NIVOLUMAB
RISK MANAGEMENT PLAN

Version Number: 42.1

Data-lock Point for this RMP: 01-May-2024

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LIST OF ABBREVIATIONS

Term	Definition
1L	First-line
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
ADCC	Antibody dependent cellular cytotoxicity
AE(s)	Adverse event(s)
AIDS	Acquired immunodeficiency syndrome
ALK	Anaplastic lymphoma kinase
APC	Adenomatous polyposis coli
ARs	Adverse reactions
ARCD	Acquired renal cystic disease
ASCT	Autologous stem cell transplant
AST	Aspartate transaminase AST
AUC	Area under the curve
AYA	Adolescent and Young Adult
BMS	Bristol-Myers Squibb
CD	Cluster of differentiation
CDC	Complement dependent cytotoxicity
CHO	Chinese Hamster Ovary
CIMP	CpG island methylator phenotype
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disorder
CPS	Combined positive score
CSR	Clinical Study Report
CRC	Colorectal cancer
CTLA	Cytotoxic T-Lymphocyte Antigen
DALY	Disability-adjusted life years
DM	Diabetes mellitus
dMMR	Mismatch repair deficient
DMTR	Dutch Melanoma Treatment Registry
DTIC	Dacarbazine
EBV	Epstein Barr Virus
EC	Esophageal cancer
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiography

Term	Definition
ECL	Electrochemiluminescence
EGFR	epidermal growth factor receptor
eGFR	Estimated glomerular filtration rate
ePPND	Enhanced pre- and postnatal development study
ESCC	Esophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
EU	European Union
GC	Gastric cancer
GCP	Good Clinical Practice
GDP	Gross domestic product
GEJC	Gastro-oesophageal Junction Cancer
GERD	Gastroesophageal reflux disease
GD	Gestation day
GI	Gastrointestinal
GLP	Good Laboratory Practice
GPV&E	Global Pharmacovigilance and Epidemiology
GVHD	Graft versus host disease
HA	Health authority
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCP	Healthcare Provider
HCV	Hepatitis C virus
HDI	Human Development Index
HIV-cHL	Human immunodeficiency virus-associated classical Hodgkin Lymphoma
HLA-DR	Human leukocyte antigen, DR subregion
HNPCC	Hereditary nonpolyposis colorectal cancer
HPV	Human papilloma virus
HSCT	Haematopoietic stem cell transplant
HuMAb	Human monoclonal immunoglobulin G4 antibody
IARC	International Agency for Research on Cancer
IB	Investigator Brochure
ICH	International Conference on Harmonization
ICSR	Individual case safety reports
IND	Investigational new drug

Term	Definition
IgG4	Immunoglobulin G4
IFN	Interferons
ILD	Interstitial lung disease
IPI	Ipilimumab
irAR	Immune-related adverse reaction
IRB	Institutional review board
IV	Intravenous
LD	Lymphocyte-depleted
LFT	Liver function tests
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MC	Mixed cellularity
MedDRA	Medical Dictionary for Regulatory Activities
MIUC	Muscle Invasive Urothelial Carcinoma
MPM	Malignant pleural mesothelioma
MSI-H	Microsatellite instability-high
N/A	Not applicable
NCCN	National Comprehensive Care Network
NCI	National Cancer Institute
NK	Natural killer
NOAEL	No Observed Adverse Effect Level
NSCLC	Non-small cell lung cancer
NSCHL	Nodular sclerosis classical Hodgkin lymphoma
NSQ	Non-squamous
OAC	Oesophageal adenocarcinoma
OC	Oesophageal Cancer
OS	Overall survival
OSCC	Oesophageal squamous cell carcinoma
PAES	Post-authorization Efficacy Study
PAHs	Polycyclic aromatic hydrocarbons
PCE	Trichloroethylene
PD-1	Programmed death–1
PD-L1	Predominant ligand, programmed death–ligand 1
PD-L2	Predominant ligand, programmed death–ligand 2
PFS	Progression-free survival

Term	Definition
PI	Package Insert
PIL	Patient Information Leaflet
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QOL	Quality of life
QPPV	Qualified Person Responsible for Pharmacovigilance
QxW	Once every x weeks
RCC	Renal cell carcinoma
RMP	Risk Management Plan
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SEER	Surveillance, Epidemiology, and End Results
SIR	Standardized incidence ratio
SmPC	Summary of Product Characteristics
SQ	Squamous
ST	Solid tumours
TEN	Toxic epidermal necrolysis
TSH	Thyroid-stimulating hormone
TRM	Treatment-related mortality
UC	Urothelial carcinoma
US	United States
2QW	Twice weekly
WHO	World Health Organization
WOCBP	Women of childbearing potential

EU RISK MANAGEMENT PLAN (RMP) FOR NIVOLUMAB

RMP version to be assessed as part of this application:

Version Number: 42.1

Data-lock Point for this RMP: 01-May-2024

Date of Final Sign-off: 24-Feb-2025

Rationale for submitting an updated RMP: Removal of the post-authorisation safety study (PASS) CA209234 from the RMP.

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part I Product Overview	NA	V41.1 / 30-Jan-2025
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	NA	V41.1 / 30-Jan-2025
SII Non-clinical part of the safety specification	NA	V6.3 / 23-Mar-2017
SIII Clinical trial exposure	NA	V41.1 / 30-Jan-2025
SIV Populations not studied in clinical trials	NA	V41.1 / 30-Jan-2025
SV Post-authorisation experience	NA	V35.1 / 23-May-2024
SVI Additional EU requirements for the safety specification	NA	V6.3 / 23-Mar-2017
SVII Identified and potential risks	NA	V41.1 / 30-Jan-2025
SVIII Summary of the safety concerns	NA	V30.1 / 26-Apr-2023
Part III Pharmacovigilance Plan	Removal of Study CA209234 from Table 3.2-1 and Table 3.3-1	V42.1 / pending
Part IV Plan for post-authorisation efficacy studies	NA	V43.1 / 17-Dec-2024
Part V Risk Minimisation Measures	Removal of Study CA209234 from Table 5.3-1	V42.1 / pending
Part VI Summary of the Risk Management Plan	Updated to align with changes in the RMP	V42.1 / pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Updated to move Study CA209234 from list of ongoing studies to completed studies.	V42.1 / pending
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	Updated to remove Study CA209234	V42.1 / pending
ANNEX 4 Specific adverse drug reaction follow-up forms	NA	V15.2 / 23-Apr-2020
ANNEX 5 Protocols for proposed and ongoing studies in RMP Part IV	NA	V43.1 / 17-Dec-2024
ANNEX 6 Details of proposed additional risk minimisation activities	NA	V15.2 / 23-Apr-2020
ANNEX 7 Other supporting data	NA	V 29.1 / 27-Oct-2022
ANNEX 8 Summary of changes to the risk management plan over time	Updated to include v42.1	V42.1 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
V36.1	24-May-2024	EMEA/H/C/003985/II/141: Type II Variation for treatment of adult patients with resectable NSCLC with OPDIVO in combination with platinum-based chemotherapy as neoadjuvant treatment followed by OPDIVO as monotherapy adjuvant treatment after surgical resection; based on CA20977T.
V40.1	27-Nov-2024	EMEA/H/C/003985/X/144: Extension Application to introduce a new pharmaceutical form (solution for injection) associated with new strength (600 mg) and new route of administration (subcutaneous use) across multiple previously approved nivolumab IV adult solid tumor indications in monotherapy, monotherapy maintenance phase following the completion of nivolumab and ipilimumab combination therapy, in combination with chemotherapy and in combination with cabozantinib.

Details of the currently approved RMP:

Version number: 41.1

Approved with procedure: EMEA/H/C/WS2717

Date of approval: 30-Jan-2025 (Opinion date)

EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Nivolumab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, monoclonal antibodies (L01FF01)
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	OPDIVO
Marketing authorization procedure	Centralized
Brief description of the product	Nivolumab is a highly specific PD-1 immune checkpoint inhibitor. The PD-1 receptor is a key regulator of T-cell activity that has been shown to control tumor-specific inhibition of T-cell responses to tumors. Engagement of the PD-1 co-inhibitory receptor on activated T-cells through PD-L1 and PD-L2, results in inhibition of T-cell proliferation, survival and cytokine secretion. Nivolumab is a IgG4 HuMAb that potentiates in vitro T-cell responses through dual ligand blockade of PD-L1 and PD-L2, and does not mediate ADCC. Expression of PD-L1 and PD-L2 by malignant cells or other cells, including immune cells, allows multiple tumor types to evade immune mediated destruction. Nivolumab restores T-cell activity either by preventing inactivation or by reactivating T-cells to mount a direct T-cell immune attack against tumor cells, including an increase in cytotoxic CD8 T-cells in the tumor, without any measurable increase in activated circulating T-cells peripheral to the tumor. Nivolumab is produced from large-scale cell culture using a CHO cell line.
Hyperlink to the Product Information	Refer to proposed PI
Indication(s) in the EEA	**Current** • 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. Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumor PD-L1 expression (see section 4.4 and 5.1 of SmPC). • OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults. • OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults. • OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

Table 1-1: Product Details

- OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1 of SmPC).
- OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.
- OPDIVO as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see section 5.1 of SmPC).
- OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.
- OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.
- OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based combination chemotherapy.
- OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (see Section 5.1 of SmPC).
- OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.
- OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) colorectal cancer (CRC) in the following settings:
  - first-line treatment of unresectable or metastatic CRC
  - treatment of metastatic CRC after prior fluoropyrimidine based combination chemotherapy (see section 5.1 of SmPC)
- OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal, or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.
- OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.
- OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1 of SmPC).
- OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC with tumour cell PD-L1 expression ≥ 1%.

Table 1-1: Product Details

	• OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC with tumour cell PD-L1 expression ≥ 1%. • OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1% (see section 5.1 of SmPC for selection criteria). • OPDIVO in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma. • OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma. **Proposed** None
Dosage in the EEA	**Current** **OPDIVO as monotherapy** The recommended dose of OPDIVO is either nivolumab 240 mg every 2 weeks **or** 480 mg every 4 weeks depending on the indication and population (see sections 5.1 and 5.2 of the SmPC), as presented in Table 1.

Table 1-1: Product Details

Table 1: Recommended dose and infusion time for intravenous administration of nivolumab monotherapy

Indication*	Recommended dose and infusion time
Melanoma (advanced or adjuvant treatment)	Adults and adolescents (12 years of age and older weighing at least 50 kg): 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes or over 30 minutes (adjuvant melanoma, see section 5.1)
	Adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30 minutes **or** 6 mg/kg every 4 weeks over 60 minutes
Renal Cell Carcinoma Muscle invasive urothelial carcinoma (MIUC) (adjuvant treatment)	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Oesophageal or Gastro-oesophageal Junction Cancer (adjuvant treatment)	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks, followed by 480 mg every 4 weeks over 30 minutes
Non-Small Cell Lung Cancer Classical Hodgkin lymphoma Squamous Cell Cancer of the Head and Neck Urothelial Carcinoma Esophageal Squamous Cell Carcinoma	240 mg every 2 weeks over 30 minutes

*As per monotherapy indication (Section 4.1 of SmPC)

If melanoma, RCC, OC, GEJC or MIUC (adjuvant treatment) patients need to be switched from the 240 mg every 2 weeks schedule to the 480 mg every 4 weeks schedule, the first 480 mg dose should be administered two weeks after the last 240 mg dose. Conversely, if patients need to be switched from the 480 mg every 4 weeks schedule to the 240 mg every 2 weeks schedule, the first 240 mg dose should be administered four weeks after the last 480 mg dose.

Table 1-1: Product Details

OPDIVO in combination with ipilimumab

Melanoma

In adults and adolescents 12 years of age and older and weighing at least 50 kg, the recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks (see sections 5.1 and 5.2 of the SmPC), as presented in Table 2. For the monotherapy phase, the first dose of nivolumab should be administered:

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks; **or**
- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480 mg every 4 weeks.

In adolescents 12 years of age and older weighing less than 50 kg, the recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 3 mg/kg every 2 weeks **or** 6 mg/kg every 4 weeks (see sections 5.1 and 5.2 of the SmPC), as presented in Table 2. For the monotherapy phase, the first dose of nivolumab should be administered:

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 3 mg/kg every 2 weeks; **or**
- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 6 mg/kg every 4 weeks.

Table 1-1: Product Details

Table 2: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for melanoma

	Combination phase, every 3 weeks for 4 dosing cycles	Monotherapy phase
Nivolumab	Adults and adolescents 12 years of age and older: 1 mg/kg over 30 minutes	Adults and adolescents (12 years of age and older and weighing at least 50 kg): 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes Adults and adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30 minutes **or** 6 mg/kg every 4 weeks over 60 minutes
Ipilimumab	Adults and adolescents 12 years of age and older: 3 mg/kg over 30 minutes	-

RCC

The recommended dose is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks, (RCC only) as presented in Table 3. For the monotherapy phase, the first dose of nivolumab should be administered;

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks; or
- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480 mg every 4 weeks.

Table 3: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for RCC

	Combination phase, every 3 weeks for 4 dosing cycles	Monotherapy phase
Nivolumab	3 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes (RCC only)
Ipilimumab	1 mg/kg over 30 minutes	-

Table 1-1: Product Details

dMMR or MSI-H colorectal cancer
The recommended dose for first-line treatment of dMMR or MSI-H CRC is 240 mg of nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for a maximum of 4 doses, followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks, as presented in Table 4. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.
The recommended dose in patients who received prior fluoropyrimidine based combination chemotherapy for dMMR or MSI-H CRC is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab monotherapy administered intravenously 240 mg every 2 weeks, as presented in Table 4. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab.

Table 4: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for dMMR or MSI-H CRC

		Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	First-line	240 mg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes
	After prior fluoropyrimidine-based combination chemotherapy	3 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes
Ipilimumab		1 mg/kg over 30 minutes	-

Table 1-1: Product Details

MPM

The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks. Treatment is continued for up to 24 months in patients without disease progression.

OSCC

The recommended dose of nivolumab in combination with ipilmumab for unresectable advanced, recurrent or metastatic OSCC with tumour cell PD-L1 expression ≥ 1% is either 3 mg/kg nivolumab every 2 weeks or 360 mg nivolumab every 3 weeks administered intravenously over 30 minutes in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

HCC

The recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for up to 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks, as presented in Table 5. For the monotherapy phase, the first dose of nivolumab should be administered:

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks or 480 mg every 4 weeks.

Table 5: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for HCC

	Combination phase, every 3 weeks for 4 dosing cycles	Monotherapy phase
Nivolumab	1 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes
Ipilimumab	3 mg/kg over 30 minutes	-

Table 1-1: Product Details

OPDIVO in combination with cabozantinib

RCC

The recommended dose is nivolumab administered intravenously at either 240 mg every 2 weeks or 480 mg every 4 weeks in combination with 40 mg cabozantinib administered orally every day.

Table 5: Recommended doses and infusion times for intravenous administration of nivolumab in combination with oral adminitration of cabozantinib for RCC

	Combination phase
Nivolumab	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Cabozantinib	40 mg once daily

Duration of treatment

Treatment with OPDIVO, either as a monotherapy or in combination with ipilimumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (and up to maximum duration of therapy if specified for an indication).

For adjuvant therapy, the maximum treatment duration with OPDIVO is 12 months.

For OPDIVO in combination with cabozantinib as first-line treatment of adult patients with advanced renal cell carcinoma, OPDIVO should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Cabozantinib should be continued until disease progression or unacceptable toxicity. Refer to SmPC for cabozantinib.

Dose escalation or reduction is not recommended for OPDIVO as monotherapy or in combination with other therapeutic agents. Dosing delay or discontinuation may be required based on individual safety and tolerability.

Atypical responses (ie, an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab or nivolumab in combination with ipilimumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Table 1-1: Product Details

	OPDIVO in combination with ipilimumab and chemotherapy The recommended dose of nivolumab in combination with ipilimumab and chemotherapy for NSCLC is nivolumab 360 mg administered as an intravenous infusion over 30 minutes every 3 weeks and ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes every 6 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression. When administered with ipilimumab and chemotherapy, nivolumab is administered first followed by ipilimumab and then histology-based platinum doublet chemotherapy on the same day, every 3 weeks (for 2 cycles). **OPDIVO in combination with chemotherapy** • The recommended dose for gastric, gastro-oesophageal junction or oesophageal adenocarcinoma is 360 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 3 weeks or 240 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 2 weeks. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. • The recommended dose of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy for unresectable advanced, recurrent or metastatic OSCC with tumour cell PD-L1 ≥ 1% is 240 mg every 2 weeks or 480 mg every 4 weeks administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. • The recommended dose for neoadjuvant treatment of NSCLC is 360 mg nivolumab administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for 3 cycles. • The recommended dose for first-line treatment of unresectable or metastatic urothelial carcinoma is 360 mg nivolumab administered intravenously over 30 minutes in combination with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks over 30 minutes **or** at 480 mg every 4 weeks over 30 minutes (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months from first dose, whichever comes first. **Proposed:** None
Pharmaceutical form (s) and strength(s)	**Current** Concentrate for solution for infusion; 10 mg/mL Presentations: 120 mg/12 mL vial (10 mg/mL), 100 mg/10 mL vial (10 mg/mL), 40 mg/4 mL vial (10 mg/mL), and 240 mg/24 mL vial (10 mg/mL)
Is/will the product be subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

2.1.1 Melanoma

Table 2.1.1-1: Epidemiologic Characteristics of Melanoma

Advanced Melanoma	
Incidence	Worldwide incidence of melanoma has steadily increased over the last several decades.[1,2,3,4,5] An analysis of data from 18 European cancer registries showed that between 1995 and 2012 the incidence of both invasive and in situ melanoma increased annually by 4 and 7.7 percent, respectively, in men and by 3 and 6.3 percent, respectively, in women.[6] The overall increase in the incidence of invasive melanoma was predominantly due to an increase in the incidence of thin tumors. Incidence of melanoma is rare in paediatric populations, particularly in youngest children, and incidence increases with age with an estimated rate of 13 per million per year in the ages 15-19 adolescent patients.[7] Since 1970, the increase in incidence of paediatric melanoma is on average 2-2.9% per year with higher rates of melanoma occurring among children of older ages. [8,9] From 1982 to 2011, melanoma incidence rates doubled in the US, while mortality rates remained constant.[3] In 2011, the overall age-adjusted incidence of melanoma was 19.7 per 100,000. In the period 2010 to 2014, the average annual incidence among non-Hispanic whites aged ≥15 years was 33/100,000 (41.7/100,000 men and 27.2/100,000 women); among women only, melanoma incidence decreased significantly among those aged 15 to 34 years and increased significantly among those aged ≥ 45 years.[10] Annual incidence has risen as rapidly as 4–6% in many fair-skinned populations that predominate regions like North America, Northern Europe, Australia, and New Zealand. Increases in incidence rates vary considerably across populations of different ethnicity and geographical location, and even within populations across age and gender.[2,11,12,13,14,15]
Prevalence	Prevalence of melanoma, like incidence, varies widely worldwide. Recent data are limited. According to GLOBOCAN 2018 and the IARC, the most recent source of global prevalence data, the approximate 1 year prevalence figures for melanoma are:[16] • World : 258,656 cases • Europe: 132,097 cases • United States: 67,682 cases • Eastern Asia: 8,229 cases • Australia/New Zealand: 16,344 cases • Central America: 2,719 cases • South America: 11,115 cases
Demographics of the population: age, gender, racial and/or ethnic origin	In a SEER analysis, 85% of melanoma cases age <18 years of age were non-Hispanic white, 5% were Hispanic and 2% were Asian/Pacific Islanders.[9]

Table 2.1.1-1: Epidemiologic Characteristics of Melanoma

Advanced Melanoma	
	In the overall population, incidence and mortality were higher in men than women[17,18]except in Europe where the opposite was observed.[17,19] For example, in the US and Australia, the number of deaths from melanoma was approximately twice as high in men as in women.[17,20] Incidence, poorer prognosis, and mortality all increased with increasing age.[17] The biology and pathogenesis of melanoma in the pediatric setting is poorly investigated; however, the immune system reactivity known to diminish with age represents a biological factor believed to contribute to better prognosis of melanoma in pediatric ages compared to adults.[21] Incidence increased in white populations residing at lower latitudes (eg, incidence rates were higher among Australians than among Europeans). In an analysis on health insurance claims data from 10,316 patients with advanced or metastatic melanoma in US, 61% were men, and mean ± SD age was 62 ±15. However, the age distribution was likely to be under-estimated for the melanoma population in US due to under-representation of individuals of age 65 or older due to insurance coverage choices (BMS study CA209161).
Risk factors for the disease	Risk factors for melanoma of the skin may be genetic or environmental:[22,23,24,25,26,27] • Large number of atypical nevi (moles) - strongest risk factor for malignant melanoma in fair-skinned populations • Fair complexion, blue eyes, red or fair hair • High, intermittent exposure to ultraviolet radiation • Family history • Genetic alterations (mutation of BRAF or KIT gene; amplification of cyclin D1 or cyclin-dependent kinase 4 gene) • Geographic location Epidemiologic studies suggest a positive association with history of sunburn, particularly sunburn at an early age. Several factors have been linked to the rising worldwide incidence of melanoma. These include: increased exposure to ultraviolet radiation; behavioral change (such as increased sunning or use of tanning beds); increased surveillance and detection.[22]
Main treatment options	Since the approval of first therapeutic agents for melanoma there has been rapid and ongoing evolution as new regimens are explored. These are best summarized in "living documents" such as: • NCCN guideline: Melanoma Cutaneous v3.2022.[28] • ESMO guideline: Cutaneous Melanoma: ESMO Clinical Practice Guidelines.[29] • NCCN guideline: AYA Oncology v3.2023.[30] Per the NCCN guidelines for AYA oncology, conventional melanomas in AYAs have a similar behavior and genomic signature when compared to melanomas in older patients, and these patients should be offered similar treatment options.[28,30] Immunotherapy has become a cornerstone of the melanoma treatment armamentarium. An unmet need exists in adolescent patients, in whom current therapeutic strategies for adults are applied due to the similarity of disease and a

Table 2.1.1-1: Epidemiologic Characteristics of Melanoma

Advanced Melanoma	
	paucity of dedicated clinical trials, to further understand treatment outcomes in patients with adolescent melanoma.
Mortality and morbidity (natural history)	Melanoma mortality trends are variable and, as with incidence, are influenced by geography, ethnicity, age, and sex.[31,32,33,34,3,13] Melanoma mortality rates have marginally increased among fair-skinned populations.[13] Same with melanoma incidence, among fair-skinned populations, melanoma mortality rate is highest in low-latitude regions.[2] In high-risk regions like New Zealand, Australia, North America, and Europe, mortality rates historically increased until the 1980s, peaked between 1988 and 1990, and then gradually maintained a slow increase. Over the last decade, mortality rate has steadily increased at 1.5% in the highest observed countries of New Zealand and Australia.[13] In Scandinavia, mortality rate has also steadily increased over the last decade, with annual ASR in Norway at 6×10^{-5} per person and 4×10^{-5}/ person in Sweden. In the United Kingdom, mortality rate has risen steadily at 1.59% per year. The US mortality rate has slowed to a 0.20% annual increase. Similar trends have also been reported in East Asian populations.[35]
Important co-morbidities	There are no identified comorbid conditions specifically or more frequently associated with metastatic melanoma than in the general population. Patients over 40 years of age diagnosed with advanced melanoma share with all individuals in this age range the susceptibility to chronic diseases prevalent among this age group.

2.1.2 NSCLC

Table 2.1.2-1: Epidemiologic Characteristics of NSCLC

NSCLC	
Incidence	Lung cancer is the most common cancer in the world with an estimated 2.1 million new cases annually. The age-standardized incidence rate (ASR) of lung cancer worldwide was estimated to be 22.4 per 100,000 in 2020 (31.5 per 100,000 men and 14.6 per 100,000 women). Generally, incidence is falling among men and increasing among women, with only a few countries showing signs of a peak and decline among women. Given these differential trends by sex, rates of lung cancer in men and women are converging in several European countries. In the United States, lung cancer incidence rates are now higher among young women than among young men.[36] According to GLOBOCAN 2020,[37] ASRs per 100,000 for lung cancer are highest in North America (32.6), Eastern Asia (34.4), and Europe (29.4). Rates are lowest in Africa overall (6.2), but with variability across regions: from Western Africa (with the lowest rate at 2.2) to Southern Africa (with the highest rate at 16.9). Due to its size and high incidence rate, China accounts for 35% of all incident cases. • Europe: 29.4/100,000 • Western Europe: 32.7/100,000 • Northern Europe: 29.7/100,000 • Southern Europe: 28.7/100,000 • Central and Eastern Europe: 26.9/100,000 • North America: 32.6/100,000 • South America: 13.6/100,000 • Central America: 5.2/100,000 • Asia: 22.9/100,000 • Eastern Asia: 34.4/100,000 • Australia/New Zealand: 25.2/100,000 • Africa: 6.2/100,000 Most lung cancer statistics include both small cell lung cancer (SCLC) and NSCLC. Approximately 84% of lung cancers are NSCLC.[38] For NSCLC specifically, US age-adjusted incidence rates are 38.05 per 100,000 (42.33 per 100,000 men and 34.88 per 100,000 women).[39]
Prevalence	According to GLOBOCAN 2020,[37] 5-year prevalence rates per 100,000 are highest in North America (78.1), Europe (66.9), Australia, and New Zealand (58.9), and Eastern Asia (57.0). Rates are lowest in Africa overall (3.0), but with variability across regions: from Western Africa (0.9) to Southern Africa (12.0). Worldwide prevalence is 27.9 per 100,000. China accounts for 34% of all prevalent cases. • World: 27.9/100,000 • Europe: 66.9/100,000 • Western Europe: 84.1/100,000 • Northern Europe: 76.0/100,000 • Southern Europe: 67.6/100,000 • Central and Eastern Europe: 51.7/100,000

Table 2.1.2-1: Epidemiologic Characteristics of NSCLC

NSCLC	
	• North America: 78.1/100,000 • South America: 15.3/100,000 • Central America: 5.4/100,000 • Asia: 26.6/100,000 • Eastern Asia: 57.0/100,000 • Australia/New Zealand: 58.9/100,000 • Africa: 3.0/100,000
Demographics of the population: age, gender, racial and/or ethnic origin	In a study of 20,461 patients with NSCLC in Denmark,[40] the age distribution was 17%, 32%, 35%, and 15% for ages < 60, 60-69, 70-79, and 80+ years, respectively. Fifty-three percent were men. Based on US SEER data through 2017, the median age at diagnosis for cancer of the lung and bronchus in the US is 71 years of age with 1.1% diagnosed prior to age 45, 6.6% diagnosed between 45 and 54; 21.8% between5 5 and 64; 31.4% between 65 and 74; 26.6% between 75 and 84; and 9.7% after age 85.[41]
Risk factors for the disease	Tobacco use is a major risk factor for lung cancer, accounting for > 90% of lung cancer in men and 75-85% of lung cancer in women.[42] Secondhand tobacco smoke can explain 1.6% of lung cancer[43] and based on a systematic review, a relative risk of 1.14-5.20 was reported for non-smokers who lived with a smoker.[44] Urban air pollution, such as emission rich in various PAH compounds, may account for 11% of lung cancer.[43] Occupational exposures to crystalline silica, chrysotile asbestos, and radioactive particulate mass (eg, uranium miners and nuclear plant workers) are also risk factors of lung cancer.[45] Hereditary genetic risk factors include TP53 germline sequence variations, germline EGFR T790M sequence variation. A marker on chromosome 15 coding for subunits of the nicotinic acetylcholine receptor may increase nicotine addiction and in turn the risk of developing lung cancer.[46,47] Never-smokers who developed NSCLC were more likely to be young female (mostly, adenocarcinoma) and have poorly differentiated tumors with higher max standardized uptake value on positron emission tomography than smokers.[48] Hyperthyroid function was associated with a 2-3 fold increased risk of lung cancer in a prospective study of 29,691 individuals, whereas hypothyroidism was not found to be a risk factor.[49]
Main treatment options	Since the approval of first therapeutic agents for NSCLC there has been rapid and ongoing evolution as new regimens are explored. These are best summarized in “living documents” such as: • NCCN guideline: Non-Small Cell Lung Cancer v1.202250 v5.2018. • ESMO guideline: Early-Stage and Locally Advanced (non-metastatic) Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines.51 • ESMO Clinical Practice Guideline: Metastatic Non-Small-Cell Lung Cancer.[52]

Table 2.1.2-1: Epidemiologic Characteristics of NSCLC

NSCLC	
Mortality and morbidity (natural history)	Lung cancer is the leading cause of cancer mortality worldwide, accounting for 1.8 million deaths in 2020, 18% of all cancer deaths that year.[37] Mortality rates vary widely. According to GLOBOCAN 2020,[37] the highest death rates in men were reported in Central and Eastern Europe (42.0), Eastern Asia (39.7), while the highest mortality rates for women were reported in Eastern Asia (17.8), Northern Europe (17.5), and North America (16.9). • Europe: 22.6/100,000 – Western Europe: 23.8/100,000 – Northern Europe: 20.1/100,000 – Southern Europe: 21.9/100,000 – Central and Eastern Europe: 22.7/100,000 • North America: 19.3/100,000 • South America: 11.8/100,000 • Central America: 4.8/100,000 • Asia: 19.3/100,000 – Eastern Asia: 28.2/100,000 • Australia/New Zealand: 16.2/100,000 • Africa: 5.6/100,000
Important co-morbidities	Co-morbidities in patients with NSCLC may include adverse effects or sequela of previous cancer therapies, and diseases/conditions that share common risk factors with lung cancer such as hypertension, ischemic heart disease, cerebrovascular disease, and COPD. Febrile neutropenia is a major complication of chemotherapy and can be life-threatening. Risk for developing febrile neutropenia is greater in patients with poor performance status, advanced-stage disease, of age ≥ 65, and those who had previous chemotherapy. [53] Use of chemotherapy/radiation was associated with increased risks of ischemic heart diseases, conduction disorders, cardiac dysfunction, and heart failure.[54]

2.1.3 MPM

Table 2.1.3-1: Epidemiologic Characteristics of MPM

Advanced MPM	
Incidence	MPM is a rare but aggressive malignancy of the pleural surface, commonly associated with occupational asbestos exposure.[55] Mesothelioma can have a very long latency period and cases continue to be diagnosed in countries that have banned asbestos.[56] In fact, some countries have continued to see increased incidence 30-40 years after banning asbestos.[57,58,59] In 2018, there were an estimated 30,443 new cases of mesothelioma. Most cases are accounted for by 8

Table 2.1.3-1: Epidemiologic Characteristics of MPM

Advanced MPM	
	countries: the US (13.5%), the UK (10.2%), China (10.1%), Japan (7.0%), Italy (6.4%), Germany (5.8%), India (5.5%), and France (4.6%). Cases are more common in men (21,662 cases) than women (8,781 cases). Data quality and completeness is uneven across the world. A study of the WHO Mortality Database (1994-2014) found that of 230 countries, 59 had mesothelioma mortality data of sufficient quality to use for reference rates, 45 countries had poor quality data, and 126 countries had no data.[60] A similar study had consistent findings and concluded that 1 mesothelioma case has been overlooked for every 4-5 reported cases.[61]
Prevalence	Of the estimated 31,250 5-year prevalent cases, most are concentrated in 8 countries: the US (13.7%), China (10.2), the UK (9.5%), Japan (6.8%), Italy (6.3%), India (5.8%), Germany (5.5%), and France (4.4%).[93]
Demographics of the population: age, gender, racial and/or ethnic origin	Male rates for mesothelioma are much higher than female rates and industrialized countries have much higher rates than non-industrialized countries. These disparities arise from the use of asbestos in industry and the predominance of male workers in the production of asbestos-containing materials.[55] However, the burden among women cannot be discounted. A study in Italy found that 32% of pleural mesothelioma cases were in women, which the authors attributed to non-occupational asbestos exposures and the presence of women in the workforce in several industrial settings (such as textiles).[62] Due to the long latency period, risk increases with age.[62]
Risk factors for the disease	Strong epidemiological evidence, including biological plausibility, has determined that mesothelioma of the pleura and peritoneum is predominantly caused by exposure to asbestos.[58] Other causes may include exposure to erionite (an asbestos-type silicate mineral) and chest wall radiation.[63] An oncogenic virus (simian virus 40) may be an independent causal factor or a contributing factor in those with asbestos exposure.[64]
Main treatment options	Patients may be undertreated. A US study found that 20–30% of patients with malignant mesothelioma received no cancer-directed therapy and only 60% received systemic therapy.[65] Since the approval of the first therapeutic agents for malignant pleural mesothelioma, there has been rapid and ongoing changes to the treatment landscape. These are best summarized in "living documents" such as: 1) NCCN guideline: Malignant Pleural Mesothelioma. v1.2020.[66] 2) ESMO guideline: Malignant Pleural Mesothelioma. ESMO Clinical Practice Guidelines.[67]
Mortality and morbidity (natural history)	Patients with MPM usually have a very poor prognosis with an expected survival of 9-12 months after diagnosis,[55] although newer treatments have extended median survival.[66]

Table 2.1.3-1: Epidemiologic Characteristics of MPM

Advanced MPM	
	As with incidence and prevalence, the majority of the estimated 25,576 fatal cases in 2018 were concentrated in 8 countries:[93] the UK (11.2%), China (10.3%), the US (9.6%), Italy (7.3%), Japan (6.7%), Germany (6.5%), India (6.2%), and France (5.0%).
Important co-morbidities	Poorer all-cause survival among patients with MPM is associated with: older age (70+ years), sarcomatoid histology (versus epithelioid), and higher stage at diganosis.[64]

2.1.4 RCC

Table 2.1.4-1: Epidemiologic Characteristics of RCC

Advanced RCC	
Incidence	The incidence of RCC is increasing worldwide and is positively correlated with gross domestic product per capita,[68] also globally it varies widely from region to region,[69] with the highest rates observed in the Czech Republic and North America.[70] In the US, there are approximately 74,000 new cases and almost 15,000 deaths from RCC each year.[71] In the EU, there were approximately 137,000 cases of RCC and 55,000 deaths due to kidney cancer in 2018.[72] RCC is approximately 50 percent more common in men compared with women.[73] RCC occurs predominantly in the sixth to eighth decade of life with median age at diagnosis around 64 years of age, according to the 2020 NCI US SEER Cancer Statistics Review; [74] it is unusual in patients under 40 years of age and rare in children.[75] Within the US, Asian Americans or Pacific Islanders have the lowest incidence of renal cancers compared with American Indians/Alaska natives, Hispanic/ Latinos, Whites, or African Americans.[76] • World: 4/100,000 • Europe: 8.1/100,000 • EU: 8.0/100,000 • North America: 11.8/100,000 – US: 12.1/100,000 – Canada: 8.4/100,000 • South America: 3.1/100,000 • Central America: 3.4/100,000 • Asia: 2.1/100,000 – Eastern Asia: 2.8/100,000 • Australia/New Zealand: 8.1/100,000 • Africa: 1.2/100,000 The incidence of RCC varies widely among European countries, with the highest incidence rates reported for the Czech Republic, with up to 15.3 cases per 100,000 among males.[77] Although RCC incidence rates range widely among

Table 2.1.4-1: Epidemiologic Characteristics of RCC

Advanced RCC	
	individual regions, the incidence rate for men is consistently approximately twice that observed for women across all regions examined.[77]

Prevalence	According to GLOBOCAN 2018, IARC, the most recent source identified that provided prevalence data, the approximate 5-year prevalence figures for kidney cancer are:[78]
	• World: 13.4 /100,000
	• Europe: 48.6 /100,000
	  o Western Europe: 56.4 /100,000
	  o Northern Europe: 54.5 /100,000
	  o Southern Europe: 46.4 /100,000
	  o Central and Eastern Europe: 42.5 /100,000
	• North America: 52.5/100,000
	• US: 52.3 /100,000
	• Canada: 54.0 /100,000
	• South America: 14.2 /100,000
	• Central America: 7.3 /100,000
	• Asia: 7.7 /100,000
	• Eastern Asia: 15.3 /100,000
	• Australia/New Zealand: 47.1 /100,000
	• Africa: 2.3/100,000

Demographics of the population: age, gender, racial and/or ethnic origin	RCC occurs approximately twice as frequently in men as in women, and incidence appears to be the highest for black males.[79] The average age at diagnosis is in the early 60's.[79] The incidence of RCC is highest in Europe, North America, and Australia/New Zealand, and is lowest in Asia and Africa.[79]
Risk factors for the disease	Smoking, obesity, hypertension, ARCD, and family history/genetics are established risk factors for RCC.[79, 80,81,82,83,84,85] A diet high in fruits/vegetables appeared to be associated with a lower risk of RCC, but no particular nutrient components were identified to be protective against RCC.[86]
Main treatment options	Since the approval of first therapeutic agents for RCC there has been rapid and ongoing evolution as new regimens are explored. These are best summarized in "living documents" such as: 3) NCCN guideline: Kidney Cancer Version 2.2020.[87] 4) ESMO guideline: Renal Cell Carcinoma, updated February 2020.[88]
Mortality and morbidity (natural history)	RCC has the highest mortality rate of the genitourinary cancers and accounts for approximately 1.5% of all cancer deaths. More than a third of patients with RCC will die from the disease.[80,89] Although rates vary regionally, the overall mortality rates for RCC are highest in North America, Australia/New Zealand, and Europe and are lowest in Africa and Asia.[90] As with incidence, the mortality rate for women is approximately half that observed for men.[80] According to GLOBOCAN 2018 data the estimated global age-standardized mortality rates for kidney cancer were: [78] • World: 1.8/100,000

Table 2.1.4-1: Epidemiologic Characteristics of RCC

Advanced RCC	
	• Europe: 12.8 /100,000 – Central and Eastern Europe: 3.0 /100,000 – Western Europe: 3.1 /100,000 – Northern Europe: 2.7 /100,000 – Southern Europe: 2.3 /100,000 • North America: 2.5 /100,000 – US: 2.5 /100,000 – Canada: 2.4 /100,000 • South America: 2.1 /100,000 • Central America: 2.7 /100,000 • Asia: 1.4 /100,000 – Eastern Asia: 1.6 /100,000 • Australia/New Zealand: 2.5 /100,000 • Africa: 1.2 /100,000 Mortality rates are stable or decreasing in the majority of Western countries, however, the decline is more pronounced in Western compared to Eastern Europe and North compared to South America.[72] RCC mortality continues to rise in Eastern Europe, however, renal cancer contributes to a greater average number of years of life lost (a measure of cancer burden dependent on patient age at death and the number of deaths at each age) than both colorectal and prostate cancer.[91]
Important co-morbidities	Comorbidity is common among RCC patients. A US-based case-control study of over 1,000 RCC patients found that 24% of patients had at least 2 significant comorbid conditions at the time of cancer diagnosis.[72] Hypertension was identified in 58% of RCC cases, while DM was present at a frequency of 17% among RCC patients.[72] Moreover, RCC may present with a variety of paraneoplastic syndromes (eg, polycythemia secondary to excessive secretion of erythropoietin, hypercalcemia secondary to derangement of serum factors regulating calcium, and hepatic dysfunction such as Stauffer syndrome).[92]

2.1.5 cHL

Table 2.1.5-1: Epidemiologic Characteristics of cHL

Relapsed/Refractory cHL	
Incidence	cHL is a rare human cancer with an estimated worldwide crude incidence rate of 0.9 / 100,000. Approximately 17,000 new cases occur in Europe annually, and 9,000 in Northern America.[93] According to GLOBOCAN 2018, IARC, the estimated global ASR for cHL are: • World: 0.98/100,000 • Europe: 2.4/100,000

Table 2.1.5-1: Epidemiologic Characteristics of cHL

Relapsed/Refractory cHL	
	• US: 2.5/100,000 • Canada: 2.1/100,000 • South America: 1.5/100,000 • Central America: 1.6/100,000 • Asia: 0.59/100,000 • Eastern Asia: 0.35/100,000 • Australia/New Zealand: 2.5/100,000 • Africa: 0.92/100,000 According to GLOBOCAN 2018, IARC, the estimated global age-standardized risk incidence rates for cHL in the world is: • 0.8 (33,431 cases) for females • 1.1 (46,559 cases) for male
Prevalence	The number of new cases of Hodgkin lymphoma was 2.5 per 100,000 men and women per year. The number of new cases in US during 2018 was 8500 (SEER). According to GLOBOCAN 2018, IARC, the most recent source of global prevalence data, the approximate 5-year prevalence figures for cHL are:[93] • World: 3.6/100,000 • Europe: 10.4/100,000 • US: 12.1/100,000 • Canada: 10.2/100,000 • South America: 5.7/100,000 • Central America: 5.5/100,000 • Asia: 2.0/100,000 • Eastern Asia: 1.5/100,000 • Australia/New Zealand: 12.2/100,000 • Africa: 2.0/100,000 In 2015, there were an estimated 208,805 people living with Hodgkin lymphoma in the US (SEER)
Demographics of the population: age, gender, racial and/or ethnic origin	Overall, cHL has a bimodal age distribution impacting young adults and older adults more than middle aged adults.[94,95,96] cHL is the most commonly diagnosed cancer in adolescents 15-19 years of age.[94] cHL occurs more often in males than females; however, some variation appears by subtype.[97] Over two-thirds of cHL cases in developed countries are the NSCHL subtype.[95]
Risk factors for the disease	EBV infection increases the risk of cHL by 3-4 fold.[95,98] HIV-infected individuals (especially those with AIDS) have an up to 10-fold increase in incidence of cHL. HIV-cHL is usually MC or LD type cHL, is of advanced stage at diagnosis and has a near-universal association with EBV infection.[95,98,99]

Table 2.1.5-1: Epidemiologic Characteristics of cHL

Relapsed/Refractory cHL	
Main treatment options	Since the approval of first therapeutic agents for Hodgkin lymphoma, there has been a rapid and ongoing evolution as new regimens are explored. These are best summarized in" living documents" such as: 1) NCCN guideline: Hodgkin lymphoma, v3.2018 - 16-Apr-2018[100] 2) ESMO guideline: Hodgkin lymphoma: ESMO Clinical Practice guidelines.[101]
Mortality and morbidity (natural history)	According to GLOBOCAN 2018, IARC, the estimated global age-standardized mortality rates for cHL are:[93] • World: 0.30/100,000 • Europe: 0.33/100,000 • North America: 0.19/100,000 • US: 0.19/100,000 • Canada: 0.19/100,000 • South America: 0.33/100,000 • Central America: 0.39/100,000 • Asia: 0.27/100,000 • Eastern Asia: 0.13/100,000 • Australia/New Zealand: 0.20/100,000 • Africa: 0.48/100,000 According to GLOBOCAN 2018, IARC, the estimated global age-standardized risk mortality rates for cHL in the world is: • 0.2 (10,397 cases) for females • 0.4 (15,770 cases) for male
Important co-morbidities	cHL has a bimodal age distribution and comorbidities typical for each age group are found. However, limited research into the impact of comorbidity presence in elderly cHL patients has identified several frequently occurring comorbidities that may influence the use of chemotherapy and overall outcome of elderly cHL patients.[102,103] Serious comorbidities identified by van Spronsen were: cardiovascular disease, hypertension, COPD, and DM.

2.1.6 SCCHN

Table 2.1.6-1: Epidemiologic Characteristics of SCCHN

Recurrent/metastatic SCCHN	
Incidence	According to GLOBOCAN 2018, there were 888,000 incident cases of head and neck cancer in 2018, including:[104] • Cancer of the oral cavity (including lip) (C00-06): 355,000 • Cancer of the salivary glands (C07-08): 53,000 • Cancer of the oropharynx (C09-10): 93,000 • Cancer of the nasopharynx (C11): 129,000 • Cancer of the hypopharynx (C12-13): 81,000 • Cancer of the larynx (C32): 177,000 In GLOBOCAN 2012, 10.5% of cancers of the oral cavity were cancer of the lip and 3% of all head and neck cancers were in other or ill-defined sites (C14).[105] Applying these estimates to 2018 data reduces the estimated cancers of the oral cavity to 318,000. Cancers of other and ill-defined sites would total 28,000. Thus, the estimated global number of head and neck cancers (excluding the lip) is 879,000.[106]
Prevalence	The 5-year prevalence of head and neck cancer is 30.0 per 100,000, with the highest proportions in Europe (65.1/100,000) and North America (61.6/100,000).[104] Based on the GLOBOCAN project, the estimated 5-year prevalence of head and neck cancer (cancers of the larynx, the lip and oral cavity, the nasopharynx, and other pharynx, including the hypopharynx, the oropharynx, and the tonsil) in 2012 is shown below.
Demographics of the population: age, gender, racial and/or ethnic origin	Age patterns are changing due to the shifting balance of HPV+ and HPV- head and neck cancers. This is being driven by a dramatic increase in HPV+ oropharyngeal squamous cell carcinoma detected in white men under 60 years of age in North America and Europe.[107]
Risk factors for the disease	HPV- head and neck cancers are commonly associated with heavy use of tobacco and alcohol and, currently, are usually diagnosed in older patients.[108] HPV+ head and neck cancers are increasing in incidence, predominantly in North America and northern Europe, reflecting a latency of 10 to 30 years after oral-sex exposure. Since the 1980s, the percentage of US head and neck cancers diagnosed as HPV+ has increased from 16.3% to 72.7% (although this is in part due to enhanced diagnostic evaluation for HPV). The impact of prophylactic HPV vaccination on trends is unknown and may not be evident for decades.[108]
Main treatment options	Since the approval of first therapeutic agents for SCCHN there has been rapid and ongoing evolution as new regimens are explored. These are best summarized in "living documents" such as: 1) NCCN guideline: Head and Neck Cancers v3.2019 - 16-Sep-2019.[109] 2) ESMO guideline: Head and Neck Cancers. ESMO Clinical Practice Guidelines.[110]

Table 2.1.6-1: Epidemiologic Characteristics of SCCHN

Recurrent/metastatic SCCHN	
Mortality and morbidity (natural history)	GLOBOCAN 2018 estimates more than 450,000 deaths from head and neck cancer worldwide in 2018, with the highest age-standardized mortality rates in Asia (5.8/100,000) and Europe (5.0/100,000).[104] The morbidity profile of the disease has been changing due to the shifting balance of HPV+ and HPV- head and neck cancers. HPV+ patients are generally younger and healthier, with fewer comorbid conditions.
Important co-morbidities	HCV- head and neck cancer occurs most commonly in older patients with a history of heavy tobacco and/or alcohol use. No specific comorbidities, beyond those associated with patients in this age demographic (eg, cardiovascular disease, asthma/COPD, depression), are clinically significant for HCV+ head and neck cancer.

2.1.7 UC

Table 2.1.7-1: Epidemiologic Characteristics of UC

Advanced UC	
Incidence	Bladder cancer is the ninth most common cancer worldwide, affecting men 3 times more often than women.[111] UC is generally a disease of older adults, with the highest rates observed in those aged ≥ 65 years. The highest incidence of bladder cancer is in Europe and North America and the lowest is in Africa, Asia, and South America.[112] Between 2004 and 2014 the incidence of UC was falling in the US, was stable in Germany and the Netherlands, and increased in England and the Nordic countries [111] According to GLOBOCAN 2020, age-standardized incidence rates are as follows:[113] World: 5.6 per 100,000 North America: 10.9 per 100,000 Europe: 11.3 per 100,000 South America: 4.7 per 100,000 Africa: 4.5 per 100,000 Asia: 3.6 per 100,000
Prevalence	The 5-year prevalence of UC according to GLOBOCAN 2020 shows that it affects approximately 1.7 million people worldwide.[113] In individual countries, the 5-year prevalence of bladder cancer is as follows:[113] Italy:150.0 per 100,000 Bulgaria: 78.7 per 100,000 Ireland: 69.6 per 100,000 Germany: 142.4 per 100,000 Denmark: 135.6 per 100,000 Finland: 75.7 per 100,000
Demographics of the population: age, gender, racial and/or ethnic origin	The median age of UC diagnosis is 73 years old with 44% of US patients[114] and 54% of UK patients age ≥ 75 at time of diagnosis[115]

Table 2.1.7-1: Epidemiologic Characteristics of UC

Advanced UC	
	Based on US SEER data, age at diagnosis was distributed as follows: <0.1% were diagnosed under age 20; 0.4% age 20-34; 1.2% age 35-44; 5.8% age 45-54; 18.0% age 55-64; 30.9%% age 65-74; 28.5% age 75-84; and 15.1% age > 84 years.[116] .[117] Approximately 75% of new cases each year occur in men. Reasons for the difference between genders are not understood.[117,118] Rate of UC by subtype:[118] 90% transitional cell carcinomas 2% to 7% squamous cell carcinomas 2% adenocarcinomas Rarely, sarcomas
Risk factors for the disease	Tobacco Smoking is considered the most significant risk factor for UC. An estimated 37-50% of UC cases are attributed to smoking.[115,119] Occupational exposures are the next most significant risk factor as a group in UC. Estimated risk attribution of occupational exposures in UC ranges from 6-20%.[115,119] Occupational exposure risk factors include:[115,118,120] Aromatic amines (eg, benzidine, 4-aminobiphenyl, 2-naphthylamine, and 4-chloro-o-toluidineare) used in production of dyes, rubber, and textiles PAHs (eg, combustion of fossil and carbon-containing fuels such as wood, coal, diesel, and fat by products, coal-tar pitch, and soot) PCE used in dry cleaning Working in aluminium production, auramine production, magenta production, rubber production, painting, dry cleaning, textile manufacturing, printing processes, or working as a hairdresser/barber, leatherworker, shoemaker, painter, or metalworker
Main treatment options	Since the approval of the first therapeutic agents for UC, there has been a rapid and ongoing evolution in treatments as new regimens are explored. These are best summarized in "living documents" such as: 1) NCCN guideline: Bladder Cancer v3.2020[121] 2) ESMO guideline: Bladder cancer ESMO Clinical; Practice Guidelines[122]
Mortality and morbidity (natural history)	Bladder cancer is the 13th leading cause of death. Mortality rates have been decreasing in developed countries, with the exception of countries undergoing rapid economic transition, including in Central and South America, Europe, and the Baltic countries.[123] According to GLOBOCAN 2020, the age-standardized mortality rates in 2020 are as follows:[113] World: 1.9 per 100,000 North America: 2.1 per 100,000 Europe: 3.0 per 100,000 South America: 1.6 per 100,000

Table 2.1.7-1: Epidemiologic Characteristics of UC

Advanced UC	
	Africa: 2.7 per 100,000 Asia: 1.5 per 100,000
Important co-morbidities	Cardiovascular disease, chronic pulmonary disease/COPD, hypertension, and DM are the most common comorbidities reported among patients with UC; and in all reports identified, these conditions were observed in ≥ 5% of UC patients.[124,125,126,127] Diabetes mellitus may also be considered a risk factor for development of UC.[128]

2.1.8 OSCC

Table 2.1.8-1: Epidemiologic Characteristics of Oesophageal Cancer

Advanced OC	
Incidence	According to data from GLOBOCAN database, worldwide an estimated 604,100 new oesophageal cancer cases were predicted to be diagnosed in 2020.[129] Oesophageal cancer accounts for 3.2% of new cancer cases.[130] The age-standardized incidence rate was 6.3 per 100,000 person-years.[129] Incidence rates of oesophageal cancer vary internationally by nearly 16-fold, with the highest rates found in Southern and Eastern Africa and Eastern Asia, and the lowest rates in Western and Middle Africa and Central America.[131] The age standardized incidence rates of oesophageal cancer worldwide are:[130] • Europe: 3.3/100,000 person-years • North America: 2.9/100,000 person-years • South America: 2.8/100,000 person-years • Africa: 3.6/100,000 person-years • Asia: 8.5/100,000 person-years • Eastern Asia: 12.3/100,000 person-years • Australia/New Zealand: 3.1/100,000 person-years In the US, the age-adjusted incidence rate of oesophageal cancer is 4.3 per 100,000 person-years based on 2012-2016 data from SEER. Over the last 10 years, the incidence rates have been falling on average 1.2% each year. In 2019, the estimated number of new cases of oesophageal cancer was 17,650, which accounts for 1% of all new cancer cases. Based on data from 2014 to 2016, approximately 0.5 percent of the US population can be diagnosed with oesophageal cancer at some point during their lifetime.[129] The 2 distinct histologic types of OC are OSCC and EAC. Globally, OSCC remains the predominant histological subtype; however, the incidence of OSCC has been decreasing, while the incidence of EAC has been increasing rapidly, particularly in Western Europe, North America, and Australia.[132]
Prevalence	According to data from GLOBOCAN database in 2020, the 5-year worldwide prevalence of oesophageal cancer is 7.2/100,000. The 5-year prevalence in different regions are:[130] • Europe: 8.6/100,000 person-years

Table 2.1.8-1: Epidemiologic Characteristics of Oesophageal Cancer

Advanced OC	
	• North America: 7.1/100,000 person-years • South America: 3.8/100,000 • Africa: 2.3/100,000 person-years • Asia: 11.3/100,000 person-years ○ Eastern Asia: 23.2/100,000 person-years • Australia/New Zealand: 7.8/100,000 person-years
Demographics of the population: age, gender, racial and/or ethnic origin	In the US, OC is more common in men than women, and it is associated with older age, heavy alcohol use and tobacco use.[129] OC is most frequently diagnosed among people aged 65-74, and the median diagnosis age is 68.[129] The incidence is higher in urban areas compared that in rural areas, particularly among African-American men.[133,134] The worldwide statistics indicates that there is no gender specificity in high incidence areas.[133] Lower socioeconomic status is associated with oesophageal cancer.[135]
Risk factors for the disease	Hereditary factors, smoking, alcohol consumption, dietary factors (e.g., foods containing N-nitroso compounds, chewing of areca nuts or betel quid, high temperature foods and beverages including hot tea, etc.), underlying oesophageal disease (e.g., achalasia and caustic strictures), oesophageal injury, prior gastrectomy, atrophic gastritis, HPV infection, history of head or neck cancer, Barrett's esophagus, poor oral hygiene, history of radiotherapy, and medication use (eg, Bisphosphonates), etc.[133,136,137,138,139,140,141,142,143,144]
Main treatment options	Since the approval of first therapeutic agents for OC, there has been a rapid and ongoing evolution as new regimens are explored. These are best summarized in "living documents" such as: 1) NCCN Guideline: [O]esophageal and [O]esophagogastric Junction Cancer, v2.2021[145] 2) ESMO guideline: [O]esophageal cancer[146]
Mortality and morbidity (natural history)	OC is the sixth most common cause of deaths worldwide, accounting for over 500,000 deaths annually.[129] In the US, the age adjusted mortality rate of oesophageal cancer is 4.0 per 100,000 person-years based on 2012-2016 deaths. The estimated deaths from OC was 16,080 in 2019, which accounted for 2.6% of all cancer deaths. Around 19.9% patients can survive 5 years based on data 2009-2015.[129] In the worldwide, 544,076 people with OC were projected to die in 2018, which accounted for 5.5% of all cancer deaths according to data from GLOBOCAN. The mortality rate is 6.3 per 100,000 person-years globally. The mortality rates in different areas are:[130] • Europe: 2.7/100,000 person-years • North America: 2.4/100,000 person-years • South America: 2.6/100,000 person-years • Africa: 3.4/100,000 person-years • Asia: 7.6/100,000 person-years • Australia/New Zealand: 2.4/100,000 person-years
Important co-morbidities	Underlying oesophageal diseases, obesity, and metabolic syndrome[133]

2.1.9 CRC

Table 2.1.9-1: Epidemiologic Characteristics of CRC

Advanced CRC	
Incidence	According to GLOBOCAN 2022, IARC, the most recent source of global epidemiological data, CRC is the third most commonly diagnosed cancer in both men and women.[147] Globally, 1.9 million people (1,069,446 men and 856,979 women) were newly diagnosed with CRC in 2022, accounting for 9.6% of all incident cancers.[147] The incidence of CRC varies widely worldwide with the highest estimated rates, per GLOBOCAN 2022, in Australia/New Zealand (35.3), Northern Europe (32.0), and Southern Europe (31.5). CRC incidence generally corresponds to level of socioeconomic development and CRC incidence rises with increasing socioeconomic development in countries undergoing such transitions.[148] This association suggests the influence of "Western lifestyle" factors such as unhealthy diet, obesity, and sedentariness. Based on data from the IARC, the source of the most recent cancer incidence data worldwide, the estimated numbers of incident cases of CRC and the ASRs for both genders in 2022 by HDI and world region are presented.[147] HDI is a measure of socioeconomic development where countries are ranked into four tiers based on life expectancy, education and per capita income.

	Male	**Females**	**Total**	**ASR per 100,000**
Very high HDI	530,863	453,893	984,756	28.6
High HDI	432,925	320,755	753,680	18.1
Medium HDI	81,645	60,859	142,504	6.7
Low HDI	23,745	21,143	44,888	6.4
WHO African Region	27,820	25,966	53,786	8.2
WHO Region of the Americas	170,019	158,661	328,680	21.0
WHO Eastern Mediterranean Region	29,964	23,977	53,941	8.9
WHO European Region	308,390	266,563	574,953	28.8
WHO South-East Asia Region	87,265	61,023	148,288	6.9

Table 2.1.9-1: Epidemiologic Characteristics of CRC

Advanced CRC

WHO Western Pacific Region	445,720	320,460	766,180	22.1

Three patterns of CRC incidence and mortality trends have been suggested, corresponding to position and movement on the HDI:[149]

1. Increases in both incidence and mortality, mainly in countries rapidly transitioning to medium or high HDI, including those in the Baltic region, Russia, China and Brazil.
2. Increases in incidence but decreases in mortality in high HDI countries such as Canada, the UK, Denmark and Singapore
3. Decreases in both incidence and mortality in the highest HDI countries, including the USA and France.

Worldwide, the crude number of incident cases per year is expected to grow 36.6% by 2030 due to demographic shifts, lifestyle patterns, and better and earlier detection.

The majority of CRCs occur in people older than 50. For colon cancer, the average age at the time of diagnosis for men is 67 and for women is 71. For rectal cancer, it is age 62 for men and 63 for women.[150]. An increasing trend for CRC has been reported for younger adults (age <50 years) in the US, where one in five new cases occur in this age group.[151] However, this may be due to increased screening and/or issues with the representativeness of the data.[152]

Prevalence

According to GLOBOCAN 2022, the 5-year prevalence of CRC in 2022 was as follows:

	Male	**Female**	**Total**	**Proportion per 100,000**
Very high HDI	1,704,898	1,458,490	3,163,388	192.7
High HDI	1,229,048	926,639	2,155,687	78.1
Medium HDI	202,990	155,474	358,464	15.8
Low HDI	46,820	43,422	90,242	7.5
WHO African Region	62,626	60,816	123,442	10.5
WHO Region of the Americas	538,289	505,624	1,043,913	100.6
WHO Eastern Mediterranean Region	79,300	64,773	144,073	19.0
WHO European Region	969,653	839,892	1,809,545	193.2

Table 2.1.9-1: Epidemiologic Characteristics of CRC

Advanced CRC

WHO South-East Asia Region	228,991	164,434	393,425	19.1
WHO Western Pacific Region	1,304,897	948,486	2,253,383	117.9

Demographics of the population: age, gender, racial and/or ethnic origin

The majority of CRC cases (56%) were diagnosed after age 65. Compared to women, men have a 30% higher risk for CRC.[150]

Risk factors for the disease

Risk factors for CRC are multifaceted, including hereditary predisposition, ulcerative colitis/inflammatory bowel disease, environmental exposure and lifestyle (eg, tobacco use, alcohol intake, dietary pattern, and physical inactivity) that may lead to somatic mutation. [153,154, 155]

In the Global Burden of Disease Study, a diet low in calcium/milk and alcohol use had the highest percentages of attributable age-standardized DALY globally. This pattern differed by gender. For males, alcohol use, a diet low in calcium, and smoking were the top contributing risk factors. For females, a diet low in calcium, milk and fiber were the top risk factors.[156] Tobacco use has been found to be associated with P53, KRAS, and BRAF mutations, MSI positivity, and CIMP positivity and with an increased risk of CRC.[157,158,159]

Unlike many other cancers, hereditary predisposition may account for only 5% of CRC risk[160]. APC gene is the most frequent gene that mutates in familial/inherited and sporadic colon cancer whereas HNPCC primarily derives from mutations in genes involved in DNA mismatch repair. [161,162,163] In population-based studies, the prevalence of MSI-H is 10-20% in sporadic cases of CRC and is more common among stage II tumors compared to metastatic CRC, where MSI is prevalent in 4% of tumors. [164, 165] Lynch syndrome, a hereditary syndrome characterized by an increased risk for CRC as well as other cancers, affects about 3% of CRC cases and accounts for 15-20% of MSI CRC tumors.[166]

Long-term follow-up studies have found associations between UC and inflammatory bowel disease and an increased risk of CRC .[167]

Main treatment options

Since the approval of first therapeutic agents for CRC there has been a rapid and ongoing evolution as new regimens are explored. These are best summarized in "living documents" such as:

1) NCCN guideline: Rectal Cancer, v4.2023.[168]
2) NCCN guideline: Colon Cancer, v2.2023.[169]

Table 2.1.9-1: Epidemiologic Characteristics of CRC

Advanced CRC

3) ESMO guideline: eUpdate – Metastatic Colorectal Cancer Treatment Recommendations.[170]

Mortality and morbidity (natural history)

According to GLOBOCAN 2022, CRC is the second leading cause of cancer mortality worldwide and is estimated to have caused 904,019 deaths worldwide in 2022, constituting 9% of cancer deaths.[147]. The global ASR for CRC was 8.1 per 100,000.

In contrast to incidence rates, there was less variation in mortality rates worldwide; mortality was highest in Eastern Europe (14.1 per 100,000), Southern Europe (11.4 per 100,000) and Caribbean (10.2 per 100,000). Mortality rates by HDI showed a clear bifurcation with higher rates per 100,000 in countries with very high HDI (10.5) or high HDI (8.3) and lower rates in countries with medium HDI (3.9) and low HDI (4.5).

Across WHO regions, CRC mortality in 2022 was as follows:

	Males	**Females**	**Both Sexes**	**ASR per 100,000**
WHO African Region	18,709	17,999	36,708	5.8
WHO Region of the Americas	72,708	66,873	139,581	8.1
WHO Eastern Mediterranean Region	16,463	13,455	29,918	5.1
WHO European Region	143,816	123,539	267,355	11.7
WHO South-East Asia Region	49,087	34,358	83,445	3.9
WHO Western Pacific Region	198,811	147,825	346,636	9.0

CRC mortality has been decreasing in recent years in developed countries like the US, France, and Australia and increasing in developing countries such as Brazil and Mexico.[171]

Table 2.1.9-1: Epidemiologic Characteristics of CRC

Advanced CRC	
Important co-morbidities	Approximately one-third of newly diagnosed CRC patients had severe comorbidities with poorer survival outcomes. Major comorbidities of CRC patients are similar to those in the general population of older adults, such as cardiovascular disease, hypertension, DM, cancer, and adverse outcomes from cancer therapies. [172,173,174]

2.1.10 Gastric Cancer including Gastro-oesophageal Junction Cancer and Oesophageal Adenocarcinoma

Table 2.1.10-1: Epidemiological Characteristics of Gastric Cancer including Gastro oesophageal Junction Cancer and Oesophageal Adenocarcinoma

Advanced GC including GEJC and OAC	
Incidence	GEJCs may be classified as GC or OC depending on their extension in the stomach. [175] For example, the American Joint Committee on Cancer considers GEJCs to be oesophageal unless they arise in an areas of the stomach that is > 5 cm from the gastroesophageal junction. However, the continuum of oesophageal cancer, GEJC, and GC leads to substantial variability in estimates of incidence and prevalence of GEJC.[176] The worldwide age-adjusted incidence of GC, which includes cancers of the gastric cardia such as GEJC as well as noncardia gastric cancers, was 15.7 per 100,000 for men and 7.0 per 100,000 for women in 2018. In the same year, GC comprised 5.7% of all new malignancies, or approximately 1.03 million cases of GC, making GC the fifth most common cancer worldwide.[177] In Europe, the age-standardized annual incidence rate was 8.1 cases per 100,000. European countries with the highest incidence (per 100,000) included Belarus (16.5) and the Russian Federation (13.3) in Central and Eastern Europe, Lithuania (13.3), Latvia (12.9) in Northern Europe, and Portugal (11.0) in Southern Europe. Lower incidence rates (per 100,000) were found in Sweden (3.3) and the UK (3.9). The incidence rates on other continents varied; the incidence per 100,000 in North America (4.1) and Africa (4.2) approached the lowest rates in Europe. The incidence in South America (8.7) was higher than in Europe. The highest per 100,000 incidence rates among all continents and regions was found in Asia, where the ASR was 14.3, rising to 22.4 in Eastern Asia (particularly Mongolia, Japan, and South Korea).[178] Although cardia and noncardia GC are grouped in many epidemiological summaries, the conditions have distinct geographical distributions and risk factors. Cancers of the gastric cardia such as GEJC have epidemiological characteristics similar to those of oesophageal adenocarcinoma, which typically occurs in the distal third of the esophagus.[179] The incidence of these cancers has been increasing relative to other GC types, particularly in high‐income countries.[177,180]
Prevalence	Worldwide, there were 576,347 1-year prevalent cases (7.6 per 100,000) and 1,589,752 5-year prevalent cases (20.8 per 100,000) cases of GC.[177]

Table 2.1.10-1: Epidemiological Characteristics of Gastric Cancer including Gastro oesophageal Junction Cancer and Oesophageal Adenocarcinoma

Advanced GC including GEJC and OAC	
Demographics of the population: age, gender, racial and/or ethnic origin	Prevalence patterns for GC largely followed incidence patterns, with 5-year prevalence very high in Eastern Asia (61.7 per 100,000) As a whole, Europe had a 5-year prevalence of 26.2 per 100,000, similar to Asia as a whole: 26.7 per 100,000. Within Europe, prevalence was highest in Central and Eastern Europe and lowest in Northern Europe. Five-year prevalence per 100,000 was lower in South America (13.7), North America (12.8), and Oceania (12.4) and lowest in Africa (3.1).[181] GC has been diagnosed primarily in patients age 50 years or older. Incidence rates increase with age between 55 and 80 years of age.[182] GC incidence is 2 times greater among males.[178] In the US, the incidence of GC varies across racial groups. In an analysis of SEER 9 data, including registry data through 2015, observed incidence rates among Whites (men: 7.5 per 100,000/year; women: 4.2 per 100,000/year) were lower than that for Blacks (men: 13.5 per 100,000/year; women: 7.1 per 100,000/year).[183] Age at diagnosis and stage at diagnosis also vary across racial/ethnic groups.[184,185] In a retrospective cohort study of the Kaiser Permanente Northern California cancer registry, mean age of newly diagnosed noncardia gastric adenocarcinoma was 66 for Asians, 63 for Hispanics, and 72 for Whites.[185] In a retrospective analysis of 638 patients (1999-2013),[184] 18% of non-Hispanic White patients had stage I disease compared with 9% of Hispanic patients; in contrast, at diagnosis, 48% of Hispanic patients had stage IV disease compared with 36% of non-Hispanic White patients.
Risk factors for the disease	Risk factors for these cancer types include older age, with the association more pronounced for OACs.[179,185 ,186,187] GC incidence is two times higher among males[178] and OAC is 7- to 10-times higher in males.[179] First-degree family history was found to be a risk factor of GC in both Western and Asian studies.[188,189,190] Based on the US SEER data, GC incidence among Whites was approximately half the incidence among other groups, including African Americans, Asian Americans, and Hispanics.[183] *Helicobacter pylori* is the predominant risk factor for stomach cancer and estimated to be the cause of nearly 90% of new cases of noncardia gastric cancer.[178] Prevalence of *H. pylori* explains a significant amount of geographic variation in GC incidence. However, dietary factors are also important including consumption of foods preserved by salting and low fruit intake. Alcohol consumption and active tobacco smoking are additional well-established risk factors.[191] There is no apparent association of *H. pylori* and cancers of the gastric cardia (such as GEJC),[192] which show patterns similar to OACs. In fact, there is some evidence of reduced risk for OAC with *H. pylori* infection due to its impact on reducing acid production and reflux.[179]

Table 2.1.10-1: Epidemiological Characteristics of Gastric Cancer including Gastro oesophageal Junction Cancer and Oesophageal Adenocarcinoma

Advanced GC including GEJC and OAC	
	Important risk factors for both GC and oesophageal adenocarcinoma include obesity and GERD/Barrett esophagus. GEJC-type cancers are more common in high-income countries.[178] A nationwide cohort study in Denmark, using medical databases, found that the SIR associated with being overweight or obesity for gastric cancer is 1.37 (95% CI; 1.21–1.56). [193] An earlier meta-analysis of cohort studies, reported that the RR for noncardia cancer was 1.26 (95% CI: 0.89-1.78) while the RR for cardia cancer was reported as 2.06 (95% CI: 1.63-2.61).[194] Intake of saturated fats and total cholesterol were also found to have independent positive associations with GC. [195] In a systematic review, cases were 2-fold more likely to have a high salt intake than control subjects.[196] Moderate protective associations have been reported in studies of fruit and vegetable intake among both noncardia and cardia cancer patients.[197]
Main treatment options	Since the approval of first therapeutic agents for GCs there has been a rapid and ongoing evolution as new regimens are explored. These are best summarized in "living documents" such as those listed below. The treatment approach for GC, GEJC and oesophageal adenocarcinoma overlap considerably: • NCCN guideline: Gastric Cancer, v4.2019.[198] • NCCN guideline: Esophageal and Esophagogastric Junction Cancer, v4.2019.[199] • ESMO guideline: eUpdate – Gastric Cancer Treatment Recommendations.[200] ESMO guideline: Oesophageal Cancer - ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up[201]
Mortality and morbidity (natural history)	According to the WHO/IARC GLOBOCAN project, stomach cancer is the third leading cause of cancer death, causing an estimated 783,000 deaths, or 1 in every 12 deaths globally.[178] The worldwide ASR for GC is 8.2 per 100,000.[202] In Europe, there were 102,167 deaths (ASR of 5.9 per 100,000) in 2018 with the highest mortality rates in Central and Eastern Europe. Of all GC deaths, 57.9% occurred in Eastern Asia, where the mortality rate was 15.9 per 100,000. Although it has a lower number of deaths, OC has disproportionately higher mortality, primarily because it is often found only after it has advanced or metastasized.[179] Reliable breakdowns for mortality of OAC versus oesophageal squamous cell carcinoma are not available in the literature.
Important co-morbidities	Very few studies presented data describing the incidence of post-diagnosis comorbidities among cases. In one study of 12,612 gastric cancer patients (approximately 34% of whom were diagnosed at Stage III or Stage IV), the comorbidities of importance during the 12 months after diagnosis were: anemia, atrial fibrillation, congestive heart failure, COPD, electrolyte disorder, infectious disease, hypertension, gastric ulcers, pneumonia, and thromboembolism. Each of these comorbidities affected at least 100 cases per 100 person-years within 12 months of diagnosis.[203]

2.1.11 HCC

Table 2.1.11-1: Epidemiological Characteristics of HCC

HCC	
Incidence	Liver cancer is the 6th most common malignancy with an estimated 866,136 new cancer cases occurring worldwide in 2022.[204] According to GLOBOCAN 2022, 607,361 cases (70.1%) of all new liver cancer cases occurred in Asia, with 367,657 cases (42.4%) in China.[204] The age standardized incidence rate (ASR) per 100,000 of liver cancer worldwide according to GLOBOCAN 2022 was estimated as follows:[204] • World: 8.6/100,000 • Europe: 5.1/100,000 – Eastern Europe: 4.2/100,000 – Northern Europe: 4.7/100,000 – Southern Europe: 6.2/100,000 – Western Europe: 5.5/100,000 • North America: 6.7/100,000 – US: 6.8/100,000 – Canada: 5.9/100,000 • South America: 4.4/100,000 • Central America: 6.4/100,000 • Asia: 10.0/100,000 – Eastern Asia: 14.7/100,000 • Australia/New Zealand: 6.7/100,000 • Africa: 8.5/100,000 HCC primarily occurs in patients with underlying liver disease, mostly as a result of hepatitis B or C virus infection or alcohol abuse.[205] Recent increases in non-alcoholic fatty liver disease (NAFLD) accompanied by metabolic syndrome and obesity increase the risk of liver cancer and these conditions may soon become the leading cause of liver cancer in Western countries.[206]
Prevalence	The 5-year prevalence of liver cancer was estimated at 1,163,723 worldwide according to GLOBOCAN 2022 with regional data as follows:[204]

	5-year prevalence	Per 100,000
WHO African Region	65,646	5.6
WHO Region of the Americas	112,830	10.9
WHO Eastern Mediterranean Region	67,851	8.9
WHO European Region	116,103	12.4
WHO South-East Asia Region	142,623	6.9

Table 2.1.11-1: Epidemiological Characteristics of HCC

HCC

	WHO Western Pacific Region	658,670	34.5

Demographics of the population: age, gender, racial and/or ethnic origin

The incidence of HCC is higher in men than in women.[207,208,209,210]

The incidence of HCC increases with age, but the median age at diagnosis varies by region, skewing younger in Asia and Africa and older in other regions. In Japan, North America, and Europe, the median age of onset is above 60 years. In other Asian countries HCC is commonly diagnosed before age 60.[211]

In the US the incidence of HCC is highest among Asian/Pacific Islanders and lowest among Whites.[212]

Risk factors for the disease

The major risk factors for HCC are chronic hepatitis B virus (HBV)/hepatitis C virus (HCV) infection, alcohol consumption, non-alcoholic fatty liver disease (NAFLD), obesity, diabetes mellitus, and metabolic dysfunction associated fatty liver disease (MAFLD).[205,213,214]

In high-resource countries, often HCC develops as an outcome following the development of liver cirrhosis due to chronic HBV or HCV infection and non-alcoholic steatohepatitis associated with metabolic syndrome or diabetes.[205,215,216]
In Eastern Asia and most African countries where HBV is endemic, HBV-associated HCC most often occurs in the absence of cirrhotic liver disease, 30-50% of HCC cases.[205,217]

Main treatment options

Since the approval of the first therapeutic agents for HCC there has been a rapid and ongoing evolution in treatments as new regimens are explored. These are best summarized in "living documents" such as:

- European Association for the Study of the Liver (EASL) guideline: Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma[218]
- ESMO Clinical Practice Guidelines: Hepatocellular Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up[219]
  - eUpdate 5 March 2021: Updated Hepatocellular Carcinoma Treatment Recommendations[220]
- NCCN Guideline: Hepatocellular Carcinoma, v1.2024[221]

American Association for the Study of Liver Diseases (AASLD) Practice Guidance on Prevention, Diagnosis and Treatment of Hepatocellular Carcinoma[222]

Mortality and morbidity (natural history)

Liver cancer is the third most common cause of death from cancer worldwide; estimated to be responsible for 758,725 deaths in 2022.[204]

Crude mortality rates and ASRs per 100,000 individuals in 2022 with regional data were estimated as follows:[204]

	Crude	ASR
WHO African Region	3.4	5.8
WHO Region of the Americas	7.2	4.5
WHO Eastern Mediterranean Region	6.2	8.1

Table 2.1.11-1: Epidemiological Characteristics of HCC

HCC			
	WHO European Region	9.5	4.3
	WHO South-East Asia Region	5.0	4.8
	WHO Western Pacific Region	21.2	12.1
	Primary prevention of HCC includes strategies such as preventing chronic HBV and HCV carriage, maintaining a healthy lifestyle and avoiding HCC risk factors.[205] An effective secondary prevention strategy is HCC surveillance which has shown to reduce the burden of HCC among patients at high risk for HCC through early detection and effective early management.[205] HCC surveillance is indicated in patients with liver cirrhosis or chronic HBV infection. Taiwan, and Japan both have intensive surveillance programs and have expected survival times of 5 years or more after treatment initiation. Most other regions have median survival times of less than 3 years.[205,210]		
Important co-morbidities	Conditions reported by multiple sources as comorbidities among patients with HCC include: heart disease, cerebrovascular disease, hypertension, pulmonary disease/COPD, and renal disease.[223,224,225,226,227,228] However, these conditions occur frequently with advancing age.		

2.2 Nonclinical Part of the Safety Specification

The scope and results of the nonclinical toxicity and exposure studies support the clinical use of IV nivolumab at the proposed dose and dosing regimen. Risks of inflammatory AEs, immunogenicity, and effects on maintenance of pregnancy and infant viability were identified in the nonclinical program (Table 2.2-1). No nivolumab-related findings were observed in standard clinical evaluations of cardiovascular, respiratory, and neurologic function conducted in cynomolgus monkeys. Anti-drug (nivolumab) antibody was detected in patients treated with nivolumab with low titers and low rate of persistent positive and low incidence of neutralizing antibodies. The presence of ADA did not have significant impact on safety or PK.

The nonclinical combination toxicity studies predicted the most common clinical toxicities observed in humans (GI toxicity). At present, the cause of adverse pregnancy outcome and infant mortality associated with nivolumab administration in monkeys is unknown. While the clinical implications of these findings are unclear, nivolumab is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk.

Safety specifications for nonclinical findings are summarized in Table 2.2-1. A summary of preclinical safety is provided in Appendix 2.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
Inflammatory AEs: Nivolumab administration alone was not associated with AEs. However, when administered in combination with other immunomodulatory agents (ipilimumab, anti-LAG-3 antibody) inflammatory AEs, including GI toxicity and vasculitis, were observed.	Increased incidences and severities of inflammatory AEs involving several organ systems have been observed in patients treated with nivolumab or nivolumab in combination with other agents in clinical trials.
Immunogenicity: Nivolumab was not appreciably immunogenic in monkeys. When immunogenicity was observed, antibodies occasionally correlated with increased elimination of nivolumab. Immunogenicity of human proteins in animals may not be predictive of clinical immunogenicity.	Immunogenicity of nivolumab may potentially increase the risk for reduced exposure and efficacy, and for AEs on safety (eg, infusion reactions, immune complex formation/deposition). Immunogenicity monitoring is employed in all nivolumab monotherapy and combination clinical studies.
Reproductive Toxicity: Effects of nivolumab on prenatal and postnatal development were investigated in ePPND study in pregnant cynomolgus monkeys. Nivolumab treatment at 10 mg/kg and 50 mg/kg (administered 2QW) dosed from GD 20-22 through parturition was associated with increases in third trimester abortions, stillbirths, and/or death/euthanasia of premature infants. No AEs were observed in surviving offspring through the 6 month evaluation phase. Systemic (AUC) exposures to nivolumab relative to the AUC at the clinical dose of 3 mg/kg, Q2W, are approximately 8 and 35× at 10 and 50 mg/kg, respectively.	The cause of adverse pregnancy outcomes and infant mortality associated with nivolumab administration are unknown as are the clinical implications of these findings. There are no data on the use of nivolumab in pregnant women. Nivolumab is not recommended during pregnancy unless the clinical benefit outweighs the potential risk. Women of childbearing potential should use effective contraception if treatment with nivolumab is recommended. It is unknown whether nivolumab is secreted in human milk. Secretion of IgGs in human milk is generally limited and IgGs have a low oral bioavailability. Significant systemic exposure of the infant is not expected and no effects on the breastfed newborn/infant are anticipated. However, because of the potential for ARs in nursing infants, a decision must be made whether to discontinue breast-feeding or to discontinue from nivolumab therapy taking into account the benefit of breast-feeding for the child and the benefit of nivolumab therapy for the woman.

2.3 Clinical Trial Exposure

Nivolumab has been studied in a comprehensive clinical development program in multiple Phase 1, 2, and 3 studies with nivolumab as a single agent and in combination with other cancer therapies. An overview of the nivolumab clinical program summarized in this RMP supporting the safe and effective use of nivolumab is in Table 2.3-1.

Table 2.3-1: Nivolumab Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number (Indication)	Study Title	Number Treated Subjects
Nivolumab Monotherapy (3 mg/kg)		
CA209037[229,230] (melanoma)	Phase 3, randomized, open-label study of nivolumab and investigator's choice (dacarbazine or carboplatin and paclitaxel) in subjects with advanced (unresectable or metastatic) melanoma who progressed on or after anti- CTLA-4 therapy, and for those with BRAF V600 mutations, who progressed on or after a BRAF inhibitor in addition to anti-CTLA-4-therapy	Nivolumab: 268 Investigator's Choice: 102
CA209066[231] (melanoma)	Phase 3, randomized, double-blind study of nivolumab vs DTIC in subjects with previously untreated, unresectable or metastatic melanoma who are BRAF WT	Nivolumab: 206 DTIC: 205
CA209067[232,233] (melanoma)	Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab in combination with IPI versus IPI monotherapy in previously untreated subjects with advanced (unresectable or metastatic) melanoma	Nivolumab:313 Nivolumab+IPI: 314 IPI: 315
CA209238[234,235] (adj. melanoma)	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	Nivolumab:452 IPI: 453
CA209017[236] (NSCLC)	Phase 3, randomized study of nivolumab vs docetaxel in subjects with previously treated locally advanced or metastatic SQ NSCLC	Nivolumab: 131 Docetaxel: 129
CA209057[237] (NSCLC)	Phase 3 randomized, open-label study of nivolumab vs docetaxel in subjects with NSQ NSCLC whose disease has progressed during or after one prior platinum doublet-based chemotherapy regimen	Nivolumab: 287 Docetaxel: 268
CA209063[238,239] (NSCLC)	Phase 2, single-arm study of nivolumab in subjects with previously treated locally advanced or metastatic SQ NSCLC	Nivolumab:117
CA209025[240] (RCC)	Phase 3, randomized, open-label study of nivolumab vs everolimus for advanced or metastatic RCC who received prior anti-angiogenic therapy	Nivolumab: 406 Everolimus: 397
CA209010[241] (RCC)	Phase 2, randomized, blinded, dose-ranging study of nivolumab treated at 0.3, 2, or 10 mg/kg in subjects with progressive advanced/metastatic clear-cell RCC who have received prior anti-angiogenic therapy	Nivolumab: 167
CA209205,[242,243] (cHL)	Phase 2, non-comparative, open-label, multi-cohort study of nivolumab in subjects with cHL (Cohort A - brentuximab vedotin-naïve, Cohort B - prior brentuximab vedotin treatment as a salvage therapy after failure of ASCT, and Cohort C - prior ASCT and brentuximab vedotin in any treatment order)	Nivolumab Cohort A+B+C: 243

Table 2.3-1: Nivolumab Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number (Indication)	Study Title	Number Treated Subjects
CA209039[244] (cHL)	Phase 1, open-label, multi-center, dose-escalation, and multi-dose study of nivolumab and nivolumab in combination with other therapies in subjects with relapsed/refractory hematologic malignancy, with expansion cohorts in selected hematologic malignancies including HL	Nivolumab cHL cohort: 23
CA209141[245] (SCCHN)	Phase 3, randomized, open-label study of nivolumab versus investigator's choice therapy (cetuximab, methotrexate, or docetaxel) in adults with recurrent or metastatic SCCHN who had progressed on or within 6 months of the last dose of a platinum-containing therapy	Nivolumab: 236 Investigator's Choice: 111
CA209275[246] (UC)	Phase 2, single arm study of nivolumab 3 mg/kg Q2W in subjects with metastatic or surgically unresectable UC who have progressed or recurred following treatment with a platinum agent	Nivolumab: 270
CA209032[247] (UC)	Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors	Nivolumab monotherapy UC cohort: 78
MDX1106-03[248]/ CA209003 (Multiple Tumor)	Phase 1b, multiple ascending-dose, dose-escalation study in multiple selected advanced or recurrent malignancies	Nivolumab: 306[a]
ONO-4538-24[249] (CA209473) (ESCC)	Phase 3, multicenter, randomized, open-label study in which subjects with unresectable, advanced, recurrent, or metastatic ESCC refractory or intolerant to fluoropyrimidine and platinum-based chemotherapy were randomized in a 1:1 ratio to nivolumab monotherapy or chemotherapy	Nivolumab: 209 Chemotherapy: 208
CA209274[250] (MIUC)	Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma.	Nivolumab: 353 Placebo: 356
CA209577[251] (OC/GEJC)	Phase 3, randomized, multicenter, double-blind study of adjuvant nivolumab or placebo in subjects with resected oesophageal, or gastro-oesophageal junction cancer	Nivolumab: 532 Placebo: 260
CA209070/ ADVL1412[252] (ST/Haematologic Tumours)	Phase 1/2 study of nivolumab in children, adolescents, and young adults with recurrent or refractory solid tumors as a single agent and in combination with ipilimumab.	Nivolumab: 80 Nivolumab+IPI: 46
CA20976K[253] (melanoma)	Phase 3, randomized, double-blind study to evaluate the use of adjuvant immunotherapy with nivolumab versus placebo after complete resection of Stage IIB/C melanoma in adults and adolescent subjects ≥ 12 years old.	Nivolumab: 524 Placebo: 264
CA2098FC[254,255] (melanoma)	Phase 1, randomized, double-blind, parallel study to compare the pharmacokinetics of [redacted] nivolumab Process D to nivolumab Process C after complete resection of stage IIIa/b/c/d or stage IV melanoma	Nivolumab Process C: 129 Nivolumab Process D: 132

Table 2.3-1: Nivolumab Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number (Indication)	Study Title	Number Treated Subjects
Nivolumab (1 mg/kg) Combined with Ipilimumab (3 mg/kg)		
CA209067[232,233] (melanoma)	Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab in combination with IPI versus IPI monotherapy in previously untreated subjects with advanced (unresectable or metastatic) melanoma	Nivolumab:313 Nivolumab+IPI: 314 IPI: 315
CA209069[256] (melanoma)	Phase 2, randomized, double-blind study of nivolumab + IPI vs ipilimumab in previously untreated subjects with advanced (unresectable or metastatic) melanoma	Nivolumab+IPI: 94 IPI: 46
CA209004[257] (melanoma)	Phase 1b, dose-escalation, open-label, multi-center, multi-dose study of nivolumab in combination with IPI in subjects with advanced (unresectable or metastatic) melanoma	Nivolumab Cohort 8: 41
CA2099DW[258] (HCC)	Phase 3, randomized, open-label, multi-center study of nivolumab in combination with ipilimumab compared to sorafenib or lenvatinib as first-line treatment in participants with advanced HCC	Nivolumab+IPI: 332 Lenvatinib: 275 Sorafenib: 50
Nivolumab (3 mg/kg or 240 mg) Combined with Ipilimumab (1 mg/kg)		
CA2098HW[259]	A Phase 3 randomized clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with MSI-H or dMMR mCRC[b]	Nivolumab + IPI: 200 Chemotherapy: 88
CA209214[260,261] (RCC)	Phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects treated subjects in the sunitinib group with previously untreated, advanced or mRCC	Nivolumab + IPI:547 Sunitinib: 535
CA209016[262] (RCC)	Phase 1, study of nivolumab plus sunitinib, pazopanib, or ipilimumab in subjects with mRCC	Nivolumab+IPI: 47 (Arm I-1)
CA209142 (CRC)[263]	Nivolumab in combination with ipilimumab CA209142 ad-hoc safety report for MSI-H or dMMR mCRC	Nivolumab + IPI: 119
CA209743[264] (MPM)	Phase 3, randomized study of nivolumab plus ipilimumab versus pemetrexed plus cisplatin or carboplatin as first-line therapy in subjects with unresectable MPM	Nivolumab+IPI: 300
CA209648[265] (OSCC)	Phase 3, randomized study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated OSCC	Nivolumab+IPI: 322 Nivolumab+Chemotherapy: 310 Chemotherapy: 304
CA209070/ ADVL1412[266] (ST/Haematologic Tumours)	Phase 1/2 study of nivolumab in children, adolescents, and young adults with recurrent or refractory solid tumors as a single agent and in combination with ipilimumab.	Nivolumab: 80 Nivolumab+IPI: 46

Table 2.3-1: Nivolumab Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number (Indication)	Study Title	Number Treated Subjects
Nivolumab (360 mg) Combined with Ipilimumab (1 mg/kg) Combined with Platinum-doublet chemotherapy		
CA209568 Part 2[267] (NSCLC)	A study of nivolumab in combination with ipilimumab (Part 1); and nivolumab plus ipilimumab in combination with chemotherapy (Part 2) as first line therapy in stage NSCLC.	Nivolumab + IPI + Chemotherapy: 36
CA2099LA[268] (NSCLC)	A study of nivolumab plus ipilimumab in combination with chemotherapy vs chemotherapy alone as first line therapy in stage IV NSCLC	Nivolumab + IPI + Chemotherapy: 358 Chemotherapy: 349
Nivolumab (240 mg) Combined with Cabozantinib (40 mg)		
CA2099ER (RCC)[269]	Phase 3, randomized study of nivolumab combined with cabozantinib versus sunitinib in subjects with previously untreated advanced or metastatic RCC	Nivo+cabo: 320 Sunitinib: 320
Nivolumab (240 mg or 360 mg) Combined with Chemotherapy		
CA209649[270] (gastric/GEJC/OAC)	Randomized, multicenter, open-label, Phase 3 study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine versus oxaliplatin plus fluoropyrmidine in subjects with previously untreated advanced or metastatic gastric or gastroesophageal junction cancer	Nivolumab + chemotherapy: 782 Chemotherapy: 767
CA209648 (OSCC)[271]	Phase 3, randomized study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated OSCC	Nivolumab + chemotherapy: 310 Nivolumab + IPI: 322 Chemotherapy: 304
CA209816[272] (NSCLC)	Randomized, open-label, Phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in early-stage NSCLC [c]	Nivolumab + chemotherapy: 176 Chemotherapy: 176
CA209901 substudy[273]	Nivolumab + Chemotherapy for Urothelial Carcinoma in Cisplatin Eligible Patients	Nivolumab + chemotherapy: 304 Chemotherapy: 288

[a] Study MDX1106-03 included multiple dose levels: 0.1 mg/kg (N = 17), 0.3 mg/kg (N = 18), 1 mg/kg (N = 86), 3 mg/kg (N = 54), 10 mg/kg (N = 131) and multiple tumor types including NSCLC (N = 129), melanoma (N = 107), RCC (N = 34), CRC (N = 19), and metastatic prostate cancer (N = 17). Of the 107 subjects with melanoma were treated with nivolumab doses ranging from 0.1 to 10 mg/kg (17 subjects with 0.1 mg/kg, 18 subjects with 0.3 mg/kg, 35 subjects with 1 mg/kg, 17 subjects with 3 mg/kg, and 20 subjects with 10 mg/kg). Of these 129 subjects with tumor type NSCLC, 33 (15 SQ and 18 NSQ NSCLC) were treated with nivolumab 1 mg/kg, 37 (18 SQ and 19 NSQ NSCLC) were treated with nivolumab 3 mg/kg, and 59 (21 SQ and 37 NSQ NSCLC; one unknown) were treated with nivolumab 10 mg/kg.

[b] In Study CA2098HW, 1L subjects only from Arm B (Nivo + Ipi) and Arm C (Chemo) have been unblinded by the 15-Nov-2023 DBL.

[c] Per the CA209816 Revised Protocol 03, randomization into the nivo+ipi arm (Arm A) was closed, and subjects were randomized into the remaining nivo+chemo or chemo arms in a 1:1 ratio.

2.3.1 Nivolumab Monotherapy

Pooled analyses for nivolumab monotherapy are in Table 2.3.1-1 through Table 2.3.1-5. Clinical trial exposure analyses for individual studies are provided in Appendix 3. Clinical trial exposure analyses for Study CA209070 are provided in Table 2.3.1-6 through Table 2.3.1-9.

<u>Nivolumab Monotherapy Pooled Studies:</u> <1 mg/kg: MDX1106-003, CA209010. 1mg/kg: MDX1106-003. 2mg/kg: CA209010. 3mg/kg: CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205 (Cohorts A+B+C), CA209141, CA209275, CA209032 (BC cohort), CA209238, MDX1106-003. 10mg/kg: CA209010, MDX1106-003. 240 mg Q2W: CA209473 (ONO-4538-24), CA209577, CA209274, 480 mg Q4W: CA20976K, CA2098FC.

Table 2.3.1-1: Clinical Exposure in Person Time; All Subjects Treated with Nivolumab Monotherapy (Pooled)

	Nivolumab N = 5380	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	122 (2.3)	
0 - < 2 MONTHS	720 (13.4)	
0 - < 3 MONTHS	1257 (23.4)	
0 - < 4 MONTHS	1711 (31.8)	
0 - < 5 MONTHS	2091 (38.9)	
0 - < 6 MONTHS	2310 (42.9)	
0 - <= 41.7 MONTHS (A)	5380 (100.0)	46738.50

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, CA209141, CA209275, CA209032 (BC cohort), CA209238, CA209577, MDX1106-03, CA209010, CA209274, ONO-4538-24 CA20976K and CA2098FC.
For CA20976K, study therapy is narrowed to blinded study phase and one subject received an unknown dose.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-pt-durtrt.sas 19SEP2023:06:56:18

Table 2.3.1-2: Clinical Exposure in Person Time by Dose Level; All Subjects Treated with Nivolumab Monotherapy (Pooled)

Dose Level	Nivolumab N = 5380	
	Persons (%)	Person Time of Exposure (1) (Months)
< 1 MG/KG	94 (1.7)	868.34
1 MG/KG	86 (1.6)	718.23
2 MG/KG	54 (1.0)	488.64
3 MG/KG	3345 (62.2)	27583.84
10 MG/KG	185 (3.4)	1451.76
240 MG Q2W	1092 (20.3)	6113.02
480 MG Q4W	1120 (20.8)	9510.34
TOTAL	5380 (100.0)	46738.50

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Monotherapy Pooled group consists of nivolumab monotherapy treatment group from following studies divided by dose regimens:
<1 mg/kg: MDX1106-03, CA209010. 1mg/kg: MDX1106-03. 2mg/kg: CA209010.
3mg/kg: CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, CA209141, CA209275, CA209032 (BC cohort), CA209238, MDX1106-03, CA2098FC.
10mg/kg: CA209010, MDX1106-03. 240 mg Q2W: ONO-4538-24, CA209577, CA209274.
480 mg Q4W: CA20976K, CA209577 and CA2098FC.
For CA20976K, study therapy is narrowed to blinded study phase and one subject received an unknown dose. The dose level percentages sum to over 100% because one patient could receive two different doses.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-pt-durtrt-by-dose.sas 19SEP2023:09:44:29

Table 2.3.1-3: Cumulative Dose of Nivolumab by Dose-Level; All Subjects Treated with Nivolumab Monotherapy (Pooled)

	Nivolumab			
	< 1 MG/KG N = 94	1 MG/KG N = 86	2 MG/KG N = 54	3 MG/KG N = 3345
NUMBER OF DOSES RECEIVED / SUBJECT				
MEAN (SD)	14.3 (15.5)	16.4 (15.8)	12.2 (14.4)	16.4 (15.2)
MEDIAN	6.5	10.0	7.5	10.0
MIN - MAX	1 - 57	1 - 48	1 - 57	1 - 79
CUMULATIVE DOSE (MG) / SUBJECT				
MEAN (SD)	436.4 (546.6)	1442.7 (1474.6)	2239.0 (2755.5)	3969.2 (4022.7)
MEDIAN	170.5	792.0	1277.1	2453.7
MIN - MAX	24 - 3129	68 - 5611	96 - 12676	36 - 26075
CUMULATIVE DOSE (MG/KG) / SUBJECT				
MEAN (SD)	5.02 (6.37)	16.30 (15.64)	24.37 (28.85)	49.00 (45.41)
MEDIAN	1.80	10.05	15.00	30.00
MIN - MAX	0.3 - 35.7	1.0 - 48.4	2.0 - 114.0	0.5 - 237.8

Table 2.3.1-3: Cumulative Dose of Nivolumab by Dose Level; All Subjects Treated with Nivolumab Monotherapy (Pooled)

	Nivolumab			
	10 MG/KG N = 185	240 MG Q2W N = 1092	480 MG Q4W N = 1120	TOTAL N = 5380
NUMBER OF DOSES RECEIVED / SUBJECT				
MEAN (SD)	13.2 (14.2)	10.8 (8.5)	8.9 (3.6)	13.8 (13.0)
MEDIAN	8.0	8.0	9.0	9.0
MIN - MAX	1 - 61	1 - 60	1 - 14	1 - 79
CUMULATIVE DOSE (MG) / SUBJECT				
MEAN (SD)	11011.9 (12564.0)	2602.3 (2032.8)	4278.9 (1746.7)	3887.9 (4189.3)
MEDIAN	5824.0	1920.0	4320.0	2637.6
MIN - MAX	169 - 68506	240 - 14400	480 - 6720	24 - 68506
CUMULATIVE DOSE (MG/KG) / SUBJECT				
MEAN (SD)	131.77 (141.66)			50.86 (56.98)
MEDIAN	78.20			29.95
MIN - MAX	2.5 - 610.0			0.3 - 610.0

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
In CA2098FC, 3 mg/kg from Week 1-17 480 mg Q4W from Week 19-51; CA209577, 240 mg Q2W 16 Weeks then 480mg Q4W.
Monotherapy Pooled group consists of nivolumab monotherapy treatment group from following studies divided by dose regimens:
<1 mg/kg: MDX1106-03, CA209010. 1mg/kg: MDX1106-03. 2mg/kg: CA209010.
3mg/kg: CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects),
CA209205, CA209141, CA209275, CA209032 (BC cohort), CA209238, MDX1106-03, CA2098FC.
10mg/kg: CA209010, MDX1106-03. 240 mg Q2W: ONO-4538-24, CA209577, CA209274.
480 mg Q4W: CA20976K, CA209577 and CA2098FC.
For CA20976K, study therapy is narrowed to blinded study phase and one subject received an unknown dose.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-cumdos.sas 19SEP2023:15:05:26

Table 2.3.1-4: Clinical Exposure in Person Time by Age Group and Sex; All Subjects Treated with Nivolumab Monotherapy (Pooled)

Treatment Group: Nivolumab

Age Category	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 3713	Female N = 1667	Total N = 5380	Male N = 3713	Female N = 1667	Total N = 5380
>= 18 AND < 65	2217 (59.7)	1108 (66.5)	3325 (61.8)	19707.24	9860.76	29568.00
>= 65 AND < 75	1125 (30.3)	406 (24.4)	1531 (28.5)	9587.38	3274.41	12861.80
>= 75 AND < 85	349 (9.4)	139 (8.3)	488 (9.1)	2958.32	1025.12	3983.44
>= 85	22 (0.6)	14 (0.8)	36 (0.7)	222.32	102.93	325.26
TOTAL	3713 (100.0)	1667 (100.0)	5380 (100.0)	32475.27	14263.23	46738.50

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, CA209141, CA209275, CA209032 (BC cohort), CA209238, CA209577, MDX1106-03, CA209010, CA209274, ONO-4538-24, CA20976K and CA2098FC.
For 76K, study therapy is narrowed to blinded study phase and one subject received an unknown dose.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-pt-age-eu.sas 19SEP2023:07:54:13

Table 2.3.1-5: Clinical Exposure in Person Time by Racial Origin and Gender; All Subjects Treated with Nivolumab Monotherapy (Pooled)

Treatment Group: Nivolumab

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 3713	Female N = 1667	Total N = 5380	Male N = 3713	Female N = 1667	Total N = 5380
WHITE	3170 (85.4)	1493 (89.6)	4663 (86.7)	28512.89	12959.54	41472.43
BLACK OR AFRICAN AMERICAN	59 (1.6)	27 (1.6)	86 (1.6)	448.59	148.73	597.32
ASIAN	407 (11.0)	122 (7.3)	529 (9.8)	2866.56	924.29	3790.85
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (<0.1)	2 (0.1)	3 (<0.1)	3.32	25.53	28.85
OTHER	69 (1.9)	23 (1.4)	92 (1.7)	583.06	205.14	788.21
NOT REPORTED	7 (0.2)	0	7 (0.1)	60.85	0	60.85
TOTAL	3713 (100.0)	1667 (100.0)	5380 (100.0)	32475.27	14263.23	46738.50

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, CA209141, CA209275, CA209032 (BC cohort), CA209238, CA209577, MDX1106-03, CA209010, CA209274, ONO-4538-24, CA20976K and CA2098FC.
For CA20976K, study therapy is narrowed to blinded study phase and one subject received an unknown dose.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-pt-race.sas 20SEP2023:11:27:20

Table 2.3.1-6: Clinical Exposure in Person Time; All Subjects Treated with Nivolumab Monotherapy in Study CA209070

Duration of Exposure	Nivolumab N = 80 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	9 (11.3)	
0 - < 2 MONTHS	45 (56.3)	
0 - < 3 MONTHS	58 (72.5)	
0 - < 4 MONTHS	61 (76.3)	
0 - < 5 MONTHS	64 (80.0)	
0 - < 6 MONTHS	70 (87.5)	
0 - < 12 MONTHS	77 (96.3)	
0 - < 24 MONTHS	78 (97.5)	
0 - <= 52.5 MONTHS (a)	80 (100.0)	312.48

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(a) max clinical exposure
Subjects were to be treated with Nivolumab 3 mg/kg Q2W for Part A/B, Nivolumab 1 mg/kg + Ipilimumab 1 mg/kg for Part C1 and Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg for Part C2/D
Program Source: /opt/zfs002/prd/bms255736/stats/eu_rmp/prog/tables/rt-ex-pt-durtrt.sas 02JUN2022:04:38:51

Table 2.3.1-7: Cumulative Dose of Nivolumab; All Subjects Treated with Nivolumab Monotherapy in Study CA209070

	Nivolumab N = 80
NUMBER OF CYCLES RECEIVED/ SUBJECT	
MEAN (SD)	3.7 (6.8)
MEDIAN	1.5
(MIN - MAX)	(1 - 45)
NUMBER OF DOSES RECEIVED/ SUBJECT	
MEAN (SD)	6.9 (13.4)
MEDIAN	2.0
(MIN - MAX)	(1 - 89)
CUMULATIVE DOSE (MG/KG)/ SUBJECT	
MEAN (SD)	20.73 (40.31)
MEDIAN	6.08
(MIN - MAX)	(3.0 - 266.7)

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /opt/zfs002/prd/bms255736/stats/eu_rmp/prog/tables/rt-ex-cumdos.sas 02JUN2022:04:38:14

Table 2.3.1-8: Clinical Exposure in Person Time by Age Group and Gender; All Subjects Treated with Nivolumab Monotherapy in Study CA209070

Treatment Group: Nivolumab

Age Category	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 49	Female N = 31	Total N = 80	Male N = 49	Female N = 31	Total N = 80
>=1 - <18	37 (75.5)	27 (87.1)	64 (80.0)	89.63	133.98	223.61
>=12 - <18	21 (42.9)	12 (38.7)	33 (41.3)	48.72	60.42	109.14
>=18	12 (24.5)	4 (12.9)	16 (20.0)	79.18	9.69	88.87
>=1 - <12	16 (32.7)	15 (48.4)	31 (38.8)	40.90	73.56	114.46
TOTAL	49 (100.0)	31 (100.0)	80 (100.0)	168.80	143.67	312.48

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.

Program Source: /opt/zfs002/prd/bms255736/stats/eu_rmp/prog/tables/rt-ex-pt-age.sas 07JUN2022:08:09:54

Table 2.3.1-9: Clinical Exposure in Person Time by Racial Origin and Gender; All Subjects Treated with Nivolumab Monotherapy in Study CA209070

Treatment Group: Nivolumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Race Category	Male N = 49	Female N = 31	Total N = 80	Male N = 49	Female N = 31	Total N = 80
WHITE	39 (79.6)	21 (67.7)	60 (75.0)	94.13	68.73	162.86
BLACK OR AFRICAN AMERICAN	3 (6.1)	6 (19.4)	9 (11.3)	58.74	54.90	113.64
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0	0	0	0
ASIAN	3 (6.1)	3 (9.7)	6 (7.5)	9.26	3.88	13.14
UNKNOWN	3 (6.1)	1 (3.2)	4 (5.0)	4.21	16.16	20.37
NOT REPORTED	1 (2.0)	0	1 (1.3)	2.46	0	2.46
TOTAL	49 (100.0)	31 (100.0)	80 (100.0)	168.80	143.67	312.48

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs002/prd/bms255736/stats/eu_rmp/prog/tables/rt-ex-pt-race.sas 02JUN2022:04:39:13

2.3.2 Nivolumab (1 mg/kg) Combined with Ipilimumab (3 mg/kg)

Pooled analyses for nivolumab (1 mg/kg) in combination with ipilimumab (3 mg/kg) are in Table 2.3.2-1 through Table 2.3.2-4. Clinical trial exposure analyses for individual studies are presented in Appendix 3.

Nivolumab (1 mg/kg) in Combination Therapy with Ipilimumab (3 mg/kg) Pooled Studies: CA2099DW, CA209067, CA209069, and CA209004

Table 2.3.2-1: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab in Combination Therapy with Ipilimumab (Pooled)

	Pooled Nivo + Ipi N = 780	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	15 (1.9)	
0 - < 2 MONTHS	174 (22.3)	
0 - < 3 MONTHS	270 (34.6)	
0 - < 4 MONTHS	364 (46.7)	
0 - < 5 MONTHS	411 (52.7)	
0 - < 6 MONTHS	440 (56.4)	
0 - < 12 MONTHS	573 (73.5)	
0 - < 18 MONTHS	627 (80.4)	
0 - < 24 MONTHS	650 (83.3)	
0 - < 30 MONTHS	734 (94.1)	
0 - < 36 MONTHS	777 (99.6)	
0 - <= 36.4 MONTHS (A)	780 (100.0)	7222.64

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment,
and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Pooled group includes the following studies: CA2099DW, CA209069, CA209004 (cohort 8), CA209067 (combo arm)
Program Source: /projects/bms211280/stats/smpc_scs_rmp9dw/prog/tables/rt-ex-pt-durtrt.sas 10APR2024:04:31:14

Table 2.3.2-2: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects with Nivolumab in Combination Therapy with Ipilimumab (Pooled)

	Pooled Nivo + Ipi N = 780	
	Nivolumab N = 780	Ipilimumab N = 780
NUMBER OF DOSES RECEIVED		
MEAN (SD)	13.3 (17.04)	3.2 (1.04)
MEDIAN	5.0	4.0
MIN - MAX	1 - 76	1 - 4
CUMULATIVE DOSE (MG/KG)		
MEAN (SD)	24.38 (49.829)	9.65 (3.148)
MEDIAN	4.00	11.95
MIN - MAX	1.0 - 220.0	2.9 - 15.7
CUMULATIVE DOSE (MG)		
MEAN (SD)	5750.5 (4109.83)	
MEDIAN	4800.0	
MIN - MAX	65 - 11520	

Cumulative dose: the sum of doses administered to a subject during the flat-dose (mg) or weight-based dose (mg/kg) treatment period.
Flat (mg) doses of Nivolumab (only in CA2099DW) were not re-calculated to total doses in mg/kg, therefore the mg/kg summary for Nivolumab apply only to weight-based period.
Pooled group includes the following studies: CA2099DW, CA209069, CA209004 (cohort 8), CA209067 (combo arm)
Program Source: /projects/bms211280/stats/smpc_scs_rmp9dw/prog/tables/rt-ex-cumdos.sas 24APR2024:04:02:07

Table 2.3.2-3: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab in Combination Therapy with Ipilimumab (Pooled)

Treatment group: NIVOLUMAB+IPILIMUMAB

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 555	Female N = 225	Total N = 780	Male N = 555	Female N = 225	Total N = 780
>= 18 AND < 65	286 (51.5)	141 (62.7)	427 (54.7)	2970.81	1165.17	4135.98
>= 65 AND < 75	200 (36.0)	59 (26.2)	259 (33.2)	1765.59	464.89	2230.47
>= 75 AND < 85	64 (11.5)	20 (8.9)	84 (10.8)	678.01	144.03	822.05
>= 85	5 (0.9)	5 (2.2)	10 (1.3)	17.08	17.05	34.14
TOTAL	555 (100.0)	225 (100.0)	780 (100.0)	5431.49	1791.15	7222.64

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Pooled group includes the following studies: CA2099DW, CA209069, CA209004 (cohort 8), CA209067 (combo arm)
Program Source: /projects/bms211280/stats/smpc_scs_rmp9dw/prog/tables/rt-ex-ptage.sas 10APR2024:04:09:36

Table 2.3.2-4: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab in Combination Therapy with Ipilimumab (Pooled)

Treatment group: NIVOLUMAB+IPILIMUMAB

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 555	Female N = 225	Total N = 780	Male N = 555	Female N = 225	Total N = 780
WHITE	430 (77.5)	184 (81.8)	614 (78.7)	4188.02	1375.38	5563.40
BLACK OR AFRICAN AMERICAN	8 (1.4)	3 (1.3)	11 (1.4)	88.94	53.49	142.42
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.2)	0	1 (0.1)	24.84	0	24.84
ASIAN	109 (19.6)	34 (15.1)	143 (18.3)	1040.26	325.82	1366.08
ASIAN INDIAN	2 (0.4)	1 (0.4)	3 (0.4)	32.62	1.02	33.64
CHINESE	59 (10.6)	17 (7.6)	76 (9.7)	610.07	252.81	862.88
JAPANESE	21 (3.8)	3 (1.3)	24 (3.1)	186.55	5.29	191.84
ASIAN OTHER	27 (4.9)	9 (4.0)	36 (4.6)	211.02	45.57	256.59
NOT REPORTED	0	4 (1.8)	4 (0.5)	0	21.13	21.13
OTHER	7 (1.3)	4 (1.8)	11 (1.4)	89.43	36.47	125.90
TOTAL	555 (100.0)	225 (100.0)	780 (100.0)	5431.49	1791.15	7222.64

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Pooled group includes the following studies: CA2099DW, CA209069, CA209004 (cohort 8), CA209067 (combo arm)
Program Source: /projects/bms211280/stats/smpc_scs_rmp9dw/prog/tables/rt-ex-pt.sas 10APR2024:04:09:25

2.3.3 Nivolumab (3 mg/kg or 240 mg) Combined with Ipilimumab (1 mg/kg)

Pooled studies with nivolumab (3 mg/kg or 240mg) in combination with ipilimumab (1 mg/kg) are presented in Table 2.3.3-1 through Table 2.3.3-9. Clinical trial exposure analyses for Study CA209070 are provided in Table 2.3.3-10 through Table 2.3.3-13.

Clinical trial exposure analyses for individual studies are presented in Appendix 3.

Pooled Studies with Nivolumab (3 mg/kg or 240mg) in Combination Therapy with Ipilimumab (1 mg/kg): CA2098HW, CA209142, CA209214 and CA209016

Table 2.3.3-1: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (3 mg/kg or 240mg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

	Pooled Nivo + Ipi N = 913	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	10 (1.1)	
0 - < 2 MONTHS	95 (10.4)	
0 - < 3 MONTHS	165 (18.1)	
0 - < 4 MONTHS	263 (28.8)	
0 - < 5 MONTHS	295 (32.3)	
0 - < 6 MONTHS	331 (36.3)	
0 - <= 58.7 MONTHS (A)	913 (100.0)	12693.72

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Pooled Nivolumab + Ipilimumab group consists of Nivolumab + Ipilimumab treatment group from studies CA2098HW, CA209214, CA209142 (cohort 2, dMMR/MSI-H CRC), and CA209016 (arm I-1).
For CA2098HW, only first line subjects are included.
Program Source: /projects/bms211280/stats/smpc_scs_rmp8hw/prog/tables/rt-ex-pt-durtrt.sas 09JAN2024:03:14:35

Table 2.3.3-2: Clinical Exposure in Person Time by Dose Level; All Treated Subjects with Nivolumab (3mg/kg or 240mg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

	Pooled Nivo + Ipi N = 913	
Nivolumab Dose Level	**Persons (%)**	**Person Time of Exposure (1) (Months)**
3 MG/KG	713 (78.1)	9870.55
240 MG Q3W THEN 480 MG Q4W	200 (21.9)	2823.16
TOTAL	913 (100.0)	12693.72

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Pooled Nivolumab + Ipilimumab group consists of Nivolumab + Ipilimumab treatment group from following studies divided by Nivolumab dose regimens: 3mg/kg: CA209214, CA209142 (cohort 2, dMMR/MSI-H CRC), and CA209016 (arm I-1);
240 mg Q3W then 480mg Q4W: CA2098HW.
For CA2098HW, only first line subjects are included.
Program Source: /projects/bms211280/stats/smpc_scs_rmp8hw/prog/tables/rt-ex-pt-doselev-ebr381.sas 05FEB2024:04:24:06

Table 2.3.3-3: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects with Nivolumab (3 mg/kg or 240mg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

	Pooled Nivo + Ipi N = 913	
	Nivolumab N = 913	Ipilimumab N = 913
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	23.5 (24.01)	3.6 (0.83)
MEDIAN	16.0	4.0
MIN - MAX	1 - 122	1 - 4
CUMULATIVE DOSE (1) / SUBJECT		
MEAN (SD)	6399.173 (6242.8363)	3.632 (0.8456)
MEDIAN	4320.000	4.000
MIN - MAX	163.50 - 33730.50	0.97 - 7.53

Cumulative dose is sum of the doses administered to a subject during the treatment period.
(1) Dose units: Nivolumab in mg and Ipilimumab in mg/kg.
Pooled Nivolumab + Ipilimumab group consists of Nivolumab + Ipilimumab treatment group from studies CA2098HW, CA209214, CA209142 (cohort 2, dMMR/MSI-H CRC), and CA209016 (arm I-1).
For CA2098HW, only first line subjects are included.
Program Source: /projects/bms211280/stats/smpc_scs_rmp8hw/prog/tables/rt-ex-cumdos-ebr381.sas 05FEB2024:04:23:47

Table 2.3.3-4: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (3 mg/kg or 240mg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

Treatment Group: Nivolumab with Ipilimumab

Age Category	Persons (%) Male N = 608	Persons (%) Female N = 305	Persons (%) Total N = 913	Person Time of Exposure (Months) (1) Male N = 608	Person Time of Exposure (Months) (1) Female N = 305	Person Time of Exposure (Months) (1) Total N = 913
< 65	398 (65.5)	179 (58.7)	577 (63.2)	5669.32	2791.46	8460.78
>= 65 AND < 75	166 (27.3)	76 (24.9)	242 (26.5)	1962.45	1108.63	3071.08
>= 75 AND < 85	40 (6.6)	48 (15.7)	88 (9.6)	460.88	638.59	1099.47
>= 85	4 (0.7)	2 (0.7)	6 (0.7)	19.58	42.81	62.39
TOTAL	608 (100.0)	305 (100.0)	913 (100.0)	8112.23	4581.49	12693.72

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Pooled Nivolumab + Ipilimumab group consists of Nivolumab + Ipilimumab treatment group from studies CA2098HW, CA209214, CA209142 (cohort 2, dMMR/MSI-H CRC), and CA209016 (arm I-1).
For CA2098HW, only first line subjects are included.
Program Source: /projects/bms211280/stats/smpc_scs_rmp8hw/prog/tables/rt-ex-pt-age.sas 09JAN2024:03:15:05

Table 2.3.3-5: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (3 mg/kg or 240mg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

Treatment Group: Nivolumab with Ipilimumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 608	Female N = 305	Total N = 913	Male N = 608	Female N = 305	Total N = 913
WHITE	538 (88.5)	274 (89.8)	812 (88.9)	7181.04	4121.63	11302.67
BLACK OR AFRICAN AMERICAN	6 (1.0)	5 (1.6)	11 (1.2)	91.76	44.29	136.05
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.2)	0	1 (0.1)	49.94	0	49.94
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.2)	0	1 (0.1)	24.64	0	24.64
ASIAN	52 (8.6)	18 (5.9)	70 (7.7)	601.92	290.66	892.58
CHINESE	3 (0.5)	3 (1.0)	6 (0.7)	45.57	34.43	80.00
JAPANESE	7 (1.2)	6 (2.0)	13 (1.4)	116.80	102.51	219.30
NOT REPORTED	42 (6.9)	9 (3.0)	51 (5.6)	439.56	153.72	593.28
OTHER	9 (1.5)	8 (2.6)	17 (1.9)	162.00	124.91	286.92
NOT REPORTED	1 (0.2)	0	1 (0.1)	0.92	0	0.92
TOTAL	608 (100.0)	305 (100.0)	913 (100.0)	8112.23	4581.49	12693.72

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Pooled Nivolumab + Ipilimumab group consists of Nivolumab + Ipilimumab treatment group from studies CA2098HW, CA209214, CA209142 (cohort 2, dMMR/MSI-H CRC), and CA209016 (arm I-1).
For CA2098HW, only first line subjects are included.
Program Source: /projects/bms211280/stats/smpc_scs_rmp8hw/prog/tables/rt-ex-pt-race.sas 09JAN2024:03:14:45

Pooled Studies with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg): CA209743 and CA209648

Table 2.3.3-6: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

	Nivo + Ipi Pooled	
	Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 622	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	21 (3.4)	
0 - < 2 MONTHS	143 (23.0)	
0 - < 3 MONTHS	201 (32.3)	
0 - < 4 MONTHS	269 (43.2)	
0 - < 5 MONTHS	321 (51.6)	
0 - < 6 MONTHS	343 (55.1)	
0 - <= 27.2 MONTHS (A)	622 (100.0)	4683.89

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Nivo + Ipi group consists of Nivo + Ipi treatment group from studies CA209743 and CA209648.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-pt-durtrt.sas 30APR2021:08:59:25

Table 2.3.3-7: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

	Nivo + Ipi Pooled	
	Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 622	
	Nivolumab N = 622	Ipilimumab N = 622
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	14.0 (13.9)	4.8 (4.5)
MEDIAN	9.0	3.0
MIN - MAX	1 - 55	1 - 19
CUMULATIVE DOSE (MG) / SUBJECT		
MEAN (SD)	2861.4 (3037.7)	324.2 (323.6)
MEDIAN	1778.8	209.0
MIN - MAX	120 - 14943	32 - 1666
CUMULATIVE DOSE (MG/KG) / SUBJECT		
MEAN (SD)	42.01 (41.15)	4.82 (4.51)
MEDIAN	26.83	3.06
MIN - MAX	2.9 - 165.4	0.9 - 21.0

Cumulative dose is sum of the doses administered to a subject during the treatment period.
Nivo + Ipi group consists of Nivo + Ipi treatment group from studies
CA209743 and CA209648.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-cumdos.sas 30APR2021:08:59:04

Table 2.3.3-8: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

Treatment Group: Nivolumab with Ipilimumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 499	Female N = 123	Total N = 622	Male N = 499	Female N = 123	Total N = 622
>= 18 AND < 65	200 (40.1)	53 (43.1)	253 (40.7)	1398.05	300.29	1698.33
>= 65 AND < 75	212 (42.5)	55 (44.7)	267 (42.9)	1604.50	566.54	2171.04
>= 75 AND < 85	84 (16.8)	15 (12.2)	99 (15.9)	699.63	90.55	790.18
>= 85	3 (0.6)	0	3 (0.5)	24.34	0	24.34
TOTAL	499 (100.0)	123 (100.0)	622 (100.0)	3726.52	957.37	4683.89

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Nivo + Ipi group consists of Nivo + Ipi treatment group from studies CA209743 and CA209648.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-pt-age.sas 30APR2021:08:59:28

Table 2.3.3-9: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

Treatment Group: Nivolumab with Ipilimumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 499	Female N = 123	Total N = 622	Male N = 499	Female N = 123	Total N = 622
WHITE	251 (50.3)	89 (72.4)	340 (54.7)	2075.56	729.33	2804.90
BLACK OR AFRICAN AMERICAN	4 (0.8)	0	4 (0.6)	26.58	0	26.58
AMERICAN INDIAN OR ALASKA NATIVE	2 (0.4)	1 (0.8)	3 (0.5)	28.45	2.46	30.92
ASIAN	227 (45.5)	29 (23.6)	256 (41.2)	1454.75	177.77	1632.53
ASIAN INDIAN	1 (0.2)	0	1 (0.2)	3.32	0	3.32
CHINESE	69 (13.8)	5 (4.1)	74 (11.9)	411.73	13.01	424.74
JAPANESE	129 (25.9)	24 (19.5)	153 (24.6)	848.30	164.76	1013.06
ASIAN OTHER	28 (5.6)	0	28 (4.5)	191.41	0	191.41
OTHER	15 (3.0)	4 (3.3)	19 (3.1)	141.17	47.80	188.98
TOTAL	499 (100.0)	123 (100.0)	622 (100.0)	3726.52	957.37	4683.89

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Nivo + Ipi group consists of Nivo + Ipi treatment group from studies CA209743 and CA209648.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-pt-race.sas 25MA

Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) Individual Study: CA209070

Table 2.3.3-10: Clinical Exposure in Person Time; All Subjects Treated with Nivolumab in Combination with Ipilimumab in Study CA209070

Duration of Exposure	Nivolumab + Ipilimumab N = 46 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	4 (8.7)	
0 - < 2 MONTHS	32 (69.6)	
0 - < 3 MONTHS	36 (78.3)	
0 - < 4 MONTHS	40 (87.0)	
0 - < 5 MONTHS	41 (89.1)	
0 - < 6 MONTHS	42 (91.3)	
0 - < 12 MONTHS	45 (97.8)	
0 - <= 12.5 MONTHS (a)	46 (100.0)	111.28

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(a) max clinical exposure
Subjects were to be treated with Nivolumab 3 mg/kg Q2W for Part A/B, Nivolumab 1 mg/kg + Ipilimumab 1 mg/kg for Part C1 and Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg for Part C2/D
Program Source: /opt/zfs002/prd/bms255736/stats/eu_rmp/prog/tables/rt-ex-pt-durtrt.sas 02JUN2022:04:38:51

Table 2.3.3-11: Cumulative Dose of Nivolumab and Ipilimumab; All Subjects Treated with Nivolumab in Combination with Ipilimumab in Study CA209070

	Nivolumab + Ipilimumab N = 46	
	Nivolumab N = 46	Ipilimumab N = 46
NUMBER OF CYCLES RECEIVED/ SUBJECT		
MEAN (SD)	2.8 (2.5)	2.3 (1.1)
MEDIAN	2.0	2.0
(MIN - MAX)	(1 - 14)	(1 - 4)
NUMBER OF DOSES RECEIVED/ SUBJECT		
MEAN (SD)	3.4 (4.2)	2.3 (1.1)
MEDIAN	2.0	2.0
(MIN - MAX)	(1 - 24)	(1 - 4)
CUMULATIVE DOSE (MG/KG)/ SUBJECT		
MEAN (SD)	9.66 (12.78)	2.31 (1.09)
MEDIAN	6.00	2.00
(MIN - MAX)	(1.0 - 72.1)	(1.0 - 4.0)

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /opt/zfs002/prd/bms255736/stats/eu_rmp/prog/tables/rt-ex-cumdos.sas 02JUN2022:04:38:14

Table 2.3.3-12: Clinical Exposure in Person Time by Age Group and Gender; All Subjects Treated with Nivolumab in Combination with Ipilimumab in Study CA209070

Treatment Group: Nivolumab + Ipilimumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 30	Female N = 16	Total N = 46	Male N = 30	Female N = 16	Total N = 46
>=1 - <18	20 (66.7)	13 (81.3)	33 (71.7)	35.38	34.10	69.49
>=12 - <18	14 (46.7)	6 (37.5)	20 (43.5)	25.13	22.31	47.44
>=18	10 (33.3)	3 (18.8)	13 (28.3)	35.06	6.74	41.79
>=1 - <12	6 (20.0)	7 (43.8)	13 (28.3)	10.25	11.79	22.05
TOTAL	30 (100.0)	16 (100.0)	46 (100.0)	70.44	40.84	111.28

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs002/prd/bms255736/stats/eu_rmp/prog/tables/rt-ex-pt-age.sas 07JUN2022:08:09:54

Table 2.3.3-13: Clinical Exposure in Person Time by Racial Origin and Gender; All Subjects Treated with Nivolumab in Combination with Ipilimumab in Study CA209070

Treatment Group: Nivolumab + Ipilimumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Race Category	Male N = 30	Female N = 16	Total N = 46	Male N = 30	Female N = 16	Total N = 46
WHITE	21 (70.0)	12 (75.0)	33 (71.7)	43.50	25.72	69.22
BLACK OR AFRICAN AMERICAN	2 (6.7)	2 (12.5)	4 (8.7)	3.19	7.95	11.14
AMERICAN INDIAN OR ALASKA NATIVE	0	1 (6.3)	1 (2.2)	0	1.02	1.02
ASIAN	1 (3.3)	1 (6.3)	2 (4.3)	4.21	6.14	10.35
UNKNOWN	3 (10.0)	0	3 (6.5)	4.53	0	4.53
NOT REPORTED	3 (10.0)	0	3 (6.5)	15.01	0	15.01
TOTAL	30 (100.0)	16 (100.0)	46 (100.0)	70.44	40.84	111.28

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs002/prd/bms255736/stats/eu_rmp/prog/tables/rt-ex-pt-race.sas 02JUN2022:04:39:13

2.3.4 Nivolumab (360 mg) in Combination with Ipilimumab (1 mg/kg) and Chemotherapy

Pooled analyses for nivolumab (360 mg Q3W) + ipilimumab (1 mg/kg Q6W) + 2 cycles of platinum doublet chemotherapy are in Table 2.3.4-1 through Table 2.3.4-4.

Clinical trial exposure analyses for all individual studies are provided in Appendix 3.

Nivolumab (360 mg Q3W) in Combination with Ipilimumab (1 mg/kg Q6W) and 2 Cycles of Platinum Doublet Chemotherapy in Pooled Studies: CA2099LA and CA209568 Part 2.

Table 2.3.4-1: Clinical Exposure in Person Time: Subjects Treated with Nivolumab + Ipilimumab + Platinum Doublet Chemotherapy, CA2099LA and CA209568 Studies (pooled)

	Nivolumab + Ipilimumab + Chemotherapy N = 394	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	9 (2.3)	
0 - < 2 MONTHS	38 (9.6)	
0 - < 3 MONTHS	70 (17.8)	
0 - < 4 MONTHS	112 (28.4)	
0 - < 5 MONTHS	140 (35.5)	
0 - < 6 MONTHS	179 (45.4)	
0 - < 12 MONTHS	326 (82.7)	
0 - <= 20.6 MONTHS (A)	394 (100.0)	2968.41

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(a) max clinical exposure
Includes data from CA2099LA (Global Population) and CA209568 (Part 2) studies.
Program Source: /opt/zfs001/prd/bms214682/stats/rmp_9la_568/prog/tables/rt-ex-pt-durtrt.sas 02DEC2019:17:11:31

Table 2.3.4-2: Cumulative Dose of Nivolumab, Ipilimumab and Chemotherapy: Subjects Treated with Nivolumab + Ipilimumab + Platinum Doublet Chemotherapy, CA2099LA and CA209568 Studies (pooled)

	Nivolumab + Ipilimumab + Chemotherapy		
	Nivolumab N = 394	Ipilimumab N = 394	Paclitaxel N = 128
NUMBER OF DOSES RECEIVED / SUBJECT			
MEAN (SD)	10.2 (6.6)	5.2 (3.3)	1.9 (0.3)
MEDIAN	9.0	4.0	2.0
MIN - MAX	1 - 29	1 - 15	1 - 2
CUMULATIVE DOSE (1) / SUBJECT			
MEAN (SD)	3639.77 (2385.43)	5.16 (3.31)	376.60 (70.08)
MEDIAN	3240.00	4.11	397.43
MIN - MAX	360.0 - 10440.0	0.1 - 15.2	74.9 - 766.0

	Nivolumab + Ipilimumab + Chemotherapy		
	Cisplatin N = 75	Carboplatin N = 319	Pemetrexed N = 268
NUMBER OF DOSES RECEIVED / SUBJECT			
MEAN (SD)	1.9 (0.3)	1.9 (0.3)	1.9 (0.3)
MEDIAN	2.0	2.0	2.0
MIN - MAX	1 - 2	1 - 2	1 - 2
CUMULATIVE DOSE (1) / SUBJECT			
MEAN (SD)	155.96 (84.87)	10.38 (2.03)	946.11 (142.40)
MEDIAN	149.08	10.07	995.52
MIN - MAX	74.6 - 697.9	1.2 - 17.6	145.9 - 1047.2

(1) Dose units: Nivolumab in mg; Ipilimumab in mg/kg, Paclitaxel, Cisplatin, and Pemetrexed in mg/ m^2, and Carboplatin in AUC. Cumulative dose (in mg, mg/kg, mg/ m^2 or AUC) is sum of the doses (in mg, mg/kg, mg/ m^2 or AUC) administered to a subject during the treatment period.
Includes data from CA2099LA (Global Population) and CA209568 (Part 2) studies.
Program Source: /opt/zfs001/prd/bms214682/stats/rmp_9la_568/prog/tables/rt-ex-cumdos.sas 02DEC2019:17:11:34

Table 2.3.4-3: Clinical Exposure in Person Time by Age Group and Gender: Subjects Treated with Nivolumab + Ipilimumab + Platinum Doublet Chemotherapy, CA2099LA and CA209568 Studies (pooled).

Treatment Group: Nivolumab + Ipilimumab + Chemotherapy

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 274	Female N = 120	Total N = 394	Male N = 274	Female N = 120	Total N = 394
>= 18 AND < 65	118 (43.1)	69 (57.5)	187 (47.5)	932.99	500.90	1433.89
>= 65 AND < 75	124 (45.3)	39 (32.5)	163 (41.4)	945.51	339.19	1284.70
>= 75 AND < 85	32 (11.7)	11 (9.2)	43 (10.9)	152.15	94.95	247.10
>= 85	0	1 (0.8)	1 (0.3)	0	2.73	2.73
TOTAL	274 (100.0)	120 (100.0)	394 (100.0)	2030.65	937.76	2968.41

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Includes data from CA2099LA (Global Population) and CA209568 (Part 2) studies.
Program Source: /opt/zfs001/prd/bms214682/stats/rmp_9la_568/prog/tables/rt-ex-pt-age.sas 02DEC2019:17:11:29

Table 2.3.4-4: Clinical Exposure in Person Time by Racial Origin and Gender: Subjects Treated with Nivolumab + Ipilimumab + Platinum Doublet Chemotherapy, CA2099LA and CA209568 Studies (pooled).

Treatment Group: Nivolumab + Ipilimumab + Chemotherapy

	Persons (%)			Person Time of Exposure (Months) (1)		
Race Category	Male N = 274	Female N = 120	Total N = 394	Male N = 274	Female N = 120	Total N = 394
WHITE	240 (87.6)	111 (92.5)	351 (89.1)	1831.13	846.46	2677.59
BLACK OR AFRICAN AMERICAN	4 (1.5)	5 (4.2)	9 (2.3)	21.09	63.34	84.44
ASIAN	27 (9.9)	3 (2.5)	30 (7.6)	170.48	16.16	186.64
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.4)	0	1 (0.3)	3.12	0	3.12
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	0	0	0
OTHER	2 (0.7)	1 (0.8)	3 (0.8)	4.83	11.79	16.62
TOTAL	274 (100.0)	120 (100.0)	394 (100.0)	2030.65	937.76	2968.41

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Includes data from CA2099LA (Global Population) and CA209568 (Part 2) studies.
Program Source: /opt/zfs001/prd/bms214682/stats/rmp_9la_568/prog/tables/rt-ex-pt-race.sas 02DEC2019:17:11:27

2.3.5 Nivolumab (240 mg) Combined with Cabozantinib (40 mg)

Studies with nivolumab (240 mg) in combination therapy with cabozantinib (40 mg) are presented in Table 2.3.5-1 through Table 2.3.5-4.

Clinical trial exposure analyses for individual studies are presented in Appendix 3.

Studies with Nivolumab (240 mg) in Combination Therapy with Cabozantinib (40 mg)

Table 2.3.5-1: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (240 mg) in Combination Therapy with Cabozantinib (40 mg) CA2099ER

	Nivolumab + Cabozantinib N = 320	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	2 (0.6)	
0 - < 2 MONTHS	10 (3.1)	
0 - < 3 MONTHS	21 (6.6)	
0 - < 4 MONTHS	30 (9.4)	
0 - < 5 MONTHS	36 (11.3)	
0 - < 6 MONTHS	46 (14.4)	
0 - < 12 MONTHS	116 (36.3)	
0 - < 24 MONTHS	312 (97.5)	
0 - <= 27.3 MONTHS (A)	320 (100.0)	4423.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(a) max clinical exposure
Subjects were to be treated with Nivolumab 240 mg Q2W + Cabozantinib 40 mg daily
Program Source: /opt/zfs001/prd/bms237293/stats/eu_smpc_rmp/prog/tables/rt-ex-pt-durtrt.sas 15MAY2020:03:24:37

Table 2.3.5-2: Cumulative Dose of Nivolumab and Cabozantinib; All Treated Subjects with Nivolumab (240 mg) in Combination Therapy with Cabozantinib (40 mg) CA2099ER

	Nivolumab + Cabozantinib	
	Nivolumab N = 320	Cabozantinib N = 320
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	25.9 (14.1)	341.1 (188.6)
MEDIAN	27.5	352.5
MIN - MAX	1 - 53	5 - 820
CUMULATIVE DOSE (1) / SUBJECT		
MEAN (SD)	6201.76 (3368.69)	10841.80 (6485.84)
MEDIAN	6600.00	10120.00
MIN - MAX	240.0 - 12720.0	200.0 - 29080.0

(1) Dose units: Nivolumab and Cabozantinib in mg
Cumulative dose (in mg) is sum of the doses (in mg) administered to a subject during the treatment period.
Program Source: /opt/zfs001/prd/bms237293/stats/eu_smpc_rmp/prog/tables/rt-ex-cumdos.sas 15MAY2020:03:25:01

Table 2.3.5-3: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (240 mg) in Combination Therapy with Cabozantinib (40 mg) CA2099ER

Treatment Group: Nivolumab + Cabozantinib

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 247	Female N = 73	Total N = 320	Male N = 247	Female N = 73	Total N = 320
>= 18 AND < 65	157 (63.6)	32 (43.8)	189 (59.1)	2266.38	486.21	2752.59
>= 65 AND < 75	73 (29.6)	29 (39.7)	102 (31.9)	998.77	329.07	1327.84
>= 75 AND < 85	16 (6.5)	11 (15.1)	27 (8.4)	211.65	116.34	327.98
>= 85	1 (0.4)	1 (1.4)	2 (0.6)	2.96	12.22	15.18
TOTAL	247 (100.0)	73 (100.0)	320 (100.0)	3479.75	943.84	4423.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms237293/stats/eu_smpc_rmp/prog/tables/rt-ex-pt-age.sas 15MAY2020:03:25:29

Table 2.3.5-4: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (240 mg) in Combination Therapy with Cabozantinib (40 mg) CA2099ER

Treatment Group: Nivolumab + Cabozantinib

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 247	Female N = 73	Total N = 320	Male N = 247	Female N = 73	Total N = 320
WHITE	209 (84.6)	55 (75.3)	264 (82.5)	2990.78	722.17	3712.95
BLACK OR AFRICAN AMERICAN	0	1 (1.4)	1 (0.3)	0	23.43	23.43
ASIAN	16 (6.5)	10 (13.7)	26 (8.1)	197.98	106.61	304.59
OTHER	22 (8.9)	7 (9.6)	29 (9.1)	290.99	91.63	382.62
TOTAL	247 (100.0)	73 (100.0)	320 (100.0)	3479.75	943.84	4423.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms237293/stats/eu_smpc_rmp/prog/tables/rt-ex-pt-race.sas 15MAY2020:03:25:54

2.3.6 Nivolumab (240 mg Q2W or 360 mg Q3W) Combined with Chemotherapy

Studies with Nivolumab (240 mg Q2W or 360 mg Q3W) in Combination Therapy with chemotherapy are presented in Table 2.3.6-1 through Table 2.3.6-4. Of note, in CA209816, nivolumab was dosed for 3 cycles in combination with platinum-based chemotherapy in subjects with resectable NSCLC. In CA209648, nivolumab was dosed for up to 2 years, in combination with fluorouracil and cisplatin, in subjects with metastatic or advanced esophageal cancer. In CA209649, nivolumab was dosed for up to 2 years, in combination with FOLFOX or XELOX chemotherapy, in subjects with metastatic or advanced GC/GEJC/OAC. In CA209901 substudy, nivolumab was dosed in combination with cisplatin-based chemotherapy for up to 6 cycles followed by nivolumab monotherapy for up to 2 years from first dose in subjects with previously untreated unresectable or metastatic UC.

Clinical trial exposure analyses for individual studies are presented in Appendix 3.

Table 2.3.6-1: Clinical Exposure in Person Time; All Nivolumab and Chemotherapy Treated Subjects (CA209816, CA209648, CA209649 and CA209901 Substudy)

Duration of Exposure	Pooled Nivo + Chemo Including CA209901 Substudy N = 1572	
	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	23 (1.5)	
0 - < 2 MONTHS	117 (7.4)	
0 - < 3 MONTHS	375 (23.9)	
0 - < 4 MONTHS	484 (30.8)	
0 - < 5 MONTHS	583 (37.1)	
0 - < 6 MONTHS	681 (43.3)	
0 - <= 48.9 MONTHS (A)	1572 (100.0)	13982.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Pooled Nivolumab + Chemotherapy Including CA209901 substudy treatment group consists of Nivolumab + Chemotherapy treatment group from studies CA209648, CA209649, CA209816 and CA209901 Substudy.
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp901sub/prog/tables/rt-ex-pt-durtrt.sas 28JUL2023:10:05:21

Table 2.3.6-2: Cumulative Dose of Nivolumab; All Nivolumab and Chemotherapy Treated Subjects (CA209816, CA209648, CA209649, and CA209901 Substudy)

	Pooled Nivo + Chemo Including CA209901 Substudy N = 1572
	Nivolumab N = 1572
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	13.0 (11.4)
MEDIAN	9.0
MIN - MAX	1 - 54
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	3937.4 (3334.8)
MEDIAN	2880.0
MIN - MAX	240 - 14640

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period
Pooled Nivolumab + Chemotherapy Including CA209901 substudy treatment group consists of Nivolumab + Chemotherapy treatment group from studies CA209648, CA209649, CA209816 and CA209901 Substudy.
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp901sub/prog/tables/rt-ex-cumdos.sas 28JUL2023:10:05:44

Table 2.3.6-3: Clinical Exposure in Person Time by Age Group and Gender; All Nivolumab and Chemotherapy Treated Subjects (CA209816, CA209648, CA209649, and CA209901 Substudy)

Treatment Group: Pooled Nivo + Chemo Including CA209901 Substudy

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 1140	Female N = 432	Total N = 1572	Male N = 1140	Female N = 432	Total N = 1572
>= 18 AND < 65	612 (53.7)	263 (60.9)	875 (55.7)	5558.08	2136.77	7694.85
>= 65 AND < 75	417 (36.6)	130 (30.1)	547 (34.8)	3734.57	1210.71	4945.28
>= 75 AND < 85	104 (9.1)	38 (8.8)	142 (9.0)	947.98	314.05	1262.03
>= 85	7 (0.6)	1 (0.2)	8 (0.5)	77.27	3.15	80.43
TOTAL	1140 (100.0)	432 (100.0)	1572 (100.0)	10317.90	3664.69	13982.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Pooled Nivolumab + Chemotherapy Including CA209901 substudy treatment group consists of Nivolumab + Chemotherapy treatment group from studies CA209648, CA209649, CA209816 and CA209901 Substudy.
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp901sub/prog/tables/rt-ex-pt-age.sas 28JUL2023:10:06:05

Table 2.3.6-4: Clinical Exposure in Person Time by Racial Origin and Gender; All Nivolumab and Chemotherapy Treated Subjects (CA209816, CA209648, CA209649, and CA209901 Substudy)

Treatment Group: Pooled Nivo + Chemo Including CA209901 Substudy

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 1140	Female N = 432	Total N = 1572	Male N = 1140	Female N = 432	Total N = 1572
WHITE	664 (58.2)	266 (61.6)	930 (59.2)	6323.25	2175.08	8498.33
BLACK OR AFRICAN AMERICAN	5 (0.4)	7 (1.6)	12 (0.8)	28.32	60.09	88.41
ASIAN	428 (37.5)	138 (31.9)	566 (36.0)	3567.97	1263.64	4831.61
AMERICAN INDIAN OR ALASKA NATIVE	7 (0.6)	8 (1.9)	15 (1.0)	48.49	58.35	106.84
OTHER	36 (3.2)	13 (3.0)	49 (3.1)	349.86	107.53	457.40
TOTAL	1140 (100.0)	432 (100.0)	1572 (100.0)	10317.90	3664.69	13982.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Pooled Nivolumab + Chemotherapy Including CA209901 substudy treatment group consists of Nivolumab + Chemotherapy treatment group from studies CA209648, CA209649, CA209816 and CA209901 Substudy.
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp901sub/prog/tables/rt-ex-pt-race.sas 28JUL2023:10:06:27

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Autoimmune Disease	Further immune activation may be potentially life-threatening.	Yes	NA
Pregnancy or breast feeding women	Effect on foetus and nursing baby were unknown.	No	Included as important potential risk (Table 2.7.3.1-3)
Patients with brain metastases: – Advanced melanoma, SCCHN, and UC – active brain or leptomeningeal metastases – NSCLC – active brain metastases – RCC – any history of or concurrent brain metastases	Subpopulation with a significantly worse prognosis.	No	This patient population is addressed in the SmPC (Sections 4.4, and 5.1). There are no risk minimisation activities recommending specific clinical measures, and no risk minimisation measures beyond the PI.
Ocular/Uveal Melanoma	Subpopulation with a significantly worse prognosis.	No	Based on the mechanism of action as well as clinical responses, ocular/uveal melanoma may be responsive to nivolumab. Limited treatment options available for this disease type.
Prior select ipilimumab ARs	Subpopulation may be a greater risk for ARs.	No	No clinical study in subjects with select ipilimumab ARs. AE frequency and severity appears similar in metastatic melanoma subjects with or without prior ipilimumab experience, based on safety results from clinical studies.
Subjects with symptomatic interstitial lung disease	Could complicate evaluation or management of	No	Included as important identified risk (see Section 2.7.3.1)

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
	nivolumab-related pneumonitis in subjects with low pulmonary reserve.		
Subjects requiring systemic treatment with corticosteroids before starting nivolumab	Systemic corticosteroids could interfere with the nivolumab mechanism of action	Yes	NA

NA = as already included as Missing Information

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme for nivolumab is unlikely to detect rare and very rare inflammatory ARs that may occur with nivolumab exposure. Continuing clinical development and post-marketing safety monitoring will support the identification of new inflammatory ARs related to nivolumab.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women: Based on animal reproductive studies, nivolumab is not recommended during pregnancy unless the clinical benefit outweighs the potential risk	No clinical studies conducted
Breastfeeding women: It is not known if nivolumab is secreted in human milk; however, immunoglobulins are known to be secreted in human milk and therefore, the potential for infant exposure to nivolumab via breast milk exists.	No clinical studies conducted
Patients with relevant comorbidities:	
Patients with hepatic impairment	Included in the clinical development program (CA2099DW)
Patients with renal impairment	No clinical studies conducted
Patients with cardiovascular impairment	No clinical studies conducted
Immunocompromized patients	No clinical studies conducted
Patients with a disease severity different from inclusion criteria in clinical trials:	

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
– ECOG PS of 2 and CNS metastases in patients with NSCLC	ECOG PS 2: 103 subjects (533 person-months[a])[274] CNS metastases: 32 subjects (165 person-months[a])[274]
– ECOG PS of 2, ocular melanoma, and CNS metastases in patients with melanoma	ECOG PS 2: 66 subjects (341 person-months[a])[275] Ocular/uveal melanoma: 103 subjects (533 person-months[a])[275] CNS metastases: 165 subjects (853 person-months[a])[275]
Population with relevant different ethnic origin	Nivolumab has been approved in Japan and other Asian countries based on demonstrated efficacy and safety in local populations.
Subpopulations carrying relevant genetic polymorphisms	No clinical studies conducted
Patients Treated with Influenza Vaccine	Nested case control study using claims data - CA20999J is completed
Other	
– Paediatric patients < 18 years o with ST/Haematologic Tumours ≥ 1 and < 18 years	Two PIPs have been agreed by the EMA ST/Haematologic Tumours: Nivo: 64 subjects (223.61 person-months[a]) Nivo+Ipi: 33 subjects (69.49 person-months[a])
– Elderly patients ≥ 65 years	Included in the clinical development program (Refer to Section 2.3 and Appendix 3).

[a] Estimated using the median duration of exposure of 5.17 person-months/patient (median duration of exposure is based on pooled monotherapy exposure).

2.5 Post-Authorisation Experience

OPDIVO (nivolumab, BMS-936558, Ono-4538, or MDX1106) has been approved in the EU, US, Japan, and several other countries for the treatment of multiple tumor types.

2.5.1 Post-Authorisation Exposure

2.5.1.1 Method Used to Calculate Exposure

There is no readily available information on the number of patients treated with marketed nivolumab. However, an estimate of the number of treated patients can be derived from available sales figures.

Third parties/vendors provide nivolumab sales figures to the Company on a quarterly basis that are generally available 3 months after the close of a calendar quarter. Although these data represent the bulk of the Company's worldwide nivolumab sales, they are only an estimation of the total quantity of product sold based on the total amount of product distributed in all countries worldwide. The sales data only capture an estimated 80% - 85% of the true total worldwide sales data. Additionally, the sales data from third parties/vendors may vary from one reporting period to another because of changes in subscription agreements and changes to the number of data channels available within a given country.

2.5.1.2 Exposure

Nivolumab as monotherapy and in combination with ipilimumab has a well-characterized safety profile that is consistent across approved indications (see Section 2.7.3.1). The cumulative postmarketing patient exposure to nivolumab across indications is available to 31-Mar-2023.[276] The postmarketing sales data for nivolumab were received from 2 different sources:

- The third party/vendor data Worldwide (excluding Japan)
- [redacted].

The total cumulative, post-marketing patient exposure to nivolumab was estimated to be 1,093,607 patients ([redacted] patients worldwide [excluding Japan] + [redacted] patients in Japan). The estimated patient-month exposure to nivolumab was estimated to be 5,653,948 patient-months ([redacted] worldwide [excluding Japan] and [redacted] in Japan).

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Nivolumab is not a controlled substance. It is administered by medical personnel in a hospital or clinic environment. Therefore, the potential for misuse as a recreational drug is not applicable. Additionally, as an anti-PD-1 antibody, nivolumab is a T-cell potentiator and its mechanism of action makes it a poor candidate for a drug of abuse. Withdrawal/rebound potential has not specifically been studied or reported in nivolumab clinical trials.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP are summarized in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	Immune-related pneumonitis
	Immune-related colitis
	Immune-related hepatitis
	Immune-related nephritis or renal dysfunction
	Immune-related endocrinopathies
	Immune-related rash

Table 2.7.1-1: Safety Concerns in the Initial RMP

	Other immune-related ARs Severe infusion reactions
Important potential risks	Embryofetal toxicity
	Immunogenicity
	Cardiac arrhythmias
Missing information	Paediatric patients <18 years of age
	Patients with severe hepatic and/or renal impairment
	Patients with autoimmune disease
	Patients already receiving systemic immunosuppressants before starting nivolumab

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Nivolumab as monotherapy and in combination with ipilimumab has a well-characterized safety profile that is consistent across approved indications and is reflected in the SmPC under Sections 4.4 and 4.8. New safety findings that are not categorized as either identified or potential risks in the list of safety concerns will be described, as applicable.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune-related rash Other immune-related ARs	The most clinically significant treatment-related ARs associated with nivolumab are immune-related ARs, which are inflammatory in nature. Severe immune-related ARs are of low frequency. Immune-related adverse reactions can be serious and life-threatening. Prompt recognition of signs and symptoms and implementation of the recommended management guidelines may prevent serious complications.
Severe infusion reactions	Serious acute infusion reactions are infrequent. However, life-threatening reactions may occur.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important potential risks	
Embryofetal toxicity	Nivolumab may cause fetal harm when administered to a pregnant woman. Preclinical results suggested potential risk of third trimester fetal loss and premature birth with increased neonatal mortality if exposed to nivolumab during pregnancy.
Immunogenicity	Low rates of immunogenicity have been observed with no impact observed on safety or efficacy even following prolonged dose interruptions and rechallenge. No association was observed between the presence of nivolumab antibodies and the occurrence of hypersensitivity and infusion related reactions.
Cardiac Arrhythmias	In one study comparing nivolumab with anti-CTLA4 medicines or BRAF inhibitors, the incidence of arrhythmias was higher in subjects given nivolumab. The most common arrhythmias were tachycardia and atrial fibrillation, Grade 1-2, and not considered drug-related. Cardiac arrhythmia can be serious or life threatening.
Missing Information	
Paediatric patients <18 years of age	Safety and efficacy of nivolumab in the paediatric population have not been established. Two PIPs are agreed by the EMA.
Patients with severe hepatic and/or renal impairment	No study has been conducted.
Patients with autoimmune disease	No study has been conducted.
Patients already receiving systemic immunosuppressants before starting nivolumab	No study has been conducted.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns or reclassification of safety concerns with the submission of the updated RMP.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important Identified Risks

- Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)
- Severe infusion reactions

Important Potential Risks

- Embryofetal toxicity
- Immunogenicity

- Risk of GVHD with nivolumab after allogeneic HSCT

Missing Information

- Patients with severe renal and/or hepatic impairment
- Patients with autoimmune disease
- Patients already receiving systemic immunosuppressants before starting nivolumab
- Long-term safety in adolescent patients ≥ 12 years of age

2.7.3.1 Presentation of Important Identified and Important Potential Risks

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	
Potential mechanisms	Nivolumab specifically blocks the inhibitory signal of PD-1, resulting in activation of T-lymphocytes. Upregulation of T-lymphocyte activity has been associated with AEs in multiple organ systems characterized by an inflammatory process. Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone.
Evidence source and strength of evidence	**Pneumonitis** Immune-related pneumonitis has been reported in subjects with a variety of tumor types and in subjects with and without lung metastases. The majority of cases reported were Grade 1-2 and subjects presented with either asymptomatic radiographic changes (eg, focal ground glass opacities, patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3-4 pulmonary toxicities were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. Severe pneumonitis can be life-threatening if not diagnosed early and managed appropriately. Death due to pulmonary toxicity, including pulmonary embolism, has been reported with nivolumab in combination with ipilimumab.[277] **Colitis** Immune-related colitis has been reported in subjects with a variety of tumor types. The majority of subjects had mild to moderate (Grade 1-2) diarrhea or colitis. Grade 3-4 cases were more common with nivolumab in combination with ipilimumab. Diarrhea/colitis was manageable using the established management guidelines. The majority of cases resolved with drug interruption and, in severe cases, with steroids treatment. Severe or persistent diarrhea and colitis can be life-threatening if not recognized early and managed appropriately. **Hepatitis** Immune-related hepatitis has been reported in subjects with a variety of tumor types. Subjects may be asymptomatic. In clinical studies, hepatotoxicities manifesting as transaminase elevations were detectable with liver function testing and signs and symptoms monitoring. Most were Grade 1-2 transaminase elevation or hepatitis. Immune-related hepatitis can be serious or life-threatening and even fatal if not treated promptly. Subjects with immune-related hepatitis are generally managed clinically with steroid therapy with resolution of the event. Prompt review of blood tests, recognition of signs and symptoms, and implementation of the recommended management guidelines may prevent serious complications. **Nephritis and renal dysfunction**

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	
	Immune-related nephritis and renal dysfunction have been reported in subjects with a variety of tumor types. Most patients present with asymptomatic increase in serum creatinine. Most were Grade 1-2 severity. Immune-related nephritis and renal dysfunction can be serious or life-threatening. Subjects with immune-related nephritis and renal dysfunction are generally managed clinically with steroid therapy with resolution of the event. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications. **Endocrinopathies** Immune-related endocrinopathies have been reported in subjects with a variety of tumor types. Immune-related endocrinopathies have been observed with nivolumab monotherapy and the most common disorder was hypothyroidism with Grade 1-2 severity in majority of the cases. Endocrinopathies were more frequent with nivolumab in combination with ipilimumab. Less frequently observed endocrinopathies included adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis. Patients are typically managed with hormone replacement and/or steroid treatment. Lifelong hormone replacement may be required. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications. **Skin ARs** Immune-related skin ARs have been reported in subjects with a variety of tumor types. Mild to moderate (Grade 1-2) immune-related skin ARs are common with nivolumab monotherapy, while severe (Grade 3-4) immune-related skin ARs are of low frequency with nivolumab monotherapy and more frequent with nivolumab in combination with ipilimumab. Rare cases of SJS and TEN, some with fatal outcome, have been observed. Early detection and timely treatment are key to recovery and to prevent severe complications. **Other irARs** Selected other irARs, which are uncommon but considered important identified risks, include uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis, encephalitis, solid organ transplant rejection, and Vogt-Koyanagi-Harada. Other irARs can be serious and life-threatening. Patients are usually clinically managed with steroids and the events generally resolved. Severe (Grade 3-4) irARs are reported in minority of patients.
Characterization of risk *(Percent; All Treated)*	Refer to Appendix 4 for single study safety data (by indication) for studies included in the pooled safety analyses. **Pneumonitis** **I. Pooled Nivolumab Monotherapy (N = 4646)** (CA209017, CA209057, CA209063, CA209141, CA209037, CA209066, CA209067, CA209238, CA209025, CA209205 (Cohorts A+B+C), CA209039 (cHL subjects), CA209275, CA209032 (BC subjects), CA209473 (ONO-4538-24), CA209577, CA209274, and CA20976K). • Any Grade: 3.3% • Grade 3-4: 0.7% • Grade 5: < 0.1%

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070			
Any Grade	0	NA	NA
Grade 3-4	0	NA	NA

II. Pooled Nivolumab Combined with Ipilimumab (+/-Chemo) (N = 2626) (CA209004 (cohort 8), CA209067, CA209069, CA209142 [dMMR or MSI-H CRC], CA2099DW, CA2098HW, CA209214, CA209648, CA209743 and CA2099LA*. Studies marked with * have chemo included in the regimen)

- Any Grade: 6.0%
- Grade 3-4: 1.3%
- Grade 5: 0%

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070[a]			
Any Grade	2.2	NA	NA
Grade 3-4	0	NA	NA

[a] nivolumab 3 mg/kg + ipilimumab 1 mg/kg: 40 subjects treated; nivolumab 1 mg/kg + ipilimumab 1 mg/kg: 6 subjects treated

III. Nivolumab (240 mg) Combined with Cabozantinib (40 mg)

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099ER			
Any Grade	5.3	0.3	5.0 (2.6, 8.0)
Grade 3-4	1.6	0.3	1.3 (-0.4, 3.3)

IV. Pooled Nivolumab (240 mg Q2W or 360 mg Q3W) Combined with Chemotherapy (N = 1572) (CA209649, CA209648, CA209816, CA209901 Substudy)

- Any Grade: 4.3%
- Grade 3-4: 1.1%
- Grade 5: 0%

Colitis

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

I. Pooled Nivolumab Monotherapy (N = 4646) (CA209017, CA209057, CA209063, CA209141, CA209037, CA209066, CA209067, CA209238, CA209025, CA209205 (Cohorts A+B+C), CA209039 (cHL subjects), CA209275, CA209032 (BC subjects), CA209473 (ONO-4538-24), CA209577, CA209274, and CA20976K.)

- Any Grade: 15.4%
- Grade 3-4: 1.5%
- Grade 5: 0

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070			
Any Grade	7.5	NA	NA
Grade 3-4	0	NA	NA

II. Pooled Nivolumab Combined with Ipilimumab (+/-Chemo) (N = 2626) (CA209004 (cohort 8), CA209067, CA209069, CA209142 [dMMR or MSI-H CRC], CA2099DW, CA2098HW, CA209214, CA209648, CA209743 and CA2099LA*. Studies marked with * have chemo included in the regimen)

- Any Grade:26.0%
- Grade 3-4: 6.5%
- Grade 5: <0.1%

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070[a]			
Any Grade	6.5	NA	NA
Grade 3-4	0	NA	NA

[a] nivolumab 3 mg/kg + ipilimumab 1 mg/kg: 40 subjects treated; nivolumab 1 mg/kg + ipilimumab 1 mg/kg: 6 subjects treated

III. Nivolumab (240 mg) Combined with Cabozantinib (40 mg)

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099ER			
Any Grade	57.5	42.5	15.0 (7.3, 22.5)
Grade 3-4	5.9	4.4	1.6 (-2.0, 5.2)

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)
IV. Pooled Nivolumab (240 mg Q2W or 360 mg Q3W) Combined with Chemotherapy (N = 1572) (CA209649, CA209648, CA209816, CA209901 Substudy) • Any Grade: 24.0% • Grade 3-4: 3.6% • Grade 5: 0%

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Hepatitis

I. Pooled Monotherapy (N = 4646) (CA209017, CA209057, CA209063, CA209141, CA209037, CA209066, CA209067, CA209238, CA209025, CA209205 (Cohorts A+B+C), CA209039 (cHL subjects), CA209275, CA209032 (BC subjects), CA209473 (ONO-4538-24), CA209577, CA209274, and CA20976K.)

- Any Grade: 8.0%
- Grade 3-4: 1.9%
- Grade 5: 0

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070			
Any Grade	40.0	NA	NA
Grade 3-4	1.3	NA	NA

II. Pooled Nivolumab Combined with Ipilimumab (+/-Chemo) (N = 2626) (CA209004 (cohort 8), CA209067, CA209069, CA209142 [dMMR or MSI-H CRC], CA2099DW, CA2098HW, CA209214, CA209648, CA209743 and CA2099LA*. Studies marked with * have chemo included in the regimen)

- Any Grade: 21.2%
- Grade 3-4: 9.6%
- Grade 5: 0%

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070[a]			
Any Grade	28.3	NA	NA
Grade 3-4	4.3	NA	NA

[a] nivolumab 3 mg/kg + ipilimumab 1 mg/kg: 40 subjects treated; nivolumab 1 mg/kg + ipilimumab 1 mg/kg: 6 subjects treated

III. Nivolumab (240 mg) Combined with Cabozantinib (40 mg)

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099ER			
Any Grade	40.0	21.9	18.1 (11.0, 25.0)
Grade 3-4	10.3	3.4	6.9 (3.0, 11.0)

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

IV. Pooled Nivolumab (240 mg Q2W or 360 mg Q3W) Combined with Chemotherapy (N = 1572) (CA209649, CA209648, CA209816, CA209901 Substudy)

- Any Grade: 18.6%
- Grade 3-4: 2.9%
- Grade 5: 0%

Nephritis and renal dysfunction

I. Pooled Nivolumab Monotherapy (N = 4646) (CA209017, CA209057, CA209063, CA209141, CA209037, CA209066, CA209067, CA209238, CA209025, CA209205 (Cohorts A+B+C), CA209039 (cHL subjects), CA209275, CA209032 (BC subjects), CA209473 (ONO-4538-24), CA209577, CA209274, and CA20976K)

- Any Grade: 2.6%
- Grade 3-4: 0.4%
- Grade 5: 0

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070			
Any Grade	8.8	NA	NA
Grade 3-4	0	NA	NA

II. Pooled Nivolumab Combined with Ipilimumab (+/-Chemo) (N = 2626) (CA209004 (cohort 8), CA209067, CA209069, CA209142 [dMMR or MSI-H CRC], CA2099DW, CA2098HW, CA209214, CA209648, CA209743 and CA2099LA*. Studies marked with * have chemo included in the regimen)

- Any Grade: 5.4%
- Grade 3-4: 1.2%
- Grade 5: 0%

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070[a]			
Any Grade	15.2	NA	NA
Grade 3-4	0	NA	NA

[a] nivolumab 3 mg/kg + ipilimumab 1 mg/kg: 40 subjects treated; nivolumab 1 mg/kg + ipilimumab 1 mg/kg: 6 subjects treated

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

III. Nivolumab (240 mg) Combined with Cabozantinib (40 mg)

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099ER			
Any Grade	9.7	8.1	1.6 (-2.9, 6.1)
Grade 3-4	1.3	0.3	0.9 (-0.7, 2.9)

IV. Pooled Nivolumab (240 mg Q2W or 360 mg Q3W) Combined with Chemotherapy (N = 1572) (CA209649, CA209648, CA209816, CA209901 Substudy)

- Any Grade: 10.8%
- Grade 3-4: 1.7%
- Grade 5: 0%

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Endocrinopathies

I. Pooled Nivolumab Monotherapy (N = 4646) (CA209017, CA209057, CA209063, CA209141, CA209037, CA209066, CA209067, CA209238, CA209025, CA209205 (Cohorts A+B+C), CA209039 (cHL subjects), CA209275, CA209032 (BC subjects), CA209473 (ONO-4538-24), CA209577, CA209274, and CA20976K)

- Any Grade 14.3%
  (thyroid disorder 13.0%, adrenal disorder 0.8%, pituitary disorder 0.6%, , and diabetes 0.3%)
- Grade 3-4: 0.8%
  (pituitary disorder 0.2%, adrenal disorder 0.2%, thyroid disorder 0.2%, and diabetes 0.2%)
- Grade 5: 0

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070			
Any Grade	23.8	NA	NA
(Nivolumab: thyroid disorder 23.8%, adrenal disorder 0%, pituitary disorder 0%, and diabetes 0%)			
Grade 3-4	0	NA	NA
(Nivolumab: thyroid disorder 0%, adrenal disorder 0%, pituitary disorder 0%, and diabetes 0%)			

II. Pooled Nivolumab Combined with Ipilimumab (+/-Chemo) (N = 2626) (CA209004 (cohort 8), CA209067, CA209069, CA209142 [dMMR or MSI-H CRC], CA2099DW, CA2098HW, CA209214, CA209648, CA209743 and CA2099LA*. Studies marked with * have chemo included in the regimen)

- Any Grade: 28.3%
  - *(thyroid disorder 23.2%, pituitary disorder 5.1%, adrenal disorder 4.9%, and diabetes 0.8%)*
- Grade 3-4: 4.8%
  - *(pituitary disorder 2.1%, adrenal disorder 1.8%, thyroid disorder 1.0%, and diabetes 0.5%)*
- Grade 5: 0

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)			
CA209070[a]			
Any Grade	23.9	NA	NA
(Nivolumab: thyroid disorder 23.9%, adrenal disorder 0%, pituitary disorder 0%, and diabetes 0%)			
Grade 3-4	0	NA	NA
(Nivolumab: thyroid disorder 0%, adrenal disorder 0%, pituitary disorder 0%, and diabetes 0%)			

[a] nivolumab 3 mg/kg + ipilimumab 1 mg/kg: 40 subjects treated; nivolumab 1 mg/kg + ipilimumab 1 mg/kg: 6 subjects treated

III. Nivolumab (240 mg) Combined with Cabozantinib (40 mg)

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099ER			
Any Grade	42.8	33.1	9.7 (2.2, 17.1)
(Nivolumab: thyroid disorder 42.2%, adrenal disorder 3.8%, pituitary disorder 0.6%)			
Grade 3-4	2.5	0.3	2.2 (0.3, 4.6)
(Nivolumab: adrenal disorder 1.9%, thyroid disorder 0.9%, pituitary disorder 0.3%)			

IV. Pooled Nivolumab (240 mg Q2W or 360 mg Q3W) Combined with Chemotherapy (N = 1572) (CA209649, CA209648, CA209816, CA209901 Substudy)

- Any Grade: 13.9%
  - *(thyroid disorder 12.7%, adrenal disorder 0.8%, pituitary disorder 0.7%, and diabetes 0.4%)*
- Grade 3-4: 0.9%
  - *(pituitary disorder 0.4%, adrenal disorder 0.3% , diabetes 0.2%, and thyroid disorder <0.1)*
- Grade 5: 0%

Skin ARs

I. Pooled Nivolumab Monotherapy (N = 4646) (CA209017, CA209057, CA209063, CA209141, CA209037, CA209066, CA209067, CA209238, CA209025, CA209205 (Cohorts A+B+C), CA209039 (cHL subjects), CA209275, CA209032 (BC subjects), CA209473 (ONO-4538-24), CA209577,CA209274, and CA20976K)

- Any Grade: 30.0%
- Grade 3-4: 1.3%
- Grade 5: 0%
-

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070			
Any Grade	20.0	NA	NA
Grade 3-4	1.3	NA	NA

II. Pooled Nivolumab Combined with Ipilimumab (+/-Chemo) (N = 2626) (CA209004 (cohort 8), CA209067, CA209069, CA209142 [dMMR or MSI-H CRC], CA2099DW, CA2098HW, CA209214, CA209648, CA209743 and CA2099LA*. Studies marked with * have chemo included in the regimen)

- Any Grade: 46.1%
- Grade 3-4: 4.7%
- Grade 5: 0%

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070[a]			
Any Grade	23.9	NA	NA
Grade 3-4	2.2	NA	NA

[a] nivolumab 3 mg/kg + ipilimumab 1 mg/kg: 40 subjects treated; nivolumab 1 mg/kg + ipilimumab 1 mg/kg: 6 subjects treated

III. Nivolumab (240 mg) Combined with Cabozantinib (40 mg)

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099ER			
Any Grade	62.2	47.2	15.0 (7.3, 22.5)
Grade 3-4	10.6	7.5	3.1 (-1.4, 7.7)

IV. Pooled Nivolumab (240 mg Q2W or 360 mg Q3W) Combined with Chemotherapy (N = 1572) (CA209649, CA209648, CA209816, CA209901 Substudy)

- Any Grade: 25.6%
- Grade 3-4: 2.5%
- Grade 5: 0%

Other irARs

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

I. Pooled Nivolumab Monotherapy (N = 4646) (CA209017, CA209057, CA209063, CA209141, CA209037, CA209066, CA209067, CA209238, CA209025, CA209205 (Cohorts A+B+C), CA209039 (cHL subjects), CA209275, CA209032 (BC subjects), CA209473 (ONO-4538-24), CA209577,CA209274, and CA20976K)

	Nivolumab
Any Grade	
uveitis	0.5
pancreatitis	0.6
graft versus host disease	0.2
demyelination	< 0.1
Guillain-Barre	< 0.1
myasthenic syndrome	< 0.1
myocarditis	0.2
encephalitis	< 0.1
myositis/ rhabdomyolysis	0.3
Grade 3 - 4	
pancreatitis	0.4
uveitis	< 0.1
graft versus host disease	< 0.1
demyelination	< 0.1
Guillain-Barre	< 0.1
myasthenic syndrome	< 0.1
encephalitis	< 0.1
myocarditis	0.2
myositis/ rhabdomyolysis	0.1
Grade 5	0

Paediatric and Young Adult ST/Haematologic Tumours	**Nivolumab**	**Comparator**
CA209070		
No myasthenic syndrome, uveitis, demyelination, Guillain-Barre syndrome, myositis, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade		
pancreatitis	2.5	NA
graft versus host disease	1.3	NA
Grade 3-4		
graft versus host disease	1.3	NA

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

II. Pooled Nivolumab Combined with Ipilimumab (+/-Chemo) (N = 2626) (CA209004 (cohort 8), CA209067, CA209069, CA209142 [dMMR or MSI-H CRC], CA2099DW, CA2098HW, CA209214, CA209648, CA209743 and CA2099LA*. Studies marked with * have chemo included in the regimen)

	Nivolumab Combined with Ipilimumab (+/-Chemo)
No Graft versus Host Disease	
Any Grade	
pancreatitis	1.7
uveitis	0.6
myositis/ rhabdomyolysis	0.7
encephalitis	0.5
myocarditis	0.4
Guillain-Barre Syndrome	<0.1
myasthenic syndrome	0.2
Vogt-Koyanagi-Harada disease	<0.1
demyelination	<0.1
Grade 3 - 4	
pancreatitis	0.9
encephalitis	0.4
myositis/ rhabdomyolysis	0.3
uveitis	0.2
Guillain-Barre Syndrome	<0.1
myasthenic syndrome	0.2
myocarditis	0.3
Grade 5	
encephalitis	<0.1
pancreatitis	<0.1

Paediatric and Young Adult ST/Haematologic Tumours	**Nivolumab**	**Comparator**
CA209070[a]		
No myasthenic syndrome, demyelination, Guillain-Barre syndrome, myositis, myocarditis, rhabdomyolysis, graft versus host disease, or encephalitis reported		
Any Grade		NA
pancreatitis	2.2	NA
uveitis	2.2	NA
Grade 3-4		NA
pancreatitis	2.2	NA

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

[a] nivolumab 3 mg/kg + ipilimumab 1 mg/kg: 40 subjects treated; nivolumab 1 mg/kg + ipilimumab 1 mg/kg: 6 subjects treated

III. Nivolumab (240 mg) Combined with Cabozantinib (40 mg)

RCC	Nivolumab	Comparator
CA2099ER		
No myositis, demyelination, rhabdomyolysis and graft versus host disease reported		
Any Grade		
Pancreatitis	0.6	0
Encephalitis	0.6	0
Myasthenic Syndrome	0.3	0
Guillain-Barre Syndrome	0.3	0
Uveitis	0.3	0.3
Myocarditis	0.3	0
Grade 3-4		
Pancreatitis	0.3	0
Encephalitis	0.3	0
Guillain-Barre Syndrome	0.3	0
Uveitis	0.3	0.3
Myocarditis	0.3	0

IV. Pooled Nivolumab (240 mg Q2W or 360 mg Q3W) Combined with Chemotherapy (N = 1572) (CA209649, CA209648, CA209816, CA209901 Substudy)

	Nivolumab Combined with Chemo
No demyelination, myasthenic syndrome, or Graft versus Host Disease	
Any Grade	
uveitis	0.1
Guillain-Barre syndrome	<0.1
autoimmune pancreatitis	<0.1
pancreatitis	0.3
pancreatitis acute	<0.1
chorioretinitis	<0.1
encephalitis	<0.1
encephalitis autoimmune	<0.1
autoimmune myocarditis	<0.1
immune-mediated myocarditis	<0.1

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	
myocarditis	0.2
myositis	<0.1
rhabdomyolysis	0.1
Grade 3-4	
Guillain-Barre syndrome	<0.1
pancreatitis	0.3
pancreatitis acute	<0.1
chorioretinitis	<0.1
encephalitis	<0.1
encephalitis autoimmune	<0.1
autoimmune myocarditis	<0.1
immune-mediated myocarditis	<0.1
myocarditis	<0.1
rhabdomyolysis	0.1
Grade 5	0

Risk factors and risk groups

Pneumonitis

ILD can develop or exacerbate as a consequence of radiotherapy, chemotherapy, or pulmonary resection.[278] Other risk factors for ILD include older age, reduced normal lung on computed tomography scan, smoking history, and concomitant or previous lung infection.[279,280]

Colitis

Patients with active inflammatory bowel disease.

Hepatitis

Active autoimmune hepatitis, which may also be associated with previous chemotherapy or immunotherapy, such as IL-2 or IFN.

Nephritis and renal dysfunction

Active autoimmune diseases with potential for renal involvement.

Endocrinopathies

Active autoimmune diseases of the endocrine glands may also be associated with previous chemotherapy or immunotherapy, such as IL-2, IFN, or anti-CTLA4.

Skin ARs

Active autoimmune skin disorders.

Other irARs

Active autoimmune diseases may also be associated with previous chemotherapy or immunotherapy, such as IL-2, IFN, or anti-CTLA4.

Preventability

In the event of immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs), prompt recognition of signs and symptoms and implementation of the recommended

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	
	management guidelines may prevent serious complications. Monitor patients for signs and symptoms of immune-related adverse reactions. Refer to Section 5 for details on risk minimisation measures.
Impact on the risk-benefit balance of the product	Nivolumab can increase the risk of immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs). Early recognition and appropriate management are important to prevent more severe complications and ensure the benefits of the medicine continue to outweigh the risks. The product label adequately addresses appropriate management guidelines, and additional patient material is intended to ensure that patients are aware of these risks.
Public health impact	All available data suggest that nivolumab has a consistent AE profile across tumor types. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids as instructed in the management guidelines.
MedDRA terms	Refer to Annex 7

Table 2.7.3.1-2: Important Identified Risk: Severe Infusion Reactions

Severe Infusion Reactions	
Potential mechanisms	Infusion reactions may occur with treatment with any injectable protein, including nivolumab, which is a fully human IgG4 anti-PD-1 mAb.
Evidence source and strength of evidence	As with any other intravenous administered drugs, infusion-related reactions can occur with nivolumab. Premedications were generally not required prior to nivolumab administration during clinical trials with nivolumab. Severe infusion reactions were uncommon but can lead to discontinuation.
Characterization of risk *(Percent; All Treated)*	Refer to Appendix 4 for single study safety data (by indication) for studies included in the pooled safety analyses. **I. Pooled Nivolumab Monotherapy** (N = 4646) (CA209017, CA209057, CA209063, CA209141, CA209037, CA209066, CA209067, CA209238, CA209025, CA209205 (Cohorts A+B+C), CA209039 (cHL subjects), CA209275, CA209032 (BC subjects), CA209473 (ONO-4538-24), CA209577, CA209274, and CA20976K) • Any Grade: 4.0% • Grade 3-4: 0.3% • Grade 5: 0

Paediatric and Young Adult ST/Haematologic Tumours	**Nivolumab**	**Comparator**	**DIFF (95% CI)**

Table 2.7.3.1-2: Important Identified Risk: Severe Infusion Reactions

Severe Infusion Reactions			
CA209070			
Any Grade	5.0	NA	NA
Grade 3-4	0	NA	NA

II. Pooled Nivolumab Combined with Ipilimumab (+/-Chemo) (N = 2626) (CA209004 (cohort 8), CA209067, CA209069, CA209142 [dMMR or MSI-H CRC], CA2099DW, CA2098HW, CA209214, CA209648, CA209743 and CA2099LA*. Studies marked with * have chemo included in the regimen)

- Any Grade: 4.5%
- Grade 3-4: 0.3%
- Grade 5: 0

Paediatric and Young Adult ST/Haematologic Tumours	Nivolumab	Comparator	DIFF (95% CI)
CA209070[a]			
Any Grade	4.3	NA	NA
Grade 3-4	0	NA	NA

[a] nivolumab 3 mg/kg + ipilimumab 1 mg/kg: 40 subjects treated; nivolumab 1 mg/kg + ipilimumab 1 mg/kg: 6 subjects treated

III. Nivolumab (240 mg) Combined with Cabozantinib (40 mg)

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099ER			
Any Grade	2.5	0.3	2.2 (0.3, 4.6)
Grade 3-4	0	0	N.A.

IV. Pooled Nivolumab (240 mg Q2W or 360 mg Q3W) Combined with Chemotherapy (N = 1572) (CA209649, CA209648, CA209816, CA209901 Substudy)

- Any Grade: 8.5%
- Grade 3-4: 1.3%
- Grade 5: 0%

Risk factors and risk groups	None.
Preventability	Acute infusion reactions are usually easily recognized and can usually be managed by interruption of the infusion and medical treatment. Pretreatment with antihistamines and/or steroids is not necessary or recommended.
Impact on the risk-benefit balance of the product	No impact as infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon.

Table 2.7.3.1-2: Important Identified Risk: Severe Infusion Reactions

Severe Infusion Reactions	
Public health impact	No impact as infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon.
MedDRA terms	See Annex 7

Table 2.7.3.1-3: Important Potential Risk: Embryofetal Toxicity

Embryofetal Toxicity	
Potential mechanisms	Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase foetal loss.
Evidence source and strength of evidence	Contraception is required for WOCBP. Preclinical study suggested potential risk of third trimester fetal loss and premature birth with increased neonatal mortality if exposed to nivolumab during pregnancy.
Characterization of risk *(Percent; All Treated)*	None
Risk factors and risk groups	Exposure during pregnancy.
Preventability	Preventable with contraception.
Impact on the risk-benefit balance of the product	Dosing during pregnancy is prohibited. WOCBP receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab.
Public health impact	None
MedDRA terms	SOC Pregnancy, puerperium and perinatal conditions

Table 2.7.3.1-4: Important Potential Risk: Immunogenicity

Immunogenicity	
Potential mechanisms	Nivolumab is protein product, thus might be recognized as foreign by the recipient subject. However, it is a fully human IgG4, thus its immunogenic potential is very low.
Evidence source and strength of evidence	No increased risk of hypersensitivity or infusion reaction in patients with positive ADA vs negative ADA subjects. No life threatening or fatal outcomes have been reported. Low rates of immunogenicity have been observed and no impact has been observed on safety or efficacy even following prolonged dose interruptions and rechallenge.
Characterization of risk *(Percent; All Treated)*	**Integrated (Pooled) Analyses of Immunogenicity** Nivolumab Monotherapy (3 mg/kg or 240 mg): Of the 3529 subjects who were treated with nivolumab monotherapy 3 mg/kg or 240 mg every 2 weeks and evaluable for the presence of anti-product-antibodies, 328 subjects (9.3%) tested positive for treatment emergent anti product antibodies with 21 subjects (0.6%) testing positive for neutralizing antibodies.

Table 2.7.3.1-4: Important Potential Risk: Immunogenicity

Immunogenicity	
	Nivolumab (1 mg/kg) in Combination with Ipilimumab (3 mk/kg): Of the 394 subjects who were treated with nivolumab in combination therapy with ipilimumab from clinical studies (CA209067 [combination group], CA209069, and CA209004 [Cohort 8]) and evaluable for the presence of ADA, 149 (37.8%) subjects tested positive for ADA by an ECL assay. Only 18 (4.6%) subjects were persistent positive. Neutralizing antibodies were detected in only 18 (4.6% of the total) subjects.[281] In an updated analysis in CA209067,[282] the incidence of nivolumab ADA was 12.3% (36/292 subjects) and 44% (128/291 subjects) following nivolumab monotherapy and nivolumab and ipilimumab combination therapy, respectively. One (0.3%) subject following nivolumab monotherapy and 15 (5.2%) subjects following nivolumab and ipilimumab combination therapy were persistent positive. There was low to minimal impact on ipilimumab immunogenicity when ipilimumab was administered in combination with nivolumab. Of the ADA evaluable subjects in the nivolumab+ipilimumab group, 24/290 (8.3%) were ipilimumab ADA positive after treatment. This incidence of ADA to ipilimumab was similar to the ipilimumab monotherapy group (5.7%). **Immunogenicity and Safety** Nivolumab Monotherapy (3 mg/kg): Of the subjects evaluable for the presence of ADA (studies CA209037, CA209063, CA209066, CA209017, CA209057, CA209067 [nivolumab monotherapy arm], CA209025, CA209039, CA209205 CA209141, CA209032 [UC subjects only], and CA209275), a total of 116 experienced hypersensitivity/infusion reactions. Of the 116 subjects who experienced hypersensitivity/infusion reactions, 5 were positive for nivolumab ADA and 111 were negative for nivolumab ADA. A total of 5/241 (2.07%) ADA positive subjects experienced adverse events in the hypersensitivity/infusion reaction category. In CA209238: Of the 426 nivolumab-treated subjects who had evaluable ADA data at baseline and post-baseline, 27 (6.3%) subjects were ADA-positive at baseline. After initiation of treatment with nivolumab, 10 (2.3%) subjects were ADA-positive, of which 3 (0.7%) subjects were considered persistent positive; and 416 (97.7%) subjects were ADA-negative. Neutralizing antibodies were not detected in any of the positive samples. In CA209577: Of the 464 nivolumab ADA evaluable subjects in the nivolumab arm, 20 (4.3%) subjects were nivolumab ADA positive at baseline. After initiation of treatment with nivolumab, 21 (4.5%) subjects were ADA positive, of which none were considered persistent positive, 1 (0.2%) subject was neutralizing ADA positive, 1 (0.2%) subject was neutralizing ADA negative, and 442 (95.3%) subjects were ADA negative. In CA209070: In combined cohorts treated with nivolumab monotherapy, 3/51 (5.9%) subjects were tested positive for ADA at baseline, and 1/51 (2.0%) subject was tested positive post baseline but was not persistently positive or NAb positive. In CA2098FC[254,255]: *Nivolumab Process C arm* Of the 118 nivolumab ADA-evaluable subjects, 5 (4.2%) subjects were nivolumab ADA-positive at baseline, and 3 (2.5%) subjects were nivolumab

Table 2.7.3.1-4: Important Potential Risk: Immunogenicity

Immunogenicity	
	ADA-positive after the start of treatment. No subjects were considered persistent positive or developed neutralizing antibody. *Nivolumab Process D arm* Of the 123 nivolumab ADA-evaluable subjects, 5 (4.1%) subjects were nivolumab ADA-positive at baseline, and 8 (6.5%) subjects were nivolumab ADA-positive after the start of treatment. 2 (1.6%) subjects were considered persistent positive, and no subjects developed neutralizing antibodies. Immunogenicity profiles of nivolumab Process D and Process C were consistent with the historical immunogenicity profile of nivolumab when administered as monotherapy, and there were no unexpected safety or efficacy concerns in subjects who developed ADAs to nivolumab. Nivolumab (1 mg/kg) in Combination with Ipilimumab (3 mg/kg): In studies CA209004 and CA209069, the safety profiles of the 4 persistent positive subjects and 1 NAb positive subject were similar to those observed in nivolumab ADA negative subjects. There were no hypersensitivity, acute infusion reactions, and new AEs observed in persistent or NAb positive subjects compared to ADA negative subjects. In CA209067: 1/36 (2.8%) nivolumab ADA positive and 16/256 (6.3%) nivolumab ADA negative subjects in the nivolumab group and 8/128 (6.3%) nivolumab ADA positive and 7/163 (4.3%) nivolumab ADA negative subjects in the nivolumab and ipilimumab combination group experienced AEs in the hypersensitivity/infusion reaction category. Overall, in the analysis of select AEs (hypersensitivity/infusion reaction) by nivolumab or ipilimumab ADA status (positive, negative) in all treated subjects who were ADA positive or negative, the findings suggest that nivolumab or ipilimumab ADA occurrence did not impact safety. No association was observed between the presence of nivolumab or ipilimumab antibodies and the occurrence of hypersensitivity and infusion-related reactions. In CA209070: In combined cohorts treated with nivolumab + ipilimumab, 2/35 (5.7%) subjects were tested positive for nivolumab ADA at baseline, and 1/35 (2.9%) subject was tested positive post baseline but was not persistently positive or NAb positive. In CA2099DW: Of the 224 nivo ADA-evaluable subjects in the nivo+ipi arm, 19 (8.5%) subjects were nivo ADA positive at baseline, and 100 (44.6%) subjects were treatment-emergent nivo ADA-positive. 11 (4.9%) subjects were persistent positive, and 16 (7.1%) subjects were neutralizing ADA positive. Of the 244 ipi ADA-evaluable subjects in the nivo+ipi arm, 18 (7.4%) subjects were ipi ADA positive at baseline and 13 (5.3%) subjects were treatment-emergent ipi ADA-positive. 1 (0.4%) subject was persistent positive, and no subject was neutralizing ADA-positive. Most ADA positivity occurred early (within the first 5 cycles) during the nivo or ipi treatment period. The presence of nivo or ipi ADA did not appear to have an effect on the efficacy or safety of nivo+ipi regimen.

Table 2.7.3.1-4: Important Potential Risk: Immunogenicity

Immunogenicity	
	Nivolumab (3 mg/kg or 240mg) in Combination with Ipilimumab (1 mg/kg): CA209016: With nivolumab, ADA were detected in 5 (13.2%) subjects, of whom 1 (2.6%) subject was considered as persistent positive, 3 (7.9%) subjects were ADA positive only at last sample, 1 (2.6%) subject was other positive, and 33 (86.8%) subjects were ADA negative. No subjects were neutralizing ADA positive. The presence of ADA was not associated with the occurrence of hypersensitivity and/or infusion-related reactions. CA209214: The incidence of nivolumab ADA was 25.4% (101/398 subjects) in subjects with at least one ADA positive sample relative to baseline at any time after initiation of treatment of nivolumab + ipilimumab. Only 1 subject was NAb ADA positive and 5 subjects (1.3%) were considered persistent positive. The incidence of ipilimumab ADA was 5.7% (23/401 subjects) in subjects with at least one ADA positive sample relative to baseline at any time after initiation of treatment, which is similar to what has been previously observed. No subject was neutralizing ADA positive or considered persistent positive. The presence of nivolumab or ipilimumab ADA was not associated with the occurrence of hypersensitivity and/or infusion-related reactions. CA209142: There were 109 subjects that were ADA evaluable for nivolumab and 107 subjects ADA evaluable for ipilimumab in CA209142 combination arm from DBL on 19-Feb-2019. The incidence of nivolumab ADA was 25.7% (n=28) with no persistent-positive subject and 2 neutralizing antibody-positive subjects. Among the 28 patients with positive ADA, there was no patient experiencing adverse events of hypersensitivity/infusion reaction. The incidence of ipilimumab ADA was 4.7% (n=5) with no persistent-positive subject and no neutralizing antibody-positive subjects. Among the 5 patients with positive ADA, there was no patient experiencing adverse events of hypersensitivity/infusion reaction. CA2098HW: There were 177 1L subjects that were ADA-evaluable for nivolumab and 173 1L subjects that were ADA evaluable for ipilimumab in the CA2098HW combination arm (Nivo + Ipi) from DBL on 15-Nov-2023. The incidence of nivolumab ADA was 14.1% (n=25) with no persistent-positivity and no treatment-emergent neutralizing antibody-positive subjects. Among the 25 subjects with positive ADA, there was 1 (4.0%) subject reported with adverse events of hypersensitivity/infusion reaction compared to 9/152 (5.9%) ADA negative subjects. The incidence of ipilimumab ADA was 8.1% (n=14) with 1 (0.6%) persistent-positivity and 1 (0.6%) treatment-emergent neutralizing antibody-positive subject. Among the 14 subjects with positive ADA, there was 1 (7.1%) subject reported with adverse events of hypersensitivity/infusion reaction compared to 9/159 (5.7%) ADA negative subjects. Overall, in the nivo+ipi arm, the frequency of nivolumab ADA and ipilimumab ADA did not appear to impact the safety of the nivo+ipi regimen. In CA209743: 17/269 (6.3%) nivolumab ADA positive at baseline and 69/269 (25.7%) subjects were nivolumab ADA positive after the start of treatment. Few subjects were persistent positive (1.9%) and positive for neutralizing ADA (0.7%). The highest titer value recorded was 64 which occurred in one subject. No association was observed between the presence of nivolumab or

Table 2.7.3.1-4: Important Potential Risk: Immunogenicity

Immunogenicity	
	ipilimumab antibodies and the occurrence of hypersensitivity and infusion-related reactions. Of the 271 ipilimumab ADA evaluable subjects in the nivo+ipi arm, 12 (4.4%) were ipilimumab ADA positive at baseline and 37 (13.7%) were ipilimumab ADA positive after start of treatment. Few subjects were persistent positive (3 subjects, 1.1%) and positive for neutralizing ADA (1 subject, 0.4%). The highest titer value recorded was 32, which occurred in one subject. CA209648: Of the 281 nivolumab ADA-evaluable subjects in the nivo + ipi arm in CA209648, 19 (6.8%) subjects were nivolumab ADA positive at baseline, and 68 (24.2%) subjects were nivolumab ADA positive after start of treatment. One (0.4%) subject was considered persistent positive, and 6 (2.1%) subjects were neutralizing ADA positive. Two subjects were positive for nivolumab ADA at baseline, but the titers of post-baseline ADA and neutralizing ADA samples did not exceed ≥ 4-fold titer increase from baseline. Thus, both subjects were not qualified for the definition of ADA-positive or NAb-positive. The highest nivolumab ADA titer values observed were 256 and 512, which occurred in 1 subject each. All other titers were low, ranging from 1 to 64. Of the 282 ipilimumab ADA-evaluable subjects in the nivo + ipi arm, 6 (2.1%) subjects were ipilimumab ADA-positive at baseline and 17 (6.0%) subjects were ipilimumab ADA positive after the start of treatment. One (0.4%) subject was considered persistent positive for ipilimumab ADA only, and 1 (0.4%) subject was NAb-positive for ipilimumab ADA only. Ipilimumab ADA titers were low, ranging from 1 to 64. Nivolumab in Combination with Ipilimumab and Chemotherapy: In study CA2099LA, following administration of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy, the incidence of nivolumab ADA was 33.8% and the incidence of ipilimumab ADA was 7.5%. A total of 8 (2.6%) subjects were nivolumab neutralizing positive and 5 (1.6%) subjects were ipilimumab neutralizing positive.[283] In CA2099LA, the incidence of nivolumab or ipilimumab immunogenicity did not appear to have an effect on the efficacy or safety of the nivo+ipi+chemo regimen. Of the nivo+ipi+chemo-treated subjects who were evaluable for ADA, hypersensitivity/infusion reaction AEs were experienced by 16 (7.8%) nivolumab ADA-negative subjects, 5 (4.8%) nivolumab ADA-positive subjects, 20 (7.1%) ipilimumab ADA-negative subjects and 2 (8.7%) ipilimumab ADA-positive subjects.[283] The presence of nivolumab or ipilimumab ADA did not appear to be associated with the occurrence of hypersensitivity/infusion reaction AEs. Nivolumab in Combination with Cabozantinib: In Study CA2099ER, 13/263 (4.9%) subjects were nivolumab treatment-emergent ADA positive after the start of treatment. Of those who were ADA positive, 1 (0.4%) subject was considered persistent positive and 1 (0.4%) subject was neutralizing ADA positive. Of all the nivo+cabo treated subjects who were evaluable for ADA,

Table 2.7.3.1-4: Important Potential Risk: Immunogenicity

Immunogenicity	
	hypersensitivity/infusion reaction were experienced by 4% (10/250) nivolumab ADA-negative subjects, and no nivolumab ADA-positive subjects. Overall, the incidence of treatment-emergent nivolumab ADA was low relative to historical nivolumab monotherapy and did not appear to have an effect on safety. Nivolumab in Combination with Chemotherapy: Low immunogenicity incidence (8.8% [60/681]) was observed in nivo+chemo arm in CA209649. Among the 60 patients with positive nivolumab ADA, only 2 patients developed neutralizing ADA. The incidence of ADA did not appear to have effects on the efficacy or safety of nivo+chemo in this population. Overall, the immunogenicity results observed in 1L gastric/GEJC/OAC following nivo+chemo treatment are consistent with those observed in other tumor types following either nivolumab monotherapy or nivolumab in combination with chemotherapy.[270] Of the 276 nivolumab ADA-evaluable subjects in the nivo+chemo arm in CA209648, 15 (5.4%) subjects were nivolumab ADA-positive at baseline, and 12 (4.3%) subjects were nivolumab ADA-positive after start of treatment. No subjects were considered persistent positive, and 3 (1.1%) subjects were neutralizing ADA positive. The highest titer observed among nivolumab ADA-positive subjects was 32, which occurred in 2 subjects. All other titers were low, ranging from 1 to 16. Of the 252 ADA-evaluable subjects in the nivo+chemo arm of CA209901 substudy, 8 (3.2%) subjects were nivolumab ADA-positive at baseline and 6 (2.4%) subjects were nivolumab ADA-positive after the start of treatment. Of the ADA-evaluable subjects, no subjects were considered persistent positive. One (0.4%) subject was neutralizing ADA-positive.[273]
Risk factors and risk groups	Occurrence of immunogenicity is dependent on several factors related to drugs of interest and patient characteristics, such as drug characteristics, processing, doses, and route of administration, and patients' age, genetic factors, immune status, disease status, concomitant medications.
Preventability	No impact of has been observed on safety even following prolonged dose interruptions and rechallenge.
Impact on the risk-benefit balance of the product	There is no evidence of altered toxicity profile associated with ADA development and there is no apparent casual effect of neutralizing antibodies on loss of efficacy.
Public health impact	None
MedDRA terms	NA

Table 2.7.3.1-5: Important Potential Risk: Risk of GVHD with Nivolumab after Allogeneic HSCT

Risk of GVHD with Nivolumab after Allogeneic HSCT	
Potential mechanisms	The rapid re-emergence of previous acute GVHD following single dose therapy is highly suggestive of an anti-PD-1 mechanism. Likewise, the rapid onset after 1 to 2 doses, increased severity, and steroid refractory course indicate an association between anti-PD-1 use and severe and sometimes fatal GVHD in patients who previously had allogeneic HSCT.
Evidence source and strength of evidence	The scenario in which nivolumab is used as a therapy for patients who relapse following allogeneic HSCT has not been formally studied in company trials, however spontaneous case reports of GVHD in patients treated with nivolumab after prior allogeneic HSCT were identified in the corporate safety database and in the scientific literature. The rapid onset after 1 to 2 doses, increased severity, and steroid refractory course, along with the rapid re-emergence of previous acute GVHD following single dose therapy indicate an association between anti-PD-1 use and severe and sometimes fatal GVHD in patients who previously had allogeneic HSCT.
Characterization of risk *(Percent; All Treated)*	The MAH does not have company-sponsored trials that enroll patients following allogeneic transplant. In an assessment of cases from the corporate safety database (all sources) and of patients with evidence of GVHD where nivolumab was given after allogenic HSCT, there were 30 spontaneous cases where nivolumab use post allogeneic HSCT was clearly documented, of these, there were 7 cases that described recurrence of GVHD, and 3 of these noted a fatal outcome. Also notable is the rapid recurrence of GVHD after the first dose of nivolumab in 5 of the cases. These cases indicate that rapid and severe recurrence of GVHD can occur following nivolumab but the frequency of this ADR is difficult to estimate outside the context of a clinical study. A review of the scientific literature resulted in 31 articles of which 8 were relevant case reports and 2 were multi-center case series describing nivolumab use in patients following allogeneic HSCT. The 2 multicenter retrospective case series contained important descriptive analysis.[284,285] The rapid re-emergence of previous acute GVHD following single dose therapy is highly suggestive of an anti-PD-1 mechanism.[284] Likewise, the rapid onset after 1 to 2 doses, increased severity, and steroid refractory course indicate an association between anti-PD-1 use and severe and sometimes fatal GVHD in patients who previously had allogeneic HSCT.
Risk factors and risk groups	patients who have previously undergone allogeneic HSCT
Preventability	Various regimens of GVHD prophylaxis or T cell depletion regimens can diminish or prevent GVHD.
Impact on the risk-benefit balance of the product	There is no impact on the benefit-risk balance for the approved indications except for in the potential situation in which a patients previously underwent an allogeneic HSCT for an unrelated malignancy.
Public health impact	There is no public health impact.
MedDRA terms	See Annex 7

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information

Population in need of further characterization:	Evidence Source
Patients with severe hepatic and/or renal impairment	No study has been conducted.
Patients with autoimmune disease	Safety data from this patient population is too limited to draw conclusions.
Patients already receiving systemic immunosuppressants before starting nivolumab	No study has been conducted.
Long-term safety in adolescent patients ≥ 12 years of age	Long-term safety of nivolumab and nivolumab in combination with ipilimumab in adolescent patients 12 years of age and older is not known.

2.8 Summary of the Safety Concerns

In the clinical development program, BMS prospectively identified categories of AEs based on potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy. The overall safety concerns, including important identified and potential risks and missing information for nivolumab, are listed in Table 2.8-1.

Table 2.8-1: Summary of Safety Concerns

Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)
	Severe infusion reactions
Important potential risks	Embryofetal toxicity
	Immunogenicity
	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

3 PART III: PHARMACOVIGILANCE PLAN

The PV plan provides details of PV activities/studies that are intended to proactively identify and/or characterize safety concerns and will inform risk mitigation strategies for the important and potential risks.

3.1 Routine Pharmacovigilance Activities

There are no activities beyond adverse reaction reporting and signal detection.

3.2 Additional Pharmacovigilance Activities

A summary of ongoing Category 1-3 safety studies included in the nivolumab pharmacovigilance plan is provided in Table 3.2-1. A tabulated summary and protocols of planned, ongoing, and completed studies in the pharmacovigilance plan are provided in Annex 2 and Annex 3, respectively.

Table 3.2-1: Post-Authorisation Safety Studies Short Name Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)	Due Date(s)
Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the Dutch Melanoma Treatment Registry (DMTR) (CA184557)[a] Voluntary post-authorisation safety study (PASS) Category 3	Rationale: Limited clinical data due to the rarity of the paediatric melanoma population. Data on long-term outcomes are lacking. Objectives: To assess safety and long-term outcomes in children and adolescents.	Observational, national, retrospective study	Paediatric patients consisting of 2 cohorts (12 to < 18 and < 12 years of age) treated with ipilimumab, nivolumab, or nivolumab in combination with ipilimumab for advanced (unresectable or metastatic) melanoma or with nivolumab as adjuvant treatment of melanoma	1. Submission of protocol[a] 2. Interim Study Report 3. Final report of study results	Q4 2023 Q4 2026 Q4 2033

[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.

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
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 Planned	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	Q4 2023 Q4 2026 Q4 2033

[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.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Studies included as a condition to the MA and are listed in Table 4-1.

Table 4-1: List of Studies in Post-authorisation Development Plan

Study / Status	Summary of objectives	Efficacy concerns addressed	Milestone(s)	Due dates (s)
Efficacy studies which are conditions of the marketing authorisation				
PAES-CA2098Y8: In order to further elucidate the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab and ipilimumab, the MAH should conduct and submit the results of a randomised, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels. This study should be conducted according to an agreed protocol. / Ongoing	Final CSR to report the efficacy and safety of the combination of nivolumab and ipilimumab compared to nivolumab monotherapy	Efficacy of the combination relative to nivolumab monotherapy in first-line RCC	Final Study Report	28-Feb-2026
PAES for study CA209577: A Phase III study evaluating the efficacy and safety of nivolumab vs. placebo in the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer - The MAH should submit the OS data from the second interim analysis - The MAH should submit the final OS data	CSR to report second interim analysis for OS	Efficacy of nivolumab monotherapy in adj OC or GEJC	OS interim analysis 2 CSR	30-Sep-2022
	CSR to report final analysis for OS	Efficacy of nivolumab monotherapy in adj OC or GEJC	OS final analysis CSR	30-Jun-2025
PAES for study CA209274: A Phase III study evaluating the efficacy and safety of nivolumab vs. placebo in the adjuvant treatment of adult patients with high risk invasive urothelial carcinoma, in all randomised patients and all randomised patients with tumour cell PD-L1 expression ≥ 1% - The MAH should submit the OS data from the second interim analysis in all randomised patients with tumour cell PD-L1 expression ≥ 1%	CSR to report second interim analysis for OS	Efficacy of nivolumab monotherapy in adj UC (PD-L1 ≥ 1%)	OS interim analysis 2 CSR	31-Jul-2025
	CSR to report final analysis for OS	Efficacy of nivolumab monotherapy in adj UC (PD-L1 ≥ 1%)	OS final analysis CSR (timelines will be reassessed at the time of the 1st PAM submission and	31-Dec-2027

Table 4-1: List of Studies in Post-authorisation Development Plan

Study / Status	Summary of objectives	Efficacy concerns addressed	Milestone(s)	Due dates (s)
Efficacy studies which are conditions of the marketing authorisation				
- The MAH should submit the final OS data in all randomised patients with tumour cell PD-L1 expression ≥ 1%			due date will be updated accordingly)	
PAES for study CA209816: In order to further characterize the efficacy of nivolumab as neoadjuvant treatment of adults with NSCLC, the MAH should submit the OS data from the final OS analysis of the Phase 3 study CA209816.	CSR to report final analysis for OS	Efficacy of nivolumab as neoadjuvant treatment of adults with NSCLC	OS final analysis CSR	30-Jun-2025
PAES for Study CA20976K: In order to further characterise the efficacy of nivolumab as adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or stage IIC melanoma, the MAH should submit the OS data from the first interim OS analysis of the Phase III study CA20976K.	CSR to report first interim analysis for OS	Efficacy of nivolumab as adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or stage IIC melanoma	OS interim analysis CSR	31-Mar-2029
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Routine Risk Minimisation Measures

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	**Routine risk communication:** The SmPC warns of the risks of immune-related ARs in Section 4.4 (Special warnings and precautions for use) and ADRs in Section 4.8. In addition, the package leaflet also includes specific warnings and descriptions of the most important safety information in the language suitable for patients. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on monitoring and management, including treatment delay or discontinuation and intervention with corticosteroids, are provided in Sections 4.2, and 4.4, as appropriate. **Other routine risk minimisation measures beyond the Product Information:** None
Severe Infusion Reactions	**Routine risk communication:** The SmPC warns the risk of severe infusion reactions in Section 4.4 and ADR in Section 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: The SmPC provides specific guidance on management and monitoring of severe infusion reactions in Section 4.4 **Other routine risk minimisation measures beyond the Product Information:** None
Embryofetal Toxicity	**Routine risk communication:** SmPC includes embryofetal toxicity in Section 4.6 Fertility, pregnancy and lactation and Section 5.3 Preclinical safety data. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Immunogenicity	**Routine risk communication:** Related information is found in Section 4.8 of the SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Risk of GVHD with nivolumab after allogeneic HSCT	**Routine risk communication:** SmPC Section 4.4 provides warnings of the increased risk of severe GVHD and death in patients who have had prior allogeneic HSCT. Related information is found in SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Patients with severe hepatic and/or renal impairment	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration: Patients with hepatic or renal impairment. SmPC Section 5.2 Pharmacokinetic properties: Hepatic or renal impairment. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Patients with autoimmune disease	**Routine risk communication:** SmPC Section 4.4 provides cautionary information for patients with an autoimmune disease. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Patients already receiving systemic immunosuppressants before starting nivolumab	**Routine risk communication:** SmPC Sections 4.4 Special populations and 4.5 Systemic Immunosuppressants. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None Other routine risk minimisation measures beyond the Product Information: None
Long-term safety in adolescent patients ≥ 12 years of age	**Routine risk communication:** SmPC Section 4.8, Paediatric Population **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None

5.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are provided in Table 5.2-1. Details of proposed additional risk minimisation activities are provided in Annex 6.

Table 5.2-1: Additional Risk Minimisation Measures

Additional Risk Minimisation:	Objectives/Rationale
Patient Alert Card	**Objectives:** To further raise awareness of patients on signs and symptoms of important risks of immune-related ARs. **Rationale for the additional risk minimisation activity:** This tool will provide the opportunity for reinforcing key messages of early recognition and appropriate management of important identified risks of

Table 5.2-1: Additional Risk Minimisation Measures

Additional Risk Minimisation:	Objectives/Rationale
	immune-related ARs to maintain favorable benefit-risk profile of nivolumab with postmarketing use. **Target audience and planned distribution path:** Patients via HCPs. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Routine pharmacovigilance activities will provide information on any changes in the occurrence, severity, and outcome of important identified risks as it relates to the established safety profile and will be reported in future regulatory safety reports (eg, PSUR).

5.3 Summary Table of Risk Minimisation Measures

A summary of risk minimisation measures is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: Patient Alert Card	Additional pharmacovigilance activities: None
Severe Infusion Reactions	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Embryofetal toxicity	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimisation measures: SmPC Section 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimisation measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimisation measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Long-term safety in adolescent patients ≥ 12 years of age	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: Long-term follow-up of ipilimumab, nivolumab, and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR (CA184557).

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for OPDIVO (nivolumab).

This is a summary of the risk management plan (RMP) for OPDIVO. The RMP details important risks of OPDIVO, how these risks can be minimized, and how more information will be obtained about OPDIVO's risks and uncertainties (missing information).

OPDIVO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how OPDIVO should be used.

This summary of the RMP for OPDIVO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of OPDIVO's RMP.

I. The medicine and what it is used for

OPDIVO is authorized for the treatment of adults and adolescents 12 years of age and older with advanced melanoma (unresectable or metastatic), and the adjuvant treatment of Stage IIB, or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see SmPC for the full indication).

OPDIVO is also authorized for the treatment of adults with advanced melanoma, melanoma after complete resection, advanced or metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin Lymphoma (cHL), squamous cell cancer of the head and neck (SCCHN), urothelial carcinoma (UC), esophageal squamous cell carcinoma (ESCC), unresectable malignant pleural mesothelioma (MPM), mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (CRC), unresectable or advanced hepatocellular carcinoma (HCC), oesophageal cancer or gastro-oesophageal junction cancer (OC or GEJC), gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma (OAC) muscle invasive urothelial carcinoma (MIUC) (adjuvant treatment), unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC), and resectable NSCLC (neoadjuvant treatment) (see SmPC for the full indication).

It contains nivolumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of OPDIVO’s benefits can be found in OPDIVO’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo.

II. Risks associated with the medicine and activities to minimise or further characterize the risks

Important risks of OPDIVO, together with measures to minimise such risks and the proposed studies for learning more about OPDIVO’s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of OPDIVO, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of OPDIVO is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of OPDIVO are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of OPDIVO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin adverse reactions [ARs], and other immune-related adverse reactions [irARs]) Severe infusion reactions
Important potential risks	Embryofetal toxicity Immunogenicity Risk of GVHD with nivolumab after allogeneic haematopoietic stem cell transplant (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

II.B Summary of important risks

Important identified risks

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	
Evidence for linking the risk to the medicine	**Pneumonitis** Immune-related pneumonitis has been reported in subjects with a variety of tumor types and in subjects with and without lung metastases. The majority of cases reported were Grade 1-2 and subjects presented with either asymptomatic radiographic changes (eg, focal ground glass opacities, patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3-4 pulmonary toxicities were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. Severe pneumonitis can be life-threatening if not diagnosed early and managed appropriately. Death due to pulmonary toxicity, including pulmonary embolism, has been reported with nivolumab in combination with ipilimumab. **Colitis** Immune-related colitis has been reported in subjects with a variety of tumor types. The majority of subjects had mild to moderate (Grade 1-2) diarrhea or colitis. Grade 3-4 cases were more common with nivolumab in combination with ipilimumab. Diarrhea/colitis was manageable using the established management guidelines. The majority of cases resolved with drug interruption and, in severe cases, with steroids treatment. Severe or persistent diarrhea and colitis can be life-threatening if not recognized early and managed appropriately. **Hepatitis** Immune-related hepatitis has been reported in subjects with a variety of tumor types. Subjects may be asymptomatic. In clinical studies, hepatotoxicities manifesting as transaminase elevations were detectable with liver function testing and signs and symptoms monitoring. Most were Grade 1-2 transaminase elevation or hepatitis. Immune-related hepatitis can be serious or life-threatening and even fatal if not treated promptly. Subjects with immune-related hepatitis are generally managed clinically with steroid therapy with resolution of the event. Prompt review of blood tests, recognition of signs and symptoms, and implementation of the recommended management guidelines may prevent serious complications. **Nephritis and renal dysfunction** Immune-related nephritis and renal dysfunction have been reported in subjects with a variety of tumor types. Most patients present with asymptomatic increase in serum creatinine. Most were Grade 1-2 severity. Immune-related nephritis and renal dysfunction can be serious or life-threatening. Subjects with immune-related nephritis and renal dysfunction are generally managed clinically with steroid therapy with resolution of the event. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications. **Endocrinopathies** Immune-related endocrinopathies have been reported in subjects with a variety of tumor types. Immune-related endocrinopathies have been observed with nivolumab monotherapy and the most common disorder was hypothyroidism with Grade 1-2 severity in majority of the cases. Endocrinopathies were more frequent with nivolumab in combination with ipilimumab. Less frequently observed endocrinopathies included adrenal insufficiency, hypophysitis,

Important identified risks

	diabetes mellitus, and diabetic ketoacidosis. Patients are typically managed with hormone replacement and/or steroid treatment. Lifelong hormone replacement may be required. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications. **Skin ARs** Immune-related skin ARs have been reported in subjects with a variety of tumor types. Mild to moderate (Grade 1-2) immune-related skin ARs are common with nivolumab monotherapy, while severe (Grade 3-4) immune-related skin ARs are of low frequency with nivolumab monotherapy and more frequent with nivolumab in combination with ipilimumab. Rare cases of SJS and TEN, some with fatal outcome, have been observed. Early detection and timely treatment are key to recovery and to prevent severe complications. **Other irARs** Selected other irARs, which are uncommon but considered important identified risks, include uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis, encephalitis, solid organ transplant rejection, and Vogt-Koyanagi-Harada. Other irARs can be serious and life-threatening. Patients are usually clinically managed with steroids and the events generally resolved. Severe (Grade 3-4) immune-related ARs are reported in minority of patients.
Risk factors and risk groups	**Pneumonitis** Interstitial lung disease (ILD) can develop or exacerbate as a consequence of radiotherapy, chemotherapy, or pulmonary resection. Other risk factors for ILD include older age, reduced normal lung on computed tomography scan, smoking history, and concomitant or previous lung infection. **Colitis** Patients with active inflammatory bowel disease. **Hepatitis** Active autoimmune hepatitis, which may also be associated with previous chemotherapy or immunotherapy, such as IL-2 or IFN. **Nephritis and renal dysfunction** Active autoimmune diseases with potential for renal involvement. **Endocrinopathies** Active autoimmune diseases of the endocrine glands may also be associated with previous chemotherapy or immunotherapy, such as IL-2, IFN, or anti-CTLA4. **Skin ARs** Active autoimmune skin disorders. **Other irARs** Active autoimmune diseases may also be associated with previous chemotherapy or immunotherapy, such as IL-2, IFN, or anti-CTLA4.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimisation measures: Patient Alert Card

Important identified risks

Additional pharmacovigilance activities	None
Severe infusion reactions	
Evidence for linking the risk to the medicine	As with any other intravenous administered drugs, infusion-related reactions can occur with nivolumab. Premedications were generally not required prior to nivolumab administration during clinical trials with nivolumab. Severe infusion reactions were uncommon but can lead to discontinuation.
Risk factors and risk groups	None.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8 Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Important potential risks

Embryofetal toxicity	
Evidence for linking the risk to the medicine	Contraception is required for women of childbearing potential (WOCBP). Preclinical study suggested potential risk of third trimester fetal loss and premature birth with increased neonatal mortality if exposed to nivolumab during pregnancy.
Risk factors and risk groups	Exposure during pregnancy.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3
Additional pharmacovigilance activities	None
Immunogenicity	
Evidence for linking the risk to the medicine	No increased risk of hypersensitivity or infusion reaction in patients with positive anti-drug antibodies (ADA) vs negative ADA subjects. No life threatening or fatal outcomes have been reported. Low rates of immunogenicity have been observed and no impact has been observed on safety or efficacy even following prolonged dose interruptions and rechallenge.
Risk factors and risk groups	Occurrence of immunogenicity is dependent on several factors related to drugs of interest and patient characteristics, such as drug characteristics, processing, doses, and route of administration, and patients' age, genetic factors, immune status, disease status, concomitant medications.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8
Additional pharmacovigilance activities	None

Important potential risks

Risk of GVHD with nivolumab after allogeneic HSCT	
Evidence for linking the risk to the medicine	In patients treated with nivolumab post allogeneic HSCT, rapid-onset and severe GVHD, some with fatal outcome, have been reported in the post-marketing setting.
Risk factors and risk groups	Patients who have previously undergone allogeneic HSCT prior to nivolumab therapy.
Risk minimisation measures	SmPC Section 4.4 provides warnings of the increased risk of severe GVHD and death in patients who have had prior allogeneic HSCT. Related information is found in SmPC Section 4.8 Undesirable effects
Additional pharmacovigilance activities	None

Missing information

Patients with severe hepatic and/or renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2
Patients with autoimmune disease	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4
Patients already receiving systemic immunosuppressants before starting nivolumab	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.5
Long-term safety in adolescent patients ≥ 12 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8
Additional pharmacovigilance activity	Additional pharmacovigilance activity: Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the Dutch Melanoma Treatment Registry (DMTR) (CA184557). See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Planned and ongoing post-authorisation efficacy studies

Study short name and title	Summary of objectives
Efficacy studies which are conditions of the marketing authorisation	
Final clinical study report for CA2098Y8: a randomized, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels.	To further evaluate the efficacy and safety of the combination of nivolumab and ipilimumab compared to nivolumab monotherapy.
Final clinical study report for CA209577: A randomized study evaluating the efficacy and safety of nivolumab vs. placebo in the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer.	To further evaluate the efficacy and safety of OPDIVO compared to placebo in the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer.
Final clinical study report for CA209274: A Phase III study evaluating the efficacy and safety of nivolumab vs. placebo in the adjuvant treatment of adult patients with high risk invasive urothelial carcinoma, in all randomised patients and all randomised patients with tumour cell PD-L1 expression ≥ 1%.	To further evaluate the efficacy of OPDIVO compared to placebo in the adjuvant treatment of adult patients with high risk invasive urothelial carcinoma, in all randomised patients with tumour cell PD-L1 expression ≥ 1%.
Final clinical study report for CA209816: A randomized, Phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in early-stage NSCLC.	To further characterize the efficacy of nivolumab as neoadjuvant treatment of adults with NSCLC
Final clinical study report for CA20976K: A Phase 3, randomized, double-blind study to evaluate the use of adjuvant immunotherapy with nivolumab versus placebo after complete resection of Stage IIB/C melanoma in adults and adolescent subjects ≥ 12 years old.	To further characterize the efficacy of nivolumab as adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or stage IIC melanoma.
Efficacy studies which are Specific Obligations	
None	NA

II.C.2 Other studies in post-authorisation development plan

Category 3 ongoing and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
CA184557: Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR.	To assess safety and long-term outcomes in children and adolescents.

APPENDIX 2: Nonclinical Safety Summary

8 page(s) excluding cover page

APPENDIX 2: NONCLINICAL SAFETY SUMMARY

Non-Clinical Toxicology: The nonclinical toxicity of nivolumab was well characterized in a comprehensive drug-safety evaluation program which evaluated repeat-dose toxicities, including combination toxicity studies with other immunomodulatory agents (ie, lymphocyte activation gene-3 [LAG-3] and ipilimumab), immunogenicity, immunotoxicity, safety pharmacology, tissue binding characteristics, and antibody dependent cellular cytotoxicity [ADCC]/complement dependent cytotoxicity [CDC] assays. In addition, an enhanced pre- and postnatal development toxicity study in cynomolgus monkeys was conducted. Mutagenicity, carcinogenicity, and specific local tolerance studies have not been conducted in accordance with International Conference on Harmonization (ICH) guidelines for biotechnology derived products.[1] The pivotal toxicology studies were conducted in compliance with Good Laboratory Practice (GLP) regulations and according to ICH guidelines.

Nivolumab is pharmacologically active in cynomolgus monkeys, the toxicology species utilized, and was evaluated at doses up to 50 mg/kg administered as intravenous (IV) injections, up to twice weekly (up to 17× greater doses and up to 4x more frequent nivolumab administration relative to ongoing Phase 3 clinical trials where humans are administered up to 3 mg/kg IV every 2 weeks [Q2W]). Rodent toxicity studies were not performed due to lack of cross-reactivity of nivolumab in mice and rats.

Nivolumab was well tolerated at doses up to 50 mg/kg administered weekly for 1 month and at doses up to 50 mg/kg administered twice weekly for 3 months with no AEs on clinical observations and body weights or electrocardiogram (ECG), clinical, and anatomic pathology parameters.[2,3] Although nivolumab was not appreciably immunogenic in monkeys (6 of 30 in the 1-month toxicity study and 1 of 24 in the 3-month toxicity study), occasionally immunogenicity correlated with increased elimination of nivolumab. Twice weekly IV injections at doses up to 50 mg/kg (estimated 2× mean sex combined AUC [0-T] of ≤ 534,000 μg•h/mL) resulted in exposure margins ≤ 35× those observed in patients at 3 mg/kg Q2W (corrected for differences in dosing frequencies and based on steady state toxicokinetic data from the enhanced pre- and postnatal development [ePPND] study, see below).

Although nivolumab was well tolerated in toxicity studies when administered alone, combination toxicity studies conducted with ipilimumab and an anti-LAG-3 monoclonal antibody have revealed the potential for toxicity when multiple immunomodulatory agents are combined.

A 1-month toxicity study was conducted in cynomolgus monkeys to determine the potential toxicity of nivolumab in combination with ipilimumab at low (10 mg/kg / 3 mg/kg) and at high dose (50 mg/kg / 10 mg/kg) combinations of nivolumab / ipilimumab.[4] Nivolumab and ipilimumab were administered as consecutive IV injections once weekly for 4 consecutive weeks. The high dose combination was associated with mortality (1 animal on Day 23). This early death was attributed to acute gastric dilatation, although there was no evidence of colitis in this animal. The combination was also associated with GI toxicity (characterized by diarrhea, low food consumption, inflammatory changes in the large intestine, enlargement of the colonic or pelvic

lymph nodes, minimal degeneration/regeneration of the overlying mucosal epithelium, rare dilation of mucosal glands, and/or minimal neutrophilic infiltrates). GI-associated lymphoid tissue in these animals was often atypical with disorganized follicles and indistinct germinal centers. Large histiocytic cells were mixed with mature lymphocytes throughout the lymphoid follicles. Atypical lymphoid follicles were also seen in other lymph nodes (eg, inguinal, mandibular, and mesenteric). In the spleen, there were mild increases in size/number of lymphoid follicles and mild expansion of the marginal zone in the red pulp. Nivolumab in combination with ipilimumab was also associated with lymphoid hypocellularity of the cortex and medulla of the thymus and acinar cell degranulation in the pancreas. While GI toxicity/colitis has not been observed in cynomolgus monkeys administered nivolumab alone, it has been observed, albeit rarely in monkeys receiving ipilimumab, and in humans receiving nivolumab or ipilimumab as monotherapy or in combination trials with nivolumab and ipilimumab.

A 1-month combination toxicity study in cynomolgus monkeys was also conducted to determine the potential toxicity of nivolumab in combination with BMS-986016, a fully human monoclonal (IgG4) antibody that inhibits the function of LAG-3 on the surface of activated CD4 and CD8 T-cells and a subset of natural killer (NK) cells.[5] Doses for this study were selected based upon results from a prior non-GLP 1-month combination toxicity study where weekly IV administration of both nivolumab and BMS-986016, at up to 50 mg/kg, was well tolerated. In this study, BMS-986016 or nivolumab alone, and in combination (100 mg/kg BMS-986016 and 50 mg/kg nivolumab) were administered to groups of 5 monkeys per sex for a total of 5 weekly doses.

While no nivolumab-related AEs on any parameters were noted, administration of the combination resulted in the moribundity of 1 monkey on Day 29. Clinical signs of toxicity included elevated body temperature, shivers, red or clear nasal discharge, fecal changes (unformed, scant or absent feces), decreased feeding behavior, mild dehydration, sneezing, decreased activity, and hunched posture. This monkey was euthanatized for humane reasons on Day 29. Histopathological findings in this monkey included: lymphoplasmacytic inflammation of the choroid plexus (slight); lymphohistiocytic inflammation of the vasculature of the brain parenchyma (moderate), meninges (mild), spinal cord (cervical and lumbar; minimal); and mixed cell inflammation of the epididymis (moderate), seminal vesicles (slight) and testes (minimal). Clinical pathology changes at necropsy indicated decreases in red blood cell count, hemoglobin concentration and hematocrit whose cause was unclear, and a notable increase in fibrinogen correlating with the inflammation observed in the central nervous system and male reproductive tract. Moribundity of this animal was attributed to central nervous system (CNS) vasculitis and considered related to administration of BMS-986016 and nivolumab.

BMS-986016 and/or nivolumab-related anatomical pathology findings in other animals were limited to minimal to slight lymphoplasmacytic inflammation of the choroid plexus in the brain at 50 mg/kg nivolumab alone and in the combination group, and minimal lymphohistiocytic inflammation of the vasculature of the brain parenchyma in 1 male monkey in the combination group. There was no evidence of reversibility after a 4-week treatment free recovery period, which was likely due to the long half-lives of BMS-986016 and nivolumab that resulted in continued exposure to the test articles throughout the recovery period.

In monkeys treated with 50 mg/kg nivolumab alone, lymphoplasmacytic inflammation was restricted to the choroid plexus with lower severity and incidence as compared to the combination therapy group at end-of-dose and recovery periods. Histologically, there were no other pathological sequelae (eg, vasculitis in the brain parenchyma or degenerative changes in the choroid epithelium). Presence of lymphoplasmacytic cells within the choroid plexus in cynomologus monkeys is a well recognized and documented spontaneous finding with no adverse consequences.[6,7] Therefore, in the monkeys treated with 50 mg/kg nivolumab alone, lower severity/incidence of the lymphoplasmacytic inflammation, lack of vasculitis and lack of tissue destruction with absence of clinical signs during the course of treatment suggest an exaggerated immunostimulatory pharmacologic effect of nivolumab without any AEs on the tissue/organ involved.

All test article-related histopathological findings in this study are likely the result of the immunostimulatory mechanism of action of the nivolumab alone and/or in combination with BMS-986016,[8,9,10] since no treatment-related histopathological changes were noted with BMS-986016 alone. In the case of the CNS vascular lesions and epididymitis, the mechanism may involve a loss of tolerance to self antigens based on the synergistic role of PD-1 and LAG-3 in maintaining self-tolerance.[10] These findings were observed at nivolumab exposures that are approximately 13× greater than those observed in humans at 3 mg/kg, Q2W.

Immunotoxicity: As a selective immunomodulator, nivolumab is expected to have effects on the immune system. The immunologic effects of nivolumab were studied in the pivotal repeat dose toxicity studies as well as the combination toxicity studies with ipilimumab and BMS-986016. In addition to routine hematologic assessments, the following immunologic and pharmacologic assessments were conducted in one or more of these studies: immunogenicity, peripheral blood lymphocyte phenotyping, T-cell-dependent antibody responses (TDAR) to keyhole limpet hemocyanin (KLH) and Hepatitis B Surface Antigen (HBsAg), splenic T-lymphocyte subset phenotyping, and ex-vivo recall responses to KLH and HBsAg.

In the 3-month toxicity study,[3] immunophenotyping analysis at the end of the study identified pharmacologically mediated changes in splenic T-cell populations consisting of increases in splenic CD3+ T cells and in circulating and splenic T-cell subpopulations. Specifically, there were increases in circulating CD4+ and CD8+ effector memory T cells at ≥ 10 mg/kg, and increases in circulating CD8+ central memory T cells and CD4+ and CD25+ regulatory T cells, and in splenic CD8+ central memory T cells at 50 mg/kg. These changes were not considered adverse and are consistent with the expected immunomodulatory action of nivolumab.

In a combination toxicity study with nivolumab (50 mg/kg) and BMS-986016 (10 or 50 mg/kg), similar T-cell changes were observed and included increases in CD4+ T lymphocytes expressing CD25 in the peripheral blood and spleen, increases in splenic CD4+ central memory T lymphocytes with a corresponding decrease in CD4+ naive T lymphocytes, and increases in splenic CD3+ lymphocytes expressing HLA-DR only at the high dose combination. Additional changes consisted of increased splenic size, weight, and/or lymphoid hyperplasia, and lymphoid hyperplasia in the colonic lymph node and lungs in males, only at the high dose combination. In a

second combination study, similar T-cell changes were observed. In addition, analysis of ex-vivo recall responses to KLH was conducted in a second combination toxicity study with nivolumab (50 mg/kg) and BMS-986016 (100 mg/kg). Test article-related changes included reversible increases in mean percent of $CD69^+$, TNF-α^+, and $CD69^+$TNF-α^+ $CD4^+CD8^-$ T-cells, and IFN-γ^+, $CD69^+$IFN-γ^+, and $CD69^+$TNF-α^+IFN-γ^+ $CD4^+CD8^-$ T-cells. No effects on TDAR to KLH or HBsAg were observed after either nivolumab alone or in combination with BMS-986016. These changes in the peripheral blood, lymphoid tissues, and in ex-vivo recall responses were again considered pharmacologically mediated, nonadverse, and consistent with inhibition of PD-1 and/or LAG-3 signaling.

Genotoxicity: As detailed in ICH guideline S6 (Guideline for Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals),[11] the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals since it is not expected that these substances would interact directly with DNA or other chromosomal material. Thus, mutagenicity and genotoxicity studies were not conducted for nivolumab.

Carcinogenicity: As detailed in ICH guidelines S1A (Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals) [12] and S9 (Guideline on Nonclinical Evaluation for Anticancer Pharmaceuticals), [13] carcinogenicity studies are generally not required for oncolytic agents intended for treatment of advanced systemic disease. In addition, the lack of cross-reactivity of nivolumab was confirmed in rodents and the difficulties of achieving and maintaining sufficient exposures of nivolumab, a fully human antibody, in rodents for extended durations due to anti-drug antibody formation and possible resulting immune-complex-mediated toxicity would preclude an adequate evaluation of target-organ toxicity. Thus, carcinogenicity studies for nivolumab were not conducted.

Reproductive and Developmental Toxicity: An enhanced pre- and postnatal development study in cynomolgus monkeys with a 6-month postnatal evaluation was conducted.[14] Nivolumab (10 or 50 mg/kg) or saline was administered twice weekly to pregnant cynomolgus monkeys (16 per group) by slow IV injection. Dosing was initiated at the onset of organogenesis (gestation day [GD] 20, 21, or 22) and continued to parturition or confirmation of pregnancy loss. During gestation, the adult females were evaluated for viability, clinical signs, food consumption, body weights, pregnancy status, clinical pathology, and immunology parameters (including immunogenicity, peripheral blood lymphocyte phenotyping, serum immunoglobulin, and serum anti-nuclear antibodies). The females were allowed to deliver vaginally and to rear their infants until 6 months of age. Criteria for infant evaluations include viability, clinical signs, growth indices, serum concentrations of nivolumab, external and skeletal morphology, clinical pathology, immunology parameters (including T-cell dependent antibody response), organ weights, and gross and microscopic pathology.

Nivolumab was well tolerated at both doses and there were no nivolumab-related effects on viability, clinical signs, food consumption, body weights, immunological endpoints, or clinical/anatomic pathology parameters in these females throughout the study.

However, in the offspring, maternal nivolumab administration at both doses was associated with fetal/neonatal mortality characterized by: 1) dose-dependent increases in third trimester fetal losses (12.5% and 33.3% at 10 and 50 mg/kg, respectively, relative to 7.1% in controls), which occurred predominately after GD 120; and 2) increased neonatal mortality at 10 mg/kg, which was noted in 3 infants with extreme prematurity during the first 2 postnatal weeks. The cause(s) of these fetal losses and infant prematurity could not be determined. There were no premonitory signs of pregnancy complications or developmental abnormalities observed in affected dams or their offspring, and there were no gross or microscopic lesions clearly attributable to nivolumab.

Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance is consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice.[15] In these models, maternal regulatory T cells are thought to be the principal mediators of fetal tolerance via suppression of autoimmune reactions directed towards the fetus. PD-1 signaling can support placental expansion of regulatory T cells and/or suppress effector T-cell function. Abrogation of PD-1 signaling (eg, PD-L1 knockout, nivolumab administration, etc) may eliminate the suppressive activity of regulatory T cells in the placenta, resulting in increased inflammatory reactions towards the fetus and associated decreased fetal survival rates. Considering that regulatory T cells are also thought to play a role in pregnancy maintenance in humans,[16] the effects observed in this ePPND study may also represent a risk in humans. The potential risk to pregnant women will be addressed with appropriate wording in the product label.

In a single fetus from the 10-mg/kg dam that aborted on GD 124, moderate interstitial inflammation and follicular-cell hypertrophy/hyperplasia were noted in the thyroid gland. Despite its single occurrence in this study and lack of dose dependency (not observed in fetuses or infants at 50 mg/kg), the relationship of these thyroid changes to treatment cannot be completely excluded because they were consistent with the pharmacology of nivolumab (ie, immune stimulation).

Three abortions were noted in dams at 50 mg/kg during the first trimester. The relationship of these early pregnancy losses to nivolumab is considered equivocal because first trimester abortions were also observed in 2 control females and the incidence at 50 mg/kg (3/16, 18.8%) was minimally increased relative to the upper range of the testing facility historical control data (16.7%). The remaining offspring of nivolumab-treated females survived to scheduled termination and there were no nivolumab-related effects on any of the parameters evaluated throughout the 6-month postnatal period.

In conclusion, nivolumab was a selective developmental toxicant when administered 2QW to pregnant monkeys from the period of organogenesis to parturition at 10 or 50 mg/kg 2QW. Maternal nivolumab administration at ≥ 10 mg/kg was associated with fetal/neonatal mortality, characterized by dose-dependent increases in third trimester fetal losses and mortality in 3 infants with extreme prematurity during the first 2 postnatal weeks. However, there were no nivolumab-related changes in surviving infants at either dose tested throughout the 6-month postnatal period. Based on these results, the no-observed-adverse-effect-level (NOAEL) for maternal toxicity was 50 mg/kg (AUC[0-168h] 541,000 μg•h/mL). A NOAEL for developmental

toxicity was not identified. The lowest-observed-adverse-effect level (LOAEL) for developmental toxicity was 10 mg/kg (AUC[0-168h] 117,000 µg•h/mL), which is approximately ×8the exposures in humans at the recommended dose of 3 mg/kg Q2W. While these nonclinical findings suggest a potential pregnancy risk to humans, they do not alter the benefit risk profile of nivolumab for the treatment of cancer in the setting of conservative contraception guidance. In addition, AEs on pregnancy outcomes and infant losses are not entirely unexpected based on previous experience with the anti-CTLA4 monoclonal antibody ipilimumab, where similar increases in third trimester fetal deaths and infant losses were observed in cynomolgus monkeys.[17]

Human IgG4 crosses the placental barrier, particularly during the third trimester. Therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. Although it is not known if nivolumab is excreted in human milk, immunoglobulins are known to be excreted in human milk and the potential for infant exposure to nivolumab via breast milk exists.

Local Tolerance: In the IV repeat dose toxicity studies of nivolumab in monkeys, irritation was not observed at the injection sites at concentrations up to 50 mg/kg (17 ×the clinical dose of 3 mg/kg).[2,3,18]

Safety Pharmacology: No drug-related findings were observed in standard clinical evaluations of cardiovascular, respiratory, and neurologic function conducted in cynomolgus monkeys as part of the repeat-dose toxicity studies for up to 3 months with nivolumab.[2,3] In addition, the potential cardiovascular effect of nivolumab was also evaluated in a single-dose IV cardiovascular safety study in conscious cynomolgus monkeys.[19] The single IV bolus administration of nivolumab at doses of 10 mg/kg or 50 mg/kg was well tolerated. There were no effects on clinical signs, body weights, body temperatures, mean arterial blood pressures, electrocardiograms, or cardiovascular parameters during the study.

APPENDIX 3: CLINICAL TRIAL EXPOSURE

1 NIVOLUMAB MONOTHERAPY

Clinical trial exposure analyses include cumulative dose and clinical exposure by duration, age, gender, and racial origin. For nivolumab monotherapy, individual clinical trial exposure analyses are presented in the following tables:

- Table 1-1 through Table 1-4 for CA209037 (melanoma)
- Table 1-5 through Table 1-8 for CA209066 (melanoma)
- Table 1- 9 through Table 1-12 for CA209017 (NSCLC)
- Table 1-13 through Table 1-16 for CA209057 (NSCLC)
- Table 1-17 through Table 1-20 for CA209063 (NSCLC)
- Table 1-21 through Table 1-25 for MDX1106-03 (multiple tumors)
- Table 1-26 through Table 1-29 for CA209025 (RCC)
- Table 1-30 through Table 1-33 for CA209010 (RCC)
- Table 1-34 through Table 1-37 for CA209067 (melanoma)
- Table 1-38 through Table 1-41 for CA209205 (cHL)
- Table 1-42 through Table 1-45 for CA209039 (cHL)
- Table 1-46 through Table 1-49 for CA209141 (SCCHN)
- Table 1-50 through Table 1-53 for CA209275 (UC)
- Table 1-54 through Table 1-57 for CA209032 (UC)
- Table 1-58 through Table 1-61 for CA209238 (adjuvant melanoma)
- Table 1-62 through Table 1-65 for Ono-4538-24 (CA209473 ESCC)
- Table 1-66 through Table 1-69 for CA209577 (adjuvant OC/GEJC)
- Table 1-70 through 1-73 for CA209274 (MIUC)
- Table 1-74 through 1-76 for CA20976K (Stage IIB/C adjuvant melanoma)
- Table 1-77 through Table 1-84 for CA2098FC (melanoma)

CA209037 (Melanoma)

Table 1-1: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209037)

Duration of Exposure	Nivolumab 3mg/kg N = 268 Persons (%)	Person Time of Exposure (1) (months)
0 - < 1 MONTH	11 (4.1)	
0 - < 2 MONTHS	37 (13.8)	
0 - < 3 MONTHS	88 (32.8)	
0 - < 4 MONTHS	108 (40.3)	
0 - < 5 MONTHS	123 (45.9)	
0 - < 6 MONTHS	137 (51.1)	
0 - <= 20.7 MONTHS (A)	268 (100.0)	1943.03

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
(A) Max clinical exposure.
Program Source: /projects/bms214677/stats/iss/prog/tables/rt-ex-pt-durtrt.sas 19JAN2015:09:17:02

Table 1-2: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209037)

	Nivolumab 3 mg/kg N = 268
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	14.3 (11.58)
MEDIAN	10.0
MIN - MAX	1 - 45
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	3447.3 (2979.17)
MEDIAN	2277.4
MIN - MAX	115 - 14406
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	43.01 (34.691)
MEDIAN	29.98
MIN - MAX	3.0 - 135.0

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms214677/stats/iss/prog/tables/rt-ex-cumdos.sas 19JAN2015:09:16:01

Table 1-3: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209037)

	Persons (%)			Person Time of Exposure (months) (1)		
Age Category	Male N = 175	Female N = 93	Total N = 268	Male N = 175	Female N = 93	Total N = 268
< 65	105 (60.0)	70 (75.3)	175 (65.3)	707.81	492.02	1199.84
>= 65 AND < 75	40 (22.9)	14 (15.1)	54 (20.1)	341.36	90.38	431.74
>= 75 AND < 85	28 (16.0)	7 (7.5)	35 (13.1)	201.82	52.11	253.93
>= 85	2 (1.1)	2 (2.2)	4 (1.5)	34.10	23.43	57.53
TOTAL	175 (100.0)	93 (100.0)	268 (100.0)	1285.09	657.94	1943.03

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
Program Source: /projects/bms214677/stats/iss/prog/tables/rt-ex-pt-age.sas 19JAN2015:09:16:25

Table 1-4: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209037)

	Persons (%)			Person Time of Exposure (months) (1)		
Race	Male N = 175	Female N = 93	Total N = 268	Male N = 175	Female N = 93	Total N = 268
WHITE	172 (98.3)	93 (100.0)	265 (98.9)	1264.16	657.94	1922.10
BLACK OR AFRICAN AMERICAN	1 (0.6)	0	1 (0.4)	2.40	0	2.40
ASIAN	2 (1.1)	0	2 (0.7)	18.53	0	18.53
OTHER	0	0	0	0	0	0
TOTAL	175 (100.0)	93 (100.0)	268 (100.0)	1285.09	657.94	1943.03

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
Program Source: /projects/bms214677/stats/iss/prog/tables/rt-ex-pt-race.sas 19JAN2015:09:17:21

CA209066 (Melanoma)

Table 1-5: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209066)

Duration of Exposure	Nivolumab 3mg/kg N = 206 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	4 (1.9)	
0 - < 2 MONTHS	26 (12.6)	
0 - < 3 MONTHS	50 (24.3)	
0 - < 4 MONTHS	70 (34.0)	
0 - < 5 MONTHS	89 (43.2)	
0 - < 6 MONTHS	103 (50.0)	
0 - <= 16.6 MONTHS (A)	206 (100.0)	1449.10

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
(A) Max clinical exposure.
Program Source: /projects/bms214677/stats/iss/prog/tables/rt-ex-pt-durtrt.sas 19JAN2015:09:17:08

Table 1-6: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209066)

	Nivolumab 3 mg/kg N = 206
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	14.2 (9.65)
MEDIAN	12.0
MIN - MAX	1 - 36
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	3381.9 (2522.87)
MEDIAN	2909.7
MIN - MAX	200 - 12066
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	42.71 (28.965)
MEDIAN	36.00
MIN - MAX	3.0 - 108.0

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms214677/stats/iss/prog/tables/rt-ex-cumdos.sas 19JAN2015:09:16:05

Table 1-7: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209066)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 117	Female N = 89	Total N = 206	Male N = 117	Female N = 89	Total N = 206
< 65	58 (49.6)	46 (51.7)	104 (50.5)	421.19	309.45	730.64
>= 65 AND < 75	44 (37.6)	31 (34.8)	75 (36.4)	333.50	205.77	539.27
>= 75 AND < 85	14 (12.0)	12 (13.5)	26 (12.6)	101.45	71.82	173.27
>= 85	1 (0.9)	0	1 (0.5)	5.91	0	5.91
TOTAL	117 (100.0)	89 (100.0)	206 (100.0)	862.06	587.04	1449.10

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
Program Source: /projects/bms214677/stats/iss/prog/tables/rt-ex-pt-age.sas 19JAN2015:09:16:39

Table 1-8: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209066)

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 117	Female N = 89	Total N = 206	Male N = 117	Female N = 89	Total N = 206
WHITE	116 (99.1)	89 (100.0)	205 (99.5)	853.32	587.04	1440.36
BLACK OR AFRICAN AMERICAN	0	0	0	0	0	0
ASIAN	0	0	0	0	0	0
OTHER	1 (0.9)	0	1 (0.5)	8.74	0	8.74
TOTAL	117 (100.0)	89 (100.0)	206 (100.0)	862.06	587.04	1449.10

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
Program Source: /projects/bms214677/stats/iss/prog/tables/rt-ex-pt-race.sas 19JAN2015:09:17:27

CA209017 (NSCLC)

Table 1-9: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209017)

Duration of Exposure	Nivolumab 3mg/kg N = 131 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	4 (3.1)	
0 - < 2 MONTHS	26 (19.8)	
0 - < 3 MONTHS	55 (42.0)	
0 - < 4 MONTHS	61 (46.6)	
0 - < 5 MONTHS	72 (55.0)	
0 - < 6 MONTHS	80 (61.1)	
0 - <= 22.1 MONTHS (A)	131 (100.0)	884.99

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
(A) Max clinical exposure.
Program Source: /projects/bms214677/stats/iss/prog/tables/iss003017063lungRMP/rt-ex-pt-durtrt.sas 12FEB2015:10:28:42

Table 1-10: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209017)

	Nivolumab 3 mg/kg N = 131
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	13.2 (12.66)
MEDIAN	8.0
MIN - MAX	1 - 48
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	3105.7 (3272.55)
MEDIAN	1620.0
MIN - MAX	153 - 15806
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	39.53 (37.768)
MEDIAN	24.00
MIN - MAX	2.9 - 143.3

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms214677/stats/iss/prog/tables/iss003017063lungRMP/rt-ex-cumdos.sas 12FEB2015:10:27:28

Table 1-11: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209017)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 107	Female N = 24	Total N = 131	Male N = 107	Female N = 24	Total N = 131
< 65	60 (56.1)	16 (66.7)	76 (58.0)	432.85	103.72	536.57
>= 65 AND < 75	38 (35.5)	6 (25.0)	44 (33.6)	270.92	33.54	304.46
>= 75 AND < 85	8 (7.5)	2 (8.3)	10 (7.6)	31.57	6.70	38.28
>= 85	1 (0.9)	0	1 (0.8)	5.68	0	5.68
TOTAL	107 (100.0)	24 (100.0)	131 (100.0)	741.03	143.97	884.99

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
Program Source: /projects/bms214677/stats/iss/prog/tables/iss003017063lungRMP/rt-ex-pt-age.sas 12FEB2015:10:28:06

Table 1-12: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209017)

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 107	Female N = 24	Total N = 131	Male N = 107	Female N = 24	Total N = 131
WHITE	97 (90.7)	21 (87.5)	118 (90.1)	646.80	119.82	766.62
BLACK OR AFRICAN AMERICAN	4 (3.7)	2 (8.3)	6 (4.6)	48.33	2.04	50.37
ASIAN	3 (2.8)	1 (4.2)	4 (3.1)	13.34	22.11	35.45
OTHER	1 (0.9)	0	1 (0.8)	5.29	0	5.29
NOT REPORTED	2 (1.9)	0	2 (1.5)	27.27	0	27.27
TOTAL	107 (100.0)	24 (100.0)	131 (100.0)	741.03	143.97	884.99

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
Program Source: /projects/bms214677/stats/iss/prog/tables/iss003017063lungRMP/rt-ex-pt-race.sas 12FEB2015:10:28:57

CA209057 (NSCLC)

Table 1-13: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209057)

Duration of Exposure	Nivolumab N = 287 Persons (%)	Nivolumab N = 287 Person Time of Exposure (1) (Month)
0 - < 1 MONTH	10 (3.5)	
0 - < 2 MONTHS	70 (24.4)	
0 - < 3 MONTHS	129 (44.9)	
0 - < 4 MONTHS	156 (54.4)	
0 - < 5 MONTHS	174 (60.6)	
0 - < 6 MONTHS	191 (66.6)	
0 - <= 25.0 MONTHS (A)	287 (100.0)	1880.02

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-durtrt.sas 02JUN2015:06:29:37

Table 1-14: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209057)

	Nivolumab N = 287
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	12.6 (13.49)
MEDIAN	6.0
MIN - MAX	1 - 52
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	2746.3 (3161.75)
MEDIAN	1385.0
MIN - MAX	146 - 16503
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	37.76 (40.433)
MEDIAN	18.02
MIN - MAX	3.0 - 156.0

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-cumdos.sas 02JUN2015:06:30:18

Table 1-15: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209057)

Treatment group: NIVOLUMAB

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 148	Female N = 139	Total N = 287	Male N = 148	Female N = 139	Total N = 287
>= 18 AND < 65	88 (59.5)	94 (67.6)	182 (63.4)	611.84	584.31	1196.16
>= 65 AND < 75	48 (32.4)	37 (26.6)	85 (29.6)	316.78	243.48	560.26
>= 75	12 (8.1)	8 (5.8)	20 (7.0)	95.38	28.22	123.60
TOTAL	148 (100.0)	139 (100.0)	287 (100.0)	1024.00	856.02	1880.02

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-age.sas 02JUN2015:06:30:24

Table 1-16: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209057)

Treatment group: NIVOLUMAB

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 148	Female N = 139	Total N = 287	Male N = 148	Female N = 139	Total N = 287
WHITE	138 (93.2)	124 (89.2)	262 (91.3)	956.19	766.49	1722.68
BLACK OR AFRICAN AMERICAN	1 (0.7)	6 (4.3)	7 (2.4)	1.02	34.66	35.68
ASIAN	5 (3.4)	4 (2.9)	9 (3.1)	41.66	32.79	74.45
OTHER	4 (2.7)	5 (3.6)	9 (3.1)	25.13	22.08	47.21
TOTAL	148 (100.0)	139 (100.0)	287 (100.0)	1024.00	856.02	1880.02

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-age.sas 02JUN2015:06:31:58

CA209063 (NSCLC)

Table 1-17: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209063)

Duration of Exposure	Nivolumab 3mg/kg N = 117 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	4 (3.4)	
0 - < 2 MONTHS	33 (28.2)	
0 - < 3 MONTHS	55 (47.0)	
0 - < 4 MONTHS	75 (64.1)	
0 - < 5 MONTHS	78 (66.7)	
0 - < 6 MONTHS	82 (70.1)	
0 - <= 16.1 MONTHS (A)	117 (100.0)	569.10

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
(A) Max clinical exposure.
Program Source: /projects/bms214677/stats/iss/prog/tables/iss003017063lungRMP/rt-ex-pt-durtrt.sas 12FEB2015:10:28:37

Table 1-18: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209063)

	Nivolumab 3 mg/kg N = 117
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	9.3 (8.97)
MEDIAN	6.0
MIN - MAX	1 - 34
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	2197.5 (2243.04)
MEDIAN	1222.0
MIN - MAX	102 - 8768
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	27.95 (26.811)
MEDIAN	18.00
MIN - MAX	1.4 - 102.1

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms214677/stats/iss/prog/tables/iss003017063lungRMP/rt-ex-cumdos.sas 12FEB2015:10:27:21

Table 1-19: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209063)

Age Category	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 85	Female N = 32	Total N = 117	Male N = 85	Female N = 32	Total N = 117
< 65	42 (49.4)	16 (50.0)	58 (49.6)	192.92	64.33	257.25
>= 65 AND < 75	32 (37.6)	11 (34.4)	43 (36.8)	182.08	37.82	219.89
>= 75 AND < 85	10 (11.8)	5 (15.6)	15 (12.8)	58.05	20.07	78.13
>= 85	1 (1.2)	0	1 (0.9)	13.83	0	13.83
TOTAL	85 (100.0)	32 (100.0)	117 (100.0)	446.88	122.22	569.10

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
Program Source: /projects/bms214677/stats/iss/prog/tables/iss003017063lungRMP/rt-ex-pt-age.sas 12FEB2015:10:27:49

Table 1-20: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209063)

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 85	Female N = 32	Total N = 117	Male N = 85	Female N = 32	Total N = 117
WHITE	70 (82.4)	29 (90.6)	99 (84.6)	366.85	109.40	476.25
BLACK OR AFRICAN AMERICAN	8 (9.4)	3 (9.4)	11 (9.4)	46.95	12.81	59.76
ASIAN	2 (2.4)	0	2 (1.7)	10.02	0	10.02
OTHER	5 (5.9)	0	5 (4.3)	23.06	0	23.06
TOTAL	85 (100.0)	32 (100.0)	117 (100.0)	446.88	122.22	569.10

(1) Sum of subject's exposure time. Subject's exposure is defined as the minimum between subject's follow up and duration of treatment + 30 days.
Program Source: /projects/bms214677/stats/iss/prog/tables/iss003017063lungRMP/rt-ex-pt-race.sas 12FEB2015:10:28:53

MDX1106-03 (Multiple Tumor Type)

Table 1-21: Clinical Exposure in Person Time; Nivolumab Treated Subjects (MDX1106-03)

Duration of Exposure	Nivolumab N = 107 Persons (%)	Person Time of Exposure (1) (months)
0 - < 1 MONTH	2 (1.9)	
0 - < 2 MONTHS	12 (11.2)	
0 - < 3 MONTHS	24 (22.4)	
0 - < 4 MONTHS	32 (29.9)	
0 - < 5 MONTHS	49 (45.8)	
0 - < 6 MONTHS	54 (50.5)	
0 - <= 28.6 MONTHS (A)	107 (100.0)	1004.25

(1) Sum of subject's exposure time. Subject's exposure time is defined as time between first dose date and minimum between last known alive date and last dose date + 30 days.
(A) Max clinical exposure.
Program Source: /projects/bms211264/stats/rmp/prog/tables/rt-ex-pt-durtrt.sas 11JUL2014:03:50:03

Table 1-22: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (MDX1106-03)

	Nivolumab			
	< 3 mg/kg N = 70	3 mg/kg N = 17	10 mg/kg N = 20	Total N = 107
NUMBER OF DOSES RECEIVED / SUBJECT				
MEAN (SD)	19.4 (16.05)	20.0 (15.75)	13.0 (14.31)	18.3 (15.77)
MEDIAN	13.5	11.0	8.0	11.0
MIN - MAX	1 - 48	1 - 48	1 - 48	1 - 48
CUMULATIVE DOSE (MG) / SUBJECT				
MEAN (SD)	1257.3 (1365.16)	4901.4 (4859.81)	10761.5 (12013.27)	3612.7 (6649.74)
MEDIAN	737.5	3520.0	6076.0	1450.0
MIN - MAX	28 - 5136	251 - 18295	653 - 39792	28 - 39792
CUMULATIVE DOSE (MG/KG) / SUBJECT				
MEAN (SD)	14.72 (15.637)	59.09 (45.569)	129.44 (142.048)	43.21 (77.903)
MEDIAN	8.74	33.70	78.68	15.55
MIN - MAX	0.4 - 48.4	3.0 - 137.7	10.0 - 468.1	0.4 - 468.1

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms211264/stats/rmp/prog/tables/rt-ex-cumdos.sas 07JUL2014:08:19:47

Table 1-23: Clinical Exposure in Person Time by Dose Level; Nivolumab Treated Subjects (MDX1106-03)

	Nivolumab N = 107	
Dose Level	Persons (%)	Person Time of Exposure (1) (months)
< 3 MG/KG	70 (65.4)	692.86
3 MG/KG	17 (15.9)	171.01
10 MG/KG	20 (18.7)	140.39
TOTAL	107 (100.0)	1004.25

(1) Sum of subject's exposure time. Subject's exposure time is defined as time between first dose date and minimum between last known alive date and last dose date + 30 days.
Program Source: /projects/bms211264/stats/rmp/prog/tables/rt-ex-pt-doselev.sas 07JUL2014:08:19:57

Table 1-24: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (MDX1106-03)

	Persons (%)			Person Time of Exposure (months) (1)		
Age Category	Male N = 72	Female N = 35	Total N = 107	Male N = 72	Female N = 35	Total N = 107
18 TO < 65	43 (59.7)	19 (54.3)	62 (57.9)	370.76	158.46	529.22
65 TO < 75	20 (27.8)	6 (17.1)	26 (24.3)	234.35	62.52	296.87
>= 75	9 (12.5)	10 (28.6)	19 (17.8)	74.81	103.36	178.17
TOTAL	72 (100.0)	35 (100.0)	107 (100.0)	679.92	324.34	1004.25

(1) Sum of subject's exposure time. Subject's exposure time is defined as time between first dose date and minimum between last known alive date and last dose date + 30 days.
Program Source: /projects/bms211264/stats/rmp/prog/tables/rt-ex-pt-age.sas 07JUL2014:08:19:54

Table 1-25: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (MDX1106-03)

Race	Persons (%) Male N = 72	Female N = 35	Total N = 107	Person Time of Exposure (months) (1) Male N = 72	Female N = 35	Total N = 107
WHITE	67 (93.1)	35 (100.0)	102 (95.3)	637.17	324.34	961.51
BLACK OR AFRICAN AMERICAN	3 (4.2)	0	3 (2.8)	18.23	0.00	18.23
ASIAN	0	0	0	0.00	0.00	0.00
OTHER	2 (2.8)	0	2 (1.9)	24.51	0.00	24.51
TOTAL	72 (100.0)	35 (100.0)	107 (100.0)	679.92	324.34	1004.25

(1) Sum of subject's exposure time. Subject's exposure time is defined as time between first dose date and minimum between last known alive date and last dose date + 30 days.
Program Source: /projects/bms211264/stats/rmp/prog/tables/rt-ex-pt-race.sas 07JUL2014:08:20:07

Study CA209025 (RCC)

Table 1-26: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209025)

Duration of Exposure	Nivolumab N = 406 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	6 (1.5)	
0 - < 2 MONTHS	42 (10.3)	
0 - < 3 MONTHS	87 (21.4)	
0 - < 4 MONTHS	112 (27.6)	
0 - < 5 MONTHS	158 (38.9)	
0 - < 6 MONTHS	180 (44.3)	
0 - <= 30.1 MONTHS (A)	406 (100.0)	3939.15

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure.
Subjects were to be treated with nivolumab 3 mg/kg every 2 weeks.
Program Source: /projects/bms217252/stats/mRCC_EURMP/prog/tables/rt-ex-pt-durtrt-025.sas 27AUG2015:03:18:06

Table 1-27: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209025)

	Nivolumab N = 406
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	19.2 (16.25)
MEDIAN	12.0
MIN - MAX	1 - 65
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	4938.2 (4565.26)
MEDIAN	3071.0
MIN - MAX	36 - 22252
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	57.72 (49.025)
MEDIAN	36.03
MIN - MAX	0.5 - 195.1

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms217252/stats/mRCC_EURMP/prog/tables/rt-ex-cumdos-025.sas 27AUG2015:03:19:13

Table 1-28: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209025)

Treatment Group: NIVOLUMAB

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 312	Female N = 94	Total N = 406	Male N = 312	Female N = 94	Total N = 406
>= 18 AND < 65	198 (63.5)	56 (59.6)	254 (62.6)	1977.82	500.99	2478.82
>= 65 AND < 75	90 (28.8)	28 (29.8)	118 (29.1)	939.79	241.35	1181.14
>= 75	24 (7.7)	10 (10.6)	34 (8.4)	200.71	78.49	279.20
TOTAL	312 (100.0)	94 (100.0)	406 (100.0)	3118.32	820.83	3939.15

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms217252/stats/mRCC_EURMP/prog/tables/rt-ex-pt-age.sas 27AUG2015:03:20:10

Table 1-29: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209025)

Treatment Group: NIVOLUMAB

Race	Persons (%) Male N = 312	Persons (%) Female N = 94	Persons (%) Total N = 406	Person Time of Exposure (Months) (1) Male N = 312	Person Time of Exposure (Months) (1) Female N = 94	Person Time of Exposure (Months) (1) Total N = 406
WHITE	271 (86.9)	79 (84.0)	350 (86.2)	2629.78	706.92	3336.71
BLACK OR AFRICAN AMERICAN	1 (0.3)	0	1 (0.2)	4.24	0	4.24
ASIAN	30 (9.6)	12 (12.8)	42 (10.3)	393.56	104.05	497.61
OTHER	10 (3.2)	3 (3.2)	13 (3.2)	90.74	9.86	100.60
TOTAL	312 (100.0)	94 (100.0)	406 (100.0)	3118.32	820.83	3939.15

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms217252/stats/mRCC_EURMP/prog/tables/rt-ex-pt-age.sas 27AUG2015:03:20:55

Study CA209010 (RCC)

Table 1-30: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209010)

Duration of Exposure	Nivolumab N = 167 Persons (%)	Nivolumab N = 167 Person Time of Exposure (1) (Months)
0 - < 1 MONTH	1 (0.6)	
0 - < 2 MONTHS	42 (25.1)	
0 - < 3 MONTHS	50 (29.9)	
0 - < 4 MONTHS	66 (39.5)	
0 - < 5 MONTHS	84 (50.3)	
0 - < 6 MONTHS	93 (55.7)	
0 - <= 41.7 MONTHS (A)	167 (100.0)	1646.03

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure.
Subjects were to be treated with nivolumab 0.3 mg/kg, 2 mg/kg or 10 mg/kg every 3 weeks.
Program Source: /projects/bms217252/stats/mRCC_EURMP/prog/tables/rt-ex-pt-durtrt-025.sas 27AUG2015:03:18:24

Table 1-31: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209010)

	Nivolumab			
	0.3 mg/kg N = 59	2 mg/kg N = 54	10 mg/kg N = 54	Total N = 167
NUMBER OF DOSES RECEIVED / SUBJECT				
MEAN (SD)	13.3 (16.48)	12.2 (14.42)	14.5 (16.43)	13.3 (15.76)
MEDIAN	6.0	7.5	8.0	6.0
MIN - MAX	1 - 57	1 - 57	1 - 61	1 - 61
CUMULATIVE DOSE (MG) / SUBJECT				
MEAN (SD)	366.8 (469.91)	2239.0 (2755.52)	12996.4 (15576.49)	5056.0 (10529.65)
MEDIAN	158.1	1277.1	6832.0	1321.0
MIN - MAX	24 - 1624	96 - 12676	513 - 68506	24 - 68506
CUMULATIVE DOSE (MG/KG) / SUBJECT				
MEAN (SD)	3.98 (4.943)	24.37 (28.847)	144.95 (164.340)	56.16 (112.954)
MEDIAN	1.80	15.00	80.00	16.00
MIN - MAX	0.3 - 17.1	2.0 - 114.0	10.0 - 610.0	0.3 - 610.0

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms217252/stats/mRCC_EURMP/prog/tables/rt-ex-cumdos-025.sas 27AUG2015:03:19:16

Table 1-32: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209010)

Treatment Group: NIVOLUMAB (0.3 MG/KG)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 41	Female N = 18	Total N = 59	Male N = 41	Female N = 18	Total N = 59
>= 18 AND < 65	22 (53.7)	14 (77.8)	36 (61.0)	191.90	52.21	244.11
>= 65 AND < 75	16 (39.0)	4 (22.2)	20 (33.9)	185.36	77.80	263.16
>= 75	3 (7.3)	0	3 (5.1)	69.45	0	69.45
TOTAL	41 (100.0)	18 (100.0)	59 (100.0)	446.72	130.00	576.72

Treatment Group: NIVOLUMAB (2 MG/KG)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 40	Female N = 14	Total N = 54	Male N = 40	Female N = 14	Total N = 54
>= 18 AND < 65	31 (77.5)	10 (71.4)	41 (75.9)	361.07	28.71	389.78
>= 65 AND < 75	6 (15.0)	3 (21.4)	9 (16.7)	47.70	34.53	82.23
>= 75	3 (7.5)	1 (7.1)	4 (7.4)	12.88	3.75	16.62
TOTAL	40 (100.0)	14 (100.0)	54 (100.0)	421.65	66.99	488.64

Treatment Group: NIVOLUMAB (10 MG/KG)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 40	Female N = 14	Total N = 54	Male N = 40	Female N = 14	Total N = 54
>= 18 AND < 65	25 (62.5)	10 (71.4)	35 (64.8)	230.70	121.49	352.20
>= 65 AND < 75	11 (27.5)	4 (28.6)	15 (27.8)	135.06	36.83	171.89
>= 75	4 (10.0)	0	4 (7.4)	56.57	0	56.57
TOTAL	40 (100.0)	14 (100.0)	54 (100.0)	422.34	158.32	580.67

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms217252/stats/mRCC_EURMP/prog/tables/rt-ex-pt-age.sas 27AUG2015:03:21:16

Table 1-33: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209010)

Treatment Group: NIVOLUMAB (0.3 MG/KG)

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 41	Female N = 18	Total N = 59	Male N = 41	Female N = 18	Total N = 59
WHITE	41 (100.0)	16 (88.9)	57 (96.6)	446.72	111.18	557.90
BLACK OR AFRICAN AMERICAN	0	0	0	0	0	0
ASIAN	0	2 (11.1)	2 (3.4)	0	18.83	18.83
OTHER	0	0	0	0	0	0
TOTAL	41 (100.0)	18 (100.0)	59 (100.0)	446.72	130.00	576.72

Treatment Group: NIVOLUMAB (2 MG/KG)

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 40	Female N = 14	Total N = 54	Male N = 40	Female N = 14	Total N = 54
WHITE	36 (90.0)	12 (85.7)	48 (88.9)	403.02	62.23	465.25
BLACK OR AFRICAN AMERICAN	2 (5.0)	0	2 (3.7)	10.32	0	10.32
ASIAN	2 (5.0)	1 (7.1)	3 (5.6)	8.31	1.02	9.33
OTHER	0	1 (7.1)	1 (1.9)	0	3.75	3.75
TOTAL	40 (100.0)	14 (100.0)	54 (100.0)	421.65	66.99	488.64

Treatment Group: NIVOLUMAB (10 MG/KG)

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 40	Female N = 14	Total N = 54	Male N = 40	Female N = 14	Total N = 54
WHITE	37 (92.5)	14 (100.0)	51 (94.4)	374.57	158.32	532.90
BLACK OR AFRICAN AMERICAN	1 (2.5)	0	1 (1.9)	32.46	0	32.46
ASIAN	2 (5.0)	0	2 (3.7)	15.31	0	15.31
OTHER	0	0	0	0	0	0
TOTAL	40 (100.0)	14 (100.0)	54 (100.0)	422.34	158.32	580.67

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms217252/stats/mRCC_EURMP/prog/tables/rt-ex-pt-age.sas 27AUG2015:03:21:19

Study CA209067 (Melanoma)

Table 1-34: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209067)

Duration of Exposure	Nivolumab N = 313 Persons (%)	Nivolumab N = 313 Person Time of Exposure (1) (Month)	Nivolumab + Ipilimumab N = 313 Persons (%)	Nivolumab + Ipilimumab N = 313 Person Time of Exposure (1) (Month)
0 - < 1 MONTH	9 (2.9)		7 (2.2)	
0 - < 2 MONTHS	32 (10.2)		77 (24.6)	
0 - < 3 MONTHS	51 (16.3)		116 (37.1)	
0 - < 4 MONTHS	94 (30.0)		160 (51.1)	
0 - < 5 MONTHS	119 (38.0)		178 (56.9)	
0 - < 6 MONTHS	131 (41.9)		184 (58.8)	
0 - <= 18.8 MONTHS (A)	313 (100.0)	2609.68	313 (100.0)	2102.18

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
In the mono arm, subjects were to be treated with nivolumab 3 mg/kg every 2 weeks.
In the combo arm, subjects were to be treated with nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for 4 doses then with nivolumab 3 mg/kg every 2 weeks.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-durtrt.sas 02JUN2015:06:28:36

Table 1-35: Cumulative Dose of Nivolumab and Ipilimumab; Nivolumab Treated Subjects (CA209067)

	Nivolumab N = 313	Nivolumab+Ipilimumab N = 313	
		Nivolumab	Ipilimumab
NUMBER OF DOSES RECEIVED / SUBJECT			
MEAN (SD)	17.0 (11.14)	11.0 (10.80)	3.2 (1.06)
MEDIAN	15.0	4.0	4.0
MIN - MAX	1 - 38	1 - 39	1 - 4
CUMULATIVE DOSE (MG) / SUBJECT			
MEAN (SD)	4312.7 (3089.45)	2205.6 (2663.27)	789.6 (306.71)
MEDIAN	3484.8	371.6	800.0
MIN - MAX	163 - 13299	59 - 10512	177 - 1517
CUMULATIVE DOSE (MG/KG) / SUBJECT			
MEAN (SD)	51.22 (33.827)	26.66 (31.187)	9.59 (3.222)
MEDIAN	45.00	4.00	12.00
MIN - MAX	3.0 - 124.7	1.0 - 109.0	2.9 - 17.8

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-cumdos.sas 02JUN2015:06:29:54

Table 1-36: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209067)

Treatment group: NIVOLUMAB

Age Category	Persons (%) Male N = 200	Persons (%) Female N = 113	Persons (%) Total N = 313	Person Time of Exposure (Months) (1) Male N = 200	Person Time of Exposure (Months) (1) Female N = 113	Person Time of Exposure (Months) (1) Total N = 313
>= 18 AND < 65	116 (58.0)	80 (70.8)	196 (62.6)	1002.02	603.76	1605.78
>= 65 AND < 75	57 (28.5)	21 (18.6)	78 (24.9)	534.28	158.03	692.30
>= 75	27 (13.5)	12 (10.6)	39 (12.5)	244.44	67.15	311.59
TOTAL	200 (100.0)	113 (100.0)	313 (100.0)	1780.73	828.94	2609.68

Treatment group: NIVOLUMAB+IPILIMUMAB

Age Category	Persons (%) Male N = 205	Persons (%) Female N = 108	Persons (%) Total N = 313	Person Time of Exposure (Months) (1) Male N = 205	Person Time of Exposure (Months) (1) Female N = 108	Person Time of Exposure (Months) (1) Total N = 313
>= 18 AND < 65	115 (56.1)	70 (64.8)	185 (59.1)	815.21	419.75	1234.96
>= 65 AND < 75	67 (32.7)	27 (25.0)	94 (30.0)	492.19	162.53	654.72
>= 75	23 (11.2)	11 (10.2)	34 (10.9)	178.00	34.50	212.50
TOTAL	205 (100.0)	108 (100.0)	313 (100.0)	1485.40	616.77	2102.18

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214677/stats/iss/prog/tables/issIMRMP/rt-ex-pt-age.sas 02JUN2015:06:28:26

Table 1-37: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209067)

Treatment group: NIVOLUMAB

Race	Persons (%) Male N = 200	Persons (%) Female N = 113	Persons (%) Total N = 313	Person Time of Exposure (Months) (1) Male N = 200	Person Time of Exposure (Months) (1) Female N = 113	Person Time of Exposure (Months) (1) Total N = 313
WHITE	194 (97.0)	111 (98.2)	305 (97.4)	1727.44	816.36	2543.80
BLACK OR AFRICAN AMERICAN	0	0	0	0	0	0
ASIAN	1 (0.5)	1 (0.9)	2 (0.6)	11.79	1.97	13.77
OTHER	5 (2.5)	1 (0.9)	6 (1.9)	41.49	10.61	52.11
TOTAL	200 (100.0)	113 (100.0)	313 (100.0)	1780.73	828.94	2609.68

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-age.sas 02JUN2015:06:31:26

Study CA209205 (Classical Hodgkin Lymphoma)

Table 1-38: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209205)

Duration of Exposure	Nivolumab, Cohort B N = 80 Persons (%)	Nivolumab, Cohort B N = 80 Person Time of Exposure (1) (Months)	Nivolumab, Cohort A+B+C N = 240 Persons (%)	Nivolumab, Cohort A+B+C N = 240 Person Time of Exposure (1) (Months)
0 - < 1 MONTH	0		22 (9.2)	
0 - < 2 MONTHS	1 (1.3)		51 (21.3)	
0 - < 3 MONTHS	4 (5.0)		74 (30.8)	
0 - < 4 MONTHS	6 (7.5)		99 (41.3)	
0 - < 5 MONTHS	14 (17.5)		130 (54.2)	
0 - < 6 MONTHS	18 (22.5)		151 (62.9)	
0 - <= 11.7 MONTHS (A)	80 (100.0)	628.21	240 (100.0)	1218.46

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure.
Subjects were to be treated with Nivolumab 3 mg/kg every 2 weeks.
Program Source: /projects/bms211280/stats/RMP/prog/tables/rt-ex-pt-durtrt.sas 23DEC2015:08:07:41

Table 1-39: Cumulative Dose of Nivolumab and Ipilimumab; Nivolumab Treated Subjects (CA209205)

	Nivolumab	
	Cohort B N = 80	Cohort A+B+C N = 240
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	16.1 (5.82)	10.9 (6.57)
MEDIAN	17.0	10.0
MIN - MAX	3 - 25	1 - 25
CUMULATIVE DOSE (MG) / SUBJECT		
MEAN (SD)	3811.2 (1826.98)	2504.0 (1742.80)
MEDIAN	3927.0	2038.0
MIN - MAX	636 - 9525	152 - 9525
CUMULATIVE DOSE (MG/KG) / SUBJECT		
MEAN (SD)	47.91 (17.295)	32.26 (19.487)
MEDIAN	50.88	29.68
MIN - MAX	9.0 - 75.8	2.9 - 75.8

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms211280/stats/RMP/prog/tables/rt-ex-cumdos.sas 23DEC2015:08:07:46

Table 1-40: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209205)

Treatment Group: Nivolumab, Cohort B

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 51	Female N = 29	Total N = 80	Male N = 51	Female N = 29	Total N = 80
>= 18 AND < 65	49 (96.1)	28 (96.6)	77 (96.3)	378.78	224.66	603.43
>= 65 AND < 75	2 (3.9)	1 (3.4)	3 (3.8)	15.54	9.23	24.77
>= 75	0	0	0	0	0	0
TOTAL	51 (100.0)	29 (100.0)	80 (100.0)	394.32	233.89	628.21

Treatment Group: Nivolumab, Cohort A+B+C

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 141	Female N = 99	Total N = 240	Male N = 141	Female N = 99	Total N = 240
>= 18 AND < 65	136 (96.5)	97 (98.0)	233 (97.1)	669.86	512.99	1182.85
>= 65 AND < 75	5 (3.5)	2 (2.0)	7 (2.9)	23.10	12.52	35.61
>= 75	0	0	0	0	0	0
TOTAL	141 (100.0)	99 (100.0)	240 (100.0)	692.96	525.50	1218.46

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211280/stats/RMP/prog/tables/rt-ex-pt-age.sas 23DEC2015:08:08:04

Table 1-41: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209205)

Treatment Group: Nivolumab, Cohort B

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 51	Female N = 29	Total N = 80	Male N = 51	Female N = 29	Total N = 80
WHITE	43 (84.3)	28 (96.6)	71 (88.8)	325.19	224.10	549.29
BLACK OR AFRICAN AMERICAN	3 (5.9)	1 (3.4)	4 (5.0)	28.78	9.79	38.57
ASIAN	1 (2.0)	0	1 (1.3)	5.62	0	5.62
OTHER	4 (7.8)	0	4 (5.0)	34.73	0	34.73
NOT REPORTED	0	0	0	0	0	0
TOTAL	51 (100.0)	29 (100.0)	80 (100.0)	394.32	233.89	628.21

Treatment Group: Nivolumab, Cohort A+B+C

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 141	Female N = 99	Total N = 240	Male N = 141	Female N = 99	Total N = 240
WHITE	120 (85.1)	88 (88.9)	208 (86.7)	565.32	472.74	1038.06
BLACK OR AFRICAN AMERICAN	8 (5.7)	4 (4.0)	12 (5.0)	46.62	17.38	64.00
ASIAN	4 (2.8)	5 (5.1)	9 (3.8)	21.72	26.58	48.30
OTHER	9 (6.4)	2 (2.0)	11 (4.6)	59.30	8.80	68.11
NOT REPORTED	0	0	0	0	0	0
TOTAL	141 (100.0)	99 (100.0)	240 (100.0)	692.96	525.50	1218.46

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211280/stats/RMP/prog/tables/rt-ex-pt-age.sas 23DEC2015:08:08:06

Study CA2090039 (Classical Hodgkin Lymphoma)

Table 1-42: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209039)

Duration of Exposure	Nivolumab N = 23 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	0	
0 - < 2 MONTHS	0	
0 - < 3 MONTHS	0	
0 - < 4 MONTHS	2 (8.7)	
0 - < 5 MONTHS	5 (21.7)	
0 - < 6 MONTHS	6 (26.1)	
0 - <= 23.9 MONTHS (A)	23 (100.0)	275.15

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure.
Subjects were to be treated with Nivolumab 3 mg/kg every 2 weeks.
Program Source: /projects/bms211280/stats/RMP/prog/tables/rt-ex-pt-durtrt.sas 23DEC2015:08:07:42

Table 1-43: Cumulative Dose of Nivolumab and Ipilimumab; Nivolumab Treated Subjects (CA209039)

	Nivolumab N = 23
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	23.2 (15.13)
MEDIAN	18.0
MIN - MAX	6 - 48
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	5736.1 (4768.16)
MEDIAN	4564.0
MIN - MAX	1236 - 21112
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	68.72 (44.428)
MEDIAN	53.97
MIN - MAX	18.0 - 137.8

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms211280/stats/RMP/prog/tables/rt-ex-cumdos.sas 23DEC2015:08:07:47

Table 1-44: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209039)

Treatment Group: Nivolumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 12	Female N = 11	Total N = 23	Male N = 12	Female N = 11	Total N = 23
>= 18 AND < 65	12 (100.0)	11 (100.0)	23 (100.0)	141.83	133.32	275.15
>= 65 AND < 75	0	0	0	0	0	0
>= 75	0	0	0	0	0	0
TOTAL	12 (100.0)	11 (100.0)	23 (100.0)	141.83	133.32	275.15

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211280/stats/RMP/prog/tables/rt-ex-pt-age.sas 23DEC2015:08:07:53

Table 1-45: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209039)

Treatment Group: Nivolumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 12	Female N = 11	Total N = 23	Male N = 12	Female N = 11	Total N = 23
WHITE	9 (75.0)	11 (100.0)	20 (87.0)	110.46	133.32	243.78
BLACK OR AFRICAN AMERICAN	2 (16.7)	0	2 (8.7)	27.76	0	27.76
ASIAN	0	0	0	0	0	0
OTHER	1 (8.3)	0	1 (4.3)	3.61	0	3.61
NOT REPORTED	0	0	0	0	0	0
TOTAL	12 (100.0)	11 (100.0)	23 (100.0)	141.83	133.32	275.15

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211280/stats/RMP/prog/tables/rt-ex-pt-age.sas 23DEC2015:08:07:59

Study CA209141 (SCCHN)

Table 1-46: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209141)

Duration of Exposure	Nivolumab N = 236 Persons (%)	Nivolumab N = 236 Person Time of Exposure (1) (Months)
0 - < 1 MONTH	20 (8.5)	
0 - < 2 MONTHS	66 (28.0)	
0 - < 3 MONTHS	132 (55.9)	
0 - < 4 MONTHS	152 (64.4)	
0 - < 5 MONTHS	172 (72.9)	
0 - < 6 MONTHS	185 (78.4)	
0 - <= 16.1 MONTHS (A)	236 (100.0)	947.58

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure.
Subjects were to be treated with nivolumab 3 mg/kg every 2 weeks.
Program Source: /projects/bms214682/stats/RMP/prog/tables/rt-ex-pt-durtrt-141.sas 29APR2016:07:24:29

Table 1-47: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209141)

	Nivolumab N = 236
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	7.6 (6.71)
MEDIAN	5.0
MIN - MAX	1 - 34
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	1562.8 (1522.99)
MEDIAN	969.0
MIN - MAX	134 - 9372
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	22.81 (20.149)
MEDIAN	14.99
MIN - MAX	3.0 - 101.9

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms214682/stats/RMP/prog/tables/rt-ex-cumdos.sas 29APR2016:07:24:33

Table 1-48: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209141)

Treatment Group: Nivolumab

Age Category	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 194	Female N = 42	Total N = 236	Male N = 194	Female N = 42	Total N = 236
>= 18 AND < 65	131 (67.5)	37 (88.1)	168 (71.2)	536.54	119.69	656.23
>= 65 AND < 75	53 (27.3)	3 (7.1)	56 (23.7)	249.36	4.21	253.57
>= 75	10 (5.2)	2 (4.8)	12 (5.1)	30.29	7.49	37.78
TOTAL	194 (100.0)	42 (100.0)	236 (100.0)	816.20	131.38	947.58

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214682/stats/RMP/prog/tables/rt-ex-pt-age-race.sas 29APR2016:07:24:58

Table 1-49: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209141)

Treatment Group: Nivolumab

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 194	Female N = 42	Total N = 236	Male N = 194	Female N = 42	Total N = 236
WHITE	157 (80.9)	35 (83.3)	192 (81.4)	654.59	101.98	756.57
BLACK OR AFRICAN AMERICAN	7 (3.6)	3 (7.1)	10 (4.2)	31.84	6.57	38.41
ASIAN	26 (13.4)	3 (7.1)	29 (12.3)	110.16	18.07	128.23
OTHER	4 (2.1)	1 (2.4)	5 (2.1)	19.61	4.76	24.38
NOT REPORTED	0	0	0	0	0	0
TOTAL	194 (100.0)	42 (100.0)	236 (100.0)	816.20	131.38	947.58

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214682/stats/RMP/prog/tables/rt-ex-pt-age-race.sas 29APR2016:07:25:24

Study CA209275 (Urothelial Carcinoma)

Table 1-50: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209275)

Duration of Exposure	Nivolumab N = 270 Persons (%)	Nivolumab N = 270 Person Time of Exposure (1) (Months)
0 - < 1 MONTH	19 (7.0)	
0 - < 2 MONTHS	63 (23.3)	
0 - < 3 MONTHS	113 (41.9)	
0 - < 4 MONTHS	131 (48.5)	
0 - < 5 MONTHS	162 (60.0)	
0 - < 6 MONTHS	168 (62.2)	
0 - <= 13.4 MONTHS (A)	270 (100.0)	1300.04

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure.
Subjects were to be treated with nivolumab 3 mg/kg every 2 weeks.
Program Source: /projects/bms217252/stats/bladder_EU_RMP/prog/tables/rt-ex-pt-durtrt.sas 24NOV2016:05:06:37

Table 1-51: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209275)

	Nivolumab N = 270
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	9.3 (7.15)
MEDIAN	7.0
MIN - MAX	1 - 30
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	2161.9 (1821.74)
MEDIAN	1436.0
MIN - MAX	126 - 7467
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	27.82 (21.310)
MEDIAN	21.06
MIN - MAX	3.0 - 89.0

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms217252/stats/bladder_EU_RMP/prog/tables/rt-ex-cumdos.sas 24NOV2016:05:01:04

Table 1-52: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209275)

Treatment Group: Nivolumab

Age Category	Persons (%) Male N = 211	Persons (%) Female N = 59	Persons (%) Total N = 270	Person Time of Exposure (Months) (1) Male N = 211	Person Time of Exposure (Months) (1) Female N = 59	Person Time of Exposure (Months) (1) Total N = 270
>= 18 AND < 65	93 (44.1)	29 (49.2)	122 (45.2)	403.25	150.67	553.92
>= 65 AND < 75	89 (42.2)	21 (35.6)	110 (40.7)	450.69	87.33	538.02
>= 75 AND < 85	27 (12.8)	8 (13.6)	35 (13.0)	155.50	39.56	195.06
>= 85	2 (0.9)	1 (1.7)	3 (1.1)	10.64	2.40	13.04
TOTAL	211 (100.0)	59 (100.0)	270 (100.0)	1020.09	279.95	1300.04

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms217252/stats/bladder_EU_RMP/prog/tables/rt-ex-pt-age-race.sas 24NOV2016:05:03:25

Table 1-53: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209275)

Treatment Group: Nivolumab

Race	Persons (%) Male N = 211	Persons (%) Female N = 59	Persons (%) Total N = 270	Person Time of Exposure (Months) (1) Male N = 211	Person Time of Exposure (Months) (1) Female N = 59	Person Time of Exposure (Months) (1) Total N = 270
WHITE	182 (86.3)	49 (83.1)	231 (85.6)	874.38	225.54	1099.93
BLACK OR AFRICAN AMERICAN	2 (0.9)	0	2 (0.7)	16.89	0	16.89
ASIAN	21 (10.0)	9 (15.3)	30 (11.1)	105.03	45.14	150.18
OTHER	2 (0.9)	1 (1.7)	3 (1.1)	2.96	9.26	12.22
NOT REPORTED	4 (1.9)	0	4 (1.5)	20.83	0	20.83
TOTAL	211 (100.0)	59 (100.0)	270 (100.0)	1020.09	279.95	1300.04

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms217252/stats/bladder_EU_RMP/prog/tables/rt-ex-pt-age-race.sas 24NOV2016:05:05:36

Study CA209032 (Urothelial Carcinoma)

Table 1-54: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209032)

Duration of Exposure	Nivolumab N = 78 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	2 (2.6)	
0 - < 2 MONTHS	16 (20.5)	
0 - < 3 MONTHS	29 (37.2)	
0 - < 4 MONTHS	36 (46.2)	
0 - < 5 MONTHS	43 (55.1)	
0 - < 6 MONTHS	47 (60.3)	
0 - <= 20.7 MONTHS (A)	78 (100.0)	529.35

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Crossover subjects from CA209032 are truncated at the first dose date of crossover period.
(A) Max clinical exposure.
Subjects were to be treated with nivolumab 3 mg/kg every 2 weeks.
Program Source: /projects/bms217252/stats/bladder_EU_RMP/prog/tables/rt-ex-pt-durtrt.sas 24NOV2016:05:06:50

Table 1-55: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209032)

	Nivolumab N = 78
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	13.6 (12.24)
MEDIAN	8.5
MIN - MAX	1 - 46
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	3631.9 (3605.16)
MEDIAN	1927.0
MIN - MAX	227 - 13888
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	40.55 (36.241)
MEDIAN	25.88
MIN - MAX	3.0 - 138.1

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Crossover subjects from CA209032 are truncated at the first dose date of crossover period.
Program Source: /projects/bms217252/stats/bladder_EU_RMP/prog/tables/rt-ex-cumdos.sas 24NOV2016:05:00:47

Table 1-56: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209032)

Treatment Group: Nivolumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 54	Female N = 24	Total N = 78	Male N = 54	Female N = 24	Total N = 78
>= 18 AND < 65	24 (44.4)	13 (54.2)	37 (47.4)	204.19	58.71	262.90
>= 65 AND < 75	21 (38.9)	10 (41.7)	31 (39.7)	128.43	48.56	176.99
>= 75 AND < 85	8 (14.8)	1 (4.2)	9 (11.5)	78.26	3.78	82.04
>= 85	1 (1.9)	0	1 (1.3)	7.43	0	7.43
TOTAL	54 (100.0)	24 (100.0)	78 (100.0)	418.30	111.05	529.35

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Crossover subjects from CA209032 are truncated at the first dose date of crossover period.
Program Source: /projects/bms217252/stats/bladder_EU_RMP/prog/tables/rt-ex-pt-age-race.sas 24NOV2016:05:02:50

Table 1-57: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209032)

Treatment Group: Nivolumab

Race	Persons (%) Male N = 54	Persons (%) Female N = 24	Persons (%) Total N = 78	Person Time of Exposure (Months) (1) Male N = 54	Person Time of Exposure (Months) (1) Female N = 24	Person Time of Exposure (Months) (1) Total N = 78
WHITE	50 (92.6)	22 (91.7)	72 (92.3)	378.12	103.56	481.68
BLACK OR AFRICAN AMERICAN	3 (5.6)	1 (4.2)	4 (5.1)	24.97	1.48	26.45
ASIAN	0	1 (4.2)	1 (1.3)	0	6.01	6.01
OTHER	1 (1.9)	0	1 (1.3)	15.21	0	15.21
NOT REPORTED	0	0	0	0	0	0
TOTAL	54 (100.0)	24 (100.0)	78 (100.0)	418.30	111.05	529.35

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Crossover subjects from CA209032 are truncated at the first dose date of crossover period.
Program Source: /projects/bms217252/stats/bladder_EU_RMP/prog/tables/rt-ex-pt-age-race.sas 24NOV2016:05:04:52

Study CA209238 (Adjuvant Melanoma)

Table 1-58: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209238)

Duration of Exposure	Nivolumab N = 452 Persons (%)	Nivolumab N = 452 Person Time of Exposure (1) (Months)
0 - < 1 MONTH	0	
0 - < 2 MONTHS	15 (3.3)	
0 - < 3 MONTHS	23 (5.1)	
0 - < 4 MONTHS	61 (13.5)	
0 - < 5 MONTHS	81 (17.9)	
0 - < 6 MONTHS	95 (21.0)	
0 - <= 15.5 MONTHS (a)	452 (100.0)	4492.75

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(a) max clinical exposure
Subjects were to be treated with nivolumab 3 mg/kg every 2 weeks.
Program Source: /unblinded/bms233672/stats/RMP/prog/tables/rt-ex-ptdurtrt.sas 06SEP2017:08:31:23

Table 1-59: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209238)

	Nivolumab N = 452
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	19.6 (7.94)
MEDIAN	24.0
MIN - MAX	1 - 26
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	2822.7 (2340.97)
MEDIAN	2500.0
MIN - MAX	19 - 13000
CUMULATIVE DOSE (MG/KG) / SUBJECT	
MEAN (SD)	58.90 (23.827)
MEDIAN	72.00
MIN - MAX	3.0 - 80.1

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /unblinded/bms233672/stats/RMP/prog/tables/rt-ex-cumdos.sas 06SEP2017:08:27:07

Table 1-60: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209238)

Treatment Group: Nivolumab

	Persons (%)			Person Time of Exposure (Months) (1)		
AGE CATEGORY	Male N = 257	Female N = 195	Total N = 452	Male N = 257	Female N = 195	Total N = 452
>= 18 AND < 65	177 (68.9)	155 (79.5)	332 (73.5)	1783.89	1547.79	3331.68
>= 65 AND < 75	68 (26.5)	35 (17.9)	103 (22.8)	681.00	308.04	989.04
>= 75 AND < 85	12 (4.7)	5 (2.6)	17 (3.8)	113.58	58.45	172.02
>= 85	0	0	0	0	0	0
TOTAL	257 (100.0)	195 (100.0)	452 (100.0)	2578.46	1914.28	4492.75

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /unblinded/bms233672/stats/RMP/prog/tables/rt-ex-pt-age.sas 06SEP2017:08:28:23

Table 1-61: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209238)

Treatment Group: Nivolumab

	Persons (%)			Person Time of Exposure (Months) (1)		
RACE	Male N = 257	Female N = 195	Total N = 452	Male N = 257	Female N = 195	Total N = 452
WHITE	242 (94.2)	183 (93.8)	425 (94.0)	2454.74	1787.14	4241.87
BLACK OR AFRICAN AMERICAN	0	0	0	0	0	0
ASIAN	13 (5.1)	11 (5.6)	24 (5.3)	107.43	114.63	222.06
OTHER	2 (0.8)	1 (0.5)	3 (0.7)	16.30	12.52	28.81
TOTAL	257 (100.0)	195 (100.0)	452 (100.0)	2578.46	1914.28	4492.75

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /unblinded/bms233672/stats/RMP/prog/tables/rt-ex-pt-age.sas 06SEP2017:08:30:21

Study Ono-4538-24 (CA209473 Esophageal squamous cell carcinoma)

Table 1-62: Clinical Exposure in Person Time; Nivolumab Treated Subjects (Ono-4538-24)

	Nivolumab N = 209	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	10 (4.8)	
0 - < 2 MONTHS	64 (30.6)	
0 - < 3 MONTHS	78 (37.3)	
0 - < 4 MONTHS	116 (55.5)	
0 - < 5 MONTHS	130 (62.2)	
0 - < 6 MONTHS	141 (67.5)	
0 - <= 29.6 MONTHS (A)	209 (100.0)	1205.85

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(a) max clinical exposure
Subjects were to be treated with nivolumab 3 mg/kg and 240 mg every 2 weeks.
Program Source: /projects/bms211280/stats/ono24_tlf/prog/tables/rt-ex-pt-durtrt.sas 03JUN2019:12:20:59

Table 1-63: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (Ono-4538-24)

	Nivolumab N = 209
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	10.8 (11.7)
MEDIAN	6.0
MIN - MAX	1 - 60
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	2585.1 (2816.1)
MEDIAN	1440.0
MIN - MAX	240 - 14400

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms211280/stats/ono24_tlf/prog/tables/rt-ex-cumdos.sas 03JUN2019:12:20:55

Table 1-64: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (Ono-4538-24)

Treatment group: Nivolumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 178	Female N = 31	Total N = 209	Male N = 178	Female N = 31	Total N = 209
>= 18 AND < 65	96 (53.9)	16 (51.6)	112 (53.6)	539.17	101.36	640.53
>= 65 AND < 75	72 (40.4)	11 (35.5)	83 (39.7)	395.93	81.58	477.50
>= 75 AND < 85	10 (5.6)	4 (12.9)	14 (6.7)	62.42	25.40	87.82
>= 85	0	0	0	0	0	0
TOTAL	178 (100.0)	31 (100.0)	209 (100.0)	997.52	208.33	1205.85

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211280/stats/ono24_tlf/prog/tables/rt-ex-pt.sas 03JUN2019:12:21:01

Table 1-65: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (Ono-4538-24)

Treatment group: Nivolumab

Race Category	Persons (%) Male N = 178	Persons (%) Female N = 31	Persons (%) Total N = 209	Person Time of Exposure (Months) (1) Male N = 178	Person Time of Exposure (Months) (1) Female N = 31	Person Time of Exposure (Months) (1) Total N = 209
WHITE	4 (2.2)	5 (16.1)	9 (4.3)	16.92	13.83	30.75
BLACK OR AFRICAN AMERICAN	0	0	0	0	0	0
ASIAN	174 (97.8)	26 (83.9)	200 (95.7)	980.60	194.50	1175.10
OTHER	0	0	0	0	0	0
NOT REPORTED	0	0	0	0	0	0
TOTAL	178 (100.0)	31 (100.0)	209 (100.0)	997.52	208.33	1205.85

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211280/stats/ono24_tlf/prog/tables/rt-ex-pt.sas 03JUN2019:12:21:03

Study CA209577 (Adjuvant OC/GEJC)

Table 1-66: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209577)

Duration of Exposure	Nivolumab N = 532 Persons (%)	Nivolumab N = 532 Person Time of Exposure (1) (Months)
0 - < 1 MONTH	3 (0.6)	
0 - < 2 MONTHS	46 (8.6)	
0 - < 3 MONTHS	79 (14.8)	
0 - < 4 MONTHS	142 (26.7)	
0 - < 5 MONTHS	169 (31.8)	
0 - < 6 MONTHS	189 (35.5)	
0 - <= 15.2 MONTHS (A)	532 (100.0)	4522.05

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Subjects were to be treated with nivolumab 240mg every 2 weeks for 16 weeks (8 doses) followed by nivolumab 480mg every 4 weeks.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp577/prog/tables/rt-ex-pt-durtrt.sas 02OCT2020:12:18:37

Table 1-67: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209577)

	Nivolumab N = 532
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	12.2 (5.4)
MEDIAN	15.0
MIN - MAX	1 - 17
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	4167.7 (2239.2)
MEDIAN	5280.0
MIN - MAX	240 - 6240

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp577/prog/tables/rt-ex-cumdos.sas 02OCT2020:12:18:18

Table 1-68: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209577)

Treatment Group: Nivolumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 449	Female N = 83	Total N = 532	Male N = 449	Female N = 83	Total N = 532
>= 18 AND < 65	283 (63.0)	50 (60.2)	333 (62.6)	2488.34	428.48	2916.83
>= 65 AND < 75	147 (32.7)	28 (33.7)	175 (32.9)	1189.88	256.99	1446.87
>= 75 AND < 85	19 (4.2)	5 (6.0)	24 (4.5)	133.72	24.64	158.36
>= 85	0	0	0	0	0	0
TOTAL	449 (100.0)	83 (100.0)	532 (100.0)	3811.94	710.11	4522.05

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp577/prog/tables/rt-ex-pt-age.sas 02OCT2020:12:18:09

Table 1-69: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209577)

Treatment Group: Nivolumab

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 449	Female N = 83	Total N = 532	Male N = 449	Female N = 83	Total N = 532
WHITE	370 (82.4)	62 (74.7)	432 (81.2)	3184.10	530.63	3714.73
BLACK OR AFRICAN AMERICAN	5 (1.1)	2 (2.4)	7 (1.3)	34.96	2.89	37.85
ASIAN	68 (15.1)	15 (18.1)	83 (15.6)	533.75	126.82	660.57
OTHER	6 (1.3)	4 (4.8)	10 (1.9)	59.14	49.77	108.91
TOTAL	449 (100.0)	83 (100.0)	532 (100.0)	3811.94	710.11	4522.05

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp577/prog/tables/rt-ex-pt-race.sas 02OCT2020:12:18:17

Study CA209274 (Muscle Invasive Urothelial Carcinoma)

Table 1-70: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA209274)

	Nivolumab N = 351
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	16.7 (9.0)
MEDIAN	19.0
MIN - MAX	1 - 27
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	3997.7 (2155.9)
MEDIAN	4560.0
MIN - MAX	240 - 6480

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp274/prog/tables/rt-ex-cumdos.sas 23AUG2021:17:08:35

Table 1-71: Clinical Exposure in Person Time by Age Group and Sex; Nivolumab Treated Subjects (CA209274)

Treatment Group: Nivolumab

Age Category	Persons (%) Male N = 264	Persons (%) Female N = 87	Persons (%) Total N = 351	Person Time of Exposure (Months) (1) Male N = 264	Person Time of Exposure (Months) (1) Female N = 87	Person Time of Exposure (Months) (1) Total N = 351
>= 18 AND < 65	123 (46.6)	32 (36.8)	155 (44.2)	1162.64	265.89	1428.53
>= 65 AND < 75	93 (35.2)	37 (42.5)	130 (37.0)	831.61	249.76	1081.36
>= 75 AND < 85	47 (17.8)	15 (17.2)	62 (17.7)	380.62	90.38	471.00
>= 85	1 (0.4)	3 (3.4)	4 (1.1)	10.22	9.43	19.65
TOTAL	264 (100.0)	87 (100.0)	351 (100.0)	2385.08	615.46	3000.54

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp274/prog/tables/rt-ex-pt-age.sas 23AUG2021:17:09:02

Table 1-72: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209274)

Duration of Exposure	Nivolumab N = 351 Persons (%)	Nivolumab N = 351 Person Time of Exposure (1) (Months)
0 - < 1 MONTH	5 (1.4)	
0 - < 2 MONTHS	32 (9.1)	
0 - < 3 MONTHS	50 (14.2)	
0 - < 4 MONTHS	81 (23.1)	
0 - < 5 MONTHS	101 (28.8)	
0 - < 6 MONTHS	113 (32.2)	
0 - <= 13.5 MONTHS (A)	351 (100.0)	3000.54

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Subjects were to be treated with nivolumab 240mg every 2 weeks until recurrence or discontinuation from study for a maximum of 1 year
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp274/prog/tables/rt-ex-pt-durtrt.sas 23AUG2021:17:08:49

Table 1-73: Clinical Exposure in Person Time by Racial Origin and Sex; Nivolumab Treated Subjects (CA209274)

Treatment Group: Nivolumab

Race	Persons (%) Male N = 264	Persons (%) Female N = 87	Persons (%) Total N = 351	Person Time of Exposure (Months) (1) Male N = 264	Person Time of Exposure (Months) (1) Female N = 87	Person Time of Exposure (Months) (1) Total N = 351
WHITE	203 (76.9)	59 (67.8)	262 (74.6)	1889.45	444.68	2334.13
BLACK OR AFRICAN AMERICAN	2 (0.8)	0	2 (0.6)	11.14	0	11.14
ASIAN	53 (20.1)	27 (31.0)	80 (22.8)	458.45	160.49	618.94
OTHER	6 (2.3)	1 (1.1)	7 (2.0)	26.05	10.28	36.34
TOTAL	264 (100.0)	87 (100.0)	351 (100.0)	2385.08	615.46	3000.54

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.

Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp274/prog/tables/rt-ex-pt-race.sas 23AUG2021:17:08:44

Study CA20976K (Stage IIB/C Adjuvant Melanoma)

Table 1-74: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA20976K)

Duration of Exposure	Nivolumab 480 mg Q4W N = 524 Persons (%)	Nivolumab 480 mg Q4W N = 524 Person Time of Exposure (1) (Months)
0 - < 1 MONTH	7 (1.3)	
0 - < 2 MONTHS	41 (7.8)	
0 - < 3 MONTHS	56 (10.7)	
0 - < 4 MONTHS	70 (13.4)	
0 - < 5 MONTHS	89 (17.0)	
0 - < 6 MONTHS	101 (19.3)	
0 - <= 13.1 MONTHS (A)	524 (100.0)	5064.08

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on blinded phase treatment.
(A) Max clinical exposure
Last dose date and start dose date are dose dates relative to study phase.
For CA20976K, there were 2 subjects who received unknown doses, 1 during Cycle 10 and 1 during Cycle 7, who are not counted in the dosing summary.

Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp76k/prog/tables/rt-ex-pt-durtrt.sas 11OCT2022:14:11:38

Table 1-75: Clinical Exposure in Person Time by Age Group and Sex; Nivolumab Treated Subjects (CA20976K)

Treatment Group: Nivolumab 480 mg Q4W

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 320	Female N = 204	Total N = 524	Male N = 320	Female N = 204	Total N = 524
< 18	0	0	0	0	0	0
>= 18 AND < 65	178 (55.6)	127 (62.3)	305 (58.2)	1826.66	1262.23	3088.89
>= 65 AND < 75	84 (26.3)	55 (27.0)	139 (26.5)	761.99	524.62	1286.60
>= 75 AND < 85	56 (17.5)	21 (10.3)	77 (14.7)	491.47	172.98	664.44
>= 85	2 (0.6)	1 (0.5)	3 (0.6)	12.09	12.06	24.15
TOTAL	320 (100.0)	204 (100.0)	524 (100.0)	3092.21	1971.88	5064.08

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Last dose date and start dose date are dose dates relative to study phase.
For CA20976K, there were 2 subjects who received unknown doses, 1 during Cycle 10 and 1 during Cycle 7, who are not counted in the dosing summary.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp76k/prog/tables/rt-ex-pt-age.sas 11OCT2022:14:13:55

Table 1-76: Clinical Exposure in Person Time by Racial Origin and Sex; Nivolumab Treated Subjects (CA20976K)

Treatment Group: Nivolumab 480 mg Q4W

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 320	Female N = 204	Total N = 524	Male N = 320	Female N = 204	Total N = 524
WHITE	313 (97.8)	200 (98.0)	513 (97.9)	3035.66	1924.27	4959.93
BLACK OR AFRICAN AMERICAN	0	2 (1.0)	2 (0.4)	0	22.41	22.41
ASIAN	0	1 (0.5)	1 (0.2)	0	12.71	12.71
OTHER	6 (1.9)	1 (0.5)	7 (1.3)	43.79	12.48	56.28
NOT REPORTED	1 (0.3)	0	1 (0.2)	12.75	0	12.75
TOTAL	320 (100.0)	204 (100.0)	524 (100.0)	3092.21	1971.88	5064.08

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Last dose date and start dose date are dose dates relative to study phase.
For CA20976K, there were 2 subjects who received unknown doses, 1 during Cycle 10 and 1 during Cycle 7, who are not counted in the dosing summary.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp76k/prog/tables/rt-ex-pt-race.sas 11OCT2022:14:14:35

Study CA2098FC (Melanoma)

Table 1-77: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA2098FC Process C)

Duration of Exposure	Nivolumab Process C N = 129 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	0	
0 - < 2 MONTHS	4 (3.1)	
0 - < 3 MONTHS	7 (5.4)	
0 - < 4 MONTHS	17 (13.2)	
0 - < 5 MONTHS	23 (17.8)	
0 - < 6 MONTHS	26 (20.2)	
0 - <= 15.7 MONTHS (A)	129 (100.0)	1317.32

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Subjects were to be treated with nivolumab 3 mg/kg IV Q2W for Week 1 to Week 17 followed by 480 mg IV Q4W for Week 19 to Week 51 until recurrence or discontinuation from study.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-pt-durtrt.sas 18OCT2022:12:20:24

Table 1-78: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA2098FC Process D)

Duration of Exposure	Nivolumab Process D N = 132 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	0	
0 - < 2 MONTHS	6 (4.5)	
0 - < 3 MONTHS	8 (6.1)	
0 - < 4 MONTHS	11 (8.3)	
0 - < 5 MONTHS	14 (10.6)	
0 - < 6 MONTHS	16 (12.1)	
0 - <= 15.7 MONTHS (A)	132 (100.0)	1429.29

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Subjects were to be treated with nivolumab 3 mg/kg IV Q2W for Week 1 to Week 17 followed by 480 mg IV Q4W for Week 19 to Week 51 until recurrence or discontinuation from study.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-pt-durtrt.sas 18OCT2022:12:20:27

Table 1-79: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA2098FC Process C)

	Nivolumab	
	3 MG/KG IV Q2W N = 129	480 MG IV Q4W N = 105
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	8.4 (1.5)	7.9 (2.3)
MEDIAN	9.0	9.0
MIN - MAX	2 - 9	1 - 9
CUMULATIVE DOSE (MG) / SUBJECT		
MEAN (SD)	2059.0 (590.5)	3768.7 (1099.7)
MEDIAN	2051.0	4320.0
MIN - MAX	480 - 3919	480 - 4320
CUMULATIVE DOSE (MG/KG) / SUBJECT		
MEAN (SD)	25.10 (4.51)	
MEDIAN	26.99	
MIN - MAX	6.1 - 27.4	

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
3 mg/kg IV Q2W is for Week 1 to Week 17 and 480 mg IV Q4W is for Week 19 to Week 51.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-cumdos.sas 19DEC2022:06:08:43

Table 1-80: Cumulative Dose of Nivolumab; Nivolumab Treated Subjects (CA2098FC Process D)

	Nivolumab	
	3 MG/KG IV Q2W N = 132	480 MG IV Q4W N = 117
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	8.5 (1.6)	7.9 (2.2)
MEDIAN	9.0	9.0
MIN - MAX	1 - 9	1 - 9
CUMULATIVE DOSE (MG) / SUBJECT		
MEAN (SD)	2062.6 (602.3)	3802.3 (1046.2)
MEDIAN	2080.5	4320.0
MIN - MAX	241 - 3774	480 - 4320
CUMULATIVE DOSE (MG/KG) / SUBJECT		
MEAN (SD)	25.50 (4.85)	
MEDIAN	27.00	
MIN - MAX	3.0 - 34.1	

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
3 mg/kg IV Q2W is for Week 1 to Week 17 and 480 mg IV Q4W is for Week 19 to Week 51.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-cumdos.sas 19DEC2022:06:08:45

Table 1-81: Clinical Exposure in Person Time by Age Group and Sex; Nivolumab Treated Subjects (CA2098FC Process C)

Treatment Group: Nivolumab Process C

Age Category	Persons (%) Male N = 87	Persons (%) Female N = 42	Persons (%) Total N = 129	Person Time of Exposure (Months) (1) Male N = 87	Person Time of Exposure (Months) (1) Female N = 42	Person Time of Exposure (Months) (1) Total N = 129
>= 18 AND < 65	56 (64.4)	32 (76.2)	88 (68.2)	537.07	368.76	905.82
>= 65 AND < 75	26 (29.9)	9 (21.4)	35 (27.1)	268.81	83.15	351.97
>= 75 AND < 85	5 (5.7)	1 (2.4)	6 (4.7)	46.69	12.85	59.53
>= 85	0	0	0	0	0	0
TOTAL	87 (100.0)	42 (100.0)	129 (100.0)	852.57	464.76	1317.32

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-pt-age-eu.sas 18OCT2022:12:21:28

Table 1-82: Clinical Exposure in Person Time by Age Group and Sex; Nivolumab Treated Subjects (CA2098FC Process D)

Treatment Group: Nivolumab Process D

Age Category	Persons (%) Male N = 78	Persons (%) Female N = 54	Persons (%) Total N = 132	Person Time of Exposure (Months) (1) Male N = 78	Person Time of Exposure (Months) (1) Female N = 54	Person Time of Exposure (Months) (1) Total N = 132
>= 18 AND < 65	55 (70.5)	34 (63.0)	89 (67.4)	576.20	404.40	980.60
>= 65 AND < 75	17 (21.8)	16 (29.6)	33 (25.0)	196.90	157.67	354.56
>= 75 AND < 85	6 (7.7)	3 (5.6)	9 (6.8)	60.09	24.21	84.30
>= 85	0	1 (1.9)	1 (0.8)	0	9.82	9.82
TOTAL	78 (100.0)	54 (100.0)	132 (100.0)	833.18	596.11	1429.29

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-pt-age-eu.sas 18OCT2022:12:21:32

Table 1-83: Clinical Exposure in Person Time by Racial Origin and Sex; Nivolumab Treated Subjects (CA2098FC Process C)

Treatment Group: Nivolumab Process C

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 87	Female N = 42	Total N = 129	Male N = 87	Female N = 42	Total N = 129
WHITE	85 (97.7)	41 (97.6)	126 (97.7)	835.32	462.75	1298.07
OTHER	2 (2.3)	1 (2.4)	3 (2.3)	17.25	2.00	19.25
TOTAL	87 (100.0)	42 (100.0)	129 (100.0)	852.57	464.76	1317.32

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-pt-race.sas 18OCT2022:12:21:54

Table 1-84: Clinical Exposure in Person Time by Racial Origin and Sex; Nivolumab Treated Subjects (CA2098FC Process D)

Treatment Group: Nivolumab Process D

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 78	Female N = 54	Total N = 132	Male N = 78	Female N = 54	Total N = 132
WHITE	76 (97.4)	51 (94.4)	127 (96.2)	809.92	557.04	1366.97
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	1 (1.9)	1 (0.8)	0	13.01	13.01
OTHER	2 (2.6)	2 (3.7)	4 (3.0)	23.26	26.05	49.31
TOTAL	78 (100.0)	54 (100.0)	132 (100.0)	833.18	596.11	1429.29

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/rmp8fc/prog/tables/rt-ex-pt-race.sas 18OCT2022:12:21:58

2 NIVOLUMAB COMBINED WITH IPILIMUMAB

For nivolumab in combination therapy with ipilimumab, individual clinical trial exposure analyses are presented in the following tables:

Tables 2-1 - 2-4 for CA209067 (melanoma)

Tables 2-5 - 2-8 for CA209069 (melanoma)

Tables 2-9 - 2-12 for CA209004 (melanoma)

Tables 2-13 - 2-16 for CA209214 (RCC)

Tables 2-17 - 2-20 for CA209016 (RCC)

Tables 2-21 - 2-24 for CA209743 (MPM)

Tables 2-25 - 2-28 for CA209142 (CRC)

Tables 2-29 - 2-32 for CA209648 (OSCC)

Tables 2-33 - 2-36 for CA2098HW (CRC)

Table 2-37 - 2-40 for CA2099DW (HCC)

Study CA209067 (Melanoma)

Table 2-1: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209067)

Duration of Exposure	Nivolumab N = 313 Persons (%)	Nivolumab N = 313 Person Time of Exposure (1) (Month)	Nivolumab + Ipilimumab N = 313 Persons (%)	Nivolumab + Ipilimumab N = 313 Person Time of Exposure (1) (Month)
0 - < 1 MONTH	9 (2.9)		7 (2.2)	
0 - < 2 MONTHS	32 (10.2)		77 (24.6)	
0 - < 3 MONTHS	51 (16.3)		116 (37.1)	
0 - < 4 MONTHS	94 (30.0)		160 (51.1)	
0 - < 5 MONTHS	119 (38.0)		178 (56.9)	
0 - < 6 MONTHS	131 (41.9)		184 (58.8)	
0 - <= 18.8 MONTHS (A)	313 (100.0)	2609.68	313 (100.0)	2102.18

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
In the mono arm, subjects were to be treated with nivolumab 3 mg/kg every 2 weeks. In the combo arm, subjects were to be treated with nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for 4 doses then with nivolumab 3 mg/kg every 2 weeks.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-durtrt.sas 02JUN2015:06:28:36

Table 2-2: Cumulative Dose of Nivolumab and Ipilimumab; Nivolumab Treated Subjects (CA209067)

	Nivolumab N = 313	Nivolumab+Ipilimumab N = 313	
		Nivolumab	Ipilimumab
NUMBER OF DOSES RECEIVED / SUBJECT			
MEAN (SD)	17.0 (11.14)	11.0 (10.80)	3.2 (1.06)
MEDIAN	15.0	4.0	4.0
MIN - MAX	1 - 38	1 - 39	1 - 4
CUMULATIVE DOSE (MG) / SUBJECT			
MEAN (SD)	4312.7 (3089.45)	2205.6 (2663.27)	789.6 (306.71)
MEDIAN	3484.8	371.6	800.0
MIN - MAX	163 - 13299	59 - 10512	177 - 1517
CUMULATIVE DOSE (MG/KG) / SUBJECT			
MEAN (SD)	51.22 (33.827)	26.66 (31.187)	9.59 (3.222)
MEDIAN	45.00	4.00	12.00
MIN - MAX	3.0 - 124.7	1.0 - 109.0	2.9 - 17.8

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-cumdos.sas 02JUN2015:06:29:54

Table 2-3: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209067)

Treatment group: NIVOLUMAB

Age Category	Persons (%) Male N = 200	Persons (%) Female N = 113	Persons (%) Total N = 313	Person Time of Exposure (Months) (1) Male N = 200	Person Time of Exposure (Months) (1) Female N = 113	Person Time of Exposure (Months) (1) Total N = 313
>= 18 AND < 65	116 (58.0)	80 (70.8)	196 (62.6)	1002.02	603.76	1605.78
>= 65 AND < 75	57 (28.5)	21 (18.6)	78 (24.9)	534.28	158.03	692.30
>= 75	27 (13.5)	12 (10.6)	39 (12.5)	244.44	67.15	311.59
TOTAL	200 (100.0)	113 (100.0)	313 (100.0)	1780.73	828.94	2609.68

Treatment group: NIVOLUMAB+IPILIMUMAB

Age Category	Persons (%) Male N = 205	Persons (%) Female N = 108	Persons (%) Total N = 313	Person Time of Exposure (Months) (1) Male N = 205	Person Time of Exposure (Months) (1) Female N = 108	Person Time of Exposure (Months) (1) Total N = 313
>= 18 AND < 65	115 (56.1)	70 (64.8)	185 (59.1)	815.21	419.75	1234.96
>= 65 AND < 75	67 (32.7)	27 (25.0)	94 (30.0)	492.19	162.53	654.72
>= 75	23 (11.2)	11 (10.2)	34 (10.9)	178.00	34.50	212.50
TOTAL	205 (100.0)	108 (100.0)	313 (100.0)	1485.40	616.77	2102.18

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214677/stats/iss/prog/tables/issIMRMP/rt-ex-pt-age.sas 02JUN2015:06:28:26

Table 2-4: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209067)

Treatment group: NIVOLUMAB

Race	Persons (%) Male N = 200	Persons (%) Female N = 113	Persons (%) Total N = 313	Person Time of Exposure (Months) (1) Male N = 200	Person Time of Exposure (Months) (1) Female N = 113	Person Time of Exposure (Months) (1) Total N = 313
WHITE	194 (97.0)	111 (98.2)	305 (97.4)	1727.44	816.36	2543.80
BLACK OR AFRICAN AMERICAN	0	0	0	0	0	0
ASIAN	1 (0.5)	1 (0.9)	2 (0.6)	11.79	1.97	13.77
OTHER	5 (2.5)	1 (0.9)	6 (1.9)	41.49	10.61	52.11
TOTAL	200 (100.0)	113 (100.0)	313 (100.0)	1780.73	828.94	2609.68

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-age.sas 02JUN2015:06:31:26

Study CA209069 (Melanoma)

Table 2-5: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209069)

Duration of Exposure	Nivolumab + Ipilimumab N = 94 Persons (%)	Nivolumab + Ipilimumab N = 94 Person Time of Exposure (1) (Month)
0 - < 1 MONTH	5 (5.3)	
0 - < 2 MONTHS	25 (26.6)	
0 - < 3 MONTHS	35 (37.2)	
0 - < 4 MONTHS	55 (58.5)	
0 - < 5 MONTHS	59 (62.8)	
0 - < 6 MONTHS	64 (68.1)	
0 - <= 10.2 MONTHS (A)	94 (100.0)	407.39

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Subjects were to be treated with nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-durtrt.sas 02JUN2015:06:29:00

Table 2-6: Cumulative Dose of Nivolumab and Ipilimumab; Nivolumab Treated Subjects (CA209069)

	Nivolumab + Ipilimumab N = 94	
	Nivolumab	Ipilimumab
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	6.4 (5.48)	3.2 (1.09)
MEDIAN	4.0	4.0
MIN - MAX	1 - 20	1 - 4
CUMULATIVE DOSE (MG) / SUBJECT		
MEAN (SD)	1060.8 (1294.70)	801.2 (330.91)
MEDIAN	315.6	813.9
MIN - MAX	62 - 6000	187 - 1928
CUMULATIVE DOSE (MG/KG) / SUBJECT		
MEAN (SD)	12.95 (15.083)	9.51 (3.282)
MEDIAN	4.00	12.00
MIN - MAX	1.0 - 52.0	3.0 - 12.0

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-cumdos.sas 02JUN2015:06:30:00

Table 2-7: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects (CA209069)

Treatment group: NIVOLUMAB+IPILIMUMAB

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 63	Female N = 31	Total N = 94	Male N = 63	Female N = 31	Total N = 94
>= 18 AND < 65	31 (49.2)	17 (54.8)	48 (51.1)	155.27	58.61	213.88
>= 65 AND < 75	23 (36.5)	11 (35.5)	34 (36.2)	110.00	39.69	149.68
>= 75	9 (14.3)	3 (9.7)	12 (12.8)	29.77	14.06	43.83
TOTAL	63 (100.0)	31 (100.0)	94 (100.0)	295.03	112.36	407.39

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-age.sas 02JUN2015:06:29:21

Table 2-8: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209069)

Treatment group: NIVOLUMAB+IPILIMUMAB

Race	Persons (%) Male N = 63	Persons (%) Female N = 31	Persons (%) Total N = 94	Person Time of Exposure (Months) (1) Male N = 63	Person Time of Exposure (Months) (1) Female N = 31	Person Time of Exposure (Months) (1) Total N = 94
WHITE	63 (100.0)	28 (90.3)	91 (96.8)	295.03	94.29	389.32
BLACK OR AFRICAN AMERICAN	0	0	0	0	0	0
ASIAN	0	1 (3.2)	1 (1.1)	0	2.53	2.53
OTHER	0	2 (6.5)	2 (2.1)	0	15.54	15.54
TOTAL	63 (100.0)	31 (100.0)	94 (100.0)	295.03	112.36	407.39

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-age.sas 02JUN2015:06:31:39

Study CA2090004 (Melanoma)

Table 2-9: Clinical Exposure in Person Time; Nivolumab Treated Subjects from Cohort 8 (CA209004)

Duration of Exposure	Nivolumab + Ipilimumab N = 41 Persons (%)	Nivolumab + Ipilimumab N = 41 Person Time of Exposure (1) (Month)
0 - < 1 MONTH	1 (2.4)	
0 - < 2 MONTHS	5 (12.2)	
0 - < 3 MONTHS	9 (22.0)	
0 - < 4 MONTHS	13 (31.7)	
0 - < 5 MONTHS	16 (39.0)	
0 - < 6 MONTHS	19 (46.3)	
0 - <= 11.5 MONTHS (A)	41 (100.0)	258.60

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Subjects were to be treated with nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-durtrt.sas 02JUN2015:06:29:20

Table 2-10: Cumulative Dose of Nivolumab and Ipilimumab; Nivolumab Treated Subjects from Cohort 8 (CA209004)

	Nivolumab + Ipilimumab N = 41	
	Nivolumab	Ipilimumab
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	9.6 (6.79)	3.1 (1.04)
MEDIAN	8.0	4.0
MIN - MAX	1 - 22	1 - 4
CUMULATIVE DOSE (MG) / SUBJECT		
MEAN (SD)	1725.0 (1606.22)	731.5 (300.94)
MEDIAN	1302.8	760.0
MIN - MAX	70 - 6340	210 - 1360
CUMULATIVE DOSE (MG/KG) / SUBJECT		
MEAN (SD)	22.42 (19.455)	9.41 (3.101)
MEDIAN	16.75	11.60
MIN - MAX	1.0 - 60.9	3.0 - 12.3

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-cumdos.sas 02JUN2015:06:30:13

Table 2-11: Clinical Exposure in Person Time by Age Group and Gender; Nivolumab Treated Subjects from Cohort 8 (CA209004)

Treatment group: NIVOLUMAB+IPILIMUMAB

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 18	Female N = 23	Total N = 41	Male N = 18	Female N = 23	Total N = 41
>= 18 AND < 65	13 (72.2)	19 (82.6)	32 (78.0)	78.16	113.97	192.13
>= 65 AND < 75	4 (22.2)	3 (13.0)	7 (17.1)	36.47	15.18	51.65
>= 75	1 (5.6)	1 (4.3)	2 (4.9)	5.59	9.23	14.82
TOTAL	18 (100.0)	23 (100.0)	41 (100.0)	120.21	138.38	258.60

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-age.sas 02JUN2015:06:29:53

Table 2-12: Clinical Exposure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects from Cohort 8 (CA209004)

Treatment group: NIVOLUMAB+IPILIMUMAB

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 18	Female N = 23	Total N = 41	Male N = 18	Female N = 23	Total N = 41
WHITE	17 (94.4)	20 (87.0)	37 (90.2)	117.88	108.22	226.10
BLACK OR AFRICAN AMERICAN	0	0	0	0	0	0
ASIAN	0	1 (4.3)	1 (2.4)	0	9.23	9.23
OTHER	1 (5.6)	2 (8.7)	3 (7.3)	2.33	20.93	23.26
TOTAL	18 (100.0)	23 (100.0)	41 (100.0)	120.21	138.38	258.60

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms214677/stats/iss/prog/tables/issLMRMP/rt-ex-pt-age.sas 02JUN2015:06:31:48

Study CA209214 (RCC)

Table 2-13: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209214)

Duration of Exposure	Nivolumab 3 + Ipilimumab 1 N = 547	
	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	7 (1.3)	
0 - < 2 MONTHS	60 (11.0)	
0 - < 3 MONTHS	110 (20.1)	
0 - < 4 MONTHS	170 (31.1)	
0 - < 5 MONTHS	193 (35.3)	
0 - < 6 MONTHS	218 (39.9)	
0 - <= 30.7 MONTHS (A)	547 (100.0)	6242.40

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure.
Subjects were to be treated with nivolumab 3 mg/kg every 3 weeks for 4 doses followed by every 2 weeks.
Program Source: /projects/bms211276/stats/rmp/prog/tables/rt-ex-ptdurtrt.sas 05SEP2017:04:13:18

Table 2-14: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209214)

	Nivolumab 3 + Ipilimumab 1 N = 547	
	Nivolumab	Ipilimumab
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	20.9 (18.69)	3.6 (0.81)
MEDIAN	14.0	4.0
MIN - MAX	1 - 63	1 - 4
CUMULATIVE DOSE (MG) / SUBJECT		
MEAN (SD)	5213.9 (4913.22)	298.0 (96.06)
MEDIAN	3325.0	308.0
MIN - MAX	164 - 20910	55 - 612
CUMULATIVE DOSE (MG/KG) / SUBJECT		
MEAN (SD)	62.39 (55.779)	3.63 (0.817)
MEDIAN	41.03	4.00
MIN - MAX	2.9 - 188.3	1.0 - 6.0

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms211276/stats/rmp/prog/tables/rt-ex-cumdos.sas 05SEP2017:04:13:23

Table 2-15: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209214)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 411	Female N = 136	Total N = 547	Male N = 411	Female N = 136	Total N = 547
>= 18 AND < 65	251 (61.1)	87 (64.0)	338 (61.8)	3035.89	1050.71	4086.60
>= 65 AND < 75	126 (30.7)	37 (27.2)	163 (29.8)	1346.56	333.44	1680.00
>= 75	34 (8.3)	12 (8.8)	46 (8.4)	342.74	133.06	475.79
TOTAL	411 (100.0)	136 (100.0)	547 (100.0)	4725.19	1517.21	6242.40

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211276/stats/rmp/prog/tables/rt-ex-ptage-ptrace.sas 05SEP2017:04:13:36

Table 2-16: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209214)

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 411	Female N = 136	Total N = 547	Male N = 411	Female N = 136	Total N = 547
WHITE	361 (87.8)	122 (89.7)	483 (88.3)	4165.98	1357.21	5523.19
BLACK OR AFRICAN AMERICAN	5 (1.2)	2 (1.5)	7 (1.3)	72.34	31.21	103.56
ASIAN	39 (9.5)	7 (5.1)	46 (8.4)	418.33	69.59	487.92
OTHER	5 (1.2)	5 (3.7)	10 (1.8)	67.61	59.20	126.82
NOT REPORTED	1 (0.2)	0	1 (0.2)	0.92	0	0.92
TOTAL	411 (100.0)	136 (100.0)	547 (100.0)	4725.19	1517.21	6242.40

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211276/stats/rmp/prog/tables/rt-ex-ptage-ptrace.sas 05SEP2017:04:13:44

Study CA209214 (RCC)

Table 2-17: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209016)

	Nivolumab 3 + Ipilimumab 1 N = 47	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	0	
0 - < 2 MONTHS	7 (14.9)	
0 - < 3 MONTHS	10 (21.3)	
0 - < 4 MONTHS	17 (36.2)	
0 - < 5 MONTHS	20 (42.6)	
0 - < 6 MONTHS	21 (44.7)	
0 - <= 35.0 MONTHS (A)	47 (100.0)	520.94

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure.
Program Source: /projects/bms217252/stats/renal_1L_EU_RMP_SMPC/prog/tables/rt-ex-ptdurtrt.sas 08FEB2017:08:30:21

Table 2-18: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209016)

	Nivolumab 3 + Ipilimumab 1 N = 47	
	Nivolumab	Ipilimumab
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	18.6 (20.34)	3.5 (0.98)
MEDIAN	10.0	4.0
MIN - MAX	1 - 71	1 - 4
CUMULATIVE DOSE (MG) / SUBJECT		
MEAN (SD)	5458.8 (7037.62)	316.7 (127.81)
MEDIAN	2542.5	336.8
MIN - MAX	256 - 33731	56 - 623
CUMULATIVE DOSE (MG/KG) / SUBJECT		
MEAN (SD)	55.86 (61.140)	3.50 (0.979)
MEDIAN	29.75	4.00
MIN - MAX	2.9 - 213.1	1.0 - 4.1

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /projects/bms217252/stats/renal_1L_EU_RMP_SMPC/prog/tables/rt-ex-cumdos.sas 08FEB2017:08:16:08

Table 2-19: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209016)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 33	Female N = 14	Total N = 47	Male N = 33	Female N = 14	Total N = 47
>= 18 AND < 65	29 (87.9)	14 (100.0)	43 (91.5)	283.70	202.87	486.57
>= 65 AND < 75	4 (12.1)	0	4 (8.5)	34.37	0	34.37
>= 75	0	0	0	0	0	0
TOTAL	33 (100.0)	14 (100.0)	47 (100.0)	318.06	202.87	520.94

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms217252/stats/renal_1L_EU_RMP_SMPC/prog/tables/rt-ex-ptage-ptrace.sas 08FEB2017:08:21:51

Table 2-20: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209016)

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 33	Female N = 14	Total N = 47	Male N = 33	Female N = 14	Total N = 47
WHITE	31 (93.9)	13 (92.9)	44 (93.6)	299.93	200.44	500.37
BLACK OR AFRICAN AMERICAN	0	1 (7.1)	1 (2.1)	0	2.43	2.43
ASIAN	2 (6.1)	0	2 (4.3)	18.14	0	18.14
OTHER	0	0	0	0	0	0
TOTAL	33 (100.0)	14 (100.0)	47 (100.0)	318.06	202.87	520.94

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms217252/stats/renal_1L_EU_RMP_SMPC/prog/tables/rt-ex-ptage-ptrace.sas 08FEB2017:08:27:17

Study CA209743 (MPM)

Table 2-21: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) CA209743

	Nivolumab + Ipilimumab N = 300	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	7 (2.3)	
0 - < 2 MONTHS	55 (18.3)	
0 - < 3 MONTHS	75 (25.0)	
0 - < 4 MONTHS	100 (33.3)	
0 - < 5 MONTHS	126 (42.0)	
0 - < 6 MONTHS	133 (44.3)	
0 - < 12 MONTHS	222 (74.0)	
0 - < 24 MONTHS	279 (93.0)	
0 - <= 27.2 MONTHS (A)	300 (100.0)	2643.32

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(a) max clinical exposure
Subjects were to be treated with Nivolumab 3 mg/kg every 2 weeks + Ipilimumab 1 mg/kg every 6 weeks.
Program Source: /opt/zfs001/prd/bms214682/stats/scs_smpc_rmp_743/prog/tables/rt-ex-pt-durtrt.sas 20MAY2020:08:51:54

Table 2-22: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) CA209743

	Nivolumab + Ipilimumab	
	Nivolumab N = 300	Ipilimumab N = 300
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	16.5 (14.5)	5.4 (4.6)
MEDIAN	12.0	4.0
MIN - MAX	1 - 55	1 - 19
CUMULATIVE DOSE (1) / SUBJECT		
MEAN (SD)	49.12 (43.07)	5.43 (4.67)
MEDIAN	35.93	4.00
MIN - MAX	2.9 - 165.4	1.0 - 21.0

(1) Dose units: Nivolumab in mg/kg; Ipilimumab in mg/kg
Cumulative dose (in mg/kg, mg/kg) is sum of the doses (in mg/kg, mg/kg) administered to a subject during the treatment period.
Program Source: /opt/zfs001/prd/bms214682/stats/scs_smpc_rmp_743/prog/tables/rt-ex-cumdos.sas 20MAY2020:08:51:33

Table 2-23: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) CA209743

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 232	Female N = 68	Total N = 300	Male N = 232	Female N = 68	Total N = 300
>= 18 AND < 65	52 (22.4)	19 (27.9)	71 (23.7)	435.58	144.13	579.71
>= 65 AND < 75	116 (50.0)	35 (51.5)	151 (50.3)	1019.20	430.98	1450.18
>= 75 AND < 85	61 (26.3)	14 (20.6)	75 (25.0)	503.26	85.82	589.08
>= 85	3 (1.3)	0	3 (1.0)	24.34	0	24.34
TOTAL	232 (100.0)	68 (100.0)	300 (100.0)	1982.39	660.93	2643.32

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms214682/stats/scs_smpc_rmp_743/prog/tables/rt-ex-pt-age.sas 20MAY2020:08:51:40

Table 2-24: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) CA209743

	Persons (%)			Person Time of Exposure (Months) (1)		
Race Category	Male N = 232	Female N = 68	Total N = 300	Male N = 232	Female N = 68	Total N = 300
WHITE	201 (86.6)	62 (91.2)	263 (87.7)	1689.72	613.75	2303.47
BLACK OR AFRICAN AMERICAN	0	0	0	0	0	0
ASIAN	21 (9.1)	5 (7.4)	26 (8.7)	166.14	40.71	206.85
AMERICAN INDIAN OR ALASKA NATIVE	2 (0.9)	0	2 (0.7)	28.45	0	28.45
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	0	0	0
OTHER	8 (3.4)	1 (1.5)	9 (3.0)	98.07	6.47	104.54
TOTAL	232 (100.0)	68 (100.0)	300 (100.0)	1982.39	660.93	2643.32

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms214682/stats/scs_smpc_rmp_743/prog/tables/rt-ex-pt-race.sas 20MAY2020:08:53:20

Study CA209142 (CRC)

Table 2-25: Clinical Exposure in Person Time; All dMMR/MSI-H Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209142)

	Nivolumab with Ipilimumab N = 119	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	1 (0.8)	
0 - < 2 MONTHS	11 (9.2)	
0 - < 3 MONTHS	15 (12.6)	
0 - < 4 MONTHS	27 (22.7)	
0 - < 5 MONTHS	29 (24.4)	
0 - < 6 MONTHS	32 (26.9)	
0 - <= 44.1 MONTHS (a)	119 (100.0)	2435.75

(1) Sum of subjects' exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(a) Max clinical exposure.
Program Source: /opt/zfs001/prd/bms211280/stats/EBR_214_142_016/prog/tables/rt-ex-c2ptdurtrt-sas.sas 22APR2020:10:43:50

Table 2-26: Cumulative Dose of Nivolumab and Ipilimumab: All dMMR/MSI-H Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) CA209142

	Nivolumab with Ipilimumab	
	Nivolumab N = 119	Ipilimumab N = 119
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	40.3 (28.62)	3.7 (0.81)
MEDIAN	51.0	4.0
MIN - MAX	1 - 93	1 - 4
CUMULATIVE DOSE (MG) / SUBJECT		
MEAN (SD)	9396.8 (7187.26)	270.2 (87.93)
MEDIAN	10796.3	280.0
MIN - MAX	170 - 26485	58 - 496
CUMULATIVE DOSE (MG/KG) / SUBJECT		
MEAN (SD)	119.39 (84.780)	3.70 (0.815)
MEDIAN	147.03	4.00
MIN - MAX	3.0 - 278.9	1.0 - 4.2

Cumulative dose (in mg/kg) is sum of the doses (in mg/kg) administered to a subject during the treatment period.
Program Source: /opt/zfs001/prd/bms211280/stats/EBR_214_142_016/prog/tables/rt-ex-c2cumdos-sas.sas 22APR2020:10:44:50

Table 2-27: Clinical Exposure in Person Time by Age Group and Gender: All dMMR/MSI-H Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209142)

Treatment Group: Nivolumab with Ipilimumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 70	Female N = 49	Total N = 119	Male N = 70	Female N = 49	Total N = 119
>= 18 AND < 65	52 (74.3)	29 (59.2)	81 (68.1)	1061.45	609.74	1671.20
>= 65 AND < 75	13 (18.6)	14 (28.6)	27 (22.7)	260.63	351.70	612.34
>= 75 AND < 85	4 (5.7)	6 (12.2)	10 (8.4)	68.27	80.95	149.22
>= 85	1 (1.4)	0	1 (0.8)	2.99	0	2.99
TOTAL	70 (100.0)	49 (100.0)	119 (100.0)	1393.35	1042.40	2435.75

(1) Sum of subjects' exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/EBR_214_142_016/prog/tables/rt-ex-c2pt-sas.sas 22APR2020:10:45:49

Table 2-28: Clinical Exposure in Person Time by Racial Origin and Gender: All dMMR/MSI-H Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209142)

Treatment Group: Nivolumab with Ipilimumab

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 70	Female N = 49	Total N = 119	Male N = 70	Female N = 49	Total N = 119
WHITE	65 (92.9)	45 (91.8)	110 (92.4)	1298.92	932.17	2231.10
BLACK OR AFRICAN AMERICAN	1 (1.4)	1 (2.0)	2 (1.7)	19.42	3.09	22.51
ASIAN	1 (1.4)	2 (4.1)	3 (2.5)	3.09	64.82	67.91
OTHER	3 (4.3)	1 (2.0)	4 (3.4)	71.92	42.32	114.23
NOT REPORTED	0	0	0	0	0	0
TOTAL	70 (100.0)	49 (100.0)	119 (100.0)	1393.35	1042.40	2435.75

(1) Sum of subjects' exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/EBR_214_142_016/prog/tables/rt-ex-c2pt-sas.sas 22APR2020:10:46:05

Study CA209648 (OSCC)

Table 2-29: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209648)

	Nivo + Ipi N = 322		Nivo + Chemo N = 310	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	14 (4.3)		3 (1.0)	
0 - < 2 MONTHS	88 (27.3)		23 (7.4)	
0 - < 3 MONTHS	126 (39.1)		54 (17.4)	
0 - < 4 MONTHS	169 (52.5)		90 (29.0)	
0 - < 5 MONTHS	195 (60.6)		115 (37.1)	
0 - < 6 MONTHS	210 (65.2)		133 (42.9)	
0 - <= 31.5 MONTHS (A)	322 (100.0)	2040.57	310 (100.0)	2570.81

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Subjects treated with Nivo + Ipi received Nivolumab 3 mg/kg every 2 weeks.
Subjects treated with Nivo + Chemo received Nivolumab 240 mg every 2 weeks.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-pt-durtrt.sas 30APR2021:08:58:49

Table 2-30: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209648)

	CA209648		Nivo + Ipi Pooled	
	Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 322		Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 622	
	Nivolumab N = 322	Ipilimumab N = 322	Nivolumab N = 622	Ipilimumab N = 622
NUMBER OF DOSES RECEIVED / SUBJECT				
MEAN (SD)	11.8 (12.9)	4.3 (4.3)	14.0 (13.9)	4.8 (4.5)
MEDIAN	6.0	3.0	9.0	3.0
MIN - MAX	1 - 52	1 - 18	1 - 55	1 - 19
CUMULATIVE DOSE (MG) / SUBJECT				
MEAN (SD)	2150.2 (2534.2)	258.4 (285.1)	2861.4 (3037.7)	324.2 (323.6)
MEDIAN	1086.5	144.0	1778.8	209.0
MIN - MAX	120 - 13535	32 - 1493	120 - 14943	32 - 1666
CUMULATIVE DOSE (MG/KG) / SUBJECT				
MEAN (SD)	35.40 (38.16)	4.26 (4.28)	42.01 (41.15)	4.82 (4.51)
MEDIAN	18.86	2.88	26.83	3.06
MIN - MAX	2.9 - 155.0	0.9 - 18.1	2.9 - 165.4	0.9 - 21.0

Cumulative dose is sum of the doses administered to a subject during the treatment period.
Nivo + Ipi group consists of Nivo + Ipi treatment group from studies CA209743 and CA209648.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-cumdos.sas 17MAY2021:08:17:20

Table 2-31: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209648)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 267	Female N = 55	Total N = 322	Male N = 267	Female N = 55	Total N = 322
>= 18 AND < 65	148 (55.4)	34 (61.8)	182 (56.5)	962.46	156.16	1118.62
>= 65 AND < 75	96 (36.0)	20 (36.4)	116 (36.0)	585.30	135.56	720.85
>= 75 AND < 85	23 (8.6)	1 (1.8)	24 (7.5)	196.37	4.73	201.10
>= 85	0	0	0	0	0	0
TOTAL	267 (100.0)	55 (100.0)	322 (100.0)	1744.13	296.44	2040.57

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-pt-age.sas 30APR2021:08:58:58

Table 2-32: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) (CA209648)

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 267	Female N = 55	Total N = 322	Male N = 267	Female N = 55	Total N = 322
WHITE	50 (18.7)	27 (49.1)	77 (23.9)	385.84	115.58	501.42
BLACK OR AFRICAN AMERICAN	4 (1.5)	0	4 (1.2)	26.58	0	26.58
AMERICAN INDIAN OR ALASKA NATIVE	0	1 (1.8)	1 (0.3)	0	2.46	2.46
ASIAN INDIAN	1 (0.4)	0	1 (0.3)	3.32	0	3.32
CHINESE	67 (25.1)	4 (7.3)	71 (22.0)	405.78	10.78	416.56
JAPANESE	110 (41.2)	20 (36.4)	130 (40.4)	688.10	126.29	814.39
ASIAN OTHER	28 (10.5)	0	28 (8.7)	191.41	0	191.41
OTHER	7 (2.6)	3 (5.5)	10 (3.1)	43.10	41.33	84.44
TOTAL	267 (100.0)	55 (100.0)	322 (100.0)	1744.13	296.44	2040.57

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-pt-race.sas 30APR2021:08:58:54

Study CA2098HW (CRC)

Table 2-33: Clinical Exposure in Person Time; All First Line Nivolumab and Ipilimumab Treated Subjects in CA2098HW

	Nivo + Ipi: 1L N = 200	
Duration of Exposure	Persons (%)	Person Time of Exposure (Months) (1)
0 - < 1 MONTH	2 (1.0)	
0 - < 2 MONTHS	17 (8.5)	
0 - < 3 MONTHS	30 (15.0)	
0 - < 4 MONTHS	49 (24.5)	
0 - < 5 MONTHS	53 (26.5)	
0 - < 6 MONTHS	60 (30.0)	
0 - <= 33.3 MONTHS (A)	200 (100.0)	2823.16

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Program Source: /projects/bms211280/stats/smpc_scs_rmp8hw/prog/tables/rt-ex-pt-durtrt.sas 09JAN2024:03:14:34

Table 2-34: Cumulative Dose Summary; All First Line Nivolumab and Ipilimumab Treated Subjects in CA2098HW

	Nivo + Ipi: 1L N = 200	
	Nivo (mg) N = 200	Ipi (mg/kg) N = 200
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	15.5 (9.89)	3.6 (0.86)
MEDIAN	16.0	4.0
MIN - MAX	1 - 37	1 - 4
CUMULATIVE DOSE (1) / SUBJECT		
MEAN (SD)	6568.800 (4647.4436)	3.629 (0.9067)
MEDIAN	6720.000	3.994
MIN - MAX	240.00 - 16800.00	0.98 - 7.53

Cumulative dose is sum of the doses administered to a subject during the treatment period.
(1) Dose units: Nivolumab in mg, Ipilimumab in mg/kg.
Program Source: /projects/bms211280/stats/smpc_scs_rmp8hw/prog/tables/rt-ex-cumdos-8hw.sas 09JAN2024:03:15:28

Table 2-35: Clinical Exposure in Person Time by Age Group and Gender; All First Line Nivolumab and Ipilimumab Treated Subjects in CA2098HW

Treatment Group: Nivo + Ipi: 1L

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 94	Female N = 106	Total N = 200	Male N = 94	Female N = 106	Total N = 200
< 65	66 (70.2)	49 (46.2)	115 (57.5)	1015.16	767.93	1783.10
>= 65 AND < 75	23 (24.5)	25 (23.6)	48 (24.0)	269.08	287.80	556.88
>= 75 AND < 85	5 (5.3)	30 (28.3)	35 (17.5)	38.24	402.14	440.38
>= 85	0	2 (1.9)	2 (1.0)	0	42.81	42.81
TOTAL	94 (100.0)	106 (100.0)	200 (100.0)	1322.48	1500.68	2823.16

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211280/stats/smpc_scs_rmp8hw/prog/tables/rt-ex-pt-age.sas 09JAN2024:03:15:06

Table 2-36: Clinical Exposure in Person Time by Racial Origin and Gender; All First Line Nivolumab and Ipilimumab Treated Subjects in CA2098HW

Treatment Group: Nivo + Ipi: 1L

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 94	Female N = 106	Total N = 200	Male N = 94	Female N = 106	Total N = 200
WHITE	81 (86.2)	94 (88.7)	175 (87.5)	1090.73	1337.92	2428.65
BLACK OR AFRICAN AMERICAN	0	1 (0.9)	1 (0.5)	0	7.56	7.56
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (1.1)	0	1 (0.5)	24.64	0	24.64
ASIAN	10 (10.6)	9 (8.5)	19 (9.5)	162.37	136.94	299.30
CHINESE	3 (3.2)	3 (2.8)	6 (3.0)	45.57	34.43	80.00
JAPANESE	7 (7.4)	6 (5.7)	13 (6.5)	116.80	102.51	219.30
OTHER	2 (2.1)	2 (1.9)	4 (2.0)	44.75	18.27	63.01
TOTAL	94 (100.0)	106 (100.0)	200 (100.0)	1322.48	1500.68	2823.16

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211280/stats/smpc_scs_rmp8hw/prog/tables/rt-ex-pt-race.sas 09JAN2024:03:14:47

Study CA2099DW (HCC)

Table 2-37: Clinical Exposure in Person Time; All Nivolumab and Ipilimumab Treated Subjects in CA2099DW

Duration of Exposure	Nivo + Ipi N = 332 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	2 (0.6)	
0 - < 2 MONTHS	67 (20.2)	
0 - < 3 MONTHS	110 (33.1)	
0 - < 4 MONTHS	136 (41.0)	
0 - < 5 MONTHS	158 (47.6)	
0 - < 6 MONTHS	173 (52.1)	
0 - < 12 MONTHS	222 (66.9)	
0 - < 18 MONTHS	256 (77.1)	
0 - < 24 MONTHS	270 (81.3)	
0 - <= 25.4 MONTHS (A)	332 (100.0)	3210.38

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment,
and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Program Source: /projects/bms211280/stats/smpc_scs_rmp9dw/prog/tables/rt-ex-pt-durtrt.sas 10APR2024:04:31:16

Table 2-38: Cumulative Dose; All Nivolumab and Ipilimumab Treated Subjects in CA2099DW

	Nivo + Ipi N = 332	
	Nivolumab N = 332	Ipilimumab N = 332
NUMBER OF DOSES RECEIVED		
MEAN (SD)	10.5 (9.41)	3.3 (1.02)
MEDIAN	6.0	4.0
MIN - MAX	1 - 28	1 - 4
CUMULATIVE DOSE (MG/KG)		
MEAN (SD)	3.31 (1.084)	9.81 (3.096)
MEDIAN	3.97	11.88
MIN - MAX	1.0 - 10.0	3.0 - 12.9
CUMULATIVE DOSE (MG)		
MEAN (SD)	5750.5 (4109.83)	
MEDIAN	4800.0	
MIN - MAX	65 - 11520	

Cumulative dose: the sum of doses administered to a subject during the flat-dose (mg) or weight-based dose (mg/kg) treatment period.
Flat (mg) doses of Nivolumab (only in CA2099DW) were not re-calculated to total doses in mg/kg, therefore the mg/kg summary for Nivolumab apply only to weight-based period.
Program Source: /projects/bms211280/stats/smpc_scs_rmp9dw/prog/tables/rt-ex-cumdos.sas 24APR2024:04:02:09

Table 2-39: Clinical Exposure in Person Time by Age Group and Sex; All Nivolumab and Ipilimumab Treated Subjects in CA2099DW

Treatment Group: Nivo + Ipi

Age Category	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 269	Female N = 63	Total N = 332	Male N = 269	Female N = 63	Total N = 332
>= 18 AND < 65	127 (47.2)	35 (55.6)	162 (48.8)	1316.30	313.72	1630.03
>= 65 AND < 75	106 (39.4)	18 (28.6)	124 (37.3)	914.33	178.96	1093.29
>= 75 AND < 85	33 (12.3)	9 (14.3)	42 (12.7)	372.11	102.28	474.38
>= 85	3 (1.1)	1 (1.6)	4 (1.2)	11.66	1.02	12.68
TOTAL	269 (100.0)	63 (100.0)	332 (100.0)	2614.41	595.98	3210.38

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211280/stats/smpc_scs_rmp9dw/prog/tables/rt-ex-ptage.sas 10APR2024:04:09:37

Table 2-40: Clinical Exposure in Person Time by Race and Sex; All Nivolumab and Ipilimumab Treated Subjects in CA2099DW

Treatment Group: Nivo + Ipi

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 269	Female N = 63	Total N = 332	Male N = 269	Female N = 63	Total N = 332
WHITE	147 (54.6)	30 (47.6)	177 (53.3)	1406.36	237.80	1644.16
BLACK OR AFRICAN AMERICAN	8 (3.0)	3 (4.8)	11 (3.3)	88.94	53.49	142.42
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.4)	0	1 (0.3)	24.84	0	24.84
ASIAN	109 (40.5)	30 (47.6)	139 (41.9)	1040.26	304.69	1344.95
ASIAN INDIAN	2 (0.7)	1 (1.6)	3 (0.9)	32.62	1.02	33.64
CHINESE	59 (21.9)	17 (27.0)	76 (22.9)	610.07	252.81	862.88
JAPANESE	21 (7.8)	3 (4.8)	24 (7.2)	186.55	5.29	191.84
ASIAN OTHER	27 (10.0)	9 (14.3)	36 (10.8)	211.02	45.57	256.59
OTHER	4 (1.5)	0	4 (1.2)	54.01	0	54.01
TOTAL	269 (100.0)	63 (100.0)	332 (100.0)	2614.41	595.98	3210.38

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment + 30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /projects/bms211280/stats/smpc_scs_rmp9dw/prog/tables/rt-ex-pt.sas 10APR2024:04:09:26

3 NIVOLUMAB COMBINED WITH IPILIMUMAB AND CHEMOTHERAPY

For nivolumab plus ipilimumab in combination with chemotherapy, individual clinical trial exposure analyses are presented in the following tables:

Table 3-1 - Table 3-4 for CA2099LA (NSCLC)

Nivolumab (360 mg Q3W) plus Ipilimumab (1 mg/kg Q6W) in Combination with 2 Cycles of Platinum Doublet Chemotherapy: CA2099LA

Table 3-1: Clinical Exposure in Person Time: Subjects Treated with Nivolumab + Ipilimumab + Platinum Doublet Chemotherapy, CA2099LA, Global Population

	Nivolumab + Ipilimumab + Chemotherapy N = 358	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	9 (2.5)	
0 - < 2 MONTHS	35 (9.8)	
0 - < 3 MONTHS	64 (17.9)	
0 - < 4 MONTHS	104 (29.1)	
0 - < 5 MONTHS	128 (35.8)	
0 - < 6 MONTHS	162 (45.3)	
0 - < 12 MONTHS	303 (84.6)	
0 - <= 19.8 MONTHS (A)	358 (100.0)	2644.90

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(a) max clinical exposure
Subjects were to be treated with Nivolumab 360 mg Q3W + Ipilimumab 1 mg/kg Q6W + 2 cycles platinum doublet chemotherapy
Program Source: /opt/zfs001/prd/bms214682/stats/rmp_9la_568/prog/tables/rt-ex-pt-durtrt.sas 02DEC2019:17:11:33

Table 3-2: Cumulative Dose of Nivolumab, Ipilimumab and Chemotherapy: Subjects Treated with Nivolumab + Ipilimumab + Platinum Doublet Chemotherapy, CA2099LA, Global Population.

	Nivolumab + Ipilimumab + Chemotherapy		
	Nivolumab N = 358	Ipilimumab N = 358	Paclitaxel N = 116
NUMBER OF DOSES RECEIVED / SUBJECT			
MEAN (SD)	10.0 (6.5)	5.2 (3.3)	1.9 (0.3)
MEDIAN	9.0	4.0	2.0
MIN - MAX	1 - 28	1 - 14	1 - 2
CUMULATIVE DOSE (1) / SUBJECT			
MEAN (SD)	3587.35 (2327.02)	5.15 (3.26)	374.39 (73.09)
MEDIAN	3240.00	4.24	396.17
MIN - MAX	360.0 - 10080.0	0.1 - 14.1	74.9 - 766.0

	Nivolumab + Ipilimumab + Chemotherapy		
	Cisplatin N = 74	Carboplatin N = 284	Pemetrexed N = 244
NUMBER OF DOSES RECEIVED / SUBJECT			
MEAN (SD)	1.9 (0.3)	1.9 (0.3)	1.9 (0.3)
MEDIAN	2.0	2.0	2.0
MIN - MAX	1 - 2	1 - 2	1 - 2
CUMULATIVE DOSE (1) / SUBJECT			
MEAN (SD)	156.03 (85.45)	10.37 (2.06)	943.79 (145.17)
MEDIAN	149.07	10.07	995.02
MIN - MAX	74.6 - 697.9	1.2 - 17.6	145.9 - 1047.1

(1) Dose units: Nivolumab in mg; Ipilimumab in mg/kg, Paclitaxel, Cisplatin, and Pemetrexed in mg/ m^2, and Carboplatin in AUC. Cumulative dose (in mg, mg/kg, mg/ m^2 or AUC) is sum of the doses (in mg, mg/kg, mg/ m^2 or AUC) administered to a subject during the treatment period.
Program Source: /opt/zfs001/prd/bms214682/stats/rmp_9la_568/prog/tables/rt-ex-cumdos.sas 02DEC2019:17:11:35

Table 3-3: Clinical Exposure in Person Time by Age Group and Gender: Subjects Treated with Nivolumab + Ipilimumab + Platinum Doublet Chemotherapy, CA2099LA, Global Population.

Treatment Group: Nivolumab + Ipilimumab + Chemotherapy

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 251	Female N = 107	Total N = 358	Male N = 251	Female N = 107	Total N = 358
>= 18 AND < 65	112 (44.6)	62 (57.9)	174 (48.6)	872.38	453.98	1326.36
>= 65 AND < 75	110 (43.8)	37 (34.6)	147 (41.1)	811.37	307.19	1118.55
>= 75 AND < 85	29 (11.6)	8 (7.5)	37 (10.3)	132.70	67.29	199.98
>= 85	0	0	0	0	0	0
TOTAL	251 (100.0)	107 (100.0)	358 (100.0)	1816.44	828.45	2644.90

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms214682/stats/rmp_9la_568/prog/tables/rt-ex-pt-age.sas 02DEC2019:17:11:31

Table 3-4: Clinical Exposure in Person Time by Racial Origin and Gender: Subjects Treated with Nivolumab + Ipilimumab + Platinum Doublet Chemotherapy, CA2099LA, Global Population.

Treatment Group: Nivolumab + Ipilimumab + Chemotherapy

	Persons (%)			Person Time of Exposure (Months) (1)		
Race Category	Male N = 251	Female N = 107	Total N = 358	Male N = 251	Female N = 107	Total N = 358
WHITE	219 (87.3)	100 (93.5)	319 (89.1)	1628.85	765.24	2394.09
BLACK OR AFRICAN AMERICAN	2 (0.8)	3 (2.8)	5 (1.4)	9.17	35.25	44.42
ASIAN	27 (10.8)	3 (2.8)	30 (8.4)	170.48	16.16	186.64
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.4)	0	1 (0.3)	3.12	0	3.12
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	0	0	0
OTHER	2 (0.8)	1 (0.9)	3 (0.8)	4.83	11.79	16.62
TOTAL	251 (100.0)	107 (100.0)	358 (100.0)	1816.44	828.45	2644.90

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms214682/stats/rmp_9la_568/prog/tables/rt-ex-pt-race.sas 02DEC2019:17:11:29

4 NIVOLUMAB COMBINED WITH CABOZANTINIB

For nivolumab in combination therapy with cabozantinib, individual clinical trial exposure analyses are presented in the following tables:

Tables 4-1 - 4-4 for CA2099ER (RCC)

CA2099ER (RCC)

Table 4-1: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (240 mg) in Combination Therapy with Cabozantinib (40 mg) CA2099ER

	Nivolumab + Cabozantinib N = 320	
Duration of Exposure	Persons (%)	Person Time of Exposure (Months) (1)
0 - < 1 MONTH	2 (0.6)	
0 - < 2 MONTHS	10 (3.1)	
0 - < 3 MONTHS	21 (6.6)	
0 - < 4 MONTHS	30 (9.4)	
0 - < 5 MONTHS	36 (11.3)	
0 - < 6 MONTHS	46 (14.4)	
0 - < 12 MONTHS	116 (36.3)	
0 - < 24 MONTHS	312 (97.5)	
0 - <= 27.3 MONTHS (A)	320 (100.0)	4423.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(a) max clinical exposure
Subjects were to be treated with Nivolumab 240 mg Q2W + Cabozantinib 40 mg daily
Program Source: /opt/zfs001/prd/bms237293/stats/eu_smpc_rmp/prog/tables/rt-ex-pt-durtrt.sas 15MAY2020:03:24:37

Table 4-2: Cumulative Dose of Nivolumab and Cabozantinib; All Treated Subjects with Nivolumab (240 mg) in Combination Therapy with Cabozantinib (40 mg) CA2099ER

	Nivolumab + Cabozantinib	
	Nivolumab N = 320	Cabozantinib N = 320
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	25.9 (14.1)	341.1 (188.6)
MEDIAN	27.5	352.5
MIN - MAX	1 - 53	5 - 820
CUMULATIVE DOSE (1) / SUBJECT		
MEAN (SD)	6201.76 (3368.69)	10841.80 (6485.84)
MEDIAN	6600.00	10120.00
MIN - MAX	240.0 - 12720.0	200.0 - 29080.0

(1) Dose units: Nivolumab and Cabozantinib in mg
Cumulative dose (in mg) is sum of the doses (in mg) administered to a subject during the treatment period.
Program Source: /opt/zfs001/prd/bms237293/stats/eu_smpc_rmp/prog/tables/rt-ex-cumdos.sas 15MAY2020:03:25:01

Table 4-3: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (240 mg) in Combination Therapy with Cabozantinib (40 mg) CA2099ER

Treatment Group: Nivolumab + Cabozantinib

Age Category	Persons (%) Male N = 247	Persons (%) Female N = 73	Persons (%) Total N = 320	Person Time of Exposure (Months) (1) Male N = 247	Person Time of Exposure (Months) (1) Female N = 73	Person Time of Exposure (Months) (1) Total N = 320
>= 18 AND < 65	157 (63.6)	32 (43.8)	189 (59.1)	2266.38	486.21	2752.59
>= 65 AND < 75	73 (29.6)	29 (39.7)	102 (31.9)	998.77	329.07	1327.84
>= 75 AND < 85	16 (6.5)	11 (15.1)	27 (8.4)	211.65	116.34	327.98
>= 85	1 (0.4)	1 (1.4)	2 (0.6)	2.96	12.22	15.18
TOTAL	247 (100.0)	73 (100.0)	320 (100.0)	3479.75	943.84	4423.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms237293/stats/eu_smpc_rmp/prog/tables/rt-ex-pt-age.sas 15MAY2020:03:25:29

Table 4-4: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (240 mg) in Combination Therapy with Cabozantinib (40 mg) CA2099ER

Treatment Group: Nivolumab + Cabozantinib

Race	Persons (%) Male N = 247	Persons (%) Female N = 73	Persons (%) Total N = 320	Person Time of Exposure (Months) (1) Male N = 247	Person Time of Exposure (Months) (1) Female N = 73	Person Time of Exposure (Months) (1) Total N = 320
WHITE	209 (84.6)	55 (75.3)	264 (82.5)	2990.78	722.17	3712.95
BLACK OR AFRICAN AMERICAN	0	1 (1.4)	1 (0.3)	0	23.43	23.43
ASIAN	16 (6.5)	10 (13.7)	26 (8.1)	197.98	106.61	304.59
OTHER	22 (8.9)	7 (9.6)	29 (9.1)	290.99	91.63	382.62
TOTAL	247 (100.0)	73 (100.0)	320 (100.0)	3479.75	943.84	4423.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms237293/stats/eu_smpc_rmp/prog/tables/rt-ex-pt-race.sas 15MAY2020:03:25:54

5 NIVOLUMAB COMBINED WITH CHEMOTHERAPY

For nivolumab in combination with chemotherapy, individual clinical trial exposure analyses are presented in the following tables:

Table 5-1 - Table 5-4 for CA209649 (1L GC/GEJ/OAC)

Table 5-5 - Table 5-8 for CA209648 (OSCC)

Table 5-9 through Table 5-12 for CA209816 (NSCLC)

Table 5-13 through Table 5-16 for CA209901 substudy (UC)

Nivolumab (240 mg Q2W or 360 mg Q3W) in Combination with Chemotherapy: CA209649

Table 5-1: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (240 mg Q2W or 360 mg Q3W) in Combination Therapy with Chemotherapy CA209649

Duration of Exposure	Nivolumab+XELOX N = 360 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	8 (2.2)	
0 - < 2 MONTHS	33 (9.2)	
0 - < 3 MONTHS	56 (15.6)	
0 - < 4 MONTHS	88 (24.4)	
0 - < 5 MONTHS	117 (32.5)	
0 - < 6 MONTHS	154 (42.8)	
0 - < 12 MONTHS	253 (70.3)	
0 - < 24 MONTHS	341 (94.7)	
0 - <= 33.7 MONTHS (A)	360 (100.0)	3416.71

Duration of Exposure	Nivolumab+FOLFOX N = 422 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	6 (1.4)	
0 - < 2 MONTHS	31 (7.3)	
0 - < 3 MONTHS	58 (13.7)	
0 - < 4 MONTHS	86 (20.4)	
0 - < 5 MONTHS	116 (27.5)	
0 - < 6 MONTHS	148 (35.1)	
0 - < 12 MONTHS	292 (69.2)	
0 - < 24 MONTHS	406 (96.2)	
0 - <= 30.0 MONTHS (A)	422 (100.0)	4083.15

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Subjects treated with nivolumab + FOLFOX received Nivolumab 240 mg every 2 weeks.
Subjects treated with nivolumab + XELOX received Nivolumab 360 mg every 3 weeks.
Program Source: /opt/zfs001/prd/bms237859/stats/eu/prog/tables/rt-ex-pt-durtrt.sas 13SEP2020:07:51:12

Table 5-1: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (240 mg Q2W or 360 mg Q3W) in Combination Therapy with Chemotherapy CA209649

Duration of Exposure	Overall N = 782 Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	14 (1.8)	
0 - < 2 MONTHS	64 (8.2)	
0 - < 3 MONTHS	114 (14.6)	
0 - < 4 MONTHS	174 (22.3)	
0 - < 5 MONTHS	233 (29.8)	
0 - < 6 MONTHS	302 (38.6)	
0 - < 12 MONTHS	545 (69.7)	
0 - < 24 MONTHS	747 (95.5)	
0 - <= 33.7 MONTHS (A)	782 (100.0)	7499.86

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Subjects treated with nivolumab + FOLFOX received Nivolumab 240 mg every 2 weeks.
Subjects treated with nivolumab + XELOX received Nivolumab 360 mg every 3 weeks.
Program Source: /opt/zfs001/prd/bms237859/stats/eu/prog/tables/rt-ex-pt-durtrt.sas 13SEP2020:07:51:12

Table 5-2: Cumulative Dose of Nivolumab and Chemotherapy; All Treated Subjects With Nivolumab (240 mg Q2W or 360 mg Q3W) in Combination Therapy With Chemotherapy CA209649

	Nivo + Chemo N = 782		
	Nivolumab+XELOX N1 = 360		
	Nivolumab (mg) N = 360	Oxaliplatin (mg/m^2) N = 360	Capecitabine (mg/m^2) N = 360
NUMBER OF DOSES RECEIVED/SUBJECT			
MEAN (SD)	11.36 (9.23)	6.48 (4.13)	10.88 (9.38)
MEDIAN	8.00	6.00	7.00
MIN - MAX	1.0 - 35.0	1.0 - 34.0	1.0 - 47.0
CUMULATIVE DOSE/SUBJECT			
MEAN (SD)	4090.71 (3324.92)	759.27 (447.29)	252602.25 (211230.13)
MEDIAN	2880.00	726.60	176388.81
MIN - MAX	240.0 - 12600.0	78.1 - 3676.0	1822.9 - 1059942.2

	Nivolumab+FOLFOX N1 = 422				
	Nivolumab (mg) N = 422	Oxaliplatin (mg/m^2) N = 422	Leucovorin (mg/m^2) N = 422	5-Fluorouracil (mg/m^2) N = 420	5-Fluorouracil Continuous (mg/m^2) N = 422
NUMBER OF DOSES RECEIVED/SUBJECT					
MEAN (SD)	17.17 (12.73)	9.37 (4.81)	14.67 (11.41)	13.92 (11.06)	15.25 (11.36)
MEDIAN	13.50	10.00	12.00	11.00	12.00
MIN - MAX	1.0 - 53.0	1.0 - 36.0	1.0 - 59.0	1.0 - 59.0	1.0 - 59.0
CUMULATIVE DOSE/SUBJECT					
MEAN (SD)	4152.01 (3104.86)	764.90 (509.50)	5041.41 (4101.22)	5395.60 (4758.13)	36021.25 (28989.81)
MEDIAN	3240.00	749.20	3992.99	4004.53	27615.35
MIN - MAX	240.0 - 12720.0	83.2 - 6841.7	117.6 - 22096.0	393.4 - 44880.8	1195.9 - 233700.9

Cumulative dose is sum of the doses administered to a subject during the treatment period.
Program Source: /opt/zfs001/prd/bms237859/stats/eu/prog/tables/rt-ex-cumdos.sas
13SEP2020:07:50:18

Table 5-3: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (240 mg Q2W or 360 mg Q3W) in Combination Therapy with Chemotherapy CA209649

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 533	Female N = 249	Total N = 782	Male N = 533	Female N = 249	Total N = 782
>= 18 AND < 65	303 (56.8)	167 (67.1)	470 (60.1)	2938.81	1420.55	4359.36
>= 65 AND < 75	169 (31.7)	66 (26.5)	235 (30.1)	1809.97	598.34	2408.31
>= 75 AND < 85	59 (11.1)	16 (6.4)	75 (9.6)	575.11	130.10	705.22
>= 85	2 (0.4)	0	2 (0.3)	26.97	0	26.97
TOTAL	533 (100.0)	249 (100.0)	782 (100.0)	5350.87	2148.99	7499.86

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms237859/stats/eu/prog/tables/rt-ex-pt-age.sas 13SEP2020:07:50:44

Table 5-4: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (240 mg Q2 W or 360 kg Q3W) in Combination Therapy with Chemotherapy CA209649

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 533	Female N = 249	Total N = 782	Male N = 533	Female N = 249	Total N = 782
WHITE	388 (72.8)	163 (65.5)	551 (70.5)	3784.54	1363.81	5148.35
BLACK OR AFRICAN AMERICAN	3 (0.6)	4 (1.6)	7 (0.9)	23.52	43.76	67.29
ASIAN	118 (22.1)	67 (26.9)	185 (23.7)	1342.95	624.56	1967.51
OTHER	24 (4.5)	15 (6.0)	39 (5.0)	199.85	116.86	316.71
TOTAL	533 (100.0)	249 (100.0)	782 (100.0)	5350.87	2148.99	7499.86

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms237859/stats/eu/prog/tables/rt-ex-pt-race.sas 13SEP2020:07:51:39

Nivolumab (240 mg Q2W) in Combination with Chemotherapy: CA209648

Table 5-5: Clinical Exposure in Person Time; Nivolumab Treated Subjects (CA209648)

Duration of Exposure	Nivo + Ipi N = 322 Persons (%)	Nivo + Ipi N = 322 Person Time of Exposure (1) (Months)	Nivo + Chemo N = 310 Persons (%)	Nivo + Chemo N = 310 Person Time of Exposure (1) (Months)
0 - < 1 MONTH	14 (4.3)		3 (1.0)	
0 - < 2 MONTHS	88 (27.3)		23 (7.4)	
0 - < 3 MONTHS	126 (39.1)		54 (17.4)	
0 - < 4 MONTHS	169 (52.5)		90 (29.0)	
0 - < 5 MONTHS	195 (60.6)		115 (37.1)	
0 - < 6 MONTHS	210 (65.2)		133 (42.9)	
0 - <= 32.9 MONTHS (A)	322 (100.0)	2127.97	310 (100.0)	2686.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Subjects treated with Nivo + Ipi received Nivolumab 3 mg/kg every 2 weeks.
Subjects treated with Nivo + Chemo received Nivolumab 240 mg every 2 weeks.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-pt-durtrt.sas 27OCT2021:11:37:36

Table 5-6: Cumulative Dose and Relative Dose Intensity of Nivolumab and Chemotherapy; All Nivolumab and Chemotherapy Treated Subjects (CA209648)

	Nivo + Ipi N = 322		Nivo + Chemo N = 310		
	Nivolumab N = 322	Ipilimumab N = 322	Nivolumab N = 310	Cisplatin N = 310	Fluorouracil N = 310
DURATION OF THERAPY (MONTHS)					
MEAN	5.70	5.09	7.59	4.27	6.12
(SD)	(6.91)	(6.86)	(6.64)	(3.20)	(5.80)
MEDIAN	2.79	2.76	5.62	4.04	4.80
(MIN - MAX)	(0.0 - 24.1)	(0.0 - 24.0)	(0.0 - 24.7)	(0.0 - 24.0)	(0.1 - 32.8)
NUMBER OF DOSES RECEIVED					
MEAN	12.3	4.4	15.9	5.2	6.8
(SD)	(13.9)	(4.7)	(13.5)	(3.2)	(5.9)
MEDIAN	6.0	3.0	12.0	5.0	6.0
(MIN - MAX)	(1 - 52)	(1 - 18)	(1 - 54)	(1 - 27)	(1 - 36)
CUMULATIVE DOSE (1)					
MEAN	36.79	4.40	3819.07	371.71	25794.73
(SD)	(41.12)	(4.59)	(3242.58)	(218.23)	(22656.05)
MEDIAN	18.86	2.88	2880.00	322.39	20203.17
(MIN - MAX)	(2.9 - 155.0)	(0.9 - 18.1)	(240.0 - 12960.0)	(23.7 - 1248.6)	(828.4 - 149341.2)
RELATIVE DOSE INTENSITY (%)					
>= 110%	2 (0.6)	3 (0.9)	0	1 (0.3)	0
90% TO < 110%	245 (76.1)	278 (86.3)	209 (67.4)	171 (55.2)	181 (58.4)
70% TO < 90%	62 (19.3)	37 (11.5)	87 (28.1)	79 (25.5)	93 (30.0)
50% TO < 70%	10 (3.1)	4 (1.2)	13 (4.2)	51 (16.5)	32 (10.3)
< 50%	3 (0.9)	0	1 (0.3)	8 (2.6)	4 (1.3)

(1) Dose units: Arm Nivo+Ipi: Nivolumab and Ipilimumab in mg/kg; Arm Nivo+Chemo and Chemo: Nivolumab in mg, Fluorouracil and Cisplatin in mg/ m^2.
Program Source: /opt/zfs001/prd/bms239897/stats/hafu/prog/tables/rt-ex-rdi.sas 07OCT2021:16:33:41

Table 5-6: Cumulative Dose and Relative Dose Intensity of Nivolumab and Chemotherapy; All Nivolumab and Chemotherapy Treated Subjects (CA209648)

	Chemotherapy N = 304	
	Cisplatin N = 304	Fluorouracil N = 302
DURATION OF THERAPY (MONTHS)		
MEAN	3.53	4.15
(SD)	(3.01)	(3.57)
MEDIAN	2.91	3.35
(MIN - MAX)	(0.0 - 17.4)	(0.1 - 19.5)
NUMBER OF DOSES RECEIVED		
MEAN	4.5	5.0
(SD)	(2.9)	(3.6)
MEDIAN	4.0	4.0
(MIN - MAX)	(1 - 17)	(1 - 21)
CUMULATIVE DOSE (1)		
MEAN	339.95	19473.74
(SD)	(218.31)	(14090.54)
MEDIAN	317.74	16123.79
(MIN - MAX)	(73.3 - 1348.7)	(1206.7 - 89185.5)
RELATIVE DOSE INTENSITY (%)		
>= 110%	1 (0.3)	0
90% TO < 110%	206 (67.8)	230 (76.2)
70% TO < 90%	72 (23.7)	62 (20.5)
50% TO < 70%	23 (7.6)	7 (2.3)
< 50%	2 (0.7)	3 (1.0)

(1) Dose units: Arm Nivo+Ipi: Nivolumab and Ipilimumab in mg/kg; Arm Nivo+Chemo and Chemo: Nivolumab in mg, Fluorouracil and Cisplatin in mg/ m^2.
Program Source: /opt/zfs001/prd/bms239897/stats/hafu/prog/tables/rt-ex-rdi.sas 07OCT2021:16:33:41

Table 5-7: Clinical Exposure in Person time by Age Group and Gender; Nivolumab Treated Subjects (CA209648)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 244	Female N = 66	Total N = 310	Male N = 244	Female N = 66	Total N = 310
>= 18 AND < 65	130 (53.3)	34 (51.5)	164 (52.9)	1045.03	294.64	1339.66
>= 65 AND < 75	91 (37.3)	26 (39.4)	117 (37.7)	814.49	308.27	1122.76
>= 75 AND < 85	20 (8.2)	6 (9.1)	26 (8.4)	136.67	45.27	181.95
>= 85	3 (1.2)	0	3 (1.0)	42.22	0	42.22
TOTAL	244 (100.0)	66 (100.0)	310 (100.0)	2038.41	648.18	2686.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-pt-age.sas 27OCT2021:11:37:29

Table 5-8: Clinical Expsoure in Person Time by Racial Origin and Gender; Nivolumab Treated Subjects (CA209648)

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 244	Female N = 66	Total N = 310	Male N = 244	Female N = 66	Total N = 310
WHITE	58 (23.8)	22 (33.3)	80 (25.8)	498.66	193.51	692.17
BLACK OR AFRICAN AMERICAN	0	1 (1.5)	1 (0.3)	0	10.61	10.61
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.4)	1 (1.5)	2 (0.6)	2.69	9.26	11.96
ASIAN	182 (74.6)	40 (60.6)	222 (71.6)	1507.35	427.04	1934.39
ASIAN INDIAN	3 (1.2)	1 (1.5)	4 (1.3)	32.13	1.18	33.31
CHINESE	67 (27.5)	7 (10.6)	74 (23.9)	553.49	77.83	631.33
JAPANESE	95 (38.9)	26 (39.4)	121 (39.0)	793.20	273.54	1066.74
ASIAN OTHER	17 (7.0)	6 (9.1)	23 (7.4)	128.53	74.48	203.01
OTHER	3 (1.2)	2 (3.0)	5 (1.6)	29.70	7.75	37.45
TOTAL	244 (100.0)	66 (100.0)	310 (100.0)	2038.41	648.18	2686.59

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms211280/stats/smpc_scs_rmp648/prog/tables/rt-ex-pt-race.sas 27OCT2021:11:36:31

CA209816 (NSCLC)

Table 5-9: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab in Combination Therapy with Chemotherapy, CA209816

	Nivolumab + Chemotherapy N = 176	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	0	
0 - < 2 MONTHS	7 (4.0)	
0 - < 3 MONTHS	173 (98.3)	
0 - < 4 MONTHS	176 (100.0)	
0 - < 5 MONTHS	176 (100.0)	
0 - < 6 MONTHS	176 (100.0)	
0 - < 12 MONTHS	176 (100.0)	
0 - < 24 MONTHS	176 (100.0)	
0 - <= 33.7 MONTHS (A)	176 (100.0)	442.22

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp816/prog/tables/rt-ex-pt-durtrt2.sas 21OCT2022:05:52:45

Table 5-10: Cumulative Dose of Nivolumab; All Treated Subjects With Nivolumab in Combination Therapy With Chemotherapy, CA209816

	Nivolumab + Chemotherapy N = 176
	Nivolumab N = 176
NUMBER OF DOSES RECEIVED	
MEAN (SD)	2.9 (0.4)
MEDIAN	3.0
MIN - MAX	1 - 3
CUMULATIVE DOSE (MG)	
MEAN (SD)	1047.3 (129.2)
MEDIAN	1080.0
MIN - MAX	360 - 1080

Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp816/prog/tables/rt-ex-rdil2.sas 21OCT2022:05:52:45

Table 5-11: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab in Combination Therapy with Chemotherapy, CA209816

Treatment Group: CA209816 Nivolumab + Chemotherapy

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 127	Female N = 49	Total N = 176	Male N = 127	Female N = 49	Total N = 176
>= 18 AND < 65	61 (48.0)	30 (61.2)	91 (51.7)	153.40	75.63	229.03
>= 65 AND < 75	61 (48.0)	14 (28.6)	75 (42.6)	153.72	35.42	189.14
>= 75 AND < 85	5 (3.9)	5 (10.2)	10 (5.7)	12.75	11.30	24.05
>= 85	0	0	0	0	0	0
TOTAL	127 (100.0)	49 (100.0)	176 (100.0)	319.87	122.35	442.22

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp816/prog/tables/rt-ex-pt-age2.sas 21OCT2022:05:52:44

Table 5-12: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab in Combination Therapy with Chemotherapy, CA209816

Treatment Group: CA209816 Nivolumab + Chemotherapy

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 127	Female N = 49	Total N = 176	Male N = 127	Female N = 49	Total N = 176
WHITE	53 (41.7)	35 (71.4)	88 (50.0)	133.52	86.14	219.66
BLACK OR AFRICAN AMERICAN	2 (1.6)	2 (4.1)	4 (2.3)	4.80	5.72	10.51
ASIAN	72 (56.7)	12 (24.5)	84 (47.7)	181.55	30.49	212.04
ASIAN INDIAN	0	1 (2.0)	1 (0.6)	0	2.40	2.40
CHINESE	40 (31.5)	3 (6.1)	43 (24.4)	99.75	7.36	107.10
JAPANESE	27 (21.3)	5 (10.2)	32 (18.2)	69.19	13.04	82.23
ASIAN OTHER	5 (3.9)	3 (6.1)	8 (4.5)	12.62	7.69	20.30
TOTAL	127 (100.0)	49 (100.0)	176 (100.0)	319.87	122.35	442.22

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of, time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp816/prog/tables/rt-ex-pt-race2.sas 21OCT2022:05:52:51

Nivolumab (360 mg Q3W) in Combination with Chemotherapy: CA209901 substudy

Table 5-13: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab in Combination Therapy with Chemotherapy - CA209901 Substudy

	Nivo + Chemo N = 304	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	6 (2.0)	
0 - < 2 MONTHS	23 (7.6)	
0 - < 3 MONTHS	34 (11.2)	
0 - < 4 MONTHS	44 (14.5)	
0 - < 5 MONTHS	59 (19.4)	
0 - < 6 MONTHS	70 (23.0)	
0 - <= 48.9 MONTHS (A)	304 (100.0)	3353.92

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
(A) Max clinical exposure
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp901sub/prog/tables/rt-ex-pt-durtrt.sas 28JUL2023:10:05:17

Table 5-14: Cumulative Dose of Nivolumab and Chemotherapy; All Treated Subjects With Nivolumab in Combination Therapy With Chemotherapy - CA209901 Substudy

	Nivo + Chemo N = 304
	Nivolumab N = 304
NUMBER OF DOSES RECEIVED / SUBJECT	
MEAN (SD)	12.2 (7.9)
MEDIAN	10.0
MIN - MAX	1 - 32
CUMULATIVE DOSE (MG) / SUBJECT	
MEAN (SD)	5251.6 (3707.4)
MEDIAN	4080.0
MIN - MAX	360 - 14640

Cumulative dose (in mg or mg/kg) is sum of the doses (in mg or mg/kg) administered to a subject during the treatment period.
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp901sub/prog/tables/rt-ex-cumdos.sas 28JUL2023:10:05:38

Table 5-15: Clinical Exposure in Person Time by Age Group and Sex; All Treated Subjects with Nivolumab in Combination Therapy with Chemotherapy - CA209901 Substudy

Treatment Group: Nivolumab + Chemotherapy

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 236	Female N = 68	Total N = 304	Male N = 236	Female N = 68	Total N = 304
>= 18 AND < 65	118 (50.0)	32 (47.1)	150 (49.3)	1420.85	345.95	1766.80
>= 65 AND < 75	96 (40.7)	24 (35.3)	120 (39.5)	956.39	268.68	1225.07
>= 75 AND < 85	20 (8.5)	11 (16.2)	31 (10.2)	223.44	127.38	350.82
>= 85	2 (0.8)	1 (1.5)	3 (1.0)	8.08	3.15	11.24
TOTAL	236 (100.0)	68 (100.0)	304 (100.0)	2608.76	745.17	3353.92

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp901sub/prog/tables/rt-ex-pt-age.sas 28JUL2023:10:06:00

Table 5-16: Clinical Exposure in Person Time by Racial Origin and Sex; All Treated Subjects with Nivolumab in Combination Therapy with Chemotherapy - CA209901 Substudy

Treatment Group: Nivolumab + Chemotherapy

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 236	Female N = 68	Total N = 304	Male N = 236	Female N = 68	Total N = 304
WHITE	165 (69.9)	46 (67.6)	211 (69.4)	1906.53	531.61	2438.14
ASIAN	56 (23.7)	19 (27.9)	75 (24.7)	536.11	181.55	717.67
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.4)	0	1 (0.3)	9.69	0	9.69
OTHER	14 (5.9)	3 (4.4)	17 (5.6)	156.42	32.00	188.42
TOTAL	236 (100.0)	68 (100.0)	304 (100.0)	2608.76	745.17	3353.92

(1) Sum of subject's exposure time. Subject's exposure time is defined as the minimum of time between first dose date and last known date alive and duration of treatment +30 days, for subjects who are off treatment, and as time between first dose date and last known date alive for subjects who are still on treatment.
Program Source: /opt/zfs001/prd/bms214682/stats/smpc_scs_rmp901sub/prog/tables/rt-ex-pt-race.sas 28JUL2023:10:06:21

APPENDIX 4: SINGLE STUDY SAFETY TABLES

Single study safety analysis (by indication) for the Important Identified Risk of Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs) are presented in Tables 4-1 through 4-7. Single study safety analysis (by indication) for the Important Identified Risk of severe infusion reaction is presented in Table 4-8.

Table 4-1: Immune-related ARs: Immune-related Pneumonitis

Immune-related Pneumonitis

Characterization of risk *(Percent; All Treated)*

I. Nivolumab Monotherapy

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209066			
Any Grade	1.5	0	1.5 (-0.6, 4.2)
Grade 3-4	0	0	NA
CA209067			
Any Grade	1.6	1.9	-0.3 (-2.7, 2.0)
Grade 3-4	0.3	0.3	0 (-1.5, 1.5)
CA209037			
Any Grade	3.0	0	3.0 (-0.9, 5.8)
Grade 3-4	0	0	NA
MDX1106-03			
Any Grade	0	3.7	NA
Grade 3-4	0	0	NA
CA209238 (adjuvant melanoma)			
Any Grade	1.3	2.4	-1.1 (-3.1, 0.8)
Grade 3-4	0	0.9	-0.9 (-2.2, 0.1)
CA20976K (Stage IIB/C adjuvant melanoma)			
Any Grade	1.3	0.4	1.0 (-0.9, 2.4)
Grade 3-4	0.2	0	0.2 (-1.3, 1.1)

CA2098FC	Nivolumab		
	Process C	Process D	DIFF (95% CI)
Any Grade	3.1	2.3	-0.8 (-5.7, 3.8)
Grade 3-4	0	0	NA

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209017			
Any Grade	4.6	0.8	3.8 (-0.5, 5.9)
Grade 3-4	0	0	NA
CA209057			
Any Grade	3.5	0.4	3.1 (0.8, 5.9)
Grade 3-4	1.4	0.4	1.0 (-0.9, 3.2)
CA209063			
Any Grade	5.1	NA	NA
Grade 3-4	3.4	NA	NA
MDX1106-03 3mg/kg			
Any Grade	5.6 SQ 0 NSQ	NA	NA

Table 4-1: Immune-related ARs: Immune-related Pneumonitis

Immune-related Pneumonitis

Grade 3-4	0 SQ 0 NSQ	NA	NA
All dose-levels			
Any Grade	7.0	NA	NA
Grade 3-4	2.3	NA	NA

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209025			
Any Grade	4.4	17.6	-13.2 (-17.6, -9.0)
Grade 3-4	1.5	3.3	-1.8 (-4.2, 0.04)

cHL	Nivolumab	Comparator	DIFF (95% CI)
CA209205 Cohort B			
Any Grade	5.0	NA	NA
Grade 3-4	0	NA	NA
CA209205 Cohort A+B+C			
Any Grade	4.9	NA	NA
Grade 3-4	0	NA	NA
CA209039			
Any Grade	4.3	NA	NA
Grade 3-4	4.3	NA	NA

SCCHN	Nivolumab	Comparator	DIFF (95% CI)
CA209141			
Any Grade	2.1	0.9	1.2 (-3.0, 4.1)
Grade 3-4	0.8	0	0.8 (-2.6, 3.0)

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209275			
Any Grade	4.1	NA	NA
Grade 3-4	1.1	NA	NA
CA209032			
Any Grade	2.6	NA	NA
Grade 3-4	0	NA	NA
CA209274			
Any Grade	5.4	1.4	4.0 (1.3, 7.0)
Grade 3-4	1.4	0	1.4 (0.1, 3.3)

ESCC	Nivolumab	Comparator	DIFF (95% CI)
ONO-4538-24 (CA209473)			
Any Grade	5.7	4.3	1.4 (-3.0, 5.9)

Table 4-1: Immune-related ARs: Immune-related Pneumonitis

Immune-related Pneumonitis			
Grade 3-4	1.0	1.9	-1.0 (-4.0, 1.8)

OC/GEJC	Nivolumab	Comparator	DIFF (95% CI)
CA209577			
Any Grade	4.3	1.5	2.8 (0.0, 5.1)
Grade 3-4	1.1	0.4	0.7 (-1.1, 2.1)

II. Nivolumab Combined with Ipilimumab (+-Chemo)

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209067			
Any Grade	7.3	1.9	5.4 (2.2, 9.0)
Grade 3-4	1.0	0.3	0.6 (-1.0, 2.5)
CA209069			
Any Grade	9.6	2.2	7.4 (-2.8, 15.2)
Grade 3-4	2.1	0	2.1 (-5.7, 7.4)
CA209004			
Any Grade	4.9	NA	NA
Grade 3-4	2.4	NA	NA

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209214			
Any Grade	6.2	0.2	6.0% (4.1, 8.4)
Grade 3-4	1.1	0	1.1% (0.2, 2.4)
CA209016			
Any Grade	6.4	NA	NA
Grade 3-4	0	NA	NA

MPM	Nivolumab	Comparator	DIFF (95% CI)
CA209743			
Any Grade	6.7	0	6.7% (4.0, 10.1)
Grade 3-4	0.7	0	0.7% (-0.8, 2.4)

CRC	Nivolumab	Comparator	DIFF (95% CI)
CA209142			
Any Grade	5.9	NA	NA
Grade 3-4	0.8	NA	NA
CA2098HW			
Any Grade	2.5	0	2.5 (-1.9, 5.7)
Grade 3-4	1.0	0	1.0 (-3.2, 3.6)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	8.1	0.7	7.4 (4.4, 10.9)
Grade 3-4	2.8	0	2.8 (1.0, 5.2)

Table 4-1: Immune-related ARs: Immune-related Pneumonitis

Immune-related Pneumonitis

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA2099LA			
Any Grade	5.3	1.1	4.2 (1.6, 7.1)
Grade 3-4	1.7	0.3	1.4 (-0.2, 3.3)

HCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099DW			
Any Grade	2.1	0	2.1 (0.5, 4.3)
Grade 3-4	0.3	0	0.3 (-0.9, 1.7)

IV. Nivolumab Combined with Chemotherapy

Gastric/GEJC/OAC	Nivolumab	Comparator	DIFF (95% CI)
CA209649			
Any Grade	5.1	0.5	4.6 (3.0, 6.4)
Grade 3-4	1.8	0.1	1.7 (0.7, 2.9)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	6.1	0.3	5.8 (3.2, 9.1)
Grade 3-4	0.6	0	0.6 (-0.7, 2.3)

Resectable NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209816			
Any Grade	1.1	0	1.1 (-1.2, 4.0)
Grade 3-4	0	0	N.A.

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209901 substudy			
Any Grade	2.0	0	2.0 (0.3, 4.2)
Grade 3-4	0.0	0	0.3 (-1.0, 1.8)

Table 4-2: Immune-related AR: Immune-related Colitis

Immune-related Colitis

Characterization of risk
(Percent, All Treated)

I. Nivolumab Monotherapy

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209066			
Any Grade	17.0	15.6	1.4 (-5.8, 8.6)
Grade 3-4	1.5	0.5	1.0 (-1.5, 3.7)
CA209067			
Any Grade	22.4	37.6	-15.3 (-22.2, -8.1)
Grade 3-4	3.5	11.6	-8.1 (-12.4, -4.0)
CA209037			
Any Grade	18.7	15.7	3.0 (-6.3, 10.7)
Grade 3-4	1.1	2.0	-0.8 (-5.8, 1.7)
MDX1106-03			
Any Grade	11.8	NA	NA
Grade 3-4	0	NA	NA
CA209238 (adjuvant melanoma)			
Any Grade	25.2	48.3	-23.1 (-29.1, -16.9)
Grade 3-4	2.0	16.8	-14.8 (-18.6, -11.2)
CA20976K (Stage IIB/C adjuvant melanoma)			
Any Grade	16.2	9.5	6.8 (1.7, 11.3)
Grade 3-4	1.1	0	1.1 (-0.4, 2.5)
CA2098FC	**Nivolumab**		
	Process C	**Process D**	**DIFF (95% CI)**
Any Grade	14.0	18.2	4.2 (-4.8, 13.2)
Grade 3-4	0.8	3.0	2.3 (-1.7, 6.8)

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209017			
Any Grade	8.4	20.2	-11.8 (-20.3, -3.3)
Grade 3-4	0.8	2.3	-1.6 (-5.9, 2.2)
CA209057			
Any Grade	7.7	21.3	-15.3 (-21.4, -9.5)
Grade 3-4	0.7	1.1	-0.4 (-2.6, 1.5)
CA209063			
Any Grade	10.3	NA	NA
Grade 3-4	2.6	NA	NA
MDX1106-03			
3mg/kg			
Any Grade	16.7 SQ 1.05 NSQ	NA	NA
Grade 3-4	0 SQ 0 NSQ	NA	NA
All dose-levels			
Any Grade	11.6	NA	NA
Grade 3-4	0.8	NA	NA

Table 4-2: Immune-related AR: Immune-related Colitis

Immune-related Colitis

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209025			
Any Grade	12.6	21.2	-8.6 (-13.8, -3.4)
Grade 3-4	2.0	1.3	0.7 (-1.2, 2.7)

cHL	Nivolumab	Comparator	DIFF (95% CI)
CA209205 Cohort B			
Any Grade	13.8	NA	NA
Grade 3-4	0	NA	NA
CA209205 Cohort A+B+C			
Any Grade	15.2	NA	NA
Grade 3-4	1.2	NA	NA
CA209039			
Any Grade	17.4	NA	NA
Grade 3-4	4.3	NA	NA

SCCHN	Nivolumab	Comparator	DIFF (95% CI)
CA209141			
Any Grade	6.8	14.4	-7.6 (-15.8, -1.0)
Grade 3-4	0	1.8	-1.8 (-6.3, 0.3)

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209275			
Any Grade	9.3	NA	NA
Grade 3-4	2.2	NA	NA
CA209032			
Any Grade	10.3	NA	NA
Grade 3-4	1.3	NA	NA
CA209274			
Any Grade	18.5	11.2	7.3 (2.0, 12.6)
Grade 3-4	1.7	0.9	0.8 (-1.0, 2.9)

ESCC	Nivolumab	Comparator	DIFF (95% CI)
ONO-4538-24 (CA209473)			
Any Grade	10.5	9.6	0.9 (-5.0, 6.8)
Grade 3-4	1.0	1.0	0.0 (-2.6, 2.6)

OC/GEJC	Nivolumab	Comparator	DIFF (95% CI)
CA209577			
Any Grade	17.1	15.4	1.7 (-4.0, 6.9)
Grade 3-4	0.8	1.2	-0.4 (-2.6, 1.0)

Table 4-2: Immune-related AR: Immune-related Colitis

Immune-related Colitis

II. Nivolumab Combined with Ipilimumab (+-Chemo)

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209067			
Any Grade	47.9	37.6	10.3 (2.5, 17.9)
Grade 3-4	15.3	11.6	3.8 (-1.6, 9.1)
CA209069			
Any Grade	46.8	32.6	14.2 (-3.2, 29.6)
Grade 3-4	19.1	10.9	8.3 (-5.6, 19.3)
CA209004			
Any Grade	36.6	NA	NA
Grade 3-4	19.5	NA	NA

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209214			
Any Grade	28.2	23.8	-23.8 (-29.3,-18.0)
Grade 3-4	4.9	5.2	- 0.3 (-3.0, 2.4)
CA209016			
Any Grade	25.5	NA	NA
Grade 3-4	4.3	NA	NA

MPM	Nivolumab	Comparator	DIFF (95% CI)
CA209743			
Any Grade	22.0	8.1	13.9 (8.2, 19.6)
Grade 3-4	5.3	1.1	4.3 (1.4, 7.5)

CRC	Nivolumab	Comparator	DIFF (95% CI)
CA209142			
Any Grade	25.2	NA	NA
Grade 3-4	3.4	NA	NA
CA2098HW			
Any Grade	23.0	52.3	-29.3 (-40.7, -17.2)
Grade 3-4	4.5	5.7	-1.2 (-8.4, 3.8)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	11.8	15.5	-3.7 (-9.1, 1.7)
Grade 3-4	1.6	2.3	-0.7 (-3.3, 1.6)

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA2099LA			
Any Grade	22.3	12.0	10.3 (4.8, 15.8)
Grade 3-4	5.3	1.1	4.2 (1.6, 7.1)

HCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099DW			

Table 4-2: Immune-related AR: Immune-related Colitis

Immune-related Colitis				
	Any Grade	16.9	35.1	-18.2 (-24.7, -11.6)
	Grade 3-4	5.1	3.1	2.0 (-1.1, 5.3)

IV. Nivolumab Combined with Chemotherapy

Gastric/GEJC/ OAC	Nivolumab	Comparator	DIFF (95% CI)
CA209649			
Any Grade	33.5	27.0	6.5 (1.9, 11.1)
Grade 3-4	5.5	3.3	2.2 (0.2, 4.3)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	20.3	15.5	4.9 (-1.2, 10.9)
Grade 3-4	2.3	2.3	0.0 (-2.7, 2.6)

Resectable NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209816			
Any Grade	5.7	11.9	-6.3 (-12.4, -0.3)
Grade 3-4	0.6	2.3	-1.7 (-5.2, 1.2)

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209901 substudy			
Any Grade	13.8	8.7	5.1 (0.0, 10.3)
Grade 3-4	2.0	0	2.0 (0.3, 4.2)

Table 4-3: Immune-related AR: Immune-related Hepatitis

Immune-related Hepatitis

Characterization of risk
(Percent; All Treated)

I. Nivolumab Monotherapy

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209066			
Any Grade	3.4	3.9	-0.5 (-4.5, 3.4)
Grade 3-4	1.5	1.0	0.5 (-2.2, 3.3)
CA209067			
Any Grade	7.7	7.4	0.3 (-4.0, 4.5)
Grade 3-4	2.6	1.6	0.9 (-1.5, 3.5)
CA209037			
Any Grade	10.8	5.9	4.9 (-2.2, 10.3
Grade 3-4	2.6	0	2.6 (-1.3, 5.3)
MDX1106-03			
Any Grade	11.8	NA	NA
Grade 3-4	5.9	NA	NA
CA209238 (adjuvant melanoma)			
Any Grade	9.1	21.2	-12.1 (-16.7, -7.5)
Grade 3-4	1.8	10.8	-9.0 (-12.4, -6.0)
CA20976K (Stage IIB/C adjuvant melanoma)			
Any Grade	11.3	6.1	5.2 (0.9, 9.0)
Grade 3-4	2.7	0.8	1.9 (-0.3, 3.8)

CA2098FC	Nivolumab		
	Process C	Process D	DIFF (95% CI)
Any Grade	14.0	18.9	5.0 (-4.1, 14.0)
Grade 3-4	0.8	2.3	1.5 (-2.3, 5.7)

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209017			
Any Grade	3.1	2.3	0.7 (-3.9, 5.5)
Grade 3-4	0	0.8	-0.8 (-4.3, 2.1)
CA209057			
Any Grade	5.2	1.9	3.4 (0.2, 6.7)
Grade 3-4	1.0	0.7	0.3 (-1.8, 2.4)
CA209063			
Any Grade	0.9	NA	NA
Grade 3-4	0	NA	NA
MDX1106-03			
3mg/kg			
Any Grade	5.6 SQ 0 NSQ	NA	NA
Grade 3-4	5.6 SQ 0 NSQ	NA	NA
All dose-levels			
Any Grade	4.7	NA	NA
Grade 3-4	0.8	NA	NA

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209025			

Table 4-3: Immune-related AR: Immune-related Hepatitis

Immune-related Hepatitis

Any Grade	11.3	7.1	4.3 (0.3, 8.3)
Grade 3-4	2.7	0.5	2.2 (0.4, 4.3)

cHL	Nivolumab	Comparator	DIFF (95% CI)
CA209205 Cohort B			
Any Grade	16.3	NA	NA
Grade 3-4	6.3	NA	NA
CA209205 Cohort A+B+C			
Any Grade	11.9	NA	NA
Grade 3-4	4.5	NA	NA
CA209039			
Any Grade	8.7	NA	NA
Grade 3-4	0	NA	NA

SCCHN	Nivolumab	Comparator	DIFF (95% CI)
CA209141			
Any Grade	2.1	3.6	-1.5 (-6.9, 2.0)
Grade 3-4	0.8	0.9	-0.1 (-4.1, 2.3)

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209275			
Any Grade	3.7	NA	NA
Grade 3-4	1.9	NA	NA
CA209032			
Any Grade	5.1	NA	NA
Grade 3-4	1.3	NA	NA
CA209274			
Any Grade	8.3	4.9	3.4 (-0.3, 7.2)
Grade 3-4	1.7	0.3	1.4 (-0.2, 3.4)

ESCC	Nivolumab	Comparator	DIFF (95% CI)
ONO-4538-24 (CA209473)			
Any Grade	6.7	3.8	2.9 (-1.6, 7.5)
Grade 3-4	0.5	1.9	-1.4 (-4.4, 1.0)

OC/GEJC	Nivolumab	Comparator	DIFF (95% CI)
CA209577			
Any Grade	9.2	6.9	2.3 (-2.1, 6.0)
Grade 3-4	1.1	1.5	-0.4 (-2.8, 1.2)

Table 4-3: Immune-related AR: Immune-related Hepatitis

Immune-related Hepatitis

II. Nivolumab Combined with Ipilimumab (+-Chemo)

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209067			
Any Grade	32.6	7.4	25.2 (19.2, 31.1)
Grade 3-4	19.8	1.6	18.2 (13.6, 23.1)
CA209069			
Any Grade	24.5	2.2	22.3 (10.4, 32.0)
Grade 3-4	11.7	0	11.7 (2.5, 19.8)
CA209004			
Any Grade	14.6	NA	NA
Grade 3-4	12.2	NA	NA

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209214			
Any Grade	18.5	14.4	4.1 (-0.4, 8.5)
Grade 3-4	8.2	3.7	4.5 (1.7, 7.4)
CA209016			
Any Grade	19.1	NA	NA
Grade 3-4	6.4	NA	NA

MPM	Nivolumab	Comparator	DIFF (95% CI)
CA209743			
Any Grade	12.0	2.1	9.9 (5.9, 14.2)
Grade 3-4	5.3	0	5.3 (2.9, 8.5)

CRC	Nivolumab	Comparator	DIFF (95% CI)
CA209142			
Any Grade	23.5	NA	NA
Grade 3-4	11.8	NA	NA
CA2098HW			
Any Grade	19.5	5.7	13.8 (5.3, 20.7)
Grade 3-4	4.5	0	4.5 (-0.2, 8.3)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	13.0	3.9	9.1 (4.8, 13.5)
Grade 3-4	4.3	0.7	3.7 (1.3, 6.5)

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA2099LA			
Any Grade	13.4	7.4	6.0 (1.4, 10.5)
Grade 3-4	4.5	0.9	3.6 (1.2, 6.3)

HCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099DW			
Any Grade	34.3	18.8	15.6 (8.8, 22.1)

Table 4-3: Immune-related AR: Immune-related Hepatitis

Immune-related Hepatitis				
	Grade 3-4	16.9	4.9	11.9 (7.3, 16.7)

IV. Nivolumab Combined with Chemotherapy

Gastric/GEJC/OAC	Nivolumab	Comparator	DIFF (95% CI)
CA209649			
Any Grade	26.0	17.5	8.5 (4.4, 12.6)
Grade 3-4	3.7	2.1	1.6 (-0.1, 3.4)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	10.3	3.9	6.4 (2.3, 10.6)
Grade 3-4	2.3	0.7	1.6 (-0.5, 4.0)

Resectable NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209816			
Any Grade	8.0	11.4	-3.4 (-9.8, 2.9)
Grade 3-4	0.6		-1.7 (-5.2, 1.2)

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209901 substudy			
Any Grade	13.2	8.3	5.1 (0.0, 10.3)
Grade 3-4	2.6	0.7	2.0 (0.3, 4.2)

Table 4-4: Immune-related AR: Immune-related Nephritis and Renal Dysfunction

Immune-related Nephritis and Renal Dysfunction

Characterization of risk *(Percent; All Treated)*

I. Nivolumab Monotherapy

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209066			
Any Grade	1.9	0.5	1.5 (-1.1, 4.4)
Grade 3-4	0.5	0	0.5 (-1.4, 2.7)
CA209067			
Any Grade	1.0	2.6	-1.6 (-4.1, 0.6)
Grade 3-4	0.3	0.3	0 (-1.5, 1.5)
CA209037			
Any Grade	1.9	1.0	0.9 (-3.6, 3.4)
Grade 3-4	0.7	0	0.7 (-2.9, 2.7)
MDX1106-03			
Any Grade	0	NA	NA
Grade 3-4	0	NA	NA
CA209238 (adjuvant melanoma)			
Any Grade	1.3	1.5	-0.2 (-2.0, 1.5)
Grade 3-4	0	0	NA
CA20976K (Stage IIB/C adjuvant melanoma)			
Any Grade	1.7	0	1.7 (0.1, 3.2)
Grade 3-4	0.4	0	0.4 (-1.1, 1.4)
CA2098FC	**Nivolumab**		
	Process C	**Process D**	**DIFF (95% CI)**
Any Grade	2.3	2.3	-0.1 (-4.6, 4.4)
Grade 3-4	0	0	NA

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209017			
Any Grade	3.1	2.3	0.7 (-3.9, 5.5)
Grade 3-4	0.8	0	0.8 (-2.2, 4.2)
CA209057			
Any Grade	2.4	0.4	2.1 (-0.1, 4.6)
Grade 3-4	0	0	NA
CA209063			
Any Grade	3.4	NA	NA
Grade 3-4	0	NA	NA
MDX1106-03			
3mg/kg			
Any Grade	0 SQ 5.3 NSQ	NA	NA
Grade 3-4	0 SQ 0 NSQ	NA	NA
All dose-levels			
Any Grade	3.1	NA	NA
Grade 3-4	0	NA	NA

Table 4-4: Immune-related AR: Immune-related Nephritis and Renal Dysfunction

Immune-related Nephritis and Renal Dysfunction

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209025			
Any Grade	6.9	8.8	-1.9 (-5.7, 1.8)
Grade 3-4	1.0	0.5	0.5 (-1.0, 2.0)

cHL	Nivolumab	Comparator	DIFF (95% CI)
CA209205 Cohort B			
Any Grade	2.5	NA	NA
Grade 3-4	0	NA	NA
CA209205 Cohort A+B+C			
Any Grade	2.1	NA	NA
Grade 3-4	0.4	NA	NA
CA209039			
Any Grade	0	NA	NA
Grade 3-4	0	NA	NA

SCCHN	Nivolumab	Comparator	DIFF (95% CI)
CA209141			
Any Grade	0.4	1.8	-1.4 (-5.9, 1.0)
Grade 3-4	0	0.9	-0.9 (-4.9, 0.9)

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209275			
Any Grade	1.1	NA	NA
Grade 3-4	0.4	NA	NA
CA209032			
Any Grade	9.0	NA	NA
Grade 3-4	1.3	NA	NA
CA209274			
Any Grade	7.1	3.4	3.7 (0.3, 7.2)
Grade 3-4	1.1	0	1.1 (-0.2, 2.9)

ESCC	Nivolumab	Comparator	DIFF (95% CI)
ONO-4538-24 (CA209473)			
Any Grade	1.4	0	1.4 (-0.6, 4.1)
Grade 3-4	0.5	0	0.5 (-1.4, 2.7)

Table 4-4: Immune-related AR: Immune-related Nephritis and Renal Dysfunction

Immune-related Nephritis and Renal Dysfunction

OC/GEJC	Nivolumab	Comparator	DIFF (95% CI)
CA209577			
Any Grade	1.3	0.8	0.5 (-1.6, 2.0)
Grade 3-4	0.2	0	0.2 (-1.3, 1.1)

II. Nivolumab Combined with Ipilimumab (+-Chemo)

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209067			
Any Grade	6.7	2.6	4.1 (0.8, 7.7)
Grade 3-4	1.9	0.3	1.6 (-0.2, 3.8)
CA209069			
Any Grade	2.1	2.2	0 (-9.3, 5.5)
Grade 3-4	1.1	0	1.1 (-6.7, 5.8)
CA209004			
Any Grade	0	NA	NA
Grade 3-4	0	NA	NA

Table 4-4: Immune-related AR: Immune-related Nephritis and Renal Dysfunction

Immune-related Nephritis and Renal Dysfunction

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209214			
Any Grade	8.8	8.6	0.2 (-3.2, 3.6)
Grade 3-4	1.3	1.1	0.2 (-1.3, 1.6)
CA209016			
Any Grade	19.1	NA	NA
Grade 3-4	4.3	NA	NA

MPM	Nivolumab	Comparator	DIFF (95% CI)
CA209743			
Any Grade	5.0	6.7	-1.7 (-5.7, 2.2)
Grade 3-4	1.3	0.4	1.0 (-0.8, 3.0)

CRC	Nivolumab	Comparator	DIFF (95% CI)
CA209142			
Any Grade	5.9	NA	NA
Grade 3-4	1.7	NA	NA
CA2098HW			
Any Grade	3.5	2.3	1.2 (-4.7, 5.1)
Grade 3-4	0.5	0	0.5 (-3.7, 2.8)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	2.5	18.8	-16.3 (-21.2, -11.6)
Grade 3-4	0.6	1.6	-1.0 (-3.2, 0.8)

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA2099LA			
Any Grade	7.0	5.7	1.3 (-2.4, 5.0)
Grade 3-4	2.2	1.1	1.1 (-1.0, 3.3)

HCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099DW			
Any Grade	1.8	3.4	-1.6 (-4.3, 1.0)
Grade 3-4	0.3	0.6	-0.3 (-1.9, 1.1)

IV. Nivolumab + Chemotherapy

Gastric/GEJC/ OAC	Nivolumab	Comparator	DIFF (95% CI)
CA209649			
Any Grade	3.3	1.0	2.3 (0.8, 3.9)
Grade 3-4	0.8	0.1	0.6 (-0.1, 1.5)

Table 4-4: Immune-related AR: Immune-related Nephritis and Renal Dysfunction

Immune-related Nephritis and Renal Dysfunction

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	23.5	18.8	4.8 (-1.7, 11.2)
Grade 3-4	2.6	1.6	0.9 (-1.6, 3.5)

Resectable NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209816			
Any Grade	7.4	10.2	-2.8 (-9.0, 3.2)
Grade 3-4	0.6	0	0.6 (-1.6, 3.1)

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209901 substudy			
Any Grade	19.1	18.8	0.3 (-6.0, 6.6)
Grade 3-4	3.6	1.0	2.6 (0.0, 5.4)

Table 4-5: Immune-related AR: Immune-related Endocrinopathies

Immune-related Endocrinopathies

Characterization of risk *(Percent; All Treated)*

I. Nivolumab Monotherapy

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209066			
Any Grade	7.8	0.5	7.3 (3.6, 11.8)
(Nivolumab: thyroid disorder 6.3%, diabetes 1.0%, and pituitary disorder 0.5%; Comparator: thyroid disorder 0.5)			
Grade 3-4	1.5	0	1.5 (-0.6, 4.2)
(Nivolumab: thyroid disorder 0.5%, diabetes 0.5%, and pituitary disorder 0.5%)			
CA209067			
Any Grade	17.3	11.6	5.7 (0.1, 11.2)
(Nivolumab: adrenal disorder 1.0%, thyroid disorder 15.0%, pituitary disorder 1.0%, and diabetes 0.6%; Comparator: adrenal disorder 1.6%, thyroid disorder 6.1%, and pituitary disorder 5.1%)			
Grade 3-4	1.6	2.6	-1.0 (-3.6, 1.5)
(Nivolumab: adrenal disorder 0.3%, pituitary disorder 1.0%, and diabetes 0.3%; Comparator: adrenal disorder 0.3% and pituitary disorder 2.3%)			
CA209037			
Any Grade	9.7	1.0	8.7 (3.4, 12.9)
(Nivolumab: thyroid disorder 9.0%, adrenal disorder 0.7%, pituitary disorder 0.4%; Comparator: thyroid disorder 1.0%)			
Grade 3-4	0	0	NA
MDX1106-03			
3mg/kg			
Any Grade	17.6	NA	NA
(Nivolumab: hypothyroidism 5.9%; hyperthyroidism 5.9%, thyroiditis 5.9%)			
Grade 3-4	0	NA	NA
All dose-levels			
Any Grade			
(Nivolumab: hypothyroidism 5.6%; hyperthyroidism 1.9%, thyroiditis 0.9%, hypophysitis 0.9%, adrenal insufficiency 0.9%, secondary adrenal insufficiency 0.9%, diabetes mellitus 0.9%)			
Grade 3-4			
(Nivolumab: hypothyroidism 0.9%; hyperthyroidism 0.9%, hypophysitis 0.9%, adrenal insufficiency 0.9%, secondary adrenal insufficiency 0.9%			
CA209238 (adjuvant melanoma)			
Any Grade	22.6	21.2	1.4 (4.0, 6.8)
(Nivolumab: adrenal disorder 1.3%, thyroid disorder 20.4%, diabetes 0.4%, and pituitary disorder 1.8%; Comparator: adrenal disorder 2.9%, thyroid disorder 12.6%, diabetes 0.2%, and pituitary disorder 12.4%)			
Grade 3-4	*1.5*	*4.2*	*-2.6 (5.0, -0.4)*
(Nivolumab: adrenal disorder 0.4%, thyroid disorder 0.7%, diabetes 0.2%, and pituitary disorder 0.4%; Comparator: 4.2% (adrenal disorder 0.9%, thyroid disorder 0.9%, and pituitary disorder 2.9%)			

Table 4-5: Immune-related AR: Immune-related Endocrinopathies

Immune-related Endocrinopathies

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA20976K (Stage IIB/C adjuvant melanoma)			
Any Grade	20.6	4.9	15.7 (11.0, 19.9)
(Nivolumab: adrenal disorder 2.1%, thyroid disorder 17.0%, diabetes 0.6%, and pituitary disorder 1.1%; Comparator: adrenal disorder 1.1%, thyroid disorder 3.4%, diabetes 0%, and pituitary disorder 0.8%)			
Grade 3-4	1.7	0	1.7 (0.1, 3.2)
(Nivolumab: adrenal disorder 0.6%, thyroid disorder 0.2%, diabetes 0.6%, and pituitary disorder 0.4%)			

CA2098FC	Nivolumab		
	Process C	Process D	DIFF (95% CI)
Any grade	33.3	28.0	-5.3 (-16.3, 5.8)
(Nivolumab Process C: adrenal disorder 1.6%, diabetes 0.8%, pituitary disorder 0.8%, thyroid disorder 31.0%; Nivolumab Process D: adrenal disorder 1.5%, diabetes 1.5%, pituitary disorder 1.5%, thyroid disorder 25.8%)			
Grade 3-4	1.6	2.3	0.7 (-3.5, 5.1)
(Nivolumab Process C: adrenal disorder 0.8%, diabetes 0.8%; Nivolumab Process D: adrenal disorder 0.8%, diabetes 0.8%, thyroid disorder 0.8%)			

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209017			
Any Grade	3.8	0	3.8 (0.2, 8.6)
(Nivolumab: thyroid disorder 3.8%)			
Grade 3-4	0	0	NA
CA209057			
Any Grade	9.4	0.4	9.0 (5.7, 13.0)
(Nivolumab: thyroid disorder 9.4%; Comparator: diabetes 0.4%)			
Grade 3-4	0	0	NA
CA209063			
Any Grade	6.0	NA	NA
(Nivolumab: thyroid disorder 8.6%, adrenal disorder 0.4%)			
Grade 3-4	0.9	NA	NA
(Nivolumab: adrenal insufficiency 0.9%)			
MDX1106-03			
3mg/kg			
Any Grade	11.1 SQ	NA	NA
(Nivolumab: Blood TSH increased 11.1%)	0 NSQ		
Grade 3-4	0 SQ	NA	NA
	0 NSQ		
All dose levels			
Any Grade	6.2	NA	
(Nivolumab: Blood TSH increased 2.3%, hypothyroidism 1.6%, autoimmune thyroiditis 0.8%, hyperthyroidism 0.8%, thyroiditis 0.8%)			
Grade 3-4	0	NA	

Table 4-5: Immune-related AR: Immune-related Endocrinopathies

Immune-related Endocrinopathies

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209025			
Any Grade	9.6	2.8	6.8 (3.6, 10.3)
(Nivolumab: adrenal disorder 1.5%, thyroid disorder 8.4%, diabetes 0.2%, and pituitary disorder 0.5%; Comparator: thyroid disorder 1.8% and diabetes 1.0%)			
Grade 3-4	1.0	0.3	0.7 (-0.6, 2.3)
(Nivolumab: hypothyroidism 8.8%, primary hypothyroidism 3.8%, thyroiditis 2.5%, hyperthyroidism 1.3%, blood TSH increased 1.3 % Comparator: diabetes 0.3%)			

cHL	Nivolumab	Comparator	DIFF (95% CI)
CA209205 Cohort B			
Any Grade	16.3	NA	NA
(Nivolumab: hypothyroidism 8.8%, primary hypothyroidism 3.8%, thyroiditis 2.5%, hyperthyroidism 1.3%, blood TSH increased 1.3 %)			
Grade 3-4	0	NA	NA
CA209205 Cohort A+B+C			
Any Grade	13.2	NA	NA
(Nivolumab: hypothyroidism 7.0%, primary hypothyroidism 2.9%, hyperthyroidism 2.1%, Blood TSH increased 1.2%, thyroiditis 0.8%)			
Grade 3-4	0	NA	NA
CA209039			
Any Grade	13.0	NA	NA
(Nivolumab: hypothyroidism 8.7%, hyperthyroidism 4.3%)			
Grade 3-4	0	NA	NA

SCCHN	Nivolumab	Comparator	DIFF (95% CI)
CA209141			
Any Grade	7.6	0.9	6.7 (1.9, 10.9)
(Nivolumab: adrenal disorder 0.4%, thyroid disorder 7.2%, and pituitary disorder 0.8%; Comparator: thyroid disorder 0.9%)			
Grade 3-4	0.4	0	0.4 (-2.9, 2.4)
(Nivolumab: adrenal disorder 0.4% and pituitary disorder 0.4%)			

Table 4-5: Immune-related AR: Immune-related Endocrinopathies

Immune-related Endocrinopathies

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209275			
Any Grade	14.4	NA	NA
(Nivolumab: thyroid disorder 13.0%, adrenal disorder 0.7%, pituitary disorder 0.7%, and diabetes 0.4%)			
Grade 3-4	0.4	NA	NA
(Nivolumab: pituitary disorder 0.4%)			
CA209032			
Any Grade	7.7	NA	NA
(Nivolumab: thyroid disorder 7.7%)			
Grade 3-4	0	NA	NA
CA209274			
Any Grade	19.1	3.7	15.4 (10.8, 20.0)
(Nivolumab: thyroid disorder 18.5%, adrenal disorder 0.6%, and diabetes 0.3%)			
Grade 3-4	0.3	0	0.3 (-0.8, 1.6)
(Nivolumab: diabetes 0.3%)			

ESCC	Nivolumab	Comparator	DIFF (95% CI)
ONO-4538-24 (CA209473)			
Any Grade	11.0	0.5	10.5 (6.3, 15.5)
(Nivolumab thyroid disorder 5.3%, pituitary disorder 0.5%; Comparator: thyroid disorder 0.5%)			
Grade 3-4	0	0	N.A.

OC/GEJC	Nivolumab	Comparator	DIFF (95% CI)
CA209577			
Any Grade	17.5	2.3	15.2 (11.2, 18.8)
(Nivolumab: thyroid disorder 16.7%, adrenal disorder 0.6%, pituitary disorder 0%, and diabetes 0.6%)			
Grade 3-4	0.9	0	0.9 (-0.6, 2.2)
(Nivolumab: thyroid disorder 0.4%, diabetes 0.4%, adrenal disorder 0.2%, and pituitary disorder 0%)			

Table 4-5: Immune-related AR: Immune-related Endocrinopathies

Immune-related Endocrinopathies

II. Nivolumab Combined with Ipilimumab (+-Chemo)

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209067			
Any Grade	33.2	11.6	21.7 (15.2, 27.9)
(Nivolumab: thyroid disorder 27.8%, pituitary disorder 8.6%, adrenal disorder 4.5%, and diabetes 1.0%; Comparator: thyroid disorder 6.1%, pituitary disorder 5.1%, and adrenal disorder 1.6%)			
Grade 3-4	6.4	2.6	3.8 (0.5, 7.3)
(Nivolumab: pituitary disorder 2.6%, adrenal disorder 1.9%, thyroid disorder 1.6%, and diabetes 0.6%; Comparator: pituitary disorder 2.3% and adrenal disorder 0.3%)			
CA209069			
Any Grade	28.7	13.0	15.7 (0.6, 27.7)
(Nivolumab: adrenal disorder 4.3%, diabetes 1.1%, thyroid disorder 20.2%, and pituitary disorder 12.8%; Comparator: adrenal disorder 4.3%, thyroid disorder 8.7%, and pituitary disorder 6.5%)			
Grade 3-4	5.3	4.3	1.0 (.7, 8.2)
(Nivolumab: adrenal disorder 1.1%, thyroid disorder 1.1%, diabetes 1.1%, and pituitary disorder 2.1%; Comparator: adrenal disorder 2.2% and pituitary disorder 4.3%)			
CA209004			
Any Grade	29.3	NA	NA
(Nivolumab: hypothyroidism 14.6%; hyperthyroidism 4.9%; hypophysitis 9.8%, adrenal insufficiency 2.4%)			
Grade 3-4	2.4	NA	NA
(Nivolumab: hypophysitis 2.4%, adrenal insufficiency 2.4%)			

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209214			
Any Grade	32.5	30.5	2.1(-3.5, 7.6)
(Nivolumab: thyroid disorder 27.2%, adrenal disorder 6.0%, pituitary disorder 4.4%, and diabetes 1.8%; Comparator: thyroid disorder 30.5%)			
Grade 3-4	6.9	0.2	6.8 (4.7, 9.2)
(Nivolumab: pituitary disorder 2.7%, adrenal disorder 2.6%, thyroid disorder 1.3%, and diabetes 1.1%; Comparator: thyroid disorder 0.2%)			
CA209016			
Any Grade	27.7		
(Nivolumab: thyroid disorder 23.4%, adrenal disorder 4.3%, and pituitary disorder 2.1%;			
Grade 3-4	4.3		
(Nivolumab: thyroid disorder 2.1%, and pituitary disorder 2.1%;			

Table 4-5: Immune-related AR: Immune-related Endocrinopathies

Immune-related Endocrinopathies

MPM	Nivolumab	Comparator	DIFF (95% CI)
CA209743			
Any Grade	17.3	0	17.3 (13.2, 22.0)
(Nivolumab: thyroid disorder 14.3%, adrenal disorder 2.0%, and pituitary disorder 4.0%)			
Grade 3-4	1.3	0	1.3 (-0.2, 3.4)
(Nivolumab: pituitary disorder 1.0%, and adrenal disorder 0.3%;			

CRC	Nivolumab	Comparator	DIFF (95% CI)
CA209142			
Any Grade	31.9		
(Nivolumab: thyroid disorder 25.2%, adrenal disorder 7.6% and pituitary disorder 3.4%)			
Grade 3-4	5.9		
(Nivolumab: thyroid disorder 3.4%, adrenal disorder 1.7% and pituitary disorder 1.7%)			
CA2098HW			
Any Grade	33.5	0	
(Nivolumab: thyroid disorder 24.0%, adrenal disorder 10.5%, pituitary disorder 5.0% and diabetes 1.0%)			
Grade 3-4	5.5	0	
(Nivolumab: adrenal disorder 3.0%, pituitary disorder 2.5%, and thyroid disorder 1.5%)			

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	27.3	0.3	27.0 (22.2, 32.1)
(Nivolumab: thyroid disorder 21.7%, pituitary disorder 6.5%, adrenal disorder 5.3%, diabetes 1.6%)			
Grade 3-4	5.9	0	5.9 (3.5, 9.0)
(Nivolumab: pituitary disorder 3.1%, adrenal disorder 2.5%, thyroid disorder 0.9%, diabetes 0.6%)			

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA2099LA			
Any Grade	24.0	0.3	23.7 (19.4, 28.4)
(Nivolumab: thyroid disorder 20.7%, pituitary disorder 2.0%, adrenal disorder 3.4%, Comparator: thyroid disorder 0.3%			
Grade 3-4	2.8	0	2.8 (1.1, 5.1)
(Nivolumab: adrenal disorder 1.4%, pituitary disorder 1.1%, thyroid disorder 0.3%; Comparator: none)			

HCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099DW			
Any Grade	28.3	31.4	-3.1 (-10.0, 3.9)

Table 4-5: Immune-related AR: Immune-related Endocrinopathies

Immune-related Endocrinopathies			
(Nivolumab: thyroid disorder 24.7%, pituitary disorder 2.4%, adrenal disorder 4.2%, diabetes 0.6%)			
Grade 3-4	3.6	0	3.6 (1.7, 6.2)
(Nivolumab: pituitary disorder 1.2%, adrenal disorder 1.2%, thyroid disorder 0.9%, diabetes 0.6%)			

IV. Nivolumab Combined with Chemotherapy

Gastric/GEJC/ OAC	Nivolumab	Comparator	DIFF (95% CI)
CA209649			
Any Grade	13.7	0.4	13.3 (10.9, 15.9)
(Nivolumab: thyroid disorder 12.3%, pituitary disorder 0.8%, adrenal disorder 0.5%, diabetes 0.3%, Comparator: thyroid disorder 0.4%			
Grade 3-4	0.6	0	0.6 (0.0, 1.5)
(Nivolumab: pituitary disorder 0.4%, adrenal disorder 0.1%, diabetes 0.1%; Comparator: none)			

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	12.3	0.3	11.9 (8.4, 16.1)
(Nivolumab: thyroid disorder 10.3%, adrenal disorder 2.3%, diabetes 0.6%, pituitary disorder 0.6%)			
Grade 3-4	1.6	0	1.6 (0.1, 3.7)
(Nivolumab: diabetes 0.6%, adrenal disorder 0.6%, pituitary disorder 0.3%)			

Resectable NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209816			
Any Grade	5.7	0	5.7 (2.3, 10.1)
(Nivolumab: thyroid disorder 5.1%, diabetes 0.6%)			
Grade 3-4	0	0	N.A.

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209901 substudy			
Any Grade	21.1	0	21.1 (16.6, 26.0)
(Nivolumab: thyroid disorder 20.4%, pituitary 1.0%, adrenal 0.7%, diabetes 0.3%)			
Grade 3-4	1.3	0	1.3 (-0.2, 3.3)
(Nivolumab: thyroid disorder 0.3%, pituitary 0.7%, adrenal 0.3%, diabetes 0%)			

Table 4-6: Immune-related AR: Immune-related Skin ARs

Immune-related Skin ARs

Characterization of risk *(Percent; All Treated)*

I. Nivolumab Monotherapy

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209066			
Any Grade	37.4	14.1	23.2 (14.9, 31.2)
Grade 3-4	1.5	0	1.5 (-0.6, 4.2)
CA209067			
Any Grade	45.7	55.3	-9.6 (-17.3, -1.8)
Grade 3-4	2.2	2.9	-0.7, -3.4, 2.0)
CA209037			
Any Grade	38.8	11.8	27.0 (17.5, 34.8)
Grade 3-4	1.5	0	1.5 (-2.2, 3.8)
MDX1106-03			
Any Grade	41.2	NA	NA
Grade 3-4	0	NA	NA
CA209238 (adjuvant melanoma)			
Any Grade	44.5	59.8	-15.4 (-21.7, -8.9)
Grade 3-4	1.1	6.0	-4.9 (-7.5, -2.5)
CA20976K (Stage IIB/C adjuvant melanoma)			
Any Grade	34.5	17.8	16.7 (10.3, 22.6)
Grade 3-4	1.1	0	1.1 (-0.4, 2.5)
CA2098FC	**Nivolumab**		
	Process C	**Process D**	
Any Grade	40.3	56.1	15.8 (3.6, 27.2)
Grade 3-4	1.6	0.8	-0.8 (-4.8, 2.8)

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209017			
Any Grade	9.2	8.5	0.6 (-6.6, 7.8)
Grade 3-4	0	1.6	-1.6 (-5.5, 1.5)
CA209057			
Any Grade	17.8	13.1	4.7 (-1.3, 10.7)
Grade 3-4	0.7	0	0.7 (-0.8, 2.5)
CA209063			
Any Grade	15.4	NA	NA
Grade 3-4	1.7	NA	NA
MDX1106-03			
3mg/kg			
Any Grade	16.7 SQ 10.5 NSQ	NA	NA
Grade 3-4	0 SQ 0 NSQ	NA	NA
All dose-levels			
Any Grade	15.5	NA	NA
Grade 3-4	0	NA	NA

Table 4-6: Immune-related AR: Immune-related Skin ARs

Immune-related Skin ARs

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209025			
Any Grade	24.9	38.5	-13.7 (-19.9, -7.2)
Grade 3-4	1.0	1.3	-0.3 (-2.0, 1.4)

cHL	Nivolumab	Comparator	DIFF (95% CI)
CA209205 Cohort B			
Any Grade	28.8	NA	NA
Grade 3-4	2.5	NA	NA
CA209205 Cohort A+B+C			
Any Grade	21.8	NA	NA
Grade 3-4	1.2	NA	NA
CA209039			
Any Grade	21.7	NA	NA
Grade 3-4	0	NA	NA

SCCHN	Nivolumab	Comparator	DIFF (95% CI)
CA209141			
Any Grade	15.7	12.6	3.1 (-5.4, 10.2)
Grade 3-4	0	1.8	-1.8 (-6.3, 0.3)

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209275			
Any Grade	17.4	NA	NA
Grade 3-4	1.5	NA	NA
CA209032			
Any Grade	42.3	NA	NA
Grade 3-4	2.6	NA	NA
CA209274			
Any Grade	40.7	17.8	22.9 (16.3, 29.3)
Grade 3-4	1.7	0	1.7 (0.3, 3.7)

ESCC	Nivolumab	Comparator	DIFF (95% CI)
ONO-4538-24 (CA209473)			
Any Grade	20.6	20.2	0.4 (-7.4, 8.1)
Grade 3-4	1.9	1.0	1.0 (-1.8, 3.9)

OC/GEJC	Nivolumab	Comparator	DIFF (95% CI)
CA209577			
Any Grade	24.4	10.8	13.7 (8.1, 18.7)
Grade 3-4	1.3	0.4	0.9 (-1.0, 2.3)

II. Nivolumab Combined with Ipilimumab (+-Chemo)

Table 4-6: Immune-related AR: Immune-related Skin ARs

Immune-related Skin ARs

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209067			
Any Grade	61.3	55.3	6.0 (-1.7, 13.7)
Grade 3-4	6.1	2.9	3.2 (-0.1, 6.7)
CA209069			
Any Grade	71.3	54.3	16.9 (0.2, 33.3)
Grade 3-4	8.5	0	8.5 (-0.2, 15.9)
CA209004			
Any Grade	82.9	NA	NA
Grade 3-4	17.1	NA	NA

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209214			
Any Grade	48.8	56.8	-8.0 (-13.9, -2.1)
Grade 3-4	3.7	9.9	- 6.3(-9.3, -3.3)
CA209016			
Any Grade	48.9	NA	NA
Grade 3-4	0	NA	NA

MPM	Nivolumab	Comparator	DIFF (95% CI)
CA209743			
Any Grade	36.0	9.9	26.1 (19.5, 32.4)
Grade 3-4	3.0	0.4	2.6 (0.5, 5.3)

CRC	Nivolumab	Comparator	DIFF (95% CI)
CA209142			
Any Grade	35.3	NA	NA
Grade 3-4	4.2	NA	NA
CA2098HW			
Any Grade	34.5	20.5	14.0 (2.6, 23.9)
Grade 3-4	2.5	2.3	0.2 (-5.6, 3.8)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	34.2	3.6	30.5 (24.9, 36.1)
Grade 3-4	4.0	0	4.0 (2.0, 6.8)

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA2099LA			
Any Grade	37.7	6.9	30.8 (25.0, 36.4)
Grade 3-4	4.5	0.3	4.2 (2.0, 6.9)

HCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099DW			

Table 4-6: Immune-related AR: Immune-related Skin ARs

Immune-related Skin ARs			
Any Grade	51.8	42.8	9.0 (1.4, 16.5)
Grade 3-4	5.7	4.9	0.8 (-2.8, 4.4)

IV. Nivolumab Combined with Chemotherapy

Gastric/GEJC/ OAC	Nivolumab	Comparator	DIFF (95% CI)
CA209649			
Any Grade	27.4	13.7	13.7 (9.7, 17.6)
Grade 3-4	3.3	0.8	2.5 (1.2, 4.1)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	17.1	3.9	13.1 (8.4, 18.0)
Grade 3-4	0.3	0	0.3 (-1.0, 1.8)

Resectable NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209816			
Any Grade	22.2	8.5	13.6 (6.2, 21.1)
Grade 3-4	2.3	0	2.3 (-0.3, 5.7)

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209901 substudy			
Any Grade	31.6	6.6	25.0 (18.9, 30.9)
Grade 3-4	2.6	0.3	2.3 (0.2, 4.8)

Table 4-7: Immune-related AR: Other irARs

Other irARs

Characterization of risk *(Percent; All Treated)*

I. Nivolumab Monotherapy

Melanoma	Nivolumab	Comparator
CA209066		
No pancreatitis, demyelination, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade		
Guillain-Barre syndrome	0.5	0
uveitis	0.5	0
Grade 3-4		
Guillain-Barre syndrome	0.5	0
CA209067		
No Guillain-Barre syndrome, demyelination, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade		
myasthenic syndrome	0	0.3
myositis	0.6	0
pancreatitis	1.6	1.0
uveitis	1.3	1.0
Grade 3-4		
myositis	0.3	
pancreatitis	1.6	0.3
uveitis	0	0.3
CA209037		
No Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade		
demyelination	0.4	0
pancreatitis	1.5	0
uveitis	1.5	0
Grade 3-4		
demyelination	0.4	0
pancreatitis	0.7	0
MDX1106-03		
No demyelination, Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade		
uveitis	5.9	0
Grade 3-4	0	0
CA209238 (adjuvant melanoma)		
No myasthenic syndrome, demyelination,, myocarditis, or rhabdomyolysis reported)		
Any Grade		
pancreatitis	0.7	0.7
uveitis	0.4	0.7
myositis	0	0.7
Guillain-Barre syndrome	0	0.2
encephalitis	0	0.2
Grade 3-4		
pancreatitis	0.4	0.7
Guillain-Barre syndrome	0	0.2

Table 4-7: Immune-related AR: Other irARs

Other irARs

encephalitis	0	0.2
CA20976K (Stage IIB/C adjuvant melanoma)		
No myasthenic syndrome, demyelination, Guillain-Barre syndrome, encephalitis, graft versus host disease, autoimmune cytopenia, autoimmune eye disorder, or immune-mediated arthritis reported.		
Any Grade		
pancreatitis	1.5	0
uveitis	0.4	0
myocarditis	0.6	0
myositis/rhabdomyolysis	1.5	0.8
Grade 3-4		
pancreatitis	0.4	0
myocarditis	0.4	0
myositis/rhabdomyolysis	1.0	0.4
CA2098FC	**Nivolumab**	
	Process C	**Process D**
No myasthenic syndrome, demylineation, Guillain-Barre syndrome, myositis, or encephalitis reported		
Any Grade		
pancreatitis	0	1.5
myocarditis	0	1.5
uveitis	0.8	0.8
myositis	0	0.8
rhabdomyolysis	0.8	0
Grade 3-4		
myocarditis	0	1.5
pancreatitis	0	0.8

Table 4-7: Immune-related AR: Other irARs

Other irARs

NSCLC	Nivolumab	Comparator
CA209017		
No uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myositis, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade		
myasthenic syndrome	0.8	0
Grade 3-4		
myasthenic syndrome	0.8	0
CA209057		
No myasthenic syndrome uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myositis, myocarditis, or rhabdomyolysis reported		
Any Grade		
encephalitis	0.3	0
Grade 3-4		
encephalitis	0.3	0
CA209063		
No uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade	0	0
Grade 3-4	0	0
MDX1106-03		
3mg/kg		
No uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade SQ		
myositis	5.6	NA
Any Grade NSQ	0	NA
Grade 3-4 SQ		
myositis	5.6	NA
Grade 3-4 NSQ	0	NA
All dose-levels		
Any Grade	0	NA
Grade 3-4	0	NA

RCC	Nivolumab	Comparator
CA209025		
No demyelination, Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade		
pancreatitis	0.2	0
uveitis	0.2	0
Grade 3-4	0	0

Table 4-7: Immune-related AR: Other irARs

Other irARs

cHL	Nivolumab	Comparator
CA209205 Cohort B		
No demyelination, Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade		
pancreatitis	2.5	NA
uveitis	1.3	NA
Grade 3-4		
pancreatitis	1.3	NA
CA209205 Cohort A+B+C		
No demyelination, Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, or rhabdomyolysis reported		
Any Grade		NA
encephalitis	0.4	NA
pancreatitis	1.2	NA
uveitis	1.2	NA
Grade 3-4		
encephalitis	0.4	NA
pancreatitis	0.4	NA
CA209039		
No demyelination, Guillain-Barre syndrome, uveitis, myasthenic syndrome, myocarditis, or rhabdomyolysis reported		
Any Grade		
pancreatitis	4.3	NA
encephalitis	4.3	NA
myositis	4.3	NA
Grade 3-4		
pancreatitis	4.3	NA
encephalitis	4.3	NA

SCCHN	Nivolumab	Comparator
CA209141		
No myasthenic syndrome, uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myositis, myocarditis, rhabdomyolysis, or encephalitis reported		
Any Grade	0	0
Grade 3-4	0	0

Table 4-7: Immune-related AR: Other irARs

Other irARs

UC	Nivolumab	Comparator
CA209275		
Any Grade	0	NA
Grade 3-4	0	NA
CA209032		
Any Grade		
pancreatitis	1.3	NA
Grade 3-4		
pancreatitis	1.3	NA
CA209274		
Any Grade		
myasthenic syndrome	0.6	NA
demyelination event	0.3	NA
guillain-barre syndrome	0	NA
pancreatitis	0.3	NA
uveitis	0.3	NA
encephalitis	0	NA
myocarditis	0.9	NA
myositis/ rhabdomyolysis	0.6	NA
graft versus host disease	0	NA
Grade 3-4		
myasthenic syndrome	0.6	NA
demyelination event	0.3	NA
guillain-Barre syndrome	0	NA
pancreatitis	0.3	NA
uveitis	0	NA
encephalitis	0	NA
myocarditis	0.6	NA
myositis/ rhabdomyolysis	0	NA
graft versus host disease	0	NA

Table 4-7: Immune-related AR: Other irARs

Other irARs

ESCC	Nivolumab	Comparator	DIFF (95% CI)
ONO-4538-24 (CA209473)			
Any Grade	0	0	NA
Grade 3-4	0	0	NA

OC/GEJC	Nivolumab	Comparator
CA209577		
No demyelination, uveitis, myasthenic syndrome, encephalitis, myositis/rhabdomyolysis, or graft versus host disease reported		
Any Grade		
Guillain-Barre syndrome	0.2	0
pancreatitis	0.2	0
myocarditis	0.6	0
Grade 3-4		
Guillain-Barre syndrome	0.2	0
pancreatitis	0.2	0
myocarditis	0.6	0

II. Nivolumab Combined with Ipilimumab (+-Chemo)

Melanoma	Nivolumab	Comparator
CA209067		
No demyelination, myocarditis, or rhabdomyolysis reported		
Any Grade		
Guillain-Barre syndrome	0.3	0
pancreatitis	1.3	1.0
uveitis	1.6	1.0
myositis	1.0	0
encephalitis	0.3	0
myasthenic syndrome	0	0.3
Grade 3-4		
Guillain-Barre syndrome	0.3	
pancreatitis	0.6	0.3
encephalitis	0.3	
uveitis	0	0.3
CA209069		
No pancreatitis. demyelination, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis , or encephalitis reported		
Any Grade		
Guillain-Barre syndrome	1.1	0
pancreatitis	2.1	0
uveitis	2.1	0
Grade 3-4		
Guillain-Barre syndrome	1.1	0
pancreatitis	2.1	0
CA209004		

Table 4-7: Immune-related AR: Other irARs

Other irARs		
No demyelination, Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis , or encephalitis reported		
Any Grade		
uveitis	2.4	0
pancreatitis	2.4	0
Grade 3-4		
uveitis	2.4	0
pancreatitis	2.4	0

RCC	Nivolumab	Comparator
CA209214		
No demyelination or Guillain-Barre syndrome reported		
Any Grade		
myasthenic syndrome	0.2	0
pancreatitis	2.4	0.3
uveitis	0.4	0.2
encephalitis	0.2	0
myocarditis	0.2	0
myositis	0.5	0
rhabdomyolysis	0.2	0
Grade 3-4		
myasthenic syndrome	0.2	0
pancreatitis	1.1	0.7
encephalitis	0.2	0
myocarditis	0.2	0
myositis	0.2	0
rhabdomyolysis	0.2	0
CA209016		
No myasthenic syndrome, demyelination, Guillain-Barre syndrome, pancreatitis, or encephalitis.		
Any Grade		
uveitis	2.1	NA
Grade 3-4	0	NA

MPM	Nivolumab	Comparator
CA209743		
No demyelination, Guillain-Barre syndrome, rhabdomyolysis, or Graft versus Host Disease		
Any Grade		
myasthenic syndrome	0.7	0
pancreatitis	1.3	0
uveitis	0.7	0
encephalitis	1.0	0
myocarditis	0.3	0
myositis	0.7	0

Table 4-7: Immune-related AR: Other irARs

Other irARs		
Grade 3-4		
myasthenic syndrome	0.7	0
pancreatitis	0.3	0
uveitis	0.3	0
encephalitis	0.3	0
myocarditis	0.3	0
myositis	0.7	0

CRC	Nivolumab	Comparator
CA209142		
No myasthenic syndrome, demyelination, Guillain-Barre syndrome, myocarditis, rhabdomyolysis or graft versus host disease		
Any Grade		
pancreatitis	0.8	NA
encephalitis	0.8	NA
myositis	1.7	NA
uveitis	0.8	NA
Grade 3-4		
pancreatitis	0.8	NA
encephalitis	0.8	NA
myositis	0.8	NA
uveitis	0.8	NA
CA2098HW		
No demyelination, Guillain-Barre syndrome, uveitis or graft versus host disease		
Any Grade		
myasthenic syndrome	0.5	0
pancreatitis	1.0	0
encephalitis	1.5	0
myocarditis	1.5	0
Myositis/rhabdomyolysis	1.0	0
Grade 3-4		
myasthenic syndrome	0.5	0
pancreatitis	0	0
encephalitis	1.5	0
myocarditis	1.5	0
myositis/rhabdomyolysis	0.5	0
Grade 5		
myasthenic syndrome	0	0
pancreatitis	0.5	0
encephalitis	0	0
myocarditis	0	0
Myositis//rhabdomyolysis	0	0

OSCC	Nivolumab	Comparator
CA209648		
No myasthenic syndrome, demyelination, Guillain-Barre syndrome, or Graft versus Host Disease		

Table 4-7: Immune-related AR: Other irARs

Other irARs		
Any Grade		
pancreatitis	0.9	0
myocarditis	0.6	0
myositis	0.6	0
pancreatitis acute	0.3	0
uveitis	0.3	0
Vogt-Koyanagi-Harada disease	0.3	0
encephalitis	0.3	0
immune-mediated encephalitis	0.3	0
immune-mediated encephalopathy	0.3	0
Grade 3-4		
pancreatitis	0.6	0
pancreatitis acute	0.3	0
uveitis	0.3	
encephalitis	0.3	0
immune-mediated encephalitis	0.3	0
immune-mediated encephalopathy	0.3	0

NSCLC	Nivolumab	Comparator
CA2099LA		
No myasthenic syndrome, demyelination, uveitis, myocarditis, rhabdomyolysis, graft versus host disease or Guillain-Barre syndrome reported		
Any Grade		
pancreatitis	1.4	0
encephalitis	0.6	0
myositis	0.0	0.3
Grade 3-4		
pancreatitis	0.8	0
encephalitis	0.3	0
Grade 5	0	0

HCC	Nivolumab	Comparator
CA2099DW		
No Guillain-Barre syndrome, uveitis, encephalitis or graft versus host disease reported		
Any Grade		
pancreatitis	2.7	0.6
Myositis/ Rhabdomyolysis	1.2	0.3

Table 4-7: Immune-related AR: Other irARs

Other irARs		
myocarditis	0.9	0
demyelination	0.3	0
myasthenic syndrome	0.3	0
Grade 3-4		
pancreatitis	1.2	0.6
Myositis/ Rhabdomyolysis	0.9	0.3
myocarditis	0.6	0
myasthenic syndrome	0.3	0
demyelination	0	0
Grade 5	0	0

IV. Nivolumab Combined with Chemotherapy

Gastric/GEJC/OAC	Nivolumab	Comparator
CA209649		
No demyelination, myasthenic syndrome, myositis/rhabdomyolysis, or GVHD reported		
Any Grade		
Guillain-Barre syndrome	0.1	0
pancreatitis	0.4	0.3
uveitis	0.1	0
encephalitis	0.1	0
myocarditis	0.3	0
Grade 3-4		
Guillain-Barre syndrome	0.1	0
pancreatitis	0.3	0.1
uveitis	0.1	0
encephalitis	0.1	0
myocarditis	0.1	0

OSCC	Nivolumab	Comparator
CA209648		
No myasthenic syndrome, demyelination, Guillain-Barre syndrome, pancreatitis, encephalitis, myocarditis, or Graft versus Host Disease		
Any Grade		
uveitis	0.6	0
myositis	0.3	0
rhabdomyolysis	0.3	0
Grade 3-4		
rhabdomyolysis	0.3	0

Table 4-7: Immune-related AR: Other irARs

Other irARs

Resectable NSCLC	Nivolumab	Comparator
CA209816		
No pancreatitis, encephalitis, demyelination, myasthenic syndrome, myositis/rhabdomyolysis, graft versus host disease, Guillain-Barre syndrome, uveitis, myocarditis, or graft versus host disease reported		

UC	Nivolumab	Comparator
CA209901 substudy		
No myasthenic syndrome, demyelination, Guillain-Barre syndrome, uveitis, or graft versus host disease reported		
Any Grade		
pancreatitis	1.0	0
myocarditis	1.0	0
encephalitis	0.3	0
myositis/ rhabdomyolysis	0.3	0
Grade 3-4		
pancreatitis	1.0	0
myocarditis	0.7	0
encephalitis	0.3	0
myositis/ rhabdomyolysis	0.3	0

Table 4-8: Important Identified Risk: Severe Infusion Reactions

Severe Infusion Reactions

Characterization of risk *(Percent; All Treated)*

I. Nivolumab Monotherapy

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209066			
Any Grade	7.3	6.3	0.9 (-4.1, 6.0)
Grade 3-4	0	0	NA
CA209067			
Any Grade	4.5	2.6	1.9 (-1.1, 5.1)
Grade 3-4	0.3	0.3	0 (-1.5, 1.5)
CA209037			
Any Grade	3.7	9.8	-6.1 (-13.6, 0.8)
Grade 3-4	0.4	0	-0.4 (-3.3, 2.1)
MDX1106-03			
Any Grade	17.6	NA	NA
Grade 3-4	0	NA	NA
CA209238 (adjuvant melanoma)			
Any Grade	2.4	2.0	0.4 (-1.6, 2.5)
Grade 3-4	0.2	0	0.2 (-0.6, 1.2)
CA20976K (Stage IIB/C adjuvant melanoma)			
Any Grade	5.9	0.8	5.2 (2.6, 7.6)
Grade 3-4	0	0	NA
CA2098FC	**Nivolumab**		
	Process C	**Process D**	**DIFF (95% CI)**
Any Grade	1.6	6.1	4.5 (-0.4, 10.1)
Grade 3-4	0	0	NA

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209017			
Any Grade	0.8	2.3	-1.6 (-5.9, 2.2)
Grade 3-4	0	0.8	-0.8 (-4.3, 2.1)
CA209057			
Any Grade	2.8	4.5	-1.7 (-5.2, 1.5)
Grade 3-4	0	0.4	-0.4 (-2.1, 1.0)
CA209063			
Any Grade	4.3	NA	NA
Grade 3-4	2.6	NA	NA
MDX1106-03			
3mg/kg			
Any Grade	0 SQ 0 NSQ	NA	NA
Grade 3-4	0 SQ 0 NSQ	NA	NA
All dose-levels			
Any Grade	3.9	NA	NA
Grade 3-4	0.8	NA	NA

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209025			

Table 4-8: Important Identified Risk: Severe Infusion Reactions

Severe Infusion Reactions			
Any Grade	5.2	0.3	4.9 (2.8, 7.5)
Grade 3-4	0.2	0	-0.2 (-0.7, 1.4)

cHL	Nivolumab	Comparator	DIFF (95% CI)
CA209205 Cohort B			
Any Grade	21.3	NA	NA
Grade 3-4	0	NA	NA
CA209205 Cohort A+B+C			
Any Grade	16.0	NA	NA
Grade 3-4	0.8	NA	NA
CA209039			
Any Grade	8.7	NA	NA
Grade 3-4	0	NA	NA

SCCHN	Nivolumab	Comparator	DIFF (95% CI)
CA209141			
Any Grade	1.3	1.8	-0.5 (-5.1, 2.2)
Grade 3-4	0	0.9	-0.9 (-4.9, 0.9)

UC	Nivolumab	Comparator	DIFF (95% CI)
CA209275			
Any Grade	1.1	NA	NA
Grade 3-4	0.4	NA	NA
CA209032			
Any Grade	2.6	NA	NA
Grade 3-4	0	NA	NA
CA209274			
Any Grade	4.6	0.9	3.7 (1.3, 6.5)
Grade 3-4	0.6	0	0.6 (-0.6, 2.1)

ESCC	Nivolumab	Comparator	DIFF (95% CI)
ONO-4538-24 (CA209473)			
Any Grade	1.4	1.0	0.5 (-2.2, 3.3)
Grade 3-4	0.5	0	0.5 (-1.4, 2.7)

OC/GEJC	Nivolumab	Comparator	DIFF (95% CI)
CA209577			
Any Grade	1.9	1.2	0.7 (-1.6, 2.4)
Grade 3-4	0	0	N.A.

Table 4-8: Important Identified Risk: Severe Infusion Reactions

Severe Infusion Reactions

II. Nivolumab Combined with Ipilimumab (+/-Chemo)

Melanoma	Nivolumab	Comparator	DIFF (95% CI)
CA209067			
Any Grade	4.2	2.6	1.6 (1.4, 4.7)
Grade 3-4	0	0.3	-0.3 (-1.8, 0.9)
CA209069			
Any Grade	3.2	2.2	1.0 (-8.4, 7.1)
Grade 3-4	0	0	NA
CA209004			
Any Grade	2.4	NA	NA
Grade 3-4	0	NA	NA

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA209214			
Any Grade	4.0	1.1	2.9 (1.0, 5.0)
Grade 3-4	0	0.4	-0.4 (-1.4, 0.4)
CA209016			
Any Grade	10.6	NA	NA
Grade 3-4	0	NA	NA

MPM	Nivolumab	Comparator	DIFF (95% CI)
CA209743			
Any Grade	12.0	2.5	9.5 (5.4, 13.9)
Grade 3-4	1.3	0	1.3 (-0.2, 3.4)

CRC	Nivolumab	Comparator	DIFF (95% CI)
CA209142			
Any Grade	3.4	NA	NA
Grade 3-4	0	NA	NA
CA2098HW			
Any Grade	4.0	9.1	-5.1 (-13.2, 0.7)
Grade 3-4	0	2.3	-2.3 (-7.9, 0.2)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	2.8	0.3	2.5 (0.5, 4.9)
Grade 3-4	0	0	NA

NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA2099LA			
Any Grade	4.7	1.1	3.6 (1.1, 6.4)
Grade 3-4	0.6	0.6	0.0 (-1.6, 1.5)

HCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099DW			

Table 4-8: Important Identified Risk: Severe Infusion Reactions

Severe Infusion Reactions			
Any Grade	2.4	0	2.4 (0.7, 4.7)
Grade 3-4	0.3	0	0.3 (-0.9, 1.7)

III. Nivolumab (240 mg) Combined with Cabozantinib (40 mg)

RCC	Nivolumab	Comparator	DIFF (95% CI)
CA2099ER			
Any Grade	2.5	0.3	2.2 (0.3, 4.6)
Grade 3-4	0	0	N.A.

IV. Nivolumab + Chemotherapy

Gastric/GEJC/ OAC	Nivolumab	Comparator	DIFF (95% CI)
CA209649			
Any Grade	14.2	5.5	8.7 (5.8, 11.7)
Grade 3-4	2.2	1.4	0.7 (-0.6, 2.2)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	1.9	0.3	1.6 (-0.2, 3.8)
Grade 3-4	0	0	N.A.

Resectable NSCLC	Nivolumab	Comparator	DIFF (95% CI)
CA209816			
Any Grade	5.7	2.8	2.8 (-1.6, 7.6)
Grade 3-4	2.3	1.1	1.1 (-2.1, 4.7)

UC	Nivolumab	Comparator
CA209901 substudy		
No myasthenic syndrome, demyelination, Guillain-Barre syndrome, uveitis, or graft versus host disease reported		
Any Grade		
pancreatitis	1.0	0
encephalitis autoimmune	0.3	0
immune-mediated myocarditis	0.3	0
myocarditis	0.7	0
dermatomyositis	0	0.3
rhabdomyolysis	0.3	0
Grade 3-4		
pancreatitis	1.0	0
encephalitis autoimmune	0.3	0
immune-mediated myocarditis	0.3	0
myocarditis	0.3	0
dermatomyositis	0	0.3

Table 4-8: Important Identified Risk: Severe Infusion Reactions

Severe Infusion Reactions			
	rhabdomyolysis	0.3	0

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

The Marketing Authorization Holder shall ensure that in each Member State where OPDIVO is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use OPDIVO have access to/are provided with the patient alert card.

Key Elements of the Patient Alert Card:

- Nivolumab can cause serious adverse reactions that can affect various organ systems that can lead to death and need to be addressed immediately
- Description of the main symptoms of the important adverse reactions and highlight the importance of notifying the treating physician immediately if symptoms occur, persist or worsen
- Description of the importance of not attempting to self-treat any symptoms without consulting with healthcare professional (HCP) first
- Provides information regarding the weblink of the Package Leaflet on the EMA website
- Highlights the importance of carrying the detachable wallet-sized Patient Alert Card at all times to show at all medical visits to HCPs other than prescribers (eg, emergency HCPs)
- Alert card contains prompts to enter contact details of the treating physician and alerts other physician that the patient is treated with nivolumab

The Marketing Authorization Holder shall agree the format and content of the above material with the National Competent Authority prior to launch of OPDIVO in the Member State.