IPILIMUMAB
RISK MANAGEMENT PLAN

Version Number: 45.0

Data-lock Point for this RMP: 24-Mar-2024

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LIST OF ABBREVIATIONS

Term	Definition
AASLD	American Association for the Study of Liver Diseases
ADR	Adverse drug reaction
AE(s)	Adverse Event(s)
AIH	Autoimmune Hepatitis
APC	Adenomatous polyposis coli
ARCD	Acquired renal cystic disease
ASR	Age-standardized rate
AUC	Area Under the Curve
BMS	Bristol Myers Squibb
CIMP	CpG island methylator phenotype
CLL	Chronic Lymphocytic Leukemia
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
CSR	Clinical study report
CTLA	Cytotoxic T-lymphocyte Antigen
DALY	Disability-adjusted life years
DMTR	Dutch Melanoma Treatment Registry
DNA	Deoxyribonucleic Acid
dMMR	Mismatch repair deficient
DTIC	Dacarbazine
EAP	Expanded Access Protocol
EASL	European Association for the Study of the Liver
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GBS	Guillain-Barré Syndrome
GFR	Glomerular filtration rate

Term	Definition
GI	Gastrointestinal
HAHA	Human Anti-Human Antibody
HBV	Hepatitis B virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HCP	Healthcare Provider
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HLGT	High Level Group Term
HLT	High Level Term
HNPCC	Hereditary nonpolyposis colorectal cancer
IARC	International Agency for Research on Cancer
ICH	International conference of Harmonization
IFN	Interferon
IFNα	Interferon alpha
IARC	International Agency for Research on Cancer
Ig	Immunoglobulin
IL	Interleukin
irARs	Immune-Related Adverse Reactions
IV	Intravenous
Kg	Kilogram
LFTs	Liver Function Tests
LPLV	Last Patient Last Visit
mAb	Monoclonal Antibody
MAFLD	Metabolic dysfunction associated fatty liver disease
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated, extracellular signal-regulated kinase
Mg	Milligram
MOA	Mechanism of Action
MPM	Malignant pleural mesothelioma
mWHO	Modified World Health Organization
mL	Milliliter
MG	Myasthenia Gravis

Term	Definition
MSI-H	Microsatellite instability high
N/A, NA	Not Applicable
NAFLD	Non-alcoholic fatty liver disease
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
NMSC	Non-Melanoma Skin Cancer
NPCR	National Program of Cancer Registries
NSCLC	Non-small cell lung cancer
OAC	Oesophageal adenocarcinoma
OC	Oesophageal cancer
OSCC	Oesophageal squamous cell carcinoma
OS	Overall Survival
PAES	Post-authorisation efficacy study
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee within EMA
PFS	Progression Free Survival
PI	Package Insert
PIL	Patient Information Leaflet
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic(s)
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person Responsible for Pharmacovigilance
rIL	Recombinant Interleukin
RCC	Renal Cell Carcinoma
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease
SEER	Surveillance, Epidemiology, and End Results
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
ST	Solid Tumours

Term	Definition
TEN	Toxic Epidermal Necrolysis
TGF	Transforming Growth Factor
TNF	Tumor Necrosis Factor
UK	United Kingdom
US	United States
WHO	World Health Organization

EU RISK MANAGEMENT PLAN FOR IPILIMUMAB

RMP version to be assessed as part of this application:

Version Number: 45.0

Data-lock Point for this RMP: 24-Mar-2024

Date of Final Sign-off: 11-Aug-2025

Rationale for submitting an updated RMP: Revise the due date related to the PAES CA2098Y8 in Part IV of 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	V44.2 / 28-Feb-2025
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	NA	V44.2 / 28-Feb-2025
SII Non-clinical part of the safety specification	N/A	V10.0/ 26-Sep-2014
SIII Clinical trial exposure	NA	V44.2 / 28-Feb-2025
SIV Populations not studied in clinical trials	NA	V44.2 / 28-Feb-2025
SV Post-authorisation experience	N/A	V41.3 / 19-Dec-2024
SVI Additional EU requirements for the safety specification	N/A	V18.6/ 18-Jan-2018
SVII Identified and potential risks	NA	V44.2 / 28-Feb-2025
SVIII Summary of the safety concerns	NA	V44.2 / 28-Feb-2025
Part III Pharmacovigilance Plan	N/A	V40.1 / 07-Jun-2024
Part IV Plan for post-authorisation efficacy studies	Revise the due date related to the PAES CA2098Y8.	V45.0 / pending
Part V Risk Minimization Measures	NA	V44.2 / 28-Feb-2025
Part VI Summary of the Risk Management Plan	NA	V44.2 / pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	N/A	V40.1 / 07-Jun-2024

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	N/A	V26.2/03-Oct-2019
ANNEX 4 Specific adverse drug reaction follow-up forms	N/A	V10.0/26-Sep-2014
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	N/A	V38.1 / 31-May-2023
ANNEX 6 Details of proposed additional risk minimisation activities	NA	V44.2 / 28-Feb-2025
ANNEX 7 Other supporting data	NA	V44.2 / 28-Feb-2025
ANNEX 8 Summary of changes to the risk management plan over time	Update to include Version 45.0	V45.0 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP: Version number: 44.2

Approved with procedure: EMEA/H/C/WS2717/0115

Date of approval: 28-Feb-2025

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 authorisation 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)	Ipilimumab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, monoclonal antibodies ATC code: L01XC11
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	YERVOY®
Marketing authorisation procedure	Centralized Procedure according to Article 3(1) Indent 1 of Regulation (EC) No 726/2004
Brief description of the product	Ipilimumab is a fully human anti-CTLA-4 monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology. CTLA-4 is a negative regulator of T-cell activation. Ipilimumab is a T-cell potentiator that specifically blocks the inhibitory signal of CTLA-4, resulting in T-cell activation, proliferation, and lymphocyte infiltration into tumours, leading to tumour cell death. The mechanism of action of ipilimumab is indirect, through enhancing T-cell mediated immune response.
Hyperlink to the Product Information	Refer to eCTD sequence 0287

Table 1-1: Product Details

Indication(s) in the EEA	**Current:** **YERVOY as monotherapy** Treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older. **YERVOY in combination with nivolumab:** • Treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older. • For the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma. • For the first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM). • Treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) colorectal cancer (CRC) in the following settings: o first-line treatment of unresectable or metastatic CRC o treatment of metastatic CRC after prior fluoropyrimidine based combination chemotherapy • For the first-line treatment of patients with unresectable advanced, recurrent metastatic OSCC with tumour cell PD-L1 expression ≥ 1%. • For the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC) **YERVOY in combination with nivolumab and chemotherapy:** • YERVOY in combination with OPDIVO 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. **Proposed:** None

Table 1-1: Product Details

Dosage in the EEA	**Current:** **YERVOY as monotherapy** **Melanoma** Adults and Adolescents 12 Years of Age or Older The recommended induction regimen of YERVOY® is 3 mg/kg administered intravenously over a 30-minute period every 3 weeks for a total of 4 doses. Patients should receive the entire treatment regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response should be conducted only after completion of treatment therapy. **YERVOY in combination with nivolumab:** **Melanoma:** In adults and adolescents 12 years of age and older and weighing at least 50 kg, the recommended dose is 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab 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 1. 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 and weighing less than 50 kg, the recommended dose is 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab 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 1. 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 1: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab

	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 weighing at least 50 kg): 240 mg every 2 weeks over 30 minutes **or** 480 mg every 4 weeks over 60 minutes 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	-

Table 1-1: Product Details

RCC

The recommended dose is 1 mg/kg ipilimumab in combination with 3 mg/kg nivolumab 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, 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 ipilimumab and nivolumab if using 240 mg every 2 weeks; or
- 6 weeks after the last dose of the combination of ipilimumab and nivolumab if using 480 mg every 4 weeks

Table 2: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab 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
Ipilimumab	1 mg/kg over 30 minutes	-

dMMR/MSI-H CRC

The recommended dose for first-line treatment of dMMR or MSI-H CRC is 1 mg/kg ipilimumab in combination with 240 mg of nivolumab administered intravenously every 3 weeks for a maximum of 4 doses, followed by nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks, 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. 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 1 mg/kg ipilimumab in combination with 3 mg/kg nivolumab 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 3. For the

Table 1-1: Product Details

monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab.

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

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

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

Unresectable or advanced HCC:
The recommended dose is 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab 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 4. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months. 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 1-1: Product Details

Table 4 **Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab 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	-

YERVOY in combination with nivolumab and chemotherapy:

NSCLC

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, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab administered intravenously every 3 weeks in combination with 1 mg/kg ipilimumab every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Duration of treatment

Treatment with YERVOY® in combination with nivolumab, should be continued for the four doses of the combination therapy 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). Atypical responses (i.e., 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 YERVOY in combination with nivolumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.
LFTs and thyroid function tests should be evaluated at baseline and before each dose of YERVOY®. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with YERVOY®.

Proposed:

None

Pharmaceutical form (s) and strength(s)

Current:

5 mg/ml concentrate for solution for infusion

Table 1-1: Product Details

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 Metastatic Melanoma

Metastatic Melanoma	
Incidence	• International incidence varies 100- to 150-fold among different populations[1,2] • The highest worldwide incidence of melanoma has been reported for Australia and New Zealand. The age-standardized (world) estimated 2012 incidence rates ranged from 34.9 to 35.8 per 100,000 for Australia and New Zealand, respectively.[3,4] Analyses of US-based cancer registry data (the CDC's NPCR; NCI's SEER) estimated the age-adjusted (to 2000 US standard population) incidence of melanoma for 2012 to be 19.9 per 100,000 persons. [5] • The WHO's IARC estimated that there were approximately 104,00 incident melanoma cases in the WHO European Region in 2012. The estimated age-standardized (world) 2012 incidence rate for Europe was 8.6 per 100,000; and for the EU-28 it was 10.2 per 100,000.[3,4] The estimated age-standardized (world) 2012 incidence rates of melanoma for various regions within Europe are as follows:[3,4] o Central and Eastern Europe: 3.4 -12.6 per 100,000 o Northern Europe: 5.6 - 19.2 per 100,000 o Southern Europe: 0.9 - 16.2 per 100,000 o Western Europe: 9.9 -20.3 per 100,000 The six European countries with the highest estimated age-standardized (world) incidence rates of melanoma (2012) were as follows:[3,4] o Switzerland: 20.3 per 100,000 o The Netherlands: 19.4 per 100,000 o Denmark: 19.2 per 100,000 o Norway: 18.8 per 100,000 o Sweden: 18.0 per 100,000 o Slovenia: 16.2 per 100,000 Although the incidence of cutaneous malignant melanoma has been increasing worldwide, with annual increases estimated between 3% and 7%,[1,2,6,7,8] evidence indicates that the incidence rate has been rising at a slower rate or stabilizing in recent years in North America, Australia, New Zealand, where

Table 2.1.1-1: Epidemiologic Characteristics of Metastatic Melanoma

Metastatic Melanoma	
	reported incidence rates have been the highest, and in certain EU countries, as well. [2,8,9,10,11,12,13] 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.[1] Incidence of melanoma is rare in paediatric populations, particularly in youngest children, incidence increases with age with an estimated rate of 13 per million per year in the ages 15-19 adolescent patients.[14] 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. [15,16]
Prevalence	Prevalence of melanoma, like incidence, varies widely worldwide. According to GLOBOCAN 2012 data from the IARC, the most recent source of global prevalence data, the 1-year and 5-year prevalence estimates for melanoma for Europe were 87,280 and 391,315 per 100,000, respectively. The 1-year and 5-year prevalence estimates for the EU-28 were 72,068 and 326,156 per 100,000, respectively.[3,17] • The approximate 1 year prevalence estimates for 2012 for melanoma ranged within and across the various regions of Europe as follows: o Central and Eastern Europe: 375- 7,470 cases per 100,000 o Northern Europe: 45 -12,601 cases per 100,000 o Southern Europe: 32 - 8,719cases per 100,000 o Western Europe: 78 - 14,736 cases per 100,000 The approximate 5 year prevalence estimates for 2012 for melanoma ranged within and across these regions as follows: o Central and Eastern Europe: 1,550 - 30,786 cases per 100,000 o Northern Europe: 208 - 57,163 cases per 100,000 o Southern Europe: 149 - 40,248 cases per 100,000 o Western Europe: 361 - 66,997 cases per 100,000
Demographics of the population: age, gender, racial and/or ethnic origin	• Incidence, poorer prognosis, and mortality all increase with increasing age.[2] • Incidence increases in white populations residing at lower latitudes (e.g, incidence rates are higher among Australians than among Europeans). • In a Surveillance, Epidemiology, and End Results (SEER) analysis, 85% of melanoma cases age <18 years of age were non-Hispanic white, 5% were Hispanic and 2% were Asian/Pacific Islanders.[16] • 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.[18]
Risk factors for the disease	Risk factors for melanoma of the skin may be genetic or environmental[1,19,20,21,22,23]

Table 2.1.1-1: Epidemiologic Characteristics of Metastatic Melanoma

Metastatic Melanoma	
	• Large number of atypical nevi (moles) - strongest risk factor 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 • History of sunburn, particularly at an early age
Main treatment options	Treatment of metastatic melanoma continues to represent a considerable unmet medical need. Prior to 2011, DTIC was the only widely approved chemotherapeutic agent for metastatic melanoma. IL-2 was approved by the FDA for treatment of metastatic melanoma, but the associated toxicities are substantial. Neither IL-2 nor DTIC has demonstrated an OS benefit in a randomized trial; although this drug has never demonstrated an OS benefit. Since 2011, ipilimumab and vemurafenib for BRAF mutation positive patients have both demonstrated an OS benefit and have been widely approved. Ipilimumab has demonstrated long term OS benefit extending through 10 years in 2 randomized Phase 3 trials and in a pooled analysis of ipilimumab in advanced melanoma. More recently, the anti-PD-1 blocking agents nivolumab and pembrolizumab have demonstrated robust clinical activity, including OS benefit, leading to the approval of each for the treatment of metastatic melanoma. High dose IFN alfa-2b is currently approved by the US FDA and the EU EMA for use as adjuvant therapy in patients with high risk of relapse. Dabrafenib acts as a BRAF inhibitor and can be used in patients with melanoma that expresses the BRAF V600E gene mutation. Trametinib acts as a MEK inhibitor. It is indicated for use in patients with whose tumors express the BRAF V600E or V600K gene mutations.
Mortality and morbidity (natural history)	Although incidence rates have increased, survival rates for cutaneous melanoma overall have improved over recent decades,[2,8,24] due in part to earlier detection and treatment, and hence improved survival rates for local and regional disease. Over the past decade, 5-year relative survival rates improved in most EU countries, with a relative increase varying from 1% - 30%, with the greatest improvements observed in countries in southern and eastern Europe.[8] Examination of trends indicates that mortality from melanoma appears to be leveling off among young and middle-aged adults in the US, Australia, New Zealand, as well as in some EU countries following a steady period of increase up to the late 1980s.[8,25] Nonetheless, mortality for distant melanoma remains poor. Survival from stage IV disease, in particular, remains quite poor with median survival times across studies ranging from 3 or 4 months to about 13 months, and a 1-year OS in the range of 7% to 58%, regardless of treatment. The presence of liver or cerebral metastases generally accounts for the shortest survival periods observed. Higher 1-year survival has been observed in patients under 20 years of age.[26]

Table 2.1.1-1: Epidemiologic Characteristics of Metastatic Melanoma

Metastatic Melanoma	
	According to the WHO's IARC the estimated age-standardized (world) 2012 mortality rate for melanoma for Europe and the EU-28 was 1.6 per 100,000. [3, 4] The estimated age-standardized (world) 2012 mortality rates for melanoma for various regions within Europe are as follows: [3,4] o Central and Eastern Europe: 1.0 - 2.1 per 100,000 o Northern Europe: 1.8 - 3.6 per 100,000 o Southern Europe: 0.5 -3.2 per 100,000 o Western Europe: 1.1 - 2.8 per 100,000 The six European countries with the highest estimated age-standardized (world) mortality rates for melanoma (2012) were as follows:[3,4] o Norway: 3.6 per 100,000 o Slovenia: 3.2 per 100,000 o Sweden: 2.8 per 100,000 o The Netherlands: 2.8 per 100,000 o Switzerland: 2.4 per 100,000 o Croatia: 2.4 per 100,000
Important co-morbidities	Second primary malignancies more common in melanoma patients: • NHL • CLL • NMSC

2.1.2 Renal Cell Carcinoma

Table 2.1.2-1: Epidemiologic Characteristics of Renal Cell Carcinoma

Advanced RCC	
Incidence	Kidney cancer accounts for approximately 2-5% of all cancers[27,28,29] and is among the top ten leading cancer types in the US.[27] In recent decades the incidence of RCC has been steadily rising by 2-4% each year,[30] but international incidence rates of RCC vary up to approximately 10-fold.[29] Variation in the observed/reported incidence rates, and the apparent trend for a recent increase in incidence, may be attributed at least in part to differences in (1) frequency of diagnostic imaging, (2) access to healthcare services, (3) change in environmental or lifestyle risk factors.[31,32] Rates of kidney cancer are highest in Europe, North America, and Australia and lowest in India, Japan, Africa, and China.[33,34] According to GLOBOCAN 2008 data the estimated global age-standardized incidence rates for kidney cancer were:[33] • World: 4/100,000

Table 2.1.2-1: Epidemiologic Characteristics of Renal Cell Carcinoma

Advanced RCC	
	• 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.[34] Although RCC incidence rates range widely among individual regions, the incidence rate for men is consistently approximately twice that observed for women across all regions examined.[34]
Prevalence	According to GLOBOCAN 2008, IARC,[33] the most recent source identified that provided prevalence data, the approximate 5-year prevalence figures for kidney cancer are: • World: 15.1/100,000 • Europe: 47.6/100,000 • EU: 51.1/100,000 • North America: 67.8/100,000 • US: 69.9/100,000 • Canada: 50.1/100,000 • South America: 9.9/100,000 • Central America: 10.8/100,000 • Asia: 6.6/100,000 • Eastern Asia: 11.1/100,000 • Australia/New Zealand: 45.6/100,000 • Africa: 2.3/100,000
Demographics of the population: age, gender, racial and/or ethnic origin	Renal cell cancer occurs approximately twice as frequently in men as in women, and incidence appears to be the highest for black males.[29] The average age at diagnosis is in the early 60's.[29] The incidence of RCC is highest in Europe, North America, and Australia/New Zealand, and is lowest in Asia and Africa.[29]
Risk factors for the disease	Smoking, obesity, hypertension, ARCD, and family history/genetics are established risk factors for RCC.[28,29,35,36,37,38] 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.[39]
Main treatment options	About three quarters of people with RCC present with localized disease, and definitive local treatment (surgery) remains the gold standard for managing patients with no evidence of distant metastasis.[40] In advanced disease, the following treatment options are available:

Table 2.1.2-1: Epidemiologic Characteristics of Renal Cell Carcinoma

Advanced RCC	
	• Approved TKIs and anti-VEGF antibodies (ie, sunitinib, pazopanib, and bevacizumab) combined with IFN-α. • Temsirolimus • Axitinib or everolimus after first-line treatment with VEGF-targeted therapy. The PD-1 inhibitor nivolumab is approved (US, EU, and other countries) for use in patients with advanced RCC who received prior anti-angiogenic therapy based on improved survival rates compared with patients who received everolimus.
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.[28,41] 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.[42] As with incidence, the mortality rate for women is approximately half that observed for men.[28] According to GLOBOCAN 2008 data the estimated global age-standardized mortality rates for kidney cancer were:[33] • Europe: 3.1/100,000 • EU: 2.9 /100,000 • North America: 2.6/100,000 • US: 2.6/100,000 • Canada: 2.6 /100,000 • South America: 1.7 /100,000 • Central America: 1.8/100,000 • Asia: 1.0/100,000 • Eastern Asia: 1.0/100,000 • Australia/New Zealand: 2.7 /100,000 • Africa: 0.9/100,000
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. Hypertension was identified in 58% of RCC cases, while diabetes mellitus (DM) was present at a frequency of 17% among RCC patients.[43] Moreover, RCC may present with a variety of paraneoplastic syndromes (eg, poycythemia secondary to excessive secretion of erythropoietin, hypercalcemia secondary to derangement of serum factors regulating calcium, and hepatic dysfunction such as Stauffer syndrome).[44]

2.1.3 Non-Small Cell Lung Cancer

Table 2.1.3-1: Epidemiologic Characteristics of Non-Small Cell Lung Cancer

Advanced NSCLC	
Incidence	A total of 1.8 million new cases of lung cancer and 1.6 million related deaths were reported in 2012. The ASR of incidence and mortality was higher in more developed countries than less developed ones by 1.5 to 1.4-fold in men, and by 1.8 to 1.5-fold fold in women. The ASR of lung cancer incidence varied more than 31-fold worldwide in 2012. Among men, the highest rates were found in Central and Eastern Europe (ASR 53.5 per 100,000), Eastern Asia (50.4), Micronesia (47.5) and Southern Europe (46.4), and the lowest in Western Africa (1.7), Middle Africa (2), Eastern Africa (3.8) and Central America (10.2). Among women, the highest rates were found in Northern America (ASR 33.8 per 100,000), Northern Europe (23.7), Micronesia (22.9), Australia/New Zealand (21.7) and Western Europe (20), and the lowest in Middle Africa (0.8), Western Africa (1.1), Eastern Africa (2.2) and Northern Africa (3.1). Countries having the highest incidence to mortality ratios in men included Australia/New Zealand (1.39), North America (1.26), Western Europe (1.25) and Southern Europe (1.19), and the ratios were the highest for women in Australia (1.45), North America (1.44) and Western Europe (1.35).[45] Age-standardized incidence rate of lung cancer worldwide was estimated to be 23.1 per 100,000 (34.2 per 100,000 men and 13.6 per 100,000 women) in 2012.[46,47] Age-standardized incidence rate of lung cancer in EU was estimated to be 30.5 per 100,000 (45.1 per 100,000 men and 18.2 per 100,000 women) in 2012.[47,48,49] In Germany, the age standardized (Europe) incidence rate of lung cancer was 60.7 per 100,000 person in men and 26.5 per 100,000 per person in women in 2010.[50] Squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and large cell carcinoma account for 20-30%, 38% 14% and 3%, respectively, of lung cancer cases in the US.[51] In the past few decades, there was a growing increase in the incidence of adenocarcinoma, but a parallel decline in SQ cell carcinoma in most developed countries, most likely as a result of changes in cigarette design and composition.[52]
Prevalence	The number of lung cancer cases in China constituted 36% of the lung cancer cases in the world (n = 1,825,000), and Europe and US constitute 25% and 11.7% of lung cancer cases worldwide, respectively, in 2012.[53]
Demographics of the population: age, gender, racial and/or ethnic origin	In a study of 20,461 patients with NSCLC in Denmark,[54] 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 the US SEER data during 2006-2010, the median age at diagnosis for cancer of the lung and bronchus was 70 years of age. Approximately 0.0% were diagnosed under age 20; 0.3% for age 20-34; 1.4% for age 35-44; 8.8% for age 45-54; 21.3% for age 55-64; 31.4% for age 65-74; 28.1% for age 75-84; and 8.7% for age 85+ years.[55]
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.[56] Secondhand tobacco smoke

Table 2.1.3-1: Epidemiologic Characteristics of Non-Small Cell Lung Cancer

Advanced NSCLC	
	can explain 1.6% of lung cancer[57] and based on a systematic review, a relative risk of 1.14-5.20 was reported for non-smokers who lived with a smoker.[58] Urban air pollution, such as emission rich in various polycyclic aromatic hydrocarbon compounds, may account for 11% of lung cancer.[57] 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.[59] 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.[60,61] 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. [62] 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.[63]
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 v5.2018[64] • ESMO guideline: Early-Stage and Locally Advanced (non-metastatic) Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines[65] • ESMO guideline: Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines[66]
Mortality and morbidity (natural history)	The mortality rates varied by approximately 32-fold worldwide in 2012. In men, the highest death rates were reported in Central and Eastern Europe (47.6), Eastern Asia (44.8) and Micronesia (41.7); whilst in women, the highest mortality was also reported in Northern America (23.5), Micronesia (20.8), and Northern Europe (19.1). The lowest mortality rates were found in Western Africa (1.5), Middle Africa (1.8), and Eastern Africa (3.5) in men. These three countries also reported the lowest mortality rates among women (ASR = 1.0, 0.7, and 2.0, respectively).[67] Geographical variation in incidence and mortality was substantial between continents. The ASR of incidence and mortality were both positively correlated with levels of human development, and to a lower degree, country-specific GDP per capita. The correlation coefficients for HDI for the incidence/mortality of lung cancer were high. Most countries included into the study conducted by Wong et al. showed declining incidence in men (22 out of 38) and increasing incidence (19 out of 38) in women. Similarly for mortality, a high proportion of countries reported a decreasing trend in men (30 out of 36) and increasing trend in women (16 out of 36). These findings suggested gender and socioeconomic disparities of lung cancer incidence and mortality.[67]

Table 2.1.3-1: Epidemiologic Characteristics of Non-Small Cell Lung Cancer

Advanced NSCLC	
Important co-morbidities	Co-morbidities in patients with advanced 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 in patients with poor performance status, at advanced-stage disease, of age ≥ 65, or with previous chemotherapy.[68] Use of chemotherapy/radiation was associated with increased risks of ischemic heart diseases, conduction disorders, cardiac dysfunction, and heart failure.[69]

2.1.4 Malignant Pleural Mesothelioma

Table 2.1.4-1: Epidemiologic Characteristics of Malignant Pleural Mesothelioma

Advanced MPM	
Incidence	MPM is a rare but aggressive malignancy of the pleural surface, commonly associated with occupational asbestos exposure.[70] Mesothelioma can have a very long latency period and cases continue to be diagnosed in countries that have banned asbestos.[71] In fact, some countries have continued to see increased incidence 30-40 years after banning asbestos.[72,73,74] In 2018, there were an estimated 30,443 new cases of mesothelioma. Most cases are accounted for by 8 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.[75] A similar study had consistent findings and concluded that 1 mesothelioma case has been overlooked for every 4-5 reported cases.[76]
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%).
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.[70] 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).[77] Due to the long latency period, risk increases with age.

Table 2.1.4-1: Epidemiologic Characteristics of Malignant Pleural Mesothelioma

Advanced MPM	
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.[78] Other causes may include exposure to erionite (an asbestos-type silicate mineral) and chest wall radiation.[79] An oncogenic virus (simian virus 40) may be an independent causal factor or a contributing factor in those with asbestos exposure.[80]
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.[81] 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.[82] 2) ESMO guideline: Malignant Pleural Mesothelioma. ESMO Clinical Practice Guidelines.[83]
Mortality and morbidity (natural history)	Patients with MPM usually have a very poor prognosis with an expected survival of 9-12 months after diagnosis,[70] although newer treatments have extended median survival.[82]As with incidence and prevalence, the majority of the estimated 25,576 fatal cases in 2018 were concentrated in 8 countries[84]: 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.[80]

2.1.5 Colorectal Cancer

Table 2.1.5-1: Epidemiologic Characteristics of Colorectal Cancer

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 men and women.[85] 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.[85] 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

Table 2.1.5-1: Epidemiologic Characteristics of Colorectal Cancer

Advanced CRC

socioeconomic development in countries undergoing such transitions.[86] 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 HDA and world region are presented below.[85] 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	490,997 530,863	407,754 453,893	898,751 984,756	3028.6
High HDI	110,800 432,925	105,572 320,755	216,372 753,680	21.418.1
Medium HDI	64,946 81,645	52,314 60,859	117,260 142,504	6.7.1
Low HDI	18,491 23,745	19,556 21,143	38,047 44,888	7.26.4
WHO African Region	23,353 27,820	24,216 25,966	47,569 53,786	8.2
WHO Region of the Americas	156,934 170,019	150,843 158,661	307,777 328,680	21.10
WHO Eastern Mediterranean Region	24,031 29,964	19,762 23,977	43,793 53,941	8.39
WHO European Region	288,528 308,390	242,083 266,563	530,611 574,953	28.48
WHO South-East Asia Region	75,179 87,265	48,996 61,023	124,175 148,288	6.59
WHO Western Pacific Region	457,980 445,720	337,217 320,460	795,197 766,180	25.922.1

Three patterns of CRC incidence and mortality trends have been suggested, corresponding to position and movement on the HDI:[87]

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

Table 2.1.5-1: Epidemiologic Characteristics of Colorectal Cancer

Advanced CRC

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 colorectal cancers 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.[88] 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.[89] However, this may be due to increased screening and/or issues with the representativeness of the data.[90]

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	1,388,752704,898	1,204,885458,490	2,593,6373,163,388	186.8192.7
High HDI	264,8491,229,048	266,923926,639	531,7722,155,687	72.478.1
Medium HDI	131,435202,990	112,231155,474	243,666358,464	12.915.8
Low HDI	27,50846,820	31,36243,422	58,87090,242	7.5.8
WHO African Region	39,87862,626	43,95260,816	83,830123,442	7.810.5
WHO Region of the Americas	423,187538,289	425,867505,624	849,0541,043,913	83100.6
WHO Eastern Mediterranean Region	50,81979,300	43,83564,773	94,654144,073	13.619.0
WHO European Region	789,667969,653	691,595839,892	1,481,262809,545	160.5193.2
WHO South-East Asia Region	151,989228,991	105,596164,434	257,585393,425	1319.1
WHO Western Pacific Region	1,139,258304,897	882,979948,486	2,022,237253,383	104.6117.9

Table 2.1.5-1: Epidemiologic Characteristics of Colorectal Cancer

Advanced CRC	
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 [88]
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.[86,91,92] 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.[93] 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.[94,95,96] Unlike many other cancers, hereditary predisposition may account for only 5% of CRC risk.[97] 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.[98,99,100] In population-based studies, the prevalence of MSI 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.[101,102] 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.[103] Long-term follow-up studies have found associations between UC and IBD and an increased risk of colorectal cancer.[104]
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 Clinical Practice Guidelines in Oncology: Rectal cancer, v4.2023.[105] 2) NCCN Clinical Practice Guidelines in Oncology: Colon cancer, v2.2023.[106] 3) ESMO Consensus Guidelines: Metastatic colorectal cancer, 2023.[107] 4) Pan-Asian Adapted ESMO guideline: eUpdate – Consensus Guidelines: Metastatic colorectal cancer, 2018.[108]
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.[109] 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 Central and Eastern Europe (14.1 per 100,000), Northern Europe (11.6 per 100,000), Southern Europe (11.4 per 100,000 for men), and Caribbean (10.2 per 100,000). Mortality rates by HDI showed a clear bifurcation

Table 2.1.5-1: Epidemiologic Characteristics of Colorectal Cancer

Advanced CRC	
	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	15,77018,709	15,66617,999	31,43636,708	5.68
WHO Region of the Americas	66,12372,708	62,66466,873	128,787139,581	8.21
WHO Eastern Mediterranean Region	14,04416,463	11,40913,455	25,45329,918	4.95.1
WHO European Region	138,954143,816	120,567123,539	259,521267,355	12.211.7
WHO South-East Asia Region	50,48549,087	31,24234,358	81,72783,445	4.3.9
WHO Western Pacific Region	198,763811	154,941147,825	353,704346,636	10.89.0

	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.[110]
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.[111,112,113]

2.1.6 Oesophageal Squamous Cell Carcinoma (OSCC)

Table 2.1.6-1: Epidemiologic Characteristics of Oesophageal Cancer

Advanced Oesophageal Cancer	
Incidence	According to data from GLOBOCAN database, worldwide an estimated 604,100 new OC cases were predicted to be diagnosed in 2020.[114] OC accounts for 3.2% of new cancer cases.[115] The age-standardized incidence rate was 6.3 per 100,000 person-years.[115] 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.[116] The age standardized incidence rates of oesophageal cancer worldwide are:[115] • 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 person-years • Australia/New Zealand: 3.1/100,000 person-years In the United States, the age-adjusted incidence rate of OC 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, estimated number of new cases of OC was 17,650, which accounts for 1% of all new cancer cases. Based on data from 2014 to 2016, approximately 0.5% of US population can be diagnosed with OC at some point during their lifetime.[114] The 2 distinct histologic types of OC are OSCC and OAC. Globally, OSCC remains the predominant histological subtype; however, the incidence of OSCC has been decreasing, while the incidence of OAC has been increasing rapidly, particularly in Western Europe, North America, and Australia.[117]
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:[115] • Europe: 8.6/100,000 person-years • North America: 7.1/100,000 person-years • South America: 3.8/100,000 person-years • 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.[114] OC is most frequently diagnosed among people aged 65-74, and the median diagnosis age is 68.[114] The incidence is higher in urban areas compared to in rural areas, particularly among African-American men.[118, 119] The worldwide statistics indicate that there is no gender specificity in high incidence areas.[118] Lower socioeconomic status is associated with OC.[120]
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

Table 2.1.6-1: Epidemiologic Characteristics of Oesophageal Cancer

Advanced Oesophageal Cancer	
	disease (e.g., achalasia and caustic strictures), oesophageal injury, prior gastrectomy, atrophic gastritis, HPV infection, history of head or neck cancer, Barrett's oesophagus, poor oral hygiene, history of radiotherapy, and medication use (eg, Bisphosphonates), etc.[118, 121, 122, 123, 124, 125, 126, 127, 128, 129]
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.[130] 2) ESMO guideline: [O]esophageal cancer.[131]
Mortality and morbidity (natural history)	EC is the sixth most common cause of deaths worldwide, accounting for over 500,000 deaths annually. In the US, the age adjusted mortality rate of OC is 4.0 per 100,000 person-years based on 2012-2016 deaths. The estimated deaths from OC were 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.[114] Worldwide, 544,076 people with OC were projected to die in 2020 accounting for 5.3% 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:[114] • 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[118]

2.1.7 Hepatocellular Carcinoma

Table 2.1.7-1: Epidemiologic Characteristics of Hepatocellular Carcinoma

HCC	
Incidence	Liver cancer is the 6th most common malignancy with an estimated 866,136 new cancer cases occurring worldwide in 2022.[132] 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.[132] The age standardized incidence rate (ASR) per 100,000 of liver cancer worldwide according to GLOBOCAN 2022 was estimated as follows:[132] • World: 8.6/100,000 • Europe: 5.1/100,000 • Eastern Europe: 4.2/100,000

Table 2.1.7-1: Epidemiologic Characteristics of Hepatocellular Carcinoma

HCC

- 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.[133] 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.[134]

Prevalence

The 5-year prevalence of liver cancer was estimated at 1,163,723 worldwide according to GLOBOCAN 2022 with regional data as follows:[132]

	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
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.[135,136,137,138]

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.[139]

In the US the incidence of HCC is highest among Asian/Pacific Islanders and lowest among Whites.[140]

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).[133,141,142]

Table 2.1.7-1: Epidemiologic Characteristics of Hepatocellular Carcinoma

HCC	
	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.[133,143,144] 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.[133,145]
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.[146] • ESMO Clinical Practice Guidelines: Hepatocellular Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up[147] – eUpdate 5 March 2021: Updated Hepatocellular Carcinoma Treatment Recommendations[148] • NCCN Guideline: Hepatocellular Carcinoma, v1.2024[149] • American Association for the Study of Liver Diseases (AASLD) Practice Guidance on Prevention, Diagnosis and Treatment of Hepatocellular Carcinoma.[150]
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.[132] Crude mortality rates and ASRs per 100,000 individuals in 2022 with regional data were estimated as follows:[132]

	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
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.[133] 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.[133] 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.[138,133]

Table 2.1.7-1: Epidemiologic Characteristics of Hepatocellular Carcinoma

HCC	
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. However, these conditions occur frequently with advancing age.[151,152,153,154,155,156]

2.2 Nonclinical Part of the Safety Specification

The scope and results of the nonclinical toxicity and exposure studies support the use of IV ipilimumab at the proposed doses and frequency. Risks of immune-related adverse toxicity, immunogenicity, infusion reactions, and effects on later stage of pregnancy and infant liability were identified in the nonclinical program.

The nonclinical toxicity studies predicted the most common clinical toxicities observed in humans (ie, irARs of colitis and dermatitis/rash). These were expected and consistent with the proposed key role of CTLA-4 in maintaining self-tolerance in the immune system and the T-cell potentiation resulting from blockade of CTLA-4. At present, the cause(s) of adverse pregnancy outcome and infant mortality associated with ipilimumab administration in monkeys are unknown; and the clinical implications of these findings are unclear. Thus, ipilimumab 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**
Immune-related adverse reactions In monkeys, ipilimumab was associated with a low incidence mechanism-based AEs of immune origin irARs, which involved the GI tract and skin. The binding of ipilimumab to CTLA4 expressed on gut-associated lymphoid tissue was confirmed in human and monkey tissue-binding studies, and suggests that these lymphocytes (T-cells) exist in an activated state, making them susceptible to CTLA4 blockade by ipilimumab.	Increased incidence and severity of irARs involving several organ systems (predominantly the GI tract, endocrine glands, liver, and skin) have been observed in patients treated with ipilimumab. In addition, ipilimumab may exacerbate autoimmune diseases in humans.
Immunogenicity Ipilimumab was not appreciably immunogenic in monkeys, with a positive anti-drug antibody response rate of ~8%. When present, antibodies usually correlated with rapid elimination of circulating levels of ipilimumab.	The immunogenicity of ipilimumab may potentially increase the risk for adverse effects on exposure (reduced area under the curve, increased clearance), reduced efficacy (neutralizing antibodies), and safety (infusion reactions, antibody-antigen complex formation/deposition [serum sickness], etc).

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

Key Safety Findings	Relevance to human usage
Immunogenicity of human proteins in animals may not be predictive of its clinical immunogenicity.	
Infusion Reactions An infusion reaction occurred in a single monkey following a rapid bolus dose of ipilimumab. This reaction could not be subsequently reproduced under controlled infusion conditions in the same monkey.	As with any IV-administered protein, ipilimumab has the potential to evoke an infusion reaction that may be associated with rapid cytokine release. Severe infusion reactions were uncommon in clinical trials. In case of a severe infusion reaction, ipilimumab therapy should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab with close monitoring.
Reproductive Toxicity - Maintenance of Pregnancy The effects of ipilimumab on prenatal and postnatal development were investigated in a study in cynomolgus monkeys. Pregnant monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through delivery, at exposure (AUC) levels either similar to or higher than those associated with the clinical doses of 3 or 10 mg/kg of ipilimumab. No treatment-related adverse effects on reproduction were detected during the first 2 trimesters of pregnancy. Beginning in the third trimester, both ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and infant mortality relative to control animals; these findings were dose-dependent. Additionally, developmental external or visceral abnormalities were identified in the urogenital system of 2 infants exposed in utero to ipilimumab. One female infant had unilateral renal agenesis of the left kidney and ureter, and 1 male infant had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema. The relationship of these malformations to treatment is unclear. Ipilimumab was shown to be present at very low levels in milk from adult mothers (with mean milk/serum ipilimumab concentration ratios that were 0.002 to 0.003).	At present, the cause(s) of adverse pregnancy outcome and infant mortality associated with ipilimumab administration are unknown. The clinical implications of these findings are unclear. There are no data on the use of ipilimumab in pregnant women. Ipilimumab is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk. It is unknown whether ipilimumab 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 adverse reactions in nursing infants, a decision must be made whether to discontinue breast-feeding or to discontinue from ipilimumab therapy taking into account the benefit of breast-feeding for the child and the benefit of ipilimumab therapy for the woman.

2.2.1 Conclusions on Nonclinical Data

Table 2.2.1-1: Nonclinical Safety Concerns

Important Identified Risks (confirmed by clinical data)	
Immune-related Events	In the placebo-controlled clinical trial MDX010-020, immune-related AEs were reported in 58~61% of ipilimumab-treated groups, 32% in the gp100 control group; with severe grade in11-15% of ipilimumab-treated groups versus 3% in the gp100-control group. The most frequent on-study immune-related events were diarrhoea/colitis and rash.

Table 2.2.1-1: Nonclinical Safety Concerns

Infusion Reactions	In the clinical program, systemic infusion reactions were reported up to 2% with rare severe cases.
Important Potential Risks (not refuted by clinical data or which are of unknown significance)	
Immunogenicity	Immunogenicity: anti-drug (ipilimumab) antibody was detected in 2% tested patients, none were neutralizing. The presence of ADA did not have significant impact on clearance of ipilimumab and did not correlate with higher frequency of infusion reaction.
Missing Information	
Use in Pregnant or Nursing Women	Use in pregnant or nursing women is not recommended

2.3 Clinical Trial Exposure

Table 2.3-1 presents the cumulative number of subjects exposed to ipilimumab, active comparators, and/or placebo in completed and ongoing BMS-sponsored clinical trials of ipilimumab and ipilimumab in combination with other BMS assets from the Development International Birth Date (25-Mar-2011) through 24-Mar-2024. These exposure estimates refer to that for advanced melanoma clinical trials only.

Clinical trial exposure analyses for ipilimumab monotherapy individual studies are provided in Appendix 3 and for nivolumab in combination with ipilimumab individual studies in Appendix 4.

Table 2.3-1: Estimated Cumulative Subject Exposure in Completed and Ongoing BMS-Sponsored Clinical Trials from 25-Mar-2011 to 24-Mar-2024

Treatment	Number of Subjects (N= 42,915)
Ipilimumab monotherapy	6,903
Ipilimumab in combination with nivolumab	13,648
Ipilimumab in combination with other products (excluding nivolumab)	1,531
Active Comparator / Placebo	20,833

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)
Pregnancy or breast-feeding women	Effect to fetus and nursing baby were unknown.	No	There are no data on the use of ipilimumab in pregnant women. It is unknown whether ipilimumab is secreted in human milk. Pregnancy and breast-feeding are adequately described in Section 4.6 of the SmPC.
Autoimmune disease	Further immune activation may be potentially imminently life threatening.	No	Available evidence on the safety and efficacy pertaining to ICI treatment in patients with autoimmune disease shows that ICIs can be safely used in this population based on clinical judgement and evaluation of the potential benefit and risk on an individual basis. Patients with autoimmune disease are also adequately described in Section 4.4 of the SmPC.
Inflammatory bowel disease, including ulcerative colitis and Crohn's disease	Ipilimumab is associated with serious immune-related GI reactions.	No	Safety management guidelines including use of systemic high-dose corticosteroid with or without additional immunosuppressive therapy and permanent discontinuation of ipilimumab are provided in Section 4.4 of the SmPC.
Elevated bilirubin or liver transaminases	Ipilimumab is associated with serious immune-related hepatotoxicity.	No	Patients with hepatic impairment are adequately addressed in Sections 4.2 and 5.2 of the SmPC.
Ocular melanoma	Subpopulation with a significantly worse prognosis.	No	Limited therapeutic options for ocular melanoma.
Active brain metastasis	Subpopulation disease with a significantly worse prognosis.	No	Study CA184042 was conducted in subjects with active brain metastases.[a]
ECOG performance status > 1	A sufficient life expectancy is necessary to assess	No	Limited therapeutic options. The EAP CA184045, and 2 observational studies,

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)
	adequately the endpoints of OS (primary or secondary).		CA184332 and CA184338, included subjects with ECOG performance status 0-2.[a]
Hepatitis B, C, or HIV positive	The MOA of ipilimumab requires specific safety and efficacy analyses in each subpopulation.	No	Study MDX010-10 was conducted in subjects infected with HIV. Section 5.1 of the SmPC describes the subpopulations not studied with ipilimumab.

NA = already included as Missing Information

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

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

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 The effects of YERVOY in pregnant women are not known; it is possible that the active substance, ipilimumab, could harm an unborn baby. Ipilimumab should not be used during pregnancy unless specifically recommended by a physician	No formal clinical studies conducted
Breastfeeding women: It is not known if ipilimumab is secreted in human milk; however, significant exposure of ipilimumab to the infant through breast milk is not expected and no effects on the breastfed infant are anticipated. A decision must be made whether to discontinue breastfeeding or to discontinue from ipilimumab therapy, taking into account the benefit of breastfeeding for the child and the benefit of ipilimumab for the woman.	No formal clinical studies conducted
Patients with relevant comorbidities:	
Patients with hepatic impairment	No formal clinical studies conducted
Patients with renal impairment	No formal clinical studies conducted

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

Type of special population	Exposure
Patients with cardiovascular impairment	No formal clinical studies conducted
Immunocompromised patients	No formal clinical studies conducted
Patients with a disease severity different from inclusion criteria in clinical trials	
− Patients with advanced melanoma who have failed multiple courses of therapy or whose disease is too advanced to qualify for other protocols. Eligibility for this study was expanded to include subjects with stable brain metastases, unfavorable histologies (eg, ocular melanoma), and ECOG performance status of 2.	3,666 patients (10,998 person-months)[a] 72 patients (216 person-months)[a] 62 patients (186 person-months)[a] 85 patients (255 person-months)[a]
− Patients with advanced melanoma with active brain metastases.[157]	
− Patients with previously treated (excluding prior BRAF, CTLA 4 and PD 1 inhibitors) or untreated unresectable Stage III or Stage IV (metastatic) melanoma. Patients with ocular melanoma were not included in CA184169, but patients with brain metastases were included if they were free of neurologic symptoms related to metastatic brain lesions and if they did not require or receive systemic corticosteroid therapy in the 10 days prior to beginning ipilimumab therapy.[158]	
− Safety in previously untreated advanced melanoma from post-marketing epidemiology studies. Patient characteristics in CA184338 and CA184332 were generally similar compared to CA184024 (previously untreated subjects) and MDX010-20 (previously treated subjects), except for the higher frequency of brain metastases at baseline, which is expected based on the exclusion criteria used in the clinical trials.[159,160]	
Population with relevant different ethnic origin	No formal clinical studies conducted
Subpopulations carrying relevant genetic polymorphisms	No formal clinical studies conducted

[a] Estimated using the median duration of exposure of 3.00 person-months/patient (median duration of exposure is based on the assumption that the vast majority of ipilimumab monotherapy studies had a fixed study duration with only 4 doses given every 3 weeks to each subject).

2.5 Post-Authorisation Experience

YERVOY® (ipilimumab, BMS-734016, or MDX010) has been approved as monotherapy and in combination with nivolumab in several 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 ipilimumab. However, an estimate of the number of treated patients can be derived from available sales figures received from a third party/vendor. These figures, which represent the bulk of BMS worldwide sales, remain an approximation of the total quantity sold, because the third party/vendor does not have access to the total amount distributed in all countries. The third party/vendor's sales data from major countries are collected and maintained with the goal of capturing 80% to 85% of total world sales. However, data may vary from one reporting period to another because of certain changes in subscription agreements and the number of data channels available within a given country, eg, direct to consumer sales, hospital sales, home care sales.

The sales data and average dose and duration of treatment, based on the prescribing information, are used to calculate the approximate number of patients treated. However, the dose and duration of therapy depend on many factors including age (eg, adult, pediatric), weight, renal function, specific treatment indication, and the patient's therapeutic response. By making certain assumptions regarding average dosage and duration of treatment, it is possible to estimate the number of patients treated with ipilimumab in the post-marketing setting.

2.5.1.2 Exposure

As described in Section 2.5.1.1, patient exposure can be estimated based on sales data received from a third party/vendor.

Cumulatively, the total number of mg sold 123,506,141 mg (25-Mar-2011 through 31-Dec-2023).

The estimated number of patients exposed (through 31-Dec-2023):

- 1 mg/kg: 62,951 patients exposed (1 mg/kg ipilimumab + 3 mg/kg nivolumab-combination therapy)
- 3 mg/kg: 118,049 patients exposed (3 mg/kg), including:
  - 3 mg/kg monotherapy: 41,835 patients
  - 3 mg/kg ipilimumab + 1 mg/kg nivolumab = 76,214 patients

Taking into account the available sales data and the assumptions as described in Section 2.5.1.1, the cumulative number of patients treated from IBD (25-Mar-2011) through 31-Dec-2023 is estimated to be approximately 184,696 patients.

The median duration of treatment for ipilimumab is estimated to be 3 months based on the assumption that the vast majority of ipilimumab monotherapy studies had a fixed study duration with only 4 doses given every 3 weeks to each subject.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Since ipilimumab is not a controlled substance and is administered by medical personnel in medically controlled conditions, the potential of illegal use is low. In addition, ipilimumab, an anti-CTLA-4 monoclonal antibody, is a T-cell potentiator and thus not a likely candidate for abuse. Symptoms of withdrawal/rebound have not been investigated or reported in ipilimumab clinical studies.

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	• GI irARs (eg, diarrhoea, colitis, GI perforation) • Hepatic irARs (eg, hepatitis) • Skin irARs (eg, rash, pruritus) • Neurologic irARs (eg, neuropathy) • Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency) • Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis) • Severe infusion reactions
Important potential risks	• Immunogenicity • Difference in efficacy in women ≥50 years
Missing information	• Reproductive and lactation data • Pediatric data • Data in ethnic groups • Potential PD interaction with systemic immunosuppressants • Patients with severe hepatic impairment • Patients with severe renal impairment • Patients with autoimmune disease • Long-term safety

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

Ipilimumab has a well-characterized safety profile that 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	
• GI irARs (eg, diarrhoea, colitis, GI perforation) Hepatic irARs (eg, hepatitis) Skin irARs (eg, rash, pruritus) Neurologic irARs (eg, neuropathy) Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency) Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)	The most common treatment-related AEs associated with the use of ipilimumab were immunological in nature (irARs), reflecting the MOA of ipilimumab. IrARs were observed across all clinical trials and most frequently involved the GI tract (mostly diarrhoea and/or colitis) and the skin (mostly rash and pruritus). Less frequently reported irARs involved the liver (such as transaminase elevations), endocrine glands (primarily hypophysitis with hypopituitary or adrenal insufficiency), and the nervous system (motor neuropathy with or without sensory neuropathy). The majority of irARs were reported during the treatment period and were manageable with established treatment guidelines.
Severe infusion reactions	Serious acute infusion reactions are infrequent. However, life-threatening reactions may occur.
Important potential risks	
• Immunogenicity	Anti-ipilimumab antibodies could lead to immune complex formation with the drug and result in hypersensitivity, leading to immediate or delayed reactions after infusion. In addition, the anti-ipilimumab antibodies may increase the clearance of the drug or it may neutralize its ability to bind to its biological target CTLA4, which in turn will reduce the efficacy of ipilimumab. No life threatening or fatal outcomes have been reported.
Difference in efficacy in women ≥50 years	In clinical trials, the clinical benefit of YERVOY in women over 50 years old was inconclusive due to small numbers of subjects in the studies.
Missing Information	
Reproductive and lactation data	The effects of YERVOY in pregnant or breastfeeding women are not known; it is possible that the active substance, ipilimumab, could harm an unborn baby. Women who could become pregnant must use effective contraception (birth control) while being treated with YERVOY. YERVOY should not be used during pregnancy unless specifically recommended by a physician. It is unknown whether YERVOY is secreted in human milk. However, significant exposure of ipilimumab to the infant through breast milk is not expected, and no effects on the breastfed infant are anticipated. A decision must be made whether to discontinue breastfeeding or to discontinue from YERVOY therapy, taking into account the benefit of breastfeeding for the child and the benefit of YERVOY for the woman.

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
• Pediatric data	The effects of YERVOY in patients less than 18 years of age are not known. YERVOY should not be used in children below 18 years of age. A PIP for ipilimumab in malignant neoplasms (except melanoma, nervous system, haematopoietic, and lymphoid tissue) and a second PIP in melanoma have been completed in the EU. Melanoma is currently a PDCO class waiver for patients younger than 12 years old.
• Data in ethnic groups	In YERVOY clinical trials, the race of over 99% of patients was Caucasian. The effect of YERVOY in other ethnic groups is unknown. The number of subjects in the other racial and/or ethnic diversities was too few to permit meaningful comparison across races.
• Potential PD interaction with systemic immunosuppressants	The use of oral or IV corticosteroids before starting YERVOY should be avoided because of their potential interference with the beneficial effect of YERVOY. Use of oral or IV corticosteroids after starting YERVOY to treat inflammations does not appear to impair the beneficial effect of YERVOY.
• Patients with severe hepatic impairment	The effect of YERVOY in patients with severe liver impairment has not been studied.
• Patients with severe renal impairment	The effect of YERVOY in patients with severe renal impairment has not been studied.
• Patients with autoimmune disease	The effect of YERVOY in patients with a history of autoimmune diseases, especially active autoimmune diseases requiring systemic immunosuppressants, has not been studied. YERVOY should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening and used with caution in other patients with a history of autoimmune disease, after careful consideration of the potential risk-benefit on an individual basis.
• Long-term safety	There is limited data on the long-term safety of YERVOY.

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

The important identified and potential risks as well as missing information are listed below.

Important Identified Risks

- Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)
- Severe infusion reactions

Important Potential Risks

None

Missing Information

- 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 GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)	
Potential mechanisms	Ipilimumab specifically blocks the inhibitory signal of CTLA-4, resulting in T-cell activation and proliferation. In association with these T-cell changes, AEs characterized by inflammation have been observed in multiple organ systems.
Evidence source and strength of evidence	**GI irARs (eg, diarrhoea, colitis, GI perforation)** In clinical studies, GI irARs most often presented as diarrhoea, abdominal pain, and/or hematochezia with or without fever. Majority of subjects with GI irARs had mild to moderate (Grade 1 or 2) diarrhoea or colitis which were generally manageable and usually resolved. However, severe or persistent diarrhoea or colitis could occur. Discontinuation of ipilimumab (either temporarily or permanently) was required for subjects with Grade 3-4 events.[161] Late onset GI irARs (more than 30 days after last dose) and fatalities due to GI perforation and hemorrhagic colitis requiring colectomy have been reported. **Hepatic irARs (eg, hepatitis)** Hepatic irARs of any grade reported during the treatment period were less common than those affecting the GI tract and skin and generally resolved. In the clinical studies, hepatic irARs were most often asymptomatic but could be detected by routine laboratory monitoring. Discontinuation of ipilimumab was required in patients with high-grade events. Fatal outcome may occur if not treated promptly and appropriately.[161] **Skin irARs (eg, rash, pruritus, TEN, and DRESS)** Skin irARs during the treatment dosing period were common and consisted primarily of Grade 1-2 rash and pruritus. Skin irARs generally resolved, however can be potentially severe or fatal.[161] **Neurologic irARs (eg, neuropathy)** Neurological manifestations in subjects treated with ipilimumab may include motor and/or sensory neuropathy. Given the difficulty in definitely establishing an inflammatory etiology, alternative etiologies (eg, tumor progression) should be excluded. Fatal Guillain-Barre syndrome and cases of myasthenia gravis have been reported in clinical trials of ipilimumab. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy should be evaluated, and

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)	
	noninflammatory causes such as disease progression, infections, metabolic disorders, and medications should be excluded.[161] **Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)** Severe (Grade 3-4) endocrinopathy has been reported in minority of patients. Patients with hypophysitis and hypopituitarism typically presented with headache or fatigue, which may be incorrectly attributed to underlying malignancy. Diagnosis requires laboratory confirmation. Endocrinopathy can be serious or life-threatening. Patients are usually clinically managed with steroids and/or hormone replacement therapy. Long-term hormone replacement may be required.[161] **Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)** Selected other irARs which are considered important identified risks include, for example, pneumonitis, nephritis, and non-infectious myocarditis. Severe (Grade 3-4) irARs reported in minority of patients. Other irARs can be serious and life-threatening. Patients are usually clinically managed with steroids and the events generally resolved.[161]
Characterization of risk	Refer to Appendix 5 for additional safety data for studies included in the pooled safety analyses and studies that included 10mg/kg ipilimumab. **GI irARs (eg, diarrhoea, colitis, GI perforation)** **3 mg/kg ipilimumab** Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004) Any GI IrAR, any grade: 30.6%; Grade 3: 3.6%; Grade 4: 0.9% • Diarrhoea, Grade 3: 2.7% • Colitis, Grade 3: 1.8%; Grade 4, 0.9% • GI perforation (fatal): 1 subject (0.9%) Ipilimumab pooled monotherapy (MDX010-20, CA184004, MDX010-08, CA184022) Any GI irARs, any grade: 23.5% previously untreated, 28.7% previously treated, 22.7% chemo naive, 30.1% chemo pretreated Grade 3-4 GI irARs: 5.9% previously untreated, 6.1% previously treated, 5.3% chemo naive, 6.3% chemo pretreated Grade 5 GI irARs: 2.9% previously untreated, None previously treated, 1.3% chemo naive, None chemo pretreated • Diarrhoea (Grade 3-4): 3.6% previously untreated, 3.1% previously treated, • Colitis: (Grade 3-4): 1.8% previously untreated, 3.3% previously treated, GI perforation (fatal): 1 previously untreated subject (1.8%) Ipilimumab pooled 3 mg/kg containing regimens (MDX010-20, CA184004, MDX010-08, CA184022) Any GI irARs, any grade: 29.1% previously untreated, 29.8% previously treated, 29.1% chemo naive, 29.9% chemo pretreated

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)

Grade 3-4 GI irARs: 5.5% previously untreated, 5.3% previously treated, 5.0% chemo naive, 5.4% chemo pretreated

Grade 5 GI irARs: 1.8% previously untreated, 0.5% previously treated, 0.7% chemo naive, 0.5% chemo pretreated

- Diarrhoea (Grade 3-4): 3.6% previously untreated, 3.1% previously treated
- Colitis: (Grade 3-4): 1.8% previously untreated, 3.3% previously treated
- GI perforation (fatal): 1 previously untreated subject (1.8%)

Ipilimumab Monotherapy in Previously Untreated Advanced Melanoma (CA184332, CA184338)
CA184332
Induction:
Any GI irARs, any grade: 41.7%; most frequent: diarrhoea 19.2%
2 year follow-up:
Any GI irARs, any grade: 88.5%; most frequent: diarrhoea 30.6%

CA184338
Induction:
Any GI irARs, any grade: NR; most frequent: fatigue 22.7% and diarrhoea 15.8%
4 year follow-up:
Any GI irARs, any grade: NR; most frequent: fatigue 12.7% and diarrhoea 6.3%

Ipilimumab in Patients with Unresectable or Metastatic Melanoma (CA184143)

Melanoma	**On Study[a] (N=1,151)**	**On Treatment[b] (N=1,151)**	**Post-treatment[c] (N=653)**
CA184143		n (%)	
Any Grade	314 (27)	297 (26)	28 (4)[d,e]
Grade ≥ 3	131 (11)	126 (11)	9 (1)

[a] Numbers of patients with any post treatment GI irAEs are shown regardless of whether they occurred in at least 5% of patients, to provide context to the results.

[b] The "on treatment" period refers to the "early-onset AE window," defined as the time from the date of the first dose of ipilimumab through 90 days after the date of the last dose of ipilimumab therapy.

[c] The "on-study" period refers to the period from the time the patient received first dose of ipilimumab until the patient exited the study or the end of the study, whichever came first.

[d] The "post-treatment" period refers to the "late-onset AE window," which is defined as any time after the last dose of ipilimumab +90 days.

[e] The year of onset was wrongly entered for one colitis irAE. This event occurred on treatment rather than post treatment. The number of patients with any irAE post treatment is 65 (and not 66), and the number of patients with GI irAE post treatment is 27 (and not 28).

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)

Summary of GI irAE by PT Reported in at Least 5% of the Any Ipilimumab Patient Cohort in CA184143

Melanoma	On Study[a] (N=1,151)	On Treatment[b] (N=1,151)	Post-treatment[c] (N=653)
CA184143			
Colitis		n (%)	
Any Grade	92 (8)	89 (8)	No irAE PT occurred in at least 5% of patients
Grade ≥ 3	66 (6)	63 (5)	
Diarrhea			
Any Grade	242 (21)	231 (20)	No irAE PT occurred in at least 5% of patients
Grade ≥ 3	71 (6)	69 (6)	

[a] The "on treatment" period refers to the "early-onset AE window," defined as the time from the date of the first dose of ipilimumab through 90 days after the date of the last dose of ipilimumab therapy.

[b] The "on-study" period refers to the period from the time the patient received first dose of ipilimumab until the patient exited the study or the end of the study, whichever came first.

[c] The "post-treatment" period refers to the "late-onset AE window," which is defined as any time after the last dose of ipilimumab +90 days.

Hepatic irARs (eg, hepatitis)

3 mg/kg ipilimumab

Ipilimumab monotherapy Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004)
No hepatic irARs

Ipilimumab pooled monotherapy (MDX010-20, CA184004, MDX010-08, CA184022)
Any hepatic irARs, any grade: 3.6% previously untreated, 2.2% previously treated, 3.5% chemo naive, 2.0% chemo pretreated

Grade 3-4 hepatic irARs: 1.8% previously untreated, 0.8% previously treated, 1.4% chemo naive, 0.7% chemo pretreated

Grade 5 hepatic irARs: 0.2% previously treated, 0.2% chemo pretreated

Ipilimumab pooled 3 mg/kg containing regimens (MDX010-20, CA184004, MDX010-08, CA184022)
Any hepatic irARs, any grade: 3.6% previously untreated, 2.2% previously treated, 3.5% chemo naive, 2.0% chemo pretreated

Grade 3-4 hepatic irARs: 1.8% previously untreated, 0.8% previously treated, 1.4% chemo naive, 0.7% chemo pretreated

Grade 5 hepatic irARs: 0.2% previously treated, 0.2% chemo pretreated

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)

Ipilimumab Monotherapy in Previously Untreated Advanced Melanoma (CA184332, CA184338)
CA184332
Induction:
Any hepatic irARs, any grade: 1.9%; most frequent: hepatitis 0.6%
2 year follow-up:
Any hepatic irARs, any grade: 19.7%; most frequent: hepatitis 3.8%

CA184338
Induction:
Any hepatic irARs, any grade: NR
4 year follow-up:
Any hepatic irARs, any grade: 0.0%

Ipilimumab in Patients with Unresectable or Metastatic Melanoma (CA184143)

Melanoma	On Study[a] (N=1,151)	On Treatment[b] (N=1,151)	Post-treatment[c] (N=653)
CA184143		n (%)	
Any Grade	65 (6)	61 (5)	5 (0.8)
Grade ≥ 3	31 (3)	29 (3)	2 (0.3)

[a] The "on treatment" period refers to the "early-onset AE window," defined as the time from the date of the first dose of ipilimumab through 90 days after the date of the last dose of ipilimumab therapy.

[b] The "on-study" period refers to the period from the time the patient received first dose of ipilimumab until the patient exited the study or the end of the study, whichever came first.

[c] The "post-treatment" period refers to the "late-onset AE window," which is defined as any time after the last dose of ipilimumab +90 days.

Skin irARs (eg, rash, pruritus, TEN, and DRESS)

3 mg/kg ipilimumab

Ipilimumab monotherapy Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004)
Any skin irARs, any grade: 42.3%, most commonly Grade 1-2 rash and pruritus.

Grade 3 skin irARs: One (0.8%)

No serious skin irARs.

Ipilimumab pooled monotherapy (MDX010-20, CA184004, MDX010-08, CA184022)
Any skin irARs, any grade: 47.1% previously untreated, 42.5% previously treated, 52.0% chemo naive, 39.8% chemo pretreated

Grade 3-4 skin irARs: 2.9% previously untreated, 0.8% previously treated, 1.3% chemo naive, 1.0% chemo pretreated

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)

Grade 5 skin irARs: None

Ipilimumab pooled 3 mg/kg containing regimens (MDX010-20, CA184004, MDX010-08, CA184022)
Any skin irARs, any grade: 50.9% previously untreated, 40.4% previously treated, 49.6% chemo naive, 39.1% chemo pretreated

Grade 3-4 skin irARs: 3.6% previously untreated, 1.9% previously treated, 2.1% chemo naive, 2.0% chemo pretreated

Grade 5 skin irARs: None

Ipilimumab Monotherapy in Previously Untreated Advanced Melanoma (CA184332, CA184338)
CA184332
Induction:
Any skin irARs, any grade: 28.2%; most frequent: rash 18.0%
2 year follow-up:
Any skin irARs, any grade: 38.2%; most frequent: rash 31.8%

CA184338
Induction:
Any skin irARs, any grade: NR; most frequent: rash 15.0%; pruritus 13.2%; dermatitis 10.3%.
4 year follow-up:
Any skin irARs, any grade: NR; most frequent: rash 3.2%; pruritus 1.6%; dermatitis 0.0%.

Ipilimumab in Patients with Unresectable or Metastatic Melanoma (CA184143)

Melanoma	On Study[a] (N=1,151)	On Treatment[b] (N=1,151)	Post-treatment[c] (N=653)
CA184143		n (%)	
Any Grade	270 (23)	251 (22)	36 (6)[d]
Grade ≥ 3	30 (3)	27 (2)	6 (1)

[a] Numbers of patients with any post treatment skin irAEs are shown regardless of whether they occurred in at least 5% of patients, to provide context to the results.

[b] The "on treatment" period refers to the "early-onset AE window," defined as the time from the date of the first dose of ipilimumab through 90 days after the date of the last dose of ipilimumab therapy.

[c] The "on-study" period refers to the period from the time the patient received first dose of ipilimumab until the patient exited the study or the end of the study, whichever came first.

[d] The "post-treatment" period refers to the "late-onset AE window," which is defined as any time after the last dose of ipilimumab +90 days.

Summary of Skin irAE by PT Reported in at Least 5% of the Any Ipilimumab Patient Cohort in CA184143

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)

Melanoma	On Study[a] (N=1,151)	On Treatment[b] (N=1,151)	Post-treatment[c] (N=653)
CA184143			
Pruritus		n (%)	
Any Grade	104 (9)	98 (9)	No irAE PT occurred in at least 5% of patients
Grade ≥ 3	7 (0.6)	7 (0.6)	
Rash			
Any Grade	136 (12)	125 (11)	No irAE PT occurred in at least 5% of patients
Grade ≥ 3	18 (2)	15 (1)	

[a] The "on treatment" period refers to the "early-onset AE window," defined as the time from the date of the first dose of ipilimumab through 90 days after the date of the last dose of ipilimumab therapy.

[b] The "on-study" period refers to the period from the time the patient received first dose of ipilimumab until the patient exited the study or the end of the study, whichever came first.

[c] The "post-treatment" period refers to the "late-onset AE window," which is defined as any time after the last dose of ipilimumab +90 days.

Neurologic irARs (eg, neuropathy)

3 mg/kg ipilimumab

Ipilimumab monotherapy Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004)
Any neurologic irARs, any grade: 0%

Ipilimumab pooled monotherapy (MDX010-20, CA184004, MDX010-08, CA184022)
Any neurologic irARs, any grade: 8.8% previously untreated, 0.8% previously treated, 5.3% chemo naive, 0.5% chemo pretreated

Grade 3-4 neurologic irARs: None

Grade 5 neurologic irARs: None

Ipilimumab pooled 3 mg/kg containing regimens (MDX010-20, CA184004, MDX010-08, CA184022)
Any neurologic irARs, any grade: 9.1% previously untreated, 2.2% previously treated, 6.4% chemo naive, 1.8% chemo pretreated

Grade 3-4 neurologic irARs: 0% previously untreated, 0.2% previously treated, 0% chemo naive, 0.2% chemo pretreated

Grade 5 neurologic irARs: 0% previously untreated, 0.2% previously treated, 0% chemo naive, 0.2% chemo pretreated

Ipilimumab Monotherapy in Previously Untreated Advanced Melanoma (CA184332, CA184338)
CA184332

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)

Induction:
Any neurological irARs, any grade: 9.0%; most frequent: seizure 1.3%
2 year follow-up:
Any neurological irARs, any grade: 28.0%; most frequent: headache 7.0%

CA184338
Induction:
Any neurological irARs, any grade: NR; most frequent: neuropathy peripheral 4.8%
4 year follow-up:
Any neurological irARs, any grade: NR; most frequent: neuropathy peripheral, headache, convulsion 1.6%

Ipilimumab in Patients with Unresectable or Metastatic Melanoma (CA184143)

Melanoma	On Study[a] (N=1,151)	On Treatment[b] (N=1,151)	Post-treatment[c] (N=653)
CA184143		n (%)	
Any Grade	27 (2)	22 (2)	6 (1)
Grade ≥ 3	6 (0.5)	6 (0.5)	0 (0)

[a] The "on treatment" period refers to the "early-onset AE window," defined as the time from the date of the first dose of ipilimumab through 90 days after the date of the last dose of ipilimumab therapy.

[b] The "on-study" period refers to the period from the time the patient received first dose of ipilimumab until the patient exited the study or the end of the study, whichever came first.

[c] The "post-treatment" period refers to the "late-onset AE window," which is defined as any time after the last dose of ipilimumab +90 days.

Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)

3 mg/kg ipilimumab

Ipilimumab monotherapy Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004)
Grade 3 endocrine irARs: One case (0.9%) of hypopituitarism

Serious endocrine irARs: 2.7%

Ipilimumab pooled monotherapy (MDX010-20, CA184004, MDX010-08, CA184022)
Any endocrine irARs, any grade: 2.9% previously untreated, 5.7% previously treated, 2.7% chemo naive, 6.3% chemo pretreated

Grade 3-4 endocrine irARs: 0% previously untreated, 2.4% previously treated, 0% chemo naive, 2.9% chemo pretreated

Grade 5 endocine irARs: None

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)

Ipilimumab pooled 3 mg/kg containing regimens (MDX010-20, CA184004, MDX010-08, CA184022)
Any endocrine irARs, any grade: 9.1% previously untreated, 2.2% previously treated, 6.4% chemo naive, 1.8% chemo pretreated

Grade 3-4 endocrine irARs: 0% previously untreated, 0.2% previously treated, 0% chemo naive, 0.2% chemo pretreated

Grade 5 endocrine irARs: None

Ipilimumab Monotherapy in Previously Untreated Advanced Melanoma (CA184332, CA184338)
CA184332
Induction:
Any endocrine irARs, any grade: 3.9%; most frequent: high blood sugar 0.6%
2 year follow-up:
Any endocrine irARs, any grade: 11.5%; most frequent: high blood sugar 9.6%

CA184338
Induction:
Any endocrine irARs, any grade: 2.6%
4 year follow-up:
Any endocrine irARs, any grade: 0.0%

Ipilimumab in Patients with Unresectable or Metastatic Melanoma (CA184143)

Melanoma	On Study[a] (N=1,151)	On Treatment[b] (N=1,151)	Post-treatment[c] (N=653)
CA184143		n (%)	
Any Grade	89 (8)	76 (7)	14 (2)
Grade ≥ 3	35 (3)	32 (3)	4 (0.6)

[a] The "on treatment" period refers to the "early-onset AE window," defined as the time from the date of the first dose of ipilimumab through 90 days after the date of the last dose of ipilimumab therapy.

[b] The "on-study" period refers to the period from the time the patient received first dose of ipilimumab until the patient exited the study or the end of the study, whichever came first.

[c] The "post-treatment" period refers to the "late-onset AE window," which is defined as any time after the last dose of ipilimumab +90 days.

Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)

3 mg/kg ipilimumab

Ipilimumab monotherapy (MDX010-20)
Any other irARs, any grade: 3.8%
gp100: 2.3%. Difference between monotherapy and gp100: 1.5% (95% CI = -3.2%, 6.9%)

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)

Uveitis: 1.5%

Grade 3-4 other irARs: 1.5%. One case each (0.8%) of lipase increased and glomerulonephritis
gp100: 0.8%. Difference between monotherapy and gp100: 0.8% (95% CI= -3.0%, 4.8%)

Ipilimumab+gp 100 (MDX010-20)
Any other irARs, any grade: 2.6%

Lipase increased and blood amylase increased: 0.5%

Grade 3-4 other irARs: 1.3%

Grade 5 (fatal) other irARs: One (0.3%) multi-organ failure

Ipilimumab monotherapy Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004)
Grade 1-2 other irARs: 1.8%; Grade 3-4: None

Ipilimumab pooled monotherapy (MDX010-20, CA184004, MDX010-08, CA184022)
Any other irARs, any grade: 0% previously untreated, 3.2% previously treated, 1.3% chemo naive, 3.4 % chemo pretreated

Grade 3-4 other irARs: 0% previously untreated, 1.2% previously treated, 1.3% chemo naive, 1.0% chemo pretreated

Grade 5 other irARs: None

Ipilimumab pooled 3 mg/kg containing regimens (MDX010-20, CA184004, MDX010-08, CA184022)
Any other irARs, any grade: 1.8% previously untreated, 2.8% previously treated, 1.4% chemo naive, 3.1% chemo pretreated

Grade 3-4 other irARs: 1.8% previously untreated, 1.2% previously treated, 1.4% chemo naive, 1.3% chemo pretreated

Grade 5 other irARs: None

Ipilimumab in Patients with Unresectable or Metastatic Melanoma (CA184143)

Melanoma	On Study[a] (N=1,151)	On Treatment[b] (N=1,151)	Post-treatment[c] (N=653)
CA184143		n (%)	
Any Grade	29 (3)	22 (2)	8 (1)
Grade ≥ 3	12 (1)	10 (0.9)	2 (0.3)

[a] The "on treatment" period refers to the "early-onset AE window," defined as the time from the date of the first dose of ipilimumab through 90 days after the date of the last dose of ipilimumab therapy.

[b] The "on-study" period refers to the period from the time the patient received first dose of ipilimumab until the patient exited the study or the end of the study, whichever came first.

[c] The "post-treatment" period refers to the "late-onset AE window," which is defined as any time after the last dose of ipilimumab +90 days.

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)	
Risk factors and risk groups	**GI irARs (eg, diarrhoea, colitis, GI perforation)** Patients with active inflammatory bowel diseases **Hepatic irARs (eg, hepatitis)** Active AIH, which may also be associated with previous chemotherapy or immunotherapy, such as IL-2 or IFN. In addition to female gender, genetic factors appear to confer a predisposition for the incidence of AIH. The HLAs DR3, DR4, and DR7 have been associated with AIH.[162,163] Moreover, there is evidence to suggest that susceptibility to AIH, the severity and clinical outcome may vary according to genetic polymorphisms for the cytokines TNF-α and TGF- β1.[164,165] Certain therapies, including long-term therapy with IFN), have been reported to induce hepatocellular injury that mimics AIH.[166,167] There is mounting evidence that IFN therapy (α,β) may exacerbate or initiate certain autoimmune diseases.[168] The frequency of IFN-α associated autoimmune diseases has been reported to range from 4% to 19%.[169] Among patients with chronic myeloid leukemia, IFN-α2a associated autoimmunity has been reported to be as high as 28%.[170] The frequency of AIH is unknown. It was reported to occur in 2% (1 of 46) of chronic myeloid leukemia patients treated at one institution (detected after 38 months on therapy).[151] and there are case reports of AIH following IFN-beta therapy for multiple sclerosis[171] and following IFN-α therapy for malignant melanoma.[172] **Skin irARs (eg, rash, pruritus, TEN, and DRESS)** Active autoimmune skin disorders **Neurologic irARs (eg, neuropathy)** Previous viral or bacterial infection (eg, cytomegalovirus, *Campylobacter jejuni*, *Mycoplasma pneumoniae*, Epstein Barr virus, influenza virus) [173,174,175,176] or previous immunotherapy with IFN-alpha.[177] **Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)** Active autoimmune diseases of endocrine glands **Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)** Active autoimmune diseases
Preventability	In the event of symptoms of immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs), prompt identification of relevant symptoms and implementation of the recommended management guideline may prevent serious complications (see SmPC and Annex 6).

Table 2.7.3.1-1: Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)

Important Identified Risk: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine, and other irARs)	
Impact on the risk-benefit balance of the product	Metastatic melanoma is a life-threatening advanced malignancy with limited effective treatment options. Advanced melanoma, its complications and immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs) affect all areas of life including daily tasks, emotions, and social relationships. Sometimes serious complications can be fatal.
Public health impact	All available data suggest that ipilimumab has a consistent AE profile across tumor types. For ipilimumab 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	See Annex 7

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

Important Identified Risk Severe Infusion Reactions	
Potential mechanisms	Infusion reactions may be observed during treatment with any injectable protein including ipilimumab, which is a fully-human IgG1 anti-CTLA-4 monoclonal antibody.
Evidence source and strength of evidence	As with any other intravenous administered drugs, infusion-related reactions can occur with ipilimumab. Likely systemic infusion reactions were defined as any event from the list that occurred within 48 hours after the subject received study treatment. Premedications were not required prior to ipilimumab administration during clinical trials with ipilimumab. Severe infusion reactions can be potentially serious if associated with severe hypersensitivity reaction or anaphylaxis. No fatal events of infusion-related reactions were reported.[142]
Characterization of risk	**3 mg/kg ipilimumab** MDX010-20 and pooled Phase 2 studies, 5 of 696 subjects (0.7%)

Ipilimumab in Patients with Unresectable or Metastatic Melanoma (CA184143)

Melanoma	**On Study[a] (N=1,151)**	**On Treatment[b] (N=1,151)**	**Post-treatment[c] (N=653)**
CA184143		n (%)	
Any Grade	4 (0.3)	4 (0.3)	0 (0)
Grade ≥ 3	2 (0.2)	2 (0.2)	0 (0)

[a] The "on treatment" period refers to the "early-onset AE window," defined as the time from the date of the first dose of ipilimumab through 90 days after the date of the last dose of ipilimumab therapy.

[b] The "on-study" period refers to the period from the time the patient received first dose of ipilimumab until the patient exited the study or the end of the study, whichever came first.

[c] The "post-treatment" period refers to the "late-onset AE window," which is defined as any time after the last dose of ipilimumab +90 days.

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

Important Identified Risk Severe Infusion Reactions	
	10 mg/kg ipilimumab CA184024 (ipilimumab+DTIC) and ipilimumab monotherapy in pooled Phase 2 studies 13/611 subjects (2.1%): 9 subjects in CA184024 and 4 subjects in pooled Phase 2 studies. Ipilimumab (CA184042) No infusion reactions reported **10 mg/kg vs 3 mg/kg ipilimumab (Phase 3, CA184169)** 1 out of 364 subjects (10 mg/kg) and 1 out of 362 subjects (3 mg/kg)
Risk factors and risk groups	Infusion reactions may be observed during treatment with any injectable protein including ipilimumab, which is a fully-human IgG1 anti-CTLA-4 monoclonal antibody.
Preventability	Acute infusional events are usually easily recognized and can be managed by interruption of dosing and appropriate medical treatment. Pretreatment with antihistamines and/or steroids is not recommended.
Impact on the risk-benefit balance of the product	Infusion related reactions may have a significant impact on the patient's quality of life, if the event is severe or life threatening.
Public health impact	All available data suggest that ipilimumab has a consistent AE profile across tumor types. For ipilimumab 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	See Annex 7

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information

Missing Information	**Is the safety profile expected to be different from the general target population?**
Population in need of further characterisation:	
Long-term safety in adolescent patients ≥ 12 years of age	The effects of ipilimumab in adolescent patients greater than 12 years of age are not known. A PIP for ipilimumab in malignant neoplasms (except melanoma, nervous system, haematopoietic, and lymphoid tissue) and a second PIP in melanoma have been completed in the EU.

2.7.3.3 Ipilimumab in Combination with Nivolumab

The safety of nivolumab in combination with ipilimumab in subjects with advanced melanoma has been fully characterized in 3 studies: one Phase 1b study (CA209004),[178] one Phase 3 study (CA209067),[179] and one Phase 2 study (CA209069).[180] In summary, the safety profile of

nivolumab in combination with ipilimumab in subjects advanced melanoma was consistent with the mechanisms of action of nivolumab and ipilimumab and were consistent with that already characterized for each agent when administered as monotherapy.[181] No new safety concerns were identified.

The safety of nivolumab in combination with ipilimumab in subjects with RCC has been fully characterized in a Phase 3 study (CA209214) and Phase 1 study (CA209016) in first-line RCC. In summary, the safety profile of nivolumab in combination with ipilimumab in subjects with RCC was consistent with the established safety profile of ipilimumab monotherapy and nivolumab in combination with ipilimumab.[181] No new safety concerns were identified.

The safety of nivolumab in combination with ipilimumab in subjects with CRC has been fully characterized in a Phase 2 study (CA209142) in second-line CRC and in a Phase 3 study (CA2098HW) in first-line CRC. In summary, the safety profile of nivolumab in combination with ipilimumab in subjects with CRC was consistent with the established safety profile of ipilimumab monotherapy and nivolumab in combination with ipilimumab.[182], [183] No new safety concerns were identified.

The safety of nivolumab in combination with ipilimumab in subjects with MPM has been fully characterized in a Phase 3 study (CA209743) in first-line MPM. In summary, the safety profile of nivolumab in combination with ipilimumab in subjects with MPM was consistent with the established safety profile of ipilimumab monotherapy and nivolumab in combination with ipilimumab.[184] No new safety concerns were identified.

The safety of nivolumab in combination with ipilimumab in subjects with OSCC has been fully characterized in a Phase 3 study (CA209648) in first-line OSCC. In summary, the safety profile of nivolumab in combination with ipilimumab in subjects with OSCC was consistent with the established safety profile of ipilimumab monotherapy and nivolumab in combination with ipilimumab.[185] No new safety concerns were identified.

The safety of nivolumab in combination with ipilimumab in paediatric and young adult subjects with relapsed or refractory solid or haematologic tumors has been characterized in a Phase 1/2 study (CA209070). In summary, the safety profile of nivolumab in combination with ipilimumab in paediatric and young adult subjects with solid or haematologic tumors was consistent with the established safety profile of nivolumab in combination with ipilimumab as known in adults.[186] There were no new safety signals identified.

The safety of nivolumab in combination with ipilimumab in subjects with unresectable or advanced HCC has been fully characterized in a Phase 3 study (CA2099DW) in first-line HCC. In summary, the safety profile of nivolumab in combination with ipilimumab in subjects with unresectable or advanced HCC was consistent with the established safety profile of ipilimumab monotherapy and nivolumab in combination with ipilimumab.[187] No new safety concerns were identified.

The safety characterization of nivolumab in combination with ipilimumab is presented in Appendix 4.

2.7.3.4 Ipilimumab in Combination with Nivolumab and Platinum Doublet Chemotherapy

The safety of nivolumab in combination with ipilimumab and platinum doublet chemotherapy in subjects with NSCLC has been fully characterized in a Phase 3 study (CA2099LA)[188] with supportive data from Part 2 of a Phase 2 study (CA209568).[189] In summary, the safety profile of ipilimumab in combination with nivolumab 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 was consistent with the established safety profiles of each individual component. No new safety concerns were identified.

The safety characterization of nivolumab in combination with ipilimumab and platinum doublet chemotherapy is presented in Appendix 4.

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 ipilimumab are listed in Table 2.8-1.

Table 2.8-1: Summary of Safety Concerns

Important identified risks	• Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs) • Severe infusion reactions
Important potential risks	• None
Missing information	• Long-term safety in adolescent patients ≥ 12 years of age

3 PART III: PHARMACOVIGILANCE PLAN

The PV plan includes several integrated and complementary activities to proactively identify and characterize all safety concerns that have been identified or have potential to be associated with the use of ipilimumab. PV activities, including pharmacoepidemiology studies, are part of the overall PV plan. The ongoing proactive activities involve a comprehensive approach to signal detection and assessment of all identified and potential risks. The safety assessments included in the following sections are key elements that are part of a cohesive PV plan that will inform risk mitigation strategies for irARs and other events of special interest. The risk minimization plan is outlined in Section 5.

3.1 Routine Pharmacovigilance Activities

Routine PV activities beyond adverse reaction reporting and signal detection are summarized in Table 3.1-1.

Table 3.1-1: Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

Other forms of routine pharmacovigilance activities	
Other forms of routine PV activities for long-term safety in adolescent patients ≥ 12 years of age	A PIP for solid tumors and a PIP for melanoma have been completed in the EU. Reporting of long-term safety data in paediatric patients in studies of nivolumab and ipilimumab combination therapy (CA209070 and CA209908[a]). Monitoring of initial AEs and continued follow-up while on therapy and/or 100 days after the last dose by the treating physician. Follow-up information obtained by BMS using specified procedures (telephone interviews or mailing a questionnaire to the treating physician).

[a] The primary CSR for CA209908 was completed and reported to fulfil the obligation set out by Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation') for both OPDIVO and YERVOY. In the YERVOY PSUR #14, this study was listed as completed.

3.2 Additional Pharmacovigilance Activities

A summary of ongoing Category 1-3 safety studies included in the ipilimumab 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 Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated paediatric patients enrolled in the Dutch Melanoma Treatment Registry (DMTR) (CA184557)[a] 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	Synopsis of the DMTR	16-Apr-2018
				Submission of protocol	02-Nov-2019
				Recruitment period[b]	Q2 2019 until Q1 2029
				Start of data collection: ipilimumab monotherapy treatment group	End of Q2 2019
				Start of data collection: nivolumab monotherapy treatment group nivolumab in combination with ipilimumab treatment group	End of Q1 2024
				Progress Report: ipilimumab monotherapy treatment group	End of Q2 2022
				Interim Study Report: ipilimumab monotherapy treatment group nivolumab monotherapy treatment group nivolumab in combination with ipilimumab treatment group	Q4 2026
				End of data collection: ipilimumab monotherapy treatment group	End of Q1 2029
				Final report of study results:	End of Q3 2029

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)
				ipilimumab monotherapy treatment group	
				End of data collection: nivolumab monotherapy treatment group	End of Q1 2033
				nivolumab in combination with ipilimumab treatment group	
				Final report of study results: nivolumab monotherapy treatment group	Q4 2033
				nivolumab in combination with ipilimumab treatment group	

[a] The protocol, CA184557, which includes patients treated with ipilimumab monotherapy, was amended (29-Sep-2023) to include patients who received nivolumab monotherapy or nivolumab in combination with ipilimumab (including those receiving therapy prior to the start of data collection).

[b] The recruitment period began in Q2 2019, when the Princess Maxima Center officially confirmed its collaboration to the paediatric extension of the DMTR, but the data will include all paediatric patients entered in the DMTR who received study treatment prior to the start of data collection.

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1: On-going 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				
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 Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated paediatric patients enrolled in the DMTR (CA184557[a])[190] Ongoing	To assess safety and long-term outcomes in children and adolescents.	Long-term safety in adolescent patients ≥ 12 years of age	Synopsis of the DMTR	16-Apr-2018
			Submission of protocol	02-Nov-2019
			Recruitment period[b]	Q2 2019 until Q1 2029
			Start of data collection: ipilimumab monotherapy treatment group	End of Q2 2019
			Start of data collection: nivolumab monotherapy treatment group nivolumab in combination with ipilimumab treatment group	End of Q1 2024
			Progress Report: ipilimumab monotherapy treatment group	End of Q2 2022
			Interim Study Report: ipilimumab monotherapy treatment group nivolumab monotherapy treatment group nivolumab in combination with ipilimumab treatment group	Q4 2026

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
			End of data collection: ipilimumab monotherapy treatment group	End of Q1 2029
			Final report of study results: ipilimumab monotherapy treatment group	End of Q3 2029
			End of data collection: nivolumab monotherapy treatment group nivolumab in combination with ipilimumab treatment group	End of Q1 2033
			Final report of study results: nivolumab monotherapy treatment group nivolumab in combination with ipilimumab treatment group	Q4 2033

[a] The protocol, CA184557, which includes patients treated with ipilimumab monotherapy, was amended (29-Sep-2023) to include patients who received nivolumab monotherapy or nivolumab in combination with ipilimumab (including those receiving therapy prior to the start of data collection).

[b] The recruitment period began in Q2 2019, when the Princess Maxima Center officially confirmed its collaboration to the paediatric extension of the DMTR, but the data will include all paediatric patients entered in the DMTR who received study treatment prior to the start of data collection.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are 2 studies that are conditions for the marketing authorisation of YERVOY in combination with nivolumab.

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-2027
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation 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
Safety Concern: Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine 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 adverse drug reactions in Section 4.8. In addition, patient product information also includes specific warnings and descriptions on 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 irAR monitoring and management including dose omission or discontinuation and intervention with corticosteroids in Sections 4.2 and 4.4 and 4.8 as appropriate. **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: Severe Infusion Reactions	**Routine risk communication:** The SmPC warns the risk of severe infusion reactions in Section 4.3 (Contraindication), 4.4 (Special warnings and precautions for use), 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
Safety Concern: Long-term safety in adolescent patients ≥ 12 years of age	**Routine risk communication:** Pediatrics-related information is available in Section 4.2, 4.4, 4.8, and 5.2 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

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 Educational materials: • Patient Card	**Objectives:** To ensure that patients are aware of the severe inflammatory adverse reactions, understand the importance of early detection, and have access to appropriate treatment guidelines. **Rationale for the additional risk minimisation activity:** The educational materials will provide the opportunity for reinforcing key messages to early recognition and appropriate management of inflammatory adverse reactions to maintain favorable benefit/risk of ipilimumab in market use. **Target audience and planned distribution path:** Target audience: Patients Distribution via healthcare professionals agreed at national level. **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 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 Minimization Measures

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

Table 5.3-1: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Identified Risks Immune-related ARs (including GI, hepatic, skin, neurologic, endocrine, and other irARs)	Routine risk minimisation measures: SmPC Section 4.4 specific warning/precautions; Sections 4.2 and 4.4 guidelines on monitoring, diagnosis, dose modification, and corticosteroids intervention; and Section 4.8 ADR list	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures:Patient Card	Additional pharmacovigilance activities: None
Severe Infusion Reactions	Routine risk minimisation measures: SmPC Section 4.3 Contraindication, Section 4.4 Special warnings, Section 4.8 Undesirable effects	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: • Patient Card	Additional pharmacovigilance activities: None

Table 5.3-1: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Long-term safety in adolescent patients ≥ 12 years of age	Routine risk minimisation measures: SmPC Section 4.2, 4.4, 4.8, and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A PIP for ipilimumab in malignant neoplasms (except melanoma, nervous system, haematopoietic, and lymphoid tissue) and a second PIP in melanoma have been completed in the EU. • Reporting of long-term safety data in paediatric patients in studies of nivolumab and ipilimumab combination therapy (CA209070 and CA209908[a]). • Monitoring of initial AEs and continued follow-up while on therapy and/or 100 days after the last dose by the treating physician. Follow-up information obtained by BMS using specified procedures (telephone interviews or mailing a questionnaire to the treating physician).
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Long-term follow-up of Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated paediatric patients enrolled in the DMTR (CA184557).

[a] The primary CSR for CA209908 was completed and reported to fulfil the obligation set out by Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation') for both OPDIVO and YERVOY. In the YERVOY PSUR #14, this study was listed as completed.

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for YERVOY (ipilimumab)

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

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

This summary of the RMP for YERVOY 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 YERVOY's RMP.

I. The medicine and what it is used for

YERVOY is authorised for treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older. YERVOY in combination with OPDIVO (nivolumab) is authorised for treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older, for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma, for treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine based combination chemotherapy, for the first-line treatment of adult patients with dMMR or MSI-H unresectable or metastatic colorectal cancer, for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma, for the first-line treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC), and for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC). YERVOY in combination with OPDIVO and chemotherapy is authorised for the first-line treatment of metastatic non-small cell lung cancer in adults. It contains ipilimumab as the active substance and it is given by intravenous infusion (see SmPC for the full indication).

Further information about the evaluation of YERVOY's benefits can be found in YERVOY'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/yervoy

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

Important risks of YERVOY, together with measures to minimise such risks and the proposed studies for learning more about YERVOY'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 authorised 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 YERVOY, 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 Periodic Safety Update Report (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 YERVOY is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of YERVOY 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 YERVOY. 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 GI, hepatic, skin, neurologic, endocrine and other irARs) Severe infusion reactions
Important potential risks	None
Missing information	Long-term safety in adolescent patients ≥ 12 years of age

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risks

Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)	
Evidence for linking the risk to the medicine	**GI irARs (eg, diarrhoea, colitis, GI perforation)** In clinical studies, GI irARs most often presented as diarrhoea, abdominal pain, and/or hematochezia with or without fever. Majority of subjects with GI irARs had mild to moderate (Grade 1 or 2) diarrhoea or colitis which were generally manageable and usually resolved. However, severe or persistent diarrhoea or colitis could occur. Discontinuation of ipilimumab (either temporarily or permanently) was required for subjects with Grade 3-4 events. Late onset GI irARs (more than 30 days after last dose) and fatalities due to GI perforation and hemorrhagic colitis requiring colectomy have been reported. **Hepatic irARs (eg, hepatitis)** Hepatic irARs of any grade reported during the treatment period were less common than those affecting the GI tract and skin and generally resolved. In the clinical studies, hepatic irARs were most often asymptomatic but could be detected by routine laboratory monitoring. Discontinuation of ipilimumab was required in patients with high-grade events. Fatal outcome may occur if not treated promptly and appropriately. **Skin irARs (eg, rash, pruritus, TEN, and DRESS)** Skin irARs during the treatment dosing period were common and consisted primarily of Grade 1-2 rash and pruritus. Skin irARs generally resolved, however can be potentially severe or fatal. **Neurologic irARs (eg, neuropathy)** Neurological manifestations in subjects treated with ipilimumab may include motor and/or sensory neuropathy. Given the difficulty in definitely establishing an inflammatory etiology, alternative etiologies (eg, tumor progression) should be excluded. Fatal Guillain-Barre syndrome and cases of myasthenia gravis have been reported in clinical trials of ipilimumab. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy should be evaluated, and noninflammatory causes

Important identified risks

	such as disease progression, infections, metabolic disorders, and medications should be excluded. **Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)** Severe (Grade 3-4) endocrinopathy has been reported in minority of patients. Patients with hypophysitis and hypopituitarism typically presented with headache or fatigue, which may be incorrectly attributed to underlying malignancy. Diagnosis requires laboratory confirmation. Endocrinopathy can be serious or life-threatening. Patients are usually clinically managed with steroids and/or hormone replacement therapy. Long-term hormone replacement may be required. **Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)** Selected other irARs which are considered important identified risks include, for example, pneumonitis, nephritis, and non-infectious myocarditis. Severe (Grade 3-4) irARs reported in minority of patients. Other irARs can be serious and life-threatening. Patients are usually clinically managed with steroids and the events generally resolved.
Risk factors and risk groups	**GI irARs (eg, diarrhoea, colitis, GI perforation)** Patients with active inflammatory bowel diseases **Hepatic irARs (eg, hepatitis)** AIH, which may also be associated with previous chemotherapy or immunotherapy, such as IL-2 or IFN. In addition to female gender, genetic factors appear to confer a predisposition for the incidence of AIH. The HLAs DR3, DR4, and DR7 have been associated with AIH. Moreover, there is evidence to suggest that susceptibility to AIH, the severity and clinical outcome may vary according to genetic polymorphisms for the cytokines TNF-α and TGF- β1. Certain therapies, including long-term therapy with IFNα, have been reported to induce hepatocellular injury that mimics AIH. There is mounting evidence that IFN therapy (α,β) may exacerbate or initiate certain autoimmune diseases. The frequency of IFN-α associated autoimmune diseases has been reported to range from 4% to 19%. Among patients with chronic myeloid leukemia, IFN-α2a associated autoimmunity has been reported to be as high as 28%. The frequency of AIH is unknown. It was reported to occur in 2% (1 of 46) of chronic myeloid leukemia patients treated at one institution (detected after 38 months on therapy). and there are case reports of AIH following IFN-beta therapy for multiple sclerosis and following IFN-α therapy for malignant melanoma. **Skin irARs (eg, rash, pruritus, TEN, and DRESS)** Active autoimmune skin disorders **Neurologic irARs (eg, neuropathy)** Previous viral or bacterial infection (eg, cytomegalovirus, *Campylobacter jejuni*, *Mycoplasma pneumoniae*, Epstein Barr virus, influenza virus) or previous immunotherapy with IFN-alpha. **Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)**

Important identified risks

	Active autoimmune diseases of endocrine glands
	Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)
	Active autoimmune diseases
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 specific warning/precautions; Sections 4.2 and 4.4 guidelines on monitoring, diagnosis, dose modification, and corticosteroids intervention; and Section 4.8 ADR list.
	Additional risk minimization measures: Patient Card.
Additional PV 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 ipilimumab. Likely systemic infusion reactions were defined as any event from the list that occurred within 48 hours after the subject received study treatment. Premedications were not required prior to ipilimumab administration during clinical trials with ipilimumab. Severe infusion reactions can be potentially serious if associated with severe hypersensitivity reaction or anaphylaxis. No fatal events of infusion-related reactions were reported.
Risk factors and risk groups	Infusion reactions may be observed during treatment with any injectable protein including ipilimumab, which is a fully-human IgG1 anti-CTLA-4 monoclonal antibody.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4, and 4.8
	Additional risk minimization measures: Patient Card.
Additional PV activities	None

Missing information

Long-term safety in adolescent patients ≥ 12 years of age	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2, 4.4, 4.8, and 5.2
Additional pharmacovigilance activity	Long-term follow-up of Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated paediatric patients enrolled in the 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 study is a condition of the marketing authorisation of YERVOY in combination with nivolumab in RCC:

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 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 (CA2098Y8)	To further evaluate the efficacy and safety of the combination of nivolumab and ipilimumab compared to nivolumab monotherapy.

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
Long-term follow-up of Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated paediatric patients enrolled in the DMTR (CA184557)	To assess safety and long-term outcomes in children and adolescents.

APPENDIX 2: NONCLINICAL SAFETY SUMMARY

12 page(s) excluding cover page

APPENDIX 2: NONCLINICAL SAFETY SUMMARY

Non-Clinical Toxicology: The nonclinical toxicity of ipilimumab was well characterized in a comprehensive, drug-safety evaluation program which evaluated repeat-dose toxicities, immunogenicity, immunotoxicity, local tolerance, safety pharmacology, and tissue binding characteristics.[1] In addition, a combined study evaluating the potential effects of ipilimumab on embryo-fetal development and pre- and postnatal development in cynomolgus monkeys was conducted.[2] Ipilimumab is pharmacologically active in cynomolgus monkeys, the toxicology species utilized, and was evaluated at doses up to 10-fold greater and dosing-intervals up to 7 times more frequent than those in humans given 3 mg/kg every 21 days. Rodent studies were not performed due to lack of cross reactivity of ipilimumab to these species. In pivotal intravenous (IV) repeat-dose toxicology studies in monkeys, ipilimumab was tolerated without adverse effects at doses up to 30 mg/kg administered every 3 days for 3 doses (peak serum concentrations ≤ 682 µg/mL),[3,4,5] at 10 mg/kg (equivalent to approximately 3 times the human dose on body-weight basis) administered weekly for 1 month (mean AUC (0-168h) and AUC (0-63 days) of 31.6 µg•h/mL and 102.1 µg•h/mL, respectively),[6] at 1 mg/kg administered weekly for 10 weeks,[7,8] and at doses up to 10 mg/kg administered approximately monthly for up to 6 months.[7,8, 9 , 10] Ipilimumab was not appreciably immunogenic in monkeys following IV administration (positive anti-drug antibody response rate of 8% or 9 of 106 monkeys evaluated as a single agent or in combination with various antigens, DNA vaccines, or an anti-CD137 mAb, BMS-663513).[4,5,6,7,8,9,10] Evidence of pharmacologic activity (enhancement of antigen-specific humoral immune responses and T-cell activation) without any generalized, non-specific immune-cell activation (adverse autoimmune toxicity) was demonstrated in several studies. However, in 2 of over 100 monkeys receiving ipilimumab as a single agent or in combination with various antigens, deoxyribonucleic acid (DNA) vaccines, or BMS-663513, an anti-CD137 monoclonal antibody, serious adverse events (SAEs) occurred within the context of exploratory studies that are considered to be consistent with similar irARs observed in humans. These include colitis, which was observed in 1 of 6 monkeys receiving ipilimumab 10 mg/kg in combination with 3 vaccines (HBsAg, SK-mel, and DNP-Ficoll) in a 3-month exploratory study. The colitis led to euthanasia on Day 42. Another reported irAR was a persistent dermatitis/rash in the inguinal area accompanied by peripheral lymphadenopathy on Day 113 that occurred in 1 monkey given ipilimumab at 10 mg/kg about twice monthly in combination with another immunomodulatory antibody (BMS-663513, a fully human anti-CD137 monoclonal antibody) and simian immunodeficiency virus DNA vaccines in a 4-month pharmacology study.

The colitis was characterized by acute to subacute inflammation, crypt abscesses, and erosion of the colon extending into the rectum. Additional findings included mixed cell infiltrates in the adrenals, liver, and renal glomeruli, thickened glomerular mesangia, hyperplasia of adrenal cortex (zona fasciculata), and lymphoid depletion of thymus, spleen, and gut-associated lymphoid tissue. These findings were considered secondary to the poor physical condition of the animal and/or to infection that occurred as a result of compromise of the gut lining. The dermatitis appeared about 4 weeks after the last dose of ipilimumab and BMS-663513 and was

transiently responsive to antihistamine treatment, but returned and was eventually resolved with prednisone treatment. Skin samples obtained from biopsy of the affected area indicated mild epidermal thickening/proliferation (increased nuclear proliferation antigen $Ki67^{+}$) with the underlying dermis containing mild perivascular edema and infiltrates of lymphocytes (mostly $CD8^{+}$), macrophages ($CD68^{+}$), and mast cells. No infectious agents were present. These irARs are an expected potential consequence of inhibiting cytotoxic T-lymphocyte antigen (CTLA)-4 function and are associated with tumor response in clinical trials.

In addition, an infusion reaction, accompanied by a breathing difficulty, cyanosis, thready pulse, and muffled heart sounds, occurred in a single monkey while under ketamine sedation following a rapid bolus dose of ipilimumab in a 4-month exploratory pharmacology study. However, this reaction could not be definitively linked to a direct effect of ipilimumab because of a lack of reproducibility under controlled infusion conditions in the same monkey.

The effects of ipilimumab on reproduction and development were studied in an enhanced pre- and postnatal development study in cynomolgus monkeys. In this study, pregnant monkeys received ipilimumab every 21 days from the beginning of organogenesis in the first trimester through delivery (mean gestation length of 155-160 days), at dose levels that resulted in exposures (by AUC) that were either 2.6 (10 mg/kg) or 7.2 times (30 mg/kg) higher than the clinical exposure of ipilimumab at a dose of 3 mg/kg every 21 days or approximately 0.9 and ~2.1 times higher than the clinical exposure at a dose of 10 mg/kg every 21 days.[2] Ipilimumab was shown to be present at very low levels in milk from adult mothers (with mean milk/serum ipilimumab concentration ratios that were 0.002 to 0.003). No treatment-related adverse effects on reproduction were detected during the first 2 trimesters of pregnancy. Maternal pregnancy outcomes for the first 2 trimesters were comparable in control and drug-treated groups. Beginning in the third trimester, the ipilimumab groups experienced lower maternal body weights; higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight); and higher incidences of infant mortality in a dose-related manner, compared to controls 21% and 30% for 10 and 30 mg/kg groups, respectively; compared to 0% in the study controls and 17.6% incidence in historical controls. Some infant mortality in ipilimumab-treated groups could be attributed to extreme prematurity; however, the group mean durations of gestation were comparable in the 3 experimental groups (160, 160, and 155 days in the control, 10, and 30 mg/kg groups, respectively). Urogenital malformations were observed in 2 infants of mothers at 30-mg/kg. Infants from mothers exposed to ipilimumab at 30 mg/kg had a lower mean body weight (-15% relative to control infant values) at birth. Lower body weight persisted through 5 months of age but the rate of body-weight gain increased by 3 months of age. At 6 months of age, the group mean body weight for the 30 mg/kg infants had increased to that of the control infants. Ipilimumab did not adversely affect the ability of infants to mount a T-cell dependent antibody response to Hepatitis B surface antigen at 6 and 18 weeks of age. There were no adverse effects observed in infants related to ipilimumab-exposure in utero with respect to clinical observations, morphometric measurements, neurobehavioral and skeletal evaluations, clinical pathology, lymphocyte phenotyping, anti-nuclear antibody formation, or serum immunoglobulin levels through 6 months of age.

Combined therapy of ipilimumab and MDX-1106 (an immunostimulatory mAb to the PD-1 receptor) at doses of ≥ 3 mg/kg and ≥ 10 mg/kg, respectively, resulted in an increased incidence of immune-related adverse effects in a 1-month (qw x 4) study in monkeys,[11] relative to those observed historically in previous studies at similar doses of either test article administered as a single agent.[6,7,8,9,10,12] These effects were generally consistent with the combined pharmacologic effects of both compounds and consisted primarily of inflammation of the large intestine with associated clinical signs of diarrhea, decreased food consumption, and body-weight loss, increased follicles and marginal zone expansion in spleen; and decreased germinal centers in the spleen and lymph nodes. In addition, the rate of immunogenicity of ipilimumab in combination with MDX-1106 (32%) was higher than observed in previous studies (~8%).[4,5,6,7,8,9,10]

The tissue binding of ipilimumab was evaluated in 36 human tissues across 2 studies using a fluorescein-conjugate of the antibody and in another study using a biotin-conjugate of the antibody. The biotin conjugate was also used to evaluate species cross reactivity to a comprehensive panel of 23 tissues from cynomolgus monkeys, and mouse, rat, or rabbit lymphoid tissues. Fluorescein and/or biotin-conjugated ipilimumab specifically bound to lymphocytes expressing CTLA-4 in several normal human and/or cynomolgus monkey tissues (tonsil, GI tract, lymphoid system, lung, kidney, liver, skin, and/or peripheral blood) in tissue-binding crossreactivity studies. In addition, biotin-conjugated ipilimumab (1 and 10 μg/mL) bound specifically to connective tissue in human and cynomolgus monkey placenta and to connective tissue in cynomolgus monkey ovary; no specific binding was observed in human ovary. Ipilimumab did not bind with specificity to other monkey or human tissues or to mouse, rat, or rabbit lymphoid tissues (lymph node, spleen, and tonsil for rabbits and lymph node and spleen for mice and rats). These data support the species specificity of ipilimumab binding to cynomolgus monkey and human CTLA-4. CTLA-4 protein expression on placental fibroblasts has been previously reported.[13,14] However, the role that CTLA-4 plays is unclear, and there is no clear depiction of whether CTLA-4 expression is internal, or on the surface where any biological effects of ipilimumab binding would presumably occur.[13] Therefore, the biological relevance, if any, of the binding of ipilimumab to cynomolgus monkey and human placental tissue is unknown. In addition, despite specific binding of ipilimumab to cynomolgus monkey ovarian tissue, no gross or microscopic ovarian findings were observed in ipilimumab toxicity studies conducted in monkeys.[4,5,6,7,8,9,10] Therefore, binding of ipilimumab to connective tissue in cynomolgus monkey ovary is also not expected to have any biological or toxicological relevance, especially since similar binding was not observed with human ovaries. The lack of specific binding in the remaining human and cynomolgus monkey tissues was expected and consistent with reports that indicate that CTLA-4 is primarily transiently expressed on activated mononuclear cells.[15]

Immunotoxicity

As a selective immunomodulator, ipilimumab is expected to have effects on the immune system. The immunologic effects of ipilimumab were studied in the pivotal and exploratory repeat-dose studies in monkeys. In addition to standard immune hematologic (ie, leukocyte counts and

differentials) and clinical chemistry (ie, globulins) assessments and gross and histopathologic examinations of lymphoid tissues included in the repeat-dose studies, specialized immune parameters were incorporated into several of the studies including peripheral blood lymphocyte phenotyping (including activated T-cell and regulatory T-cell subsets),[4,5,6,7,8,9,10,11] lymphocyte phenotyping in spleen, inguinal lymph node, and colon epithelium, T cell-dependent antibody response assessments,[6,7,8,9,10,11] DTH assessments,[7,8,10] anti-nuclear antibody assessments,[6] and intracellular staining of *ex vivo* stimulated cytokine (IL-2, TNF-α and/or IFN-γ) production by monkey peripheral blood T cells.[7,8,9]

In pivotal toxicity studies of ≥ 1 month in duration at ipilimumab doses up to 10 mg/kg, there were no drug-related effects on immune clinical-pathology parameters or gross or microscopic pathology of lymphoid organs.[6,7,8,10] In the 2-week study at 30 mg/kg, minimal increases (approximate 2-fold of predose values) in white blood cell counts (primarily due to increases in lymphocyte, neutrophil, basophil, and monocyte counts), total protein (globulins, due to direct IV administration of a fully human antibody), and minimal decreases in percentages of $CD20^+$ B cells in the peripheral blood were observed.[4] These changes were consistent with the pharmacologic activity of ipilimumab.

Immunologic effects noted in all of the studies were consistent with the T-cell potentiating activity of ipilimumab, and, with the exception of 2 immune-related AEs (colitis in 1 monkey in the 3-month exploratory study and rash in 1 monkey given ipilimumab and BMS-663513 in the 4-month exploratory pharmacology study), were specific to test antigens that were coadministered. In several studies, enhancement (2- to 7-fold control across all studies) of T cell-dependent antibody responses to antigens (ie, SK-mel cells, HbsAg, KLH) administered in conjunction with ipilimumab was demonstrated.[6,7,8,9,10,11] At 1 mg/kg weekly[7,8] or 10 mg/kg monthly,[7,8,10] DTH skin reactions to SK-mel cells or HbsAg antigens were quite variable but were slightly stronger in ipilimumab-treated animals relative to vehicle-treated animals as evidenced by increased edema/induration, erythema, and reaction diameters.

In the 2-month, 79-day, and 3-month exploratory studies, antigen specific T-cell activation was examined by staining for intracellular cytokines TNF-α, IFN-γ, and/or IL-2 following overnight incubation of whole blood or cultured T cells with HbsAg antigen to which monkeys had been previously sensitized.[7,8,9] At 10 mg/kg monthly, modest increases in activated T cells expressing 1 or more of these cytokines above a baseline level (>0.2%) with a staining pattern similar to the positive control superantigen activator, Staphylococcus enterotoxin B, were seen across all groups but occurred with higher incidence in monkeys given ipilimumab compared with control monkeys. The most common cytokine expression observed among the animals was that of TNF-α production for CD8- cells, although TNF-α production from CD8+ cells and IL-2 or IFN-γ production from CD8- and/or CD8+ cells were also observed. In the 79-day study, minimal dose- or schedule-dependent increases in antigen-specific cytokine production (TNF-α or IFN-γ) by activated CD69+ T cells also occurred in individual animals at 1 mg/kg weekly or at 10 mg/kg monthly on Days 43 or 79.[7,8] No drug-related changes in antigen-specific T-cell activation were observed in a 3-month exploratory study at 10 mg/kg monthly.

Despite the drug-related antigen-specific immune effects described above, there were generally no global non-specific or multiorgan immunopotentiating or autoimmune toxicities of ipilimumab in the majority of monkeys. Peripheral-blood lymphocyte subset phenotyping analyses performed at doses up to 10 mg/kg in the pivotal 1-month, 79-day, and 6-month studies, as well as the 2-month exploratory study, demonstrated no drug-related changes or indication of a generalized T-cell activation or depletion.[6,7,8,9,10] Across all of these studies, the analyses examined 1 or more of the following lymphocyte subsets: CD2+ or $CD3^+$ (T cells), $CD20^+$ (B cells), CD3/$CD4^+$ (T-helper cells), CD3/$CD8^+$ (T-cytotoxic cells), CD3-CD16+ (natural killer [NK] cells), CD3/$CD25^+$ (activated T-cell subset), CD3/$CD29^+$ (T-cell subset), CD3/$CD69^+$ (activated T-cell subset), and CD3/HLA-DR^+ (T cells expressing MHC Class II - DR isotype) cells. In the 3-month exploratory study, an extended phenotypic analysis including B cells, T cells, monocytes, activated monocytes (CD14+CD25+), dendritic cells (CD11c+), activated T cells (CD4+CD25+, CD8+CD25+, CD3+HLA+), memory T cells (CD3+CD45RO+, CD3+CD45RA-), memory T cell subsets such as effector memory T cells (CD4+CD28-CD95+ or CD8+CD28-CD95+), central memory T cells (CD4+CD28+CD95+ or CD8+CD28+CD95+), naïve T cells (CD4+CD28+CD95- or CD8+CD28+CD95-), and Treg cells (CD4+CD25+, CD4+CD25+CTLA-4+, CD4+CD25+FoxP3+) demonstrated an increased (up to 77%, relative to controls) peripheral-blood memory T-cell population, specifically in the CD4 central memory T-cell subset (CD4+CD28+CD95+), in monkeys treated with ipilimumab. Highly variable increases in total circulating T-lymphocyte and T-helper lymphocytes were also detected in monkeys receiving ipilimumab in combination with MDX-1106 (anti-PD-1 mAb) at doses of ≥ 3 and 10 mg/kg/dose, respectively.[11] The increase in memory T cells is consistent with the pharmacology of ipilimumab and may contribute to its bioactivity (ie, enhancement of humoral and cellular immunity). No drug-related changes were noted in other peripheral-blood cell populations, including Tregs. Following a challenge dose of ipilimumab at approximately 5 months, there were also no drug-related alterations in the same immune cell subsets in blood, inguinal lymph nodes, spleen, or colon. In addition, there were no drug-related increases in anti-nuclear antibody levels in serum in the pivotal 1-month study with weekly dosing of ipilimumab alone or in combination with BMS-663513 (anti-CD137 antibody).

In 2 of over 100 monkeys dosed with ipilimumab, AEs occurred within the context of exploratory studies that are consistent with similar immune-related AEs observed in humans. These include colitis, observed in 1 monkey receiving ipilimumab at 10 mg/kg in the 3-month exploratory study, that led to euthanasia on Day 42, and a persistent dermatitis/rash in the inguinal area accompanied by peripheral lymphadenopathy on Day 113 that occurred in 1 monkey given ipilimumab at 10 mg/kg in combination with BMS-663513 in the 4-month pharmacology study. The inflammatory responses observed in these monkeys are consistent with the proposed key role of CTLA-4 in maintaining self-tolerance in the immune system and are similar in nature to the primary AEs seen with clinical ipilimumab therapy. In the clinical studies, the primary AEs were inflammatory in nature and consisted predominately of colitis and rash. Uveitis has also been observed in association with colitis, but uveitis did not occur in any monkeys dosed with ipilimumab. The binding of ipilimumab to CTLA-4 expressed on gut-

associated lymphoid tissue has been shown in human tissue binding studies, and suggests that these lymphocytes (T cells) may exist in an activated state, making them susceptible to CTLA-4 blockade by ipilimumab.

Taken together, ipilimumab increased antigen-specific humoral and cellular immune responses in monkeys, but did not cause global non-specific immunostimulatory or autoimmune toxicities in the majority of animals. In 2 monkeys given repeated doses of ipilimumab, immune-related AEs (colitis and rash) similar to those reported in clinical studies occurred and were consistent with the proposed key role of CTLA-4 in maintaining self-tolerance in the immune system.

Genotoxicity and Carcinogenicity

Since large recombinant proteins are not expected to interact directly with DNA or other chromosomal materials, genotoxicity testing was not performed and is not required per International Conference of Harmonisation (ICH) guideline S6.

The carcinogenic potential of ipilimumab has not been studied. Because of the intended patient population, carcinogenicity testing is not required according to the ICH S1A[16] and Committee for Proprietary Medicinal Products/Safety Working Party 997/96[17] guidelines and literature reports.[18]

Reproductive and Developmental Toxicity

As part of the routine histopathologic examination of organs collected in toxicity studies, the male/female reproductive organs were evaluated, including assessments of sperm and ovum morphology and maturation. There were no histopathologic changes in these organs that could be attributed to ipilimumab.

In a pre- and postnatal development study in cynomolgus monkeys, pregnant monkeys received ipilimumab every 21 days from the beginning of organogenesis in the first trimester through delivery, at dose levels either 2.6 (10 mg/kg) or 7.2 times (30 mg/kg) higher than the clinical exposure of ipilimumab at a dose of 3 mg/kg, and 0.9 or 2.1 times higher than a clinical dose of 10 mg/kg every 21 days.[18] Ipilimumab was shown to be present at very low levels in milk from adult mothers (with mean milk/serum ipilimumab concentration ratios that were 0.002 to 0.003).

There were no ipilimumab-related effects on maternal clinical observations, food consumption, body weights, clinical pathology, serum immunoglobulin (Ig) A, IgM, or anti-nuclear antibodies (ANA) levels, or lymphocyte subpopulations during gestation through 6 months postpartum. A nonadverse dose-related increase in serum IgG levels (1.2-1.4× control) occurred in adult females 72 hours after dosing on GD125-127 at both 10 and 30 mg/kg, and reversed during the dose-free postpartum period. Increases in IgG levels at 10 and 30 mg/kg are consistent with the immunostimulatory MOA of ipilimumab and its ability to promote sustained T-cell activation.

No treatment-related adverse effects on reproduction were detected during the first 2 trimesters of pregnancy. Maternal pregnancy outcomes for the first 2 trimesters were comparable in control and drug-treated groups. Beginning in the third trimester, the ipilimumab groups experienced lower maternal body weights; higher incidences of abortion, stillbirth, premature delivery (with

corresponding lower birth weight); and higher incidences of infant mortality in a dose-related manner: 21% and 30% for 10 and 30 mg/kg groups, respectively; compared to 0% in the study controls and 17.6% incidence in historical controls. Some infant mortality in ipilimumab-treated groups could be attributed to extreme prematurity; however, the group mean durations of gestation were comparable in the 3 experimental groups (160, 160, and 155 days in the control, 10, and 30 mg/kg groups, respectively).

Examination of mothers with either third trimester losses or infant losses (including pathology endpoints from the placenta, umbilical cord, of the fetus/infant itself) did not reveal a clear cause for ipilimumab-related death or pregnancy failure. Poor maternal care of the neonates and general neonatal stress as evidenced by maternal rejection were important contributory variables in the case of several infant deaths including both deceased neonatal controls, 1 of 3 deceased neonates from mothers who were dosed at 10 mg/kg and 1 of 4 deceased neonates from mothers who were dosed at 30 mg/kg. However, issues with maternal care are insufficient to explain all the observed neonatal deaths and do not explain the many observed pregnancy failures. The findings associated with the third trimester fetal losses and early infant mortality were most consistent with a nonspecific failure to thrive. Nonetheless, considering the third trimester pregnancy losses, shortened gestation length, infant prematurity, and infant loss observed in the present study combined with the MOA of ipilimumab (ie, inhibition of CTLA-4 and immunostimulation) and the localized expression of the target in the placenta, the observed developmental mortality is likely secondary to the maternal pharmacology of ipilimumab.

Urogenital malformations were observed in 2 infants of mothers treated with 30 mg/kg/dose. One female infant had unilateral renal agenesis of the left kidney and ureter. One male infant had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema. No other affected urogenital structures were noted in either animal. Infants from mothers dosed with ipilimumab at 30 mg/kg had a lower mean body weight (-15% relative to control infant values) at birth. Lower mean body weight persisted in these animals through 5 months of age but the rate of body-weight gain began to increase by 3 months of age. At 6 months of age, the group mean body weight for the 30 mg/kg infants was equivalent to that of the control infants.

Ipilimumab did not adversely affect the ability of infants to mount a T-cell dependent antibody response to Hepatitis B surface antigen at 6 and 18 weeks of age. There were no adverse effects observed in infants related to ipilimumab-exposure in utero with respect to clinical observations, morphometric measurements, organ weights, heart, histopathologic, neurobehavioral and skeletal evaluations, clinical pathology, lymphocyte phenotyping, anti-nuclear antibody formation, or serum immunoglobulin levels through 6 months of age.

Although the benefits of treatment may outweigh the risks in certain situations, the use of ipilimumab in pregnant women is generally not recommended. Women of child-bearing potential should use effective contraception during treatment with ipilimumab.

Juvenile toxicology studies were not performed with ipilimumab. Because of the lack of specific target binding of ipilimumab in rodent or rabbit tissues, evaluation of ipilimumab in standard juvenile models using these species would not be relevant.

Safety Pharmacology

As detailed in ICH guidelines S6 (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals) and S7A (Safety Pharmacology Studies for Human Pharmaceuticals), specific safety pharmacology studies are not required for biotechnology-derived products that achieve specific receptor targeting such as monoclonal antibodies. Since ipilimumab is a monoclonal antibody with a selective mechanism and does not belong to a drug or chemical class expected to cause cardiovascular effects, specific safety pharmacology studies, including cardiovascular telemetry safety pharmacology studies, were not conducted. In accordance with ICH S7, evaluations of the potential effects of IV administration of ipilimumab on the cardiovascular, central/peripheral nervous and/or respiratory systems were included as part of the pivotal GLP repeat-dose toxicity studies in monkeys (Nonclinical Pharmacology Tabulated Summary, [19] Table 2.6.3.4). No drug-related findings were observed in standard clinical evaluations of cardiovascular, respiratory and/or neurologic function (including behavior, posture, coordination, neurologic exams that included peripheral and cranial nerve evaluations, peripheral reflexes, proprioception, and/or eye movements, and in the 1-month study, electrocardiograms) conducted in monkeys as part of the pivotal repeat-dose toxicity studies for up to 6 months duration with ipilimumab.[4,5,6,7,8,10]

In the 1-month (qw x 4) intermittent-dose study of ipilimumab at 10 mg/kg alone or in combination with BMS-663513 (another immunomodulatory agent, fully human anti-CD137 antibody), detailed physical examinations were conducted prior to the first dose, at the completion of dosing on Day 22 during the time of high ipilimumab serum levels, and after an approximate 10-week dose-free observation period.[6] The physical examinations included observations of general body condition, and assessments of the respiratory, GI, integumentary, cardiovascular, lymphatic, urogenital, ophthalmologic, neurologic, and musculoskeletal systems. Body temperatures were also recorded at 1, 4, and 24 hours postdose on Day 1. Criteria for cardiovascular evaluation included heart sounds by thoracic auscultation, heart rate, and femoral pulse rate; criteria for central-nervous system evaluation included behavior, coordination/balance, movement, muscle tone, proprioception, spinal reflexes, and peripheral and cranial nerve function; and criteria for respiratory evaluation included lung sounds by thoracic auscultation, and respiratory rate. Arterial oxygen saturation was also measured using pulse oximetry by rectal probe. In addition, 10-lead electrocardiograms (ECG) were obtained from conscious monkeys using a limb-lead only configuration prior to the first dose, at the completion of dosing on Day 15 at the time of high ipilimumab serum levels, and after an approximate 10-week dose-free observation period. Quantitative ECG data collected included the following parameters: number of beats collected (number averaged), R-R interval, heart rate, P wave duration, PR interval, QRS complex duration, QT interval, corrected QT (QTcf), P wave amplitude, R wave amplitude, T wave height, T wave height negative, and ST segment elevation. Qualitative assessment of each ECG was also performed to assess for arrhythmias or other waveform abnormalities. The results of these evaluations did not demonstrate any drug-related changes in cardiovascular, neurologic, or respiratory function.

In the 6-month study in cynomolgus monkeys in which ipilimumab was administered IV (10 mg/kg, as a single agent or in conjunction with a vaccine [SK-mel cells]) on Days 0, 28, 56, 84 and 140, the mean peak concentrations of drug in plasma (measured at approximately 24 hours after the first and last doses) were 185 µg/mL and 262 µg/mL, respectively, and mean trough drug concentrations (measured on 27 and 29 days after the first and last doses) were 32 µg/mL and 54 µg/mL, respectively. These concentrations are approximately 3 times those observed in humans at a dose of 3 mg/kg every 3 weeks. Monkeys were observed twice daily (cage-side) for mortality and general condition including signs of emesis, abnormal stool, other discharges, appearance, behavior, activity, and respiration. In addition, pretest and weekly detailed physical examinations were conducted to assess general condition, eyes and respiration. No drug-related findings involving the safety pharmacology endpoints were noted.[10] Assessments of similar parameters and frequency performed in other repeat-dose studies also did not demonstrate any drug-related findings.[4,5,7,8,9]

The specificity of ipilimumab and its molecular size limit possible access to ion channels in the myocardium, and ipilimumab is not expected to affect ion currents or channel selectivity as can occur with a variety of small molecule drugs.[20] The pharmacologic target specificity and molecular size of ipilimumab also preclude its ability to directly alter intracellular protein trafficking of cardiac channel proteins, the activity of cell signaling molecules, or the expression of other proteins within the cardiovascular system. Similarly, ipilimumab is not expected to interact with cytochrome P450 isoenzymes and therefore should not be associated with drug-drug interactions (DDIs).

Immunogenicity

Ipilimumab was not appreciably immunogenic in monkeys following IV administration (positive anti-drug antibody response rate of 8% or 9 of 106 monkeys evaluated as a single agent or in combination with various antigens, DNA vaccines, or an anti-CD137 mAb, BMS-663513).[4,5,6,7,8,9,10] When administered in combination with MDX-1106 (anti-PD-1 mAb), anti-ipilimumab antibody responses were detected in 32% or 6 of 19 animals evaluated,[11] suggesting that immunostimulatory effects of MDX-1106 may have contributed to an increased humoral response to ipilimumab in monkeys. There was no evidence of a difference in immunogenicity between ipilimumab from Process A (hybridoma-derived material) or Process B (CHO cell-derived material)[7,8] or between ipilimumab from Process B and Process C (1500-L pilot scale utilizing a higher producing subclone of the Process B master cell bank and modifications to the fermentation and purification processes). The incidences of monkeys with positive ipilimumab-specific antibody responses inclusive of all processes tested were as follows: 1 of 8 (13%) evaluated in the single-dose comparability study, 2 of 12 (17%) evaluated in the 14-day studies,[4,5] 1 of 20 (5%) in the 1-month study (this animal was in a combined treatment group of 10 animals with BMS-663513),[6] 0 of 8 (0%) in the 2-month study,[9] 3 of 30 (10%) in the 79-day study,[7,8] 0 of 6 (0%) in the 3-month exploratory study, 2 of 12 (8%) in the 4-month study, 0 of 10 (0%) in the 6-month study,[10] and 6 of 19 (32%) in the 1-month combination study with MDX-1106.[11] Since ipilimumab is a human antibody and may be recognized as

foreign to monkeys, immunogenicity was not unexpected, and the presence or rate of immunogenicity in monkeys cannot be used as a predictor for immunogenicity in humans.

In the pivotal toxicity studies, the detection of ipilimumab-specific antibodies was not associated with any acute or target-organ toxicity.[4,5,6,7,8,10] However, in an exploratory pharmacology study, 1 monkey receiving ipilimumab approximately twice monthly at 10 mg/kg in combination with SIV DNA vaccines developed an infusion reaction following ipilimumab injection on Day 58. While it is possible that immunogenicity (drug-antibody immune complex formation) combined with a rapid infusion rate contributed to the infusion reaction in this monkey, other factors, including anesthesia-induced hypotension and the coadministration of vaccines may also have played a role. With the exception of 1 other monkey in this study with a weak, but positive immunogenicity response on Day 116, anti-ipilimumab antibodies were not observed in other monkeys in this study.

In summary, as expected, ipilimumab was immunogenic in a low percentage of monkeys evaluated since it is a foreign protein. However, in all studies exposure to ipilimumab was maintained during the treatment period.

Local Tolerance Studies

In the IV repeat-dose studies in monkeys with ipilimumab,[3,4,5,6,7,8,10] no substantial irritation was observed at injection sites of ipilimumab. Ipilimumab was administered from preformulated (ready-to-use) vials at the clinical concentration (generally ~5 mg/mL). However, injection rates were faster and varied from ~3 to 10 mL/min (up to 50 mg/min) in the nonclinical studies compared with 90-min clinical infusion (total dose of 210 mg for a 70 kg person, up to 2.3 mg/min); thus, providing a safety factor of approximately up to ~22-fold based on infusion rate.

APPENDIX 3: CLINICAL TRIAL EXPOSURE

13 page(s) excluding cover page

APPENDIX 3: CLINICAL TRIAL EXPOSURE

IPILIMUMAB

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

- Tables 1-2: CA184025
- Table 3: CA184029
- Table 4: CA184043
- Table 5: CA184124
- Table 6: CA184161
- Table 7: CA184202
- Table 8: CA184396
- Table 9: CA184113
- Table 10: CA184178
- Table 11: CA184169
- Table 12: CA184070

Table 1: Exposure of Ipilimumab in Patient years During Entire Study Duration - Treated Subjects (CA184025)

	PATIENT EXPOSURE YEARS			
CATEGORY	FIRST RE-INDUCTION 10 MG/KG TO 10 MG/KG N = 53	FIRST RE-INDUCTION 3.0 MG/KG TO 10 MG/KG N = 34	FIRST RE-INDUCTION 0.3 MG/KG TO 10 MG/KG N = 24	FIRST RE-INDUCTION OTHER DOSAGE TO 3.0 MG/KG OR 10 MG/KG N = 11
TOTAL PATIENT YEARS	86.533	46.374	24.123	25.484
GENDER				
MALE	48.838	36.964	21.369	23.548
FEMALE	37.695	9.410	2.754	1.936
AGE GROUP				
AGE LESS THAN 18 YEARS	0	0	0	0
AGE 18-50 YEARS	32.635	10.606	6.853	8.496
AGE 51-64 YEARS	33.355	28.159	7.206	8.370
AGE 65 YEARS AND OLDER	20.542	7.608	10.064	8.619
RACE				
WHITE	81.369	46.374	24.123	22.300
BLACK/AFRICAN AMERICAN	0.071	0	0	0
ASIAN	0	0	0	3.184
HISPANIC	0	0	0	0
OTHER	5.092	0	0	0

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Table 2: Exposure of Ipilimumab in Patient years During Entire Study Duration - Treated Subjects (CA184025)

	PATIENT EXPOSURE YEARS		
CATEGORY	EXTENDED MAINTENANCE 10 MG/KG N = 33	EXTENDED MAINTENANCE 3.0 MG/KG N = 12	EXTENDED MAINTENANCE 0.3 MG/KG N = 4
TOTAL PATIENT YEARS	98.574	34.042	8.728
GENDER			
MALE	64.137	16.490	4.764
FEMALE	34.437	17.552	3.964
AGE GROUP			
AGE LESS THAN 18 YEARS	0	0	0
AGE 18-50 YEARS	13.996	10.223	0
AGE 51-64 YEARS	36.112	0.194	3.838
AGE 65 YEARS AND OLDER	48.465	23.625	4.890
RACE			
WHITE	98.574	34.042	8.728
BLACK/AFRICAN AMERICAN	0	0	0
ASIAN	0	0	0
HISPANIC	0	0	0
OTHER	0	0	0

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Table 3: Exposure of Ipilimumab/Placebo in Patient years During Entire Study Duration - Randomized Subjects (CA184029)

	PATIENT EXPOSURE YEARS		
CATEGORY	NOT TREATED N = 6	10 MG/KG IPILIMUMAB N = 471	PLACEBO N = 474
TOTAL PATIENT YEARS	0	440.531	728.082
GENDER			
MALE	0	280.397	443.305
FEMALE	0	160.134	284.778
AGE GROUP			
AGE LESS THAN 18 YEARS	0	0	0
AGE 18-50 YEARS	0	235.677	339.480
AGE 51-64 YEARS	0	148.465	260.695
AGE 65 YEARS AND OLDER	0	56.389	127.907
RACE			
WHITE	0	438.628	728.082
BLACK/AFRICAN AMERICAN	0	0	0
ASIAN	0	0.367	0
HISPANIC	0	0	0
OTHER	0	1.536	0

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Table 4: Exposure of Ipilimumab/Placebo in Patient years During Entire Study Duration - Randomized Subjects (CA184043)

	PATIENT EXPOSURE YEARS		
CATEGORY	10 MG/KG IPILIMUMAB + RADIOTHERAPY N = 393	NOT TREATED N = 10	PLACEBO + RADIOTHERAPY N = 396
TOTAL PATIENT YEARS	172.882	0	156.739
GENDER			
MALE	172.882	0	156.739
FEMALE	0	0	0
AGE GROUP			
AGE LESS THAN 18 YEARS	0	0	0
AGE 18-50 YEARS	1.363	0	2.574
AGE 51-64 YEARS	55.428	0	54.798
AGE 65 YEARS AND OLDER	116.090	0	99.368
RACE			
WHITE	163.058	0	145.604
BLACK/AFRICAN AMERICAN	4.200	0	4.260
ASIAN	1.328	0	0.873
HISPANIC	0	0	0
OTHER	4.296	0	6.001

LIBRARY: /wwbdm/data/ca/184/043/fa01a/blinded/analysis EXTRACT DATE: 05-FEB-2013
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/iss01/val/cpp/programs/rt-ex-rmpptyrs-v01.sas RUN DATE: 10-APR-2015 10:16

Table 5: Exposure of Ipilimumab/Pemetrexed in Patient years During Entire Study Duration - Treated Subjects (CA184124)

	PATIENT EXPOSURE YEARS	
CATEGORY	10 MG/KG IPILIMUMAB N = 6	500 MG/M2 PEMETREXED N = 2
TOTAL PATIENT YEARS	0.301	0.123
GENDER		
MALE	0.241	0.063
FEMALE	0.060	0.060
AGE GROUP		
AGE LESS THAN 18 YEARS	0	0
AGE 18-50 YEARS	0.003	0
AGE 51-64 YEARS	0.181	0.123
AGE 65 YEARS AND OLDER	0.118	0
RACE		
WHITE	0.301	0.123
BLACK/AFRICAN AMERICAN	0	0
ASIAN	0	0
HISPANIC	0	0
OTHER	0	0

LIBRARY:
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/iss01/val/cpp/programs/rt-ex-rmpptyrs-v01.sas

EXTRACT DATE:
RUN DATE: 10-APR-2015 10:16

Table 6: Exposure of Ipilimumab/Vemurafenib in Patient years During Entire Study Duration - Treated Subjects (CA184161)

	PATIENT EXPOSURE YEARS		
CATEGORY	3 MG/KG IPILIMUMAB + 960 MG VEMURAFENIB N = 6	3 MG/KG IPILIMUMAB + 720 MG VEMURAFENIB N = 4	720 MG VEMURAFENIB N = 2
TOTAL PATIENT YEARS	2.943	1.949	0.602
GENDER			
MALE	1.320	1.114	0.468
FEMALE	1.624	0.835	0.134
AGE GROUP			
AGE LESS THAN 18 YEARS	0	0	0
AGE 18-50 YEARS	0.397	0.334	0
AGE 51-64 YEARS	1.188	1.615	0.134
AGE 65 YEARS AND OLDER	1.358	0	0.468
RACE			
WHITE	2.193	1.949	0.602
BLACK/AFRICAN AMERICAN	0.750	0	0
ASIAN	0	0	0
HISPANIC	0	0	0
OTHER	0	0	0

LIBRARY: /wwbdm/data/ca/184/161/fa01/blinded/analysis EXTRACT DATE: 06-JUN-2013
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/iss01/val/cpp/programs/rt-ex-rmpptyrs-v01.sas RUN DATE: 10-APR-2015 10:23

Table 7: Exposure of Ipilimumab/Dacarbazine in Patient years During Entire Study Duration - Treated Subjects (CA184202)

	PATIENT EXPOSURE YEARS
CATEGORY	10 MG/KG IPILIMUMAB + DACARBAZINE N = 15
TOTAL PATIENT YEARS	5.971
GENDER	
MALE	4.326
FEMALE	1.645
AGE GROUP	
AGE LESS THAN 18 YEARS	0
AGE 18-50 YEARS	2.278
AGE 51-64 YEARS	1.402
AGE 65 YEARS AND OLDER	2.292
RACE	
WHITE	0
BLACK/AFRICAN AMERICAN	0
ASIAN	5.971
HISPANIC	0
OTHER	0

LIBRARY: /wwbdm/data/ca/184/202/fa01/blinded/analysis EXTRACT DATE: 01-AUG-2014
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/iss01/val/cpp/programs/rt-ex-rmpptyrs-v01.sas RUN DATE: 10-APR-2015 10:35

Table 8: Exposure of Ipilimumab in Patient years During Entire Study Duration - Treated Subjects (CA184396)

	PATIENT EXPOSURE YEARS
CATEGORY	3 MG/KG IPILIMUMAB N = 20
TOTAL PATIENT YEARS	6.253
GENDER	
MALE	2.825
FEMALE	3.428
AGE GROUP	
AGE LESS THAN 18 YEARS	0
AGE 18-50 YEARS	2.459
AGE 51-64 YEARS	1.336
AGE 65 YEARS AND OLDER	2.459
RACE	
WHITE	0
BLACK/AFRICAN AMERICAN	0
ASIAN	6.253
HISPANIC	0
OTHER	0

LIBRARY: /wwbdm/data/ca/184/396/fa02a/blinded/analysis EXTRACT DATE: 21-AUG-2014
PROGRAM SOURCE: /wwbdm/clin/proj/ca/184/iss01/val/cpp/programs/rt-ex-rmpptyrs-v01.sas RUN DATE: 10-APR-2015 10:37

Table 9: Exposure of Ipilimumab in Patient years During Entire Study Duration - Treated Subjects All Treated Subjects (CA184113)

CATEGORY	PATIENT EXPOSURE YEARS IPILIMUMAB 3 MG/KG + PACLITAXEL + CARBOPLATIN N=8	 IPILIMUMAB 10 MG/KG + PACLITAXEL + CARBOPLATIN N=7
TOTAL PATIENT YEARS	1.596	2.147
GENDER		
FEMALE	0.249	0.063
MALE	1.347	2.084
AGE GROUP		
AGE 18-50 YEARS	0.003	0.222
AGE 51-64 YEARS	1.418	1.092
AGE 65 YEARS AND OLDER	0.175	0.833
RACE		
JAPANESE	1.596	2.147

Program Source: /gbs/prod/clin/programs/ca/184/113/jnda201504/rpt/rt-table-s-8-113-v01.sas 08APR2015:13:13

Table 10: Exposure of Ipilimumab in Patient Years During Entire Study Duration All Treated Subjects (CA184178)

CATEGORY	PATIENT EXPOSURE YEARS 3 MG/KG IPILIMUMAB N = 4	 10 MG/KG IPILIMUMAB N = 8
TOTAL PATIENT YEARS	1.5	2.8
GENDER		
MALE	0.7	1.7
FEMALE	0.8	1.1
AGE GROUP		
AGE LESS THAN 18 YEARS	1.5	2.8
AGE 18-50 YEARS	0.0	0.0
AGE 51-64 YEARS	0.0	0.0
AGE 65 YEARS AND OLDER	0.0	0.0
RACE		
WHITE	1.1	2.8
BLACK/AFRICAN AMERICAN	0.4	0.0
ASIAN	0.0	0.0
OTHER	0.0	0.0

Program Source: /wwbdm/clin/proj/ca/184/178/val/cpp/programs/rmpreq/rt-ex-rmpptyrs178-v01.sas 07-FEB-2017 13:59

Table 11: Exposure of Ipilimumab in Patient Years During Entire Study Duration All Treated Subjects (CA184169)

CATEGORY	PATIENT EXPOSURE YEARS 10 mg/kg Ipilimumab (N=364)	3 mg/kg Ipilimumab (N=362)
TOTAL PATIENT YEARS	158.100	169.120
GENDER		
MALE	92.854	105.240
FEMALE	65.246	63.880
AGE GROUP		
AGE LESS THAN 18 YEARS	0.000	0.000
AGE 18-50 YEARS	42.313	39.970
AGE 51-64 YEARS	53.183	48.627
AGE 65 YEARS AND OLDER	62.604	80.523
RACE		
WHITE	156.695	168.038
BLACK/AFRICAN AMERICAN	0.219	0.290
ASIAN	0.857	0.372
OTHER	0.329	0.419

PROGRAM SOURCE: S:\RHO\BMS\Ipilimumab\Studies\CA184-169\Tables\rt-ex-rmpptyrs169-v01.SAS 23DEC2016:09:12:38

Table 12: Exposure of Ipilimumab in Patient Years During Entire Study Duration All Treated Subjects (CA184070)

CATEGORY	PATIENT EXPOSURE YEARS			
	1 MG/KG IPILIMUMAB N = 3	3 MG/KG IPILIMUMAB N = 3	5 MG/KG IPILIMUMAB N = 14	10 MG/KG IPILIMUMAB N = 13
TOTAL PATIENT YEARS	0.370	0.485	3.671	2.478
GENDER				
MALE	0.142	0.342	0.068	2.042
FEMALE	0.227	0.142	3.603	0.435
AGE GROUP				
AGE LESS THAN 18 YEARS	0.085	0.227	3.261	2.119
AGE 18-50 YEARS	0.285	0.257	0.411	0.359
AGE 51-64 YEARS	0.000	0.000	0.000	0.000
AGE 65 YEARS AND OLDER	0.000	0.000	0.000	0.000
RACE				
WHITE	0.370	0.400	1.355	1.749
BLACK/AFRICAN AMERICAN	0.000	0.000	0.000	0.170
ASIAN	0.000	0.000	0.285	0.559
AMERICAN INDIAN/ALASKA NATIVE	0.000	0.085	1.911	0.000
UNKNOWN	0.000	0.000	0.120	0.000

Program Source: /wwbdm/clin/proj/ca/184/070/val/cpp/programs/rmpreq/rt-ex-rmpptyrs070-v01.sas 07-FEB-2017 14:04

APPENDIX 4: NIVOLUMAB IN COMBINATION WITH IPILIMUMAB - EXPOSURE AND SAFETY SUMMARY

61 page(s) excluding cover page

APPENDIX 4: NIVOLUMAB IN COMBINATION WITH IPILIMUMAB - EXPOSURE AND SAFETY SUMMARY

1 EXPOSURE

Table 1-1: Overview of Nivolumab in Combination with Ipilimumab Development

Study Number (Indication)	Study Title	Number Treated Subjects
Nivolumab (1 mg/kg) Combined with Ipilimumab (3 mg/kg)		
CA209004[1]	Phase 1b dose-escalation, open-label, multi-center, multi-dose study of nivolumab in combination with ipilimumab in subjects with advanced (unresectable or metastatic) melanoma. Subjects in the expansion Cohort 8 of CA209004 were treated with the same dosing schedule as CA209069 (nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses; then nivolumab 3 mg/kg Q2W).	Nivolumab + IPI: 41 in Cohort 8
CA209067[2]	Randomized (1:1:1), double-blind, Phase 3 study of nivolumab monotherapy or nivolumab in combination with ipilimumab versus ipilimumab monotherapy in previously untreated subjects with advanced (unresectable or metastatic) melanoma.	Nivolumab+IPI: 313
CA209069[3]	Randomized (2:1), double-blind, Phase 2 study of nivolumab+ipilimumab vs ipilimumab in previously untreated subjects with advanced (unresectable or metastatic) melanoma.	Nivolumab+IPI: 94
CA2099DW[4]	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) Combined with Ipilimumab (1 mg/kg)		
CA209214[5,6] (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[7] (RCC)	Phase 1, study of nivolumab plus sunitinib, pazopanib, or ipilimumab in subjects with mRCC	Nivolumab+IPI: 47 (Arm I-1)
CA209142[8] (CRC)	Ad-hoc safety report, of nivolumab in combination with ipilimumab for microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC)	Nivolumab + IPI: 119
CA209743[9] (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

Table 1-1: Overview of Nivolumab in Combination with Ipilimumab Development

Study Number (Indication)	Study Title	Number Treated Subjects
CA209648[10] (OSCC)	Phase 3, randomized study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluoorouacil plus cisplatin in subjects with unrescectable advanced, recurrent or metastatic previously untreated OSCC	Nivolumab+IPI: 322 Nivolumab+Chemotherapy: 310 Chemotherapy: 304
CA209070/ ADVL1412[11] (ST/Haematologic Tumors)	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+IPI: 46
CA2098HW[12] (mCRC)	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
Nivolumab (360 mg) Combined with Ipilimumab (1 mg/kg) combined with Platinum-doublet chemotherapy		
CA209568 Part 2[13] (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 IV non-small cell lung cancer (NSCLC)	Nivolumab+IPI+Chemotherapy: 36
CA2099LA[14] (NSCLC)	Phase 3, randomized 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

[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.

1.1 Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg

1.1.1 CA2099DW

Table 1.1.1-1: 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 1.1.1-2: 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 1.1.1-3: Clinical Exposure in Person Time by Age Group and Sex; All Nivolumab and Ipilimumab Treated Subjects in CA2099DW

Treatment Group: Nivo + Ipi

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	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 1.1.1-4: 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

1.1.2 Studies CA209004, CA209067 and CA209069 (Advanced Melanoma)

Pooled exposure analyses for nivolumab (1 mg/kg) in combination with ipilimumab (3 mg/kg) are presented in Table 1.1.2-1 through Table 1.1.2-4.

Table 1.1.2-1: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (1 mg/kg) in Combination Therapy with Ipilimumab (3 mg/kg): (Pooled)

	Nivolumab + Ipilimumab N = 448	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	13 (2.9)	
0 - < 2 MONTHS	107 (23.9)	
0 - < 3 MONTHS	160 (35.7)	
0 - < 4 MONTHS	228 (50.9)	
0 - < 5 MONTHS	253 (56.5)	
0 - < 6 MONTHS	267 (59.6)	
0 - <= 41.7 MONTHS (A)	448 (100.0)	4012.25

(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 CA209067, CA209004, and CA209069 studies.
Program Source: /projects/bms217252/stats/067_EU_RMP/prog/tables/rt-ex-ptdurtrt.sas, 22DEC2016:04:22:39

Table 1.1.2-2: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects with Nivolumab (1 mg/kg) in Combination Therapy with Ipilimumab (3 mg/kg): (Pooled)

	Nivolumab + Ipilimumab N = 448	
	Nivolumab	Ipilimumab
NUMBER OF DOSES RECEIVED / SUBJECT		
MEAN (SD)	15.5 (20.74)	3.2 (1.06)
MEDIAN	4.0	4.0
MIN - MAX	1 - 76	1 - 4
CUMULATIVE DOSE (MG) / SUBJECT		
MEAN (SD)	3344.2 (5329.77)	784.8 (309.98)
MEDIAN	400.0	796.4
MIN - MAX	59 - 23985	177 - 1928
CUMULATIVE DOSE (MG/KG) / SUBJECT		
MEAN (SD)	39.99 (61.254)	9.53 (3.184)
MEDIAN	4.00	12.00
MIN - MAX	1.0 - 220.0	2.9 - 15.7

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
Includes data from CA209067, CA209004, and CA209069 studies.
Program Source: /projects/bms217252/stats/067_EU_RMP/prog/tables/rt-ex-cumdos.sas 22DEC2016:04:16:44

Table 1.1.2-3: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (1 mg/kg) in Combination Therapy with Ipilimumab (3 mg/kg): (Pooled)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 286	Female N = 162	Total N = 448	Male N = 286	Female N = 162	Total N = 448
>= 18 AND < 65	159 (55.6)	106 (65.4)	265 (59.2)	1654.51	851.45	2505.95
>= 65 AND < 75	94 (32.9)	41 (25.3)	135 (30.1)	851.25	285.93	1137.18
>= 75 AND < 85	31 (10.8)	11 (6.8)	42 (9.4)	305.91	41.76	347.66
>= 85	2 (0.7)	4 (2.5)	6 (1.3)	5.42	16.03	21.45
TOTAL	286 (100.0)	162 (100.0)	448 (100.0)	2817.08	1195.17	4012.25

(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 CA209067, CA209004, and CA209069 studies.
Program Source: /projects/bms217252/stats/067_EU_RMP/prog/tables/rt-ex-ptage.sas 03JAN2017:05:35:04

Table 1.1.2-4: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (1 mg/kg) in Combination Therapy with Ipilimumab (3 mg/kg): (Pooled)

Treatment group: NIVOLUMAB+IPILIMUMAB

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	Male N = 286	Female N = 162	Total N = 448	Male N = 286	Female N = 162	Total N = 448
WHITE	283 (99.0)	154 (95.1)	437 (97.5)	2781.67	1137.58	3919.24
BLACK OR AFRICAN AMERICAN	0	0	0	0	0	0
ASIAN	0	4 (2.5)	4 (0.9)	0	21.13	21.13
OTHER	3 (1.0)	4 (2.5)	7 (1.6)	35.42	36.47	71.89
TOTAL	286 (100.0)	162 (100.0)	448 (100.0)	2817.08	1195.17	4012.25

(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 CA209067, CA209004, and CA209069 studies.
Program Source: /projects/bms217252/stats/067_EU_RMP/prog/tables/rt-ex-ptage.sas 03JAN2017:05:35:55

1.2 Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg

1.2.1 Studies CA209214 and CA209016 (Renal Cell Carcinoma)

Exposure analyses for nivolumab (3 mg/kg) in combination with ipilimumab (1 mg/kg) are presented in Table 1.2.1-1 through Table 1.2.1-4 for CA209214 and Table 1.2.1-5 through Table 1.2.1-8 for CA209016.

Table 1.2.1-1: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg): CA209214

	Nivolumab 3 + Ipilimumab 1 N = 547	
Duration of Exposure	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 1.2.1-2: 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 1.2.1-3: 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 1.2.1-4: 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

Table 1.2.1-5: 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

	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 1.2.1-6: 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 1.2.1-7: 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 1.2.1-8: 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

1.2.2 Study CA209142 (Colorectal Cancer)

Exposure analyses for nivolumab (3 mg/kg) in combination with ipilimumab (1 mg/kg) are presented in Table 1.2.2-1 through Table 1.2.2-4 for CA209142.

Table 1.2.2-1: 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 1.2.2-2: 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 1.2.2-3: 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 1.2.2-4: 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)

	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

1.2.3 Study CA2098HW (Colorectal Cancer)

Exposure analyses of subjects who had received nivolumab (240 mg Q3W then 480mg Q4W) in combination with ipilimumab (1 mg/kg) as first-line treatment in Study CA2098HW are presented in Table 1.2.3-1 through Table 1.2.3-4.

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

Table 1.2.3-1: Clinical Exposure in Person Time; All First Line Nivolumab and Ipilimumab Treated Subjects in CA2098HW

Duration of Exposure	Nivo + Ipi: 1L N = 200 Persons (%)	Person Time of Exposure (1) (Months)
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 1.2.3-2: 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 1.2.3-3: 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 1.2.3-4: 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

	Persons (%)			Person Time of Exposure (Months) (1)		
Race	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

1.2.4 Studies CA209142, CA209214, CA209016, and CA2098HW (Pooled Studies)

Pooled exposure analyses for nivolumab (3 mg/kg dose regimen for CA209214, CA209142, and CA209016 studies, and 240 mg dose regimen for CA2098HW study) in combination with ipilimumab (1 mg/kg) are presented in Table 1.2.4-1 through Table 1.2.4-5.

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

Table 1.2.4-1: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (3 mg/kg or 240 mg) 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 1.2.4-2: Clinical Exposure in Person Time by Dose Level; All Treated Subjects with Nivolumab (3 mg/kg or 240 mg) 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 1.2.4-3: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects with Nivolumab (3 mg/kg or 240 mg) 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 1.2.4-4: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects with Nivolumab (3 mg/kg or 240 mg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

	Persons (%)			Person Time of Exposure (Months) (1)		
Age Category	Male N = 608	Female N = 305	Total N = 913	Male N = 608	Female N = 305	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 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 1.2.4-5: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects with Nivolumab (3 mg/kg or 240 mg) in Combination Therapy with Ipilimumab (1 mg/kg) (Pooled)

	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 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

1.2.5 Studies CA209743 and CA209648 (Pooled Studies)

Exposure analyses for nivolumab (3 mg/kg) in combination with ipilimumab (1 mg/kg) are presented in Table 1.2.5-1 through Table 1.2.5-4 for CA209743 and CA209648 (pooled studies).

Table 1.2.5-1: Clinical Exposure in Person Time; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) CA209743 and CA209648 (Pooled)

	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	
Duration of Exposure	Persons (%)	Person Time of Exposure (1) (Months)	Persons (%)	Person Time of Exposure (1) (Months)
0 - < 1 MONTH	14 (4.3)		21 (3.4)	
0 - < 2 MONTHS	88 (27.3)		143 (23.0)	
0 - < 3 MONTHS	126 (39.1)		201 (32.3)	
0 - < 4 MONTHS	169 (52.5)		269 (43.2)	
0 - < 5 MONTHS	195 (60.6)		321 (51.6)	
0 - < 6 MONTHS	210 (65.2)		343 (55.1)	
0 - <= 27.2 MONTHS (A)	322 (100.0)	2040.57	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 1.2.5-2: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects with Nivolumab (3 mg/kg) in Combination Therapy with Ipilimumab (1 mg/kg) CA209743 and CA209648 (Pooled)

	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 30APR2021:08:59:04

Table 1.2.5-3: 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 and CA209648 (Pooled)

	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 1.2.5-4: 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 and CA209648 (Pooled)

	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 25MAY2021:08:11:02

1.2.6 Study CA209070 (Solid Tumors/Haematologic Tumors)

Exposure analyses for nivolumab (1 mg/kg or 3mg/kg) in combination with ipilimumab (1 mg/kg) are presented in Table 1.2.6-1 through Table 1.2.6-4.

Table 1.2.6-1: Clinical Exposure in Person Time; All Treated Subjects in CA209070 Study

	Nivolumab + Ipilimumab N = 46	
Duration of Exposure	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 1.2.6-2: Cumulative Dose of Nivolumab and Ipilimumab; All Treated Subjects in CA209070 Study

	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 1.2.6-3: Clinical Exposure in Person Time by Age Group and Gender; All Treated Subjects in CA209070 Study

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 1.2.6-4: Clinical Exposure in Person Time by Racial Origin and Gender; All Treated Subjects in CA209070 Study

Treatment Group: Nivolumab + Ipilimumab

Race Category	Persons (%) Male N = 30	Persons (%) Female N = 16	Persons (%) Total N = 46	Person Time of Exposure (Months) (1) Male N = 30	Person Time of Exposure (Months) (1) Female N = 16	Person Time of Exposure (Months) (1) 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

1.3 Nivolumab 360 mg + Ipilimumab 1 mg/kg + Platinum-doublet Chemotherapy

1.3.1 Studies CA2099LA and CA209568 Part 2

Pooled analyses for nivolumab (360 mg Q3W) + ipilimumab (1 mg/kg Q6W) + 2 cycles of platinum doublet chemotherapy are in Table 1.3.1-1 through Table 1.3.1-4.

Table 1.3.1-1: 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 1.3.1-2: 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 1.3.1-3: 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 1.3.1-4: 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 DETAILS OF IMPORTANT IDENTIFIED AND POTENTIAL RISKS FROM CLINICAL DEVELOPMENT

ARs have been identified based on findings observed in the nivolumab non-clinical and clinical programs, safety-related concerns reported for nivolumab and other PD-1 inhibitors, or theoretical considerations related to the mechanism of action of PD-1 inhibitors. The important identified and potential risks for nivolumab in combination with ipilimumab are presented below in Sections 2.1 and 2.2.

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

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

Important identified and potential risks are summarized for nivolumab in combination therapy with ipilimumab in Sections 2.1 and 2.2.

2.1 Important Identified Risks

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

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Important Identified Risk: 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

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

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.[15]

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, 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,

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

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 immune-related ARs, 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 immune-related ARs 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.

Characterization of risk *(Percent; All Treated)*

Pneumonitis

I. 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			

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

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)

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)

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

Colitis

I. 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

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			
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)

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%

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

- 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

Hepatitis

I. 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)
Grade 3-4	16.9	4.9	11.9 (7.3, 16.7)

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

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

Nephritis and renal dysfunction

I. 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

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)

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

Endocrinopathies

I. 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%;			

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	33.5 (26.0, 40.3)
(thyroid disorder 24.0%, adrenal disorder 10.5%, pituitary disorder 5.0% and diabetes 1.0%)			
Grade 3-4	5.5	0	5.5 (0.7, 9.6)
(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)
(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%)			

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%

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

- *(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)
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%, and 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

Skin ARs

I. Nivolumab Combined with Ipilimumab (+/-Chemo)

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

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

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			
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)

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]			

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

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

Other irARs

I. 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		
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

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

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
Grade 3-4		
myasthenic syndrome	0.7	0
pancreatitis	0.3	0
uveitis	0.3	0

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

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, rhabdomyolysis, 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		

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
myocarditis	0.9	0
demyelination	0.3	0
myasthenic syndrome	0.3	0
Grade 3-4		
pancreatitis	1.2	0.6

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)		
myositis/rhabdomyolysis	0.9	0.3
myocarditis	0.6	0
myasthenic syndrome	0.3	0
demyelination	0	0
Grade 5	0	0

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]		

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

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

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

Risk factors and risk groups	**Pneumonitis** ILD can develop or exacerbate as a consequence of radiotherapy, chemotherapy, or pulmonary resection.[16] Other risk factors for ILD include older age, reduced normal lung on computed tomography scan, smoking history, and concomitant or previous lung infection.[17,18] **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 management guidelines may prevent serious complications. Monitor patients for signs and symptoms of immune-related adverse reactions. Refer to the nivolumab EU RMP for additional risk minimization measures.
Impact on the risk-benefit	Nivolumab can increase the risk of immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin

Table 2.1.1-1: Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Important Identified Risk: Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	
balance of the product	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	See Table 2.1.3-1

2.1.2 Important Identified Risk - Severe Infusion Reactions

Table 2.1.2-1: Important Identified Risk: Severe Infusion Reactions; Nivolumab+Ipilimumab

Important Identified Risk: 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)*	**I. <u>Nivolumab Combined with Ipilimumab (+/-Chemo)</u>**

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			

Table 2.1.2-1: Important Identified Risk: Severe Infusion Reactions; Nivolumab+Ipilimumab

Important Identified Risk: Severe Infusion Reactions

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

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)

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)

OSCC	Nivolumab	Comparator	DIFF (95% CI)
CA209648			
Any Grade	2.8	0.3	2.5 (0.5, 4.9)
Grade 3-4	0	0	0

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			
Any Grade	2.4	0	2.4 (0.7, 4.7)
Grade 3-4	0.3	0	0.3 (-0.9, 1.7)

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)

Table 2.1.2-1: Important Identified Risk: Severe Infusion Reactions; Nivolumab+Ipilimumab

Important Identified Risk: Severe Infusion Reactions				
	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			
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.			
Public health impact	No impact as infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon.			
MedDRA terms	See Table 2.1.3-1			

2.1.3 MedDRA Terms

Table 2.1.3-1: Summary MedDRA Terms for Safety Concerns

Safety Concern	**MedDRA Terms**
Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	
Immune-related Pneumonitis	Acute respiratory distress syndrome, acute respiratory failure, autoimmune lung disease, hypersensitivity pneumonitis, idiopathic interstitial pneumonia, immune-mediated lung disease, interstitial lung disease, lung infiltration, pneumonitis
Immune-related Colitis	Autoimmune colitis, autoimmune enteropathy, colitis, colitis ulcerative, diarrhoea, duodenal perforation, enteritis, enterocolitis, enterocolitis haemorrhagic, frequent bowel movements, GI perforation, immune-mediated enterocolitis, immune-mediated gastritis, lower GI perforation, ulcerative duodenitis, upper GI perforation
Immune-related Hepatitis	Acute hepatic failure, acute on chronic liver failure, alanine aminotransferase increased, aspartame aminotransferase increased, autoimmune cholangitis, autoimmune hepatitis, biliary cirrhosis, bilirubin conjugated decreased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, cholangitis, drug-induced liver injury, gamma-glutamyl transferase increased, hepatic cytolysis, hepatic enzyme increased, hepatic failure, hepatitis, hepatitis acute, hepatotoxicity, hyperbilirubinaemia, immune-mediated cholangitis, immune-mediated cholestasis, immune-mediated hepatic disorder, immune-mediated hepatitis, liver disorder, liver function test abnormal, liver function test increased, liver injury, transaminases increased
Immune-related Nephritis and renal dysfunction	Acute kidney injury, autoimmune nephritis, blood creatinine increased, blood urea increased, creatinine renal clearance decreased, end stage renal disease, glomerulonephritis rapidly progressive, hypercreatininaemia, immune-mediated

Table 2.1.3-1: Summary MedDRA Terms for Safety Concerns

Safety Concern	MedDRA Terms
	nephritis, immune-mediated renal disorder, nephritis, nephritis allergic, paraneoplastic glomerulonephritis, renal failure, renal tubular necrosis, subacute kidney injury, tubulointerstitial nephritis, urine output decreased
Immune-related Endocrinopathies	Atrophic thyroiditis, autoimmune hypothyroidism, autoimmune thyroid disorder, autoimmune thyroiditis, adrenal insufficiency, adrenal suppression, adrenocortical insufficiency acute, basedow's disease, blood corticotrophin increased, blood corticotrophin decreased, blood thyroid stimulating hormone increased, blood thyroid stimulating hormone decreased, diabetes mellitus, diabetic ketoacidosis, diabetic ketosis, fulminant type 1 diabetes mellitus, hyperthyroidism, hypogonadism, hypoparathyroidism, hypophysitis, hypopituitarism, hypothalamic pituitary adrenal axis suppression, hypothyroidism, immune-mediated adrenal insuficiency, immune-mediated hyperthyroidism, immune-mediated hypophysitis, immune-mediated hypothyroidism, immune-mediated thyroiditis, latent autoimmune diabetes in adults, lymphocytic hypophysitis, primary adrenal insufficiency, primary hyperthyroidism, primary hypothyroidism, secondary adrenal insufficiency, thyroid function test abnormal, thyroid hormone decreased, thyroid hormone increased, thyroiditis, thyroiditis acute, thyroxine decreased, thyroxine free increased, thyroxine free decreased, thyroxine increased, tri-iodothyronine uptake increased, type 1 diabetes mellitus
Immune-related Skin ARs	Anal eczema, anal rash, autoimmune blistering disease, autoimmune dermatitis, blister, bullous haemorrhagic dermatosis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis exfoliative, drug eruption, eczema, enanthema, erythema, erythema multiforme, erythrodermic atopic dermatitis, exfoliative rash, fixed eruption, generalised bullous fixed drug eruption, guttate psoriasus, immune-mediated dermatitis, mucocutaneous disorder, mocosa vesicle, nodular rash, palmar-plantar erythrodysaesthesia syndrome, paradoxical psoriasis, pemphigoid, pemphigus, photosensitivity reaction, pruritus, pruritus allergic, psoriasis, pustular psoriasis, psoriasis, rash, rash erythematous, rash macular, rash macular-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash vesicula, SJS-TEN overlap, scrotal dermatitis, skin exfoliation, skin hypopigmentation, skin irritation, stevens-johnson syndrome, toxic epidermal necrolysis, toxic skin eruption, urticaria, urticarial dermatitis, vitiligo, vulval eczema
Immune-related Other irARs	Anti-myelin-associated glycoprotein associated polyneuropathy, demyelinating polyneuropathy, demyelination, acute disseminated encephalomyelitis, acute encephalitis with refractory, repetitive partial seizures, autoimmune encephalopathy, bickerstaff's encephalitis, encephalitis, encephalitis allergic, encephalitis autoimmune, encephalitis brain stem, encephalitis haemorrhagic, encephalitis lethargica, encephalitis toxic, immune effector cell-associated neurotoxicity syndrome, immune-mediated encephalitis, immune-mediated encephalopathy, limbic encephalitis, lupus encephalitis, noninfective encephalitis, panencephalitis, rasmussen encephalitis, subacute sclerosing panencephalitis, Guillain-Barre syndrome, Miller Fisher syndrome, myasthenia gravis, myasthenia gravis crisis, myasthenic syndrome, ocular myasthenia, autoimmune myocarditis, eosinophilic myocarditis, giant cell myocarditis, hypersensitivity myocarditis, immune-mediated myocarditis, autoimmune myositis, dermatomyositis, immune-mediated myositis, inclusion body myositis, myositis, necrotising myositis, paraneoplastic dermatomyositis, polymyositis, rhabdomyolysis, autoimmune pancreatitis, haemorrhagic necrotic pancreatitis, immune-mediated pancreatitis, pancreatitis, pancreatitis acute, pancreatitis necrotising, subacute pancreatitis, autoimmune uveitis, chorioretinitis, cyclitis, immune recovery uveitis, immune-mediated uveitis, iridocyclitis, iritis, keratouveitis, uveitis, Vogt-Koyanagi-Harada syndrome

Table 2.1.3-1: Summary MedDRA Terms for Safety Concerns

Safety Concern	MedDRA Terms
Severe Infusion Reactions	Infusion-related reaction, infusion related hypersensitivity reaction, hypersensitivity, bronchospasm, anaphylactic reaction, anaphylactic shock

2.2 Important Potential Risks

2.2.1 Important Potential Risk - Embryofetal Toxicity

Table 2.2.1-1: 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

2.2.2 Important Potential Risk - Immunogenicity

Table 2.2.2-1: 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 of 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 (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],

Table 2.2.2-1: Important Potential Risk: Immunogenicity

Immunogenicity	
	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.[19] In an updated analysis in CA209067,[20] 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 (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. 1/33 (3.0%) subject was tested positive for ipilimumab ADA at baseline, and no subjects were tested positive post baseline. 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

Table 2.2.2-1: Important Potential Risk: Immunogenicity

Immunogenicity	
	period. The presence of nivo or ipi ADA did not appear to have an effect on the efficacy or safety of nivo+ipi regimen. Nivolumab (3 mg/kg) 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.

Table 2.2.2-1: Important Potential Risk: Immunogenicity

Immunogenicity	
	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 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. In 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. <u>Nivolumab in Combination with Ipilimumab and Chemotherapy:</u> 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.[14] 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.[14] The presence of nivolumab or ipilimumab ADA did not appear to be associated with the occurrence of hypersensitivity/infusion reaction AEs.

Table 2.2.2-1: Important Potential Risk: Immunogenicity

Immunogenicity	
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

APPENDIX 5: SINGLE STUDY SAFETY TABLES

7 page(s) excluding cover page

APPENDIX 5: SINGLE STUDY SAFETY TABLES

Single study safety analysis (by dose) for the important identified risk of immune-related ARs (including including GI, hepatic, skin, neurologic, endocrine and other irARs) are presented in Tables 4-1 through 4-6.

Table 4-1: GI irARs (eg, diarrhoea, colitis, GI perforation)

GI irARs (eg, diarrhoea, colitis, GI perforation)	
Characterization of risk	**3 mg/kg ipilimumab** Ipilimumab monotherapy (MDX010-20) Any GI IrAR, any grade: 28.2% gp100: 14.5%. Difference between monotherapy and gp100: 13.9% (95% CI: 4.0%-23.7%) Grade 3: 7.6% gp100: 0.8%. Difference between monotherapy and gp100: 6.9% (95% CI: 2.4%-13.1%) • Diarrhoea, any grade: 26.7%; Grade 3: 4.6% • Colitis, any grade: 7.6%; Grade 3: 5.3% • GI perforation: One instance (0.8%) of fatal GI perforation more than 70 days after last dose Ipilimumab+gp 100 (MDX010-20) Any GI IrARs, any grade: 31.1%; Grade 3-4: 5.3% • Diarrhoea, any grade: 29.2% (ipilimumab+gp100) • Colitis, any grade: 5.0% (ipilimumab+gp100) • GI perforation: 1.3% (ipilimumab+gp100 with an outcome of death in 3 cases) **10 mg/kg ipilimumab** Ipilimumab + DTIC (Phase 3 CA184024) Any GI irAR, any grade: 35.6%; DTIC + placebo: 16.7%. Difference between ipilimumab + DTIC and placebo + DTIC: 18.9% (95% CI= 11.3-26.5%) Grade 3: 5.3%; Grade 4: 0.4%. DTIC + placebo: no Grade 3-4 irARs. Difference between ipilimumab + DTIC and placebo + DTIC: 5.7% (95% CI= 3.3-9.3%) • Diarrhoea, any grade: 32.8%. • Colitis, any grade: 4.5%. • No GI perforation or Grade 5 GI irARs. One case of Grade 5 GI hemorrhage (DTIC + placebo) Ipilimumab (Phase 2, CA184042) GI perforation (fatal): 1 subject (3.6%) **10 mg/kg vs 3 mg/kg ipilimumab (Phase 3, CA184169)** 10 mg/kg Any GI irAR, any grade: 39.0%; Grade 3-4: 14.3% • Diarrhoea, any grade: 37.4% • Colitis, any grade: 9.6% • Three cases of Grade 3-4 GI perforation (2 cases intestinal and one case large intestine) and no Grade 5 GI irARs. 3 mg/kg

Table 4-1: GI irARs (eg, diarrhoea, colitis, GI perforation)

GI irARs (eg, diarrhoea, colitis, GI perforation)	
	Any GI irAR, any grade: 25.1%; Grade 3-4: 8.6%; Grade 5: 0.3%. • Diarrhoea, any grade: 23.2% • Colitis, any grade: 5.2%. • Two cases of Grade 3-4 GI perforation (one case each GI and small intestinal). • One case of Grade 5 large intestine perforation.

Table 4-2: Hepatic irARs (eg, hepatitis)

Hepatic irARs (eg, hepatitis)	
Characterization of risk	**3 mg/kg ipilimumab** Ipilimumab monotherapy (MDX010-20) Any hepatic irARs any grade: 3.1% gp100: 3.8%. Difference between monotherapy and gp100: -0.7% (95% CI: -6.1%, 4.6%) Grade 3- 4 hepatic irARs: 0% gp100: 2.3%. Difference between monotherapy and gp100: -2.3% (95% CI: -6.8%, 0.6%) Grade 5 (fatal) hepatic irARs: 0.8% Serious hepatic irARs: 0.8% Ipilimumab+gp 100 (MDX010-20) Any hepatic irARs any grade: 2.1% Grade 3/4 hepatic irARs: 1.1% No Grade 5 hepatic irARs. Serious hepatic irARs: 0.8% **10 mg/kg ipilimumab** Ipilimumab + DTIC (Phase 3, CA184024) Any hepatic irARs any grade: 36.8%. DTIC + placebo: 6.0%. Difference between ipilimumab + DTIC and placebo + DTIC: 30.9% Grade 3: 20.2%; Grade 4: 7.7%, DTIC + placebo: Grade 3: 1.6%; Grade 4: 0.4%. Difference between ipilimumab + DTIC and placebo + DTIC: 25.9% (95% CI= 20.3-32.1%) Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004) Any hepatic irARs any grade: 8.0%. Grade 3-4 hepatic irARs: 6.8%. Grade 5 (fatal) hepatic irARs: One (0.3%) abnormal hepatic function (possibly related to study therapy). The hepatic management guideline prescribed by the protocol was not followed in this case. Ipilimumab (CA184042) Grade 1-2 hepatic irARs: One (2.0%) hepatobiliary disorder. **10 mg/kg vs 3 mg/kg ipilimumab (Phase 3, CA184169)**

Table 4-2: Hepatic irARs (eg, hepatitis)

Hepatic irARs (eg, hepatitis)	
	10 mg/kg Any hepatic irARs, any grade: 14.8%; Grade 3-4: 9.6%; no Grade 5 3 mg/kg Any hepatic irARs, any grade: 3.6%; Grade 3-4: 2.5%; no Grade 5

Table 4-3: Skin irARs (eg, rash, pruritus, TEN, and DRESS)

Skin irARs (eg, rash, pruritus, TEN, and DRESS)	
Characterization of risk	**3 mg/kg ipilimumab** Ipilimumab monotherapy (MDX010-20) Any skin irARs, grade: 42.0%, most commonly Grade 1-2 rash and pruritus gp100: 16.7%. Difference between monotherapy and gp100: 25.3% (95% CI = 14.5%, 35.7%) Grade 3-4 skin irARs: 0.8% gp100: 0%. Difference between monotherapy and gp100: 0.8% (95% CI = -2.2%, 4.6%) Serious skin irARs: 0% for monotherapy group Ipilimumab+gp 100 (MDX010-20) Any skin irARs, any grade: 38.9%, most commonly Grade 1-2 rash and pruritus Grade 3-4 skin irARs: 2.4%. One patient died of leukocytoclastic vasculitis and TEN, with both events reported as Grade 4. Serious skin irARs: 1.6% **10 mg/kg ipilimumab** Ipilimumab + DTIC (Phase 3, CA184024) Any skin irARs, any grade: 42.9%; DTIC + placebo: 10.4%. Difference between ipilimumab + DTIC and placebo + DTIC: 32.6% (95% CI= 25.2-39.8%) Grade 3 skin irARs: 3.2% Grade 4 -5 skin irARs: None DTIC + placebo: no Grade 3 -5 skin irARs. Difference between ipilimumab + DTIC and placebo + DTIC: 3.2% (95% CI= 1.5-6.5%) Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004) Any skin irARs, any grade: 53.2% Grade 3 skin irARs: 2.8% Grade 4 -5 skin irARs: None Ipilimumab (CA184042) Any skin irARs, any grade: 41.7%; 45.1% in corticosteroid-free arm; 33.3% in corticosteroid-dependent arm

Table 4-3: Skin irARs (eg, rash, pruritus, TEN, and DRESS)

Skin irARs (eg, rash, pruritus, TEN, and DRESS)	
	Grade 3-4 skin irARs,: 3 subjects (4.2%); 2 subjects in corticosteroid-free arm and 1 subject in corticosteroid-dependent arm **10 mg/kg vs 3 mg/kg ipilimumab (Phase 3, CA184169)** 10 mg/kg Any skin irARs, any grade: 45.3%; Grade 3-4: 1.9%; no Grade 5 3 mg/kg Any skin irARs, any grade: 37.3%; Grade 3-4: 1.4%; no Grade 5

Table 4-4: Neurologic irARs (eg, neuropathy)

Neurologic irARs (eg, neuropathy)	
Characterization of risk	**3 mg/kg ipilimumab** Ipilimumab monotherapy (MDX010-20) Any neurologic irARs, any grade: 0% Ipilimumab+gp 100 (MDX010-20) Any neurologic irARs, any grade: 0.5% (no Grade 1 or 2) Grade 3-5 neurologic irARs: 0.5%: 1 case of Grade 3 meningitis (resolved with IV steroids) and 1 Grade 5 (fatal) case of GBS **10 mg/kg ipilimumab** Ipilimumab + DTIC (Phase 3, CA184024) Any neurologic irARs, any grade: 2.0%; DTIC + placebo: 2.0%. Difference between ipilimumab + DTIC and placebo + DTIC: 0.03% (95% CI= -2.9-3.1%) Grade 3 neurologic irARs: 0.4% Grade 4-5 neurologic irARs: None DTIC + placebo, no Grade 3 -5 neurologic irARs. Difference between ipilimumab + DTIC and placebo + DTIC: 0.4% (95% CI= -1.2-2.4%) Ipilimumab Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004) Any neurologic irARs, any grade: 2.8% Grade 3 neurologic irARs: 0.6% (2 cases of paraesthesia) Grade 4 - 5 neurologic irARs: None Ipilimumab (CA184042) No neurologic irARs reported **10 mg/kg vs 3 mg/kg ipilimumab (Phase 3, CA184169)** 10 mg/kg Any neurologic irARs, any grade: 2.7%; Grade 3-4: 1.1%; no Grade 5 3 mg/kg

Table 4-4: Neurologic irARs (eg, neuropathy)

Neurologic irARs (eg, neuropathy)
Any neurologic irARs, any grade: 0.6%; no Grade 3-5

Table 4-5: Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)

Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)	
Characterization of risk	**3 mg/kg ipilimumab** Ipilimumab monotherapy (MDX010-20) Any endocrine irARs, any grade: 7.6% gp100: 1.5%. Difference between monotherapy and gp100: 6.1% (95% CI = 1.2%, 12.2%) Grade 3 endocrine irARs: 3.8%; most commonly hypophysitis and hypopituitarism gp100: 0%. Difference between monotherapy and gp100: 3.8% (95% CI = 0.9%,8.8%) Serious: endocrine irARs 4.6% Ipilimumab+gp 100 (MDX010-20) Any endocrine irARs, any grade: 3.4% Grade 3 endocrine irARs: 1.1% (ipilimumab+gp100), most commonly hypophysitis and hypopituitarism Grade 4 endocrine irARs: None Serious endocrine irARs: 1.1% **10 mg/kg monotherapy** Ipilimumab + DTIC (Phase 3, CA184024) Any endocrine irARs, any grade: 3.2% DTIC + placebo: 0.8%. Difference between ipilimumab + DTIC and placebo + DTIC: 2.4% (95% CI= -0.04-5.6%) Grade 3-5 endocrine irARs: None DTIC + placebo: no Grade 3 -5 endocrine irARs. Difference between ipilimumab + DTIC and placebo + DTIC: 0% (95% CI= -1.6-1.6%) Ipilimumab monotherapy Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004) Any endocrine irARs, any grade: 6.2%, Grade 3: 2.5% (most commonly hypothyroidism, hypophysitis, and hypopituitarism); no Grade 4 - 5 endocrine irARs Ipilimumab (CA184042) Any endocrine irARs, any grade: 7.0% Grade 3-4: 2.8% in corticosteroid-dependent arm; no Grade 5 irARs Ipilimumab (CA184042) Any grade: 7.0% Grade 3-4: 3.9% in corticosteroid-free group; none in corticosteroid-dependent group; no Grade 5 irARs

Table 4-5: Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)

Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)	
	10 mg/kg vs 3 mg/kg ipilimumab (Phase 3, CA184169)
	10 mg/kg
	Any endocrine irARs, any grade: 14.8%; Grade 3-4: 5.2%; no Grade 5
	3 mg/kg
	Any endocrine irARs, any grade: 9.1%; Grade 3-4: 2.2%; no Grade 5

Table 4-6: Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)

Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)	
Characterization of risk	**3 mg/kg ipilimumab**
	Ipilimumab monotherapy (MDX010-20) Any other irARs, any grade: 3.8% gp100: 2.3%. Difference between monotherapy and gp100: 1.5% (95% CI = -3.2%, 6.9%)
	Uveitis: 1.5%
	Grade 3-4 other irARs: 1.5%. One case each (0.8%) of lipase increased and glomerulonephritis gp100: 0.8%. Difference between monotherapy and gp100: 0.8% (95% CI= -3.0%, 4.8%)
	Ipilimumab+gp 100 (MDX010-20) Any other irARs, any grade: 2.6%
	Lipase increased and blood amylase increased: 0.5%
	Grade 3-4 other irARs: 1.3%
	Grade 5 (fatal) other irARs: One (0.3%) multi-organ failure
	10 mg/kg ipilimumab
	Ipilimumab + DTIC (Phase 3, CA184024)
	Any other irARs, any grade: 15.8% DTIC + placebo: 4.8%. Difference between ipilimumab + DTIC and placebo + DTIC: 11.0% (95% CI= 5.9-16.6%)
	Grade 3-4 other irARs: 3.2%, 1 case of Grade 5 systemic inflammatory response syndrome DTIC + placebo: Grade 3-4 other irARs: 0.4%, Grade 5 other irARs: None. Difference between ipilimumab + DTIC and placebo + DTIC: 2.8% (95% CI= 0.6-6.0%) Ipilimumab monotherapy Phase 2 studies, pooled (CA184008, CA184022, CA184007, CA184004)
	Any other irARs, any grade: 6.2%; Grade 3-4: 2.5%; Grade 5: 2 patients (0.6%) multi-organ failure and acute glomerulonephritis

Table 4-6: Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)

Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)
Ipilimumab (CA184042) Any grade: 5.8% in the corticosteroid-free group and none in the corticosteroid-dependent group Grade 3: one lipase increased in the corticosteroid-free group and none in the corticosteroid-dependent group **10 mg/kg vs 3 mg/kg ipilimumab (Phase 3, CA184169)** 10 mg/kg Any other irARs, any grade: 6.3%; Grade 3-4: 2.7%; no Grade 5 3 mg/kg Any other irARs, any grade: 0.8%; Grade 3-4: 0.3%; no Grade 5

ANNEX 4: NOT APPLICABLE

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

The Marketing Authorization Holder shall ensure that all physicians who are expected to prescribe ipilimumab are provided with/have access to the following to provide to their patients:

- Patient Card

Key Elements of the Patient Card:

- Ipilimumab can cause serious side effects in many parts of the body that can lead to death and need to be addressed immediately
- Request to inform the physician of relevant medical conditions before treatment
- Description of the main symptoms of irARs and severe infusion reactions and the importance of notifying their treating physician immediately if symptoms occur, persist or worsen
    - Gastrointestinal: diarrhea, bloody stool, abdominal pain, nausea, or vomiting
    - Liver: yellowing of your skin or whites of your eyes, bleeding, dark urine
    - Skin: rash, blisters and/or peeling, mouth sores
    - Nerves: weakness, numbness or tingling in legs, arms or face
    - Hormone glands: weight change, headache, feeling tired, dizziness or fainting, changes in behavior, such as less sex drive, being irritable or forgetful, excessive hunger and/or thirst, change in amount and/or frequency of urine
    - Lungs: shortness of breath, cough, chest pain
    - Eye: blurred vision, vision changes, eye pain
    - Severe infusion reactions: fever, chills, flushing, shortness of breath
- The importance of not attempting to self-treat any symptoms without consulting their HCP first.
- Placeholder including the weblink of the Package Leaflet on the EMA website
- The importance of carrying the detachable wallet-sized Patient Card at all times to show it at all medical visits to HCPs other than prescriber (eg. emergency HCPs). The Card reminds patients about key symptoms that need to be reported immediately to the physician/nurse. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is treated with ipilimumab.