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**INVESTIGATOR'S BROCHURE**  
**Nivolumab Intravenous**

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**MDX1106**

**ONO-4538**

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## CHANGES FROM THE PREVIOUS VERSION

Section	Summary of Changes	Do the Changes Affect Patient Safety, the Benefit/Risk Profiles, Toxicology, Pharmacology, or the Expectedness of Serious Adverse Events? (Y/N)
1 Summary	Minor edits	Patient Safety: N B/R Profile: N
2 Introduction	Minor edits	Patient Safety: N B/R Profile: N
3.1 Physical/Chemical Properties	Minor edits	Patient Safety: N B/R Profile: N
3.2 Pharmaceutical Properties and Formulation	None	N/A
4.1 Nonclinical Pharmacology	None	N/A
4.2 Nonclinical Pharmacokinetics	None	N/A
4.3 Nonclinical Toxicology	None	N/A
4.4 Safety Pharmacology	None	N/A
5.1 Clinical Pharmacodynamics	None	N/A
5.2 Clinical Pharmacokinetics	Minor edits	Patient Safety: N B/R Profile: N
5.3 Exposure-Response Relationship	Minor edits	Patient Safety: N B/R Profile: N



Section	Summary of Changes	Do the Changes Affect Patient Safety, the Benefit/Risk Profiles, Toxicology, Pharmacology, or the Expectedness of Serious Adverse Events? (Y/N)
5.4 Clinical Efficacy	Updated data for CA209592, CA209205, CA20976K Added data for CA20977T, CA209914, CA209901, CA2098HW, CA2097FL, CA209672 Removed data for ONO-4538-32. This study was a Phase I study and not primarily evaluated for efficacy.	Patient Safety: N B/R Profile: N
5.5 Clinical Safety	Updated data for CA20976K, CA209205, ONO-4538-32, CA209848 Added data for ONO-4538-67, ONO-4538-38, CA209672, CA209743, CA2097FL, CA20977T, CA2098HW, CA209914, ONO-4538-64, CA209901	Patient Safety: N B/R Profile: N
5.6 Immunogenicity	Minor Edits	Patient Safety: N B/R Profile: N
5.7 QT Prolongation Potential	None	N/A
5.8 Opportunistic Infections Due to Immunosuppression	None	N/A
5.9 Drug-induced Liver Injury	None	N/A
6 Marketing Experience	None	N/A
7 Summary of Data and Guidance for the Investigator	None	N/A
Appendix 1	Updated the RSI for Serious Adverse Reactions based on completed and ongoing studies of BMS-936558. A detailed summary of changes to the RSI is provided in "Explanation of Changes to the Reference Safety Information" section following the SAR tables in Appendix 1 (RSI)	Patient Safety: N B/R Profile: N Expectedness of SAEs: Y

## LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AE-DC/D	adverse events leading to discontinuation or death
AJCC	American Joint Committee on Cancer
ALC	absolute lymphocyte count
ALCL	Anaplastic Large Cell Lymphoma
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASCT	Autologous Stem Cell Transplant
APC	antigen-presenting cell
AUC	area under the concentration-time curve
AUC(0-168 h)	area under the concentration-time curve from time zero to 168 hours
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(TAU)	area-under-the-concentration-time curve over the dosing interval
BC	breast cancer
BEV	bevacizumab
BICR	blinded independent central review
BIRC	blinded independent review committee
BTLA	B and T lymphocyte attenuator
BMS	Bristol Myers Squibb Company
BOR	best overall response
BSC	best supportive care
bTMB-H	high tumor mutational burden in blood
BV	brentuximab vedotin
CAR	carboplatin
Cavg	time-averaged concentration
Cavg4	time-averaged nivolumab concentration after the fourth dose
Cavgd28	time-averaged concentration over the first 28 days
Cavgss	time-averaged concentration at steady state
CBR	Clinical Benefit Rate
CCC	clear cell carcinoma
CD28	cluster of differentiation 28
CFR	Code of Federal Regulations

Abbreviation	Definition
cHL	classical Hodgkin lymphoma
CHO	Chinese hamster ovary
CI	confidence interval
CIS	cisplatin
CL	clearance
CLss	steady-state clearance
Cmax	maximum serum concentration
Cmax1	peak concentration after the first dose
Cmaxss	peak concentration at steady-state
Cmin	minimum serum concentration
Cmind28	trough concentration at Day 28
Cminss	trough concentration at steady-state
CMR	complete metabolic response
CMV	cytomegalovirus
CNS	central nervous system
CNST	central nervous system tumor
Combo	combination
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CRu	Unconfirmed complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cutaneous T-cell lymphoma
CTLA-4	cytotoxic T lymphocyte antigen-4
CV	coefficient of variation
CXCL	chemokine (C-X-C motif) ligand
CYP	cytochrome
DBL	database lock
DC	discontinuations
DCR	disease Control rate
DFS	disease free survival
DILI	drug-induced liver injury
DLBL	diffuse large B-cell lymphoma

Abbreviation	Definition
DLT	Dose-limiting toxicity
dMMR	mismatch repair deficient
Doce	docetaxel
DOR	duration of response
DTIC	dacarbazine
EBV	Epstein Barr Virus
EC	esophageal cancer
EC50	half maximal effective concentration
ECG	electrocardiogram
ECL	Electrochemiluminescent
ECOG PS	Eastern Cooperative Oncology Group Performance Score
ED-SCLC	extensive stage disease small cell lung cancer
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
ePPND	enhanced pre- and postnatal development
ER+	estrogen receptor positive
E-R	exposure-response
ERL	erlotinib
ESCC	esophageal squamous cell carcinoma
EU	European Union
FACS	fluorescent-activated cell sorter
FBL	follicular B-cell lymphoma
FDA	Food and Drug Administration
GEJC	gastroesophageal junction cancer
GBM	glioblastoma
GC	gastric cancer
GD	gestational day
GEM	gemcitabine
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GVHD	graft-versus-host disease
GYN	gynecological
HCC	hepatocellular carcinoma

Abbreviation	Definition
HER2-	human epidermal growth factor receptor 2-negative
HGG	high grade gliomas
HLA	human leukocyte antigen
HPV	human papilloma virus
HRD+	homologous recombination deficiency positive
HSCT	hematopoietic stem cell transplantation
HuMAb	human monoclonal antibody
I-O	immuno-oncology
IB	Investigator Brochure
IC50	half maximal inhibitory concentration
ICC	investigator's choice chemotherapy
ICF	Informed consent form
ICOS	inducible co-stimulator
IFN- $\gamma$	interferon-gamma
IgG4	immunoglobulin G4
IMAE	immune-mediated adverse event
IPI	ipilimumab
IPI1	ipilimumab 1 mg/kg
IPI3	ipilimumab 3 mg/kg
IRRC	independent radiology review committee
ITT	intention to treat
IV	intravenous
JP	Japan
JPI	Japanese Package Insert
ka	association constant
KD	affinity
kd	dissociation constant
KM	Kaplan-Meier
LAG-3	lymphocyte-activation gene 3
LDH	lactate dehydrogenase
LFT	liver function test
LPLV	last patient last visit
mAb	monoclonal antibody
	
MCC	Merkel Cell carcinoma

Abbreviation	Definition
mCRC	metastatic CRC
mCRPC	metastatic castrate-resistant prostate cancer
MedDRA	medical dictionary for regulatory activities
MGMT	O-6-methylguanine DNA methyltransferase
MGZL	Mediastinal Gray Zone Lymphoma
MHC	major histocompatibility complex
MLR	mixed lymphocyte reaction
MM	multiple myeloma
MPM	malignant pleural mesothelioma
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
N-I	nivolumab in combination with Ipilimumab
N-Pd	nivolumab, pomalidomide, and dexamethasone
N1I1	nivolumab 1 mg/kg with ipilimumab 1 mg/kg
N1I3	nivolumab 1 mg/kg + ipilimumab 3 mg/kg
N3I1	nivolumab 3 mg/kg + ipilimumab 1 mg/kg
NC	not calculated
NCI	National Cancer Institute
NED	no evidence of disease
NET	neoadjuvant endocrine treatment
NHL	non-hodgkin lymphoma
NIVO+IPI	nivolumab + ipilimumab
Nivo	nivolumab
Nivo1	nivolumab 1 mg/kg
Nivo3	nivolumab 3 mg/kg
NPC	nasopharyngeal cancer
NR	not reported
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NSQ	non-squamous
NUTRFS	non-urothelial tract recurrence-free survival
OC	ovarian cancer
OECD	Organisation for Economic Cooperation and Development
OESIs	Other events of special interest



<b>Abbreviation</b>	<b>Definition</b>
ONO	Ono Pharmaceutical Co., Ltd.
OR	objective response
ORR	objective response rate
OS	overall survival
PAC	paclitaxel
PAZ	pazopanib
PBMC	peripheral blood mononuclear cells
PCNSL	primary central nervous system lymphoma
PD	pharmacodynamic(s)
PD-1	programmed death-1
PD-1-Fc	programmed death-1 protein fused to immunoglobulin constant region
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PEM	pemetrexed
PFS	progression-free survival
PFSR	progression-free survival rate
PFS2	progression-free survival through next-line systemic therapy
PK	pharmacokinetic(s)
PMBL	primary mediastinal B-cell lymphoma
PMR	partial metabolic response
PPK	population pharmacokinetic(s)
PR	partial response
PSA	prostate specific antigen
PT	preferred term
PTCL	Peripheral T-cell Lymphoma
PTL	primary testicular lymphoma
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	recurrence-free survival
RO	receptor occupancy
RRMM	Relapsed and/or Refractory Multiple Myeloma

Abbreviation	Definition
RSI	Reference Safety Information
RT	radiation therapy
SAE	serious adverse event
SARs	serious adverse reactions
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	stable disease
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SQ	squamous
SUN	sunitinib
t <sub>1/2</sub>	apparent elimination half-life
T3	triiodothyronine
T4	thyroxine
TCL	T-cell lymphoma
TEN	toxic epidermal necrolysis
TKI	tyrosine-kinase inhibitor
TMB	tumor mutational burden
TMB-H	high tumor mutational burden
TMZ	temozolomide
TNBC	Triple Negative Breast Cancer
TOR	time of response
TSH	thyroid-stimulating hormone
tTMB-H	high tumor mutational burden in tissue
TTP	time to progression
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VEGFR	vascular endothelial growth factor receptor
VKH	Vogt-Koyanagi-Harada
V <sub>ss</sub>	volume of distribution at steady state
WOCBP	women of childbearing potential

## **1 SUMMARY**

### **1.1 Introduction**

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.<sup>1</sup> Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the downregulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

OPDIVO™ (nivolumab) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (JP, Jul-2014). Nivolumab is also being investigated in various other types of cancer as monotherapy or in combination with other therapies.

### **1.2 Nonclinical Studies**

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the cluster of differentiation 28 (CD28) family.<sup>2,3</sup> Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN- $\gamma$ ) release in vitro.<sup>4,5,6</sup> Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1.<sup>2</sup> In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN- $\gamma$  release.<sup>7</sup>

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents.<sup>8</sup>

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted.<sup>9</sup> Administration of nivolumab at up to 50 mg/kg twice weekly was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at  $\geq 10$  mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC(0-168 h)] 117,000  $\mu\text{g}\cdot\text{h}/\text{mL}$ ). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these

pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice.<sup>10</sup>

### 1.3 Effects in Humans

The pharmacokinetics (PK), clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classical Hodgkin Lymphoma (cHL), urothelial carcinoma (UC), squamous cell carcinoma of the head and neck (SCCHN), hepatocellular carcinoma (HCC), colorectal cancer (CRC), small cell lung cancer (SCLC), esophageal squamous cell carcinoma (ESCC), gastric cancer (GC), gastroesophageal junction cancer (GEJC), esophageal cancer (EC), malignant pleural mesothelioma (MPM) in addition to other tumor types. This updated Investigator Brochure (IB) references the most recent US Prescribing Information (USPI) and European Union (EU) Summary of Product Characteristics (SmPC) as the basis for the current state of knowledge on nivolumab for use treating cancer in humans. See [Appendix 2](#) for USPI and [Appendix 3](#) for EU SmPC.

Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies for the treatment of several types of cancer. Single-dose nivolumab monotherapy was also investigated in a Phase 1b study and a Phase 1/2 study of subjects with sepsis who were also managed according to established best practice care for sepsis. Additional clinical activity and safety information presented in this IB focus primarily on data from clinical studies that are relevant to ongoing clinical investigations not in the approved USPI and EU SmPC.

#### 1.3.1 Clinical Pharmacokinetics

Nivolumab PK in subjects with cancer was assessed using a population PK approach for nivolumab monotherapy and in combination with ipilimumab or other therapeutic agents (eg, chemotherapy).

The PK of nivolumab as monotherapy was studied over a dose range of 0.1 to 20 mg/kg administered as a single-dose or as multiple-doses of nivolumab as a 60-minute infusion every 2 or 3 weeks. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks (Q2W). Based on a population pharmacokinetic (PPK) analysis with a time varying clearance (CL) component using data from subjects with several tumor types, including melanoma, NSCLC, and RCC, nivolumab clearance was shown to decrease over time, with a median maximal reduction from baseline values of approximately 26% resulting in a geometric mean steady-state clearance (CL<sub>ss</sub>) (% coefficient of variation [CV%]) of 7.91 mL/h (46%) in subjects with metastatic tumors. However, the decrease in CL<sub>ss</sub> is not considered to be clinically relevant. Nivolumab clearance does not decrease over time in subjects with completely resected melanoma. The geometric mean (CV%) volume of distribution at steady state (V<sub>ss</sub>) is 6.6 L (24.4%), and elimination half-life (t<sub>1/2</sub>) is 25 days (55.4%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 4-fold. PK differences across

multiple tumor types were explored, and in general there was no clinically meaningful difference, due to a flat dose/exposure-response (E-R) relationship between nivolumab and efficacy/safety.

The PK of nivolumab was assessed in the adolescent ( $\geq 12$  to 17 years) and pediatric ( $< 12$  years) subjects. Based on the covariate analysis, adolescent and younger pediatric subjects had nivolumab baseline CL values that were 20% (95% CI: 7-33%) and 44% (32-54%) lower than in adult subjects with advanced melanoma, respectively. In addition, the adolescent and pediatric subjects had 24% lower nivolumab VC than adult subjects. Refer to [Section 5.2.1.2](#) for detailed information on nivolumab exposures in pediatric and adolescent subjects.

PPK analysis demonstrated that coadministration of nivolumab and ipilimumab potentially increases nivolumab CL by up to 29% compared to nivolumab administered alone, depending on the dose and frequency of ipilimumab coadministration. These are unlikely to be clinically relevant given the flat dose-response relationship demonstrated using exposure response (E-R) analyses for efficacy and safety.

In addition, PPK analyses demonstrated that co-administration with chemotherapy, cabozantinib, ipilimumab 1mg/kg Q6W + chemotherapy, relatlimab, or ipilimumab had no clinically meaningful impact on nivolumab PK in 1L GC/GEJC, resectable NSCLC, 1L ESCC, 1L RCC, 1L NSCLC, advanced melanoma, and mCRC subjects. No covariates were found to have clinically relevant effect on nivolumab PK in these studies.

Nivolumab E-R relationships for efficacy and safety were evaluated for nivolumab monotherapy and in combination with ipilimumab or other therapeutic agents.

The dose range of 1 mg/kg Q2W to 10 mg/kg Q2W was evaluated for nivolumab monotherapy in melanoma, RCC, and NSCLC. Generally, a flat E-R relationship was observed over this dose range between nivolumab and clinical endpoints such as the hazard of death, probability of objective response (OR), adverse events (AEs) leading to discontinuation or death (AE-DC/D), and/or Grade 3+ AEs, and a 3 mg/kg Q2W dose regimen was approved for these and additional indications.

Further E-R analyses demonstrated that the benefit-risk profiles of nivolumab 240 mg Q2W and 480 mg every 4 weeks (Q4W) are comparable to 3 mg/kg Q2W; flat dose nivolumab monotherapy regimens were subsequently approved in some regions for existing and additional indications including melanoma, RCC, NSCLC, SCLC, SCCHN, CRC, UC, cHL, HCC, and esophageal squamous cell carcinoma (ESCC). Flat dose regimen 360 mg every 3 weeks (Q3W) nivolumab was similarly evaluated and recently as combination therapy with ipilimumab and platinum-doublet chemotherapy in NSCLC, GC, GEJC, and esophageal adenocarcinoma.

E-R analysis were also conducted for 1L mesothelioma (nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W), 1L RCC (nivolumab 240 mg Q2W with cabozantinib 40 mg QD), 1L GC/GEJC (nivolumab 240 mg Q2W or 360 mg Q3W in combination with fluoropyrimidine and platinum-containing chemotherapy), adjuvant EC/GEJC/EAC (nivolumab 240 mg Q2W or 480 mg Q4W 16 weeks followed by 480 mg Q4W), 1L NSCLC (nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W), and 1L NSCLC (nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy), 1L ESCC (nivolumab 240 mg Q2W + chemotherapy or nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W), adjuvant MIUC

(nivolumab 240 mg Q2W or 480 mg Q4W), and 1L mCRC (nivolumab 240 mg + ipilimumab 1 mg/kg Q3W for up to 4 doses then nivolumab 480 mg Q4W) subjects. The E-R relationship were generally flat within the exposure ranges produced by the studied regimen in each study.

### **1.3.2 Clinical Efficacy**

Nivolumab has demonstrated durable responses as monotherapy and in combination with ipilimumab in several tumor types. In confirmatory trials, nivolumab demonstrated significant clinical benefit as monotherapy, and in combination with other therapeutics such as ipilimumab, relatlimab<sup>11</sup>, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies. Please refer to [Appendix 2 \[USPI\]](#) and [Appendix 3 \[EU SmPC\]](#) for information on approved indications.

### **1.3.3 Clinical Safety**

The safety experience from clinical trials with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 32,608 subjects treated to date in unblinded clinical trials.

For monotherapy, the safety profile is similar across tumor types. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

Based on data from a completed Phase 1b study and a Phase 1/2 study, single doses of either 480 mg or 960 mg nivolumab did not result in unexpected safety findings for participants with sepsis or septic shock.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. Nivolumab as monotherapy and nivolumab in combination with other agents is approved in subjects with several tumor types (see [Appendix 2 \[USPI\]](#) and [Appendix 3 \[EU SmPC\]](#)). Results to date suggest that the safety profile of nivolumab + ipilimumab combination therapy, the most advanced combination under development, is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

## 2 INTRODUCTION

PD-1 (or CD279), a 55-kilodalton Type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that is highly expressed on activated T cells and B cells. PD-1 expression can also be detected on memory T-cell subsets with variable levels of expression. Two ligands specific for PD-1 have been identified: PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.<sup>12, 13, 14</sup> The interaction of PD-1 with its ligands, PD-L1 and PD-L2, that are expressed on antigen-presenting cells (APCs) and dendritic cells, transmits negative regulatory stimuli to down-modulate the activated T-cell immune response. The absence or inhibition of PD-1 in murine models has resulted in the development of various autoimmune phenotypes and autoimmune diseases.<sup>1</sup> Taken together, these results suggest that inhibition of PD-1 binding to its ligands has the potential to activate T-cell responses. Since these responses are variable and dependent upon various host genetic factors, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

### 2.1 PD-1 and Oncology

Tumors can express tumor-specific antigens as a result of mutational burden, and ongoing immune surveillance is believed to control the development of many tumors. One mechanism to evade an effective immune response may be the expression of ligands, which engage inhibitory receptor(s) on anti-tumor T-cells of many tumors. PD-L1 expression has been found on a number of tumors and may be a mechanism by which tumors can directly engage PD-1 to evade an effective anti-tumor immune response.<sup>15,16,17</sup> Expression of interferon-gamma (IFN- $\gamma$ ) by activated T cells is known to induce PD-L1 expression in tumors.<sup>18</sup> PD-L1 expression has been associated with poor prognoses in renal,<sup>19, 20, 21</sup> esophageal,<sup>22</sup> gastric,<sup>23</sup> ovarian,<sup>17</sup> pancreatic,<sup>24</sup> and lung cancers.<sup>25</sup> PD-1 engagement on T-cells by PD-L1-positive APC or PD-L1-positive tumor cells in the tumor microenvironment may limit effective immune responses. Conversely, PD-L1 expression may be a positive prognostic factor as it may indicate infiltration of tumor-specific T cells that secrete IFN- $\gamma$ , which upregulates PD-L1 expression. Consistent with this hypothesis is the co-localization of lymphoid cell infiltrates and PD-L1 staining observed in human melanoma lesions.<sup>26</sup>

Studies in multiple tumor models using a chimeric murine anti-mouse PD-1 antibody showed that PD-1 blockade has anti-tumor activity ([Section 4.1.3](#)).<sup>27</sup> Blocking PD-1 in PD-L1-positive tumors may reverse the inactivation of tumor-specific effector T-cells at the tumor site, as well as activate anti-tumor responses that are limited by PD-L1 expression on “host” dendritic cells or APC. The anti-tumor effects of anti-PD-1 observed in several murine models suggest that both PD-L1-positive and PD-L1-negative tumors may be targeted using this approach. In addition, in several tumor models in which anti-PD-1 has proved ineffective, PD-1 blockade can be combined with vaccines or other immunomodulatory antibodies for improved therapeutic efficacy.<sup>28,29,30</sup> PD-1 blockade by nivolumab is a promising avenue to pursue as an anti-tumor therapy for recurrent or treatment-refractory malignancies.

### 3 PHYSICAL/CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

#### 3.1 Physical/Chemical Properties

Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. Nivolumab is produced from cell culture using a CHO cell line. The physical and chemical properties of nivolumab drug substance are provided in Table 3.1-1.

**Table 3.1-1: Physical and Chemical Properties of Nivolumab Drug Substance**

BMS Number	BMS-936558-01
Other Names	nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1
Molecular Weight	146,221 daltons (143,619.17 daltons, protein portion)
Appearance	Clear to opalescent, colorless to pale yellow liquid
Solution pH	5.5 to 6.5

#### 3.2 Pharmaceutical Properties and Formulation

##### 3.2.1 Description of the Dosage Form

The nivolumab (Opdivo®) dosage forms are provided in [Table 3.2.1-1](#). The drug products are sterile, non-pyrogenic, single-use, isotonic aqueous solutions for intravenous (IV) infusion. Nivolumab Injection, 40 mg/Vial (10 mg/mL), 100 mg/Vial (10 mg/mL), 120 mg/Vial (10 mg/ml), and 240 mg/Vial (10 mg/mL) are also referred to as nivolumab injection.



**Table 3.2.1-1: Nivolumab Dosage Forms**

Drug Product	Placebo	Nivolumab Injection			
Strength	-	40 mg/vial	100 mg/vial	120 mg/vial <sup>a</sup>	240 mg/vial <sup>a</sup>
Appearance	Clear to opalescent, colorless to pale yellow liquid, essentially free of particles on visual inspection	Clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates			
Concentration	-	10 mg/mL			
Vial Fill <sup>b</sup>	10.7 mL /10.5 mL <sup>a</sup>	4.7 mL	10.7 mL /10.5 mL <sup>a</sup>	12.6 mL <sup>a</sup>	24.6 mL <sup>a</sup>
Vial Size	10 cc	10 cc	10 cc	25 cc <sup>a</sup>	30 cc <sup>a</sup>
Components	Sodium citrate dihydrate, sodium chloride, mannitol, pentetic acid <sup>c</sup> , polysorbate 80, and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment.	Nivolumab, sodium citrate dihydrate, sodium chloride, mannitol, pentetic acid <sup>c</sup> , polysorbate 80, and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment.			
Solution pH	5.5–6.5	5.5–6.5			
Container Closure System	Type I flint glass vials closed with fluoropolymer film-laminated rubber stoppers, and sealed with aluminum seals	Type I flint glass vials closed with fluoropolymer film-laminated rubber stoppers, and sealed with aluminum seals			

<sup>a</sup> Information on ONO drug product

<sup>b</sup> All of the drug products include an overfill to account for vial, needle, and syringe holdup

<sup>c</sup> Also referred to as diethylenetriaminepentaacetic acid

### 3.2.2 Drug Product Preparation

#### Nivolumab Injection and Placebo for Nivolumab Injection

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (eg, polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. When the dose is based on patient weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% sodium chloride injection or 5% dextrose injection to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For subjects weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kg of patient weight.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection will be provided to the clinical site. Care must be taken to ensure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride or polyolefin containers and infusion sets, and glass bottles.

The placebo for nivolumab injection is administered in a similar manner as described above for the active drug product.

### **3.2.3      *Recommended Storage and Use Conditions***

#### **Nivolumab Injection**

Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

#### **Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container**

Following the preparation of nivolumab injection, it is preferred to administer the drug product immediately. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) and protected from light for up to 7 days, including the product administration period or as described in the instructions provided to the clinical site. The infusion solution may be stored at room temperature (up to 25°C, 77°F) and room light for a maximum of 8 hours, including the product administration period.

#### **Placebo for Nivolumab Injection**

The same storage and use conditions for the active drug product also apply to the placebo for nivolumab injection.

## 4 NONCLINICAL STUDIES

### 4.1 Nonclinical Pharmacology

#### 4.1.1 *Binding of Nivolumab to Programmed Death-1*

The ability of nivolumab to bind to PD-1 was determined using Biacore, enzyme-linked immunosorbent assay, fluorescent-activated cell sorter (FACS), and Scatchard analyses using PD-1+ transfectants and activated human T cells.<sup>2,3</sup>

Nivolumab was also shown to inhibit the binding of PD-1 to its ligands, PD-L1 and PD-L2. These properties of nivolumab are summarized in Table 4.1.1-1. Nivolumab bound specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and BTLA.<sup>2,3</sup>

**Table 4.1.1-1: Properties of Nivolumab (BMS-936558 or MDX1106)**

Affinity to PD-1 (Biacore)	KD (nM)	ka × 10 <sup>4</sup> (1/ms)	kd × 10 <sup>-4</sup> (1/s)
Human PD-1	3.06	25.00	7.68
Cynomolgus PD-1	3.92	11.80	4.65
Binding to PD-1	EC50 (nM)		
PD-1-Fc fusion protein by ELISA	0.39		
Activated human T cells by FACS	0.64		
CHO/PD-1 cells by FACS	1.66		
Activated human T cells by Scatchard	2.6		
Inhibition of Ligand Binding	IC50 (nM)		
PD-L1 to CHO/PD-1	1.04		
PD-L2 to CHO/PD-1	0.97		

Sources: MDX1106-025-R<sup>2</sup> and MDX1106-28-R<sup>3</sup>

Abbreviations: CHO = Chinese hamster ovary; EC50 = half maximal effective concentration; ELISA = enzyme-linked immunosorbent assay; FACS = fluorescent-activated cell sorter; IC50 = half maximal inhibitory concentration; ka = association constant; KD = affinity; kd = dissociation constant; PD-1-Fc = PD-1 protein fused to immunoglobulin constant region.

#### 4.1.2 *Nivolumab Activity in Functional Assays*

Nivolumab was shown to promote the proliferation of human T cells in a variety of assays, which is an anticipated pharmacologic result of PD-1 inhibition.

Nivolumab blockade of the PD-1 pathway was evaluated in the MLR as assessed by T-cell proliferation and IFN-γ secretion. PD-1 blockade resulted in a reproducible concentration-dependent enhancement of both proliferation and IFN-γ release in the MLR.<sup>7</sup>

The effect of nivolumab on cytomegalovirus (CMV) antigen-specific recall responses was investigated using human peripheral blood mononuclear cells from a CMV-exposed donor. These

data demonstrated that nivolumab, versus an isotype-matched control antibody, augmented IFN- $\gamma$  secretion from CMV-specific memory T cells in a dose-dependent manner up to 10  $\mu\text{g/mL}$ .<sup>31</sup>

An investigative study was conducted to examine the ability of nivolumab to potentiate cellular immune and humoral immune responses to an HBsAg vaccine, SKMel melanoma cell vaccine and DNP-Ficoll in cynomolgus monkeys. Nivolumab administration (10 mg/kg/dose at days 1, 29, and 57) was associated with increases in delayed-type hypersensitivity responses to HBsAg and increases in anti-SKMel antibody responses compared to monkeys administered with saline.<sup>32</sup>

#### **4.1.3 Activity of Anti-programmed Death-1 Antibody in Murine Tumor Models**

The role of anti-PD-1 in generating an anti-tumor response has been tested in a number of murine transplantable tumor models. A surrogate rat anti-mouse PD-1 antibody (4H2) was derived and expressed as a chimeric IgG1 murine antibody. Antibody 4H2 inhibited the binding of murine PD-1 to its ligands and is expected to have an improved in vivo half-life over the parental rat antibody.<sup>29</sup> Results from tumor studies demonstrate that inhibition of PD-1 binding to its ligands resulted in anti-tumor activity in some models. The surrogate chimeric antibody promoted anti-tumor activity in MC38, SA1/N, and J558 syngeneic tumor models; however, Renca, 4T1, CT26, and B16F10 tumors were refractory to treatment.<sup>5, 6, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42</sup>

#### **4.2 Nonclinical Pharmacokinetics**

In cynomolgus monkeys receiving 1 mg/kg to 50 mg/kg IV single-doses of nivolumab, the apparent elimination half-life estimates were long (124 to 148 hours after 1 mg/kg doses, 223 to 267 hours after 10 or 50 mg/kg doses), and serum clearance was low.<sup>43, 44, 45</sup> Systemic exposure to nivolumab increased in an approximately dose-proportional manner. Nivolumab was immunogenic in cynomolgus monkeys; generally, exposure to nivolumab in these anti-nivolumab-positive monkeys was lower than the mean exposures in animals in the same dose group with no detectable anti-nivolumab antibodies. The low volume of distribution in cynomolgus monkeys (0.046 L/kg to 0.071 L/kg) indicates that there is little extravascular distribution of nivolumab.

No mass balance or metabolism studies with nivolumab have been conducted in animals. The expected in vivo degradation of monoclonal antibodies is to small peptides and amino acids via biochemical pathways that are independent of drug metabolism enzymes.

Nivolumab is not expected to have any effect on cytochrome (CYP) P450 or other drug-metabolizing enzymes in terms of inhibition or induction, and is, therefore, not expected to induce these types of PK-based drug interactions.

#### **4.3 Nonclinical Toxicology**

A battery of nonclinical studies (single-dose toxicity studies,<sup>43</sup> repeat-dose toxicity studies,<sup>45, 46</sup> safety pharmacology studies,<sup>47</sup> reproductive and developmental toxicity study,<sup>9</sup> binding studies,<sup>3</sup> and antibody-dependent cellular cytotoxicity/complement-dependent cytotoxicity assays<sup>2</sup>) have been completed to assess the potential toxicologic profile of nivolumab.

The pivotal toxicity and reproductive developmental studies were conducted in countries that are members of the OECD Mutual Acceptance of Data program and in accordance with the Organization for Economic Cooperation and Development (OECD) Test Guidelines and Principles of Good Laboratory Practice (GLP) or GLP regulations of the United States Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Title 21, Part 58 (21CFR58).

However, several of the studies were exploratory or investigative in nature (non-GLP) and were not conducted in full compliance with all aspects of the GLP regulations. These studies are considered scientifically valid and were used to provide useful information in designing or interpreting the GLP studies.

The potential of nivolumab to react with non-target tissues was investigated with cryosections of normal human tissues.<sup>48</sup> Nivolumab demonstrated reactivity with rare to occasional lymphocytes in the majority of tissues. The cytoplasmic staining of these rare to occasional endocrine cells in the adenohypophysis is considered to be an unexpected cross-reactivity because expression of PD-1 has not been reported in this cell type. In addition, the binding can be reduced by the addition of PD-1 to the assay, and binding to these cells is not seen with a commercial anti-PD-1 antibody. Although this reactivity is not expected, it is unlikely to result in physiological effects due to the limited exposure of cytoplasmic compartments to nivolumab in humans.

Nivolumab did not mediate antibody-dependent cell-mediated cytotoxicity on activated CD4 T cells, while the positive control anti-major histocompatibility complex (MHC) Class I antibody did.<sup>2</sup>

Nivolumab did not mediate complement-mediated cytotoxicity on activated CD4 T cells, while the positive control anti-MHC Class I antibody did.<sup>2</sup>

Addition of nivolumab + irrelevant IgG4 antibody resulted in no significant effect on the release of cytokines, while positive control anti-CD3 antibody induced dramatic increases in cytokine release.<sup>49</sup>

Single administration of nivolumab at dose levels of up to 10 mg/kg IV and repeat-dose administration of up to 50 mg/kg once weekly IV for 4 weeks and 50 mg/kg twice weekly IV for 3 months were evaluated in cynomolgus monkeys and were well tolerated at all dose levels.<sup>43</sup>

As nivolumab is a HuMAb, it is not expected that it would interact directly with deoxyribonucleic acid or other chromosomal materials. Thus, genotoxicity studies have not been conducted for nivolumab.

Carcinogenicity studies have not been conducted with nivolumab.

In an ePPND study, nivolumab was administered twice weekly at 10 or 50 mg/kg to pregnant cynomolgus monkeys from gestational day (GD) 20 to 22 until parturition.<sup>48</sup> Nivolumab was well tolerated at both doses, and there were no nivolumab-related effects on viability, clinical signs, food consumption, body weights, immunological endpoints, or clinical/anatomic pathology parameters in these females throughout the study.

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

Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance is consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice.<sup>10</sup> In these models, maternal regulatory T cells are thought to be the principal mediators of fetal tolerance via suppression of autoimmune reactions directed towards the fetus. PD-1 signaling can support placental expansion of regulatory T cells and/or suppress effector T cell function. Abrogation of PD-1 signaling (eg, PD-L1 knockout, nivolumab administration) may eliminate the suppressive activity of regulatory T cells in the placenta, resulting in increased inflammatory reactions towards the fetus and associated decreased fetal survival rates.

A 4-week toxicity study was conducted in cynomolgus monkeys to characterize the toxicity of the co-administration of nivolumab + ipilimumab.<sup>45</sup>

The result of this study demonstrated that the combination of nivolumab + ipilimumab, when co-administered at low and high (10/3 mg/kg and 50/10 mg/kg of nivolumab + ipilimumab) weekly IV doses for 4 weeks resulted in dose-dependent gastrointestinal (GI) toxicity. GI toxicity/colitis has not been observed in cynomolgus monkeys administered nivolumab alone but has been observed at a low incidence in monkeys receiving ipilimumab and in humans receiving nivolumab as monotherapy or in combination with ipilimumab.

A 1-month combination toxicity study in cynomolgus monkeys was conducted to determine the potential toxicity of nivolumab in combination with relatlimab, a fully human anti-lymphocyte-activation gene 3 (LAG-3) antibody.<sup>8</sup> Relatlimab and nivolumab, alone and in combination (100 mg/kg relatlimab and 50 mg/kg nivolumab), were administered once weekly IV.

Nivolumab alone was well tolerated. Administration of the combination resulted in the moribundity of 1 monkey on Day 29 due to central nervous system (CNS) vasculitis including lymphoplasmacytic inflammation of the choroid plexus. In monkeys treated with 50 mg/kg nivolumab alone, lymphoplasmacytic inflammation was restricted to the choroid plexus with lower severity and incidence as compared to the combination therapy group. The presence of lymphoplasmacytic cells within the choroid plexus in cynomolgus monkeys is a well-recognized and documented spontaneous finding with no adverse consequences.<sup>50, 51</sup>

#### **4.4 Safety Pharmacology**

No drug-related findings were observed in standard clinical evaluations of cardiovascular, respiratory, and neurologic function conducted in cynomolgus monkeys as part of the repeat-dose toxicity studies for up to 3 months with nivolumab. In addition, the potential cardiovascular effect of nivolumab, when administered as a single IV dose, was examined in conscious cynomolgus monkeys.<sup>47</sup> The single IV bolus administration of nivolumab at doses up to 50 mg/kg was well tolerated. There were no effects on clinical signs, body weights, body temperatures, mean arterial blood pressures, electrocardiograms (ECGs), or cardiovascular parameters.

## 5 EFFECTS IN HUMANS

This updated IB references the most recent USPI and EU SmPC as the basis for the current state of knowledge on nivolumab for use in humans with cancer. The data from supportive studies for approved indications are provided in the approved USPI and EU SmPC are referenced in [Appendix 2](#) and [Appendix 3](#), respectively.

The currently approved indications for nivolumab can be found in Table 5-1.

**Table 5-1: Currently approved indications for Nivolumab IV (BMS-936558) in US and EU**

Nivolumab Therapy	Indications (Supportive Study)
Nivolumab monotherapy	<p>Melanoma (CA209037, CA209066, CA209172 and CA209070)</p> <p>Adjuvant melanoma Stage IIB/C (CA20976K)</p> <p>Adjuvant melanoma Stage III/IV (CA209238 and CA209070)</p> <p>Squamous NSCLC (CA209063 and CA209017)</p> <p>Non-squamous NSCLC (CA209057)</p> <p>RCC (CA209025)</p> <p>cHL (CA209205 and CA209039)</p> <p>SCCHN (CA209141)</p> <p>UC (CA209275)</p> <p>Adjuvant UC (CA209274)</p> <p>CRC (CA209142)</p> <p>Adjuvant EC or GEJC (CA209577)</p> <p>ESCC (CA209473/ATTRACTION -3)</p>
Nivolumab in combination with Ipilimumab	<p>Melanoma (CA209069, CA209067 and CA209070)</p> <p>NSCLC (CA209227)</p> <p>MPM (CA209743)</p> <p>RCC (CA209214)</p> <p>CRC (CA209142)</p> <p>HCC (CA209040)</p> <p>ESCC (CA209648)</p>
Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy	NSCLC (CA2099LA)
Nivolumab in combination with cabozantinib	RCC (CA2099ER).
Nivolumab in combination with chemotherapy	<p>GC, GEJC, and esophageal adenocarcinoma (CA209649)</p> <p>Neoadjuvant NSCLC (CA209816)</p> <p>ESCC (CA209648)</p>
Nivolumab in combination with cisplatin and gemcitabine	UC (CA209901)

Clinical data included in this annual IB update are based on the available information to date. Data from clinical studies that have reported primary endpoints (ie, completed studies) and are relevant



to ongoing clinical investigations in oncology that are not in the approved USPI and EU SmPC are included in this updated IB.

Completed studies include those studies that describe the results of the primary study endpoint(s); however, in some completed studies, subjects may continue to receive treatment. Ongoing studies include studies where subjects remain on treatment or in follow-up, and where the primary endpoint has not been reported.

This IB also describes 3 different types of clinical study reports (CSRs): An interim CSR is written in certain cases, such as when data are available for endpoints or variables that predate the availability of data for the primary endpoint. A primary CSR (or final CSR) is written when data for the primary endpoint are available. An addendum to the primary CSR is written when data are available for endpoints or variables that postdate the availability of data for the primary endpoint.

The PK, clinical activity, and safety of nivolumab have been assessed in approximately 174 clinical studies sponsored by BMS or ONO. The description and status of studies with reference safety information included in [Appendix 1](#) are provided in [Appendix 5](#). Across those studies, approximately 32,608 subjects have received nivolumab monotherapy in single- or multiple-dose unblinded Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies). Results from the ongoing studies are preliminary and are subject to change.

In confirmatory trials, nivolumab demonstrated significant clinical benefit as monotherapy, and in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies.

All available data suggest that nivolumab monotherapy has a consistent AE profile across tumor types. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. The safety profile of nivolumab in combination with ipilimumab was consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs was similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs were increased with the combination. A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3-mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD.<sup>52</sup> The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, the frequency of any grade and severity of AEs were greater than that observed with either agent alone. Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash, Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN]), hepatotoxicity, and myotoxicity. 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 or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided in [Appendix 4](#).

In addition to BMS-sponsored ongoing studies, studies sponsored by ONO Pharmaceuticals, Ltd conducted in Japan, Korea, and/or Taiwan are included in the reference safety information in [Appendix 1](#). Brief descriptions of these studies are provided in [Appendix 5](#). The studies are not under any US Investigational New Drug application. Efficacy and safety information from ONO studies (ONO-4538-01, ONO-4538-04, ONO-4538-13, ONO-4538-14, ONO-4538-19, ONO-4538-23, ONO-4538-31, ONO-4538-32, ONO-4538-39, ONO-4538-54 and ONO-4538-83) are provided in [Section 5.4](#) and [Section 5.5](#). The ONO studies listed are included per ONO recommendation.

All studies were conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Food and Drug Administration Code of Federal Regulations (CFR), Title 21, Part 50 (21CFR50).

## 5.1 Clinical Pharmacodynamics

The clinical PD were assessed in subjects with cancer for nivolumab monotherapy and for nivolumab in combination with ipilimumab.

The PD effects of nivolumab in subjects with cancer were studied by assessing RO, peripheral immune cell population modulation, systemic cytokine modulation, and change in absolute lymphocyte count (ALC) in studies MDX1106-03<sup>53</sup> and/or CA209009<sup>54</sup>. Results were as follows:

- Peripheral receptor occupancy (RO) of PD-1 is saturated at doses  $\geq 0.3$  mg/kg dose levels as measured on CD3+ cells from frozen and fresh peripheral blood mononuclear cells (PBMCs).
- Nivolumab treatment had no clinically meaningful changes in activated T-cells in peripheral blood; no dose-response was evident.
- Baseline measurements of select immune cell subsets were not associated with response to nivolumab.
- Mean ALC measured over time did not change at any nivolumab dose nor was it associated with response to nivolumab.
- Median percent increase from baseline to post-dose for chemokine (C-X-C motif) ligand (CXCL) 9 (CXCL9) and CXCL10 were consistent with demonstration of immunomodulatory activity of nivolumab on these chemokines.

To understand if the effect of nivolumab in combination with ipilimumab was distinct from that of either nivolumab or ipilimumab monotherapy, changes in immunomodulatory PD biomarkers with combination nivolumab and ipilimumab treatment was assessed in study CA209004. ALC, activated CD4+ and CD8+ T cells in the periphery, and levels of inflammatory cytokines were measured in blood and serum in CA209004<sup>55</sup>. Results were as follows:

- No consistent rise in ALC was observed with combination nivolumab and ipilimumab therapy, similar to nivolumab monotherapy.
- Increases in activated CD4+ and CD8+ T cells were observed with the combination regimen, consistent with the PD effects of ipilimumab alone and distinct from the effects of nivolumab alone.

- Combination therapy resulted in increases in interferon- $\gamma$  induced serum cytokines, such as MIG (CXCL9) and IP-10 (CXCL10), which are also increased with single-agent nivolumab.

The PD effects of nivolumab in subjects with sepsis were studied by assessing RO, peripheral immune cell population modulation, systemic cytokine modulation, and change in monocyte-human leukocyte antigen-DR (HLA-DR) expression. Results were as follows:

- Peripheral RO of PD-1 is saturated with a single-dose of 480 mg and 960 mg in the majority of subjects for the duration of the observation period, ie, until exiting the study or 90 days, as measured on CD3+ cells.
- Nivolumab treatment was associated with increases in ALC and mHLA-DR expression; no dose-response was evident. Since no placebo control subjects were assessed, the clinical relevance of this finding is unknown.
- Selected cytokines, chemokines, and inflammatory markers were generally decreased following nivolumab administration, consistent with decreasing expression following a sepsis event. Importantly, in subjects with sepsis administered nivolumab, no signs of a cytokine storm were observed subsequent to dosing.

## **5.2 Clinical Pharmacokinetics**

### **5.2.1 Pharmacokinetics of Nivolumab in Subjects with Cancer**

Nivolumab PK in subjects with cancer was assessed for nivolumab monotherapy and in combination with ipilimumab or other therapeutic agents such as chemotherapy.

The PK of nivolumab as monotherapy was studied in subjects with cancer over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple-doses of nivolumab as a 60-minute infusion every 2 or 3 weeks. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. Based on a PPK analysis using data from subjects with several tumor types, including melanoma, NSCLC, and RCC, nivolumab clearance was shown to decrease over time (a time-varying CL) in subjects with metastatic tumors.<sup>56</sup> Median maximal reduction from baseline values was approximately 26%, resulting in a geometric mean CLss (% coefficient of variation [CV%]) of 7.91 mL/h (46%). However, the decrease in CLss is not considered to be clinically relevant. Nivolumab clearance was not seen to decrease over time in subjects with completely resected melanoma. The geometric mean (CV%) Vss is 6.6 L (24.4%), and elimination t<sub>1/2</sub> is 25 days (55.4%).<sup>57</sup> Steady-state concentrations of nivolumab were reached by approximately 12 weeks and systemic accumulation was approximately 4-fold when administered at 3 mg/kg Q2W.<sup>58</sup>

Pharmacokinetic differences across multiple tumor types were explored, and there were no clinically meaningful differences. Specifically, PPK analysis suggested that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC.<sup>59</sup> PPK analysis also indicated that nivolumab CL in subjects with GC was approximately 33% higher relative to subjects with NSCLC.<sup>60</sup> Nivolumab CL in adjuvant melanoma subjects was approximately 20% lower than steady-state CL in subjects with advanced melanoma.<sup>58</sup> Nivolumab CL was only marginally higher (less than 20%) in subjects with HCC and other tumor types (RCC, CRC,

prostate) than in those with NSCLC.<sup>61</sup> Nivolumab CL was similar for Adj MIUC and Adv UC, and the CL was lower Adj MIUC (14.5%) and Adv UC(8%) than 2L+ NSCLC; however the magnitude of the differences (< 20%) is not considered to be clinically relevant.<sup>62</sup> The differences in CL are not considered to be clinically relevant based on the observed safety and efficacy profiles and flat E-R relationship generated from ER analyses in subjects with different tumor types.

The PK of nivolumab were assessed using a PPK approach when nivolumab and ipilimumab were administered in combination. Coadministration of ipilimumab can potentially increase nivolumab CL by up to 29% compared to nivolumab administered alone, depending on the dose and frequency of ipilimumab coadministration (see [Appendix 2](#) [USPI]). These are unlikely to be clinically relevant given the flat dose-response relationship demonstrated using E-R analyses for efficacy and safety.

Individual nivolumab PPK analyses were conducted for 1L mesothelioma (nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg every 6 weeks [Q6W])<sup>63</sup>, 1L RCC (nivolumab 240 mg Q2W with cabozantinib 40 mg QD)<sup>64</sup>, 1L GC/GEJC (nivolumab 240 mg Q2W or 360 mg Q3W in combination with fluoropyrimidine and platinum-containing chemotherapy)<sup>65</sup> and adjuvant EC/GEJC/EAC (nivolumab 240 mg Q2W or 480 mg Q4W 16 weeks followed by 480 mg Q4W)<sup>66</sup>, 1L NSCLC (nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W)<sup>67</sup>, 1L NSCLC (nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy)<sup>68</sup>, resectable NSCLC (nivolumab 360 mg Q3W + 3 cycles of platinum-doublet chemotherapy)<sup>69</sup>, advanced melanoma (nivolumab 480 mg + relatlimab 160 mg fixed dose combination Q4W)<sup>70</sup>, adjuvant MIUC (nivolumab 240 mg Q2W or 480 mg Q4W)<sup>71</sup>, 1L ESCC (nivolumab 240 mg Q2W + chemotherapy or nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W)<sup>72</sup>, and 1L mCRC (nivolumab 240 mg + ipilimumab 1 mg/kg Q3W for up to 4 doses then nivolumab 240 mg Q2W or 480 mg Q4W)<sup>73</sup>. Nivolumab PK in these analyses were similar and consistent with the known nivolumab PK (see [Appendix 2](#) [USPI]). Co-administration with ipilimumab 1 mg/kg Q6W, chemotherapy, cabozantinib, ipilimumab 1mg/kg Q6W + chemotherapy, or relatlimab had no clinically meaningful impact on nivolumab PK in 1L mesothelioma or 1L ESCC, 1L GC/GEJC or resectable NSCLC or 1L ESCC, 1L RCC, 1L NSCLC, and advanced melanoma subjects, respectively. No covariates were found to have clinically relevant effect on nivolumab PK in these studies.

#### **5.2.1.1 Ethnic Sensitivity Assessments of Nivolumab Pharmacokinetics**

The PK of nivolumab was studied in Japanese subjects with cancer (ONO-4538-01). Dose proportional PK was observed over the dose range of 1 mg/kg to 20 mg/kg, while showing large inter-subject variability in maximum serum concentration (C<sub>max</sub>) in the 20 mg/kg group. Based on the comparison of C<sub>max</sub> and AUC (0-21 d) observed in MDX1106-01 and ONO-4538-01 studies, the PK of nivolumab is similar in US and Japanese subjects.<sup>74</sup>

The PK of nivolumab was evaluated in Chinese subjects with advanced solid tumors in study CA209077 for monotherapy and CA209672 for combination therapy with ipilimumab.<sup>75, 76</sup> The

geometric mean nivolumab C<sub>max</sub> and area-under-the-concentration-time curve over the dosing interval (AUC[TAU]) were similar between Chinese subjects (Study CA209077) and global subjects (Study CA209003<sup>77</sup>). A pooled PPK analysis, using data from 12 studies including two Chinese studies, characterized the PK of nivolumab in Chinese subjects with CRC relative to other Asian and non-Asian subjects, and in Asian subjects with RCC, relative to non-Asian subjects. Nivolumab exposures in Asian and non-Asian subjects with CRC or RCC were similar when nivolumab was administered in combination with ipilimumab (< 20% difference in geometric means).<sup>78</sup>

#### **5.2.1.2 Pharmacokinetics of Nivolumab in Pediatrics**

PPK analyses were conducted to assess nivolumab pharmacokinetics (PK) in pediatric subjects with solid tumors, CNS tumors and hematological malignancies.<sup>79</sup>

The pooled analysis included nivolumab PK data from pediatric (n = 275, age range: 1 to 17 years) and adult clinical trials. The pediatric population consisted of 79 pediatric solid tumor subjects (one subject with melanoma), 46 pediatric lymphoma subjects (31 chronic Hodgkin lymphoma, 6 Hodgkin lymphoma, 9 non-Hodgkin lymphoma) and 150 pediatric CNS tumor (CNST) subjects. Effects of age on nivolumab baseline CL were evaluated using a categorical variable (eg, adults: ≥ 18 years, adolescents: ≥ 12 to < 18 years, and young pediatrics: 1 to < 12 years) and were described separately for each tumor type using adult melanoma subjects as a reference, the adolescents and young pediatrics with solid tumors showed 20% and 44% lower nivolumab baseline CL, respectively, after accounting for the effect of body weight. For subjects with lymphoma, baseline CL values were similar between adolescents and young pediatrics. Therefore, the effects of age were combined for adolescent and young pediatrics. The pediatric lymphoma subjects (1 to < 18 years) had 34% lower baseline CL which was similar to adult lymphoma subjects whose baseline CL was 32% lower than adult melanoma subjects. Similarly, for subjects with CNS tumors, baseline CL values were similar between adolescent and young pediatrics and the effects of age for the two age categories were combined. The pediatric subjects with CNS tumors (1 to < 18 years) showed 55% lower baseline CL. Comparatively, nivolumab baseline CL in adults with glioblastoma (GBM) was 44% lower than adult melanoma. In addition, the effect of age on volume of distribution (V<sub>c</sub>) was evaluated with all tumor types combined, since V<sub>c</sub> is not expected to vary by tumor type. Both adolescents and young pediatrics were found to have 24% lower V<sub>c</sub> than adult subjects. A follow up population PK analysis was conducted to evaluate nivolumab PK in adolescent subjects treated in the adjuvant melanoma. Adolescent subjects treated in the adjuvant melanoma setting had a 19% lower CL than adult melanoma subjects treated in the adjuvant setting and 47% lower CL than adult melanoma subjects.<sup>80</sup>

Similar findings were also seen with the ipilimumab PPK analysis in adults and pediatric subjects with solid tumors.<sup>79</sup> The ipilimumab PPK model was based on 23 pediatric melanoma subjects, 72 pediatric CNST subjects, and 43 pediatric 'other' tumors (including Ewing sarcoma [N=5], neuroblastoma [N=1], osteosarcoma [N=8], renal cell carcinoma [N=2], rhabdomyosarcoma [N=6], solid tumor [N=11] and others [N=10]). Adolescents and young pediatrics (1 to < 12 years) were found to have similar ipilimumab CL values and therefore were described as a combined age



group. Ipilimumab CL was found to be about 29% lower in pediatric (1 to < 18 years) melanoma subjects as compared to adult melanoma subjects when effects of body weight were accounted for; The pediatric (1 to < 18 years) and adult subjects with CNS tumors had similar CL values and were approximately 48-49% lower than adult melanoma subjects. In addition, Vc was about 20% and 26% lower in adolescents and young pediatrics, respectively, as compared to adults.

Model-based simulations were performed to predict nivolumab exposures in adolescents and young pediatrics with solid tumors and in the adjuvant, melanoma setting as monotherapy and in combination with ipilimumab. Simulations were performed across body weight bands for adolescents from 30 kg to  $\geq 110$  kg and for young pediatrics from 10 kg to  $\geq 60$ kg, in 10 kg increments. The simulated geometric mean exposure parameters in adolescents and young pediatrics for each weight band were compared to the adult reference range of geometric means exposures simulated based on adult body weight range of 40 kg to  $\geq 110$  kg.

#### Nivolumab 240 mg Q2W or 480 mg Q4W Dosing Considerations in Adolescent Subjects

Simulation findings in adolescents are described below, followed by findings in young pediatrics 1 to < 12 years old. For nivolumab monotherapy, either de novo or as maintenance following nivolumab and ipilimumab combination, flat dosing regimens (eg, 240 mg Q2W or 480 mg Q4W) for adolescents weighing 40 kg and above (note flat dosing should not be given to subjects < 40 kg), are expected to produce higher nivolumab steady-state C<sub>max</sub>, C<sub>avg</sub> and C<sub>min</sub> values by up to 42%, 33% and 32%, respectively, than those in adults with advanced melanoma receiving the corresponding flat dose. The upper range of these exposure differences is expected in only in adolescents within the lowest body weight band receiving a flat dose (40 to 50 kg). For adolescents treated in the adjuvant melanoma setting, higher nivolumab steady state C<sub>max</sub>, C<sub>avg</sub>, and C<sub>min</sub> were predicted with values up to 25%, 15%, and 15% higher, respectively, than those in adults treated in the adjuvant melanoma setting with either 240 mg Q2W or 480 mg Q4W. Despite higher adolescent exposures compared with adult using the approved adult dosing regimens, a comprehensive exposure-response safety analysis evaluating time to first GR2+IMAE in a pooled adolescent, pediatric and adult dataset, predicted GR2+IMAEs to be lower in adolescent versus adult.<sup>81</sup> This combined with the information that the geometric mean exposures across all body weight bands in adolescents are well below the exposures observed with the clinically tolerated dose of nivolumab 10 mg/kg Q2W in adults, supports the use of adult flat dosing regimens of 240 mg Q2W or 480 mg Q4W in adolescents  $\geq 40$  kg in advanced and adjuvant subjects in melanoma. Body weight-based dosing 3 mg/kg Q2W or 6 mg/kg Q4W is still recommended for low body weight adolescents < 40 kg to avoid further exposure increases. In adolescents receiving a nivolumab flat dosing regimen when used in combination with another therapeutic agent (e.g, relatlimab or bempedaldesleukin), higher nivolumab exposures of similar magnitude to the above-described monotherapy are expected.

#### Nivolumab 3 mg/kg Q2W or 6 mg/kg Q4W Dosing Considerations in Adolescent Subjects

Following nivolumab weight-based dosing regimens, including subjects < 40 kg, with or without a fixed maximum dose corresponding to a body weight cutoff of 80 kg (ie, 3 mg/kg up to 240 mg Q2W or 6 mg/kg up to 480 mg Q4W), nivolumab exposures in adolescents in advanced melanoma

and in the adjuvant melanoma setting are expected to be similar (less than 20% higher) to those in adults receiving a flat dose regimen.

#### Nivolumab in Combination with Ipilimumab Dosing Considerations in Adolescent Subjects

In adolescents receiving nivolumab in combination with ipilimumab (nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W or nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W), nivolumab C<sub>max</sub>, C<sub>avg</sub> and C<sub>min</sub> values following the 4<sup>th</sup> combination dose (C<sub>max4</sub>, C<sub>avg4</sub> and C<sub>min4</sub>) are predicted to be up to 27%, 16% and 20% higher, respectively, than those in adult subjects receiving the same regimen. Ipilimumab C<sub>max4</sub>, C<sub>avg4</sub> and C<sub>min4</sub> values are predicted to be up to 36%, 41% and 63% higher, respectively, compared to adults receiving the same regimen.

In the context of weight-based combination therapy, capping the nivolumab dose to a fixed maximum corresponding to a body weight cutoff of 80 kg (ie, maximum dose of 80 mg for 1 mg/kg regimen or maximum dose of 240 mg for 3 mg/kg regimen) is predicted to result in nivolumab exposure values to be similar (less than 20% higher) to those in adults. Similarly, capping the ipilimumab dose is predicted to result in ipilimumab C<sub>max4</sub> and C<sub>avg4</sub> values that are similar (less than 20% higher) to those in adults. Although ipilimumab C<sub>min4</sub> is predicted to be up to 40% higher compared to that in adults even after dose capping, predictions from exposure-response safety (Gr2+IMAEs) analysis described above indicated probability of GR2+IMAEs were the same with or without a maximum dose cap for the nivolumab 1 mg/kg Q3W+ ipilimumab 3 mg/kg Q3W for 4 doses, followed by nivolumab monotherapy and lower than the GR2+IMAEs for adults using the same regimen.<sup>81</sup>

#### Nivolumab 240 mg Q2W or 480 mg Q4W Dosing Considerations Young Pediatric Subjects (1 to < 12 years)

In young pediatrics 1 to < 12 years old receiving nivolumab monotherapy, either de novo or as maintenance following nivolumab and ipilimumab combination, with a flat dosing regimen (eg, 240 mg Q2W or 480 mg Q4W) for subjects weighing 40 kg and above (note flat dosing should not be given to subjects < 40 kg), nivolumab exposures are expected to be markedly higher (up to 115% higher) than those in adults receiving the same flat dose, due to the greater pediatric effect on nivolumab PK parameters. The upper range of these exposure differences is expected in subjects within the lowest body weight band receiving flat dose (40 to 50 kg).

Nivolumab exposures in young pediatrics 1 to < 12 years old receiving flat dose are predicted to be near or potentially exceed (by approximately 10%) the exposures in adults receiving the 10 mg/kg Q2W dose. As mitigation, weight-based dosing of 3 mg/kg Q2W with a fixed maximum dose corresponding to a body weight cutoff of 80 kg in young pediatrics (weighting 10 kg to ≥ 60 kg) is predicted to result in similar nivolumab steady-state C<sub>max</sub> and C<sub>avg</sub> values (less than 20% higher) and C<sub>min</sub> up to 24% higher, compared to those in adults. The slight increase in nivolumab C<sub>min</sub> is unlikely to be clinically relevant. Weight-based dosing of 6 mg/kg Q4W with a fixed maximum dose in young pediatrics is predicted to result in nivolumab steady-state C<sub>max</sub>, C<sub>avg</sub> and C<sub>min</sub> values up to 10%, 25% and 44% higher, compared to those in adults.

### Nivolumab in combination with Ipilimumab Dosing Considerations in Young Pediatric Subjects (1 to < 12 years)

Following nivolumab in combination with ipilimumab using body weight-based dosing, nivolumab C<sub>max</sub>4, C<sub>avg</sub>4 and C<sub>min</sub>4 values are expected to be up to 27%, 43% and 72% higher, respectively, than those in adults receiving the same body weight-based regimens. Ipilimumab C<sub>max</sub>4 and C<sub>avg</sub>4 are predicted to be similar (less than or equal to 20% higher) to those in adults receiving the same regimen, with C<sub>min</sub>4 up to 26% higher. Capping the nivolumab dose to a fixed maximum dose corresponding to a body weight cutoff of 80 kg is expected to result in nivolumab C<sub>max</sub>4, C<sub>avg</sub>4 and C<sub>min</sub>4 values to be up to 23%, 39% and 66% higher, respectively, than the corresponding adult values. This modest overall effect of dose capping is due to the low likelihood of young pediatrics in this age range to have body weight greater than 80 kg. Similarly, capping the ipilimumab dose results in C<sub>min</sub>4 to be up to 21% higher compared to that in adults. The slight increase in ipilimumab C<sub>min</sub>4 is unlikely to be clinically relevant.

Nivolumab administered using weight-based dosing alone and in combination with ipilimumab (nivolumab 3 mg/kg with ipilimumab 1 mg/kg) demonstrated acceptable safety profiles in pediatric subjects in two clinical studies [CA209070 (1 to 17 years), [Section 5.5.2.4](#); CA209908 ( $\geq 6$  months and < 22 years)]. The safety profile was consistent with that observed in adults and no new safety signals were identified. Limited data with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg is available in pediatric subjects. No clinical data is available with nivolumab flat dosing in pediatric subjects.



**Table 5.2.1.2-1: Simulated nivolumab and ipilimumab exposures in adolescents (≥ 12 to 17 years) and young pediatrics (1 to < 12 years) with solid tumor vs adults with melanoma and adolescent's vs adults in the adjuvant treatment of melanoma**

Regimen	Pediatric Population*	% by which exposure in pediatrics exceeds that in adults**	Considerations
Nivo mono flat dosing (de novo and maintenance)	Adolescents (≥ 40 kg) (≥ 12 to 17 years)	<u>Advanced Melanoma</u> 240 mg Q2W Cmaxss, Cavgss, and Cminss values up to 32%, 27% and 27% higher 480 mg Q4W Cmaxss, Cavgss and Cminss values up to 42%, 33% and 32% higher	Exposures are within the well-tolerated dose of 10 mg/kg Q2W in adults. Exposure-response safety analysis predicted lower GR2+IMAEs in adolescent subjects compared with adult subjects for the flat dosing regimens of 240 mg Q2W or 480 mg Q4W.  No clinical trial data with flat dose in adolescents to date
	Young Pediatrics (≥ 40 kg) (1 to < 12 years)	<u>Adjuvant Treatment of Melanoma</u> 240 mg Q2W Cmaxss, Cavgss, and Cminss values up to 13%, 9.6 % and 9.5% higher 480 mg Q4W Cmaxss, Cavgss and Cminss values up to 25%, 15% and 15% higher	
Nivo mono weight-based dosing (de novo)	Adolescents (≥ 12 to 17 years)	<u>Advanced Melanoma</u> 3 mg/kg Q2W: Cmaxss, Cavgss and Cminss values up to 8%, 3% and 3% higher 6 mg/kg Q4W: Cmaxss, Cavgss and Cminss values up to 15%, 10% and 8% higher <u>Adjuvant Treatment of Melanoma</u> 3 mg/kg Q2W: exposures are within adult range 6 mg/kg Q4W: exposures are within adult range	Exposures are similar to those in adults (within 20%)  3 mg/kg Q2W well-tolerated in CA209070, CA209908 <a href="#">(Section 5.5.2.12)</a>
	Young Pediatrics (1 to < 12 years)	3 mg/kg Q2W: Cmaxss, Cavgss and Cminss values up to 8%, 11% and 19% higher 6 mg/kg Q4W: Cmaxss, Cavgss and Cminss values up to 13%, 29% and 44% higher	

**Table 5.2.1.2-1: Simulated nivolumab and ipilimumab exposures in adolescents (≥ 12 to 17 years) and young pediatrics (1 to < 12 years) with solid tumor vs adults with melanoma and adolescent's vs adults in the adjuvant treatment of melanoma**

Regimen	Pediatric Population*	% by which exposure in pediatrics exceeds that in adults**	Considerations
Nivo mono weight-based dosing up to a maximum dose (de novo)	Adolescents (≥ 12 to 17 years)	3 mg/kg up to 240 mg Q2W: exposures are within adult range 6 mg/kg up to 480 mg Q4W: exposures are within adult range	
	Young Pediatrics (1 to < 12 years)	3 mg/kg up to 240 mg Q2W: C <sub>max</sub> ss, C <sub>avg</sub> ss and C <sub>min</sub> ss values up to 5%, 10% and 19% higher 6 mg/kg up to 480 mg Q4W: C <sub>max</sub> ss, C <sub>avg</sub> ss and C <sub>min</sub> ss values up to 10%, 25% and 39% higher	Exposures after 3 mg/kg are similar to those in adults (within 20%) Exposures after 3 mg/kg Q2W or 6 mg/kg Q4W are within those in adults receiving 10 mg/kg Q2W
Nivo mono weight-based dosing up to a maximum dose (maintenance)	Adolescents (≥ 12 to 17 years)	3 mg/kg up to 240 mg Q2W: exposures are impacted within adult range 6 mg/kg up to 480 mg Q4W: exposures are impacted within adult range	
	Young Pediatrics (1 to < 12 years)	3 mg/kg up to 240 mg Q2W: C <sub>max</sub> ss, C <sub>avg</sub> ss and C <sub>min</sub> ss values up to 10%, 14% and 24% higher 6 mg/kg up to 480 mg Q4W: C <sub>max</sub> ss, C <sub>avg</sub> ss and C <sub>min</sub> ss values up to 8%, 25% and 44% higher	Exposures after 3 mg/kg are similar to those in adults (within 20%) except C <sub>min</sub> (24% higher) Exposures after 3 mg/kg Q2W or 6 mg/kg Q4W are within those in adults receiving adult 10 mg/kg Q2W
Nivo + ipi Q3W weight-based dosing	Adolescents (≥ 12 to 17 years)	Nivo 1 mg/kg Q3W with ipi 3mg/kg: Nivo: C <sub>max</sub> 4, C <sub>avg</sub> 4 and C <sub>min</sub> 4 values up to 27%, 16% and 20% higher Ipi: C <sub>max</sub> 4, C <sub>avg</sub> 4 and C <sub>min</sub> 4 values up to 36%, 39% and 56% higher Nivo 3 mg/kg Q3W with ipi 1mg/kg: Nivo: C <sub>max</sub> 4, C <sub>avg</sub> 4 and C <sub>min</sub> 4 values up to 25%, 17% and 19% higher Ipi: C <sub>max</sub> 4, C <sub>avg</sub> 4 and C <sub>min</sub> 4 values up to 35%, 41% and 63% higher	Overlapping side effect profile Simultaneous increased exposure of both. Exposure-response safety analysis predicted lower GR2+IMAEs in adolescent subjects treated with N1I3 compared with adult subjects. N3I1 is well-tolerated in ADVL1412/CA209070 and CA209908 ( <a href="#">Section 5.5.2.12</a> )
	Young Pediatrics (1 to < 12 years)	Nivo 1 mg/kg Q3W with ipi 3mg/kg: Nivo: C <sub>max</sub> 4, C <sub>avg</sub> 4 and C <sub>min</sub> 4 values up to 27%, 43% and 72% higher Ipi: C <sub>max</sub> 4, C <sub>avg</sub> 4 and C <sub>min</sub> 4 values up to 20%, 15% and 22% higher Nivo 3 mg/kg Q3W with ipi 1mg/kg: Nivo: C <sub>max</sub> 4, C <sub>avg</sub> 4 and C <sub>min</sub> 4 values up to 26%, 38% and 61% higher Ipi: C <sub>max</sub> 4, C <sub>avg</sub> 4 and C <sub>min</sub> 4 values up to 20%, 16% and 26% higher	Overlapping side effect profile Simultaneous increased exposure of both However, N3I1 well-tolerated in ADVL1412/CA209070 and CA209908

**Table 5.2.1.2-1: Simulated nivolumab and ipilimumab exposures in adolescents (≥ 12 to 17 years) and young pediatrics (1 to < 12 years) with solid tumor vs adults with melanoma and adolescent's vs adults in the adjuvant treatment of melanoma**

Regimen	Pediatric Population*	% by which exposure in pediatrics exceeds that in adults**	Considerations
Nivo + ipi Q3W weight-based dosing with a fixed maximum	Adolescents (≥ 12 to 17 years)	<p>Nivo 1 mg/kg up to 80 mg Q3W with ipi 3mg/kg up to 240 mg Q3W:</p> <p>Nivo: C<sub>max</sub>4, C<sub>avg</sub>4 and C<sub>min</sub>4 values up to 11%, 6% and 10% higher</p> <p>Ipi: C<sub>max</sub>4, C<sub>avg</sub>4 and C<sub>min</sub>4 values up to 10%, 16% and 33% higher</p> <p>Nivo 3 mg/kg up to 240 mg Q3W with ipi 1mg/kg up to 80mg Q3W:</p> <p>Nivo: C<sub>max</sub>4, C<sub>avg</sub>4 and C<sub>min</sub>4 values up to 10%, 5% and 8% higher</p> <p>Ipi: C<sub>max</sub>4, C<sub>avg</sub>4 and C<sub>min</sub>4 values up to 10%, 18% and 40% higher</p>	<p>Exposures are similar to adult (within 20%) except for ipilimumab C<sub>min</sub>4</p> <p>Moderate increase in ipilimumab C<sub>min</sub>4 (&lt;40%)</p> <p>Exposure-response safety analysis predicted lower GR2+IMAEs in adolescent subjects treated with N1I3 with a fixed maximum dose compared with adult subjects.</p> <p>However, N3I1 well-tolerated in ADVL1412/CA209070 and CA209908</p>
	Young Pediatrics (1 to < 12 years)	<p>Nivo 1 mg/kg up to 80 mg Q3W with ipi 3mg/kg up to 240 mg Q3W:</p> <p>Nivo: C<sub>max</sub>4, C<sub>avg</sub>4 and C<sub>min</sub>4 values up to 23%, 39% and 66% higher</p> <p>Ipi: C<sub>max</sub>4, C<sub>avg</sub>4 and C<sub>min</sub>4 values up to 15%, 11% and 18% higher</p> <p>Nivo 3 mg/kg up to 240 mg Q3W with ipi 1mg/kg up to 80mg Q3W:</p> <p>Nivo: C<sub>max</sub>4, C<sub>avg</sub>4 and C<sub>min</sub>4 values up to 22%, 34% and 57% higher</p> <p>Ipi: C<sub>max</sub>4, C<sub>avg</sub>4 and C<sub>min</sub>4 values up to 16%, 12% and 21% higher</p>	<p>Cap does not fully mitigate Overlapping side effect profile</p> <p>Simultaneous increased exposure of both</p> <p>However, N3I1 well-tolerated in ADVL1412/CA209070 and CA209908</p>

Abbreviations: C<sub>avg</sub>ss, C<sub>max</sub>ss and C<sub>min</sub>ss: time-averaged concentration, peak concentrations and trough concentrations at steady state, respectively; C<sub>avg</sub>4, C<sub>max</sub>4 and C<sub>min</sub>4: C<sub>avg</sub>, C<sub>max</sub> and C<sub>min</sub> following the 4th combination dose, respectively.

\* Nivolumab and ipilimumab exposures in adolescents were simulated for body weight ranging from 30 kg to ≥ 110 kg in 10 kg increments; exposures in young pediatrics were simulated for body weight ranging from 10 to ≥ 60 kg in 10 kg increments.

\*\* Exposures relative to adult were calculated as a percent difference between the geometric mean for adolescent or young pediatrics for each weight band and the upper or lower bound of adult geometric mean values across all body weights. Adult upper bound was used if adolescent or young pediatrics value was above the adult range; Adult lower bound was used if adolescent or young pediatrics value was below the adult range. Among the simulated adolescent or young pediatrics weight bands, only the highest percent exposure differences (indicated as "up to") were listed.

Nivolumab PK has been characterized in pediatric subjects with lymphoma including cHL, HL and non-hodgkin lymphoma (NHL). Nivolumab monotherapy with a flat dosing regimen (240 mg Q2W or 480 mg Q4W) in pediatric (1 to < 18 years) lymphoma subjects ≥ 40 kg is expected to result in nivolumab exposures similar (within 20%) to those in adults receiving the same regimen except for subjects with body weight between 40 to 50 kg. C<sub>max</sub>ss values in the latter subjects are expected to be up to 33% higher compared to adults. With a body weight-based dosing regimen (3 mg/kg Q2W or 6 mg/kg Q4W), nivolumab exposures in pediatric lymphoma subjects are expected to be similar to adults across the body weight range except for 10 to 20 kg (the lowest

simulated body weight band). In these low body weight subjects, nivolumab C<sub>max</sub>ss, C<sub>min</sub>ss and C<sub>avg</sub>ss following the body weight-based regimen are predicted to be up to 1%, 35% and 21% lower compared to those in adults.

**Table 5.2.1.2-2: Simulated nivolumab exposure in pediatric subjects (1 to < 18 years) with lymphoma vs adult lymphoma subjects\***

Regimen	% by which exposure in pediatrics exceeds that in adults**	Considerations
Nivo mono flat dosing in pediatric subjects $\geq$ 40 kg	240 mg Q2W C <sub>max</sub> ss, C <sub>avg</sub> ss and C <sub>min</sub> ss values up to 25%, 17%, and 14% higher 480 mg Q4W C <sub>max</sub> ss, C <sub>avg</sub> ss and C <sub>min</sub> ss values up to 33%, 18% and 15% higher	Highest exposure differences only expected in 40 to 50 kg subjects Exposures are similar (within 20%) between pediatrics and adults in other weight categories Body weight-based dosing fully mitigates the exposure differences
Nivo weight based dosing	3 mg/kg Q2W: C <sub>max</sub> ss, C <sub>avg</sub> ss and C <sub>min</sub> ss values up to 1%, 18% and 24% lower 6 mg/kg Q4W: C <sub>avg</sub> ss and C <sub>min</sub> ss values up to 21% and 35% lower; C <sub>max</sub> ss expected to be in adult range	Highest exposure difference only expected in 10 to 20 kg subjects Exposures are similar (within 20%) between pediatrics and adults in other weight categories

Abbreviations: C<sub>avg</sub>ss, C<sub>max</sub>ss and C<sub>min</sub>ss: time-averaged concentration, peak concentrations and trough concentrations at steady state, respectively.

\* Nivolumab exposures in pediatrics were simulated for body weight ranging from 10 kg to  $\geq$  110 kg in 10 kg increments.

\*\* Exposures relative to adult were calculated as a percent difference between the geometric mean for pediatrics for each weight band and the upper or lower bound of adult geometric mean values across all body weights. Adult upper bound was used if the pediatric value was above the adult range; Adult lower bound was used if the pediatric value was below the adult range. Among the simulated pediatric weight bands, only the highest percent exposure differences (indicated as "up to") were listed.

### 5.2.1.3 Drug-Drug Interaction Potential with the Treatment of Nivolumab

Although monoclonal antibodies are not direct inhibitors/inducers of metabolizing enzymes, recent literature reports suggest that therapeutic proteins that are modulators of cytokines may indirectly affect expression of CYP enzymes.<sup>82</sup> The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes, at single and multiple-doses of 0.3 to 10 mg/kg Q3W from CA209009 in subjects with RCC.

There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2, and 10 mg/kg) during the course of treatment. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system).<sup>83</sup> These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab.

#### **5.2.1.4 Renal Impairment**

The effect of renal impairment on the CL of nivolumab was evaluated in cancer subjects with mild (glomerular filtration rate [GFR]  $< 90$  and  $\geq 60$  mL/min/1.73 m<sup>2</sup>; n = 1399), moderate (GFR  $< 60$  and  $\geq 30$  mL/min/1.73 m<sup>2</sup>; n = 651), or severe (GFR  $< 30$  and  $\geq 15$  mL/min/1.73 m<sup>2</sup>; n = 6) renal impairment compared to subjects with normal renal function (GFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>; n = 1354) in the PPK analysis.<sup>56</sup> No clinically important differences in the CL of nivolumab were found between subjects with mild or moderate renal impairment and subjects with normal renal function. Data from subjects with severe renal impairment are too limited to draw conclusions on this population.

#### **5.2.1.5 Hepatic Impairment**

The effect of hepatic impairment on the CL of nivolumab was evaluated in subjects with different tumor types (NSCLC, SCLC, melanoma, RCC, SCCHN, UC, GC, and cHL) with mild hepatic impairment (total bilirubin 1.0 to 1.5 times upper limit of normal [ULN] or aspartate aminotransferase (AST)  $> \text{ULN}$  as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 351) and in subjects with moderate hepatic impairment (total bilirubin  $> 1.5$  to 3 times ULN and any AST; n = 10) compared to subjects with normal hepatic function (total bilirubin and AST  $\leq \text{ULN}$ ; n = 3,096).<sup>84</sup> No clinically important differences in the CL of nivolumab were found between subjects with mild or moderate hepatic impairment and normal hepatic function. Similar results were observed in subjects with HCC (mild hepatic impairment: n = 152; moderate hepatic impairment: n = 13).<sup>85</sup> Nivolumab has not been studied in subjects with severe hepatic impairment (total bilirubin  $> 3$  times ULN and any AST).

#### **5.2.1.6 Nivolumab Maintenance Dosing after Nivolumab + Ipilimumab Combination**

For indications where nivolumab + ipilimumab are given for 4 doses Q3W, followed by nivolumab maintenance dosing (240 mg Q2W or 480 mg Q4W), no additional washout period, *ie*, 6 weeks vs standard 3 weeks, is recommended between the last dose of nivolumab + ipilimumab combination and the start of the first nivolumab maintenance dose. The combination regimens include nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses for melanoma and hepatocellular carcinoma and nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses for renal cell carcinoma and MSI-H/dMMR colorectal cancer.

There is no clinically meaningful increase in safety events expected when nivolumab maintenance dosing (240 mg Q2W or 480 mg Q4W) is started 3 weeks vs 6 weeks after nivolumab + ipilimumab combinations. A comprehensive pooled exposure-response safety analysis was conducted evaluating time to first GR2+IMAE (a pharmacological based-safety endpoint) that included pediatric subjects [N=97 ( $< 18$  years); N=42 ( $< 12$  years); N=55 ( $\geq 12$  to  $< 18$  years)] and adult subjects (N=3410) across nivolumab monotherapy (N=2006), ipilimumab monotherapy (N=839) and nivo + ipi combinations (nivolumab 1 mg/kg + ipilimumab 3 mg/kg and nivolumab 3 mg/kg + ipilimumab 1 mg/kg) (N=662).<sup>81</sup> Nivolumab daily C<sub>avg</sub> was not a significant predictor of time to GR2+ IMAEs for monotherapy or when in combination with ipilimumab. Ipilimumab daily

Cavg was a significant predictor of time to GR2+ IMAEs for monotherapy and in combination with nivolumab, however the magnitude of the effect was small.

The model predicted median cumulative probability of GR2+IMAES at week 12 after 4 doses of nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W was 0.526 with a narrow 90% PI of 0.490 to 0.558 across the nivolumab and ipilimumab exposure ranges in the combination regimen.<sup>81</sup> A narrow 90% PI (which was also observed at 2 and 4 weeks after dosing) suggested a relatively flat exposure-response for safety for the combinations. Given lack of nivolumab exposure dependence for both monotherapy and in combination with ipilimumab and the relatively flat ipilimumab E-R for the combination, introducing nivolumab 240 mg Q2W or 480mg Q4W maintenance dosing 3 weeks after the last combination dose is not expected to increase GR2+IMAES.

#### **5.2.1.7 Pharmacokinetic Comparison between [REDACTED] Nivolumab Process D and Nivolumab Process C**

CA2098FC is an ongoing phase 1, randomized, double-blinded study serving to establish a new [REDACTED] long-term manufacture of nivolumab ([REDACTED] referred to in this study as Process D).<sup>86,87</sup> [REDACTED]

[REDACTED] The current nivolumab drug substance manufacturing Process C serves as the global clinical/commercial supply of nivolumab. Process D supplies are expected to be commercially used following depletion of Process C supplies.

[REDACTED]

In addition, the overall safety profile of Process D nivolumab is consistent with the known adverse event profile of nivolumab reported with Process C. The overall nivolumab safety profile between Process C and D is comparable with similar all causality and drug-related AEs (any-grade) between the two processes. No new safety concerns were identified in this study and the overall benefit-risk profile is unchanged. Please refer to [section 5.5.1.3](#) for detailed safety results.

#### **5.2.2 Pharmacokinetics of Nivolumab in Subjects with Sepsis**

A single dose of nivolumab monotherapy (480 mg or 960 mg) in participants with sepsis and low ALC was studied.<sup>88</sup> The mean t<sub>1/2</sub> ranged from 353 to 378 h (14.7 to 15.8 days). C<sub>max</sub> values for



the 480 mg and 960 mg doses were 82 and 196  $\mu\text{g/mL}$ , respectively, and area under the concentration-time curve from time zero extrapolated to infinite time [AUC(INF)] was 18,961 and 36,190  $\mu\text{g} \times \text{h/mL}$ , respectively. Mean terminal CL values for nivolumab 480 mg and 960 mg were 0.025 and 0.027 L/h, respectively; mean Vss values were 10.9 L and 10.4 L, respectively.

### 5.3 Exposure-Response Relationship

Nivolumab E-R relationships for efficacy and safety were evaluated for nivolumab monotherapy and in combination with ipilimumab or other therapeutic agents such as chemotherapy. The dose range of 1 mg/kg Q2W to 10 mg/kg Q2W was evaluated for nivolumab monotherapy in melanoma, RCC, and NSCLC. Generally, a flat E-R relationship was observed over this dose range between nivolumab and clinical endpoints such as the hazard of death, probability of OR, AE-DC/D, and/or Grade 3+ AEs, and a 3 mg/kg Q2W dose regimen was approved for these and additional indications. For NSCLC, there was a trend of additional benefit (especially in ORR) at 3 mg/kg Q2W, when compared to 1 mg/kg Q2W, which had a small sample size. Therefore, a flat E-R relationship could only be confirmed from 3 mg/kg Q2W to 10 mg/kg Q2W for NSCLC. Further E-R analyses demonstrated that the benefit-risk profiles of nivolumab 240 mg Q2W and 480 mg Q4W are comparable to 3 mg/kg Q2W; flat dose nivolumab monotherapy regimens were subsequently approved in some regions for existing and additional indications including melanoma, RCC, NSCLC, SCCHN, CRC, UC, cHL, HCC, ESCC, GC, and adjuvant EC and GEJC. A nivolumab flat dose regimen of 360 mg Q3W was similarly evaluated and approved recently as combination therapy with ipilimumab and platinum-doublet chemotherapy in NSCLC (see 5.3.1 for details).<sup>89</sup>

Exposure-response relationship (E-R) analysis were also conducted for 1L mesothelioma (nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W)<sup>63, 90</sup>, 1L RCC (nivolumab 240 mg Q2W with cabozantinib 40 mg QD)<sup>64, 91</sup>, 1L GC/GEJC (nivolumab 240 mg Q2W or 360 mg Q3W in combination with fluoropyrimidine and platinum-containing chemotherapy)<sup>65, 92</sup>, adjuvant EC/GEJC/EAC (nivolumab 240 mg Q2W or 480 mg Q4W 16 weeks followed by 480 mg Q4W)<sup>68, 93</sup>, 1L NSCLC (nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W)<sup>67, 94</sup> and 1L NSCLC (nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy)<sup>68, 95</sup>, 1L ESCC (nivolumab 240 mg Q2W + chemotherapy or nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W)<sup>96</sup>, adjuvant MIUC (nivolumab 240 mg Q2W or 480 mg Q4W)<sup>97</sup>, and 1L mCRC (nivolumab 240 mg + ipilimumab 1 mg/kg Q3W for up to 4 doses then nivolumab 480 mg Q4W) subjects<sup>98</sup>. The E-R relationship were generally flat within the exposure ranges produced by the studied regimen in each study. In subjects with resectable NSCLC (nivolumab 360 mg Q3W + chemotherapy), higher nivolumab exposure was associated with significantly better efficacy than subjects with lower nivolumab exposures<sup>99</sup>. In addition, in subjects with adjuvant muscle invasive urothelial carcinoma (240 mg Q2W with prior neo-adjuvant cisplatin), higher nivolumab exposure was associated with significantly better efficacy and higher risk of Grade 2+ IMAEs than subjects with lower nivolumab exposures.<sup>100</sup>

### 5.3.1 ***Flat Dose Regimens and Dosing Frequency***

Based on a comprehensive characterization of nivolumab PK, safety, efficacy, and E-R relationships across indications, the benefit-risk profiles of nivolumab 240 mg Q2W and 480 mg Q4W are comparable to 3 mg/kg Q2W as monotherapy.<sup>65, 89, 101, 102</sup> Given that nivolumab has linear PK over a dose range of 0.1 to 10 mg/kg across multiple tumor types, the 240 mg Q2W regimen was selected based on the approximate median bodyweight of 80 kg for subjects treated in nivolumab clinical trials. The 480 mg Q4W regimen was also selected based on nivolumab's dose proportional PK and because it translates to the same dose intensity of the 240 mg flat dose given Q2W while offering more convenience to subjects due to reduced hospital visits.

Using a previously developed PPK model, the geometric means of key summary measures of exposure achieved with nivolumab 240 mg Q2W including peak (C<sub>max</sub>), time-averaged (C<sub>avg</sub>) and trough (C<sub>min</sub>) concentrations after the first dose or at steady-state were similar (<6% difference) to the corresponding exposures achieved with nivolumab 3 mg/kg Q2W. The magnitude of the difference is not expected to be clinically significant. In comparing nivolumab 480 mg Q4W to 3 mg/kg Q2W, the geometric mean time-averaged concentration over the first 28 days (C<sub>avgd28</sub>) was approximately 27% higher with 480 mg Q4W, whereas the geometric mean steady-state time-averaged concentration (C<sub>avgss</sub>) for both dosing regimens was similar. Nivolumab geometric mean trough concentrations at Day 28 (C<sub>mind28</sub>) and at steady state (C<sub>minss</sub>) were 22% and 16% lower, respectively, with 480 mg Q4W dosing. Conversely, geometric mean peak nivolumab concentrations after the first dose (C<sub>max1</sub>) and at steady state (C<sub>maxss</sub>) were 111% and 43.4% higher, respectively, with 480 mg Q4W dosing.

Extensive E-R analyses were conducted for OS, OR, and tumor growth dynamics to bridge efficacy of nivolumab 240 mg Q2W and 480 mg Q4W to the clinically evaluated 3 mg/kg Q2W dosing regimen. The hazard ratios with nivolumab 240 mg Q2W or 480 mg Q4W were predicted to be similar to 3 mg/kg Q2W across multiple tumor types (melanoma, RCC, squamous [SQ] and non-squamous [NSQ] NSCLC). There were no differences in predicted response rates with nivolumab 240 mg Q2W or 480 mg Q4W compared to 3 mg/kg Q2W.<sup>89</sup>

To evaluate safety, the exposure margin of nivolumab 240 mg Q2W and 480 mg Q4W relative to the safe and well-tolerated dose of 10 mg/kg Q2W was determined. In addition, extensive E-R analyses for AE-DC/D, AE-Grade 3+, and Grade 2+ immune mediated adverse event (IMAE Grade 2+) were conducted with pooled safety data across multiple tumor types (melanoma, RCC, SQ NSCLC, NSQ NSCLC, SCCHN, cHL, UC, ESCC, GC, and adjuvant EC and GEJC). Exposure margins with 240 mg Q2W or 480 mg Q4W were below that achieved with nivolumab 10 mg/kg Q2W indicating that these dosing regimens are expected to be safe and tolerable. In addition, the risk of AE-DC/D, AE-Grade 3+, and IMAE Grade 2+ showed a flat exposure-response relationship for C<sub>avgd28</sub> or C<sub>max1</sub> in the E-R analyses.

Clinical safety data across multiple studies and tumors (CA209511 [Part 2], CA209384, CA209017, CA209025, CA209057, CA209066, CA209743, CA2099ER, CA209649, and CA209577) support the modeling above<sup>63, 64, 65, 66, 102, 103, 104, 105, 106, 107</sup>. In addition, these studies suggest that there are no substantive differences in the safety profiles of nivolumab 3 mg/kg



or 240 mg Q2W compared with 480 mg Q4W in terms of Grade 3/4 AEs, serious adverse events (SAEs), AEs leading to discontinuation, and IMAEs. No new safety concerns were identified. These data show that the safety profiles of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W were similar, despite the increase in the maximum concentration (C<sub>max</sub>) with 480 mg Q4W.

The clinical data from study CA209907 in which nivolumab 480 mg Q4W was given de novo to subjects with NSCLC were used to externally validate the previous PPK and E-R analysis. This analysis demonstrated that the observed exposures and efficacy (OS and ORR) were consistent with the model predictions from both the previous models and the re-estimated models, thereby confirming the original simulation analysis.<sup>108</sup>

Nivolumab 360 mg Q3W is also under evaluation as monotherapy and in combination therapy studies across a number of tumor types. The C<sub>avgss</sub> following nivolumab 360 mg Q3W is predicted to be similar to that following 3 mg/kg Q2W or 240 mg Q2W dosing, while C<sub>minss</sub> is predicted to be approximately 6% lower and is not considered clinically relevant. Following nivolumab 360 mg Q3W, C<sub>maxss</sub> is predicted to be approximately 23% higher relative to that following nivolumab 3 mg/kg Q2W; however, the range of exposures across body weights (35 to 160 kg) is predicted to be well below corresponding exposures observed at the well-tolerated dosing regimen of 10 mg/kg Q2W.<sup>68</sup>

Based on E-R modeling and simulation results as well as the totality of data from nivolumab studies, the less frequent dosing schedules: nivolumab 360 mg Q3W plus ipilimumab 1 mg/kg Q6W and 480 mg Q4W plus cabozantinib 40 mg QD were approved as 1L treatment option for subjects with mesothelioma<sup>90</sup> and RCC<sup>91</sup>, respectively. Additionally, comparable benefit-risk profiles were also demonstrated for nivolumab 240 mg Q2W + chemotherapy (fluoropyrimidine- or platinum-containing) and nivolumab 360 mg Q3W + chemotherapy (fluoropyrimidine- or platinum-containing) for subjects with 1L GC/GEJC<sup>92</sup>.

### 5.3.2 Infusion Duration

Administration of nivolumab using a 30-minute or 60-minute infusion time has been evaluated in subjects with cancer. Previous clinical studies of nivolumab monotherapy for the treatment of cancer have used a 60-minute infusion duration wherein nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across the nivolumab clinical program. In CA209010, a dose association was observed for drug-related events: infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 20.4% at 10 mg/kg). All the events were Grade 1-2 and were manageable.<sup>109</sup> An infusion duration of 30 minutes for nivolumab 3 mg/kg (30% of the dose provided at 10 mg/kg), 240 mg, or 480 mg was shown to not present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. The safety of nivolumab 3 mg/kg administered as a 30-min infusion was assessed in CA209153 in subjects (n = 322) with previously treated advanced NSCLC (see [Section 5.5.1.4](#)). Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in subjects with cancer administered nivolumab over a 30 min infusion compared with that reported for subjects

with the 60 min infusion. Thus, it was shown in study CA209153 that nivolumab can be safely infused over 30 min in subjects with cancer.

### **5.3.3 E-R Analysis in Support of Adolescent Dosing Regimen**

E-R analysis of safety was performed to support the dosing regimen recommendations for adolescent patients ( $\geq 12$  to  $< 18$  years) for nivolumab +/- ipilimumab in advanced melanoma and nivolumab monotherapy in the adjuvant treatment of melanoma.<sup>81</sup>

The E-R model for Gr2+ IMAEs adequately characterized the cumulative probability of the time to first occurrence of a Gr2+ IMAE in adults with melanoma treated in the advanced and adjuvant setting and adolescents with solid tumors, including melanoma.

The risk of Gr2+ IMAEs was not significantly associated with nivolumab exposure (daily Cavg) but was significantly associated with ipilimumab exposure (daily Cavg) and interaction between nivolumab and ipilimumab exposure. However, the magnitude of the ipilimumab exposure-response and interaction of ipilimumab and nivolumab exposure on the risk of Gr2+ IMAEs for the N1I3 Q3W combination is predicted to be minimal; The range of predicted Gr2+ IMAEs is narrow at Week 12 with a median (P05, P95) of 0.526 (0.490, 0.558) across the range of nivolumab and ipilimumab daily Cavg for this combination regimen.

The E-R model predicted Gr2+ IMAEs of potential dosing regimens in adolescents with advanced melanoma:

- Nivolumab monotherapy: Model predicted Gr2+ IMAEs for adolescents receiving nivolumab 3 mg/kg Q2W ( $< 40$  kg), 240 mg ( $\geq 40$  kg) Q2W or nivolumab 3 mg/kg Q2W with and without a dose cap are similar and lower than that for adults using the approved 240 mg Q2W dosing regimen. Similarly, model predicted Gr2+ IMAEs for adolescents receiving nivolumab 6 mg/kg Q4W ( $< 40$  kg), 480 mg ( $\geq 40$  kg) Q4W or nivolumab 6 mg/kg Q4W with and without a dose cap are similar and lower than that for adults using the approved 480 mg Q4W dosing regimen.
- Nivolumab + ipilimumab combination: Model-predicted Gr2+ IMAEs for adolescents receiving N1I3 combination therapy followed by either nivolumab Q2W or Q4W maintenance with or without dose cap are similar and lower than that for adults using the approved N1I3 dosing regimen followed by nivolumab maintenance.

The E-R model predicted Gr2+ IMAEs of potential dosing regimens in adolescents with adjuvant treatment of melanoma:

- Nivolumab monotherapy: Model-predicted Gr2+ IMAEs for adolescents receiving nivolumab 3 mg/kg Q2W ( $< 40$  kg), 240 mg ( $\geq 40$  kg) Q2W or nivolumab 3 mg/kg Q2W with and without a dose cap are similar and lower than that for adults using the approved 240 mg Q2W dosing regimen. Similarly, model predicted Gr2+ IMAEs for adolescents receiving nivolumab 6 mg/kg Q4W ( $< 40$  kg), 480 mg ( $\geq 40$  kg) Q4W or nivolumab 6 mg/kg Q4W with and without a dose cap are similar and lower than that for adults using the approved 480 mg Q4W dosing regimen.

## 5.4 Clinical Efficacy

Nivolumab has demonstrated clinical activity in subjects with a variety of malignancies as described in the USPI ([Appendix 2](#)) and EU SmPC ([Appendix 3](#)). Refer to [Table 5-1](#) for the complete list of approved indication of nivolumab in the USPI and EU SmPC. In addition to studies presented in the approved labels, results of other clinical studies of nivolumab alone and in combination are summarized with available data for the indications listed below.

### **NSCLC (Section 5.4.1)**

- CA209026: completed Phase 3 study of nivolumab in subjects with Stage IV or recurrent PD-L1+ NSCLC
- CA209012: completed Phase 1 study with nivolumab in combination with ipilimumab, platinum-based chemotherapy or erlotinib in subjects with treatment-naïve Stage IIIB/IV NSCLC
- CA209384: completed Phase 3b/4 study of nivolumab monotherapy in subjects with advanced/metastatic (Stage IIIB/IV) NSCLC (non-squamous and squamous)
- CA209907: completed Phase 2, open-label, single-arm safety study of nivolumab in participants with advanced or metastatic NSCLC who have progressed during or after receiving at least one prior systemic regimen
- ONO-4538-04: completed Phase 1, open-label study of nivolumab in combination with chemotherapy in Japanese subjects with Stage IIIB/IV or recurrent NSCLC
- CA209592: completed two-part, open-label, exploratory Phase 2 trial of nivolumab in combination with ipilimumab in subjects with no prior systemic anticancer therapy, given as primary therapy for advanced or metastatic NSCLC
- CA209568: completed two-part, Phase 2 study to evaluate the efficacy and safety of nivolumab plus ipilimumab and nivolumab plus ipilimumab in combination with chemotherapy in adult subjects with stage IV NSCLC who had received no prior systemic therapy for advanced disease
- CA20977T: ongoing Phase 3, randomized, double-blind study of neoadjuvant chemotherapy plus nivolumab versus neoadjuvant chemotherapy plus placebo, followed by surgical resection and adjuvant Treatment with nivolumab or placebo for participants with resectable stage II-IIIB non-small cell lung cancer

### **Melanoma (Section 5.4.2)**

- CA209915: completed, Phase 3 randomized, double-blind study of nivolumab plus ipilimumab vs nivolumab monotherapy in adult and pediatric subjects with completely resected stage IIIB/c/d or stage IV no evidence of disease (NED) melanoma
- ONO-4538-31: completed Phase II Study: A multicenter, randomized, open-label study in patients with advanced malignant melanoma
- CA209204: completed multi-center phase 2 open-label study to evaluate safety and efficacy in subjects with melanoma metastatic to the brain treated with nivolumab in combination with ipilimumab followed by nivolumab monotherapy

- CA20976K: ongoing Phase 3, randomized, double-blind study to evaluate the use of adjuvant immunotherapy with nivolumab versus placebo after complete resection of Stage IIB/C melanoma in adults and adolescent subjects 12 years old

#### **RCC (Section 5.4.3)**

- CA209016: completed, Phase 1, dose-escalation study of nivolumab in combination with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitors (TKIs) or ipilimumab in subjects with metastatic RCC
- CA209914: ongoing, Phase 3, double-blind, randomized trial of adjuvant nivolumab plus ipilimumab combination therapy (hereafter referred to as nivo + ipi) versus placebo infusions (Part A) and adjuvant nivolumab monotherapy (hereafter referred to as nivo) versus placebo infusions (Part B) in subjects with early-stage localized renal cell carcinoma (RCC) with a predominantly clear cell histology who underwent radical or partial nephrectomy

#### **cHL (Section 5.4.4)**

- CA209205: completed, Phase 2, non-comparative, parallel-cohort, single-arm study in subjects with cHL
- CA209744: ongoing, Phase 2, open-label study of nivolumab + BV, followed by BV + bendamustine for suboptimal response, in children, adolescents, and young adults with low or standard risk relapsed/refractory cHL
- CA209812: completed randomized, open-label, phase 3 trial of nivolumab plus BV versus BV alone in participants with relapsed refractory or ineligible for autologous stem cell transplant (ASCT) advanced stage cHL

#### **SCCHN (Section 5.4.5)**

- CA209714: completed, Phase 2, double-blind, randomized, two-arm study of nivolumab in combination with ipilimumab versus nivolumab in combination with placebo in recurrent or metastatic SCCHN
- CA209651: completed open label, randomized, two arm phase 3 study of nivolumab in combination with ipilimumab versus EXTREME study regimen (cetuximab + cisplatin/carboplatin + fluorouracil) as first line therapy in recurrent or metastatic SCCHN

#### **UC (Section 5.4.6)**

- CA209032: ongoing, Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab at different dose levels in subjects with several types of advanced or metastatic solid tumors, including UC
- CA209901: ongoing Phase 3, open-label, randomized study of nivolumab combined with ipilimumab, or with SOC chemotherapy, versus SOC chemotherapy in subjects with previously untreated unresectable or metastatic urothelial cancer (UC)

#### **SCLC (Section 5.4.7)**

- CA209032: ongoing Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors, including SCLC

- CA209331: completed, Phase 3, open-label study of nivolumab monotherapy in subjects with relapsed SCLC who had been treated with first-line, platinum-based chemotherapy
- CA209451: completed Phase 3, randomized, multicenter, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab as maintenance therapy in subjects with extensive-stage disease SCLC (ED-SCLC) after completion of platinum-based first-line chemotherapy

#### **Gastric and Esophageal Cancer (Section 5.4.8)**

- CA209032: ongoing Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors, including GC

#### **Hepatocellular Carcinoma (Section 5.4.9)**

- CA209459: completed open-label, randomized, Phase 3 study comparing nivolumab monotherapy with sorafenib as first-line therapy in adult (> 18 years) male and female subjects with advanced HCC

#### **Colorectal Cancer (Section 5.4.10)**

- CA209142: ongoing Phase 2 open-label, multi-center, multi-cohort trial of nivolumab, or nivolumab combinations, in MSI-H and non-MSI-H recurrent and metastatic CRC
- CA2098HW: ongoing Phase 3, randomized, 3-arm open-label study of nivolumab monotherapy (nivo: Arm A), nivolumab plus ipilimumab combination therapy (nivo+ipi: Arm B) or investigator's choice chemotherapy (chemo: Arm C) for the treatment of subjects with microsatellite instability high (MSI-H)/ deficient mismatch repair (dMMR) metastatic colorectal cancer (mCRC)

#### **Glioblastoma (Section 5.4.11)**

- CA209143: ongoing Phase 3, randomized, open-label study of nivolumab versus BEV(Bevacizumab) and a safety study of nivolumab or nivolumab in combination with ipilimumab in adult subjects with recurrent glioblastoma multiforme
- CA209498: completed Phase 3, open-label study of nivolumab vs temozolomide (TMZ), each in combination with radiation therapy (RT) in newly diagnosed adult subjects with unmethylated O-6-methylguanine DNA methyltransferase (MGMT) GBM
- ONO-4538-19: completed Phase II Study: A Multicenter Open-Label, Non-Comparative Study of ONO-4538 in Patients with First Recurrence of Glioblastoma

#### **Combined Malignant Tumors (Section 5.4.12)**

- ONO-4538-01: completed Phase 1, dose-escalation study of nivolumab monotherapy in subjects with advanced or recurrent malignant tumors
- ONO-4538-39: completed Phase 2, open label non-controlled study in patients with uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma

- CA209627: completed, open-label, multicenter, Phase 2 study, was designed to evaluate the efficacy and safety of nivolumab 240 mg Q2W for 8 doses followed by nivolumab 480 mg Q4W in multiple established and emerging cancer types

#### **Pancreatic Cancer(Section 5.4.14)**

- CA209032: ongoing, Phase 1/2, open-label study of nivolumab monotherapy, nivolumab combined with ipilimumab, or nivolumab with ipilimumab and cobimetinib in subjects with several types of advanced or metastatic solid tumors, including Pancreatic Cancer

#### **Primary Central Nervous System Lymphoma (Section 5.4.15)**

- CA209647: completed, Phase 2 study of nivolumab monotherapy in subjects with relapsed/refractory primary central nervous system lymphoma (PCNSL) or primary testicular lymphoma (PTL) who progressed after or did not respond to at least 1 line of systemic therapy

#### **Prostate Cancer (Section 5.4.16)**

- CA209650: ongoing, Phase 2, open-label study of same-day sequential dosing of nivolumab followed by ipilimumab, in subjects with metastatic castration-resistant prostate cancer (mCRPC)
- CA2099KD: ongoing, Phase 2 trial of nivolumab combined with rucaparib, docetaxel, or enzalutamide in men with mCRPC.

#### **Non-Hodgkin Lymphoma (NHL) (Section 5.4.17)**

- CA209436: completed, Phase 1/2 study to evaluate the safety and preliminary efficacy of nivolumab in combination with BV in subjects with relapsed/refractory Non-Hodgkin Lymphomas

#### **Hematologic Malignancies (Section 5.4.18)**

- CA209039: ongoing, multiple Phase 1/2 cohorts of nivolumab monotherapy or nivolumab combination regimens across relapsed/refractory hematologic malignancies
- CA209602: completed phase 3 multicenter, randomized, open label study to evaluate the clinical benefit and safety of the combination therapy of nivolumab, pomalidomide, and dexamethasone, when compared to pomalidomide and dexamethasone in subjects with Relapsed and/or Refractory Multiple Myeloma (RRMM)

#### **CNS Malignancies (Section 5.4.18.2)**

- CA209908: completed open-label, sequential-arm, Phase 1b/2 clinical study of nivolumab monotherapy and nivolumab + ipilimumab in pediatric subjects with high-grade primary central nervous system (CNS) malignancies

#### **Ovarian Cancer (Section 5.4.20)**

- CA209032: ongoing signal-detection Phase 1/2 open-label study to evaluate the efficacy and safety of nivolumab as a single agent or in combination with ipilimumab for treatment of advanced or metastatic cancer of the 6 tumor types, including ovarian cancer (OC)
- ONO-4538-23: completed Phase III Study: A Multicenter, Randomized, Open-Label Study in Ovarian Cancer Patients



### **Breast Cancer ([Section 5.4.21](#))**

- CA209032: ongoing signal-detection Phase 1/2 open-label study to evaluate the efficacy and safety of nivolumab as a single agent or in combination with ipilimumab for treatment of advanced or metastatic cancer of the 6 tumor types, including Triple Negative Breast Cancer (TNBC)
- CA2097FL: ongoing Phase 3, randomized, global study assessing the efficacy and safety of nivolumab vs nivolumab placebo combined with standard neoadjuvant anthracycline-taxane-based chemotherapy, followed by nivolumab or nivolumab placebo combined with ET as adjuvant treatment, in subjects with high-risk, ER+, HER2- primary BC

### **Solid Tumors ([Section 5.4.22](#))**

- CA209358: ongoing Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab or relatlimab or daratumumab in subjects with virus-positive and virus-negative solid tumors
- CA209848: ongoing randomized, open-label, phase 2 study of nivolumab in combination with ipilimumab or nivolumab monotherapy in participants with advanced or metastatic solid tumors of high tumor mutational burden (TMB-H)
- CA209672: ongoing open-label trial of nivolumab in combination with ipilimumab in adult Chinese subjects with histologically confirmed recurrent or metastatic MSI-H/dMMR CRC, who had shown progression during, after, or have been intolerant to  $\geq 1$  line treatment(s) for metastatic disease (included at least a fluoropyrimidine, and oxaliplatin or irinotecan), and who complied to provide tumor tissue (archival or fresh biopsy specimen)

#### **5.4.1 Clinical Activity in Subjects with NSCLC**

Nivolumab monotherapy has demonstrated clinical benefit as second-line therapy in subjects with metastatic squamous and non-squamous NSCLC and has been approved for use in these populations in the US, EU, and additional regions (see [Appendix 2 \[USPI\]](#) and [Appendix 3 \[EU SmPC\]](#) for efficacy information). Nivolumab and ipilimumab combination therapy demonstrated clinical benefit in subjects with metastatic NSCLC with  $\geq 1\%$  PD-L1+ tumor expression as first-line treatment and has been approved for use in this population in the US (see [Appendix 2 \[USPI\]](#)). Additionally, nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy demonstrated clinical benefit as first-line treatment in subjects with metastatic NSCLC and has been approved for use in this population in the US and Singapore (see [Appendix 2 \[USPI\]](#)). Nivolumab in combination with carboplatin, paclitaxel, and bevacizumab also demonstrated clinical benefit as first-line therapy in subjects with metastatic non squamous NSCLC (ONO-4538-52, described in the Japanese Package Insert [JPI]). Available data for the clinical activity of nivolumab monotherapy as a first- or second-line therapy for NSCLC, for

nivolumab combination therapy in subjects with NSCLC, and for nivolumab in Japanese subjects with NSCLC are presented in the following sections.

#### **5.4.1.1 Nivolumab Monotherapy as First-line Therapy in Subjects with PD-L1+ NSCLC - CA209026**

In CA209026, an open-label, randomized, Phase 3 study of nivolumab vs investigator's choice chemotherapy (ICC) as first-line therapy for Stage IV or recurrent PD-L1+ NSCLC, nivolumab monotherapy did not demonstrate superior progression free survival (PFS) per Independent Radiologic Review Committee (IRRC) compared to the ICC (platinum-doublet chemotherapy) in subjects with  $\geq 5\%$  PD-L1+ tumor expression.<sup>110</sup>

There were 530 treated subjects (267 with nivolumab, 263 with ICC). Nivolumab was administered at 3 mg/kg Q2W by IV infusion over 60 minutes. PFS per IRRC in the all-randomized population was similar to the population with  $\geq 5\%$  PD-L1+ tumor expression. However, nivolumab monotherapy appears to have clinical activity as first-line treatment in these populations, as evidenced by similar OS with the ICC group, despite the fact that 60% of subjects in the ICC group received subsequent nivolumab. The ORR of 26% in the nivolumab group, although numerically lower than the ORR of 33.5% in the ICC group, is associated with a longer duration of response and also represents evidence of clinical activity for nivolumab monotherapy in this setting.

#### **5.4.1.2 Nivolumab Monotherapy or in Combination with Ipilimumab, Chemotherapy, or Erlotinib in Subjects with NSCLC - CA209012**

CA209012 was a Phase 1, multiple-cohort study of nivolumab as monotherapy, in combination with ipilimumab, or in combination with chemotherapy or targeted therapy, in chemotherapy-naïve adult ( $\geq 18$  years) subjects with Stage IIIB/IV NSCLC or recurrent disease.



There were 56 subjects were administered nivolumab in combination with chemotherapy (gemcitabine [GEM]/cisplatin, pemetrexed/cisplatin, carboplatin [CAR]/paclitaxel), 21 with nivolumab in combination with erlotinib, and 197 with nivolumab in combination with ipilimumab. The maximum evaluated dose was 10 mg/kg of nivolumab in combination with chemotherapy.

A summary of ORR and progression-free survival rate (PFSR) at 24 weeks for subjects treated with nivolumab + chemotherapy (N = 56, minimum follow-up 45.5 months), and nivolumab + erlotinib (N = 21, median follow-up 71.9 weeks) in CA209012 is provided in Table 5.4.1.2-1. Among responders, the median duration of responses across the nivolumab + chemotherapy groups were 10.35 months, while the median duration of response for nivolumab + erlotinib was not reached at the time of analysis. Among the erlotinib subjects, 20 of the 21 subjects had previously received an epidermal growth factor receptor (EGFR) TKI for NSCLC. All had sensitizing EGFR mutations.

**Table 5.4.1.2-1: Efficacy in Chemotherapy-naïve NSCLC Subjects Treated with Nivolumab in Combination with Chemotherapy or Erlotinib - CA209012**

Treatment Group	N	Nivo mg/kg	ORR <sup>a</sup>		PFSR at 24 weeks <sup>a</sup>		Median OS	
			n (%)	95% CI <sup>b</sup>	%	95% CI <sup>c</sup>	Months	95% CI <sup>c</sup>
Nivo + ERL	21 <sup>d</sup>	3	4 (19)	5, 42	51	28, 70	19.3	15.6, NR
Nivo + Chemotherapy								
Nivo + GEM/CIS	12	10	5 (42)	15, 72	51	19, 76	11.6	7.9, 25.2
Nivo + PEM/CIS	15	10	7 (47)	21, 73	68	36, 87	19.2	12.3, 33.2
Nivo + PAC/CAR	15	10	7 (47)	21, 73	34	11, 59	14.9	6.2, 20.6
Nivo + PAC/CAR	14	5	7 (50)	23, 77	59	28, 81	33.7	19.4, 47.5

Source: CA209012 Clinical Study Report (CSR) <sup>111</sup>, database lock date 19-Sep-2016 (Nivo+Chemotherapy); Preliminary data for CA209012, database lock date 28-Mar-2014 (Nivo+ERL)

<sup>a</sup> CR + PR; assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 by the investigator

<sup>b</sup> Based on Clopper-Pearson method

<sup>c</sup> Based on Kaplan-Meier method

<sup>d</sup> 20 subjects progressed on TKIs and 1 subject was TKI-naïve

Abbreviations: CAR = carboplatin; CI = confidence interval; CIS = cisplatin; ERL = erlotinib; GEM = gemcitabine; Nivo = nivolumab; NR = not reached; PAC = paclitaxel; PEM = pemetrexed; PFSR = progression-free survival rate

Nivolumab in combination with ipilimumab was active regardless of treatment schedule. Clinically meaningful response rates were observed with schedules using the approved dose of nivolumab (3 mg/kg) with lower and less frequent dosing of ipilimumab (1 mg/kg Q6W or Q12W) [Table 5.4.1.2-2](#).

Numerical differences in ORR between cohorts P and Q are likely not due to differences in efficacy. Although there were no obvious imbalances in demographic or baseline characteristics between the cohorts outside of fewer males and fewer never smokers in cohort P, the sample sizes were small and there was a higher proportion of subjects with rapidly progressive disease in cohort Q versus P, with the excess of rapid progressions occurring too early to be attributed to differences between the two dosing schedules.

The magnitude of benefit from nivolumab in combination with ipilimumab increased with increasing PD-L1 expression for all efficacy endpoints.

**Table 5.4.1.2-2: Summary of Key Efficacy Results- All Treated Subjects in Nivolumab + Ipilimumab -CA209012**

	Pooled Cohorts	Pooled Cohorts					IRRC-Assessed Efficacy	
	GH <sup>a</sup> N = 24	IJ <sup>b</sup> N = 25	Cohort N <sup>c</sup> N = 31	Cohort O <sup>d</sup> N = 40	Cohort P <sup>e</sup> N = 38	Cohort Q <sup>f</sup> N = 39	Cohort P <sup>e</sup> N = 38	Cohort Q <sup>f</sup> N = 39
<b>EFFICACY<sup>g</sup></b>								
<b>Best Overall Response, n (%)</b>								
CR	2 ( 8.3) <sup>h</sup>	1 ( 4.0)	0	0	4 (10.5) <sup>i</sup>	2 ( 5.1) <sup>i</sup>	2 ( 5.3)	1 ( 2.6)
PR	3 (12.5)	5 (20.0)	7 (22.6)	13 (32.5)	14 (36.8)	13 (33.3)	17 (44.7)	13 (33.3)
SD	8 (33.3)	11 (44.0)	12 (38.7)	13 (32.5)	12 (31.6)	7 (17.9)	9 (23.7)	8 (20.5)
PD	8 (33.3)	7 (28.0)	12 (38.7)	12 (30.0)	7 (18.4)	11 (28.2)	9 (23.7)	11 (28.2)
Not evaluable	3 (12.5)	1 ( 4.0)	0	2 ( 5.0)	1 ( 2.6)	6 (15.4)	1 ( 2.6)	6 (15.4)
<b>Objective Response Rate</b>								
% (95% CI)	20.8 (7.1, 42.2)	24.0 (9.4, 45.1)	22.6 (9.6, 41.1)	32.5 (18.6, 49.1)	47.4 (31.0, 64.2)	38.5 (23.4, 55.4)	50.0 (33.4, 66.6)	35.9 (21.2, 52.8)
<b>Duration of Response</b>								
Median (95% CI), months	NR (6.9, N.A.)	NR (4.83, N.A.)	NR (27.53, N.A.)	NR (2.79, N.A.)	NR (11.33, N.A.)	NR (11.17, N.A.)	NR (8.34, N.A.)	19.55 (7.75, N.A.)

**Table 5.4.1.2-2: Summary of Key Efficacy Results- All Treated Subjects in Nivolumab + Ipilimumab -CA209012**

	Pooled Cohorts	Pooled Cohorts					IRRC-Assessed Efficacy	
	GH <sup>a</sup>	IJ <sup>b</sup>	Cohort N <sup>c</sup>	Cohort O <sup>d</sup>	Cohort P <sup>e</sup>	Cohort Q <sup>f</sup>	Cohort P <sup>e</sup>	Cohort Q <sup>f</sup>
	N = 24	N = 25	N = 31	N = 40	N = 38	N = 39	N = 38	N = 39
<b>Progression-free Survival</b>								
Median (95% CI), months	3.78 (1.97, 7.98)	3.55 (2.17, 6.80)	5.16 (2.07, 12.09)	5.09 (2.73, 9.69)	8.11 (5.55, 16.69)	3.94 (2.56, 13.37)	12.78 (6.44, N.A.)	3.68 (2.60, 9.00)
<b>Overall Survival</b>								
Median (95% CI), months	19.78 (10.94, N.A.)	11.01 (3.98, 37.75)	NR (11.50, N.A.)	17.68 (11.04, N.A.)	NR (14.42, N.A.)	18.46 (13.31, N.A.)	-	-

Source: CA209012 CSR database lock date 19-Sep-2016 (Nivo+Ipi)<sup>112</sup>

Percentages based on subjects treated.

<sup>a</sup> Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W; <sup>b</sup> Nivo 3 mg/kg + Ipi 1 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W; <sup>c</sup> Nivo 1 mg/kg + Ipi 1 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W; <sup>d</sup> Nivo 1 mg/kg Q2W + Ipi 1 mg/kg Q6W; <sup>e</sup> Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q12W; <sup>f</sup> Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W <sup>g</sup> Investigator-assessed efficacy unless otherwise noted. <sup>h</sup> One of these subjects developed radiographic PR and later had excisional biopsy of radiographic residue lesion. Pathological evaluation showed no viable tumor and pathological CR was determined by investigator. The other subject in cohort GH with a CR was radiographically determined and confirmed (per RECIST v1.1 criteria).

Subjects receiving nivolumab monotherapy were enrolled in 4 cohorts.

- Cohort F: 52 chemotherapy-naïve subjects with any histology received nivolumab 3 mg/kg Q2W as a 60-minute IV infusion.
- Cohorts K and L: 13 subjects with squamous (SQ) (cohort K) or 13 subjects with NSQ (cohort L) histology who completed ≥ 4 cycles of platinum-based doublet chemotherapy and were non-progressors received nivolumab 3 mg/kg Q2W (60-minute IV infusion) as switch maintenance therapy.
- Cohort M: 12 subjects with any histology with untreated, asymptomatic brain metastases (BM; ≤ 3 cm and without evidence of cerebral edema) received nivolumab 3 mg/kg Q2W as a 60-minute IV infusion.

The summary of efficacy in subjects treated with nivolumab monotherapy is provided in [Table 5.4.1.2-3](#).

**Table 5.4.1.2-3: Summary of Key Efficacy Results- All Treated Subjects in Nivolumab Monotherapy-CA209012**

	<b>Cohort F N = 52</b>	<b>Cohort K N = 13</b>	<b>Cohort L N = 13</b>	<b>Cohort M N = 12</b>
<b>Objective Response Rate per Investigator<sup>a</sup></b>				
% (95% CI) <sup>b</sup>	23.1 (12.5, 36.8)	0 (0.0, 24.7)	15.4 (1.9, 45.4)	8.3 (0.2, 38.5)
<b>Best Overall Response, n (%)</b>				
Complete response	5 (9.6)	0	0	0
Partial response	7 (13.5)	0	2 (15.4)	1 (8.3)
Stable disease	15 (28.8)	9 (69.2)	6 (46.2)	1 (8.3)
Progressive disease	22 (42.3)	3 (23.1)	5 (38.5)	10 (83.3)
Not evaluable	3 (5.8)	1 (7.7)	0	0
<b>Duration of Response, months</b>				
Median (95% CI) <sup>c</sup>	NR (8.31, N.A.)	-	3.91 (3.61, 4.21)	NR
<b>Progression-free Survival</b>				
Events, n (%)	40 (76.9)	12 (92.3)	11 (84.6)	11 (91.7)
Median (95% CI), months <sup>c</sup>	3.58 (2.30, 6.64)	4.78 (2.17, 9.46)	4.93 (0.95, 5.29)	1.59 (0.92, 2.50)
<b>Overall Survival</b>				
Events, n (%)	36 (69.2)	7 (53.8)	11 (84.6)	8 (66.7)
Median (95% CI), months <sup>c</sup>	21.82 (15.05, 25.59)	25.56 (9.4, N.A.)	14.75 (4.93, 29.40)	7.95 (1.38, 15.51)

Source: CA209012 CSR database lock date 19-Sep-2016 (Nivo+Mono)<sup>113</sup>

Treatment: F=NIV3; K=NIV3 S SWITCH; L=NIV3 NS SWITCH; M=NIV3 BM

<sup>a</sup>Tumor responses were assessed using RECIST v1.1 criteria beginning 11 weeks ( $\pm$  5 days) after first dose, and then occurred at weeks 17 ( $\pm$  5 days) and 23 ( $\pm$  5 days), and then every 12 weeks until disease progression.

<sup>b</sup>Confidence interval computed using the Clopper-Pearson method.

<sup>c</sup>Kaplan-Meier estimate. + symbol indicates a censored value; NR=not reached due to high percentage of censored response.

### **5.4.1.3 Nivolumab Monotherapy in Subjects with Advanced/Metastatic (Stage IIb/IV) NSCLC - CA209384**

CA209384 is an open-label, randomized, Phase 3b/4 study evaluating the outcomes of nivolumab 480 mg Q4W versus nivolumab 240 mg Q2W in subjects with advanced/metastatic (Stage IIb/IV) NSCLC, NSQ and SQ, who had received up to 12 months (52 weeks) of nivolumab therapy at either 3 mg/kg or 240 mg Q2W and achieved a complete response (CR), partial response (PR), or stable disease (SD) as evidenced by at least 2 consecutive tumor assessments prior to enrollment. At enrollment, subjects were randomized 1:1 to receive either 240 mg Q2W (Arm 1) or 480 mg Q4W (Arm 2). Randomization was stratified by histology and response criteria to pre-study nivolumab at randomization (CR or PR vs SD).

A summary of key efficacy results is provided in Table 5.4.1.3-1. The efficacy of nivolumab was similar between the nivolumab 480 mg Q4W arm and the nivolumab 240 mg Q2W arm based on PFS rates (stratified by tumor histology and by response criteria before randomization) at 6 months and 12 months after randomization, as measured by investigator-assessed response. The PFS rates in all randomized subjects, not adjusted for the stratification factors, were also similar between the two treatment arms. OS rates at 6 months (stratified by tumor histology and by response criteria before randomization) were comparable between the two treatment arms. The OS rate at 12 months was numerically higher for the 240 mg Q2W arm; however, at the time of the database lock (DBL), only about 32% of OS events have been reported and therefore OS is not yet mature.

**Table 5.4.1.3-1: Summary of Efficacy of Nivolumab 480 mg Q4W and Nivolumab 240 mg Q2W in Subjects with Advanced/Metastatic NSCLC - CA209384**

	<b>Nivolumab 480 mg Q4W N = 180</b>	<b>Nivolumab 240 mg Q2W N = 183</b>
<b>Adjusted PFS (Stratified by Tumor Histology and Response Criteria before Randomization)</b>		
Events, n (%)	107 (59.4)	100 (54.6)
Median (95% CI), months <sup>a</sup>	12.68 (9.99, 17.54)	12.98 (11.10, 17.02)
HR (One-sided 95% CI) <sup>b</sup>	1.07 (0, 1.35)	
Rate at 6 months (95% CI), % <sup>c</sup>	0.76 (0.70, 0.83)	0.79 (0.73, 0.85)
Rate at 12 months (95% CI), % <sup>c</sup>	0.53 (0.46, 0.61)	0.55 (0.47, 0.62)
<b>Unadjusted PFS (all Randomized Subjects)</b>		
Rate at 6 months (95% CI), % <sup>d</sup>	0.74 (0.67, 0.81)	0.74 (0.68, 0.81)
Rate at 12 months (95% CI), % <sup>d</sup>	0.53 (0.45, 0.60)	0.54 (0.46, 0.62)
<b>Adjusted OS</b>		
Events, n (%)	64 (35.6%)	51 (27.9%)
Median (95% CI), months <sup>a</sup>	NA (27.86, NA)	NA (NA, NA)
HR (One-sided 95% CI) <sup>b</sup>	1.31 (0, 1.78)	
Rate at 6 months (95% CI), % <sup>c</sup>	0.966 (0.938, 0.993)	0.956 (0.922, 0.991)
Rate at 12 months (95% CI), % <sup>c</sup>	0.851 (0.799, 0.902)	0.908 (0.866, 0.951)
<b>Unadjusted OS (All Randomized Subjects)</b>		
Rate at 6 months (95% CI), % <sup>d</sup>	0.94 (0.91, 0.98)	0.95 (0.92, 0.99)
Rate at 12 months (95% CI), % <sup>d</sup>	0.82 (0.76, 0.88)	0.88 (0.83, 0.93)

Source: CA209384 Final CSR<sup>106</sup>; 09-Aug-2019 database lock; minimum follow-up: 12 months

- a Median PFS and OS were based on Kaplan-Meier (KM) estimates and two-sided 95% CI was calculated using Brookmeyer and Crowley method.
- b Stratified Cox proportional hazard model. (by tumor histology [SQ vs. NSQ] and response category at randomization [CR or PR vs. SD]). Hazard Ratio is Nivolumab 480 mg Q4W over Nivolumab 240 mg Q2W.
- c Based on KM Estimates. The rate and 95% CI adjusted for stratifying factors (tumor histology [SQ vs. NSQ] and response category at randomization [CR or PR vs. SD]) were calculated using inverse variance weight.
- d Based on KM Estimates. The unadjusted 95% CI was calculated using the Greenwood formula for variance derivation.

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; N = number; NA: Not Available; NSQ= non-squamous; PFS = progression free survival; OS = overall survival; PR = partial response; Q2W = every two weeks; Q4W = every four weeks; SD = stable disease; SQ = squamous

#### 5.4.1.4 Nivolumab Monotherapy in Subjects with Advanced or Metastatic NSCLC with at Least One Prior Systemic Regimen-CA209907

CA209907 is an open-label, single-arm Phase 2 safety study of nivolumab 480 mg administered IV over 30 minutes Q4W in subjects  $\geq 18$  years old with advanced or metastatic NSCLC who have progressed during or after receiving at least 1 prior systemic regimen.<sup>114, 115</sup> The primary endpoint of this study was to characterize the safety of nivolumab 480 mg IV over 30 minutes Q4W. At the DBL, a total of 184 subjects were enrolled and 129 subjects were treated. A summary of efficacy results is provided in Table 5.4.1.4-1.

**Table 5.4.1.4-1: Summary of Efficacy of Nivolumab 480 mg Q4W in Subjects with Advanced/Metastatic NSCLC - CA209907**

Efficacy Parameter	Nivolumab 480 mg Q4W N = 129
<b>Objective Response Rate<sup>a</sup></b>	
n (%)	22 (17.1%)
95% CI	11.0, 24.7
<b>Duration of Objective Response</b>	
Median (95% CI), months <sup>b</sup>	35.45 (10.87, 47.31)
Min, Max <sup>c</sup>	3.9, 47.3
<b>Progression Free Survival, Primary Definition<sup>d,e</sup></b>	
Median (95% CI), months	3.68 (3.06, 4.50)
Rate at 30 months (95% CI), %	10.9 (6.2, 17.1)
Rate at 36 months (95% CI), %	9.8 (5.3, 15.9)
<b>Overall Survival<sup>d</sup></b>	
Median (95% CI), months	10.58 (8.34, 14.69)
Rate at 30 months (95% CI), %	21.6% (14.9, 29.2)
Rate at 36 months (95% CI), %	19.9% (13.4, 27.4)

Source: CA209907 Closeout CSR<sup>115</sup>; 20-May-2022 database lock;

- <sup>a</sup> CR + PR, confidence interval based on the Clopper and Pearson method
- <sup>b</sup> Median computed using KM method
- <sup>c</sup> Symbol + indicates a censored value
- <sup>d</sup> Based on KM estimates
- <sup>e</sup> Primary definition of progression free survival (PFS; investigator-assessed) is defined as the time between the date of first treatment and the date of first document tumor progression (per investigator), or death due to any cause, whichever occurs first accounting for subsequent therapy (no new anti-cancer treatment started, or subsequent anti-cancer therapy started without death or progression reported prior or on the same day)

#### 5.4.1.5 **Nivolumab Monotherapy in NSCLC Subjects from Japan, Korea, Taiwan, China, Russia and Singapore**

Clinical activity of nivolumab monotherapy subjects from JP with advanced NSCLC (ONO-4538-05/ ONO-4538-06, described in the JPI), subjects from Korea with advanced NSCLC (ONO-4538-09), Taiwan with advanced NSCLC (ONO-4538-25) and subjects from China, Russia, and Singapore (CA209078) was consistent with efficacy reported for NSCLC in the representative USPI ([Appendix 2](#)) and EU SmPC ([Appendix 3](#)).

#### 5.4.1.6 **Nivolumab in Combination with Chemotherapy in Japanese Subjects with NSCLC - ONO-4538-04**

ONO-4538-04 was a Phase 1, open-label, uncontrolled study of nivolumab (10 mg/kg Q3W) in combination with chemotherapy in Stage IIIB/IV or recurrent NSCLC conducted solely in JP. As of the last patient last visit (LPLV) date (01-Jul-2019), 24 subjects were treated.

A summary of key efficacy results from ONO-4538-04 is provided in Table 5.4.1.6-1. Antitumor activity in Japanese subjects with Stage IIIB/IV or recurrent NSCLC was observed in all treatment groups of nivolumab in combination with chemotherapy.

**Table 5.4.1.6-1: Summary of Efficacy of Nivolumab in Combination with Chemotherapy in Japanese Subjects with NSCLC - ONO-4538-04**

	Nivo + Cis/Gem N = 6	Nivo + Cis/Pem N = 6	Nivo + Carb/Pac/Bev N = 6	Nivo + Doc N = 6
Objective Response Rate, n (%)	3 (50.0)	3 (50.0)	6 (100.0)	1 (16.7)
95% CI	11.8, 88.2	11.8, 88.2	54.1, 100.0	0.4, 64.1
Median Time to Response (Days)	64.0	66.0	65.0	62.0
Median Duration of Response (Days)	351.0	273.0	1153.0	85.0
Median PFS (95% CI) (Days)	191.0 (108.0, 1454.0)	359.5 (42.0, -)	1239.0 (160.0, -)	96.0 (59.0, 332.0)
Median TTP (95% CI) (Days)	191.0 (108.0, 1454.0)	293.0 (42.0, -)	1239.0 (160.0, -)	96.0 (59.0, 332.0)
Median OS (95% CI) (Days)	401.0 (336.0, 1686.0)	868.0 (444.0, -)	NR (737.0, -)	380.5 (297.0, 514.0)



Source: ONO-4538-04 final CSR; 1-Jul-2019 <sup>116</sup> clinical cutoff date

Note: Responses were evaluated by the investigator at each study site according to RECIST v1.1. Medians were estimated using the Kaplan–Meier method.

Abbreviations: Bev = bevacizumab; Carb = carboplatin; CI = confidence interval; Cis = cisplatin; Doc = docetaxel; NR = not reached; NSCLC = non-small cell lung cancer; Pac = paclitaxel; Pem = pemetrexed; PFS = progression-free survival; TTP = time to progression

#### **5.4.1.7 Nivolumab in Combination with Ipilimumab in Subjects with Treatment-Naive Stage IV or Recurrent NSCLC-CA209592**

CA209592 is a two-part, open-label, completed exploratory Phase 2 trial of nivolumab in combination with ipilimumab in subjects with no prior systemic anticancer therapy, given as primary therapy for advanced or metastatic NSCLC. <sup>117</sup> All subjects started treatment with nivolumab + ipilimumab at a flat dose of nivolumab 240 mg as a 30-minute IV infusion Q2W + ipilimumab 1 mg/kg as a 30-minute IV infusion Q6W.

The overall efficacy summary is provided below.

- Investigator-assessed ORR was 30.4% (95% CI: 24.6, 36.8), with a CR rate of 2.2%
- Disease control rate (DCR) was 66.1% (95% CI: 59.6, 72.2)
- Median DOR was 17.05 (95% CI: 10.74, 23.59) months
- Median PFS was 5.75 (95% CI: 4.47, 7.36) months
- Median OS was 15.74 (95% CI: 12.12, 20.30) months

Nivolumab (240 mg Q2W) plus ipilimumab (1 mg/kg Q6W) demonstrated objective response in Stage IV treatment naive or recurrent NSCLC.

Clinically meaningful improved ORRs were noted in bTMB high (21 mutations/Mb cut-point) and tTMB high (10 mutations/Mb cut-point) compared to bTMB and tTMB low subjects respectively. This trend was also reflected in improved OS, PFS and DOR in the bTMB and tTMB high compared to the respective low groups. In the PD-L1  $\geq 1\%$  group, ORR was also improved compared to the PD-L1  $< 1\%$  group regardless of TMB status. <sup>118</sup>

#### **5.4.1.8 Nivolumab in Combination with Ipilimumab and Nivolumab in Combination with Ipilimumab and Chemotherapy as First-Line Therapy in Subjects with Stage IV NSCLC-CA209568**

CA209568 was a two-part, phase 2 study to evaluate the efficacy and safety of nivolumab plus ipilimumab and nivolumab plus ipilimumab in combination with chemotherapy in adult subjects with stage IV NSCLC who had received no prior systemic therapy for advanced disease. <sup>119</sup> In Part 1, subjects received nivolumab IV over 30 minutes at 3 mg/kg Q2W + ipilimumab IV over 30 minutes at 1 mg/kg Q6W until progression, unacceptable toxicity, or other reasons specified in the protocol. In Part 2, subjects received nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W, in combination with 2 cycles of platinum-doublet chemotherapy Q3W, which was chosen based on histology.



The overall efficacy summary is provided below.

### **Part 1(288 subjects)**

- Blinded independent central review (BICR)-assessed ORR was 44.2% (61/138) in subjects with PD-L1  $\geq 1\%$  vs 17.1% (20/117) in subjects with PD-L1  $< 1\%$  (co-primary efficacy endpoints).
  - ◆ BICR-assessed ORR was 32.3% (93/288) in all treated subjects and 51.5% (35/68) in subjects with PD-L1  $\geq 50\%$ .
- The 60-month PFS rate was 19.0% in subjects with PD-L1  $\geq 1\%$  vs 10.5% in subjects with PD-L1  $< 1\%$ ; it was 28.0% in subjects with PD-L1  $\geq 50\%$ .
  - ◆ Median PFS (95% CI) was 6.80 (4.17, 10.97) months in subjects with PD-L1  $\geq 1\%$  vs 2.92 (2.17, 4.11) months in subjects with PD-L1  $< 1\%$ ; it was 5.19 (3.06, 5.82) months in all treated subjects.
- The 60-month OS rate was 32.5% in subjects with PD-L1  $\geq 1\%$  vs 14.7% in subjects with PD-L1  $< 1\%$ ; it was 45.8% in subjects with PD-L1  $\geq 50\%$ .
  - ◆ Median OS was 26.51(17.12, 43.17) months in PD-L1  $\geq 1\%$  subjects, vs 13.70 (10.71, 21.91) months in PD-L1  $< 1\%$  subjects; it was 49.41 (22.97, N.A) in subjects with PD L1  $\geq 50\%$  and 20.83 (14.46, 25.20) months in all treated subjects.
- An analysis of ORR data from this study was conducted to identify a cutoff for baseline tumor mutational burden (TMB). A baseline TMB level of 10 mut/Mb was chosen as the cutoff based on a preliminary analysis; with a higher TMB cutoff, there was no incremental ORR benefit.
  - A high baseline TMB level ( $\geq 10$  mut/Mb) was associated with improved ORR and PFS compared with low TMB ( $< 10$  mut/Mb): ORR (52.1% vs 16.0%) and PFS rates at 60 months (24.9% vs 8.2%); these improvements in ORR and PFS were observed regardless of PD-L1 expression. Note: subjects with a low baseline TMB level with PD-L1  $\geq 1\%$  was associated with improved/longer ORR and PFS compared with subjects with PD-L1  $< 1\%$ .
  - Subjects with a baseline TMB level  $\geq 10$  mut/Mb (high TMB) had an improved median OS compared with subjects with low TMB ( $< 10$  mut/Mb): 47.31 vs 11.33 months

### **Part 2 (36 subjects)**

- Investigator-assessed ORR was 50.0% (6/12) in subjects with PD-L1  $\geq 1\%$  vs 38.9% (7/18) in subjects with PD-L1  $< 1\%$ ; it was 47.2% (17/36) in all treated subjects.
- Overall, 41.7% (15/36) of subjects had partial response and stable disease and 5.6% (2/36) subjects had a complete response.

Across all endpoints, the efficacy benefit of nivolumab + ipilimumab was greater in subjects with PD-L1  $\geq 1\%$  compared with subjects with PD-L1  $< 1\%$ .

In Part 1 of CA209568, nivolumab + ipilimumab as first line therapy demonstrated clinical response in subjects with stage IV or recurrent NSCLC. Baseline tumor PD-L1 expression was associated with anti-tumor activity and durable responses were observed regardless of PD-L1 expression. Baseline high TMB level was associated with anti-tumor activity, regardless of PD-L1 expression level. Subjects with a low baseline TMB level with PD-L1  $\geq 1\%$  was associated with

improved/longer ORR and PFS compared with subjects with PD-L1 < 1%. The overall safety profile of nivolumab + ipilimumab combination therapy was manageable and consistent with the known safety profile of the combination. In Part 2 of CA209568, nivolumab + ipilimumab + chemotherapy demonstrated a meaningful response rate.

#### **5.4.1.9    *Neoadjuvant Treatment with Nivolumab plus Chemotherapy Followed by Surgical Resection and Adjuvant Treatment with Nivolumab in Subjects with Resectable Stage II-IIIB NSCLC - CA20977T***

This is a randomized, double-blind, Phase 3 study in subjects with resectable early-stage non-small cell lung cancer (NSCLC): Stage IIA (> 4 cm) to IIIB (T3N2 or T4N2). Subjects with N3 nodal disease were not eligible.<sup>120</sup> Subjects with resectable T4 tumor size with Stage IIIA or IIIB disease should have been reviewed and approved for participation in the study by the multidisciplinary team (including surgeon, medical oncologist, and radiation oncologist).

**Arm A:** nivo 360 mg Q3W + SOC platinum-based doublet chemo Q3W x 4 cycles as neoadjuvant treatment followed by surgery and post-surgical treatment with nivo 480 mg Q4W for up to 13 cycles (approximately 1 year)

**Arm B:** placebo Q3W + SOC platinum-based doublet chemo Q3W x 4 cycles as neoadjuvant treatment followed by surgery and post-surgical treatment with placebo Q4W for up to 13 cycles (approximately 1 year).

The primary endpoint was to compare EFS (by BICR) in Arm A vs Arm B. The secondary endpoints were to assess PCR rate, MPR rate, safety and tolerability in Arm A vs Arm B.

As of 26-Jul-2023, 735 subjects were enrolled, 461 subjects were randomized at 86 sites in 18 countries.

#### **Efficacy Results:**

The median follow-up (median of the time from randomization to the clinical cutoff date) was 25.4 months and the minimum follow up (time from the last subject's randomization date to the clinical cutoff date) was 15.7 months for all randomized subjects in the global population.

#### **Overall Efficacy Summary**

A statistically significant and clinically meaningful improvement was observed in EFS per Blinded Independent Central Review (BICR, primary endpoint), with nivo+chemo/nivo vs placebo + chemo/placebo in subjects with resectable stage IIA-IIIB NSCLC (Table 5.4.1.9-1). Results for EFS per BICR favored nivo+chemo/nivo over placebo+chemo/placebo across subgroups of tumor PD-L1 (< 1%, ≥ 1%), histology (NSQ, SQ), and disease stage (stage II, stage III).

The results for the primary endpoint (EFS per BICR) were supported by clinically meaningful improvements in pathologic complete response (pCR) and major pathologic response (MPR) per Blinded Independent Pathological Review (BIPR, secondary endpoints) with nivo+chemo/nivo vs placebo+chemo/placebo.

**Table 5.4.1.9-1: Summary of Efficacy - All Randomized Subjects in the Global Population**

	Arm A Nivo+Chemo/Nivo N = 229	Arm B Placebo+Chemo/Placebo N = 232
Primary Endpoint		
Event-Free Survival per BICR, primary definition		
Events, n (%)	76 (33.2)	113 (48.7)
Median EFS (95% CI), mo. <sup>a</sup>	Not Reached (28.94, NA)	18.43 (13.63, 28.06)
HR (97.36% CI) <sup>b</sup>	0.58 (0.42, 0.81); p = 0.00025 <sup>c</sup>	
HR (95% CI) <sup>b</sup>	0.58 (0.43, 0.78)	
EFS rates (95% CI), % <sup>a</sup>		
6 months	84.6 (79.1, 88.8)	79.9 (73.8, 84.7)
12 months	73.4 (66.8, 78.9)	59.2 (52.2, 65.6)
18 months	70.2 (63.4, 76.0)	50.0 (42.9, 56.7)
Secondary Endpoints		
Pathologic Complete Response <sup>d</sup> per BIPR		
N responders/all randomized subjects (%)	58/229 (25.3)	11/232 (4.7)
95% CI <sup>e</sup>	(19.8, 31.5)	(2.4, 8.3)
Difference (95% CI), % <sup>f,g</sup>	20.5 (14.3, 26.6)	
Estimate of odds ratio (95% CI) <sup>g,h</sup>	6.64 (3.40, 12.97)	
Major Pathologic Response <sup>d</sup> per BIPR		
N responders/all randomized subjects (%)	81/229 (35.4)	28/232 (12.1)
95% CI <sup>e</sup>	(29.2, 41.9)	(8.2, 17.0)
Difference (95% CI), % <sup>f,g</sup>	23.2 (15.8, 30.6)	
Estimate of odds ratio (95% CI) <sup>g,h</sup>	4.01 (2.48, 6.49)	

<sup>a</sup> Based on Kaplan-Meier estimates

<sup>b</sup> HR of Arm A to Arm B from a Cox proportional hazard model stratified by randomization stratification factors: PD-L1 status ( $\geq 1\%$  vs  $< 1\%$  / NE/indeterminate), disease stage (II vs III), histology (SQ vs NSQ) per IRT

<sup>c</sup> Log-rank test stratified by same factors (per IRT) as used in the Cox proportional hazard model. The p-value threshold for statistical significance was 0.0264.

<sup>d</sup> Randomized subjects who were no longer eligible for surgery, or who were on alternative anti-cancer therapy before surgery, or who discontinued the study before surgery were all counted as non-responders.

<sup>e</sup> Confidence interval based on the Clopper and Pearson method.

<sup>f</sup> Strata adjusted difference based on Cochran-Mantel-Haenszel (CMH) method of weighting.

<sup>g</sup> Stratified by randomization stratification factors: PD-L1 status ( $\geq 1\%$  vs  $< 1\%$  / not evaluable/indeterminate), disease stage (II vs III), histology (SQ vs NSQ) per IRT

<sup>h</sup> Strata adjusted odds ratio using Mantel-Haenszel method.

Source:CA20977T Primary CSR<sup>120</sup> Clinical data cutoff was 26-Jul-2023. Minimum follow-up (date the last subject was randomized to the date of the clinical data cutoff) was 15.7 months.

Abbreviations: BICR - Blinded Independent Central Review, BIPR - Blinded Independent Pathological Review, chemo - chemotherapy, CI - confidence interval, EFS - event-free survival, HR - hazard ratio, IRT - interactive response technology, NA - not available, NE - not evaluable, nivo - nivolumab, NSQ - non- squamous, PD-L1 - programmed death ligand 1, SQ - squamous

#### **5.4.2 Clinical Activity in Subjects with Melanoma**

Nivolumab has demonstrated clinical benefit in subjects with unresectable or metastatic melanoma as monotherapy or in combination with ipilimumab and has been approved for use in the US (including adolescent patients  $\geq 12$  years to  $< 18$  years), EU, and additional regions (see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information).

Nivolumab has also demonstrated clinical benefit in subjects with melanoma with lymph node who have undergone complete resection in the adjuvant setting and has been approved for use in the US (including adolescent patients  $\geq 12$  years to  $< 18$  years), EU, (see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information).

In addition, the clinical activity of nivolumab monotherapy or in combination with ipilimumab in Japanese subjects with unresectable or recurrent melanoma (ONO-4538-02, ONO-4538-08, and ONO-4538-17 as described in the JPI) was consistent with efficacy reported for melanoma in the representative USPI and EU SmPC.

##### **5.4.2.1 Nivolumab in Combination with Ipilimumab in Subjects with completely resected stage IIIb/c/d or stage IV No Evidence of Disease Melanoma - Study CA209915**

CA209915 was a Phase 3 randomized, double-blind study of nivolumab plus ipilimumab (hereafter nivolumab + ipilimumab) vs nivolumab monotherapy in adult and pediatric subjects ( $\geq 12$  years of age) with completely resected stage IIIb/c/d or stage IV NED melanoma. The study originally included an ipilimumab monotherapy treatment arm, which was removed after the implementation of global protocol amendment. Per the amended protocol, subjects originally randomized to ipilimumab monotherapy were unblinded and could continue open-label treatment with either ipilimumab or nivolumab monotherapy.<sup>121</sup>

The primary end point of the study was to compare efficacy as measured by recurrence-free survival (RFS). The secondary end points of the study were to compare efficacy as measured by OS, to evaluate the association between tumor PD-L1 expression and RFS and to evaluate investigator-assessed outcomes on next-line therapies.

The primary study objective of demonstrating improved RFS with nivolumab + ipilimumab vs nivolumab as adjuvant therapy in all randomized subjects or in all randomized subjects with tumor PD-L1  $< 1\%$  with completely resected stage IIIb/c/d or stage IV NED melanoma was not met.

##### **All randomized subjects:**

- A total of 715 RFS events had occurred in all randomized subjects.

- Nivolumab + ipilimumab did not demonstrate a statistically significant and clinically meaningful improvement in the primary endpoint of RFS vs nivolumab (HR = 0.90 [95% CI: 0.78, 1.04]).
- RFS results for nivolumab + ipilimumab vs nivolumab were similar across the baseline tumor PD-L1 expression level subgroups.
- There was no significant difference in OS between the nivolumab + ipilimumab and nivolumab treatment group in the all randomized subjects
- There was no improvement in Distant Metastasis-free Survival (DMFS) with nivolumab + ipilimumab vs nivolumab.

**All randomized subjects with tumor PD-L1 expression < 1%:**

- As per the 24 months exploratory follow-up RFS data analysis, the results in the PD-L1 < 1% population were consistent with those in the overall population (all randomized subjects). There was no improvement in RFS with nivolumab + ipilimumab vs nivolumab (HR = 0.91 [95% CI: 0.73, 1.14]).
- As per the data monitoring committee recommendation in Nov-2019, nivolumab + ipilimumab did not demonstrate a statistically significant improvement in the primary endpoint of RFS vs nivolumab.
- There was no improvement in DMFS with nivolumab + ipilimumab vs nivolumab.

**5.4.2.2 Nivolumab in Subjects with Advanced Malignant Melanoma - ONO-4538-31**

ONO-4538-31 was a multicenter, randomized, open-label study intended to evaluate the efficacy and safety of nivolumab monotherapy at doses of 3 mg/kg at 2-week intervals (group A) and 2 mg/kg at 3-week intervals (group B) in subjects with advanced malignant melanoma. <sup>122</sup>

As of the LPLV of 15-Oct-2018, the following are the key efficacy results:

- The ORRs (centralized measurement; [primary endpoint]) in groups A and B were 14.3% (1/7 subjects, 90% CI: [0.7, 52.1]) and 20.0% (1/5, 90% CI [1.0, 65.7]), respectively.
- The median OS in groups A and B were 22.90 months (90% CI: [4.34, 22.90]) and 17.87 months (90% CI [6.24, not applicable (NA)]), respectively. The 6-month survival rates estimated by the Kaplan–Meier method in groups A and B were 85.7% (90% CI [44.9, 97.1]) and 100.0% (90% CI [100.0, 100.0]), respectively. The 12-month survival rates in groups A and B were 68.6% (90% CI [29.1, 89.1]) and 80.0% (90% CI [31.4, 95.8]), respectively. The 18-month survival rates in groups A and B were 68.6% (90% CI [29.1, 89.1]) and 30.0% (90% CI [2.8, 66.6]), respectively.
- The median PFS (centralized measurement) in groups A and B were 12.55 months (90% CI [1.12, NA]) and 1.61 months (90% CI [1.41, NA]), respectively. The 6- and 12-month PFS rates (centralized measurement) estimated by the Kaplan–Meier method were 57.1% (90% CI [23.1, 80.7]) and 20.0% (90% CI [1.8, 52.5]), respectively. The 12-month PFS rates in groups A and B were 38.1% (90% CI [9.5, 67.3]) and 20.0% (90% CI [1.8, 52.5]), respectively.

In conclusion, in this post marketing clinical study, both regimens of nivolumab, namely, “3 mg/kg (weight) at 2-week intervals” and “2 mg/kg (weight) at 3-week intervals,” had a certain level of

efficacy and were observed to be tolerable for subjects with unresectable stage III/IV or recurrent malignant melanoma.

#### **5.4.2.3 Nivolumab in Subjects with Advanced Malignant Melanoma - CA209204**

CA209204 is a completed multi-center phase 2 open-label study to evaluate safety and efficacy in subjects with melanoma metastatic to the brain treated with nivolumab in combination with ipilimumab followed by nivolumab monotherapy. The primary objective of the study was to assess intracranial clinical benefit rate (CBR; defined as CR + PR + SD  $\geq$  6 months) in subjects with melanoma metastatic to the brain per modified RECIST v1.1 criteria.<sup>123</sup>

Subjects were enrolled to 1 of 2 cohorts as follows:

- Cohort A (asymptomatic): Approximately 90 subjects with histologically confirmed metastatic melanoma presenting with intracranial metastases and at least 1 measurable index intracranial metastasis  $\geq$  0.5 cm and  $\leq$  3 cm in diameter that had not been irradiated previously were enrolled. No local intervention (surgery, radiosurgery, corticosteroid therapy) or other systemic therapy was required. Subjects with a history of whole brain irradiation were not eligible for this study.
- Cohort B (symptomatic): Approximately 20 subjects with histologically confirmed metastatic melanoma presenting with symptomatic intracranial metastases who could have been on steroids with doses no higher than a total daily dose of 4 mg of dexamethasone or equivalent that was stable or tapering within 10 days prior to treatment were enrolled. Subjects who were symptomatic and were not being treated with steroids were also eligible. Subjects enrolled in Cohort B must have had at least 1 measurable index intracranial metastasis  $\geq$  0.5 cm and  $\leq$  3 cm in diameter that had not been irradiated previously, did not require immediate local therapy (stereotactic radiotherapy or surgery within 3 weeks prior to first treatment), had a performance status 0 to 2, and no experience of seizure within 10 days prior to first treatment. Subjects with a history of whole brain irradiation were not eligible for this study.

All subjects were treated with the combination regimen of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks (Q3W; 4 doses), followed by nivolumab monotherapy (3 mg/kg every 2 weeks [Q2W]) for a maximum of 24 months, or until disease progression or unacceptable toxicity.

Efficacy results of nivolumab combined with ipilimumab followed by nivolumab monotherapy for the treatment of subjects with melanoma metastatic to the brain were as follows:

#### **Investigator-assessed CBR (CR + PR + SD $\geq$ 6 months)**

##### **Intracranial**

- All subjects: 51.3% (95% CI: 41.9, 60.5)
- Cohort A: 57.4% (95% CI: 47.2, 67.2)
- Cohort B: 16.7% (95% CI: 3.6, 41.4)

##### **Extracranial**

- All subjects: 48.7% (95% CI: 39.5, 58.1)
- Cohort A: 53.5% (95% CI: 43.3, 63.5)

- Cohort B: 22.2% (95% CI: 6.4, 47.6)

Global (intracranial + extracranial)

- All subjects: 50.4% (95% CI: 41.1, 59.7)
- Cohort A: 55.4% (95% CI: 45.2, 65.3)
- Cohort B: 22.2% (95% CI: 6.4, 47.6)

Nivolumab combined with ipilimumab produces durable clinical benefit in subjects with active, asymptomatic melanoma brain metastases. Data from CA209204 demonstrate that nivolumab combined with ipilimumab followed by nivolumab monotherapy provides clinically meaningful improvements in CBR, ORR, and OS, as well as PFS, in asymptomatic subjects with melanoma metastatic to the brain (Cohort A). Symptomatic subjects (Cohort B) generally progressed rapidly, but a durable response was observed in some subjects.

**5.4.2.4 Nivolumab as an Adjuvant Immunotherapy after Complete Resection of Stage IIB/C Melanoma-CA20976K**

CA20976K is a Phase 3, randomized, double-blind study designed to evaluate the use of adjuvant immunotherapy with nivolumab versus placebo after complete resection of Stage IIB/C melanoma in adults and adolescent subjects 12 years old.<sup>124</sup> Subjects received nivolumab (or matching placebo) at a dose of 480 mg as an approximately 30-minute infusion on Day 1 of each 4-week treatment cycle until unacceptable toxicity, withdrawal of consent, completion of 12 months of treatment (from first dose of study treatment), disease recurrence, or the study ends, whichever occurred first.

The efficacy results as follows:

- Adjuvant nivolumab 480 mg Q4W demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of RFS compared with placebo (stratified HR = 0.53 [95% CI: 0.40, 0.71]).
- RFS rates were higher in the nivolumab arm compared with the placebo arm: 95.1% and 88.3% at 6 months, 88.8% and 81.1% at 12 months.
- Overall, 19.4% of subjects receiving nivolumab and 31.8% of subjects receiving placebo experienced a recurrence event. The reduction in recurrence events was primarily driven by fewer distant recurrences (8.4% vs 14.8%) and regional recurrences (3.0% vs 8.7%) with nivolumab.
- Adjuvant nivolumab was associated with an improvement in DMFS per Investigator compared with placebo (HR = 0.62 [95% CI: 0.43, 0.89]).
- In all randomized subjects, 40 (7.6%) Progression-free Survival Through Next-Line Systemic Therapy (PFS2) events occurred in the nivolumab arm and 31 (11.7%) events occurred in the placebo arm. PFS2 HR favored nivolumab vs placebo: 0.63 (95% CI: 0.40, 1.01).

Adjuvant nivolumab has a favorable benefit/risk profile relative to placebo in subjects with resected Stage IIB/C melanoma who are at a high risk of disease recurrence. Nivolumab demonstrated a 47% reduction in the risk of recurrence or death compared to placebo, and in a descriptive analysis, a 38% reduction in the risk of distant metastases or death was observed.



### **5.4.3 Clinical Activity in Subjects with Renal Cell Carcinoma**

Nivolumab monotherapy has demonstrated clinical benefit in subjects with advanced RCC and has been approved for use in this population in the US, EU, and additional regions (see [Appendix 2 \[USPI\]](#) and [Appendix 3 \[EU SmPC\]](#) for efficacy information). Nivolumab in combination with ipilimumab has demonstrated clinical benefit in subjects with intermediate or poor-risk RCC and has been approved for use in this population in the US, EU, and additional regions (see [Appendix 2 \[USPI\]](#) and [Appendix 3 \[EU SmPC\]](#) for efficacy information). In addition, available data for the use of nivolumab combination therapy in subjects with advanced RCC are presented in the following section.

#### **5.4.3.1 Nivolumab in Combination with Ipilimumab, Sunitinib, or Pazopanib in Subjects with Metastatic RCC - CA209016**

A total of 100 subjects with metastatic RCC were treated with nivolumab (1 or 3 mg/kg) and ipilimumab (1 or 3 mg/kg) in CA209016 (Phase 1 dose-escalation study of nivolumab in combination with VEGFR-TKIs or ipilimumab in subjects with metastatic RCC). In addition, a total of 53 subjects with metastatic RCC were treated with nivolumab (2 or 5 mg/kg) and sunitinib or nivolumab (2 mg/kg) and pazopanib in CA209016.

Key efficacy results are provided in [Table 5.4.3.1-1](#) for all treatment groups.



**Table 5.4.3.1-1: Efficacy in Subjects with Metastatic RCC Treated with Nivolumab in Combination with Ipilimumab, Sunitinib, or Pazopanib - CA209016**

	SUN + NIVO N = 33		PAZ + NIVO2 N = 20	IPI1 + NIVO3 N = 47	IP13 + NIVO1 N = 47	IP13 + NIVO3 N = 6
	SUN + NIVO2 N = 7	SUN + NIVO5 N = 26				
<b>Objective Response Rate<sup>a</sup></b>						
n (%)	6 (85.7)	11 (42.3)	9 (45.0)	19 (40.4)	19 (40.4)	0
95% CI	(42.1, 99.6)	(23.4, 63.1)	(23.1, 68.5)	(26.4, 55.7)	(26.4, 55.7)	--
<b>Duration of Response</b>						
Median (95% CI) <sup>b</sup> (weeks)	45.6 (18.14, NA)	78.1 (36.14, NA)	30.1 (12.14, 174.14)	88.7 (37.14, NA)	85.9 (35.14, NA)	--
Min, Max <sup>b</sup>	18.1, 183.0+	36.0, 150.1+	12.1, 189.0	9.3, c.0+	12.1+, 138.0+	--
<b>Progression-free Survival</b>						
Median (95% CI) <sup>b</sup> (months)	11.3 (7.62, N.A.)	12.7 (5.55, 19.38)	7.2 (2.79, 11.07)	7.7 (3.71, 14.29)	9.4 (5.62, 18.63)	8.5 (1.31, NA)
Min, Max <sup>b</sup> (months)	7.6, 43.4+	0.0+, 35.8+	1.0, 44.8	1.1+, 33.7+	1.0, 33.1+	1.3, 21.9+
6-Month Rate <sup>b</sup> , % (95% CI) <sup>c</sup>	100 (100, 100)	72.9 (49.3, 86.8)	54.9 (29.4, 74.6)	55.6 (40.0, 68.6)	63.8 (48.4, 75.7)	NC
<b>Overall Survival</b>						
Median (95% CI) <sup>b</sup> (months)	43.8 (15.87, NA)	36.8 (30.92, NA)	27.9 (13.34, NA)	NR (26.68, NA)	32.6 (25.99, NA)	NR
Min, Max <sup>b</sup> (months)	15.9, 45.6+	8.1, 39.2+	7.0, 47.6+	3.5, 35.0+	1.1, 34.3+	4.2+, 23.0+

Sources: CA209016 CSR<sup>125</sup>; database lock date 16-Mar-2016.

Treatment: SUN=Sunitinib; PAZ=Pazopanib; IPI=Ipilimumab; NIVO=Nivolumab; +: censored; NC: Not calculated; NR: The time point at which the percent of survivor drops below 50% has not been reached due to insufficient number of events and/or follow up.

Median follow-up times as of the 16-Mar-2016 database lock date were: Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n = 47): 22.31 months//Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 47): 22.34 months//Nivolumab 3 mg/kg + ipilimumab 3 mg/kg (n = 6): 22.59 months//Nivolumab 2 mg/kg + Sunitinib (n = 7): 42.55 months//Nivolumab 5 mg/kg + Sunitinib (n = 26): 33.49 months//Nivolumab 2 mg/kg + Pazopanib (n = 20): 27.07 months

<sup>a</sup> Confirmed responses of CR + PR as per RECIST v1.1 criteria, as assessed by the investigator.

<sup>b</sup> By Kaplan-Meier Method.

<sup>c</sup> The 95% CIs are derived from Greenwood's formula.

#### **5.4.3.2    *Nivolumab Monotherapy or in Combination with Ipilimumab vs Placebo in Subjects with Renal Cell Carcinoma - CA209914***

CA209914 is a Phase 3, randomized, double-blind study of adjuvant nivolumab 240 mg once every 2 weeks (Q2W) combined with ipilimumab 1 mg/kg once every 6 weeks (Q6W) (nivo + ipi) versus placebo (Part A), or adjuvant nivolumab monotherapy 240 mg Q2W (nivo) versus placebo (Part B), in subjects with early stage localized RCC with a predominantly clear cell histology, who have undergone radical or partial nephrectomy. Part B also included a nivo + ipi arm.<sup>126</sup>

The primary endpoints of DFS per BICR of nivo + ipi versus placebo (Part A) and DFS per BICR of nivo versus placebo (Part B) did not achieve statistical significance.

#### **Efficacy Results:**

##### **Part A:**

Based on the data cutoff date of 28-Jun-2022 (minimum 15.4 months and median 37.0 months follow-up), nivo + ipi did not demonstrate a statistically significant improvement in DFS per BICR compared with placebo (HR = 0.92 (95% CI: 0.71, 1.19); p = 0.5347]. DFS rates were similar at all timepoints between the nivo + ipi and placebo arms and Kaplan-Meier (KM) curves were largely overlapping at all timepoints .

DFS results were consistent regardless of assessment type or censoring rules. There was high concordance (> 94%) between BICR and Investigator assessment of DFS.

Because DFS was not significant, no formal analysis of OS was performed.

##### **Part B:**

Based on the data cutoff date of 28-Sep-2023 (minimum 18.0 months and median 27.01 months follow-up), nivo did not demonstrate a statistically significant improvement in DFS per BICR compared with placebo (HR = 0.87 [95% CI: 0.62, 1.21]; p = 0.3962. DFS rates were similar at all timepoints between the nivo and placebo arms.

DFS results were consistent regardless of assessment type or censoring rules. There was high concordance (> 97%) between BICR and Investigator assessment of DFS.

Because DFS was not significant, no formal analysis of OS was performed.

#### 5.4.4 Clinical Activity in Subjects with Classical Hodgkin Lymphoma

Nivolumab monotherapy has demonstrated clinical benefit in subjects with cHL who have relapsed or progressed, including those who received autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin, and has been approved for use in the US, EU, and additional regions (see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information). Available data for the use of nivolumab monotherapy followed by nivolumab in combination with chemotherapy is presented in Section 5.4.4.1. Available data for the use of nivolumab in combination with brentuximab vedotin in children, adolescents, and young adults is presented in [Section 5.4.4.2](#).

In addition, the clinical activity of nivolumab monotherapy in Japanese subjects with relapsed or refractory cHL (NCCH1606 and ONO-4538-15, described in the JPI) was consistent with efficacy reported for cHL in the representative USPI and EU SmPC.

##### 5.4.4.1 Nivolumab Monotherapy Followed by Nivolumab in Combination with Chemotherapy in Newly Diagnosed, Previously Untreated cHL Subjects - CA209205 Cohort D

CA209205 is a completed study which was a non-comparative, parallel cohort, single-arm Phase 2 study in subjects with cHL. In Cohort D, newly diagnosed subjects with advanced stage cHL were treated with nivolumab monotherapy followed by nivolumab in combination with chemotherapy (adriamycin/doxorubicin, vinblastine, dacarbazine [DTIC]). Key secondary efficacy results are provided in Table 5.4.4.1-1. The all-treated population demonstrated a CR rate of 66.7% by IRRC criteria at end of therapy.

**Table 5.4.4.1-1: Efficacy of Nivolumab Monotherapy Followed by Nivolumab in Combination with Chemotherapy - CA209205 Cohort D**

Efficacy Parameter	Cohort D (N = 51)		
	End of Monotherapy	After 2 Combocycles	End of Therapy
<b>Complete Response Rate</b>			
<b>Secondary Endpoint (per IRRC)</b>			
N responders (%)	9 (17.6)	26 (51.0)	34 (66.7)
95% CI <sup>a</sup>	8.4, 30.9	36.6, 65.2	52.1, 79.2
<b>Complete Response Rate</b>			
<b>Secondary Endpoint (per Investigator)</b>			
N responders (%)	13 (25.5)	36 (70.6)	41 (80.4)
95% CI <sup>a</sup>	14.3, 39.6	56.2, 82.5	66.9, 90.2

Source: CA209205 Addendum 02 Cohort D CSR<sup>127</sup>; database lock date 12-Oct-2017

<sup>a</sup> Confidence interval based on the Clopper and Pearson method

#### 5.4.4.2 **Nivolumab in Combination with Brentuximab Vedotin in Pediatric Subjects with cHL - CA209744**

CA209744 is an ongoing, Phase 2, open-label study of nivolumab + brentuximab vedotin, followed by brentuximab vedotin + bendamustine for suboptimal response, in children, adolescents, and young adults with low (Cohort R1) or standard risk (Cohort R2) relapsed/refractory cHL. The results of Cohort R1 will be reported in the Final CSR. At the 25-Oct-2019 database lock, per blinded independent central review (BICR), complete metabolic response (CMR) was reached by 26 (59.1%) subjects in Cohort R2, and partial metabolic response (PMR) was reached by 10 (22.7%) subjects. The ORR (CMR + PMR following 4 cycles of nivolumab + brentuximab vedotin) was 81.8% (90% CI: 69.6, 90.6). For all response evaluable subjects in Cohort R2, 38 (88.4%) reached CMR, and 4 (9.3%) reached PMR by BICR assessment any time prior to high dose chemotherapy or autologous hematopoietic stem cell transplantation. Key efficacy results are presented in Table 5.4.4.2-1.

**Table 5.4.4.2-1: Efficacy of Nivolumab + Brentuximab Vedotin, followed by Brentuximab Vedotin + Bendamustine for Suboptimal Response, in Children, Adolescents, and Young Adults with Standard Risk (R2) Preliminary Results - Relapsed/Refractory cHL - CA209744**

<b>n (%)</b>	<b>BICR (N = 44)</b>	<b>Investigator (N = 44)</b>
After 4 cycles of nivolumab + BV Induction		
CMR	26 (59.1)	29 (65.9)
PMR	10 (22.7)	10 (22.7)
ORR	36 (81.8)	39 (88.6)
Any time prior to consolidation		
CMR	38 (88.4) <sup>a</sup>	39 (88.6)
PMR	N.A.	4 (9.3)

Source: CA209744 Interim CSR<sup>128</sup>; database lock date 25-Oct-2019

<sup>a</sup> Response-evaluable subjects any time prior to consolidation per BICR n=43

Abbreviations: BICR = blinded independent central review, BV = brentuximab vedotin, CMR = complete metabolic response, PMR = partial metabolic response, ORR = objective response rate

#### 5.4.4.3 **Nivolumab in Combination with Brentuximab Vedotin in Subjects with cHL-CA209812**

CA209812 is a completed randomized, open-label, phase 3 trial of nivolumab plus brentuximab vedotin versus BV alone in participants with relapsed refractory or ineligible for ASCT advanced stage cHL.<sup>129</sup>

Participants were treated in one of 2 arms. In one arm, participants received nivolumab 360 mg IV Q3W until progression or unacceptable toxicity plus BV 1.8 mg/kg IV Q3W for up to 16 cycles, or until disease progression or unacceptable toxicity, whichever occurred first. In the other arm, participants received BV alone 1.8 mg/kg Q3W for up to 16 cycles, or until disease progression, or unacceptable toxicity, whichever occurred first.

Due to a treatment paradigm shift and subsequent low enrollment, the study was terminated early and consequently there is limited data and unable to provide definitive conclusions.

The efficacy results as of the 07-Apr-2021 DBL are provided in Table 5.4.4.3-1.

**Table 5.4.4.3-1: Efficacy of Nivolumab + Brentuximab Vedotin vs Brentuximab Vedotin - All Randomized Subjects-CA209812**

Efficacy Parameter	All Randomized Subjects	
	Nivo+BV (N = 12)	BV (N = 11)
<b>PFS per Investigator</b>		
Events, n	3/12	7/11
Median PFS (95% CI) <sup>a</sup> , months	14.32 (10.12, N.A.)	7.93 (2.86, N. A.)
<b>CRR<sup>b</sup> per Investigator</b>		
Events, n (%)	4/12 (33.3)	3/11 (27.3)
(95% CI) <sup>c</sup> , months	(9.9, 65.1)	(6.0, 61.0)
<b>ORR<sup>b, d</sup> per Investigator</b>		
Events, n (%)	8/12 (66.7)	5/11 (45.5)
95% CI <sup>d</sup>	(34.9, 90.1)	(16.7, 76.6)
<b>DOR per Investigator- All Subjects with Complete or Partial Response</b>		
Events, n	2/8	2/5
Median DOR (95% CI) <sup>a</sup> , months	11.27 (7.39, 11.27)	7.00 (1.54, N.A.)
<b>DOCR per Investigator - All Subjects with Complete Response</b>		
Events, n	1/4	0/3
Median DOCR (95% CI) <sup>a</sup> , months	7.85 (N.A., N.A.)	N.A.
<b>OS per Investigator</b>		
Events, n	1/12	0/11
Median OS (95% CI) <sup>a</sup> , months	N.A. (25.40, N.A.)	N.A.

Source: Synoptic Closeout CSR-CA209812.<sup>129</sup>

<sup>a</sup> Based on Kaplan-Meier estimates

<sup>b</sup> Per Revised 2014 Lugano Classification.

<sup>c</sup> CR, confidence interval based on the Clopper and Pearson method.

<sup>d</sup> CR+PR, confidence interval based on the Clopper and Pearson method.

Abbreviations: BV - brentuximab vedotin, CI - confidence interval, CRR - complete response rate, DOCR - duration of complete response, DOR - duration of response, N.A. - Not Available, Nivo - nivolumab, ORR - objective response rate, OS - overall survival, PFS - progression-free survival.

### **5.4.5 Clinical Activity in Subjects with SCCHN**

Nivolumab monotherapy has demonstrated clinical benefit in subjects with SCCHN who have progressed on or after a platinum-based therapy, and has been approved for use in the US, EU, and additional regions (see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information). In addition, available data for the use of nivolumab + ipilimumab combination therapy are presented in section 5.4.5.1.

#### **5.4.5.1 Nivolumab in Combination with Ipilimumab in Subjects with SCCHN - CA209714**

CA209714 was a Phase 2, randomized, double-blind, two-arm study evaluating nivolumab (3 mg/kg Q2W) combined with ipilimumab (1 mg/kg Q6W) versus nivolumab (3 mg/kg Q2W) combined with ipilimumab placebo as first-line treatment in subjects with metastatic SCCHN or recurrent SCCHN not amenable to curative therapy (surgery or radiation with/without chemotherapy).<sup>130</sup> Subjects were enrolled into 2 subgroups: a platinum-refractory subgroup or a platinum-eligible subgroup. Subjects were assessed for response (per RECIST v1.1 criteria) via computerized tomography/magnetic resonance imaging (MRI) every  $6 \pm 1$  weeks during the first 48 weeks of treatment, and then every  $12 \pm 1$  weeks until disease progression or subsequent therapy.

This study did not meet its primary endpoint of ORR benefit with first line nivolumab plus ipilimumab compared to nivolumab monotherapy in platinum-refractory recurrent or metastatic SCCHN. Also, nivolumab in combination with ipilimumab did not demonstrate improvements in PFS or OS compared with nivolumab as monotherapy in this SCCHN population.

#### **5.4.5.2 Nivolumab in Combination with Ipilimumab in Subjects with SCCHN - CA209651**

CA209651 is a completed open label, randomized, two arm phase III study of nivolumab in combination with ipilimumab versus EXTREME study regimen (cetuximab + cisplatin/carboplatin + fluorouracil) as first line therapy in recurrent or metastatic SCCHN.<sup>131</sup>

This study did not meet its primary endpoints of OS benefit with first line NIVO+IPI compared to EXTREME regimen in Recurrent or Metastatic SCCHN in all randomized subjects and all randomized subjects with PD-L1 combined positive score (CPS)  $\geq 20$ . However, NIVO+IPI exhibited clinical activity in subjects with PD-L1 CPS  $\geq 20$  and CPS  $\geq 1$ , as shown by longer median OS, higher OS rates, and longer median duration of responses. NIVO+IPI did not demonstrate improvements in PFS or ORR compared with EXTREME regimen in all randomized subjects and all randomized subjects with PD-L1 CPS  $\geq 20$ .

### **5.4.6 Clinical Activity in Subjects with Urothelial Carcinoma**

Nivolumab monotherapy has demonstrated clinical benefit in subjects with UC who have progressed during or following platinum-containing chemotherapy or progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, and has been approved for use in the US, EU, and additional regions (see [Appendix 2](#) [USPI] and

[Appendix 3](#) [EU SmPC] for efficacy information). Nivolumab monotherapy for adjuvant treatment of subjects with MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter), that are at high risk of recurrence after undergoing radical resection, demonstrated a statistically significant and clinically meaningful improvement in disease free survival (DFS), and a clinically meaningful improvement in non-urothelial tract recurrence-free survival (NUTRFS), compared with placebo in all randomized subjects and in subjects with PD-L1 expression level  $\geq$  1%. In addition, available data for the use of nivolumab combination therapy are presented in the following section.

#### **5.4.6.1 Nivolumab in Combination with Ipilimumab in Subjects with Urothelial Carcinoma - CA209032**

CA209032 is a Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab at different dose levels in subjects with several types of advanced or metastatic solid tumors, including UC. The study included 3 arms:

- **Nivolumab monotherapy** (3 mg/kg) Q2W (Arm N)
- **N1I3** (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W (Arm N-I: Dose Level 2). Safety and tolerability were evaluated after 6 subjects were dosed at this level. Subsequently, additional subjects were dosed at this dose level
- **N3I1** (nivolumab 3 mg/kg + ipilimumab 1 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W (Arm N-I: Dose Level 2b)

##### Primary Endpoints (ORR)

The N1I3 arm demonstrated a numerically higher ORR relative to the nivolumab monotherapy arm and N3I1 arm, as assessed by BICR. Nivolumab monotherapy and nivolumab in combination with ipilimumab per BICR assessment had clinically meaningful activity in subjects with mUC. There was a higher ORR observed in the N1I3 arm than the other 2 treatment arms. Overall, BICR assessed efficacy results were similar to investigator-assessed results.

Key efficacy results are provided in [Table 5.4.6.1-1](#).



**Table 5.4.6.1-1: Summary of Efficacy Results - Treated Subjects with Urothelial Carcinoma-CA209032**

	<b>Nivolumab</b> N= 78	<b>ML13</b> N= 92	<b>N311</b> N= 104
<b>PRIMARY ENDPOINT</b>			
<b>OBJECTIVE RESPONSE</b>	21.8	38.0	23.1
<b>RATE (%) (1)</b> (95% CI)	(13.2, 32.6)	(28.1, 48.8)	(15.4, 32.4)
<b>SECONDARY ENDPOINTS</b>			
<b>DURATION OF OBJECTIVE RESPONSE (MONTHS)</b>			
<b>TTR (months)</b>			
NUMBER OF RESPONDERS	17	35	24
MEDIAN	1.41	1.35	1.46
MIN, MAX	1.0, 6.9	0.8, 4.0	1.1, 8.3
<b>DOR (Months)</b>			
MIN, MAX (A)	2.6, 57.0	2.7, 48.2+	1.3+, 57.4+
MEDIAN	41.63	N.A.	N.A.
(95% CI) (B)	(16.43, 57.03)	(13.83, N.A.)	(20.76, N.A.)
N EVENT/N RESP (%)	9/17 (52.9)	15/35 (42.9)	9/24 (37.5)
<b>PROGRESSION FREE SURVIVAL</b>			
# EVENTS / # SUBJECTS (%)	65/78 (83.3)	64/92 (69.6)	80/104 (76.9)
MEDIAN PFS (MONTHS)	2.76	4.34	2.46
(95% CI) (B)	(1.45, 3.94)	(2.69, 8.18)	(1.45, 3.88)
<b>OVERALL SURVIVAL</b>			
MEDIAN OS (MONTHS)	9.89	15.28	7.36
(95% CI) (B)	(7.26, 18.56)	(8.11, 25.59)	(5.59, 11.01)
# EVENTS / # SUBJECTS (%)	61/78 (78.2)	58/92 (63.0)	82/104 (78.8)
OS RATE at 12 MONTHS	47.3	53.7	38.3
OS RATE at 24 MONTHS	37.9	41.4	27.5

Sources: CA209032 Interim CSR<sup>132</sup> database lock 28-Feb-2020. (A) Symbol + indicates a censored value

(B) Median computed using Kaplan-Meier method.

#### **5.4.6.2 Nivolumab in Combination with Ipilimumab or Chemotherapy Versus Standard of Care Chemotherapy in Subjects with Urothelial Cancer**

Study CA209901 is a Phase 3, open-label, randomized study of nivolumab combined with ipilimumab, or with SOC chemotherapy, versus SOC chemotherapy in subjects with previously untreated unresectable or metastatic urothelial cancer (UC). This study has been separated into 2 independent studies: a primary study evaluating the combination of nivolumab + ipilimumab versus platinum-based chemotherapy (Arms A and B) and the substudy evaluating the combination of nivolumab + cisplatin-based chemotherapy followed by nivolumab monotherapy versus cisplatin-based chemotherapy alone (Arms C and D). These 2 studies are independently powered Phase 3 studies comparing arms A vs B in the primary study and C vs D in the substudy.<sup>133</sup>

#### **Objectives:**

The CA209901 substudy evaluates the combination of nivolumab + cisplatin-based chemotherapy versus cisplatin-based chemotherapy alone. The protocol-specified objectives for the substudy presented in this report are listed below. The main study is currently ongoing, and results are not available.



### **Primary Objectives:**

- To compare overall survival (OS) of nivolumab combined with SOC chemotherapy versus standard of care (SOC) chemotherapy.
- To compare progression-free survival (PFS) of nivolumab combined with SOC chemotherapy versus SOC chemotherapy.

### **Secondary Objectives:**

- To evaluate whether programmed death-ligand 1 (PD-L1) expression is a predictive biomarker of efficacy (OS and PFS) of nivolumab combined with SOC chemotherapy as first-line therapy.
- To evaluate changes from baseline in health-related quality of life (HRQoL) of nivolumab combined with SOC chemotherapy.

### **Efficacy Results:**

The substudy met both of its primary objectives. Both primary endpoints of OS and PFS were statistically significant and clinically meaningful in subjects with previously untreated, unresectable, or metastatic UC.

#### **Primary Endpoint of OS:**

Nivo + SOC demonstrated a statistically significant and clinically meaningful improvement in OS compared with SOC alone: HR = 0.78 (alpha-adjusted 95.59% CI: 0.63, 0.96; 95% CI: 0.63, 0.96), stratified log-rank test p-value 0.0171. Significance level was p-value < 0.0311.

- Median OS (95% CI) was longer in the nivo + SOC arm than in the SOC arm: 21.72 (18.63, 26.38) vs 18.86 (14.72, 22.44) months, respectively.
- OS rates were numerically higher in the nivo + SOC arm than in the SOC arm at different timepoints: 88.1% vs 83.9% at 6 months, 70.2% vs 62.7% at 12 months, 57.5% vs 51.7% at 18 months, and 46.9% vs 40.7% at 24 months, respectively.

#### **Primary Endpoint of PFS:**

Nivo + SOC treatment demonstrated a statistically significant and clinically meaningful improvement in PFS per BICR by primary definition (censoring by subsequent anti-cancer therapy before progression of disease) compared with SOC: HR = 0.72 (alpha-adjusted 99% CI: 0.55, 0.94; 95% CI: 0.59, 0.88), stratified log-rank test p-value = 0.0012. Significance level was p-value < 0.01.

- Median PFS per BICR was longer in the nivo + SOC arm than in the SOC arm (7.92 [95% CI: 7.62, 9.49] vs 7.56 [95% CI: 6.05, 7.75] months)
- PFS rates were higher in the nivo + SOC arm than in the SOC arm: 65.5% vs 58.1% at 6 months, 34.2% vs 21.8% at 12 months, 27.6% vs 12.7% at 18 months, and 23.5% vs 9.6% at 24 months, respectively.
- Separation of the KM curves favoring nivo + SOC occurred after the median timepoint, with continued separation at all landmarks in the PFS assessment.

- Nivo + SOC treatment also demonstrated an improvement in PFS per BICR by secondary definition (not censoring by subsequent anti-cancer therapy before progression of disease): HR = 0.74 (95% CI: 0.62, 0.89).

#### Secondary Endpoint of OS by PD-L1 $\geq 1\%$ by IHC:

- Nivo + SOC demonstrated improvement in OS in subjects with PD-L1 expression  $\geq 1\%$  compared to SOC.

#### Secondary Endpoint of PFS (per BICR) by PD-L1 $\geq 1\%$ by IHC:

- Nivo + SOC demonstrated an improvement in PFS per BICR in subjects with PD-L1 expression  $\geq 1\%$  compared to SOC

### 5.4.7 Clinical Activity in Subjects with SCLC

Available data for the use of nivolumab combination therapy in subjects with SCLC and nivolumab monotherapy in subjects with SCLC are presented in the following sections.

#### 5.4.7.1 Nivolumab Monotherapy or in Combination with Ipilimumab in Subjects with SCLC - CA209032

CA209032 is a Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab at different dose levels in subjects with several types of advanced or metastatic solid tumors, including SCLC.<sup>134</sup>

Subjects with SCLC were included if they had advanced or metastatic SCLC with progressive disease after  $\geq 1$  prior platinum-containing regimens. Key efficacy data for nivolumab monotherapy (3 mg/kg Q2W) and nivolumab + ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W) in subjects with SCLC based on a 06-Nov-2017 database lock date are provided in Table 5.4.7.1-1. Responses were observed regardless of platinum sensitivity, line of therapy, or PD-L1 status. Updates to OR, DOR, and OS for the third-line nivolumab monotherapy group were provided in Addendum 01 to the final CSR, based on a 21-Jun-2019 database lock date (Table 5.4.7.1-1).

**Table 5.4.7.1-1: Summary of Efficacy Results with Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Subjects with SCLC - CA209032**

	$\geq$ Third-Line		$\geq$ Second-Line	
	Nivo 3 (N = 109)	Nivo 1 + Ipi 3 (N = 58)	Nivo 3 (N = 245)	Nivo 1 + Ipi 3 (N = 157)
<b>Objective Response Rate (per BICR)<sup>a</sup></b>				
n (%)	13 (11.9) <sup>e</sup>	16 (27.6)	29 (11.8)	35 (22.3)
95% CI	6.5, 19.5	16.7, 40.9	8.1, 16.6	16.0, 29.6
<b>Median Duration of Response (95% CI), months<sup>b</sup></b>	42.05 <sup>e</sup> (7.92, N.A.)	10.61 (4.01, NA)	17.94 (7.92, 42.05)	10.41 (6.93, 26.48)
Min, Max <sup>c</sup>	3.0, 57.7+ <sup>e</sup>	1.8, 31.8+	1.4+, 42.1	1.5, 34.6+

**Table 5.4.7.1-1: Summary of Efficacy Results with Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Subjects with SCLC - CA209032**

	<b>≥ Third-Line</b>		<b>≥ Second-Line</b>	
	<b>Nivo 3 (N = 109)</b>	<b>Nivo 1 + Ipi 3 (N = 58)</b>	<b>Nivo 3 (N = 245)</b>	<b>Nivo 1 + Ipi 3 (N = 157)</b>
n (%) responders with DoR ≥ 6 mo. <sup>d</sup>	10 (76.9)	10 (62.5)	21 (72.4)	25 (71.4)
n (%) responders with DoR ≥ 12 mo. <sup>d</sup>	8 (61.5)	6 (37.5)	13 (44.8)	14 (40.0)
<b>Progression-Free Survival (per BICR)</b>				
Median (95% CI), months <sup>b</sup>	1.38 (1.31, 1.64)	1.87 (1.41, 2.89)	1.35 (1.31, 1.38)	1.58 (1.38, 2.33)
6-month PFS rate (95% CI) <sup>b</sup>	17.2 (10.7, 25.1)	28.1 (17.2, 40.1)	15.3 (11.0, 20.2)	24.2 (17.8, 31.2)
<b>Overall Survival</b>				
Median (95% CI), months <sup>b</sup>	5.42 <sup>e</sup> (3.09, 6.83)	8.38 (5.39, 14.46)	5.09 (3.75, 6.74)	6.67 (3.91, 8.41)
12-month OS rate (95% CI) <sup>b</sup>	28.2 <sup>e</sup> (19.9, 37.1)	41.4 (28.7, 53.6)	29.2 (23.5, 35.1)	34.4 (27.0, 41.9)
18-month OS rate (95% CI) <sup>b</sup>	20.2 <sup>e</sup> (13.0, 28.4)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)

Source: CA209032 Addendum 01 to CA209032 Final SCLC CSR,<sup>135</sup> database lock 21-Jun-2019; minimum follow-up: ~ 29.6 months

Abbreviations: BICR = blinded independent central review, CI = confidence interval, CR = complete response, CSR = clinical study report, DoR = duration of response, PR = partial response, QxW = every x weeks, RECIST = Response Evaluation Criteria in Solid Tumors, SCLC = small-cell lung cancer, Nivo 3 = nivolumab 3 mg/kg Q2W, Nivo 3 + Ipi 1 = nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W

**a** Based on RECIST v1.1, confirmation of response required. CR+PR, confidence interval based on the Clopper and Pearson method

**b** Computed using Kaplan-Meier method

**c** + symbol indicates a censored value

**d** The proportion is the number of subjects observed to be in response at that timepoint divided by the total number of responders.

#### **5.4.7.2 Nivolumab Monotherapy in Subjects with Relapsed SCLC After Platinum-based First Line Chemotherapy - CA209331**

CA209331 was a Phase 3, open-label study of nivolumab monotherapy in subjects with relapsed SCLC who had been treated with first-line, platinum-based chemotherapy (topotecan or amrubicin).<sup>136</sup>

Subjects in this study were randomized 1:1 to receive nivolumab (Group A) or chemotherapy (Group B). Nivolumab was administered at 240 mg as an IV infusion over 30 minutes Q2W until unacceptable toxicity or disease progression. A total of 781 subjects were enrolled and 547 subjects were treated (282 with nivolumab and 265 with chemotherapy).

Nivolumab did not demonstrate superior OS compared with chemotherapy in subjects with SCLC whose disease had relapsed or progressed after a prior platinum-based chemotherapy regimen: HR = 0.86 (95% CI: 0.72, 1.04), stratified log-rank p-value = 0.1144. HR of PFS was 1.41 (95% CI: 1.18, 1.69). The ORR was numerically lower with nivolumab than with chemotherapy (13.7% vs 16.5%); however, the median DoR was longer in the nivolumab group than in the chemotherapy group (8.34 vs 4.47 months).

#### **5.4.7.3 Nivolumab Monotherapy or in Combination with Ipilimumab as Maintenance Therapy in Subjects with ED-SCLC after Completion of Platinum-based First Line Chemotherapy - CA209451**

CA209451 was a randomized, double-blind, 3-arm, multicenter, Phase 3 study in adult subjects with extensive-stage disease SCLC (ED-SCLC), who achieved CR, PR, or SD after completion of platinum-based first-line chemotherapy.<sup>137</sup> The study was designed to evaluate the efficacy and safety of nivolumab in combination with ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses followed by nivolumab 240 mg Q2W), and nivolumab monotherapy (240 mg Q2W) versus placebo. This study included a separate China sub-study to allow enrollment of subjects from China (per Protocol Amendment 12). The Global Population (834 subjects) included 2 subjects from China, who were also included in the China Cohort. A total of 75 subjects were randomized in the China Cohort. Nivolumab in combination with ipilimumab did not demonstrate a statistically significant improvement in OS compared with placebo (HR = 0.92 [95% CI: 0.75, 1.12], stratified log-rank test p-value = 0.3693). As the primary endpoint did not meet statistical significance, the secondary endpoints were not formally tested. Results in the China Cohort were generally consistent with those in the Global population; nivolumab in combination with ipilimumab did not demonstrate a statistically significant improvement in OS compared with placebo (HR = 0.92 [95% CI: 0.45, 1.89]). Interpretation of the efficacy data in the China Cohort is limited due to small sample size.

#### **5.4.8 Clinical Activity in Subjects with Gastric and Esophageal Cancers**

Nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy has demonstrated clinical benefit in subjects with advanced or metastatic gastric cancer, GEJC, and esophageal adenocarcinoma and has been approved for use (see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information). In addition, nivolumab in combination with chemotherapy in subjects with unresectable advanced or recurrent gastric cancer (ONO-4538-37) has demonstrated clinical benefit and described in the JPI. Nivolumab monotherapy also has demonstrated clinical benefit as third line therapy in subjects with unresectable advanced or recurrent gastric cancer (ONO-4538-12) and has been approved for use in Japan. Available data for the use of nivolumab monotherapy therapy in subjects with gastric cancer are presented in the following sections. Nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy or in combination with ipilimumab has demonstrated clinical benefit in subjects with unresectable advanced or metastatic esophageal cancer and has been approved for use (see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information, and also described in the JPI). Nivolumab monotherapy also has demonstrated clinical benefit as second line therapy in subjects with unresectable advanced or recurrent esophageal cancer and has been approved for use

(see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information, and also described in the JPI). In addition, Nivolumab as an adjuvant treatment has demonstrated clinical benefit in subjects who received neoadjuvant chemoradiotherapy and has been approved for use (see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information, and also described in the JPI).

#### **5.4.8.1 Nivolumab Monotherapy or in Combination with Ipilimumab in Subjects with Gastric Cancer - CA209032**

CA209032 is an ongoing Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab at different dose levels in subjects with several types of advanced or metastatic solid tumors, including GC. Subjects were included if they had GC or gastroesophageal junction cancer, including adenocarcinoma of the lower esophagus, with progressive or refractory disease after  $\geq 1$  prior line of therapy.

Key efficacy data for nivolumab monotherapy (3 mg/kg Q2W IV) and nivolumab + ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg or nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W IV) in subjects with GC based on a 24-Mar-2016 database lock date (median follow-up ranged from 3.9 to 5.0 months; median duration of therapy ranged from 1.3 to 1.8 months) are provided in [Table 5.4.8.1-1](#).

**Table 5.4.8.1-1: Summary of Efficacy Results with Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab - All Randomized Subjects with Gastric Cancer in CA209032**

Efficacy Parameter	Nivo 3 N = 59	Nivo 1 + Ipi 3 N = 49	Nivo 3 + Ipi 1 N = 52
<b>Objective Response Rate<sup>a</sup></b>			
n (%)	4 (6.8)	11 (22.4)	4 (7.7)
95% CI	1.9, 16.5	11.8, 36.6	2.1, 18.5
<b>Duration of Response<sup>b</sup></b>			
Median (95% CI) (Months)	14.13 (2.83, 14.13)	5.55 (2.76, NR)	NR (2.53, NR)
Min - Max	2.8 - 14.1	2.7 - 15.0+	2.5 - 11.1+
<b>Progression-free Survival</b>			
Median (95% CI) (Months)	1.45 (1.31, 2.56)	1.43 (1.22, 3.78)	1.58 (1.38, 2.60)
12-month rate (95% CI)	9.9 (3.7, 19.8)	16.9 (7.6, 29.4)	8.2 (2.6, 17.9)
<b>Overall Survival</b>			
Median (95% CI) (Months)	5.13 (3.35, 12.91)	6.87 (3.75, 11.47)	4.83 (2.99, 9.07)
12-month rate (95% CI)	39.4 (26.3, 52.3)	34.5 (21.3, 48.1)	24.7 (13.6, 37.5)

Source: CA209032 Gastric Cancer CSR<sup>138</sup> (Nivo 3) and preliminary data for CA209032 (Nivo 1 + Ipi 3 and Nivo 3 + Ipi 1); database lock date 24-Mar-2016 for all arms.

Nivo 3 = nivolumab monotherapy (3 mg/kg) Q2W

Nivo 1 + Ipi 3 = nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W

Nivo 3 + Ipi 1 = nivolumab (3 mg/kg) + ipilimumab (1 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W

<sup>a</sup> Responses of CR + PR as per RECIST v1.1 criteria, as assessed by BICR (Nivo 3) or the investigator (Nivo1+Ipi3 and Nivo3+Ipi1).

<sup>b</sup> Determined for subjects with CR or PR. For responders who did not have reported progression or death date, DOR was censored at the last tumor assessment date and is denoted by a + symbol.

#### 5.4.9 Clinical Activity in Subjects with Hepatocellular Carcinoma

Nivolumab combination therapy with ipilimumab demonstrated clinical benefit in subjects with HCC who have been previously treated with sorafenib and has been approved for use in the US (see [Appendix 2](#) [USPI] for efficacy information).

##### 5.4.9.1 Nivolumab Monotherapy as First-Line Therapy in Subjects with Hepatocellular Carcinoma - CA209459

CA209459 is an open-label, randomized, Phase 3 study comparing nivolumab monotherapy with sorafenib as first-line therapy in adult ( $\geq 18$  years) male and female subjects with advanced HCC.<sup>139</sup> Nivolumab demonstrated a clinically meaningful increase in the primary endpoint of OS over sorafenib. Median OS was 16.39 (95% CI: 13.93, 18.37) months in the nivolumab group and 14.69 (95% CI: 11.89, 17.22) months in the sorafenib group, with HR = 0.85 (95% CI: 0.72, 1.02); however, it was not statistically significant (two-sided p-value = 0.0752 which is greater than the pre-specified statistical significance boundary 0.0419).

#### **5.4.10 Clinical Activity in Subjects with Colorectal Cancer**

Nivolumab has demonstrated clinical benefit in subjects with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan as monotherapy or in combination with ipilimumab, and has been approved for use in the US, EU and additional regions (see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information).

##### **5.4.10.1 Nivolumab, or Nivolumab Combinations, in Recurrent and Metastatic MSI-H and non-MSI-H CRC-CA209142**

CA209142 is an ongoing Phase 2 open-label, multi-center, multi-cohort trial of nivolumab, or nivolumab combinations, in MSI-H and non-MSI-H recurrent and metastatic CRC (mCRC).

Cohort 5 explored the combination of nivolumab + relatlimab, in adult subjects with dMMR/MSI-H CRC who failed at least 1 prior line of therapy for metastatic disease. A total of 50 previously treated MSI-H subjects who had not had prior anti-PD-1 therapy were treated with nivolumab 240 mg Q2W in combination with relatlimab 160 mg Q2W until disease progression, unacceptable toxicity, or withdrawal of consent.<sup>140</sup>

The efficacy summary is provided below:

#### **Primary Endpoint**

- The Investigator-assessed ORR was 50.0% (95% CI: 35.5, 64.5), with a CR rate of 10%. Median DOR was 42.71 months (95% CI: 27.70, N.A), with a range of 2.8 to 47.0 months. For the 49 subjects with a target lesion at baseline and one or more on-treatment Investigator assessments, 35 (71.4%) had a reduction in tumor burden from baseline. ORR per Investigator did not substantially differ by selected subsets, including age, sex, diagnosis of Lynch syndrome, KRAS mutational status, or baseline Eastern Cooperative Oncology Group Performance Score (ECOG PS).

#### **Secondary Endpoints**

- The BICR-assessed ORR was 48.0% (95% CI: 33.7, 62.6), with a CR rate of 16.0%. Median BICR-assessed DOR was not reached (95% CI: 21.85, N.A.), with a range of 11.1 to 46.3 months. For the 48 subjects with target lesion at baseline and one or more on-treatment assessments, 32 (66.7%) had a reduction in tumor burden from baseline per blinded independent review committee (BIRC) assessment.
- The Investigator-assessed DCR was 70.0% (95% CI: 55.4, 82.1). The BICR-assessed DCR was 64.0% (95% CI: 49.2, 77.1).

Nivolumab in combination with relatlimab demonstrated high anti-tumor activity in subjects with previously treated MSI-H/dMMR mCRC, which translated into durable PFS and OS.

##### **5.4.10.2 Nivolumab, or Nivolumab in Combination with Ipilimumab or Chemotherapy in Subjects with Colorectal Cancer - CA2098HW**

CA2098HW is an ongoing Phase 3, randomized, 3-arm open-label study of nivolumab monotherapy (nivo: Arm A), nivolumab plus ipilimumab combination therapy (nivo+ipi: Arm B) or investigator's choice chemotherapy (chemo: Arm C) for the treatment of subjects with



microsatellite instability high (MSI-H)/ deficient mismatch repair (dMMR) metastatic colorectal cancer (mCRC). In this study, subjects were enrolled and randomized based on local MSI/MMR test results; however, the primary study population consists of subjects with confirmation of MSI-H/dMMR status by central testing.<sup>141</sup>

### **Efficacy Results:**

In CA2098HW, nivo+ipi demonstrated a statistically significant and clinically meaningful improvement in PFS per BICR (primary definition) compared with chemo in 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC

Results for the first primary endpoint were supported by results for the following secondary endpoints in 1L randomized subjects, which also favored nivo+ipi over chemo:

- PFS per investigator in 1L randomized subjects with centrally confirmed MSI-H/dMMR mCRC: Not Reached (38.44, NA) vs 7.66 (4.21, 9.00) months; HR = 0.20 (95% CI: 0.14, 0.31)
- PFS per BICR in all 1L randomized subjects: median PFS (95% CI): Not Reached (34.30, not available [NA]) vs 6.21 (4.70, 9.00) months; HR = 0.32 (95% CI: 0.23, 0.46)
- Consistent results for PFS per BICR results using central polymerase chain reaction (PCR) testing (for MSI-H status) or central immunohistochemistry (IHC) testing (for dMMR status)
  - **Confirmed MSI-H status by PCR:** median PFS (95% CI): Not Reached (38.44, NA) vs 6.21 (4.70, 9.03) months; HR = 0.20 (95% CI: 0.12, 0.31)
  - **Confirmed dMMR Status by IHC:** median PFS (95% CI): Not Reached (38.44, NA) vs 5.85 (4.40, 7.79) months; HR = 0.22 (95% CI: 0.14, 0.34)

Results for the other primary endpoint (PFS per BICR for nivo+ipi vs nivo in all randomized subjects with centrally confirmed MSI-H/dMMR mCRC) was not tested yet due to not reaching required number of PFS events to trigger its analysis.

## **5.4.11 Clinical Activity in Subjects with Glioblastoma**

### **5.4.11.1 Nivolumab Monotherapy in Subjects with Recurrent Glioblastoma - CA209143**

Cohort 2 of CheckMate 143 was a randomized Phase 3, open-label study comparing nivolumab monotherapy with BEV in subjects with recurrent GBM. Based on preliminary data, nivolumab did not meet the primary endpoint of superior OS when compared with BEV (HR = 1.04; P = 0.76). ORR with nivolumab was lower than with BEV (7.8% vs 23.1%).<sup>142</sup>

Cohort 1c and Cohort 1d were included in CA209143 to evaluate the safety and tolerability profile of nivolumab monotherapy (3 mg/kg Q2W) in subjects with newly diagnosed GBM. Cohort 1c evaluated nivolumab 3 mg/kg plus RT with temozolomide (nivolumab + RT + TMZ) in newly diagnosed GBM subjects regardless of MGMT-methylation status, and Cohort 1d assessed nivolumab 3 mg/kg plus RT (nivolumab + RT) in subjects with newly diagnosed GBM with MGMT-unmethylated status. Cohort 1c and Cohort 1d consisted of Part A and Part B. In Part A of Cohort 1c, 31 subjects with newly diagnosed GBM regardless of methylation status received treatment. In Part A of Cohort 1d, 30 subjects with newly diagnosed unmethylated GBM received treatment. In Part B, only newly diagnosed unmethylated GBM subjects were randomized between



Cohorts 1c and 1d (28 subjects treated in each). Enrollment in Part A ended when Part B enrollment was initiated, and the subject population in Part A and Part B was mutually exclusive (ie, subjects in Part A did not continue into Part B).

In Part A, median OS was 22.08 months (95% CI: 16.13, 32.39) and 14.41 months (95% CI: 12.55, 17.31), in Cohort 1c and Cohort 1d, respectively.

In Part B, median OS was 14.75 months (95% CI: 10.02, 18.60) and 13.96 months (95% CI: 10.81, 18.14), in Cohort 1c and Cohort 1d, respectively.

#### **5.4.11.2 Nivolumab in Combination with Radiation Therapy in Subjects with Unmethylated MGMT Glioblastoma - CA209498**

CA209498 was a Phase 3, randomized, open-label, multicenter study to compare the OS of nivolumab + RT vs temozolomide (TMZ) + RT in subjects with newly diagnosed, unmethylated MGMT GBM.<sup>143</sup> A total of 560 subjects were randomized (280 subjects to each group), and 553 subjects were treated (278 subjects with nivolumab + RT, and 275 subjects with TMZ + RT).

The efficacy results are presented below:

- The study did not meet its primary objective of demonstrating a statistically significant OS improvement with nivolumab + RT compared to TMZ + RT (HR: 1.31[95% CI: 1.10, 1.55]; stratified log-rank descriptive p-value = 0.0024).
- Median OS was shorter with nivolumab + RT vs TMZ + RT (13.34 months [95% CI: 12.55, 14.16] vs 14.92 months [95% CI: 13.27, 16.10]).
- The OS rate in the nivolumab + RT group was lower at 24 months compared with the TMZ + RT group (10.6% vs 21.2%).
- Median PFS was 6.01 months (95% CI: 5.65, 6.21) in the nivolumab + RT group and 6.21 months (95% CI: 5.98, 6.90) in the TMZ + RT group; HR = 1.43 (95% CI: 1.19, 1.71).

Study CA209498 did not meet the primary objective of demonstrating superior OS with treatment of nivolumab + RT compared with TMZ + RT among subjects with newly diagnosed, unmethylated MGMT GBM after surgical resection.

#### **5.4.11.3 Nivolumab in Subjects with first recurrence of Glioblastoma - ONO-4538-19**

ONO-4538-19 was a phase II Study A Multicenter Open-Label, Non-Comparative Study of nivolumab in subjects with first recurrence of glioblastoma.<sup>144</sup>

As of the last observation date of 04-Dec-2020, analyses were conducted in order to prepare the clinical study report (final report) of this study. Forty-four subjects and 50 subjects were employed in the full analysis set which was the efficacy analysis set and the safety analysis set, respectively. The anti-drug antibody evaluable population consisted of 48 subjects.

The efficacy and safety of nivolumab when 3 mg/kg was intravenously administered with 2-week intervals was examined in Japanese subjects with first recurrence of GBM. The posterior mean of the 1-year survival rate which was the primary efficacy endpoint was 54.35% (90% confidence

interval [42.27, 66.21]). The probability that the 1-year survival rate of this study would exceed the threshold 1-year survival rate (34.5%), which was selected using the 1-year survival rate in the Japanese phase II study of bevacizumab (JO22506), was 99.7%, which met the pre-defined efficacy assessment criterion (93% or more).

#### **5.4.12 Clinical Activity in Subjects with Combined Malignant Tumors**

##### **5.4.12.1 Nivolumab Monotherapy in Japanese Subjects with Multiple Malignant Tumors - ONO-4538-01**

ONO-4538-01 was a Phase 1, an open-label, dose-escalation study of nivolumab in subjects with malignant tumors (lung cancer [n = 5], melanoma [n = 4], rectal cancer [n = 3], thymic cancer [n = 2], colon cancer [n = 1], esophageal cancer [n = 1], and thyroid medullary cancer [n = 1]) conducted solely in JP.<sup>145</sup> Nivolumab doses were administered in 4 steps (single-dose, multiple-dose [2 doses Q2W], extended treatment [4 doses Q2W], and long-term follow-up), at 1 mg/kg (3 subjects), 3 mg/kg (5 subjects), 10 mg/kg (6 subjects), and 20 mg/kg (3 subjects). Each subject received the same dose throughout the single- and multiple-dose phases and the extended treatment phase. As of the study end date of 03-Jun-2014 (end of follow-up of the last subject), efficacy results were as follows:

- A best overall response (BOR), according to the RECIST (v01), of CR was reported for 1 subject in the 3 mg/kg group (melanoma) and a PR was reported for 1 subject each in the 1 mg/kg group (rectal cancer) and 10 mg/kg group (thyroid medullary cancer).
- The time of response (TOR) (ie, time from start of treatment to assessment of PR) in the melanoma subject with a BOR of CR (3 mg/kg group) was 49 days, and the time to assessment of CR was 1,088 days. The duration of CR was 460 days, and the duration from PR to CR was 1,499 days.
  - The TORs in the 2 subjects with a PR were 49 days (subject with rectal cancer, 1 mg/kg group) and 47 days (subject with thyroid medullary cancer in the 10 mg/kg group). The duration of response to the data cutoff point (ie, time from assessment of PR to PD or death) was 198 days in the 1 mg/kg group and 398 days in the 10 mg/kg group.

- The durations of PFS to the data cutoff point ranged from:
  - 47 to 246 days in the 3 subjects in the 1 mg/kg group
  - 18 to 1,547 days in the 5 subjects in the 3 mg/kg group
  - 47 to 577 days in the 6 subjects in the 10 mg/kg group
  - 45 to 52 days in the 3 subjects in the 20 mg/kg group.

#### **5.4.12.2 Nivolumab in Subjects with Advanced or Recurrent Uterine Cervical Cancer, Uterine Corpus Cancer, or Soft Tissue Sarcoma-ONO-4538-39**

ONO-4538-39 was a Phase 2, open-label, non-controlled study in subjects with uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma. Nivolumab 240 mg was administered intravenously over 30 minutes two-week intervals. At the study completion, 64 subjects (20 subjects with uterine cervical cancer, 23 subjects with uterine corpus cancer, 21 subjects with soft tissue sarcoma) have been treated with nivolumab, and efficacy has been evaluated in 63 treated subjects (20 subjects with uterine cervical cancer, 22 subjects with uterine corpus cancer, 21 subjects with soft tissue sarcoma). <sup>146</sup> The primary endpoint was site investigator-assessed ORR. The results are as follows.

##### **Uterine cervical cancer**

The site investigator-assessed ORR was 25.0% (5/20 subjects) (80% CI: 12.7, 41.5), and the lower limit of the 80% CI was above the predetermined threshold response rate of 5%.

##### **Uterine corpus cancer**

The site investigator-assessed ORR was 22.7% (5/22 subjects) (80% CI: 11.5, 38.1), and the lower limit of the 80% CI was above the predetermined threshold response rate of 5%.

##### **Soft tissue sarcoma**

The site investigator-assessed ORR was 4.8% (1/21 subjects) (80% CI: 0.5, 17.3), and the lower limit of the 80% CI was below the predetermined threshold response rate of 5%.

#### **5.4.12.3 Nivolumab in Subjects with Advanced or Metastatic Malignancies CA209627**

CA209627 is an open-label, multicenter, Phase 2 study, was designed to evaluate the efficacy and safety of nivolumab 240 mg Q2W for 8 doses followed by nivolumab 480 mg Q4W in multiple established and emerging cancer types. <sup>147</sup>

Up to 350 subjects were planned to be treated; 668 subjects were enrolled (signed an informed consent form and were registered into the interactive voice response system and a total of 239 subjects were analyzed (all treated subjects, ie, subjects who received at least 1 dose of nivolumab). The study enrolled subjects in 27 groups based on tumor type, of which subjects were treated in 25 groups. In 2 groups no subjects were treated due to screening failure.

Efficacy results as of 20-Aug-2021 DBL are summarized in [Table 5.4.12.3-1](#).

**Table 5.4.12.3-1: Summary of Key Efficacy Results in Subjects with Advanced or Metastatic Malignancies Treated with Nivolumab Monotherapy - CA209627**

	Number of Subjects (%)								
	Total N = 239	Group 1 N = 11	Group 2 N = 12	Group 3 N = 10	Group 4 N = 8	Group 5 N = 8	Group 6 N = 11	Group 8 N = 4	Group 9 N = 8
BEST OVERALL RESPONSE									
COMPLETE RESPONSE (CR)	4 ( 1.7)	1 ( 9.1)	0	0	0	0	0	0	0
PARTIAL RESPONSE (PR)	15 ( 6.3)	0	1 ( 8.3)	0	1 ( 12.5)	0	1 ( 9.1)	1 ( 25.0)	1 ( 12.5)
STABLE DISEASE (SD)	100 ( 41.8)	4 ( 36.4)	3 ( 25.0)	9 ( 90.0)	1 ( 12.5)	4 ( 50.0)	6 ( 54.5)	2 ( 50.0)	5 ( 62.5)
PROGRESSIVE DISEASE (PD)	81 ( 33.9)	6 ( 54.5)	3 ( 25.0)	1 ( 10.0)	4 ( 50.0)	3 ( 37.5)	2 ( 18.2)	0	0
UNABLE TO DETERMINE (UTD)	39 ( 16.3)	0	5 ( 41.7)	0	2 ( 25.0)	1 ( 12.5)	2 ( 18.2)	1 ( 25.0)	2 ( 25.0)
Objective Response Rate (1) (95% CI)	19/239 (7.9) (4.9, 12.1)	1/11 (9.1) (0.2, 41.3)	1/12 (8.3) (0.2, 38.5)	0/10 (0.0, 30.8)	1/8 (12.5) (0.3, 52.7)	0/8 (0.0, 36.9)	1/11 (9.1) (0.2, 41.3)	1/4 (25.0) (0.6, 80.6)	1/8 (12.5) (0.3, 52.7)
	Group 11 N = 6	Group 12 N = 2	Group 13 N = 20	Group 14 N = 11	Group 15 N = 6	Group 16 N = 8	Group 17 N = 9	Group 18 N = 15	Group 19 N = 4
BEST OVERALL RESPONSE									
COMPLETE RESPONSE (CR)	0	0	1 ( 5.0)	0	1 ( 16.7)	0	0	0	0
PARTIAL RESPONSE (PR)	0	0	5 ( 25.0)	1 ( 9.1)	0	0	0	2 ( 13.3)	0
STABLE DISEASE (SD)	0	0	3 ( 15.0)	10 ( 90.9)	1 ( 16.7)	5 ( 62.5)	2 ( 22.2)	5 ( 33.3)	0
PROGRESSIVE DISEASE (PD)	5 ( 83.3)	1 ( 50.0)	6 ( 30.0)	0	3 ( 50.0)	2 ( 25.0)	6 ( 66.7)	3 ( 20.0)	4 (100.0)
UNABLE TO DETERMINE (UTD)	1 ( 16.7)	1 ( 50.0)	5 ( 25.0)	0	1 ( 16.7)	1 ( 12.5)	1 ( 11.1)	5 ( 33.3)	0
Objective Response Rate (1) (95% CI)	0/6 (0.0, 45.9)	0/2 (0.0, 84.2)	6/20 (30.0) (11.9, 54.3)	1/11 (9.1) (0.2, 41.3)	1/6 (16.7) (0.4, 64.1)	0/8 (0.0, 36.9)	0/9 (0.0, 33.6)	2/15 (13.3) (1.7, 40.5)	0/4 (0.0, 60.2)
	Group 20 N = 10	Group 21 N = 9	Group 22 N = 8	Group 23 N = 11	Group 24 N = 14	Group 26 N = 9	Group 27 N = 9	Group 25 N = 16	
BEST OVERALL RESPONSE									
COMPLETE RESPONSE (CR)	0	1 ( 11.1)	0	0	0	0	0	0	
PARTIAL RESPONSE (PR)	0	0	0	0	2 ( 14.3)	0	0	0	
STABLE DISEASE (SD)	6 ( 60.0)	4 ( 44.4)	3 ( 37.5)	3 ( 27.3)	5 ( 35.7)	6 ( 66.7)	5 ( 55.6)	8 ( 50.0)	
PROGRESSIVE DISEASE (PD)	1 ( 10.0)	4 ( 44.4)	3 ( 37.5)	7 ( 63.6)	6 ( 42.9)	3 ( 33.3)	3 ( 33.3)	5 ( 31.3)	
UNABLE TO DETERMINE (UTD)	3 ( 30.0)	0	2 ( 25.0)	1 ( 9.1)	1 ( 9.1)	0	1 ( 11.1)	3 ( 18.8)	
Objective Response Rate (1) (95% CI)	0/10 (0.0, 30.8)	1/9 (11.1) (0.3, 48.2)	0/8 (0.0, 36.9)	0/11 (0.0, 28.5)	2/14 (14.3) (1.8, 42.8)	0/9 (0.0, 33.6)	0/9 (0.0, 33.6)	0/16 (0.0, 20.6)	

Source CA209627 CSR. <sup>148</sup> LPLV- 21-Oct-2019. Treatment Group: 1=Anal Cancer, 2=Biliary tract cancer, 3=Carcinoid, 4=Squamous Cell Cancer, 5=Endometrial Cancer, 6=Non-squamous Cell Head and Neck, 8=Lynch Syndrome, 9=Medullary Thyroid Cancer, 11=Mesothelioma, 12=Nasopharyngeal Carcinoma, 13=Neuroendocrine Tumors Poor, 14=Neuroendocrine Tumors Well, 15=Non-Ling Small Cell Carcinoma, 16=Penile Cancer, 17=Rare Women's Cancers, 18=Soft-Tissue Sarcoma, 19=Testicular Cancer, 20=Thymic Carcinoma or Invasive Thymoma, 21=Thyroid Cancer Papillary or Follicular, 22=Anaplastic Thyroid Cancer, 23=Uterine Sarcoma, 24=Vulvar Cancer, 26=Adenoid Cystic carcinoma, 27=Adrenocortical Carcinoma, 25=Other malignancies. Percentages based on subjects treated.

Per RECIST 1.1, confirmation of response required. (1) CR+PR, confidence interval based on the Clopper and Pearson method.

The primary endpoint of ORR was evaluated in all treated subjects. Additionally, ORR in individual tumor types were evaluated respectively. In all treated subjects, the primary endpoint of ORR was 7.9% (95% confidence interval [CI]: 4.9, 12.1) with 19/239 subjects demonstrating complete response (CR) or partial response (PR). Of the tumor groups included in this study, subjects with poorly differentiated neuroendocrine tumors (Group 13) demonstrated an ORR of 30.0% (95% CI: 11.9, 54.3) with 6/20 subjects demonstrating CR or PR.

#### **5.4.13 Clinical Activity in Subjects with Malignant Pleural Mesothelioma**

Nivolumab in combination with ipilimumab, has demonstrated clinical benefit for adult subjects with unresectable MPM and has been approved for use in the US, EU, and additional regions (see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information). Nivolumab monotherapy also has shown the clinical benefit for the subjects with advanced or metastatic malignant pleural mesothelioma resistant or intolerant to platinum-based combination therapy with pemetrexed (ONO-4538-41) and has been approved for use in Japan.

#### **5.4.14 Clinical Activity in Subjects with Pancreatic Cancer**

##### **5.4.14.1 Nivolumab Monotherapy, Nivolumab Combined with Ipilimumab, or Nivolumab with Ipilimumab and Cobimetinib in Subjects with Pancreatic Cancer - CA209032**

CA209032 is a Phase 1/2, open-label study in subjects with several types of advanced or metastatic solid tumors, including Pancreatic Cancer. A total of 93 subjects were enrolled and 69 subjects were treated: nivolumab monotherapy (n=18), nivolumab + ipilimumab combination therapy (n=21), and nivolumab + ipilimumab + cobimetinib (n=30). The nivolumab + ipilimumab + cobimetinib treatment arm was the only arm that demonstrated objective responses (two subjects had PR per Investigator assessment - ORR of 6.7%) with durability ranging from 3.3 to 12 + months. Responses occurred in PD-L1 tumor positive (1% cutoff) and negative subjects. In addition, no subjects had an objective response in either the nivolumab monotherapy or nivolumab + ipilimumab treatment arms.<sup>149</sup>

#### **5.4.15 Clinical Activity in Subjects with Primary Central Nervous System Lymphoma**

##### **5.4.15.1 Nivolumab Monotherapy in Subjects with Relapsed/Refractory Primary Central Nervous System Lymphoma - CA209647**

CA209647 is an open-label, 2-cohort study in subjects with relapsed/refractory PCNSL or PTL who progressed after or did not respond to at least 1 line of systemic therapy. Key efficacy data are provided in [Table 5.4.15.1-1](#).

**Table 5.4.15.1-1: Summary of Efficacy in Subjects with Relapsed/Refractory Primary Central Nervous System Lymphoma Treated with Nivolumab Monotherapy- CA209647**

Efficacy Parameter	PCNSL Cohort N = 47		PTL Cohort N = 19	
	BICR- assessed (Primary Endpoint)	Investigator- assessed (Secondary Endpoint)	BICR- assessed (Primary Endpoint)	Investigator- assessed (Secondary Endpoint)
ORR <sup>a</sup>				
N responders (%)	3 (6.4%)	5 (10.6%)	5 (26.3%)	5 (26.3%)
95% CI <sup>b</sup>	(1.3, 17.5)	(3.5, 23.1)	(9.1, 51.2)	(9.1, 51.2)
<b>BOR</b>				
CR	1 (2.1%)	0	3 (15.8%)	3 (15.8%)
CRu	0	2 (4.3%)	0	0
PR	2 (4.3%)	3 (6.4%)	2 (10.5%)	2 (10.5%)
SD	2 (4.3%)	3 (6.4%)	0	0
PD	40 (85.1%)	36 (76.6%)	10 (52.6%)	13 (68.4%)
NE	2 (4.3%)	3 (6.4%)	4 (21.1%)	1 (5.3%)

Source: CA209647 Closeout CSR<sup>150</sup>; database lock date 29-Jan-2021

Abbreviations: CI= confidence interval, CR=complete response, CRu= unconfirmed complete response, BOR= best overall response, DOR= duration of response, N= number, NE= non-evaluable, ORR= objective response rate, OS= overall survival, PD=Relapsed or progressive disease, PFS= progression-free survival, PR=partial response, SD=stable disease, TTR= time to first response

<sup>a</sup> CR + CRu + PR

<sup>b</sup> CI based on the Clopper and Pearson method.

In the PCNSL Cohort, the primary endpoint, BICR-assessed ORR, was 6.4% (95% CI: 1.3, 17.5). The efficacy data confirmed that nivolumab therapy in relapsed/refractory PCNSL had limited clinical benefit, evidenced by a short-term PFS and OS. The primary endpoint, BICR-assessed ORR, of the PTL Cohort was 26.3% (95% CI: 9.1, 51.2). In these subjects with relapsed/refractory PTL had clinical benefit limited only to certain subjects without CNS involvement evidenced by a BICR-assessed ORR of 0% (95% CI: 0.0, 45.9) vs. 38.5% (95% CI: 13.9, 68.4) in subjects with and without CNS involvement, respectively.

#### **5.4.16 Clinical Activity in Subjects with Prostate Cancer**

##### **5.4.16.1 Nivolumab in Combination with Ipilimumab in Subjects with Metastatic, Castration-Resistant Prostate Cancer - CA209650**

CA209650 is an ongoing, Phase 2, open-label study of same-day sequential dosing of nivolumab followed by ipilimumab, in subjects with mCRPC.<sup>151</sup> Asymptomatic/minimally symptomatic subjects who progressed after 2nd-generation hormone therapy and have not received chemotherapy for mCRPC (Cohort B) and subjects who progressed after taxane-based

chemotherapy (Cohort C) were included. Subjects were treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses, followed by nivolumab 480 mg every 4 weeks. Key preliminary results from the 16-Jun-2022 database lock are presented in Table 5.4.16.1-1.

**Table 5.4.16.1-1: Summary of Efficacy in Subjects with mCRPC Treated with Nivolumab Followed by Ipilimumab - CA209650**

Efficacy Parameter	Cohort B	Cohort C
<b>Objective Response (measurable disease only)<sup>a</sup></b>		
<b>Subjects with measurable disease at baseline</b>	32	30
<b>Confirmed ORR, n (%)</b>	8 (25.0)	3 (10.0)
95% CI	11.5-43.4	2.1-26.5
<b>Best overall response, n (%)</b>		
Complete Response	2(6.3) <sup>b</sup>	2 (6.7)
Partial Response	6 (18.8) <sup>c</sup>	1 (3.3)
Stable Disease	13 (40.6)	11 (36.7)
Progressive Disease	9 (28.1)	13 (43.3)
Unable to determine	2 (6.3)	3 (10.0)
<b>Median time to response, months (Q1-Q3)</b>	1.9 (1.9-2.8)	2.1 (1.9-7.4)
<b>PSA Response (Subjects with baseline and ≥ 1 post-baseline PSA result)</b>		
<b>Subjects with baseline and ≥ 1 post-baseline PSA result</b>	34	40
<b>Confirmed PSA response rate, n (%)<sup>d</sup></b>	6 (17.6)	4 (10.0)
95 % CI	6.8-34.5	2.8-23.7
<b>Subjects with PSA &lt; 0.2 ng/mL, n (%)</b>	5 (14.7)	2 (5.0)
<b>Median time to confirmed PSA response, months (Q1-Q3)</b>	1.4 (0.8-1.4)	1.2 (0.8-1.4)

<sup>a</sup> Based on RECIST v1.1

<sup>b</sup> One subject with CR has persistent bone lesions

<sup>c</sup> One subject has an unconfirmed PR

<sup>d</sup> Confirmed PSA decline ≥ 50% from baseline

Abbreviations: ORR = objective response rate, PSA = prostate-specific antigen, Q = quartile

Source: CA209650 preliminary results from database lock with database lock of 16-Jun-2022

#### **5.4.16.2 Nivolumab in Combination With Either Rucaparib, Docetaxel, or Enzalutamide in Men With mCRPC -CA2099KD**

CA2099KD is an open-label Phase 2 study of nivolumab combined with rucaparib (Cohort A1 and A2), docetaxel (Cohort B), or enzalutamide (Cohort C) in men with metastatic (American Joint Committee on Cancer [AJCC] Stage IV [N1 and/or M1]) mCRPC. Cohorts A2 and C have not yet reached primary final analysis and data from Cohorts A1 and B are presented below.<sup>152</sup>



**Cohort A1 (Nivo+Ruca)**-A total of 88 subjects were treated in Cohort A1, including 58 (66%) with measurable disease at baseline and 45 (51%) were homologous recombination deficiency positive (HRD+). All subjects had received prior taxane chemotherapy and 65 (74%) received 1 or 2 prior NATs for mCRPC, including 28 (31.8%) who had 2 prior NATs.

With a median follow up of 12 months, efficacy results for the nivo+ruca combination in HRD+ mCRPC subjects with prior taxane-chemotherapy were as follows: ORR (95% CI) of 17.2% (5.8, 35.8) and confirmed RR-PSA (95% CI) of 18.2% (8.2, 32.7).

**Cohort B (Nivo+Doce)**-Cohort B had a total of 84 subjects treated, including 45 (54%) with measurable disease at baseline and 35 (42%) who were HRD+. Eligible subjects were allowed up to 2 prior NATs in the mCRPC setting and should have been eligible to start chemo. In this cohort, 10.7% subjects received prior taxane chemotherapy in a non-mCRPC setting, 36% had no prior NAT, 50% had 1 prior NAT and 14% had 2 prior NATs for mCRPC.

With a median follow up of 15 months (minimum follow up 12 months), efficacy results in chemotherapy-naïve mCRPC subjects with up to two prior NATs in cohort B (n=84) who were treated with docetaxel + nivo showed ORR 40%, confirmed RR-PSA 47%, median rPFS 9 months, and median OS 18 months. Over 50% of subjects had stable disease. Efficacy results for HRD+ and HRD- subjects were similar.

#### **5.4.17 Clinical Activity in Subjects with NHL**

##### **5.4.17.1 Nivolumab in Combination with Brentuximab Vedotin in Subjects Relapsed Refractory NHL - CA209436**

CA209436 was an open-label, multicenter phase 1/2 study examining the safety and efficacy of nivolumab in combination with BV in subjects with relapsed/refractory non-Hodgkin lymphomas.<sup>153</sup> The purpose of study CA209436 was to investigate whether nivolumab (240 mg flat dose Q3W IV) can be safely combined with B) (1.8 mg/kg Q3W IV) and to assess the clinical benefit of the combination treatment in subjects with relapsed/refractory NHL. The NHL subtypes eligible for study evaluation included Diffuse Large B-cell Lymphoma (DLBCL), Peripheral T-cell Lymphoma (PTCL) (all subtypes excluding Anaplastic Large Cell Lymphoma [ALCL]), Primary Mediastinal B-cell Lymphoma (PMBL), Mediastinal Gray Zone Lymphoma (MGZL) and Cutaneous T-cell Lymphoma (CTCL) Mycosis Fungoides/Sezary Syndromes (MF/SS).

Key primary analysis results are presented in [Table 5.4.17.1-1](#)



**Table 5.4.17.1-1: Summary of Key Efficacy Results Based on Investigator's Assessment - All Treated Subjects-CA209436**

<b>Efficacy Parameter</b>	<b>PMBL N = 30</b>	<b>DLBCL N = 42</b>	<b>PTCL N = 33</b>	<b>CTCL N = 29</b>	<b>MGZL N = 10</b>
<b>Primary Endpoint</b>					
<b>ORR (CR + PR)<sup>a</sup></b>					
N responders (%)	22 ( 73.3)	12 ( 28.6)	15 ( 45.5)	12 ( 41.4)	7 ( 70.0)
80% CI	(60.3, 83.8)	(19.4, 39.4)	(33.3, 58.0)	(28.8, 55.0)	(44.8, 88.4)
95% CI	(54.1, 87.7)	(15.7, 44.6)	(28.1, 63.6)	(23.5, 61.1)	(34.8, 93.3)
<b>Secondary Endpoints</b>					
<b>BOR<sup>b</sup></b>					
CR	12 ( 40.0)	3 ( 7.1)	11 ( 33.3)	1 ( 3.4)	5 ( 50.0)
PR	10 ( 33.3)	9 ( 21.4)	4 ( 12.1)	11 ( 37.9)	2 ( 20.0)
SD	3 ( 10.0)	8 ( 19.0)	6 ( 18.2)	11 ( 37.9)	0
RD or PD	3 ( 10.0)	17 ( 40.5)	10 ( 30.3)	1 ( 3.4)	2 ( 20.0)
UTD	2 ( 6.7)	5 ( 11.9)	2 ( 6.1)	5 ( 17.2)	1 ( 10.0)
<b>DOR, All responders</b>					
Events/Responders	5/22	9/12	8/15	4/12	2/7
Median (95% CI), month	NA (23.33, NA)	3.55 (1.18, 36.53)	4.60 (2.76, 12.75)	26.97 (2.79, NA)	20.76 (1.22, NA)
<b>Duration of CR, Subjects with CR as BOR</b>					
Events/CR Responders	1/12	2/3	5/11	0/1	0/5
Median (95% CI), month	NA (27.89, NA)	36.53 (9.92, NA)	7.39 (2.17, NA)	NA	NA

**Table 5.4.17.1-1: Summary of Key Efficacy Results Based on Investigator's Assessment - All Treated Subjects-CA209436**

<b>Efficacy Parameter</b>	<b>PMBL N = 30</b>	<b>DLBCL N = 42</b>	<b>PTCL N = 33</b>	<b>CTCL N = 29</b>	<b>MGZL N = 10</b>
<b>PFS<sup>c</sup></b>					
# Events (%)	13 (43.3)	37 (88.1)	25 (75.8)	10 (34.5)	5 (50.0)
Median PFS (months) (95% CI)	25.95 ( 2.63, NA)	2.60 ( 1.38, 2.79)	4.30 ( 1.58, 5.62)	15.61 ( 4.86, NA)	21.88 ( 0.07, NA)
PFS rate (95% CI) at					
6 months	63.5 (42.5, 78.6)	19.5 ( 8.8, 33.2)	27.7 (12.9, 44.6)	67.6 (43.3, 83.3)	52.5 (15.0, 80.4)
12 months	55.5 (32.0, 73.8)	16.2 ( 6.5, 29.7)	13.8 ( 2.9, 33.0)	67.6 (43.3, 83.3)	52.5 (15.0, 80.4)
18 months	55.5 (32.0, 73.8)	6.5 ( 1.2, 18.3)	6.9 ( 0.5, 25.6)	46.4 (18.3, 70.7)	52.5 (15.0, 80.4)
24 months	55.5 (32.0, 73.8)	6.5 ( 1.2, 18.3)	6.9 ( 0.5, 25.6)	46.4 (18.3, 70.7)	0.0 (NA, NA)
<b>OS<sup>c</sup></b>					
# Events (%)	8 (26.7)	30 (71.4)	26 (78.8)	14 (48.3)	4 (40.0)
Median OS (months) (95% CI)	NA	13.31 ( 6.57, 15.87)	11.07 ( 5.16, 15.31)	37.16 (18.63, NA)	NA ( 0.07, NA)
OS rate (95% CI) at					
6 months	86.3 (67.5, 94.6)	70.8 (54.4, 82.3)	57.6 (39.1, 72.3)	89.7 (71.3, 96.5)	80.0 (40.9, 94.6)
12 months	79.1 (59.3, 90.0)	56.9 (39.9, 70.7)	45.1 (27.7, 61.0)	78.9 (58.9, 89.9)	70.0 (32.9, 89.2)
18 months	75.5 (55.4, 87.5)	31.3 (17.2, 46.4)	25.8 (12.3, 41.6)	71.0 (50.2, 84.4)	70.0 (32.9, 89.2)
24 months	75.5 (55.4, 87.5)	25.0 (12.3, 40.0)	25.8 (12.3, 41.6)	62.9 (41.7, 78.1)	58.3 (23.0, 82.1)

<sup>a</sup> Confidence interval based on the Clopper and Pearson method<sup>b</sup> Based on Lugano Classification 2014<sup>c</sup> Median and rates computed using the KM method

Note Treatment response and disease progression-related findings are based on investigator assessment. For subjects with relapsed/refractory CTCL, response was assessed according to consensus Global Response Score as per the consensus statement of the International Society for Cutaneous Lymphoma.

Source: : CA209436 Closeout CSR; database lock date 30-Mar-2022

Nivolumab in combination with BV resulted in an Investigator-assessed ORR of 73% (95% CI: 54.1, 87.7) and 70% (95% CI: 34.8, 93.3) and a CR of 40% and 50% in the PMBL and MGZL cohorts, respectively. No safety signals or any new safety concerns were identified across all 5 cohorts. Toxicities were overall manageable and within the expected profile of the individual agents.

#### **5.4.18 Clinical Activity in Subjects with Hematologic Malignancies**

##### **5.4.18.1 Nivolumab Monotherapy or in Combination with Lirilumab in Subjects with Relapsed or Refractory Hematologic Malignancies - CA209039**

The CA209039 nivolumab monotherapy cohort is a Phase 1, open-label, multicenter, study to investigate the safety, PK, immunogenicity, and preliminary antitumor activity of nivolumab monotherapy in subjects with relapsed or refractory hematologic malignancy. The study included dose-escalation and dose-expansion phases. The dose-escalation phase aimed to include 12 to 18 subjects to be treated with nivolumab 1 or 3 mg/kg during week 1 and week 4, then every 2 weeks for up to 2 years of treatment using a 6 + 3 design. The dose-expansion phase aimed to include 92 subjects. Retreatment was permitted for up to 1 year in subjects with CR, PR, or SD at the time of nivolumab discontinuation if disease progression (PD) occurred  $\leq 1$  year of discontinuation. High ORR (87%) and durable responses (median DOR 37.29 months) were associated with nivolumab monotherapy for relapsed/refractory cHL.

CA209039 is a Phase 1/2 study of nivolumab monotherapy or nivolumab combination regimens across relapsed/refractory hematologic malignancies. The purpose of the nivolumab/lirilumab cohort was to evaluate the safety profile and tolerability of the combination of nivolumab and lirilumab in subjects with relapsed or refractory hematologic malignancies. The combination of nivolumab and lirilumab did not appear to provide improved efficacy over that observed with nivolumab monotherapy in the studied hematologic malignancies.

Key efficacy data based on a 26-Apr-2019 database lock date are presented in [Table 5.4.18.1-1](#).

**Table 5.4.18.1-1: Summary of Key Efficacy Results in Subjects with Hematologic Malignancies Treated with Nivolumab Monotherapy - CA209039**

Efficacy Parameters	cHL <sup>a</sup> N=23	DLBL N=14	FBL N=10	OBL N=7	CTL N=17	PTL N=6	Total N=77
Objective Response Rate (ORR) <sup>b</sup>	20 (87.0%)	5 (35.7%)	5 (50.0%)	0	2 (11.8%)	2 (33.3%)	34 (44.2%)
Complete Remission (CR)	5 (21.7)	2 (14.3)	1 (10.0)	0	0	0	8 (10.4)
Partial Remission (PR)	15 (65.2)	3 (21.4)	4 (40.0)	0	2 (11.8)	2 (33.3)	26 (33.8)
Stable Disease (SD)	3 (13.0)	5 (35.7)	5 (50.0)	5 (71.4)	10 (58.8)	0	28 (36.4)
No. of subjects evaluated in TTR & DOR	18	5	5	0	2	2	32
Time to response (months)							
Median	1.69	1.61	7.79	-	6.59	1.28	1.91
Min, Max	0.7, 9.2	0.7, 3.5	1.8, 9.0	-	6.0, 7.2	0.7, 1.8	0.7, 9.2
Duration of Response (DOR) [months]							
Median <sup>c</sup>	37.29	15.80	N.A.	-	13.98	5.77	22.83
95% CI	(15.51, N.A.)	(0.95, N.A.)	(N.A., N.A.)	-	(13.31, 14.65)	(0.82, 10.71)	(13.31, N.A.)
Ongoing response <sup>d</sup>	0	0	0	0	0	0	0

Source: CA209039 Final CSR<sup>154</sup>; database lock date 26-Apr-2019

Abbreviations: cHL = classic Hodgkin lymphoma, DLBL = diffuse large B-cell lymphoma, FBL = follicular B-cell lymphoma, OBL = other B-cell lymphoma, CTL = cutaneous T-cell lymphoma, PTL = peripheral T-cell lymphoma. Note: DLBL (N=14), FBL (N=10) and OBL (N=7) are disease subtypes of BCL (N=31), and CTL (N=17) and PTL (N=6) are disease subtypes of TCL (N=23). MCL (N=4), SLL (N=2), and MALT (N=1) are subcategories of OBL (N=7).

<sup>a</sup> Nivolumab has been approved for use in subjects with cHL. See USPI ([Appendix 2](#)) and EU SmPC ([Appendix 3](#)) for efficacy information.

<sup>b</sup> CR + PR

<sup>c</sup> Median computed using Kaplan-Meier method.

<sup>d</sup> Subjects with Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis, and excludes responders censored prior to 26 weeks of the clinical cutoff date

#### **5.4.18.2 Nivolumab in Subjects with Refractory Multiple Myeloma- CA209602**

Study CA209602 was a phase 3 multicenter, randomized, open label study designed to evaluate the clinical benefit and safety of the combination therapy of nivolumab, pomalidomide, and dexamethasone (N-Pd; the investigational arm A), when compared to pomalidomide and dexamethasone (Pd; the control arm B) in subjects with RRMM.<sup>155</sup>

The statistical analyses were not sufficiently powered due to the early termination of enrollment and the smaller than planned study sample size. These results were unable to demonstrate that adding nivolumab to Pd improved efficacy, similar to the results of the Keynote 183 study that evaluated the combination of the PD-1 inhibitor, pembrolizumab, with Pd versus Pd.<sup>156</sup> Although no formal comparison was performed, the median PFS was numerically lower in the NE-Pd arm compared to the N-Pd arm and compared to Elotuzumab-Pd (median PFS 6.3 months, 8.4 months, and 10.3 months respectively).

#### **5.4.19 Clinical Activity in Subjects with CNS Malignancies**

##### **5.4.19.1 Clinical Activity in Subjects with CNS Malignancies- CA209908**

CA209908 was an open-label, sequential-arm, Phase 1b/2 clinical study of nivolumab monotherapy and nivolumab + ipilimumab in pediatric subjects with high-grade primary central nervous system (CNS) malignancies, including diffuse intrinsic pontine glioma (DIPG- Cohort 1), high-grade gliomas (HGG- Cohort 2), medulloblastoma (Cohort 3), ependymoma (Cohort 4), and other high grade CNS tumors (Cohort 5).

The study consisted of 2 treatment modules: Module A included nivolumab 3 mg/kg Q2W as monotherapy, and Module B included nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W for 4 doses followed by nivolumab 3 mg/kg Q2W as monotherapy. The study consisted of a safety lead-in phase and an expansion phase. The safety lead-in phase across cohorts was implemented prior to the expansion phase, because nivolumab, as monotherapy or immediately after radiation therapy (RT) or in combination with ipilimumab, has not been studied in pediatric subjects with CNS tumors.

Efficacy results (as of database lock 13-Jan-2021) are summarized by cohort for nivolumab monotherapy (Module A) in [Table 5.4.19.1-1](#) and for nivolumab + ipilimumab (Module B) in [Table 5.4.19.1-2](#). Results were generated on small sample sizes to detect efficacy signals with nivolumab monotherapy or nivolumab + ipilimumab in different cohorts. These results were intended to be compared with historical controls. Given the limitations associated with the available historical controls (eg, single studies and small sample sizes) and the small precision on point estimates and CIs, no meaningful conclusions could be drawn based on comparison against the historical values.

**Table 5.4.19.1-1: Efficacy Summary - Nivolumab Monotherapy Treated Subjects (Module A)-CA209908**

	Nivolumab (Module A)				
	<b>Cohort 1 (DIPG) N = 23</b>	<b>Cohort 2 (HGG) N = 16</b>	<b>Cohort 3 (Medulloblastoma) N = 15</b>	<b>Cohort 4 (Ependymoma) N = 12</b>	<b>Cohort 5 (Others) N = 19</b>
<b>OS (Primary Endpoint in Cohort 1 and Secondary Endpoint in Cohorts 2-5)</b>					
Median (95% CI), Months	11.66 (9.33, 27.27).	6.67 (2.99, 14.62)	7.36 (2.46, 30.23)	5.70 (1.81, N.E.)	5.91 (1.97, 7.98)
12-month Rate (95% CI), %	48.0 (25.6, 67.3)	37.5 (15.4, 59.8)	38.9 (14.3, 63.2)	41.7 (15.2, 66.5)	N.A.
<b>PFS (Primary Endpoint in Cohort 2-5 and Secondary Endpoint in Cohort 1)</b>					
Median (95% CI), Months	6.21 (3.75, 6.54)	1.74 (1.18, 2.76)	1.38 (0.95, 1.38).	1.41 (1.35, 8.34)	1.22 (1.08, 1.31)
<b>ORR (Exploratory Endpoint in Cohorts 1-5)</b>					
Response-evaluable Subjects	2	11	13	9	12
ORR (%)	0	0	0	1 (11.1)*	0
(95% CI)	(0.0, 84.2)	(0.0, 28.5)	(0.0, 24.7)	(0.3, 48.2)	(0.0, 26.5)

Source: CA209908 Primary CSR<sup>157</sup>; database lock date 13-Jan-2021

Abbreviations: CI = confidence interval; N.A. = not available; N.E. = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

Medians and rates of OS and PFS were computed using the Kaplan-Meier method. Two-sided exact 95% CIs for ORR were computed using the Clopper-Pearson method.

\* Partial response

Subjects in Cohort 1 were considered to have non-measurable disease and therefore considered to be non-evaluable for response. Two subjects were incorrectly entered as having measurable disease at baseline in the database. These subjects' CRF pages will be updated for final analysis.

**Table 5.4.19.1-2: Efficacy Summary - Nivolumab + Ipilimumab Treated Subjects (Module B)-CA209908**

Nivolumab + Ipilimumab (Module B)					
	Cohort 1 (DIPG) N = 22	Cohort 2 (HGG) N = 15	Cohort 3 (Medulloblastoma) N = 15	Cohort 4 (Ependymoma) N = 10	Cohort 5 (Others) N = 19
<b>OS (Primary Endpoint in Cohort 1 and Secondary Endpoint in Cohorts 2-5)</b>					
Median (95% CI), Months	10.78 (9.07, 16.13).	8.54 (2.14, 13.63)	22.21 (13.77, N.A.)	9.82 (2.50, N.E.)	8.48 (3.45, 24.34)
12-month Rate (95% CI), %	42.9 (21.9, 62.3)	35.4 (11.3, 60.9)	86.7 (56.4, 96.5)	44.4 (13.6, 71.9)	N.A.
<b>PFS (Primary Endpoint in Cohort 2-5 and Secondary Endpoint in Cohort 1)</b>					
Median (95% CI), Months	4.53 (2.76, 6.44)	1.31 (0.92, 1.48)	2.76 (1.45, 4.60)	4.60 (0.85, 5.82)	1.61 (1.31, 3.45)
<b>ORR (Exploratory Endpoint Cohorts 1-5)</b>					
Response-evaluable Subjects	1	9	8	5	13
ORR (%)	0	0	0	0	0
(95% CI)	(0.0, 97.5)	(0.0, 33.6)	(0.0, 36.9)	(0.0, 52.2)	(0.0, 24.7)

Source: CA209908 Primary CSR<sup>157</sup>; database lock date 13-Jan-2021

Medians and rates of OS and PFS were computed using the Kaplan-Meier method. Two-sided exact 95% CIs for ORR were computed using the Clopper-Pearson method.

Subjects in Cohort 1 were considered to have non-measurable disease and therefore considered to be non-evaluable for response. One subject was incorrectly entered as having measurable disease at baseline in the database. These subject's CRF pages will be updated for final analysis.

Abbreviations: CI = confidence interval; N.A. = not available; N.E. = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival



**5.4.20 Clinical Activity in Subjects with Ovarian Cancer****5.4.20.1 Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab in Subjects with Advanced or Metastatic Cancers-CA209032**

CA209032 is a Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab at different dose levels in subjects with several types of advanced or metastatic solid tumors, including OC.

For OC, the study consisted of One Stage Design with a planned enrollment of 40 subjects in each arm:

- Arm N-I Dose Level 2: Nivolumab (1 mg/kg) + Ipilimumab (3 mg/kg) [Nivolumab1 + Ipilimumab3] Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W
- Arm N-I Dose Level 2b: Nivolumab (3 mg/kg) + Ipilimumab (1 mg/kg) [Nivolumab3 + Ipilimumab1] Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W
- Arm N-I Dose Level 2c: Nivolumab (3 mg/kg) Q2W + Ipilimumab (1 mg/kg) [Nivolumab3 + Ipilimumab1] Q6W

As of database lock of 12-Apr-2019, the ORR per BICR in the Nivolumab1 + Ipilimumab3 (DL 2), Nivolumab3 + Ipilimumab1 (DL 2b), and Nivolumab3 + Ipilimumab1 (DL 2c) arm was 5/41 (12.2%), 3/43 (7.0%) and 4/42 (9.5%), respectively (Table 5.4.20.1-1).

**Table 5.4.20.1-1: Best Overall Response per BICR - Treated Subjects with Ovarian Cancer-CA209908**

	Number of Subjects (%)		
	Nivo 1 + Ipi 3 (DL 2) N = 41	Nivo 3 + Ipi 1 (DL 2b) N = 43	Nivo 3 + Ipi 1 (DL 2c) N = 42
BEST OVERALL RESPONSE (A) :			
COMPLETE RESPONSE (CR)	0	2 ( 4.7)	2 ( 4.8)
PARTIAL RESPONSE (PR)	5 ( 12.2)	1 ( 2.3)	2 ( 4.8)
STABLE DISEASE (SD)	12 ( 29.3)	12 ( 27.9)	11 ( 26.2)
PROGRESSIVE DISEASE (PD)	19 ( 46.3)	20 ( 46.5)	21 ( 50.0)
UNABLE TO DETERMINE (UTD)	4 ( 9.8)	5 ( 11.6)	4 ( 9.5)
NOT REPORTED	1 ( 2.4)	3 ( 7.0)	2 ( 4.8)
OBJECTIVE RESPONSE RATE (1) (95% CI)	5/41 ( 12.2%) (4.1, 26.2)	3/43 ( 7.0%) (1.5, 19.1)	4/42 ( 9.5%) (2.7, 22.6)

Source: CA209032 Final CSR<sup>158</sup>; database lock 12-Apr-2019

Notes: RECIST 1.1, confirmation of response required.

(1) CR+PR, confidence interval based on the Clopper and Pearson method.

Confirmed BOR where response designations before start of subsequent therapy contribute to the BOR determination.

**5.4.20.2 Nivolumab in Subjects with Advanced or Recurrent Ovarian Cancer-ONO-4538-23**

ONO-4538-23 was a phase III, multicenter, randomized, open-label study in subjects with platinum-resistant, advanced or recurrent ovarian cancer. The objective of this study is to evaluate the efficacy and safety of nivolumab versus chemotherapy (liposomal doxorubicin or gemcitabine).<sup>159</sup>

Eligible subjects were randomly assigned to either the nivolumab group or the chemotherapy group in a 1:1 ratio after stratification according to histological type (clear cell carcinoma [CCC] vs. non-CCC) and prior treatment history after diagnosis of platinum resistance (number of regimens: 0 vs. 1). In the nivolumab group, 240 mg of nivolumab was administered once in 2 weeks (one cycle). In the chemotherapy group, the investigator or sub investigator chose either liposomal doxorubicin or gemcitabine at the time of enrollment in the study and administered it. Liposomal doxorubicin was administered at a dose of 50 mg/m<sup>2</sup> on Day 1, followed by a rest for 27 days (one cycle). Gemcitabine was administered at a dose of 1000 mg/m<sup>2</sup> once weekly for 3 weeks, followed by a rest for 7 days in the fourth week (one cycle).

At the study completion, 316 subjects were in ITT (157 subjects in the nivolumab group and 159 subjects in the chemotherapy group [84 subjects in the liposomal doxorubicin group and 75 subjects in the gemcitabine group]).

- In ITT population, the median OS [two-sided 95% CI], which was the primary endpoint, was 10.12 months [8.34, 14.09] in the nivolumab group and 12.09 months [9.26, 15.34] in the chemotherapy group. Hazard ratio was not statistically significant different (hazard ratio [two-sided 95% CI]: 0.98 [0.77, 1.23], stratified log-rank test: p=0.8295).
- In ITT, the overall response rate [two-sided 95% CI] according to RECIST guideline, version 1.1 was 5.7% [2.7, 10.6] (9/157 subjects) in the nivolumab group and 9.4% [5.4, 15.1] (15/159 subjects) in the chemotherapy group (p=0.2128, Cochran–Mantel–Haenszel test).

The superiority of nivolumab to chemotherapy was not verified in subjects with platinum-resistant, advanced, or recurrent ovarian cancer. In the subgroup analysis, the efficacy of nivolumab was numerically higher than that of chemotherapy in CCC, suggesting the possibility that nivolumab has clinical significance, but the number of subjects was limited precluding the ability to draw definitive conclusion.

#### **5.4.21 Clinical Activity in Subjects with Breast Cancer**

##### **5.4.21.1 Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab in Subjects with Advanced or Metastatic Cancers-CA209032**

CA209032 is a Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab at different dose levels in subjects with several types of advanced or metastatic solid tumors, including TNBC.

As of the data cutoff date of 12-Apr-2019, 18 subjects were in nivolumab 3 mg/kg monotherapy (nivolumab monotherapy) group, 3 subjects in the nivolumab 1 mg/kg + ipilimumab 1 mg/kg (N1I1) group, and 18 subjects in nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1I3) group.<sup>160</sup>

Efficacy results as of 12-Apr-2019 for subjects who received are presented in below:

- One subject (N = 1/18) in the nivolumab monotherapy arm achieved an objective response (ORR 5.6% [95% CI: 0.1, 27.3]). The baseline PD-L1 expression for this subject was < 1%. Moreover, this responder had Stage III disease at diagnosis and Stage IV disease at study entry, with the primary tumor removed at surgery after neo-adjuvant treatment.

- Median PFS in the nivolumab monotherapy, N1I1, and N1I3 arms was 1.38 months, 2.20 months, and 1.35 months, respectively.
- Median OS in the nivolumab monotherapy, N1I1, and N1I3 arms was 5.59 months, 17.61 months, and 10.61 months, respectively.

#### **5.4.21.2 Nivolumab Combined with Chemotherapy Subjects with Untreated, High-risk, Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Primary Breast Cancer**

CA2097FL is an ongoing Phase 3, randomized, global study assessing the efficacy and safety of nivolumab vs nivolumab placebo combined with standard neoadjuvant anthracycline-taxane-based chemotherapy, followed by nivolumab or nivolumab placebo combined with ET as adjuvant treatment, in subjects with high-risk, ER+, HER2- primary BC.<sup>161</sup> The primary objective is to compare efficacy of nivolumab plus chemotherapy vs nivolumab placebo plus chemotherapy as neoadjuvant treatment in terms of the absence of residual tumor disease in participants with untreated, high-risk ER+, HER2- BC. This study was designed to evaluate nivolumab (Arm A) vs nivolumab placebo (Arm B) in combination with neoadjuvant chemotherapy and adjuvant ET in newly diagnosed, treatment-naïve subjects with high-risk ER+, HER2- BC. High-risk disease was defined as a subject having either Grade 3 disease or having Grade 2 disease with low ER expression of 1-10%. As of 16-May-2022 (at the time of enrollment closure), a total of 521 subjects were randomized in a 1:1 ratio to Arm A and Arm B.

#### **Efficacy Results:**

The mITT population used for efficacy analyses included all randomized subjects excluding those from the Russian sites who discontinued due to “sponsor decision” or “study closure at country level” prior to a pCR assessment or had less than 6 months of follow-up by 01-May-2022 (5 subjects in Arm A and 2 subjects in Arm B).

The primary endpoint, pCR, depended on participants undergoing surgery. Due to the above-mentioned constraints, over half of the randomized participants from the Russian sites did not reach the surgery phase and therefore were not expected to have a pCR assessment. Of the 23 randomized participants from the Russian sites, 11 had a pCR assessment and 1 discontinued in 2021 and were counted as a non-pCR. The remaining 11 participants were either randomized in 2022 and therefore did not have sufficient time on study for a pCR assessment (n=8) or were discontinued due to the closure of the site prior to a pCR assessment (n=3).

pCR rate in the mITT population was the primary endpoint of this study, and the difference between arms was statistically significant: Arm A (24.5%, 63/257) vs Arm B (13.8%, 35/253; adjusted difference, 10.5%; 95% CI 4.0-16.9; P = 0.0021 (Table 5.4.21.2-1)

**Table 5.4.21.2-1: Efficacy Summary**

Parameter	Arm A: Nivo + Chemo / Nivo + ET	Arm B: Nivo Placebo + Chemo / ET
PRIMARY ENDPOINT		

**Table 5.4.21.2-1: Efficacy Summary**

Parameter	Arm A: Nivo + Chemo / Nivo + ET	Arm B: Nivo Placebo + Chemo / ET
<b>pCR (primary definition) in mITT population</b>		
	<b>N = 257</b>	<b>N = 253</b>
Yes, n (%)	63 (24.5)	35 (13.8)
No, n (%)	166 (64.6)	202 (79.8)
Not Assessed, n (%)	28 (10.9)	16 (6.3)
pCR rate (95% CI) (A)	24.5% (19.4, 30.2)	13.8% (9.8, 18.7)
Adjusted difference of pCR rates (95% CI) (B, C)	10.5% (4.0, 16.9)	--
Estimate of odds ratio of pCR (95% CI) (C, D)	2.05 (1.29, 3.27)	--
p-value (E)	0.0021	--
<b>KEY SECONDARY ENDPOINTS</b>		
<b>pCR (primary definition) by PD-L1 expression <math>\geq 1\%</math> population (SP142 assessment)</b>		
	<b>N = 88</b>	<b>N = 84</b>
Yes, n (%)	39 (44.3)	17 (20.2)
No, n (%)	43 (48.9)	62 (73.8)
Not assessed, n (%)	6 (6.8)	5 (6.0)
pCR rate (95% CI) (A)	44.3% (33.7, 55.3)	20.2% (12.3, 30.4)
Adjusted difference of pCR rates (95% CI) (B, C)	24.1% (10.7, 37.5)	--
Estimate of odds ratio of pCR (95% CI) (C, D)	3.11 (1.58, 6.11)	--
<b>RCB in mITT population, Radiographic Assessment</b>		
	<b>N = 257</b>	<b>N = 253</b>
RCB Class, n (%)		
RCB-0	62 (24.1)	34 (13.4)
RCB-I	17 (6.6)	20 (7.9)
RCB-II	90 (35.0)	106 (41.9)
RCB-III	57 (22.2)	73 (28.9)
Not reported	31 (12.1)	20 (7.9)
RCB 0-I Rate (95% CI)(F)	30.7% (25.2, 36.8)	21.3% (16.5, 26.9)
Adjusted difference of RCB 0-I rates (95% CI) (C, G)	9.2% (2.0, 16.5)	--
Estimate of odds ratio of RCB 0-I (95% CI) (C, D)	1.65 (1.10, 2.49)	--

**Table 5.4.21.2-1: Efficacy Summary**

Parameter	Arm A: Nivo + Chemo / Nivo + ET	Arm B: Nivo Placebo + Chemo / ET
<b>RCB by status of PD-L1 <math>\geq</math> 1% expression population (SP142 assessment)</b>		
	<b>N = 88</b>	<b>N = 84</b>
RCB Class, n (%)		
RCB-0	38 (43.2)	16 (19.0)
RCB-I	10 (11.4)	6 (7.1)
RCB-II	25 (28.4)	36 (42.9)
RCB-III	9 (10.2)	20 (23.8)
Not Reported	6 (6.8)	6 (7.1)
RCB 0-I Rate (95% CI) (F)	54.5% (43.6, 65.2)	26.2% (17.2, 36.9)
Adjusted difference of RCB 0-I rates (95% CI) (C,G)	28.5% (14.6, 42.4)	--
Estimate of odds ratio of RCB 0-I (95% CI) (C,D)	3.49 (1.82, 6.69)	--

Source: CA2097FL Primary CSR<sup>161</sup> Database lock 14-Apr-2023

The population excludes Russian sites subjects disc. due to sites closure prior to pCR assessment or with insufficient follow-up.

pCR: No invasive residual disease in breast and lymph nodes (ypT0/is, ypN0) by a local pathologist.

RCB-0: no residual disease; RCB-1: minimal residual disease; RCB-II: moderate residual disease. RCB-III: extensive residual disease.

(A) Non-pCR: subjects with pCR No or pCR Not Assessed. Confidence interval based on the Clopper and Pearson method.

(B) Strata adjusted difference in pCR (Arm A-B) based on Cochran-Mantel-Haenszel (CMH) method of weighting

(C) Stratified by PD-L1 by SP142 (< 1% vs.  $\geq$  1%), AC Dose-Frequency Chemotherapy Regimen (Q2W vs. Q3W) per IRT. Tumor Grade (Grade 2 vs. Grade 3) and Axillary Nodal Status (positive vs. negative) per IRT are excluded following SAP rule.

(D) Strata adjusted odds ratio (Arm A over Arm B) using Mantel-Haenszel method.

(E) Two-sided p-value from stratified CMH Test.

(F) Confidence interval based on the Clopper and Pearson method.

(G) Strata adjusted difference in RCB 0-I (Arm A-B) based on Cochran-Mantel-Haenszel (CMH) method of weighting

## 5.4.22 Clinical Activity in Subjects with Solid Tumors

### 5.4.22.1 Clinical Activity of Nivolumab Monotherapy or Nivolumab in Combination with Ipilimumab or Relatlimab or Daratumumab in Subjects with Virus-Positive and Virus-Negative Solid Tumors - CA209358

Study CA209358 is an open label, multicenter, Phase 1/2 trial to investigate the safety and efficacy of nivolumab (henceforth referred to as 'nivo') as a single agent or in combination with either ipilimumab (henceforth referred to as 'ipi'), relatlimab (anti-LAG3 antibody; BMS-986016; [henceforth referred to as 'relat']), or daratumumab (henceforth referred to as 'dara') in the following tumor types: Epstein Barr Virus (EBV)(+) Gastric cancer, EBV(+) nasopharyngeal

cancer (NPC), cervical cancer, Human Papilloma Virus (HPV)(+) and (-) squamous cell cancer (SCC) of the head and neck (SCCHN), HPV-associated gynecological (GYN) and anogenital cancers (vaginal, vulvar, anal canal, penile), and Polyomavirus(+) Merkel cell cancer (MCC).<sup>162</sup>

Subjects were included if they had progressive metastatic or recurrent MCC and  $\leq 2$  prior systemic therapies in the metastatic setting. A total of 963 subjects were enrolled in this study, of which 578 subjects received study treatment. Subjects were enrolled into the Neoadjuvant or Metastatic Monotherapy or assigned or randomized into the Metastatic Combination (combo) Therapy cohorts (A, B, C, and D) based on eligibility and tumor type shown in Table 5.4.22.1-1.

**Table 5.4.22.1-1: Tumor Types and Treatment Administered by Cohort-CA209358**

Cohort (number of treated subjects)	Treatment administered	Tumor Type
Neoadjuvant Therapy-Nivo (n=123)	Nivo administered IV over 30 minutes at 240 mg for 2 doses, on Day 1 and Day 15	<ul style="list-style-type: none"> <li>• HPV(+) SCCHN (N-1)</li> <li>• HPV(-) SCCHN (N-2)</li> <li>• GYN Carcinoma (N-3) <ul style="list-style-type: none"> <li>– Cervical (N-3-C)</li> <li>– Vaginal/Vulvar (N-3-V)</li> </ul> </li> <li>• MCC (N-4)</li> </ul>
Metastatic Monotherapy- Nivo (n=113)	Nivo administered IV over 30 minutes at 240 mg Q2W for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.	<ul style="list-style-type: none"> <li>• EBV(+) Gastric cancer (M-1)</li> <li>• HPV(+) SCCHN (M-2)</li> <li>• GYN Carcinoma (M-3): M-3-C + M-3-V <ul style="list-style-type: none"> <li>– Cervical (M-3-C)</li> <li>– Vaginal/Vulvar (M-3-V)</li> </ul> </li> <li>• MCC (M-4)</li> <li>• NPC (M-5)</li> </ul>
Metastatic Combo A-Nivo + Ipi [N3+I1] (n=195)	Nivo 3 mg/kg IV over 30 minutes Q2W plus ipi 1 mg/kg IV over 30 minutes Q6W for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.	<ul style="list-style-type: none"> <li>• HPV(+) SCCHN (immuno-oncology [I-O] naïve) (MC-1a)</li> <li>• Cervical Carcinoma (randomized) (MC-2a)</li> <li>• Anogenital cancers (MC-3a) (vulvar, vaginal, anal canal, penile)</li> <li>• MCC (MC-4a)</li> <li>• NPC (MC-5a)</li> </ul>
Metastatic Combo B- Nivo + Ipi [N1+I3] (n=133)	Nivo 1 mg/kg IV over 30 minutes plus ipi 3 mg/kg IV over 30 minutes Q3W for 4 doses followed by nivolumab 240 mg IV over 30 minutes Q2W for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.	<ul style="list-style-type: none"> <li>• Cervical Carcinoma (randomized) (MC-2b)</li> <li>• SCC of the Cervix (expansion) (MC-exp) <ul style="list-style-type: none"> <li>– Expansion, first line (1L) (MC-exp1)</li> <li>– Expansion, second line (2L) (MC-exp2)</li> </ul> </li> <li>• Cervical (pooled) (MC-cer): MC-2b + MC-exp1 + MC-exp2 <ul style="list-style-type: none"> <li>– Pooled, first line (1L) (MC-cer1): MC-2b + MC-exp1</li> <li>– Pooled, second line (2L) (MC-cer2): MC-2b + MC-exp2</li> </ul> </li> <li>• Anogenital cancers (MC-3b) (vulvar, vaginal, anal canal, penile)</li> </ul>

**Table 5.4.22.1-1: Tumor Types and Treatment Administered by Cohort-CA209358**

Cohort (number of treated subjects)	Treatment administered	Tumor Type
Metastatic Combo C-Nivo + relat [N+R] (n=8)	Nivo 240 mg over 30 minutes Q2W plus relat 80 mg for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.	<ul style="list-style-type: none"> <li>HPV(+) SCCHN (I-O experienced) (MC-6c)</li> </ul>
Metastatic Combination D- Nivo + dara [N+D] (n=6)	Dara 16 mg/kg IV administered weekly for the first 8 weeks. Thereafter, dara 16 mg/kg administered Q2W from Weeks 9-24. Starting at Week 3, nivo 240 mg IV over 30 minutes administered Q2W. Starting at Week 25, nivo 480 mg IV flat dose over 30 minutes Q4W; dara 16 mg/kg Q4W administered for a maximum of 24 months or until progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.	<ul style="list-style-type: none"> <li>HPV(+/-, or unknown) SCCHN (I-O naïve) (MC-7d)</li> </ul>

A summary of overall efficacy is presented below.

### **Metastatic Therapy Cohorts:**

Overall, results for all treated subjects in the Metastatic Combo C and Combo D cohorts, generated on small sample sizes, did not demonstrate clinically meaningful efficacy signals. Therefore, the efficacy results of the metastatic therapy cohorts are focused on the Monotherapy, Combo A, and Combo B cohorts and are presented by tumor indication for treatment regimen-comparison.

**Cervical Carcinoma:** In study CA209358, among all randomized subjects, ORR, OS, and PFS consistently favored Combo B (N1+I3) (ORR: 40% [95%CI: 25.7, 55.7]; median OS: 24.74 [95% CI: 16.59, 49.12] months; median PFS: 7.20 [95% CI: 3.75, 17.25] months) over Combo A (N3+I1) (ORR: 31.1% [95% CI: 18.2, 46.6]; median OS: 15.24 [95% CI: 9.03, 36.21] months; median PFS: 3.75 [95% CI: 2.07, 10.28] months).

Responses were observed regardless of tumor PD-L1 status. TPS PD-L1-positive  $\geq 1\%$  subgroups favored nivo monotherapy and Combo A (N3+I1) for all endpoints. However, the interpretation is limited due to the small sample sizes and the percent of non-evaluable for PD-L1 TPS. CPS  $\geq 1\%$  and CPS  $\geq 10\%$  were associated similarly with ORR across the treatment cohorts. However, the interpretation of response to PD-L1 positive subjects at the  $\geq 1\%$  cut-off is limited due to the small sample size of subjects with PD-L1 CPS  $< 1\%$ . CPS  $\geq 1\%$  and TPS  $\geq 1\%$  were associated similarly with ORR across the treatment cohorts.

For the 1L subgroup of Combo B, ORR of 41% was lower relative to historical data. PFS was more similar to the historical median PFS. The 2L subgroups of the Combo A and Combo B cohorts performed similarly or better compared to external data (Keynote-158) regarding anti-PD-L1 with chemotherapy combination. Given the small sample sizes for line of therapy results, interpretations were limited.



**HPV(+) SCCHN:** Among all treated subjects, nivo monotherapy demonstrated an ORR of 11.5% (95% CI: 2.4, 30.2) which was lower than the available historical ORR of 17%. The median OS was 20.44 (95% CI: 13.90, 64.59) months and the median PFS was 3.25 (95% CI: 1.84, 6.93) months, which was similar to the historical median PFS.

Combo A (N3+I1) demonstrated an ORR of 31.0% (95% CI: 17.6, 47.1) with a median DOR of 34.46 (95% CI: 10.45, N/A) months. No improvement was demonstrated in median OS (17.15 [95% CI: 9.49, 26.91] months) for Combo A (N3+I1) compared to nivo monotherapy. The median PFS (3.71 [95% CI: 1.77, 7.39] months) overlapped with the PFS 95% CI of nivo monotherapy, although the PFS 12-month (34.97% [95% CI: 20.72, 49.59]) and 24-month rates (25.43% [95% CI: 12.77, 40.22]) for Combo A (N3+I1) were more favorable versus nivo monotherapy.

**MCC:** Among all treated subjects, nivo monotherapy demonstrated clinically meaningful ORR (64% [95% CI: 42.5, 82]) as it relates to historical data. The OS signal demonstrated a positive trend (median OS: N/A [95% CI: 23.26, N/A] months and OS 24-month rate: 71.78% [95% CI: 49.72, 85.44]), and durability by PFS (median PFS: 21.32 [95% CI: 9.20, 62.52] months) and DOR (median DOR: 60.62 [95% CI: 16.72, N/A] months) was consistent and noticeable, despite early censoring and population heterogeneity.

Combo A (N3+I1) demonstrated an ORR of 58.1% (95% CI: 42.1, 73.0) which was comparable to nivo monotherapy with overlapping 95% CI. Median OS (29.83 [95% CI: 8.51, N/A] months) and median PFS (9.49 [95% CI: 3.71, 24.34] months) values for Combo A (N3+I1) were reduced compared to nivo monotherapy.

**NPC:** Among all treated subjects, nivo monotherapy demonstrated an ORR of 16.7% (95% CI: 4.7, 37.4) with a median DOR of 9.46 (95% CI: 3.68, N/A) months. The median OS was 22.74 (95% CI: 12.62, 35.29) months, demonstrating an OS signal trend up to 24 months (OS 24-month rate: 41.81% [95% CI: 21.23, 61.22]). The median PFS was 1.94 (95% CI: 1.54, 3.580 months), with a PFS 12-month and 24-month rate of 0%.

Combo A (N3+I1) demonstrated an ORR of 26.2 (95% CI: 13.9, 42.0), which was lower than the historic ORR value of Docetaxel + cisplatin (63%) but higher than the historic ORR value of Cetuximab + carboplatin (12%). The median DOR was 21.95 (95% CI: 5.55, N/A) months, and the median OS was 23.56 (95% CI: 16.82, 37.68) months. The OS 6-month rate favored Combo A (N3+I1) over nivo monotherapy (87.97% [95% CI: 73.47, 94.81] vs. 75% [95% CI: 52.62, 87.91]) and demonstrated comparable values at 24 months (47% [95% CI: 30.35, 62.00] vs. 41.81 [95% CI: 21.23, 61.22]). The OS signal demonstrated a favorable trend over Docetaxel + cisplatin (median OS: 12.4 months) and Cetuximab + carboplatin (median OS: 7.7 months). Median PFS was 4.40 (95% CI: 2.37, 9.03) months with an improved PFS 12-month rate of 24.39% (95% CI: 12.65, 38.17) and 24-month rate of 17.07% (95% CI: 7.51, 20.91).

#### **5.4.22.2 Clinical Activity of Nivolumab Monotherapy or Nivolumab in Combination with Ipilimumab in Solid Tumors of High Tumor Mutation Burden-CA209848**

CA209848 is an ongoing open-label Phase 2 study to demonstrate the clinical activity of nivolumab in combination with ipilimumab in participants with advanced or metastatic solid tumors of TMB-H in blood (bTMB-H) or tissue (tTMB-H), including salvage setting participants defined as subjects with refractory, metastatic or unresectable TMB-H malignancy who were treated with prior non-IO therapies for whom no standard treatment per local management guidelines was available.<sup>163</sup> The study randomized participants diagnosed with advanced or metastatic solid tumors (excluding melanoma, non-small cell lung cancer and renal cell carcinoma) with either tTMB-H or bTMB-H  $\geq 10$  mut/Mb. In part A, subjects were treated with nivo 240Q2W + ipi 1mg/kg Q6W up to 24 months. In part B, subjects were treated with nivo 480mg Q4W up to 24 months. As of the data base lock of 30-Jun-2022, 211 subjects were treated in the study.

The primary efficacy criteria, that the lower bound of 95% CI for ORR by BICR  $>10\%$  for the nivolumab + ipilimumab arm in both the bTMB-H and tTMB-H groups, were met in this analysis. The ORR in the bTMB-H population (N=80) was 22.5% (95% CI: 13.9, 33.2) in the nivolumab + ipilimumab treatment arm, and was 15.6% (95% CI: 6.5, 29.5) in the nivolumab monotherapy arm.

The summary of efficacy for the bTMB group is provided below:

**Primary Endpoint:** Of the 80 subjects in the nivolumab + ipilimumab Arm A, 18 had a confirmed response per BICR, with ORR = 22.5% (95% CI: 13.9, 33.2), and 7 of 45 subjects (95% CI: 6.5, 29.5) receiving nivolumab monotherapy exhibited a confirmed response; ORR = 15.6% (95% CI: 6.5, 29.5).

##### **Secondary Endpoints:**

- Responses were early and durable in both arms. The median TTR per BICR was 2.8 (2.6, 8.8) months in Arm A and 2.7 (2.5, 9.0) months in Arm B. The median DOR was not yet reached in either treatment group, but the rates were 94% (67%, 99%) and 86% (33%, 98%) for DOR of at least 6 months for Arm A and Arm B, respectively.
- The median PFS per BICR was 2.8 months in both Arm A and Arm B, with 95% confidence intervals (CI: 2.3, 3.0 and CI: 2.6, 3.3 for Arm A and Arm B, respectively). Median PFS per investigator was 3.0 (2.7, 4.3) months in Arm A and 3.0 (2.8, 5.4) months in Arm B.
- The median OS in the arm treated with nivolumab + ipilimumab (80% of events) was 8.1 (5.8 - 10.5) months and 11.2 (5.3 - 19.0) months in the nivolumab monotherapy arm (76% of events).

The summary of efficacy for tTMB group is provided below:

**Primary Endpoint:** Of the 88 subjects in the nivolumab + ipilimumab arm A, 34 had a confirmed response per BICR, with ORR = 38.6% (95% CI: 28.4, 49.6). Fourteen of 47 subjects receiving nivolumab monotherapy exhibited a confirmed response; ORR = 29.8% (95% CI: 17.3, 44.9).

##### **Secondary Endpoints:**

- Responses were early and durable in both the nivolumab + ipilimumab and nivolumab monotherapy arm. The median TTR per BICR was 2.8 (2.1, 27.6) months in Arm A and was

also 2.8 (2.5, 9.0) months in Arm B. As in the bTMB group, the median DOR was not yet reached in either treatment group, but the rate of responders was 94% (78%, 98%) and 86% (54%, 96%) for DOR of at least 6 months for Arm A and Arm B, respectively.

- The median PFS per BICR was 5.7 (3.2, 11.6) months in Arm A and 2.8 (2.7, 5.7) months in Arm B. Median PFS per investigator was 8.15 (4.8, 12.9) months in Arm A and 3.1 (2.8, 10.9) months in Arm B.
- The median OS in the arm treated with nivolumab + ipilimumab (59% of events) was 15.1 (10.2 - 29.8) months, and median OS in the nivolumab monotherapy arm (68% of events) was 14.6 (7.7 - 20.7) months.

#### **5.4.22.3 Clinical Activity of Nivolumab in Combination with Ipilimumab in Chinese Subjects with Previously Treated Metastatic or Recurrent Solid Tumors -CA209672 (Part 2)**

Part 2 of Study CA209672 is a Phase 2, open-label trial of nivolumab in combination with ipilimumab in adult Chinese subjects with histologically confirmed recurrent or metastatic MSI-H/dMMR CRC, who had shown progression during, after, or have been intolerant to  $\geq 1$  line treatment(s) for metastatic disease (included at least a fluoropyrimidine, and oxaliplatin or irinotecan), and who complied to provide tumor tissue (archival or fresh biopsy specimen).<sup>164</sup>

The Part 2 consisted of 3 periods: screening period; treatment period (until disease progression, intolerable toxicities, withdrawal of consent, completion of maximum treatment duration [up to 24 months], the study ends, or other reasons specified in the protocol, whichever occurs first); and a follow-up period (up to 100 days).

Tumor assessment was to be completed every 6 weeks from date of first dosing for the first 24 weeks, and then every 12 weeks thereafter (including treatment beyond progression) until initiation of subsequent anticancer treatment. Images were submitted to a central imaging vendor for BICR during the study.

Due to significant landscape changes and enrollment challenges, the enrollment for Part 2 was closed after 13 subjects were enrolled, out of the 33 subjects planned. Enrollment closure was not due to any safety concerns.

#### **Efficacy Results:**

The Part 2 last patient first treatment occurred on 29-Sep-2021 and the last patient last visit was 27-Oct-2022, leading to a minimum follow-up of approximately 13 months. Nivolumab in combination with ipilimumab demonstrated high anti-tumor activity in 9 Chinese subjects with previously treated MSI-H/dMMR mCRC

- The BICR-assessed ORR using RECIST 1.1 was 77.8% (7/9); of the treated subjects, 1 achieved CR and 6 achieved PR.
- The BICR-assessed DCR using RECIST 1.1 was 88.9 % (8/9); of the treated subjects, 1 achieved CR, 6 achieved PR and 1 had SD.
- The investigator-assessed ORR using RECIST 1.1 was 66.7 % (6/9), with all 6 subjects achieved PR.

- The investigator-assessed DCR using RECIST 1.1 was 88.9% (8/9); of the treated subjects, 6 achieved PR and 2 had SD.

## 5.5 Clinical Safety

Overall, the safety profile of nivolumab monotherapy in subjects with cancer is manageable and consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1-2) with relatively few drug-related high-grade (Grade 3-4) AEs. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone. The safety profile of nivolumab + ipilimumab combination therapy was consistent with the mechanisms of action of nivolumab and ipilimumab. A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3 mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD.<sup>52</sup> For nivolumab monotherapy and combination therapy, most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided in [Appendix 4](#).

The clinical safety data for nivolumab use in approved cancer indications are described in the USPI and EU SmPC ([Appendix 2](#) and [Appendix 3](#)). A summary of significant related AEs for nivolumab clinical trial treated subjects is provided in [Appendix 6](#). In addition, the following sections provide additional information on the safety profile of nivolumab monotherapy and combination therapies.

- Section 5.5.1: Nivolumab Monotherapy
- [Section 5.5.2](#): Nivolumab in Combination with Ipilimumab
- [Section 5.5.3](#): Nivolumab in Combination with Chemotherapy
- [Section 5.5.4](#): Nivolumab in Combination with Others

### **Immune-mediated Adverse Reactions**

Nivolumab or nivolumab in combination with ipilimumab is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment was required in a greater proportion of subjects receiving nivolumab in combination with ipilimumab than in those receiving nivolumab monotherapy for immune-related colitis, immune-related hepatitis, and immune-related endocrinopathies (see the USPI [[Appendix 2](#)] and the EU SmPC [[Appendix 3](#)]). The management guidelines for immune-mediated adverse reactions are described in [Section 7.1.11](#) and [Appendix 4](#) (Management Algorithms).

#### **5.5.1 Nivolumab Monotherapy**

Safety data for nivolumab monotherapy are described in the USPI ([Appendix 2](#)) for approved indications: melanoma, NSCLC, RCC, SCCHN, cHL, UC, CRC, HCC, EC, and the EU SmPC ([Appendix 3](#)) for approved indications: melanoma, NSCLC, RCC, SCCHN, cHL, UC, EC, ESCC, GEJC. The safety profile was consistent with the mechanism of action of nivolumab, and no new safety concerns were identified. In addition, available safety data for the use of a 480 mg Q4W

nivolumab treatment regimen are described in Section 5.5.1.1. Safety data for the use of a single-dose of nivolumab therapy are available in [Section 5.5.1.2](#), for multiple-dose nivolumab therapy in [Section 5.5.1.3](#), shorter infusion duration in [Section 5.5.1.4](#), for nivolumab monotherapy in Japanese, Korean, Taiwanese, and Chinese subjects in [Section 5.5.1.5](#) and for nivolumab monotherapy in Indian subjects in [Section 5.5.1.6](#).

#### **5.5.1.1 Nivolumab 480 mg Q4W Treatment Regimen**

##### **CA209384 (NSCLC)**

The study design and efficacy of CA209384 are discussed in [Section 5.4.1.3](#).

The following are the key safety findings:

- The overall safety profile was similar in the nivolumab 480 mg Q4W arm, administered as a 30 min IV infusion, as compared to the nivolumab 240 mg Q2W arm. No new safety concerns were identified in this trial.
- As of the 09-Aug-2019 clinical DBL, there were no deaths attributed to study drug toxicity in either treatment arm.
- Frequencies of all-causality AEs, drug-related AEs, AEs leading to discontinuation, and SAEs were numerically lower in the nivolumab 480 mg Q4W arm than in the nivolumab 240 mg Q2W arm (less than 5 points difference).
- Select AEs were AEs of special clinical interest meeting defined criteria and multiple event terms were grouped into select AE categories (regardless of treatment with immune-modulating medication). Additional analyses of IMAEs were conducted in order to further characterize AEs of special clinical interest and were limited to subjects who received immune-modulating medication for treatment of the event, with the exception of endocrine events. Most select AEs and IMAEs were Grade 1-2. The majority of select AEs and IMAEs resolved and were manageable using the recommended treatment guidelines for early work-up and intervention. Abnormalities in hematology laboratory results, liver tests, kidney function tests, and electrolytes in nivolumab treated subjects from both treatment arms were predominantly Grade 1 or 2.

No new safety concerns were identified in this study. The overall safety profile of nivolumab was consistent with the known safety profile of nivolumab.

##### **CA209907 (NSCLC)**

The study design and efficacy data of CA209907 are described in [Section 5.4.1.4](#).

The following are the key safety findings:

- There were 105 deaths among all 129 treated subjects, with disease progression being the most frequently reported cause of death (79.1%). There were no deaths attributed to study drug toxicity.
- There were 41 (31.8%) SAEs reported with 4 (3.1%) drug-related SAEs.
- There were 11 (8.5%) AEs leading to discontinuations (DC) and 2 (1.6%) drug-related AE leading to DC.

- Most select AEs and IMAEs were Grade 1-2. The majority of select AEs and IMAEs resolved and were manageable using the recommended treatment guidelines for early workup and intervention.
- There were 87 (67.4%) drug-related AEs reported with skin (34.1%) and hepatic (20.2%) as the most frequently reported (>15.0%) drug-related AE categories.
- Abnormalities in hematology laboratory results, liver tests, kidney function tests, and electrolytes in subjects treated with nivolumab were primarily Grade 1-2.
- The incidence of nivolumab immunogenicity was 8.8% anti-drug antibody [ADA] positive. One subject had persistent positive ADA results; no subjects had evidence of neutralizing ADAs. Nivolumab ADA did not impact safety. One nivolumab ADA-positive subject and 6 nivolumab ADA-negative subjects reported a select AE in the hypersensitivity/infusion reaction category.

The safety profile of nivolumab 480 mg Q4W administered IV over 30 minutes was consistent with the established safety profile of nivolumab 3 mg/kg Q2W in terms of the type, frequency, and severity of reported events. No new safety concerns were identified with nivolumab 480 mg Q4W treatment in this study.

#### **CA209627 (Advanced or Metastatic Malignancies)**

The study design and efficacy of CA209627 are discussed in [Section 5.4.12.3](#).

Nivolumab was well tolerated in all treatment groups with no new safety concerns identified. The following are the key safety findings:

- As of the clinical cut-off (LPLV 24-Jun-2021), across all treated subjects, there were 156 deaths. No deaths were attributed to study drug toxicity.
- SAEs were reported in 61.9% of all treated subjects.
  - 32.6% of SAEs were Grade 3-4 events
  - 25.1% of SAEs were Grade 5 events and were reported as primarily due to malignant neoplasm progression
- AEs were reported in 98.7% of all treated subjects. The most frequently reported AEs (>20%) of any grade in all treated subjects were fatigue, malignant neoplasm progression, nausea, diarrhoea and constipation.
  - 38.9% of AEs were Grade 3-4 events
  - 25.1% of AEs were Grade 5 events and were primarily reported as due to malignant neoplasm progression
- AEs leading to discontinuation of study drug were reported in 17.2% of all treated subjects.

The overall safety profile of nivolumab was consistent with expectations based on prior data, in terms of the type, frequency, and severity of reported events. The safety profile within individual tumor types could not be evaluated in detail because of the small sample size within the individual groups. No new safety concerns with nivolumab treatment were identified.



### **CA20976K(Melanoma)**

The study design and efficacy of CA20976K are discussed in [Section 5.4.2.4](#).

The overall safety results are summarized as follows:

- There were 21 (4.0%) deaths in the nivolumab arm and 16 (6.1%) deaths in the placebo arms. Death due to study drug toxicity was reported in 1(0.2%) subject in the nivo arm due to heart failure and acute kidney failure.
- Grade 3-4 AEs (regardless of causality) were reported in 119 (22.7%) subjects in the nivolumab arm, and 32 (12.1%) subjects in the placebo arm. The most frequently reported Grade 3-4 AEs (regardless of causality) were blood creatinine phosphokinase increased (1.9%) and alanine transaminase (ALT) increased, AST increased, and hypertension (1.9% each) in the nivolumab arm and headache and blood creatinine phosphokinase increased (0.8%) in the placebo arm
- Any-grade drug-related AEs were reported in 436 (83.2%) subjects in the nivolumab, and 141 (53.4%) subjects in the placebo arms. The most frequently reported drug-related AEs were fatigue (20.6%), pruritus (18.5%), and diarrhea (15.6%) in the nivolumab arm and fatigue (20.1%), pruritus, and diarrhea (9.5% each) in the placebo arm
- Grade 3-4 drug-related AEs were reported in 54 (10.3%) subjects in the nivolumab arm, and 6 (2.3%) subjects in the placebo arm. The most frequently reported Grade 3-4 drug-related AEs were AST increased and blood creatine phosphokinase increased (1.1% each) in the nivolumab arm and lipase increased (1.1%) in the placebo arm.

The safety profile of nivolumab in this setting was consistent with known safety profile of nivolumab, and acceptable in the context of the observed clinical activity.

#### **5.5.1.2 *Single-dose Nivolumab Monotherapy***

### **CA209923 (Sepsis)**

CA209923 was a Phase 1b, randomized, double-blind, multicenter study to evaluate a single dose of nivolumab in adult subjects with sepsis or septic shock who were also managed according to established best practice care for sepsis. Final database lock occurred on 11-Apr-2018, and a final clinical study report is completed. Overall, 31 subjects were randomized to receive a single dose of nivolumab 480 mg (n = 15) or 960 mg (n = 16).

The following are the key safety findings:

- Single-doses of either 480 mg or 960 mg nivolumab did not result in unexpected safety findings for participants with sepsis or septic shock.
- Death occurred in a total of 12 subjects, 6 in each dose group. All deaths were considered by the investigator to be not related to study treatment and the causes of death were not unexpected for the subject population.
- Serious adverse events (SAEs) occurred in a total of 8 subjects, 7 were in the 960 mg nivolumab dose group. One subject in the 960 mg nivolumab dose group had severe acute kidney injury, assessed as drug-related by the investigator.



- Adverse event frequency and intensity were similar across dose groups. The majority of AEs were mild to moderate. The most frequently reported AEs were anemia, pyrexia, hypotension, pleural effusion, diarrhea, and hypernatremia. AEs assessed as drug-related by investigators occurred in 6 subjects. There were no AEs leading to discontinuation in this study.
- AEs assessed as immune-mediated occurred in 21 subjects, 13 were in the 960 mg nivolumab dose group. Immune-mediated AEs were consistent with those reported in the nivolumab US Product Information. The majority of IMAEs were mild to moderate. Seven subjects had Grade 3-4 IMAEs which included acute kidney injury, diarrhea, blood bilirubin increased, blood creatinine increased, transaminase increased, renal failure, rash, and diabetic ketoacidosis.

### **MDX1106-01 (Oncology)**

MDX1106-01 was a Phase 1, open-label, multicenter, safety and pharmacokinetic dose-escalation study of nivolumab (0.3, 1, 3, or 10 mg/kg) in subjects with selected refractory or relapsed malignancies. 27 of 39 subjects received a single dose of nivolumab and 15 of those 27 received 10 mg/kg. All subjects were followed for up to 84 days after the dose of study drug.

The following are the key safety findings:

- 24 of 27 (88.9%) subjects had a drug-related AE. The most commonly reported ( $\geq 5\%$ ) drug-related AEs were fatigue, lymphopenia, proteinuria, dry mouth, fever, decreased weight, pruritus, hypocalcemia, anemia, nausea, vomiting, thyroid-stimulating hormone (TSH) increased, TSH decreased, hypokalemia, myalgia, rash. No drug-related AEs were serious. Most drug-related AEs were Grade 1 or 2. Nine (33.3%) subjects had Grade 3 or 4 drug-related AEs; the most commonly reported drug-related AEs were CD4 lymphocytes decreased (4 subjects) and lymphocyte count decreased (2 subjects).
- 7 of 27 (25.9%) subjects had an IMAE. These included rash/erythema (4 subjects), pruritus (3 subjects), arthritis (1 subject), melena (1 subject), hypersensitivity (1 subject), blood bilirubin increased (1 subject). No IMAEs were serious. All IMAEs were Grade 1 except for the case of hypersensitivity which was Grade 2.
- There was no apparent dose-related pattern with regard to the incidence, severity, or relationship of AEs.

### **MDX1106-02 (HCV)**

MDX1106-02 was a Phase 1, double-blind, randomized, multicenter, placebo-controlled, safety and pharmacokinetic dose-escalation study of a single intravenous administration of nivolumab (0.03, 0.1, 0.3, 1, 3, or 10 mg/kg) in subjects with active hepatitis C virus (HCV) infection. 45 subjects received a single dose of nivolumab, and 9 subjects received placebo. All subjects were followed for up to 84 days after the dose of study drug.

The following are the key safety findings:

- Overall, a single-dose of nivolumab (up to 10 mg/kg) was generally well tolerated. No deaths, SAEs, or discontinuations due to AEs occurred.
- 17 of 45 (37.8%) of nivolumab-treated subjects had a drug-related AE. The most commonly reported ( $\geq 5\%$ ) drug-related AEs were fatigue, headache, and diarrhea. All drug-related AEs were grade 1 or 2.

- 6 of 45 (13.3%) nivolumab-treated subjects had an IMAE. The IMAEs included diarrhea (3 subjects), hyperthyroidism (2 subjects), hypothyroidism (1 subject), blister (1 subject), urticaria (1 subject), pruritus (1 subject), and rash (1 subject). All IMAEs were Grade 1 except for the case of urticaria which was Grade 2.
- The pattern of AEs did not indicate a dose response.

### **CA209026(NSCLC)**

The study design and efficacy of CA209026 are discussed in [Section 5.4.1.1](#).

The overall safety results are summarized as follows:

- The frequency of deaths was similar in both groups: 230 (86.1%) subjects in the nivolumab group and 223 (84.8%) subjects in the ICC group died (87 died without crossover therapy and 136 died after the first dose of crossover therapy).
- The overall frequency of any grade drug-related SAEs reported was similar in the nivo (18.0%; n=48) and ICC (18.6%; n=49) groups. There were 36 (13.5%) and 43 (16.3%) grade 3-4 drug-related SAEs reported in the nivo and ICC group respectively.
- There were 30 (11.2%) and 39 (14.8%) any grade drug-related AEs leading to DC reported in the nivo and ICC group respectively, with 23(8.6%) grade 3-4 drug-related AE leading to DC in the nivo group and 20 (7.6%) in the ICC group.
- There were 195 (73.0%) any grade drug-related AEs in the nivo group compared to 243 (92.4%) in the ICC group. In the nivo group, the most frequently reported any grade drug-related AEs occurring in  $\geq 20\%$  of subjects was fatigue (22.1%). In the ICC group, the most frequently reported drug-related AEs occurring in  $\geq 20\%$  of subjects were nausea (49%), anemia (43.3%), fatigue (36.1%), decreased appetite (27.8%) and vomiting (23.2%).
- There were 52 (19.5%) grade 3-4 drug-related AEs reported in the nivo group compared to 135 (51.3%) in the ICC group. In the nivo group, the most frequently reported grade 3-4 drug-related AEs was fatigue and diarrhoea (1.5% each). In the ICC group, the most frequently reported drug-related AEs occurring in  $\geq 10\%$  of subjects were anemia (18.3%) and neutropenia (11.0%).

The safety profile of nivolumab monotherapy at 3 mg/kg Q2W was favorable compared to ICC platinum-doublet chemotherapy.

### **CA209012 (NSCLC)**

The study design and efficacy of CA209012 are discussed in [Section 5.4.1.2](#).

The summary of safety results in subjects treated with nivolumab monotherapy is provided in [Table 5.5.1.2-1](#).

**Table 5.5.1.2-1: Summary of Safety Results -Nivolumab Monotherapy-CA209012**

	Cohort F (N=52)	Cohort K (N=13)	Cohort L (N=13)	Cohort M (N=12)				
Deaths, n (%)	36 (69.2)	7 (53.8)	11 (84.6)	8 (66.7)				
Within 30 days of last dose	2 ( 3.8)	0	1 ( 7.7)	1 ( 8.3)				
Within 100 days of last dose	7 (13.5)	1 ( 7.7)	3 (23.1)	3 (25.0)				
Due to study drug toxicity	0	0	0	0				
	Number (%) Subjects							
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All Causality SAEs	23 (44.2) (30.8)	16	3 (23.1) (23.1)	3	4 (30.8) (7.7)	1	4 (33.3) (25.0)	3
Drug-related SAEs	10 (19.2) (11.5)	6	1 (7.7)	1 (7.7)	2 (15.4) (7.7)	1	0	0
All Causality AEs leading to DC	9 (17.3) (15.4)	8	3 (23.1)	0	4 (30.8) (7.7)	1	1 (8.3)	1 (8.3)
Drug-related AEs leading to DC	6 (11.5) (11.5)	6	3 (23.1)	0	2 (15.4) (7.7)	1	0	0
All Causality AEs	51 (98.1) (46.2)	24	11 (84.6) (30.8)	4	13 (100) (7.7)	1	12 (100) (50.0)	6
Drug-related AEs	36 (69.2) (19.2)	10	9 (69.2) (7.7)	1	9 (69.2) (7.7)	1	7 (58.3) (16.7)	2
Most frequent drug-related AEs (≥ 25% of Any Grade in any cohort)								
Rash	10 (19.2)	2 (3.8)	3 (23.1)	0	0	0	0	0
Fatigue	15 (28.8)	0	4 (30.8)	0	3 (23.1)	0	3 (25.0)	0
Paronychia	0	0	0	0	0	0	0	0
Cough	1 (1.9)	0	0	0	2 (15.4)	0	3 (25.0)	0
Drug-Related Select AEs, by Category								
Endocrine	8 (15.4)	1 (1.9)	3 (23.1)	0	1 (7.7)	0	1 (8.3)	0
Gastrointestinal	6 (11.5)	1 (1.9)	3 (23.1)	0	0	0	0	0
Hepatic	2 (3.8)	1 (1.9)	1 (7.7)	0	0	0	0	0
Pulmonary	3 (5.8)	1 (1.9)	1 (7.7)	0	2 (15.4)	1 (7.7)	0	0
Renal	0	0	3 (23.1)	0	0	0	0	0
Skin	13 (25.0)	2 (3.8)	4 (30.8)	0	0	0	1 (8.3)	0
Hypersensitivity/Infusion Reactions	4 (7.7)	0	1 (7.7)	0	1 (7.7)	0	0	0

Source: CA209012 CSR database lock date 19-Sep-2016 (Nivo+Mono)<sup>113</sup>

Treatment: F=NIV3; K=NIV3 S SWITCH; L=NIV3 NS SWITCH; M=NIV3 BM. MedDRA Version 19.0; CTC Version 4.0. Includes events reported between first dose and 30 days after the last dose of study therapy unless otherwise indicated.

### **5.5.1.3 Multiple-Dose Nivolumab Monotherapy**

#### **CA2098FC (Melanoma)**

CA2098FC is an ongoing randomized, double-blind, parallel, phase I study to compare the pharmacokinetics of [REDACTED] nivolumab (BMS-936558) Process D to nivolumab (BMS-936558) Process C after complete resection of stage III or stage IV melanoma [REDACTED]

[REDACTED]

[REDACTED]

Subjects received Process C or Process D nivolumab at a dose of 3 mg/kg as a 30-minute IV infusion on Day 1 of each treatment cycle Q2W for Week 1 to Week 17 and a flat dose of 480 mg IV Q4W for Week 19 to Week 51 until recurrence, unacceptable toxicity, withdrawal of consent, completion of 1 year of treatment, or the study ends, whichever occurred first.

The safety summary of CA2098FC is provided in [Table 5.5.1.3-1](#).

**Table 5.5.1.3-1: Summary of Safety - All Treated Subjects-CA2098FC**

Safety Parameters	Number of Subjects (%)			
	Nivolumab Process C (N = 129)		Nivolumab Process D (N = 132)	
<b>Deaths</b>	15 (11.6)		14 (10.6)	
<b>Primary Reason for Death</b>				
Disease	13 (10.1)		10 (7.6)	
Study Drug Toxicity	0		1 (0.8)	
Unknown	0		1 (0.8)	
Other	2 (1.6)		2 (1.5)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<b>All-causality SAEs</b>	15 (11.6)	9 (7.0)	20 (15.2)	17 (12.9)
<b>Drug-related SAEs</b>	9 (7.0)	7 (5.4)	7 (5.3)	6 (4.5)
<b>All-causality AEs leading to DC</b>	20 (15.50)	8 (6.2)	20 (15.2)	9 (6.8)
<b>Drug-related AEs leading to DC</b>	15 (11.6)	5 (3.9)	18 (13.6)	8 (6.1)
<b>All-causality AEs</b>	124 (96.1)	23 (17.8)	126 (95.5)	37 (28.0)
<b>Drug-related AEs</b>	114 (88.4)	13 (10.1)	111 (84.1)	17 (12.9)
<b>≥ 20% Drug-related AEs in Any Treatment</b>				
Rash	22 (17.1)	1 (0.8)	28 (21.2)	1 (0.8)
Pruritis	21 (16.3)	0	32 (24.2)	0
Fatigue	31 (24.0)	0	35 (26.5)	0
Hypothyroidism	26 (20.2)	0	24 (18.2)	0
<b>Drug-related Select AEs by Category</b>				
Skin	52 (40.3)	2 (1.6)	74 (56.1)	1 (0.8)
Endocrine	43 (33.3)	2 (1.6)	37 (28.0)	3 (2.3)
Gastrointestinal	18 (14.0)	1 (0.8)	24 (18.2)	4 (3.0)
Hepatic	18 (14.0)	1 (0.8)	25 (18.9)	3 (2.3)
Pulmonary	4 (3.1)	0	3 (2.3)	0
Renal	3 (2.3)	0	3 (2.3)	0
Hypersensitivity/Infusion Reactions	2 (1.6)	0	8 (6.1)	0
<b>All-causality Non-endocrine IMAEs within 100 days of last dose where Immune Modulating Medication was Initiated by Category</b>				
Rash	13 (10.1)	2 (1.6)	17 (12.9)	2 (1.5)
Diarrhea/Colitis	6 (4.7)	3 (2.3)	7 (5.3)	5 (3.8)
Hepatitis	3 (2.3)	0	8 (6.1)	4 (3.0)
Pneumonitis	3 (2.3)	0	3 (2.3)	1 (0.8)

**Table 5.5.1.3-1: Summary of Safety - All Treated Subjects-CA2098FC**

Safety Parameters	Number of Subjects (%)			
	Nivolumab Process C (N = 129)		Nivolumab Process D (N = 132)	
Nephritis and Renal Dysfunction	2 (1.6)	0	3 (2.3)	0
Hypersensitivity	1 (0.8)	0	2 (1.5)	0
<b>All-causality Endocrine IMAEs within 100 days of last dose by Category</b>				
Adrenal insufficiency	2 (1.6)	1 (0.8)	3 (2.3)	1 (0.8)
Hypothyroidism/Thyroiditis	28 (21.7)	0	27 (20.5)	0
Hypothyroidism	27 (20.9)	0	26 (19.7)	0
Hyperthyroidism	23 (17.8)	0	21 (15.9)	1 (0.8)
Thyroiditis	3 (2.3)	0	1 (0.8)	0
Diabetes Mellitus	2 (1.6)	2 (1.6)	3 (2.3)	2 (1.5)
Hypophysitis	1 (0.8)	0	2 (1.5)	0

Source: Addendum 01 CSR; data base lock 18-Feb-2022.

The overall safety profile of Process D nivolumab is consistent with the known adverse event profile of nivolumab, with no new safety concerns identified.

#### **5.5.1.4 Shorter Infusion Duration of Nivolumab Monotherapy**

##### **CA209153 (NSCLC)**

CA209153 is a Phase 3b/4 study of nivolumab in previously treated subjects with advanced or metastatic NSCLC. The safety of nivolumab 3 mg/kg was assessed when administered as a 30-min infusion (n=369) versus a 60-min infusion (n=368). The overall safety profile of nivolumab was similar between 30-minute and 60-minute infusion groups, despite the longer duration of exposure for subjects in the 30-minute infusion group (3.48 vs 1.41 months).<sup>165</sup> There were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions compared to those reported for subjects in the 60-minute infusion group. Hypersensitivity/infusion reactions were generally manageable using dosing interruptions, with only a limited impact on the total dose received for that cycle. Across both groups, systemic corticosteroids were administered in a limited number of cases (3 and 2 subjects in the 30-minute and 60-minute infusion groups, respectively) and treatment was discontinued as a result of hypersensitivity/infusion reactions in even fewer cases (1 subject and 2 subjects in the 30-minute and 60-minute infusion groups, respectively). The safety profile in both groups was consistent with the well-characterized safety profile of nivolumab as a single agent in previous studies. No new safety events were identified.

##### **CA209331 (SCLC)**

The study design and efficacy summary of CA209331 are discussed in [Section 5.4.7.2](#).

The summary of the key safety findings is shown below.

**Deaths:** In all treated subjects, a lower proportion of subjects in the nivolumab group compared with the chemotherapy group had died. There were 2 (0.7%) deaths in the nivolumab group and

3 (1.1%) deaths in the chemotherapy reported as due to study drug toxicity. Disease progression was the most frequently reported cause of death in both groups.

### **SAEs**

- The overall reported frequencies of SAEs among treated subjects were similar between the nivolumab and chemotherapy groups. The most frequently reported SAE ( $\geq 10\%$ ) was malignant neoplasm progression in both the treatment groups.
- Drug-related SAEs including Grade 3-4 events were reported in a lower proportion of subjects, in the nivolumab group than the chemotherapy group. One Grade 5 drug-related SAE of pancytopenia reported in the chemotherapy group on 30-days follow-up visit and resulted in treatment withdrawal. The most frequently reported drug-related SAEs ( $\geq 5$  subjects in either treatment group) were pneumonitis, anemia, and febrile neutropenia.

### **Drug-related AEs**

- Drug-related AEs including Grade 3-4 events were reported in a lower proportion of subjects, in the nivolumab group than the chemotherapy group. Most frequently reported drug-related AEs ( $\geq 35\%$ ) were anemia, thrombocytopenia, and neutropenia in the chemotherapy group. None of the drug-related AEs were reported in  $\geq 10\%$  subjects in the nivolumab group.
- The most frequently reported drug-related AEs leading to discontinuation in chemotherapy group were anemia (0 vs 3.4%) and febrile neutropenia (0 vs 2.6%).

Safety data for all treated subjects demonstrated that nivolumab has a differentiated safety profile compared with chemotherapy in subjects with SCLC whose disease has relapsed or progressed after one prior platinum-based chemotherapy regimen. No new safety concerns were identified with long-term safety data of nivolumab.

#### **5.5.1.5 Nivolumab Monotherapy in Japanese, Korean, Taiwanese, and Chinese Subjects**

Safety of nivolumab monotherapy in Japanese subjects with advanced NSCLC (ONO-4538-05/ONO-4538-06, described in the JPI), unresectable or recurrent melanoma (ONO-4538-02/ONO-4538-08, described in the JPI), or relapsed or refractory cHL (ONO-4538-15), uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma (ONO-4538-39), advanced malignant melanoma (ONO-4538-31), advanced or recurrent ovarian cancer (ONO-4538-23), glioblastoma (ONO-4538-19), esophageal cancer (ONO-4538-24, described in JPI), and biliary cancer (ONO-4538-32) were consistent with safety reported in the USPI ([Appendix 2](#)) and EU SmPC ([Appendix 3](#)). Additionally, results in Korean Subjects with advanced NSCLC (ONO-4538-09), and subjects from China, Russia, and Singapore (CA209078) were also found to be consistent with safety reported in the respective USPI ([Appendix 2](#)) and EU SmPC ([Appendix 3](#)).



### **Safety in Japanese Subjects - ONO-4538-01**

As of the study end date of 03-Jun-2014 (end of follow-up of the last subject), no deaths have been reported. A summary of safety is provided below:

**Serious Adverse Events:** Four subjects had an SAE reported on study (1 subject each in the 1-mg/kg and 3-mg/kg groups and 2 subjects in the 10-mg/kg group).

- The events were pain in extremity (1 subject, 1-mg/kg group); malignant neoplasm progression (1 subject, 3-mg/kg group); dehydration (1 subject, 10-mg/kg group); and ALT increased, AST increased, and blood bilirubin (1 subject, 10-mg/kg group).
- Only the event of dehydration in the 10-mg/kg group was considered possibly related to study drug, but the event improved with treatment.

**Adverse Events:** All 17 subjects receiving nivolumab developed an AE and a drug-related AE. The AEs occurring in more than 1 subject from the start of the study to the extended treatment phase were:

- 1-mg/kg group: blood creatine phosphokinase increased and eosinophil count increased at 66.7% (2 of 3 subjects) each
- 3-mg/kg group: diarrhea, blood albumin decreased, eosinophil count increased, hematocrit decreased, hemoglobin decreased, total protein decreased, and red blood cell count decreased at 60.0% (3 of 5 subjects) each; and constipation, vomiting, pain, C-reactive protein increased, lymphocyte count decreased, neutrophil count decreased, arthralgia, erythema, and rash at 40.0% (2 of 5 subjects) each
- 10-mg/kg group: lymphocyte count decreased at 83.3% (5 of 6 subjects); blood lactate dehydrogenase (LDH) increased, blood uric acid increased, and decreased appetite at 50.0% (3 of 6 subjects) each; and ventricular extrasystoles, constipation, diarrhea, fatigue, malaise, pyrexia, ALT increased, AST increased, blood albumin decreased, blood creatine phosphokinase increased, blood creatinine increased, C-reactive protein increased, eosinophil count increased, hematocrit decreased, hemoglobin decreased, pruritus, and rash at 33.3% (2 of 6 subjects) each.
- 20-mg/kg group: nausea, pyrexia, blood albumin decreased, C-reactive protein increased, lymphocyte count decreased, decreased appetite, dizziness, and upper respiratory tract inflammation at 66.7% (2 of 3 subjects) each
- The  $\geq$  Grade 3 AEs reported were pain in extremity in 1 subject (33.3%) in the 1-mg/kg group; blood albumin decreased, hematocrit decreased, hemoglobin decreased, lymphocyte count decreased, red blood cell count decreased, and malignant neoplasm progression in 1 subject (20.0%) each in the 3-mg/kg group; ALT increased, AST increased, conjugated bilirubin increased, blood bilirubin increased, and hyponatremia in 1 subject (16.7%) each in the 10-mg/kg group; and gamma-glutamyltransferase (GGT) increased, lymphocyte count decreased, blood alkaline phosphatase increased, and hypoxia in 1 subject (33.3%) each in the 20-mg/kg group. Each event was Grade 3.
- The drug-related AEs reported in  $\geq 20.0\%$  of subjects were lymphocyte count decreased at 58.8% (10 subjects), eosinophil count increased at 47.1% (8 subjects), pyrexia at 35.3% (6 subjects), blood albumin decreased and rash at 29.4% (5 subjects) each, and ventricular extrasystoles, fatigue, and blood uric acid increased at 23.5% (4 subjects) each.

**Adverse Events Leading to Discontinuation:** One subject in the 10-mg/kg group developed an AE that resulted in treatment discontinuation. The AEs that resulted in treatment discontinuation, which occurred in the same subject in the extended treatment phase, were bile duct stenosis, ALT increased, AST increased, conjugated bilirubin increased, blood LDH increased, and blood ALP increased. The events of ALT increased and AST increased were the events reported as SAEs.

#### **Japanese Subjects with Sepsis or Septic Shock - ONO-4538-54**

This was a Phase 1/2 study of nivolumab in subjects with sepsis or septic shock. Subjects were treated with a single dose of nivolumab at 480 mg (n = 5) or 960 mg (n = 8). At the date of last participant observation of 15-Mar-2018, 3 subjects died in the 960 mg arm due to progression of primary disease and 1 subject died in the 480 mg arm due to an AE occurring within 28 days after the last dose but was not considered related to study drug.

**Adverse Events:** AEs were reported in 4/5 (80.0%) subjects in the 480 mg arm and 4/8 (50.0%) subjects in the 960 mg arm.

- AEs reported in 2 subjects were diarrhoea, alanine aminotransferase increased, aspiration, decubitus ulcer, and rash.
  - Grade 3-4 event reported in 2 subjects was alanine aminotransferase increased.
- Drug-related AEs were reported in 1 (20.0%) subject in the 480 mg arm and none in the 960 mg arm.

**AEs leading to Discontinuation:** No AEs leading to discontinuation were reported.

#### **Japanese Subjects with Uterine Cervical Cancer, Uterine Corpus Cancer, Or Soft Tissue Sarcoma (ONO-4538-39)**

At the study completion, safety has been evaluated in 64 subjects (20 subjects with uterine cervical cancer, 23 subjects with uterine corpus cancer, 21 subjects with soft tissue sarcoma).

##### Uterine cervical cancer

**Deaths:** One subject (5.0%) died, and the cause of death was unrelated to the study drug.

**Serious Adverse Events:** Serious adverse events occurred in 7 subjects (35.0%), but except for pelvic venous thrombosis and spondylitis in 1 subject (5.0%) each, a causal relationship to the study drug was excluded for each event. Pelvic venous thrombosis was Grade 3 and was resolving after treatment including anticoagulant therapy. Spondylitis was Grade 3, and the outcome was not resolved after treatment with nonsteroidal anti-inflammatory drugs.

**Adverse Events:** Adverse drug reactions occurred in 13 subjects (65.0%).

- Adverse events with incidences  $\geq 10\%$  were anaemia in 35.0% (7 subjects), aspartate aminotransferase increased and pyrexia in 30.0% (6 subjects) each, alanine aminotransferase increased and arthralgia in 25.0% (5 subjects) each, upper respiratory tract infection, pruritus, and rash maculo-papular in 20.0% (4 subjects) each, blood alkaline phosphatase increased, lipase increased, cystitis, viral upper respiratory tract infection, rash, diarrhoea, malaise, hypothyroidism, and proteinuria in 15.0% (3 subjects) each, and amylase increased, blood creatinine increased, lymphocyte count decreased, gastritis, nausea, stomatitis, oedema peripheral, decreased appetite, akathisia, and femoral neck fracture in 10.0% (2 subjects) each.

- Adverse drug reactions with incidences  $\geq 10\%$  were aspartate aminotransferase increased, pruritus, diarrhoea, arthralgia, and hypothyroidism in 15.0% (3 subjects) each, alanine aminotransferase increased, lipase increased, rash maculo-papular, pyrexia, and malaise in 10.0% (2 subjects) each.

**Adverse Events Leading to Discontinuation:** Adverse events leading to discontinuation occurred in 3 subjects (15.0%), and drug-induced liver injury and rash maculo-papular in 1 subject (5.0%) each were assessed as adverse drug reactions.

#### **Japanese Subjects with Advanced Malignant Melanoma (ONO-4538-31)**

ONO-4538-31 was a multicenter, randomized, open-label study was intended to evaluate the efficacy and safety of nivolumab monotherapy at doses of 3 mg/kg at 2-week intervals (group A) and 2 mg/kg at 3-week intervals (group B) in subjects with advanced malignant melanoma.<sup>122</sup> Although grade 3 or higher adverse events, serious adverse events, and adverse events resulting in the interruption of the study treatment were observed, they were managed by interrupting the study treatment or by performing appropriate procedures. Both regimens were considered tolerable.

The safety analysis set consisted of 12 subjects (group A: 7 subjects; group B: 5 subjects). A summary of safety is provided below:

**Serious Adverse Events:** Serious adverse events were observed in one (14.3%) and one (20.0%) subject, in group A and group B respectively.

- The serious adverse events occurring in group A were hypophysitis (one subject [14.3%]) and fatigue (one subject [14.3%]).
- The serious adverse event that occurred in group B was adrenal insufficiency (one subject [20.0%]). All of them were judged as having an undeniable causal relationship with the investigational drug.

**Adverse Events:** Adverse events were observed in all 12 subjects.

- Adverse events occurring in  $\geq 2$  subjects from any treatment group were nausea (group A: one subject [14.3%]; group B: two subjects [40.0%]), constipation (group A: zero subjects [0.0%]; group B: two subjects [40.0%]), retching (group A: two subjects [28.6%]; group B: zero subjects [0.0%]), nasopharyngitis (group A: two subjects [28.6%]; group B: two subjects [40.0%]), dermatitis contact (group A: two subjects [28.6%]; group B: zero subjects [0.0%]), pyrexia (group A: two subjects [28.6%]; group B: one subject [20.0%]), lipase increased (group A: three subjects [42.9%]; group B: zero subjects [0.0%]), and vertigo (group A: two subjects [28.6%]; group B: zero subjects [0.0%]).
- No grade 5 adverse events were observed.
- In groups A and B, grade 3–4 adverse events were observed in four subjects (57.1%) and one subject (20.0%), respectively: lipase increased (group A: three subjects [42.9%]; group B: zero subjects [0.0%]), adrenal insufficiency (group A: zero subjects [0.0%]; group B: one subject [20.0%]), and hypophysitis (group A: one subject [14.3%]; group B: zero subjects [0.0%]).

#### **Japanese Subjects with Advanced or Recurrent Ovarian Cancer (ONO-4538-23)**

ONO-4538-23 was a phase III, multicenter, randomized, open-label study in subjects with platinum-resistant, advanced or recurrent ovarian cancer. The objective of this study is to evaluate

the efficacy and safety of nivolumab versus chemotherapy (liposomal doxorubicin or gemcitabine).<sup>159</sup>

For safety evaluation set, there were 311 subjects (156 subjects in the nivolumab group and 155 subjects in the chemotherapy group [82 subjects in the liposomal doxorubicin group and 73 subjects in the gemcitabine group]).

All adverse drug reactions observed in this study were manageable. Nivolumab was considered to be tolerable for subjects with platinum-resistant, advanced or recurrent ovarian cancer.

**Deaths:** The number of subjects who died was 11/156 subjects (7.1%) in the nivolumab group and 4/155 subjects (2.6%) in the chemotherapy group. The cause of all deaths was the primary disease.

#### **Serious Adverse Events:**

- The incidences of serious adverse events and adverse drug reactions were 13.5% (21/156 subjects) and 6.4% (10/156 subjects), respectively, in the nivolumab group and 15.5% (24/155 subjects) and 10.3% (16/155 subjects), respectively, in the chemotherapy group.
- Serious adverse events that occurred in two or more subjects in the nivolumab group were cerebral infarction (3/156 subjects, 1.9%) and interstitial lung disease (2/156 subjects, 1.3%). Among these, interstitial lung disease in 2/156 subjects (1.3%) and cerebral infarction in 1/156 subjects (0.6%) were adverse drug reactions.

#### **Adverse Events:**

- The incidences of adverse events and adverse drug reactions were 89.7% (140/156 subjects) and 61.5% (96/156 subjects), respectively, in the nivolumab group and 99.4% (154/155 subjects) and 98.1% (152/155 subjects), respectively, in the chemotherapy group. Adverse events with an incidence of  $\geq 10\%$  in the nivolumab group were diarrhoea (16.0%, 25/156 subjects) and nausea, pruritus, and rash (12.2%, 19/156 subjects each). Among these, rash in 10.3% (16/156 subjects), diarrhoea and nausea in 6.4% each (10/156 subjects), and pruritus in 5.8% (9/156 subjects) were adverse drug reactions. Adverse events with an incidence of  $\geq 10\%$  in the chemotherapy group were neutrophil count decreased (64.5%, 100/155 subjects), platelet count decreased (34.2%, 53/155 subjects), nausea (33.5%, 52/155 subjects), stomatitis (32.9%, 51/155 subjects), white blood cell count decreased (31.0%, 48/155 subjects), anaemia (30.3%, 47/155 subjects), palmar-plantar erythrodysesthesia syndrome (20.6%, 32/155 subjects), vomiting (16.8%, 26/155 subjects), pyrexia (15.5%, 24/155 subjects), malaise (14.8%, 23/155 subjects), constipation (14.2%, 22/155 subjects), decreased appetite (13.5%, 21/155 subjects), and rash (11.0%, 17/155 subjects).
- Regarding adverse events by grade, no subject in either treatment group experienced Grade 5 adverse events.
- Of the 156 subjects evaluable for anti-nivolumab antibody, 8 subjects (5.1%) were tested positive for anti-nivolumab antibody at baseline. Ten subjects (6.4%) were positive for anti-nivolumab antibody after the start of study treatment. None of them were persistent positive.

**Adverse Events Leading to Discontinuation:** The incidences of adverse events and adverse drug reactions leading to discontinuation of study treatment were 7.7% (12/156 subjects) and

7.1% (11/156 subjects), respectively, in the nivolumab group and 13.5% (21/155 subjects) and 10.3% (16/155 subjects), respectively, in the chemotherapy group. The adverse event leading to discontinuation of study treatment that occurred in two or more subjects in the nivolumab group was interstitial lung disease (3/156 subjects, 1.9%), and all incidents were adverse drug reactions.

### **Japanese Subjects with First Recurrence of Glioblastoma (ONO-4538-19)**

ONO-4538-19 was a phase II Study A Multicenter Open-Label, Non-Comparative Study of nivolumab in subjects with first recurrence of glioblastoma.

At the last observation date of 04-Dec-2020, the safety evaluation set, had 50 subjects and the data were consistent with the known safety profile of nivolumab.

**Deaths:** Forty-one subjects (82.0%) died from the first dose of study drug until the last observation date, the adverse event leading to death was rhabdomyolysis in 1 subject (2.0%). The subject suffered influenza after the 2nd treatment with the study drug, with persistent pyrexia, followed by the occurrence of acute kidney injury due to rhabdomyolysis, developed respiratory disorder due to pulmonary congestion, and died. Although influenza infection is the most likely etiology, it was assessed that the causality of several drugs used including nivolumab, of which rhabdomyolysis is listed in the Clinically Significant Adverse Reactions of the package inserts, could not be totally ruled out.

### **Serious Adverse Events:**

- Serious adverse events were observed in 16 subjects (32.0%), which were epilepsy in 4 subjects (8.0%), pyrexia in 2 subjects (4.0%), and large intestine polyp, cholecystitis acute, hepatic function abnormal, pharyngitis, subdural haematoma, dehydration, rhabdomyolysis, biliary neoplasm, tumour flare, haemorrhage intracranial, hemiparesis, brain oedema, and respiratory failure in 1 subject each (2.0%). Out of these, hepatic function abnormal, rhabdomyolysis, tumour flare, haemorrhage intracranial, hemiparesis, and brain oedema in 1 subject each (2.0%) were assessed to be serious drug-related adverse events.

### **Adverse Events:**

- Adverse events were observed in 45 subjects (90.0%), and drug-related adverse events were observed in 24 subjects (48.0%). The adverse events with the number of subjects (incidence) of at least 5 subjects (10.0%) were pyrexia, headache, lymphocyte count decreased, constipation, nasopharyngitis, diarrhoea,  $\gamma$ -glutamyltransferase ( $\gamma$ -GTP) increased, insomnia, and brain oedema, and the drug-related adverse events with the number of subjects (incidence) of at least 2 subjects (4.0%) were  $\gamma$ -GTP increased, lymphocyte count decreased, pyrexia, brain oedema, diarrhoea, hypopituitarism, and rash maculo-papular.
- With regard to incidences of adverse events by grade, the Grade 5 adverse event was rhabdomyolysis observed in 1 subject (2.0%).
- Endocrine disorder, gastrointestinal toxicity, hepatotoxicity, pulmonary toxicity, renal toxicity, skin toxicity, and hypersensitivity/infusion reaction were defined as categories of specific adverse events in this study. The specific adverse events were observed in 26 subjects (52.0%). Out of these, the Grade  $\geq 3$  specific adverse event was only rash maculo-papular in 1 subject (2.0%) and it was assessed to be a drug-related adverse event.

**Adverse Events Leading to Discontinuation:** Adverse events leading to treatment discontinuation were observed in 8 subjects (16.0%). An adverse event leading to withholding of doses was observed in 1 subject (2.0%).

### **Japanese Subjects with neoadjuvant NSCLC and Gastric Cancer (ONO-4538-67)**

ONO-4538-67 was a phase I Study A Multicenter Open-Label, Non-Comparative Study of neoadjuvant nivolumab monotherapy for resectable NSCLC and gastric cancer.

At the last observation date of 14-Feb-2022 for NSCLC and 15-Feb-2022 for gastric cancer, the safety evaluation set, had 26 subjects for NSCLC and 31 subjects for gastric cancer. The data were consistent with the known safety profile of nivolumab.

### **NSCLC**

**Deaths:** Four subjects (15.4%) died from the first dose of study drug until the last observation date with the cause of death reported as due to the original disease, the adverse event leading to death was not reported.

#### **Serious Adverse Events:**

- Serious adverse events were observed in 7 subjects (26.9%), which were pneumothorax in 3 subjects (11.5%), dyspnoea in 2 subjects (7.7%), and anaemia, hepatic function abnormal, function kidney abnormal, haemothorax, and interstitial pneumonia in 1 subject each (3.8%). Out of these, dyspnoea in 2 subjects (7.7%) and interstitial pneumonia in 1 subject (3.8%) were assessed to be serious drug-related adverse events.

#### **Adverse Events:**

- Adverse events were reported in 16 subjects (61.5%), and drug-related adverse events were observed in 11 subjects (42.3%). The adverse events with the number of subjects (incidence) of at least 10.0% were pneumothorax and rash maculo-papular in 4 subjects (15.4%) each, hypothyroidism and cough in 3 subjects (11.5%) each, and the drug-related adverse events with the number of subjects (incidence) of at least 10.0% were hypothyroidism in 3 subjects (11.5%).

### **Gastric Cancer**

**Deaths:** Four subjects (12.9%) died from the first dose of study drug until the last observation date due to the original disease in 3 subjects (9.7%) and other cancer in 1 subject (3.2%), the adverse event leading to death was not reported.

#### **Serious Adverse Events:**

- Serious adverse events were reported in 7 subjects (22.6%), which were fistula of small intestine in 2 subjects (6.5%), and cardiomyopathy, intussusception, pancreatic fistula, peritonitis, arterial injury, failure to anastomose, anastomotic leak, and decreased appetite in 1 subject each (3.2%). Out of these, cardiomyopathy and pancreatic fistula in 1 subject (3.2%) were assessed to be serious drug-related adverse events.

#### **Adverse Events:**

Adverse events were reported in 21 subjects (67.7%), and drug-related adverse events were reported in 7 subjects (22.6%). The adverse events with the number of subjects (incidence) of at

least 10.0% were procedural pain in 10 subjects (32.3%), insomnia in 5 subjects (16.1%), and dumping syndrome, pyrexia, and alanine aminotransferase increased in 4 subjects (12.9%) each. No drug-related adverse events with the number of subjects (incidence) of at least 10.0% was reported.

### **Korean Subjects (ONO-4538-13 and ONO-4538-14)**

#### **ONO-4538-13**

ONO-4538-13 was a Phase 1 multicenter, open-labeled, uncontrolled study of nivolumab in subjects with advanced or recurrent solid tumors who were refractory or intolerant to standard therapy or for whom no appropriate treatment was available conducted solely in Korea. Subjects were treated with a single dose of nivolumab at 1 mg/kg (n = 6), 3 mg/kg (n = 6) or 10 mg/kg (n = 6) and followed for 3 weeks after dosing. As of the database lock date of 26-Feb-2015, 2 deaths have been reported in the 18 subjects treated. Both deaths were reported as due to disease progression and not considered related to study drug.

**Serious Adverse Events:** Three SAEs were reported in 2 subjects (11.1%): blood bilirubin increased (2 subjects) and malignant neoplasm progression (1 subject). None were considered drug related.

**Adverse Events:** AEs, regardless of causality, were reported in 14 (77.8%) subjects. Of these, 4 (22.2%) subjects experienced drug-related events.

- AEs reported in  $\geq 2$  subjects included anemia (4 subjects, 22.2%), decreased appetite (4 subjects, 22.2%), pyrexia (3 subjects, 16.7%), blood bilirubin increased (2 subjects, 11.1%), and cough (2 subjects, 11.1%).
  - Grade 3 events were reported in 3 (16.7%) subjects: ascites, hyperglycemia, nausea, amylase increased, bilirubin conjugated increased, blood bilirubin increased, decreased appetite, and dyspnea.
  - Grade 4 events were reported in 2 (11.1%) subjects: blood bilirubin increased and lipase increased.
  - Only one Grade 5 event was reported; malignant neoplasm progression considered not related to study drug
- Drug-related AEs were reported in 4 (22.2%) subjects: hyperthyroidism, autoimmune thyroiditis, hypersensitivity, and blood thyroid-stimulating hormone increased. All were Grade 1 except for Grade 2 hypersensitivity.

**AEs leading to Discontinuation:** No drug-related AEs leading to discontinuation were reported.

#### **ONO-4538-14**

ONO-4538-14 was a Phase 1 multicenter, open-label, uncontrolled study of nivolumab in subjects with advanced or recurrent solid tumors who were refractory or intolerant to standard therapy or for whom no appropriate treatment was available conducted solely in Korea. Subjects were enrolled if they completed the ONO-4538-13 study and did not meet the criteria for entering the follow-up phase in that study. Subjects were treated with nivolumab 3 times with 2-week intervals



in a 6-week cycle at 1 mg/kg (n = 6), 3 mg/kg (n = 6) or 10 mg/kg (n = 6) based on treatment received in ONO-4538-13.

As of the database lock date of 7-May-2021, 2 deaths have been reported in the 18 subjects treated. Deaths were reported as due to blood bilirubin increased and malignant neoplasm progression. Both were not considered related to study drug.

**Serious Adverse Events:** 7 (38.9%) subjects experienced 9 SAEs (disease progression and blood bilirubin increased [2 subjects each], and brain neoplasm, dyspnea, musculoskeletal, pneumonitis, and malignant neoplasm progression [1 subject each]). The event of pneumonitis was considered drug related.

**Adverse Events:** AEs, regardless of causality, were reported in 18 (100.0%) subjects. Of these, 7 (38.9%) subjects experienced drug-related events.

- The most frequently reported AEs were decreased appetite (7 subjects, 38.9%), pyrexia and dyspnea (5 subjects, 27.8% each), and anemia, upper respiratory tract infection and back pain (4 subjects, 22.2%).
  - Grade 3-4 events reported in 2 or more subjects were decreased appetite, dyspnea, disease progression, and blood bilirubin increased.
  - Only one Grade 5 event was reported; malignant neoplasm progression considered not related to study drug
- Drug-related AEs were reported in 7 (38.9%) subjects and included thyroiditis and pneumonitis (2 subjects each), and eye pain, chills, pyrexia, hypersensitivity, blood thyroid stimulating hormone increased, and decreased appetite (1 subject each).

**AEs leading to Discontinuation:** 4 (22.2%) subjects had AEs leading to treatment discontinuation (disease progression and pneumonitis [2 subjects each]). Both events of pneumonitis were considered drug related.

### **Chinese Subjects - CA209077**

CA209077<sup>166</sup> was a Phase 1/2, open-label study of nivolumab monotherapy in Chinese subjects with previously treated advanced or recurrent solid tumors (nasopharyngeal cancer (NPC), NSCLC, and HCC). 46 subjects (15 subjects at 3 mg/kg Q2W, 20 subjects at 240 mg Q2W, and 11 subjects at 360 mg Q3W) received at least 1 dose of nivolumab. The overall safety profiles of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 360 mg Q3W were consistent with known nivolumab safety profile. No new safety signals were identified. As of the 20-Jan-2022 database lock, 12 deaths have been reported: 4 in the nivolumab 3 mg/kg/Q2W group, 7 in the 240 mg Q2W group and 1 in the nivolumab 480mg Q4W group. No deaths were attributed to study drug toxicity.

**Serious Adverse Events:** SAEs were reported in 40% of subjects in the 3 mg/kg Q2W group, 40% of subjects in the 240 mg Q2W group, 18.2% of subjects in the 360 mg Q3W group and 58.3% in the 480mg Q4W group. There was one drug-related SAE were reported in 3mg/kg Q2W and 240 mg Q2W group each.

**Adverse Events:** AEs, regardless of causality, were reported in 100% of subjects in all groups.

- Grade 3-4 AEs (regardless of causality) were reported in 2 (13.3%) subjects in the 3 mg/kg Q2W group, 4 (20.0%) subjects in the 240 mg Q2W group, 3 (27.3%) subjects in the 360 mg Q3W group and 5 (41.7%) subjects in the 480mg Q4W group.
- The most common (>25%) drug-related AE was reported were rash (33.3%; n=5) in 3 mg/kg Q2W group and hypothyroidism (54.5%; n= 6) and rash (36.4%; n= 4) in the 360 mg Q3W group.
- **AEs leading to discontinuation** were reported in 3 (20%) subjects in the 3 mg/kg Q2W group, 3 (15%) subjects in the 240 mg Q2W group, and 1 (9.1%) subject in the 360 mg Q3W group. Drug-related AE leading to discontinuation was only reported in 1 (6.7%) subject in the 3 mg/kg Q2W group.

### **5.5.1.6 Nivolumab Monotherapy in Indian Subjects**

#### **CA209887 (NSCLC/RCC)**

CA209887 was a completed single-arm, open-label, multi-center, prospective Phase 4 clinical study enrolled subjects with locally advanced metastatic NSCLC (Stage IIIb/IV) or advanced RCC at study sites in India.<sup>167</sup> Eligible subjects were treated with 3 mg/kg nivolumab administered intravenously over 60 minutes Q2W. Each 2-week dosing period constituted a cycle. The treatment period was comprised of 24 weeks of treatment and 2 weeks of follow-up after the final on-study dose of nivolumab.

Overall, 112 subjects were enrolled, 70 subjects with NSCLC, 30 subjects with RCC, and 12 subjects who were screen failures or lost to follow-up. Overall, 100 subjects were treated in the study, and 12 subjects did not receive study drug.

The incidence and severity of treatment-related AEs was the primary endpoint for this study. No new safety signals were observed during the study. Overall, the safety profile of nivolumab in this population was consistent with that observed in global clinical studies of nivolumab given as monotherapy.

Twenty-five (25.0%) subjects experienced treatment-related AEs; 17 (24.3%) subjects in the NSCLC group and 8 (26.7%) subjects in the RCC group. The most common treatment-related AEs of any grade were hypothyroidism, fatigue, and infusion related reaction. Treatment-related Grade 3-4 AEs were experienced by 4 (4.0%) subjects; 3 (4.3%) subjects in the NSCLC group and 1 (3.3%) subject in the RCC group. The most common treatment-related Grade 3-4 AEs were hyponatremia, lower respiratory tract infection, blood electrolytes abnormal, and pneumonitis. Treatment-related Grade 5 AEs (pneumonitis and acute respiratory distress syndrome) were each experienced by 1 (1.4%) subject in the NSCLC group.

Four (4.0%) subjects experienced treatment related SAEs; 4 (5.7%) subjects in the NSCLC group (pneumonitis, acute respiratory distress syndrome, lower respiratory tract infection, and blood electrolytes abnormal). The incidence of Grade 3-4 and Grade 5 treatment-related SAEs was low; in the NSCLC group, 4 subjects experienced 5 events (Grade 3-4 pneumonitis, Grade 3-4 lower respiratory tract infection, Grade 3-4 blood electrolytes abnormal, Grade 5 pneumonitis, and Grade 5 acute respiratory distress syndrome).

Twenty-two subjects experienced AEs leading to discontinuation, 18 in the NSCLC group and 4 in the RCC group. Of these, 2 subjects in the NSCLC group experienced 4 treatment-related AEs leading to discontinuation (leukocytosis, fatigue, transaminases increased, pneumonitis).

Treatment-related select AEs were in the hepatic (1 subject [NSCLC group], Grade 1 transaminases increased), pulmonary (2 subjects: 1 subject [NSCLC group], Grade 3 pneumonitis; 1 subject [NSCLC group], Grade 5 pneumonitis and Grade 5 acute respiratory distress syndrome), skin (2 subjects: 1 subject [NSCLC group], Grade 1 rash and 1 subject [RCC group], Grade 1 rash pruritic), and hypersensitivity/infusion reaction (3 subjects: 1 subject [NSCLC group], Grade 1 infusion related reaction; 2 subjects [1 subject in the NSCLC group, 1 subject in the RCC group], Grade 2 infusion related reaction) categories.

Immune-mediated AEs (IMAEs) where immune modulating medication was initiated were in the pneumonitis (2 subjects: 1 subject [NSCLC group], Grade 3 pneumonitis; 1 subject [NSCLC group], Grade 5 pneumonitis), hepatic (1 subject [NSCLC group], Grade 1 transaminases increased), and hypersensitivity (2 subjects: 1 subject [NSCLC group], Grade 2 infusion related reaction; 1 subject [RCC group], Grade 2 infusion related reaction) categories.

Endocrine IMAEs were in the hypothyroidism/thyroiditis (6 subjects: 2 subjects [NSCLC group], Grade 1 hypothyroidism; 2 subjects [NSCLC group], Grade 2 hypothyroidism; 1 subject [RCC group], Grade 2 hypothyroidism; 1 subject [RCC group], Grade 3 hypothyroidism), diabetes mellitus (1 subject [RCC group], Grade 1 diabetes mellitus), and hyperthyroidism (1 subject [NSCLC group], Grade 1 hyperthyroidism) categories.

### **5.5.2 Nivolumab in Combination with Ipilimumab**

Safety data for nivolumab in combination with ipilimumab in subjects with melanoma, NSCLC, MPM, RCC, CRC, HCC, and ESCC are described in the USPI ([Appendix 2](#)) and in subjects with melanoma, NSCLC, MPM, RCC, CRC and ESCC in the EU SmPC ([Appendix 3](#)). Nivolumab in combination with ipilimumab is being evaluated in subjects with UC, SCLC, SCCHN, GC, prostate cancer, pancreatic cancer, CNS malignancies, solid tumor, ovarian cancer, MPM, and breast cancer. Additional safety data for the use of nivolumab in combination with ipilimumab are presented in the below sections.

#### **5.5.2.1 Nivolumab in Combination with Ipilimumab - CA209511 (Melanoma)**

CA209511<sup>107</sup> was a Phase IIIb/IV, 2-part, 2-arm study. Part 1 evaluated nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg (N3I1; Arm A) vs nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg (N1I3; Arm B) in subjects with previously untreated, unresectable, or metastatic melanoma. Part 2 evaluated the maintenance phase dose of nivolumab 480 mg every 4 weeks. The primary endpoint database lock occurred on 01-Jun-2017 and final database lock occurred on 01-Jun-2018. Overall, 360 subjects were randomized to receive N3I1 (n = 180) or N1I3 (n = 180).

**For subjects treated in Part 1**, the safety profile of N3I1 and N1I3 was consistent with the mechanisms of action of nivolumab and ipilimumab. Per the 01-Jun-2017 DBL, the rate of drug-related Grade 3-5 AEs in the N3I1 arm was 32.8% and in the N1I3 arm was 45.5%. The

difference in Grade 3-5 drug related rates between N3I1 and N1I3 was -12.7% (95% CI: -22.7, -2.6) with a p-value of 0.0144, and was consistent with the 01-Jun-2018 DBL (-14.4%, p-value of 0.0059). No new safety concerns with N3I1 and N1I3 treatment arms were identified.

The frequencies of (all causality and drug-related, any grade and Grade 3-4) SAEs and AEs leading to discontinuation were lower in the N3I1 group than in the N1I3 group. Drug-related (any grade) AEs were also lower in the N3I1 group than in the N1I3 group. The most frequently reported drug-related AEs ( $\geq 15\%$ ) across both treatment groups were diarrhoea, fatigue, pruritus, rash, asthenia, and hypothyroidism. The frequency of drug-related Grade 3-4 AEs was lower in the N3I1 group (33.9%) than in the N1I3 group. No drug-related Grade 3-4 event in  $\geq 5\%$  of subjects were reported in the N1I3 group and the only drug-related Grade 3-4 event reported ( $\geq 5\%$ ) in the N3I1 group was diarrhoea. Most select AEs and IMAEs were Grade 1-2. The majority of select AEs and IMAEs resolved and were manageable using the recommended treatment guidelines for early work-up and intervention.

**For subjects treated in Part 2**, the overall safety profile of nivolumab fixed dose (480 mg) was similar in subjects from both the N3I1 and N1I3 treatment groups and no new safety concerns were identified. As of the 01-Jun-2018 clinical database lock, there were no deaths attributed to study drug toxicity in either the N3I1 or N1I3 treatment groups. Frequencies of (all causality and drug-related, any grade and Grade 3-4) SAEs, AEs leading to discontinuation, and all AEs were similar for subjects in the N3I1 and N1I3 groups. Most select AEs and IMAEs were Grade 1-2. All causality and drug-related hepatic select AEs (Any Grade) were higher in the N3I1 group compared to the N1I3 group. The majority of select AEs and IMAEs resolved and were manageable using the recommended treatment guidelines for early work-up and intervention.

### **CA209511 Cohort C**

Cohort C subjects were enrolled in a single arm, independently from the randomized part. Subjects were treated with nivolumab 6 mg/kg in combination with ipilimumab 1 mg/kg followed 4 weeks later by nivolumab 480 mg flat dose Q8W. Safety data from CA209511 Cohort C were consistent with the known safety profile of nivolumab in combination with ipilimumab in that no new events were identified and there were no differences in the incidences and severities of reported events. As of the 01-Jun-2018 clinical DBL, 7 deaths occurred due to progressive disease.

### **5.5.2.2 Nivolumab in Combination with Ipilimumab - CA209204 (Melanoma)**

The study design and efficacy of CA209204 are discussed in [Section 5.4.2.3](#).

Key safety findings are as follows and are presented below:

- No new safety concerns with nivolumab combined with ipilimumab followed by nivolumab monotherapy treatment were identified.
- A total of 39 (32.8%) subjects died (29 [28.7%] subjects in Cohort A and 10 [55.6%] subjects in Cohort B).
  - The most common reason for death was disease progression (29 [24.4%] subjects), including deaths occurring within 30 days of last dose and deaths occurring within

100 days of last dose; 10 (8.4%) subjects died within 30 days of last dose and 14 (11.8%) subjects died within 100 days of last dose.

- One death was attributed to study therapy toxicity (autoimmune myocarditis).
- A reason for death categorized as “other” was reported by the investigator for 3 (3.0%) subjects in Cohort A (pulmonary embolism, intracranial hemorrhage, and gastrointestinal hemorrhage) and 1 (5.6%) subject in Cohort B (neoplasm progression of disease).
- Serious AEs were reported more frequently in Cohort B (11 [61.1%] subjects) compared with Cohort A (44 [43.6%] subjects).
  - The most frequently reported SAEs were malignant neoplasm progression (8 [6.7%] subjects), colitis (6 [5.0%] subjects), and diarrhea (6 [5.0%] subjects).
  - The frequency of all-causality AEs leading to discontinuation was higher in Cohort B (33.3%) than Cohort A (30.7%).
- The frequency of drug-related SAEs were reported more frequently in Cohort A (34 [33.7%] subjects) compared with Cohort B (5 [27.8%] subjects).
- The frequency of drug-related AEs and drug-related AEs leading to discontinuation was higher for Cohort A (96.0% and 28.7%, respectively) compared with Cohort B (88.9% and 16.7%, respectively).
- The only Grade 3 IMAE categories with PTs reported by > 5% of subjects were in the hepatitis (10.9%), rash (9.2%), and diarrhea/colitis (8.4%) categories. No Grade 5 IMAEs were reported. The majority of select AEs and IMAEs resolved and were manageable using the recommended treatment guidelines for early evaluation and intervention.

These results support the use of 1 mg/kg nivolumab plus 3 mg/kg ipilimumab as standard of care for most melanoma subjects with asymptomatic brain metastases. Subjects with symptomatic brain metastases remain difficult to treat, but some can derive long-term benefit with nivolumab combined with ipilimumab.

### **5.5.2.3 Nivolumab in Combination with Ipilimumab - CA209064 (Melanoma)**

CA209064 was an open-label, randomized Phase 2 study of two schedules of nivolumab given sequentially with ipilimumab in adult subjects with advanced (unresectable Stage III) or metastatic (Stage IV) melanoma.<sup>168</sup> Eligible subjects were randomized (1:1) to receive one of two dosing schedules during Induction Periods 1 and 2:

- Cohort A: nivolumab 3 mg/kg Q2W followed by ipilimumab 3 mg/kg Q3W
- Cohort B: ipilimumab 3 mg/kg Q3W followed by nivolumab 3 mg/kg Q2W

The safety data from the DBL of 18-Mar-2021 are presented below:

- There were 35 deaths in Cohort A and 48 deaths in Cohort B, primarily attributed to disease progression.
  - In Cohort A, 32 deaths were attributed to disease progression. Two subjects died of “other” causes. One subject died of an unknown cause of death.
  - In Cohort B, 45 deaths were attributed to disease progression. Three subjects died from an unknown cause of death, and 1 died from “other” reason of natural cause.



- The number of subjects reported with any Grade SAEs was similar in both Cohorts (79.4% in Cohort A and 77.1% in Cohort B). Grade 3-4 SAEs were slightly higher in Cohort A compared to Cohort B (63.2% vs 55.7%). All Grade 5 SAEs were attributed to malignant neoplasm progression in Cohort B (7 subjects, 10.0%). Of the 3 subjects (4.4%) who were reported with Grade 5 SAEs in Cohort A, 2 (2.9%) were attributed to malignant neoplasm progression and 1 (1.5%) due to an acute kidney injury. The most frequently reported ( $\geq 5\%$ ) any Grade SAEs were:
  - Cohort A: colitis (17.6%), diarrhoea (10.3%), adrenal insufficiency (7.4%), pneumonia (5.9%), pyrexia (5.9%), pneumonitis (5.9%), and acute kidney injury (5.9%).
  - Cohort B: colitis (21.4%), fatigue (14.3%), malignant neoplasm progression (12.9%), diarrhoea (8.6%), urinary tract infection (7.1%), dehydration (7.1%), and pyrexia (5.7%).
- The number of subjects reported with any Grade AEs leading to study drug discontinuation was higher in Cohort A compared to Cohort B (50.0% vs 41.4%). The number of Grade 3-4 events that led to discontinuation of study therapy was similar across both Cohorts (29.4% in Cohort A vs 31.4%). The most frequently reported ( $\geq 3\%$ ) any Grade AEs that led to study drug discontinuation were:
  - Cohort A: colitis (11.8%), ALT increased (7.4%), pneumonitis (7.4%), and AST increased (4.4%).
  - Cohort B: colitis (18.6%).
- The number of subjects reported with any Grade drug-related AEs was similar across both Cohorts (95.6% in Cohort A vs 91.4% in Cohort B). Grade 3-4 drug-related AEs were higher in Cohort A compared to Cohort B (64.7% vs 51.4%). There was no drug-related Grade 5 AE.
- The most frequently reported ( $\geq 5\%$ ) Grade 3-4 drug-related AEs between the first dose of study drug and 30 days after last dose of study drug were:
  - Cohort A: lipase increased (19.1%), colitis (14.7%), ALT increased (10.3%), diarrhoea (10.3%), and AST increased (8.8%).
  - Cohort B: colitis (21.4%), lipase increased (20.0%), diarrhoea (8.6%), amylase increased (5.7%), and fatigue (5.7%).

There were no new safety signals identified. There were no deaths due to study drug toxicity in either cohort. No new types of AEs were identified. The overall reported safety data from CA209064 demonstrated similar types and frequencies of AEs between the two cohorts.

#### **5.5.2.4 Nivolumab in Combination with Ipilimumab - CA209915 (Melanoma)**

The study design and efficacy of CA209915 are discussed in [Section 5.4.2.1](#).

As of 16-Mar-2021 DBL, the overall frequencies of all-causality SAEs, all causality AEs leading to DC, and all causality AEs were higher in the nivolumab + ipilimumab group than in the nivolumab group. The safety profiles of nivolumab 240 mg Q2W + ipilimumab 1 mg/kg Q6W and nivolumab monotherapy (480 mg Q4W) in all treated subjects with completely resected Stage IIb/c or Stage IV melanoma were similar with those in other tumor types, with no new safety signals.

### **5.5.2.5 Nivolumab in Combination with Ipilimumab - Study CA209401 (Melanoma)**

CA209401 was a study to characterize of the safety and clinical activity of nivolumab combined with ipilimumab in subjects who received first-line therapy for advanced disease and presented with stage III unresectable or stage IV metastatic melanoma.<sup>169</sup>

The overall safety results are summarized as follows:

#### Deaths

- A total of 199 subjects (37.3%) died in the study, 35 subjects (6.6%) died within 30 days of the last dose, and 76 subjects (14.3%) died within the extended follow-up period (within 100 days of the last dose). Of the subjects who died, the primary reason for deaths was disease (disease progression; 179 subjects [33.6%]). Study drug toxicity was reported as the primary reason for death for 3 subjects (0.6%). All 3 subjects were in the ECOG PS 0-1 subgroup with 1 of the 3 subjects in the ocular/uveal disease subtype and 2 of the 3 subjects in the cutaneous disease subtype.

#### Other Serious Adverse Events

- Drug-related SAEs of Grade 3 through Grade 4 severity were reported in 219 subjects (41.1%).
- Grade 5 severity events were reported in 4 subjects (0.8%). The largest proportion of Grade 5 SAEs per subgroup occurred in subjects with ECOG PS 2 (16.4%) and in the mucosal disease subtype (31.3%). The smallest proportion of Grade 5 SAEs per subgroup occurred in subjects with ECOG PS 0-1 (9.4%) and in the cutaneous disease subtype (7.1%).
- The most frequently reported serious select AEs per category were in the gastrointestinal and hepatic categories. Drug-related serious select gastrointestinal AEs of Grade 3 through Grade 4 severity were reported in 74 subjects (13.9%); Grade 5 severity was reported in 1 subject (0.2%). Drug-related serious select hepatic AEs of Grade 3 through Grade 4 severity were reported in 50 subjects (9.4%); no Grade 5 severity events were reported. Drug-related serious select endocrine AEs of Grade 3 through Grade 4 severity were reported in 53 subjects (9.9%); no Grade 5 severity events were reported.

#### Adverse Events Leading to Discontinuation

- Drug-related AEs leading to discontinuation of study therapy of Grade 3 through Grade 4 severity were reported in 186 subjects (34.9%); Grade 5 severity events were reported in 2 subjects (0.4%).
- Drug-related select endocrine AEs leading to discontinuation of study therapy of Grade 3 through Grade 4 severity were reported in 17 subjects (3.2%); no Grade 5 severity events were reported.

### **5.5.2.6 Nivolumab in Combination with Ipilimumab - CA209817 (NSCLC)**

CA209817<sup>170</sup> is a Phase 3b/4 study of flat dose nivolumab in combination with ipilimumab in subjects with NSCLC. The combination of nivolumab 240 mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks was studied as first-line (Cohorts A, A1, C) and second line (Cohort B) for the treatment of Stage IV or recurrent NSCLC. As of the database lock 01-Mar-2018, the overall safety of nivolumab 240 mg Q2W + ipilimumab 1 mg/kg Q6W in subjects with previously untreated NSCLC in Cohort A was consistent with the known toxicity profiles and no new safety

concerns were identified. In Cohort A, 2 deaths were attributed to study drug toxicity; the investigator-assessed causes included toxicities related to heart failure due to rhabdomyolysis and Guillain-Barre syndrome. The following are key safety results in Cohort A.

**Serious Adverse Events:** SAEs were reported in 52.7% of subjects. Grade 3-4 SAEs were reported in 36.3% of subjects. The most frequently reported SAEs were malignant neoplasm progression (7.4%), pneumonitis (4.1%), pneumonia (4.1%), and dyspnea (3.1%).

**Adverse Events:** AEs (any-grade, regardless of causality) were reported in 97.4% of subjects. The most frequently reported AEs were fatigue (31.2%), diarrhea (26.6%), decreased appetite (21.0%), nausea (20.5%), cough (19.7%), dyspnea (19.7%), asthenia (17.4%), pruritus (16.9%), and pyrexia (15.3%).

**AEs leading to discontinuation** were reported in 22.8% of subjects treated with nivolumab + ipilimumab in Cohort A. Grade 3 and 4 AEs leading to discontinuation were reported in 12.5% and 3.3% of subjects, respectively.

#### **5.5.2.7 Nivolumab in Combination with Ipilimumab- CA209592 (NSCLC)**

The study design and efficacy of CA209592 are discussed in [Section 5.4.1.7](#).

The overall safety results are summarized as follows:

- Death due to study drug toxicity was reported in 4 (1.7%) subjects. These deaths were reported as due to study drug toxicities of pneumonitis (2 subjects), aplastic anaemia, and immune mediated lung disease.
- Any grade SAEs (regardless of causality) were reported in 135 (58.7%) subjects, with Grade 3-4 SAEs being reported in 84 (36.5%) subjects. Any grade drug-related SAEs were reported in 49 (21.3%) subjects, with Grade 3-4 drug-related SAEs being reported in 37 (16.1%) subjects.
- All causality AEs (any grade) leading to discontinuation were reported in 61 (26.5%) subjects. Drug-related AEs (any grade) leading to discontinuation were reported in 43 (18.7%) subjects.
- The reported frequency of all causality and drug-related AEs was 99.6% and 81.3%, respectively. The most frequently reported drug-related AEs (any grade) were diarrhoea (62 [27.0%] subjects), pruritis (56 [24.3%] subjects), fatigue (54 [23.5%] subjects), and rash (53 [23.0%]).
- Most select AEs (all causality or drug-related) were Grade 1-2. The most frequently reported select AE categories (any grade) were skin (47.0%), gastrointestinal (37.8%), and hepatic (26.1%). The most frequently reported drug-related select AE categories (any grade) were skin (41.3%), gastrointestinal (27.8%), and hepatic (20.4%).
- The most frequently reported drug-related serious select AE category was pulmonary (any grade, 10 [4.3%] subjects; Grade 3-4, 8 [3.5%] subjects). There was 1 reported drug-related serious select Grade 5 pulmonary AE.



- Most IMAEs were Grade 1-2, with the most frequently reported endocrine IMAEs being thyroiditis (21 [9.1%] subjects) followed by hyperthyroidism (19 [8.3%] subjects). The most frequently reported non-endocrine IMAEs were rash (30 [13.0%] subjects) and pneumonitis (25 [10.9%] subjects).

The safety of nivolumab plus ipilimumab in this study is consistent with the known safety profile and reflective of the mechanism of action of each of the components, with no new signals that negatively impact the benefit risk profile of the combination.

### 5.5.2.8 Nivolumab in Combination with Ipilimumab-CA209012 (NSCLC)

The study design and efficacy of CA209012 are discussed in [Section 5.4.1.2](#).

The summary of safety results of nivolumab in combination with ipilimumab cohort is presented in Table 5.5.2.8-1.

**Table 5.5.2.8-1: Summary of Key Safety Results- All Treated Subjects in Nivolumab + Ipilimumab -CA209012**

	Pooled Cohorts	Pooled Cohorts	Cohort			
	GH <sup>a</sup> N = 24	IJ <sup>b</sup> N = 25	N <sup>c</sup> N = 31	Cohort O <sup>d</sup> N = 40	Cohort P <sup>e</sup> N = 38	Cohort Q <sup>f</sup> N = 39
<b>SAFETY, n (%)</b>						
<b>Deaths</b>	15 (62.5)	17 (68.0)	14 (45.2)	17 (42.5)	15 (39.5)	20 (51.3)
Within 30 days of last dose	2 ( 8.3)	3 (12.0)	1 ( 3.2)	1 ( 2.5)	4 (10.5)	2 ( 5.1)
Within 100 days of last dose	3 (12.5)	10 (40.0)	3 ( 9.7)	6 (15.0)	8 (21.1)	7 (17.9)
Due to study drug toxicity	1 ( 4.2)	2 ( 8.0)	0	0	0	0
<b>Drug-related SAEs, Grade 3-4</b>	10 (41.7)	7 (28.0)	5 (16.1)	9 (22.5)	10 (26.3)	9 (23.1)
<b>Drug-related AEs leading to DC, Grade 3-4</b>	8 (33.3)	6 (24.0)	2 (6.5)	3 (7.5)	3 (7.9)	3 (7.7)
<b>Drug-related AEs, Grade 3-4</b>	14 (58.3)	12 (48.0)	9 (29.0)	13 (32.5)	15 (39.5)	11 (28.2)
<b>Most frequent drug-related AEs</b>						
Fatigue	2 (8.3)	1 (4.0)	0	1 (2.5)	1 (2.6)	0
Diarrhea	3 (12.5)	0	0	2 (5.0)	1 (2.6)	0
Decreased Appetite	0	0	0	0	0	0
Rash	0	1 (4.0)	4 (12.9)	2 (5.0)	0	0
<b>Drug-Related Select AEs, by Category, Grade 3-4</b>						
Endocrine	3 (12.5)	1 (4.0)	2 (6.5)	3 (7.5)	2 (5.3)	3 (7.7)
Gastrointestinal	4 (16.7)	4 (16.0)	0	2 (5.0)	2 (5.3)	2 (5.1)
Hepatic	3 (12.5)	1 (4.0)	2 (6.5)	4 (10.0)	0	2 (5.1)

**Table 5.5.2.8-1: Summary of Key Safety Results- All Treated Subjects in Nivolumab + Ipilimumab -CA209012**

	Pooled Cohorts	Pooled Cohorts	Cohort			
	GH <sup>a</sup>	IJ <sup>b</sup>	N <sup>c</sup>	Cohort O <sup>d</sup>	Cohort P <sup>e</sup>	Cohort Q <sup>f</sup>
	N = 24	N = 25	N = 31	N = 40	N = 38	N = 39
Pulmonary	1 (4.2)	1 (4.0)	1 (3.2)	0	2 (5.3)	1 (2.6)
Renal	1 (4.2)	0	0	0	2 (5.3)	1 (2.6)
Skin	0	1 (4.0)	4 (12.9)	2 (5.0)	1 (2.6)	2 (5.1)
Hypersensitivity/Infusion Reactions	0	0	0	0	0	0

Source: CA209012 CSR database lock date 19-Sep-2016 (Nivo+Ipi)<sup>112</sup>

Percentages based on subjects treated.

<sup>a</sup> Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W; <sup>b</sup> Nivo 3 mg/kg + Ipi 1 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W; <sup>c</sup> Nivo 1 mg/kg + Ipi 1 mg/kg Q3W for 4 cycles followed by Nivo 3 mg/kg Q2W; <sup>d</sup> Nivo 1 mg/kg Q2W + Ipi 1 mg/kg Q6W; <sup>e</sup> Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q12W; <sup>f</sup> Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W

### 5.5.2.9 Nivolumab in Combination with Ipilimumab - CA209451 (SCLC)

The study design and efficacy of CA209451 are discussed in [Section 5.4.7.3](#).

Safety data for all treated subjects (N = 830) in the Global Population demonstrated that the overall safety profiles of nivolumab1 + ipilimumab 3 and nivolumab were consistent with prior data in terms of the type, frequency, and severity of reported events. No new safety concerns were identified with nivolumab1 + ipilimumab 3 or with nivolumab monotherapy in this study.

As of the 12-Nov-2018 clinical database lock, 189 (68.0%) deaths occurred in the nivolumab1 + ipilimumab 3 group, 194 (69.5%) deaths occurred in the nivolumab group, and 210 (76.9%) deaths occurred in the placebo group. There were 9 deaths attributed to study drug toxicity by the investigator: 7 (2.5%) in the nivolumab1 + ipilimumab 3 group, 1 (0.4%) in the nivolumab group, and 1 (0.4%) in the placebo group. Frequencies of all causality Grade 3-4 AEs, as well as any-grade and Grade 3-4 drug-related SAEs, AEs, and AEs leading to discontinuation, were higher in the nivolumab1 + ipilimumab 3 group than in the nivolumab and placebo groups.

Most select AEs and IMAEs were Grade 1 or 2. The majority of select AEs and IMAEs resolved and were manageable using the recommended treatment guidelines for early work-up and intervention.

Abnormalities in hematology laboratory results, liver tests, kidney function tests, and electrolytes in subjects treated with nivolumab1 + ipilimumab 3 and nivolumab were primarily Grade 1 or 2.

The incidence of nivolumab ADA was higher with nivolumab1 + ipilimumab 3 relative to nivolumab monotherapy (46.2% vs 9.4%) as was the incidence of neutralizing nivolumab ADA (11.7% vs 3.1%) and of persistent positive ADA (2.0% vs 0.4%). The incidence of ipilimumab

ADA was 4.0% with no subjects with neutralizing ADA or persistent positive ADA. Overall, the incidence of immunogenicity with both nivolumab1 + ipilimumab 3 and nivolumab monotherapy was consistent with previous data.

The safety profile of the China Cohort was generally consistent with that of the Global Population.

No deaths were attributed to study drug toxicity by the investigator. In the China Cohort, frequencies of all causality Grade 3-4 AEs, as well as any-grade and Grade 3-4 drug-related SAEs and AEs were higher in the nivolumab1 + ipilimumab 3 group than in the nivolumab and placebo groups.

Most select AEs and IMAEs were Grade 1 or 2. The majority of select AEs and IMAEs resolved and were manageable using the recommended treatment guidelines for early work-up and intervention.

Abnormalities in hematology laboratory results, liver tests, kidney function tests, and electrolytes in subjects treated with nivolumab1 + ipilimumab 3 and nivolumab were primarily Grade 1 or 2.

The incidence of nivolumab ADA was high with nivolumab1 + ipilimumab 3 relative to nivolumab monotherapy (30.8% vs 0%) with no persistent ADA positive subjects or subjects with neutralizing ADAs. There were no ipilimumab ADA positive subjects.

#### **5.5.2.10 Nivolumab in Combination with Ipilimumab - CA209032 (SCLC)**

The study design and efficacy of CA209032 (SCLC) are discussed in [Section 5.4.7.1](#).

As of the 06-Nov-2017 clinical database lock, 179 (73.1%) subjects in the nivolumab group and 121 (77.1%) subjects in the nivolumab plus ipilimumab group died, and there was 1 death attributed to study drug toxicity in the nivolumab group (pneumonitis) and 4 deaths attributed to study drug toxicity in the nivolumab combination.<sup>134</sup>

The summary of the key safety findings is shown in [Table 5.5.2.10-1](#).

**Table 5.5.2.10-1: Summary of Safety Results - Subjects with SCLC-CA209032**

	Number (%) Subjects			
	Nivolumab (N=245)		Nivo 1 + Ipi 3 (N=157)	
<b>DEATHS</b>	179 ( 73.1)		121 ( 77.1)	
WITHIN 30 DAYS OF LAST DOSE	39 ( 15.9)		31 ( 19.7)	
WITHIN 100 DAYS OF LAST DOSE	114 ( 46.5)		75 ( 47.8)	
PRIMARY REASON FOR DEATH				
DISEASE PROGRESSION	166 ( 67.8)		97 ( 61.8)	
STUDY DRUG TOXICITY (a)	1 ( 0.4)		4 ( 2.5)	
UNKNOWN	6 ( 2.4)		9 ( 5.7)	
OTHER (b)	6 ( 2.4)		11 ( 7.0)	
<b>Number (%) Subjects</b>				
	Nivolumab (N=245)		Nivo 1 + Ipi 3 (N=157)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<b>ALL CAUSALITY SAEs</b>	129 ( 52.7)	83 ( 33.9)	107 ( 68.2)	69 ( 43.9)
<b>DRUG-RELATED SAEs</b>	20 ( 8.2)	17 ( 6.9)	37 ( 23.6)	30 ( 19.1)
<b>ALL CAUSALITY AEs LEADING TO DC</b>	44 ( 18.0)	29 ( 11.8)	39 ( 24.8)	25 ( 15.9)
<b>DRUG-RELATED AEs LEADING TO DC</b>	7 ( 2.9)	6 ( 2.4)	19 ( 12.1)	16 ( 10.2)
<b>ALL-CAUSALITY AEs</b>	240 ( 98.0)	115 ( 46.9)	155 ( 98.7)	97 ( 61.8)
<b>Most Frequent AEs (≥ 20% of Any Grade in either treatment group)</b>				
FATIGUE	89 ( 36.3)	7 ( 2.9)	66 ( 42.0)	5 ( 3.2)
DECREASED APPETITE	65 ( 26.5)	3 ( 1.2)	46 ( 29.3)	0
MALIGNANT NEOPLASM PROGRESSION	55 ( 22.4)	25 ( 10.2)	34 ( 21.7)	11 ( 7.0)
NAUSEA	53 ( 21.6)	1 ( 0.4)	38 ( 24.2)	1 ( 0.6)
DIARRHOEA	52 ( 21.2)	2 ( 0.8)	44 ( 28.0)	9 ( 5.7)
CONSTIPATION	49 ( 20.0)	1 ( 0.4)	30 ( 19.1)	1 ( 0.6)
DYSPNEA	49 ( 20.0)	13 ( 5.3)	27 ( 17.2)	4 ( 2.5)
COUGH	45 ( 18.4)	1 ( 0.4)	39 ( 24.8)	0
PRURITUS	33 ( 13.5)	0	39 ( 24.8)	2 ( 1.3)
<b>DRUG-RELATED AEs</b>	137 ( 55.9)	30 ( 12.2)	115 ( 73.2)	57 ( 36.3)
<b>Most Frequent Drug-related AEs (≥ 15% of Any Grade in either treatment group)</b>				
FATIGUE	26 ( 10.6)	1 ( 0.4)	33 ( 21.0)	1 ( 0.6)
PRURITUS	27 ( 11.0)	0	32 ( 20.4)	1 ( 0.6)
DIARRHEA	12 ( 4.9)	0	31 ( 19.7)	7 ( 4.5)
<b>ALL CAUSALITY SELECT AEs, BY CATEGORY</b>				
ENDOCRINE	26 ( 10.6)	0	39 ( 24.8)	5 ( 3.2)
GASTROINTESTINAL	53 ( 21.6)	3 ( 1.2)	50 ( 31.8)	14 ( 8.9)
HEPATIC	42 ( 17.1)	19 ( 7.8)	37 ( 23.6)	16 ( 10.2)
PULMONARY	12 ( 4.9)	7 ( 2.9)	12 ( 7.6)	5 ( 3.2)
RENAL	12 ( 4.9)	4 ( 1.6)	11 ( 7.0)	2 ( 1.3)
SKIN	52 ( 21.2)	1 ( 0.4)	66 ( 42.0)	10 ( 6.4)
HYPERSENSITIVITY/INFUSION REACTIONS	17 ( 6.9)	0	3 ( 1.9)	0
<b>DRUG-RELATED SELECT AEs, BY CATEGORY</b>				
ENDOCRINE	20 ( 8.2)	0	34 ( 21.7)	5 ( 3.2)
GASTROINTESTINAL	12 ( 4.9)	0	38 ( 24.2)	12 ( 7.6)
HEPATIC	15 ( 6.1)	3 ( 1.2)	21 ( 13.4)	11 ( 7.0)
PULMONARY	7 ( 2.9)	5 ( 2.0)	8 ( 5.1)	4 ( 2.5)
RENAL	2 ( 0.8)	1 ( 0.4)	2 ( 1.3)	0
SKIN	40 ( 16.3)	1 ( 0.4)	58 ( 36.9)	9 ( 5.7)
HYPERSENSITIVITY/INFUSION REACTIONS	13 ( 5.3)	0	2 ( 1.3)	0
<b>ALL-CAUSALITY IMMUNE-MEDIATED ADVERSE EVENTS WITHIN 100 DAYS OF LAST DOSE, BY CATEGORY</b>				
<b>Immune-mediated AEs Treated with Immune-modulating medication</b>				
DIARRHEA/COLITIS	5 ( 2.0)	1 ( 0.4)	20 ( 12.7)	9 ( 5.7)
HEPATITIS	5 ( 2.0)	5 ( 2.0)	10 ( 6.4)	10 ( 6.4)
PNEUMONITIS	10 ( 4.1)	6 ( 2.4)	7 ( 4.5)	5 ( 3.2)
NEPHRITIS AND RENAL DYSFUNCTION	1 ( 0.4)	1 ( 0.4)	1 ( 0.6)	0
RASH	8 ( 3.3)	0	32 ( 20.4)	9 ( 5.7)
HYPERSENSITIVITY/INFUSION REACTIONS	5 ( 2.0)	0	0	0

**Table 5.5.2.10-1: Summary of Safety Results-Subjects with SCLC-CA209032**

	Number (%) Subjects			
	Nivolumab (N=245)		Nivo 1 + Ipi 3 (N=157)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<b><i>Immune-Mediated Endocrine AEs Treated with or without Immune-Modulating Medications</i></b>				
ADRENAL INSUFFICIENCY	4 ( 1.6)	1 ( 0.4)	3 ( 1.9)	1 ( 0.6)
HYPOPHYSITIS	1 ( 0.4)	0	3 ( 1.9)	2 ( 1.3)
HYPOTHYROIDISM/THYROIDITIS	15 ( 6.1)	0	24 ( 15.3)	1 ( 0.6)
HYPERTHYROIDISM	7 ( 2.9)	0	21 ( 13.4)	1 ( 0.6)
DIABETES MELLITUS	1 ( 0.4)	0	1 ( 0.6)	0

Source: CA209032 Final SCLC CSR; database lock 06-Nov-2017. MedDRA version 20.0; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

- (a) At database lock, 1 death in the nivo 1 + ipi 3 group assessed as due to study drug toxicity has the cause of death reported as 'seizure possibly related to therapy' but was determined to be encephalitis.
- (b) 1 death in the nivo 1 + ipi 3 group reported as a combination of study drug toxicity (SAE of autoimmune colitis) and disease progression was classified as 'other' for cause of death.

### 5.5.2.11 Nivolumab in Combination with Ipilimumab - CA209714 (SCCHN)

The study design and efficacy results for CA209714 are discussed in [Section 5.4.5.1](#).

#### Platinum Refractory Subgroup

As of the 11-Mar-2022 clinical cutoff date (minimum follow-up: 47.2 months), the combination of nivo + ipi demonstrated an acceptable safety profile in subjects with platinum refractory recurrent or metastatic SCCHN.

There were no deaths attributed to study drug toxicity in either treatment group. Overall frequencies of all-causality SAEs and drug-related SAEs, as well as AEs and drug-related AEs, continued to be similar in the nivo + ipi and the nivo + ipi placebo groups. Frequencies of all-causality and drug-related AEs (any-grade and Grade 3 and 4) leading to discontinuation continued to be numerically higher in the nivo + ipi group than in the nivo + ipi placebo group. In both treatment groups, most AEs or IMAEs were reported as Grade 1 or 2 events.

- Similar proportions of subjects died in both treatment groups. There were no reported treatment-related deaths. Disease progression was the most frequently reported reason for death in both treatment groups, including deaths occurring within 30 days of last dose and 100 days of last dose.
- Overall frequencies of all-causality SAEs(54.4% vs 53.7%), all causality AEs (97.5% vs 97.6%)and drug-related AEs (62.7% vs 65.9%) were similar in the nivo + ipi and the nivo + ipi placebo groups.
  - The most frequently reported (>15.0%) drug-related AE categories were skin (28.5%, endocrine (17.7%) and gastrointestinal (16.5%) in nivo + ipi group and endocrine (15.9%) in the nivo + ipi placebo groups
- Drug-related treatment discontinuation was reported as 13.3 % and 11.0% nivolumab + ipilimumab and the nivolumab + ipi placebo groups respectively.
- In both treatment groups, the majority of select AEs or IMAEs were reported as Grade 1-2 events.

### Platinum Eligible Subgroup

As of the 11-Mar-2022 clinical cutoff date (minimum follow-up: 47.2 months), the combination of nivo + ipi demonstrated an acceptable safety profile in subjects with platinum eligible recurrent or metastatic SCCHN.

There were no deaths attributed to study drug toxicity in either treatment group. Frequencies of all-causality SAEs and drug-related SAEs (any-grade and Grade 3-4) continued to be numerically higher in the nivo + ipi group than in the nivo + ipi placebo group. Frequencies of all-causality, any-grade AEs and drug-related AEs were similar between the treatment groups. Drug-related Grade 3 and 4 AEs remained numerically higher in the nivo + ipi group than in the nivo + ipi placebo group, while the frequencies of all-causality Grade 3 and 4 AEs became similar with longer follow-up. Frequencies of all-causality and drug-related AEs (any-grade and Grade 3 and 4) leading to discontinuation continued to be numerically higher in the nivo + ipi group than in the nivo + ipi placebo group. In both treatment groups, most select AEs or IMAEs were reported as Grade 1 and 2 events.

- Similar proportions of subjects died in both treatment groups. There were no treatment-related deaths. Disease progression was the most reported reason for death in both treatment groups, including deaths occurring within 30 days of last dose and 100 days of last dose.
- Overall frequencies of all-causality SAEs (100.0% vs 96.7%), and drug-related AEs (66.4% vs 68.9%) were similar in the nivo + ipi and the nivo + ipi placebo groups.
- The frequently reported (>25.0%) drug-related AE categories were skin (37.7%) and endocrine (31.1%) in nivo + ipi group and skin and endocrine (26.2% each) in the nivo + ipi placebo groups.
- There was a higher frequency of all-causality AEs leading to DC (22.1% vs 11.5%) and drug-related AEs leading to DC (9.8% vs 3.3%) reported in the in the nivo + ipi and the nivo + ipi placebo groups.
- There was a higher frequency of all-causality SAEs (64.8% Vs 45.9%) and drug-related SAEs (14.8% vs 4.9%) reported in the in the nivo + ipi and the nivo + ipi placebo groups.

The safety profiles of nivolumab as monotherapy or in combination with ipilimumab in this SCCHN population were manageable, with no new safety signals identified after extended follow-up.

#### **5.5.2.12 Nivolumab in Combination with Ipilimumab - CA209651 (SCCHN)**

The study design and efficacy of CA209651 are discussed in [Section 5.4.5.2](#).

The summary of safety results is provided below:

- There were similar number of subjects died in the EXTREME regimen arm (86.4%) compared to nivo + ipi (82.3%). Disease progression was the most frequently reported cause of death in both groups. There were 6 (1.3%) deaths in the nivo + ipi arm and 7 (1.6%) deaths in the EXTREME regimen arm attributed to study drug toxicity for all treated subjects.

- The most frequently reported SAEs (regardless of causality) were as follows:
  - Nivo + ipi arm: malignant neoplasm progression (11.5%), pneumonia (4.3%), and tumor hemorrhage (4.1%).
  - EXTREME regimen arm: malignant neoplasm progression (10.2%), pneumonia (5.9%), and febrile neutropenia (5.4%).
- The most frequently reported drug-related SAEs were as follows:
  - Nivo + ipi arm: colitis (2.1%), diarrhea (1.1%), and pneumonitis (1.1%).
  - EXTREME regimen arm: febrile neutropenia (5.2%), anemia (2.5%), mucosal inflammation (1.6%), and acute kidney injury (1.6%).
- The most frequently reported drug-related AEs leading to discontinuation were:
  - Nivo + ipi arm: colitis (2.4%), pneumonitis (1.3%), and lipase increased (0.9%).
  - EXTREME regimen arm: anemia (1.1%), stomatitis (0.9%), and rash (0.9%).
- The most frequently reported drug-related AEs were:
  - Nivo + ipi arm: fatigue (18.2%), pruritus (15.0%), hypothyroidism (14.3%), and rash (13.9%).
  - EXTREME regimen arm: nausea (44.4%), rash (38.1%), and anemia (34.9%).

Final safety data of nivo + ipi in SCCHN remains reflective of the known safety profile and no new safety signals or toxicities were identified.

#### **5.5.2.13 Nivolumab in Combination with Ipilimumab - CA209908 (Pediatric Subjects)**

The study design and efficacy of CA209908 are discussed in [Section 5.4.19.1](#).

Safety results (as of database lock 13-Jan-2021) for nivolumab monotherapy and Nivolumab + Ipilimumab combination therapy are summarized below:

##### Nivolumab Monotherapy

In combined cohorts treated with nivolumab monotherapy: 66 (77.6%) subjects had died. No deaths were attributed to study drug toxicity. Drug-related AEs leading to discontinuation were reported in 11.8% of subjects. The frequency of drug-related AEs was 57.6%; 14.1% of subjects had Grade 3-4 drug-related AEs. Grade 3-4 drug-related AEs reported in  $\geq 2$  subjects were neutrophil count decreased (3.5%) and rash (2.4%). Laboratory abnormalities (hematology, liver tests, kidney function tests, thyroid function tests, pancreas function tests, and electrolytes) were primarily Grade 1-2. None of the 77 nivolumab ADA evaluable subjects were ADA positive post baseline.

The frequency of drug-related SAEs was 11.8%. Grade 3-4 SAEs were reported in 25 (29.4%) subjects. The most frequently reported all-causality SAEs ( $\geq 5\%$ ) was malignant neoplasm progression (16.5%). Grade 3-4 drug-related SAEs were reported in 5 (5.9%) subjects. Drug-related SAEs (any-grade) reported in  $\geq 2$  subjects were hepatitis, pyrexia, and rash (2.4% each).



### Nivolumab + Ipilimumab

In combined cohorts treated with nivolumab + ipilimumab: 59 (72.8%) subjects had died. No deaths were attributed to study drug toxicity. Drug-related AEs leading to discontinuation were reported in 17.3% of subjects. The frequency of drug-related AEs was 64.2%; 27.2% of subjects had Grade 3-4 drug-related AEs. Grade 3-4 drug-related AEs reported in  $\geq 2$  subjects were ALT increased (6.2%), aspartate aminotransferase (AST) increased (4.9%), and weight decreased (2.5%). Most select AEs and IMAEs were Grade 1-2. Select AEs and IMAEs, including those that were severe (Grade 3-4), were manageable. Laboratory abnormalities (hematology, liver tests, kidney function tests, thyroid function tests, pancreas function tests, and electrolytes) were primarily Grade 1-2. One (1.4%) of the 69 nivolumab ADA-evaluable subjects and 1 (1.4%) of the 70 ipilimumab-evaluable subjects were ADA positive post baseline.

The frequency of drug-related SAEs was 24.7%. Grade 3-4 drug-related SAEs were reported in 13 (16.0%) subjects. Drug-related SAEs (any-grade) reported in  $\geq 2$  subjects were tumor flare (4.9%), diarrhea (3.7%), colitis, headache, and immune-mediated enterocolitis (2.5% each).

#### **5.5.2.14 Nivolumab in Combination with Ipilimumab - CA209032 (Ovarian Cancer)**

The study design and efficacy of CA209032 (Ovarian Cancer) are discussed in [Section 5.4.20.1](#).

As of the 12-Apr-2019 clinical database lock, over 80% of subjects died across the 3 arms. 33 (80.5%), 37 (86.0%) and 34 (81.0%) subjects died in the nivolumab1 + ipilimumab3 (DL 2), nivolumab3 + ipilimumab1 (DL 2b), and nivolumab3 + ipilimumab1 (DL 2c) arm respectively. The most common reason for death was disease progression. There were no deaths attributed to study drug toxicity.

The most frequently reported ( $> 20\%$ ) AEs were:

- Nivolumab1 + ipilimumab3 (DL 2) arm: fatigue (51.2%), abdominal pain (43.9%), nausea (41.5%), diarrhea (34.1%), pruritus (41.5%), constipation (22.0%), rash maculo-papular (31.7%), decreased appetite (26.8%), vomiting (22.0%), pyrexia (22.0%), alanine aminotransferase increased (22.0%), and aspartate aminotransferase increased (22.0%).
- Nivolumab3 + ipilimumab1 (DL 2b) arm: fatigue (55.8%), nausea (53.5%), abdominal pain (46.5%), diarrhea (44.2%), constipation (32.6%), vomiting (32.6%), pruritus (27.9%), decreased appetite (25.6%), hypothyroidism (23.3%), anaemia (23.3%), ascites (20.9%), and pyrexia (20.9%).
- Nivolumab3 + ipilimumab1 (DL 2c) arm: fatigue (64.3%), nausea (47.6%), diarrhea (38.1%), dyspnea (38.1%), abdominal pain (33.3%), vomiting (31.0%), decreased appetite (31.0%), constipation (26.2%), headache (26.2%), aspartate aminotransferase increased (23.8%), cough (21.4%), hypomagnesaemia (21.4%), alanine aminotransferase increased (21.4%), and pruritus (21.4%).



The most frequently reported (> 20%) drug-related AEs were:

- Nivolumab1 + ipilimumab3 (DL 2) arm: pruritus (34.1%), rash maculo-papular (31.7%), fatigue (26.8%), and diarrhea (24.4%).
- Nivolumab3 + ipilimumab1 (DL 2b) arm: diarrhea (23.3%), pruritus (20.9%) and hypothyroidism (20.9%).
- Nivolumab3 + ipilimumab1 (DL 2c) arm: fatigue (38.1%), and diarrhea (26.2%).

The most frequently reported (>5%) SAEs were:

- Nivolumab1 + ipilimumab3 (DL 2) arm: urinary tract infection (7.3%) and pleural effusion (9.8%).
- Nivolumab3 + ipilimumab1 (DL 2b) arm: abdominal pain (7.0%), ascites (7.0%), constipation (7.0%), diarrhea (7.0%), intestinal obstruction (7.0%), nausea (7.0%), vomiting (7.0%), and urinary tract obstruction (7.0%).
- Nivolumab3 + ipilimumab1 (DL 2c) arm: abdominal pain (9.5%), intestinal obstruction (9.5%), malignant neoplasm progression (9.5%), ascites (7.1%), dyspnoea (7.1%), and vomiting (7.1%).

The most frequently reported (> 4%) drug-related SAEs were:

- Nivolumab1 + ipilimumab3 (DL 2) arm: adrenal insufficiency (4.9%) and hyperthyroidism (4.9%).
- Nivolumab3 + ipilimumab1 (DL 2b) arm: alanine aminotransferase increased (4.7%), aspartate aminotransferase increased (4.7%), blood alkaline phosphatase increased (4.7%), diarrhea (4.7%) and pneumonitis (4.7%).
- Nivolumab3 + ipilimumab1 (DL 2c) arm: diarrhea (4.8%).

#### **5.5.2.15 Nivolumab in Combination with Ipilimumab - CA209032 (Triple Negative Breast Cancer)**

The study design and efficacy of CA209032 (Triple Negative Breast Cancer) are discussed in [Section 5.4.21.1](#).

As of the 12-Apr-2019 clinical database lock, 94.4 % of the subjects treated in the nivolumab monotherapy arm (n=17), and 100% of the subjects in the nivolumab 1 mg/kg + ipilimumab 1 mg/kg (N1I1) [n=3] and nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1I3) [n=18] arms died, all of which were due to disease progression. There were no reported deaths due to study drug toxicity in any of the arms.

SAEs were reported in 9 (50.0%), 2 (66.7%), and 11 (61.1%) of the subjects in the nivolumab monotherapy, N1I1, and N1I3 arms, respectively. Grade 3-4 SAEs were reported in 6 (33.3%), 1 (33.3%), and 8 (44.4%) subjects in the nivolumab monotherapy, N1I1, and N1I3 arms, respectively.

Drug-related SAEs were reported in none of the subjects in the nivolumab monotherapy and N1I1 arms. There were 5 (27.8%) drug-related SAEs in the N1I3 therapy arm. Grade 3-4 drug-related SAEs were reported in 4 (22.2%) subjects in the N1I3 therapy arm. The most frequently reported

drug-related SAEs in N1I3 treatment arm were neutropenia, colitis, pyrexia, transaminases increased, myasthenic syndrome, and pneumonitis (5.6% for each).

AEs (any-grade, regardless of causality) were reported in all 18 (100.0%), 3 (100.0%), and 18 (100.0%) of the subjects in the nivolumab monotherapy, N1I1, and N1I3 arms, respectively. The most frequently reported AEs ( $\geq 35.0\%$ ) in each treatment arm were as follows:

- Nivolumab monotherapy arm: dyspnoea (55.6%), fatigue and cough (44.4% each)
- N1I1 arm: fatigue (66.7%)
- N1I3 arm: diarrhea (61.1%), fatigue, alanine aminotransferase increased, and aspartate aminotransferase increased (38.9% each).

Drug-related AEs (any grade) were reported in 8 (44.4%), 2 (66.7%), and 15 (83.3%) of the subjects in the nivolumab monotherapy, N1I1, and N1I3 arms, respectively. The most frequently reported AEs ( $\geq 15\%$ ) in each treatment arm. No subjects had Grade 3-4 drug-related AEs in the nivolumab monotherapy and N1I1 arms. Grade 3-4 drug-related AEs were reported in 8 (44.4%) of the subjects in the N1I3 arm.

No subjects had AEs or drug-related AEs leading to discontinuation in the N1I1 arm. Drug-related AEs leading to discontinuation (all grades) were reported in 1 (5.6%) subject in the nivolumab monotherapy arm and 2 (11.1%) subjects in the N1I3 arm. There were no Grade 3-4 drug-related AEs leading to discontinuation reported in the nivolumab monotherapy arm and 2 (11.1%) subjects reported in the N1I3 arm. All reported drug-related AEs leading to discontinuation ( $\geq 5.6\%$ ) were as follows: Nivolumab monotherapy arm: malignant neoplasm progression (5.6%) and pneumonitis (5.6%), N1I1 arm: no AEs leading to discontinuation, N1I3 arm: metastases to central nervous system (11.1%) and colitis, dyspnoea, pneumonia and myasthenic syndrome (5.6% each).

#### **5.5.2.16 Nivolumab in Combination with Ipilimumab - CA209650 (mCRPC)**

The study design and efficacy of CA209650 are discussed in [Section 5.4.16.1](#). There were 45 subjects in the safety population in each Cohort, with 15 (33.3%; Cohort B) and 22 (48.9%; Cohort C) total deaths.

The most frequently reported drug-related AE was diarrhoea in Cohort B (17; 37.8%) and Cohort C (24; 53.3%). The reported incidence of any grade and Grade 3-4 all causality as well as drug-related AEs, SAEs, AEs leading to discontinuation, select AEs, and other events of special interest (OESIs) were consistent with other nivo + ipi therapy and nivo monotherapy studies. No new safety concerns with nivo + ipi therapy and nivo monotherapy were identified.

#### **5.5.2.17 Nivolumab in Combination with Ipilimumab - CA209672 (Solid Tumor)**

The study design and efficacy of CA209672 are discussed in [Section 5.4.22.3](#)

#### **Safety Results:**

The median durations of therapy for both nivolumab and ipilimumab in period 1 were 9.43 weeks and was 68.29 weeks for nivolumab in maintenance period 2.

The overall safety profile of nivolumab combined with ipilimumab was manageable and well tolerated in all treated subjects (N=9) in this study with regard to the type, frequency, and severity of adverse events (AEs). No new safety signals with nivolumab combined with ipilimumab were identified (Table 5.5.2.17-1).

As of the DBL of Part 2, there was 1 death reported in Arm D due to disease progression. No drug related deaths were reported. One subject was reported with drug-related pancreatitis (Grade 4) that led to discontinuation. Serious adverse events (SAEs) were reported in 4 subjects, 3 of them were assessed as drug related. Any-grade AEs (regardless of causality) and drug-related AEs were reported in all 9 treated subjects. Grade 3-4 SAEs or AEs were reported in 2 and 4 subjects, respectively.

Other than 1 Grade 3-4 hepatic event, all select AEs and IMAEs were Grade 1-2, reported as resolved and were manageable using the recommended treatment guidelines for early work-up and intervention. One other events of special interest (OESIs) of pancreatitis (Grade 4) was reported, which led to subject discontinuation. No OESIs in other categories were reported. Abnormalities in hematology laboratory results, liver tests, kidney function tests, and electrolytes in treated subjects were primarily Grade 1 or 2.

There were no COVID-19 related AEs reported between the first dose and within 100 days of the last dose of study therapy.

**Table 5.5.2.17-1: Summary of Safety Results - All Treated Subjects (Part 2)**

Safety Parameters	NIVO 3Q3+IPI 1Q3 (N = 9)	
	No. of Subjects (%)	
<b>Deaths</b>	1 (11.1)	
Due to disease progression	1 (11.1)	
	Adverse Event Grades	
	Any Grade	Grade 3-4
<b>All-causality SAEs</b>	4 (44.4)	2 (22.2)
<b>Drug-related SAEs</b>	3 (33.3)	2 (22.2)
<b>All-causality AEs leading to DC (within 30 days from last dose)</b>	1 (11.1)	1 (11.1)
<b>Drug-related AEs leading to DC (within 30 days from last dose)</b>	1 (11.1)	1 (11.1)
<b>All-causality AEs (occurred in ≥3 subjects)</b>	9 (100.0)	5 (55.6)
Alanine aminotransferase increased	5 (55.6)	1 (11.1)
Aspartate aminotransferase increased	5 (55.6)	0
Hypothyroidism	5 (55.6)	0
Blood bilirubin increased	4 (44.4)	0
Bilirubin conjugated increased	3 (33.3)	0
Lipase increased	3 (33.3)	2 (22.2)
Neutrophil count decreased	3 (33.3)	0

**Table 5.5.2.17-1: Summary of Safety Results - All Treated Subjects (Part 2)**

Safety Parameters	NIVO 3Q3+IPI 1Q3 (N = 9)	
	No. of Subjects (%)	
Diarrhea	3 (33.3)	0
<b>Drug-related AEs (occurred in ≥3 subjects)</b>	9 (100.0)	4 (44.4)
Alanine aminotransferase increased	5 (55.6)	0
Hypothyroidism	5 (55.6)	0
Aspartate aminotransferase increased	4 (44.4)	0
Lipase increased	3 (33.3)	2 (22.2)
<b>All-causality Select AEs, by category</b>		
Endocrine	7 (77.8)	0
Gastrointestinal	3 (33.3)	0
Hepatic	7 (77.8)	1 (11.1)
Pulmonary	1 (11.1)	0
Renal	1 (11.1)	0
Skin	3 (33.3)	0
Hypersensitivity/Infusion Reactions	0	0
<b>Drug-Related Select AEs, by category</b>		
Endocrine	7 (77.8)	0
Gastrointestinal	2 (22.2)	0
Hepatic	7 (77.8)	0
Pulmonary	1 (11.1)	0
Renal	1 (11.1)	0
Skin	3 (33.3)	0
Hypersensitivity/Infusion Reactions	0	0

Source: CA209672 Primary CSR<sup>164</sup>

MedDRA Version 25.1; CTC Version 4.0

All events (except for AEs leading to discontinuation) were reported between first dose and 100 days after last dose of study therapy.

Abbreviations: AE, adverse events; DC, discontinue; SAE, serious adverse events.

**5.5.2.18 Nivolumab in Combination with Ipilimumab - CA209743 (Malignant Pleural Mesothelioma)**

CA209743 was a randomized (1:1), open-label, Phase 3 clinical trial evaluating nivolumab 3 mg/kg every 2 weeks (Q2W) combined with ipilimumab 1 mg/kg every 6 weeks (Q6W) versus 6 cycles of pemetrexed plus cisplatin or carboplatin as a first line treatment in adults (18 years and older) with untreated, unresectable malignant pleural mesothelioma (MPM).

The last patient last visit (LPLV) for safety data was 28-Apr-2023 and database lock (DBL) was 14-Jun-2023.

### Safety Results:

The median duration of therapy was longer in the nivo+ipi arm, 5.55 months, compared with 3.48 months in the chemotherapy arm; 23.7% of subjects received more than 12 months of nivo+ipi treatment. The maximum duration of treatment per protocol was 24 months for nivo+ipi, and 6 cycles of chemotherapy.

In the follow-up period inclusive of data through 14-Jun-2023, the overall frequencies of all-causality AEs and drug-related AEs were comparable between the nivo+ipi and chemotherapy arms; 99.7% vs 97.5% for all-causality AEs, and 80.0% vs 82.4% for drug-related AEs. The frequencies of all-causality Grade 3-4 SAEs and drug-related Grade 3-4 SAEs were higher for nivo+ipi arm compared with chemotherapy arm (34.7% vs 19.0% and 15.7% vs 6.0%). The frequency of deaths attributed to study drug toxicity was low and comparable for the nivo+ipi (1.0%) and chemotherapy arms (0.4%) (Table 5.5.2.18-1)

The safety profile of nivo+ipi in first-line MPM data in the follow-up period through 14-Jun-2023, was similar to the known safety profile of nivo+ipi. No new adverse events, safety signals or toxicities were identified with nivo+ipi, relative to each agent as monotherapy or in combination.

**Table 5.5.2.18-1: Summary of Safety - All Treated Subjects**

Safety Parameters	Nivolumab+ Ipilimumab N=300 n (%)	Chemotherapy N=284 n (%)		
Number Of Subjects Who Died	251 (83.7)	259 (91.2)		
Within 30 of last dose	28 (9.3)	14 (4.9)		
Within 100 days of last dose	55 (18.3)	51 (18.0)		
Adverse Event Grades				
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-Causality SAEs	165 (55.0)	104 (34.7)	73 (25.7)	54 (19.0)
Drug-related SAEs	64 (21.3)	47 (15.7)	22 (7.7)	17 (6.0)
All-Causality AEs leading to DC	87 (29.0)	60 (20.0)	58 (20.4)	28 (9.9)
Drug-related AEs leading to DC	68 (22.7)	46 (15.3)	45 (15.8)	21 (7.4)
All-Causality AEs	299 (99.7)	159 (53.0)	277 (97.5)	120 (42.3)
Drug-related AEs	240 (80.0)	95 (31.7)	234 (82.4)	93 (32.7)
All Causality Select AEs				
Gastrointestinal	98 (32.7)	18 (6.0)	34 (12.0)	3 (1.1)
Hepatic	57 (19.0)	20 (6.7)	9 (3.2)	0
Pulmonary	26 (8.7)	6 (2.0)	2 (0.7)	1 (0.4)
Renal	33 (11.0)	6 (2.0)	26 (9.2)	3 (1.1)

**Table 5.5.2.18-1: Summary of Safety - All Treated Subjects**

Safety Parameters	Nivolumab+ Ipilimumab N=300 n (%)		Chemotherapy N=284 n (%)	
Skin	135 (45.0)	11 (3.7)	40 (14.1)	1 (0.4)
Hypersensitivity	37 (12.3)	4 (1.3)	7 (2.5)	0
<b>All Causality Drug-related Select AEs</b>				
Gastrointestinal	66 (22.0)	16 (5.3)	23 (8.1)	3 (1.1)
Hepatic	40 (13.3)	17 (5.7)	6 (2.1)	0
Pulmonary	20 (6.7)	2 (0.7)	0	0
Renal	15 (5.0)	4 (1.3)	19 (6.7)	1 (0.4)
Skin	107 (35.7)	9 (3.0)	27 (9.5)	1 (0.4)
Hypersensitivity	36 (12.0)	4 (1.3)	7 (2.5)	0

Source: CA209743 CSR database lock date 14-Jun-2023<sup>171</sup>

### **5.5.3 Nivolumab in Combination with Chemotherapy**

Safety data for nivolumab in combination with chemotherapy in subjects with NSCLC and GC, GEJC and esophageal adenocarcinoma are described in the USPI ([Appendix 2](#)) and in subjects with NSCLC, ESCC, GEJC and esophageal adenocarcinoma in the EU SmPC ([Appendix 3](#)). Additional safety data for the use of nivolumab in combination with chemotherapy are presented below.

#### **5.5.3.1 Nivolumab in Combination with Chemotherapy - CA209012 (NSCLC)**

The study design and efficacy of CA209012 are discussed in [Section 5.4.1.2](#).

No dose-limiting toxicities were reported in any subjects receiving nivolumab + platinum-based chemotherapy during the protocol-defined evaluation period (first 6 weeks of treatment) and, thus, no MTD was defined. The safety profile of nivolumab in combination with chemotherapy was manageable and consistent with that reported for nivolumab monotherapy and platinum-based doublet chemotherapy alone. No new safety concerns were identified.

A summary of safety is provided in [Table 5.5.3.1-1](#).

The following were the key safety findings:

- The most frequently reported drug-related AE with nivolumab + chemotherapy was fatigue (71.4%).
- Drug-related SAEs reported in at least 2 subjects treated with nivolumab in combination with chemotherapy included pneumonitis (7.1%), anemia (5.4%), febrile neutropenia (3.6%), and rash maculo-papular (3.6%).
- Drug-related AEs leading to discontinuation reported in at least 2 subjects treated with nivolumab in combination with chemotherapy included pneumonitis (5.4%) and hypersensitivity (3.6%).
- Most deaths in CA209012 were due to disease progression. There were no deaths reported due to study drug toxicity in subjects treated with nivolumab + chemotherapy.



**Table 5.5.3.1-1: Summary of Safety in Subjects with Chemotherapy-naïve NSCLC Treated with Nivolumab + Platinum based Chemotherapy by Worst CTC Grade – CA209012**

	Number (%) Subjects	
	Pooled Cohorts ABC (N = 56)	
<b>DEATHS</b>	47 ( 83.9)	
PRIMARY REASON FOR DEATH (%)		
DISEASE	36 (64.3)	
STUDY DRUG TOXICITY	0	
UNKNOWN	8 (14.3)	
OTHER	3 ( 5.4)	
<b>WITHIN 30 DAYS OF LAST DOSE</b>	0	
<b>WITHIN 100 DAYS OF LAST DOSE</b>	2 ( 3.6)	
PRIMARY REASON FOR DEATH (%)		
DISEASE	1 ( 1.8)	
STUDY DRUG TOXICITY	0	
OTHER	1 ( 1.8)	
	Pooled Cohorts ABC (N = 56)	
	Any Grade	Grade 3-4
<b>ALL CAUSALITY SAEs</b>	31 ( 55.4)	23 ( 41.1)
<b>DRUG-RELATED SAEs</b>	18 ( 32.1)	13 ( 23.2)
<b>ALL CAUSALITY AEs LEADING TO DC</b>	10 ( 17.9)	7 ( 12.5)
<b>DRUG-RELATED AEs LEADING TO DC</b>	9 ( 16.1)	6 ( 10.7)
<b>ALL CAUSALITY AEs</b>	56 (100.0)	36 ( 64.3)
<b>Most Frequent AEs (≥ 40% of Any Grade)</b>		
FATIGUE	47 ( 83.9)	4 ( 7.1)
NAUSEA	32 ( 57.1)	2 ( 3.6)
CONSTIPATION	31 ( 55.4)	0
DECREASED APPETITE	27 ( 48.2)	1 ( 1.8)
COUGH	26 ( 46.4)	0
DYSPNOEA	26 ( 46.4)	1 ( 1.8)
DIARRHOEA	23 ( 41.1)	3 ( 5.4)
<b>DRUG-RELATED AEs</b>	53 ( 94.6)	25 ( 44.6)
<b>Most Frequent Drug-related AEs (≥ 35% of Any Grade)</b>		
FATIGUE	40 ( 71.4)	3 ( 5.4)
NAUSEA	26 ( 46.4)	1 ( 1.8)
DECREASED APPETITE	20 ( 35.7)	1 ( 1.8)

Source: CA209012 CSR<sup>111</sup>, database lock date 19-Sep-2016

Medical Dictionary for Regulatory Activities (MedDRA) version 19.0; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated. Chemotherapy includes GEM/cisplatin, paclitaxel/CAR, and pemetrexed/cisplatin.

### 5.5.3.2 Nivolumab in Combination with Chemotherapy - CA209205 (cHL)

The study design and efficacy of CA209205 are discussed in [Section 5.4.4.1](#).

CA209205 Cohort D was a non-comparative, single-arm Phase 2 study of nivolumab monotherapy followed by nivolumab in combination with chemotherapy (adriamycin/doxorubicin, vinblastine, DTIC) in subjects with untreated advanced-stage cHL. The safety profile was consistent with the known safety profile of nivolumab monotherapy and in combination with chemotherapy. No new safety concerns were identified. There were no differences in the incidences and severities of reported events for the monotherapy phase (N = 51), the combination therapy phase (N = 50), and overall (N = 51). A summary of safety is provided in [Table 5.5.3.2-1](#).

**Table 5.5.3.2-1: Summary of Safety in Subjects with cHL Treated with Nivolumab Monotherapy Followed by Nivolumab in Combination with Chemotherapy - CA209205**

No. of Subjects (%)						
Safety Parameter	Monotherapy Phase N = 51		Combination Therapy Phase N = 50		Overall N = 51	
Deaths, n (%)						5 (9.8)
Within 30 days of Last Dose	0		0		0	
Within 100 days of Last Dose	0		0		1 (2.0)	
Due to Study Drug Toxicity	0		0		1 (2.0)	
Adverse Event Grades						
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
All Causality SAEs	2 (3.9)	0	10 (2.0)	6 (12.0)	12 (23.5)	6 (11.8)
Drug-Related SAEs	2 (3.9)	0	5 (10.0)	4 (8.0)	7 (13.7)	4 (7.8)
All Causality AEs leading to DC	1 (2.0)	0	3 (6.0)	2 (4.0)	4 (7.8)	2 (3.9)
Drug-Related AEs leading to DC	1 (2.0)	0	3 (6.0)	2 (4.0)	4 (7.8)	2 (3.9)
Adverse Event Grades						
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Drug Related AEs	37 (72.5)	0	45 (90.0)	30 (60.0)	49.0 (96.1)	30 (58.8)
Most frequently reported drug-related AEs (≥ 10% of any grade)						
Pyrexia	4 (7.8)	0	3 (6.0)	1 (2.0)	6 (11.8)	1 (2.0)
Fatigue	4 (7.8)	0	11 (22.0)	0	13 (25.5)	0
Arthralgia	4 (7.8)	0	2 (4.0)	0	6 (11.8)	0
Neutropenia	1 (2.0)	0	25 (50.0)	21 (42.0)	25 (49.0)	21 (41.2)
White Blood Cell Count Decreased	0	0	7 (14.0)	1 (2.0)	7 (13.7)	1 (2.0)
Neutrophil Count Decreased	0	0	6 (12.0)	6 (12.0)	6 (11.8)	6 (11.8)

**Table 5.5.3.2-1: Summary of Safety in Subjects with cHL Treated with Nivolumab Monotherapy Followed by Nivolumab in Combination with Chemotherapy - CA209205**

Safety Parameter	No. of Subjects (%)					
	Monotherapy Phase N = 51		Combination Therapy Phase N = 50		Overall N = 51	
Nausea	2 (3.9)	0	17 (34.0)	1 (2.0)	18 (35.3)	1 (2.0)
Constipation	1 (2.0)	0	7 (14.0)	0	7 (13.7)	0
Vomiting	0	0	7 (14.0)	0	7 (13.7)	0
Diarrhea	3 (5.9)	0	3 (6.0)	0	6 (11.8)	0
Infusion Related Reactions	15 (29.4)	0	3 (6.0)	0	16 (31.4)	0
Stomatitis	0	0	6 (12.0)	0	6 (11.8)	0
Hypothyroidism	0	0	7 (14.0)	0	7 (13.7)	0

Source: CA209205 Closeout CSR Cohort D CSR<sup>172</sup>; 13-Apr-2023 database lock

MedRA Version: 25.1

CTC Version 4.0

Includes events reported between first dose of the considered therapy phase and 30 days after last dose of study therapy phase (or up to first dose of combination if any when considering the monotherapy period), unless otherwise indicated

**5.5.3.3 Nivolumab in Combination with Chemotherapy - CA209744 (cHL)**

The study design and efficacy of CA209744 are discussed in [Section 5.4.4.2](#).

A summary of key safety findings from Cohort R2 is provided in Table 5.5.3.3-1.

**Table 5.5.3.3-1: Summary of Safety in Children, Adolescents, and Young Adults with cHL Treated with Nivolumab + Brentuximab Vedotin - CA209744 Cohort R2**

N = 44			
<b>DEATH (%)</b>		1 (2.3)	
CAUSE OF DEATH (%)		1 (2.3)	
DISEASE		0	
WITHIN 30 DAYS OF LAST DOSE (%)		0	
WITHIN 100 DAYS OF LAST DOSE (%)		0	
<b>BY WORST CTC GRADE</b>	<b>Any Grade</b>	<b>Grade 3-4</b>	<b>Grade 5</b>
ALL CAUSALITY SAES	9 ( 20.5)	6 ( 13.6)	0
DRUG-RELATED SAES	5 ( 11.4)	3 ( 6.8)	0
ALL CAUSALITY AE LEADING TO DISCONTINUATION	1 ( 2.3)	1 ( 2.3)	0
Anaphylactic reaction	1 ( 2.3)	1 ( 2.3)	0
DRUG-RELATED AE LEADING TO DISCONTINUATION	1 ( 2.3)	1 ( 2.3)	0
Anaphylactic reaction	1 ( 2.3)	1 ( 2.3)	0
ALL CAUSALITY AES WITH 30 DAYS FOLLOW-UP	42 ( 95.5)	18 ( 40.9)	0
MOST FREQUENT AES (≥ 25% OF ANY GRADE)			
Nausea	25 ( 56.8)	0	0
Diarrhoea	12 ( 27.3)	0	0
Pyrexia	12 ( 27.3)	0	0
DRUG-RELATED AES WITH 30 DAYS FOLLOW-UP	32 ( 72.7)	10 ( 22.7)	0
MOST FREQUENT AES (≥ 25% OF ANY GRADE)			
Nausea	12 ( 27.3)	0	0
DRUG-RELATED AES WITH 100 DAYS FOLLOW-UP	32 ( 72.7)	11 ( 25.0)	0
MOST FREQUENT AES (≥ 25% OF ANY GRADE)			
Nausea	12 ( 27.3)	0	0

Source: CA209744 Interim CSR<sup>173</sup>; database lock date 25-Oct-2019

MedDRA Version: 22.0

CTC Version: 4.0

No safety signals were observed in subjects treated in Cohort R2. The overall frequency of AEs (regardless of causality and Grade 3-4) were generally consistent with the known safety profile of the therapeutic agents. One death due to disease progression was reported in Cohort R2 in a refractory subject who completed the induction, intensification, and consolidation phases. Grade 3-4 drug-related SAEs were reported in 3/44 (6.8%) subjects, in Cohort R2 (during induction: anaphylactic reaction, infusion-related reaction, activated thromboplastic time prolongation; and during consolidation: pulmonary veno-occlusive and organizing pneumonia).

The rate of hematologic toxicity was low for subjects treated in Cohort R2 (Grade 3 toxicity for decreased leukocytes in 3/44 [6.8%] subjects, decreased absolute lymphocytes in 7/44 [15.9%]

subjects, and decreased absolute neutrophil count in 5/44 [11.4%] subjects; Grade 4 toxicity for decreased absolute lymphocytes in 1/44 [2.3%] subjects). Abnormalities in hematology and serum chemistry tests, after the first dose and within 30 days of the last dose of study drug, were primarily Grades 1-2 in subjects treated in Cohort R2.

#### **5.5.3.4 Nivolumab in Combination with Chemotherapy - CA209436 (Non-Hodgkin Lymphoma)**

The study design and efficacy of CA209436 are discussed in [Section 5.4.17.1](#).

The following are the key safety findings:

- There were 8 (26.7%), 30 (71.4%), 26 (78.8%), 14 (48.3%) and 4 (40.0%) subjects who died in the PMBL, DLBCL, PTCL, CTCL and MGZL cohorts respectively. One subject in each of the DLBCL and PTCL cohorts died, reportedly from study drug toxicity (One subject with DLBCL was reported with concurrent infections and died due to reported progressive disease, Steven Johnson Syndrome and Sepsis and one subject with PTCL died reportedly due to pneumonitis).
- There were 10 (33.3%), 22 (55.4%), 19 (57.6%), 14 (48.3%), 4 (40.0%) all-causality SAEs reported in the PMBL, DLBCL, PTCL, CTCL and MGZL cohorts respectively.
- For the majority of subjects with most frequently reported AEs by PT (AEs reported in more than 20% of all subjects per cohort), AEs were low grade (Grade 1-2) across the 5 cohorts. Of these most frequently reported AEs, higher rates of PTs Grade 3-4 were reported for neutropenia in PMBL and PTCL cohorts and anaemia and thrombocytopenia in PTCL. The majority of AEs reported in subjects across cohorts were assessed as drug-related by the investigator.
- There were 9 (30.0%), 12 (28.6%), 11 (33.3%), 10 (34.5%) and 2 (20.0%) reported AEs leading to discontinuation in the PMBL, DLBCL, PTCL, CTCL and MGZL cohorts respectively. The 3 most common AEs leading to discontinuation across cohorts were malignant neoplasm progression, peripheral sensory neuropathy and neuropathy peripheral.
- There were 6 (20.0%), 5 (11.9%), 9 (27.3%), 8 (27.6%) and 1 (10.0%) reported drug-related AEs leading to discontinuation in the PMBL, DLBCL, PTCL, CTCL and MGZL cohorts respectively. The most frequently reported (>10%) drug-related AEs reported in PMBL, CTCL, and MGZL were peripheral sensory neuropathy and neuropathy peripheral.
- No specific patterns were identified for Select AEs and IMAEs.
- The majority of laboratory parameters were low grade (Grade 1-2).

No safety signals or any new safety concerns were identified. Toxicities were overall manageable and within the expected profile of the individual agents.

### **5.5.3.5 Nivolumab in Combination with Chemotherapy - CA2099TM (SCCHN)**

CA2099TM is a completed randomized, double-blind, placebo-controlled, phase 3 study of nivolumab or nivolumab plus cisplatin, in combination with radiotherapy in participants with cisplatin ineligible and cisplatin eligible locally advanced SCCHN. <sup>174</sup>

As of 15-Oct-2018, enrollment into the study was closed due to low enrollment. At that time, enrollment in the study was less than 5% of the target enrollment. There were 39 subjects exposed to nivolumab across all arms. Given the low enrollment and expected change in the treatment landscape, completion of the study would not have meaningfully impacted the standard of care treatment in this setting. Importantly, study closure was not due to identification of safety or efficacy concerns in the study treatment arms.

The safety results reported in this study were consistent with the known safety profile of nivolumab. No treatment related deaths were noted in the study. No new safety signals were identified.

### **5.5.3.6 Nivolumab in Combination with Chemotherapy in Japanese, Korean, and Taiwanese, and Chinese Subjects**

Safety of nivolumab in combination with chemotherapy in Japanese, Korean and Taiwanese subjects with NSCLC (ONO-4538-52, described in the JPI) and GC (ONO-4538-37, described in the JPI) were consistent with known safety profiles of nivolumab and chemotherapy. Additional safety data for the use of nivolumab in combination with chemotherapy in Japanese, Korean, Taiwanese, and Chinese subjects are presented below.

### **ONO-4538-04: Nivolumab in Combination with Chemotherapy in Japanese Subjects with Stage IIIB/IV or Recurrent NSCLC**

In this study, subjects received nivolumab (10 mg/kg Q3W) in combination with chemotherapy. As of the LPLV date (01-Jul-2019), safety was evaluated in 24 treated subjects.

**Deaths:** No subjects died from AEs reported within 28 days of the last dose of study treatment or before the start of post-study treatment.

**Serious Adverse Events:** SAEs were reported in 9 (37.5%) subjects.

- **Nivolumab 10 mg/kg + cisplatin/gemcitabine (n=6):** SAEs were observed in 2 (33.3%) subjects (atrial fibrillation in 1 subject; thyroid disorder and hypophysitis both in 1 subject), and all were considered possibly related to nivolumab and/or chemotherapy.
- **Nivolumab 10 mg/kg + cisplatin/pemetrexed (n=6):** SAEs were observed in 3 (50.0%) subjects (interstitial lung disease in 2 subjects, depression in 1 subject) and all were considered possibly related to nivolumab and/or chemotherapy.
- **Nivolumab 10 mg/kg + carboplatin/paclitaxel/bevacizumab (n=6):** 1 (16.7%) subject had a SAE of epistaxis and was considered possibly related to nivolumab and/or chemotherapy.
- **Nivolumab 10 mg/kg + docetaxel (n=6):** SAEs were observed in 3 (50.0%) subjects (pneumonia, lung infection, and infusion-related reaction); all were considered possibly related to nivolumab and/or chemotherapy.

**Adverse Events:** AEs, regardless of causality, and drug-related AEs were observed in all of 24 subjects treated with nivolumab + chemotherapy.

- **Nivolumab 10 mg/kg + cisplatin/gemcitabine (n=6):** Drug-related AEs reported in at least 2 subjects were anemia, neutrophil count decreased, platelet count decreased, and white blood cell count decreased (6 subjects, 100.0% each); nausea, GGT increased, and decreased appetite (5 subjects, 83.3% each); ALT increased, AST increased, lymphocyte count decreased, and hyponatremia (4 subjects, 66.7% each); constipation, and alopecia (3 subjects, 50.0% each); and vomiting, malaise, hypersensitivity, hyperkalemia, and rash maculo-papular (2 subjects, 33.3% each).
- **Nivolumab 10 mg/kg + cisplatin/pemetrexed (n=6):** Drug-related AEs reported in at least 2 subjects were neutrophil count decreased, white blood cell count decreased, and decreased appetite (5 subjects, 83.3% each); anemia, nausea, GGT increased, and hyponatremia (4 subjects, 66.7% each); constipation, malaise, AST increased, platelet count decreased, dry skin, and rash (3 subjects, 50.0% each); and ALT increased and interstitial lung disease (2 subjects, 33.3% each).
- **Nivolumab 10 mg/kg + carboplatin/paclitaxel/bevacizumab (n=6):** Drug-related AEs reported in at least 2 subjects were neutrophil count decreased, platelet count decreased, white blood cell count decreased, and alopecia (6 subjects, 100.0% each); decreased appetite and rash (5 subjects, 83.3%); constipation, nausea, lymphocyte count decreased, arthralgia, myalgia, peripheral sensory neuropathy, epistaxis, and hypertension (4 subjects, 66.7% each); anemia, malaise, ALT increased, and pruritus (3 subjects, 50.0% each); and diarrhea, hemorrhoids, stomatitis, infusion-related reaction, AST increased, dysgeusia, sensory disturbance, proteinuria and dry skin (2 subjects, 33.3% each).
- **Nivolumab 10 mg/kg + docetaxel (n=6):** Drug-related AEs reported in at least 2 subjects were neutrophil count decreased and white blood cell count decreased (6 subjects, 100.0% each); lymphocyte count decreased and alopecia (5 subjects, 83.3% each); anemia, constipation, nausea, and decreased appetite (3 subjects, 50.0% each); and malaise and infusion-related reaction (2 subjects, 33.3% each).

**AEs leading to Discontinuation:** Nine (37.5%) subjects discontinued nivolumab treatment due to AEs.

- **Nivolumab 10 mg/kg + cisplatin/gemcitabine (n=6):** AEs leading to nivolumab discontinuation were observed in 2 (33.3%) subjects (thyroid disorder, hypophysitis, and hypersensitivity), and all were considered possibly related to nivolumab and/or chemotherapy.
- **Nivolumab 10 mg/kg + cisplatin/pemetrexed (n=6):** AEs leading to nivolumab discontinuation were observed in 3 (50.0%) subjects (interstitial lung disease in 2 subjects, depression in 1 subject) and all were considered possibly related to nivolumab and/or chemotherapy.
- **Nivolumab 10 mg/kg + carboplatin/paclitaxel/bevacizumab (n=6):** AEs leading to nivolumab discontinuation were observed in 1 (16.7%) subject (interstitial lung disease) and interstitial lung disease was considered possibly related to nivolumab and/or chemotherapy.
- **Nivolumab 10 mg/kg + docetaxel (n=6):** AEs leading to nivolumab discontinuation were observed in 3 (50.0%) subjects (hypothyroidism, lung infection, and infusion-related reaction); all were considered possibly related to nivolumab and/or chemotherapy.

**Electrocardiograms:** The QT/QTc interval was not prolonged in any of the treatment arms.



### **ONO-4538-32: Nivolumab in Combination with Chemotherapy in Japanese Subjects with Biliary Tract Cancer**

This was a multicentre, open-label, Phase 1 trial including two cohorts: a nivolumab monotherapy cohort of subjects with unresectable or recurrent biliary tract cancer refractory or intolerant to gemcitabine-based treatment regimens and a nivolumab with cisplatin plus gemcitabine combination therapy cohort of subjects with unresectable or recurrent biliary tract cancer who have not previously had chemotherapy.

Thirty subjects were enrolled into each cohort. Data cutoff was April 11, 2022. In the monotherapy cohort, the most frequently reported treatment-related adverse events were decreased appetite (five [16.7%]), malaise (four [13.3%]), pruritus (four [13.3%]) and rash (three [10.0%]). Grade 3-4 treatment-related adverse events were reported in three (10.0%) subjects (rash, rash maculopapular, and amylase increased) and treatment-related serious adverse events were reported in two (6.7%) subjects (colitis and pleurisy). In the combined therapy cohort, the most frequently reported treatment-related adverse events were platelet count decreased (23 [76.7%]), neutrophil count decreased (22 [73.3%]), white blood cell count decreased (20 [66.7%]), anaemia (19 [63.3%]), and decreased appetite (13 [43.3%]). Grade 3-4 treatment-related adverse events were reported in 27 subjects (90.0%). Most frequent Grade 3-4 treatment-related adverse events were neutrophil count decreased (20 [66.7%]), platelet count decreased (15 [50.0%]), anaemia (14 [46.7%]), and white blood cell count decreased (13 [43.3%]). Serious adverse drug reactions were reported in six (20.0%) subjects: platelet count decreased (three [10.0%]), febrile neutropenia (two [6.7%]), interstitial lung disease, anaemia, myocarditis, pyrexia, anaphylactic reaction, neutrophil count decreased, and decreased appetite (each in one [3.3%]).

### **ONO-4538-38: Nivolumab in Combination with Chemotherapy in Japanese, Korean, Taiwanese and Chinese Subjects with Gastric Cancer**

This was a multicenter, double-blind, randomized study intended to evaluate the efficacy and safety of postoperative adjuvant chemotherapy with nivolumab in combination with tegafur-gimeracil-oteracil potassium (S-1) therapy or capecitabine + oxaliplatin (CapeOX) therapy, in comparison with placebo in combination with S-1 therapy or CapeOX therapy (hereinafter, chemotherapy), in pathological stage (pStage) III gastric cancer (including esophagogastric junction cancer) after D2 or more extensive lymph node dissection.

At the final assessment (31-Mar-2023), the ITT population consisted of 377 subjects in the nivolumab group (132 subjects in the nivolumab + S-1 therapy group and 245 subjects in the nivolumab + CapeOX therapy group) and 378 subjects in the placebo group (135 subjects in the placebo + S-1 therapy group and 243 subjects in the placebo + CapeOX therapy group). Incidences of drug-related AEs, drug-related Grade 3-4 AEs, drug-related SAEs, drug-related AEs leading to dose delay or reduction of products, and drug-related AEs leading to discontinuation of products were 98.7% (366 subjects), 54.2% (201 subjects), 25.3% (94 subjects), 81.7% (303 subjects), and 9.2% (34 subjects), respectively, in the nivolumab group. AEs leading to death reported in the nivolumab group were asphyxia (1 subject) and pneumonitis (1 subject). Of these, pneumonitis was drug related. The most frequently reported drug-related AEs by PT (incidence  $\geq 10\%$ ) in the

nivolumab group were nausea (52.0%, 193 subjects), decreased appetite (51.2%, 190 subjects), diarrhoea (46.4%, 172 subjects), neutrophil count decreased (45.0%, 167 subjects), peripheral sensory neuropathy (28.0%, 104 subjects), platelet count decreased (19.1%, 71 subjects), vomiting (18.9%, 70 subjects), white blood cell count decreased (18.1%, 67 subjects), neuropathy peripheral (17.3%, 64 subjects), malaise (16.2%, 60 subjects), alanine aminotransferase increased (15.9%, 59 subjects), aspartate aminotransferase increased (15.9%, 59 subjects), fatigue (14.8%, 55 subjects), stomatitis (14.3%, 53 subjects), dysgeusia (14.0%, 52 subjects), anemia (12.7%, 47 subjects), palmar-plantar erythrodysesthesia syndrome (12.4%, 46 subjects), rash (11.9%, 44 subjects), hypothyroidism (11.3%, 42 subjects), and weight decreased (10.2%, 38 subjects).

### **ONO-4538-83: Nivolumab in Combination with Chemotherapy in Japanese Subjects with Pancreatic Cancer**

This was a multicenter, open-label, Phase 2 study (JapicCTI-184230), evaluating the efficacy and safety of nivolumab combined with the modified FOLFIRINOX, a regimen containing oxaliplatin, levofolinate calcium, irinotecan and fluorouracil, in subjects with pancreatic cancer.

As of the data cutoff of 09-Dec-2021, there were 31 subjects in the study. Drug-related serious adverse events were reported in 9 (29.0%) subjects; one (3.2%) drug-related adverse events led to discontinuation, and none led to death within 30-day safety window. Nausea (25; 80.6%), diarrhoea (19; 61.3%), neutrophil count decreased (19; 61.3%) and peripheral sensory neuropathy (19; 61.3%) were the most frequently reported adverse events within 30-day safety window; nausea (23; 74.2%), neutrophil count decreased (19; 61.3%), peripheral sensory neuropathy (19; 61.3%), diarrhoea (18; 58.1%) and decreased appetite (18; 58.1%) were the most frequently reported drug-related adverse events within 30-day safety window. Diarrhoea (7; 22.6%), rash (4; 12.9%) and hypothyroidism (4; 12.9%) were the most frequently reported treatment-emergent adverse events of interest for nivolumab within 100-day safety window.

### **5.5.3.7 Nivolumab in Combination with Chemotherapy - CA209812 (cHL)**

The study design and efficacy of CA209812 are discussed in [Section 5.4.4.3](#).

The key safety data are presented below:

- No new safety signals or toxicities were identified with nivolumab + BV, relative to each agent as monotherapy or in combination.
- One subject died 480 days after last dose in the nivolumab + BV arm. The death was attributed to “disease”.
- All-causality SAEs were reported more frequently in the nivolumab + BV arm than in the BV alone arm. Infusion related reaction was the only SAE that was reported in more than 1 subject (2 subjects; 16.7%) in the nivolumab + BV arm. All other SAEs were singular events (1 subject; 8.3% in the nivolumab + BV arm and 1 subject; 10.0% in the BV alone arm).
- All-causality AEs that led to discontinuations were reported more frequently in the nivolumab + BV arm than in the BV alone arm. All AEs that led to discontinuation were singular events (1 subject; 8.3% in the nivolumab + BV arm and 1 subject; 10.0% in the BV alone arm).
- All 12 subjects in the nivolumab + BV arm and all 10 subjects in the BV alone arm reported at least 1 AE. Overall, the events reported in each arm were similar in terms of incidence and were mostly Grade 1-2 events.

The overall safety of nivolumab + BV and BV alone was consistent with the known safety profile of the individual treatment regimens, and no additional safety concerns were identified.

### **5.5.3.8 Nivolumab in Combination with Chemotherapy - CA2097FL (Breast Cancer)**

The study design and efficacy of CA2097FL are discussed in [Section 5.4.21.2](#).

#### **Safety Results:**

Safety data from the 517 subjects (262 in Arm A and 255 in Arm B) treated in the neoadjuvant phase of this study demonstrated that the addition of nivolumab to neoadjuvant standard of care chemotherapy resulted in an acceptable safety profile.

- Deaths: A total of 13 (2.5%) subjects died - 9 deaths in Arm A and 4 deaths in Arm B. In Arm A, the most frequently reported reason for death was ‘other’ (n = 6: 2 pulmonary embolism, 1 COVID-19 related, 1 hypovolemic shock, 1 respiratory failure and 1 cardiopulmonary arrest). Two deaths were reported as due to study drug toxicity (pneumonitis and hepatitis). All 4 deaths in Arm B were reported as due to disease.
- Other SAEs: A total of 60 (22.9%) subjects in Arm A and 33 (12.9%) subjects in Arm B were reported with SAEs; the most frequently reported events included febrile neutropenia, and infections and infestations. Drug related SAEs were reported in 38 (14.5%) subjects in Arm A and 21 (8.2%) subjects in Arm B; the most frequently reported event was febrile neutropenia.
- AEs leading to discontinuation/dose delay or reduction:
  - A total of 26 (9.9%) subjects in Arm A and 7 (2.7%) subjects in Arm B were reported with AEs that led to discontinuation; the most frequently reported events included ALT increased and nervous system disorders. Drug-related AEs leading to discontinuation were

- reported in 25 (9.5%) subjects in Arm A and 7 (2.7%) subjects in Arm B; the most frequently reported event was ALT increased.
- A total of 108 (41.2%) subjects in Arm A and 90 (35.3%) subjects in Arm B were reported with AEs that led to dose delay or reduction; the most frequently reported events included COVID-19 and neutropenia. Drug-related AEs leading to dose delay or reduction were reported in 79 (30.2%) subjects in Arm A and 70 (27.5%) subjects in Arm B; the most frequently reported event was neutropenia in Arm A.
  - OESI:
    - Related Grade 3-4 events of myocarditis, Guillain Barre syndrome, and autoimmune neuropathy were recorded in 1 subject (0.4%) for each event in Arm A; 1 (0.4%) subject in Arm B was reported with an unrelated Grade 3-4 pancreatitis. No subjects were reported with myasthenic syndrome, demyelination event, uveitis event, encephalitis event, myositis/rhabdomyolysis event, graft-vs-host-disease, autoimmune cytopenia, autoimmune eye disorders, or immune mediated arthritis.
    - A total of 33 (12.6%) subjects in Arm A and 33 (12.9%) subjects in Arm B were reported with COVID-19 related AEs; only a few subjects were reported with a COVID-19-related pneumonia or symptomatic infection.
    - A total of 104 (20.1%) of all subjects were reported with surgical complication AEs; most events were assessed as Grade 1 or Grade 2 and the most frequently reported event was procedural pain. A total of 15 (2.9%) subjects were reported with surgical complication SAEs; most events were assessed as Grade 2 or Grade 3 and the most frequently reported events included infections.
    - Most AE leading to surgery delay were assessed as Grade 1, 2 or 3, and none were assessed as Grade 5. The most common events were in the blood and lymphatic disorders SOC.
  - Overall AEs: Most subjects in both arms were reported with non-serious AEs; the most frequently reported events were in the Gastrointestinal Disorders and Skin and subcutaneous tissue disorders SOC. Overall, 39.8% of subjects were reported with a Grade 3-4 AE and 0.6% of subjects were reported with a Grade 5 event. Drug related AEs were more frequently reported in Arm A (95.3%) than in Arm B (91.7%).
  - IMAE: Endocrine IMAEs were more frequently reported in Arm A, and the most frequently reported event was hypothyroidism. Non-endocrine IMAEs were more frequently reported in Arm A, and the most frequently reported event was rash.
  - Clinical Laboratory Evaluations: Most clinical laboratory abnormalities were Grade 1-2 or within normal limits.

#### **5.5.3.9 Nivolumab in Combination with Chemotherapy - CA20977T (Non-small Cell Lung Cancer)**

The study design and efficacy of CA20977T are discussed in [Section 5.4.1.9](#).

## Safety Results:

### Overall Safety Summary

The safety profile of neoadjuvant nivo 360 mg + platinum-based doublet chemo Q3W × 4 cycles, surgery, and adjuvant treatment with nivo 480 mg Q4W for up to 13 cycles (approximately 1 year) was consistent with the known safety profiles of the immunotherapy and chemotherapy components in subjects with NSCLC (Table 5.5.3.9-1). No new safety signals or toxicities were identified.

### *Safety Summary - Overall Treatment Period*

- The overall frequency of reported all-causality AEs was similar in the 2 treatment arms. The most frequently reported drug-related AEs were events frequently associated with chemotherapy (eg, constipation, alopecia, anemia, nausea, decreased neutrophil count).
- As of the 26-Jul-2023 clinical data cutoff, a similar proportion of subjects in both arms died.
  - The most frequently reported cause of death in both arms was disease progression.
  - 2 deaths due to study drug toxicity (per investigator) were reported in the nivo+chemo/nivo arm; both subjects died with the cause of death reported as pneumonitis after completing 4 cycles of neoadjuvant treatment. No deaths due to study drug toxicity (per investigator) were reported in the placebo+chemo/placebo arm.
  - Note that 23 subjects in the nivo+chemo/nivo arm and 37 subjects in the placebo+chemo/placebo arm died > 100 days after the last treatment of study therapy.
- Select AEs and immune-mediated adverse events (IMAEs) were more frequently reported with nivo+chemo/nivo compared with placebo+chemo/placebo but were infrequent and mostly Grade 1-2. All were manageable using the established algorithms.
  - Most drug-related select AEs (non-endocrine: 71.4% - 100.0%; endocrine: 57.6%) and most IMAEs (non-endocrine: 71.4% - 100.0%; endocrine: 25.0% - 100.0%) in the nivo+chemo/nivo arm were reported as resolved at the time of database lock.
- Other events of special interest (OESIs) were reported in 4 subjects in the nivo+chemo/nivo arm and 1 subject in the placebo+chemo/placebo arm. Each subject was reported to have 1 OESI, except for 1 subject in the nivo+chemo/nivo arm reported with 2 OESIs reported (myocarditis and myositis).
- The grades and frequencies of laboratory abnormalities (hematology, liver tests, kidney function tests, and electrolytes) were similar between the nivo+chemo/nivo and placebo+chemo/placebo arms.

**Table 5.5.3.9-1: Safety in the Overall Treatment Period - All Treated Subjects in the Global Population**

	No. of Subjects (%)	
	Nivo+Chemo/Nivo N = 228	Placebo+Chemo/Placebo N = 230
<b>Deaths</b> (includes all deaths)	40 (17.5)	48 (20.9)
Primary Reason for Death		
Disease	21 (9.2)	39 (17.0)

**Table 5.5.3.9-1: Safety in the Overall Treatment Period - All Treated Subjects in the Global Population**

	No. of Subjects (%)			
	Nivo+Chemo/Nivo N = 228		Placebo+Chemo/Placebo N = 230	
Study Drug Toxicity <sup>a</sup>	2 (0.9)		0	
Unknown <sup>b</sup>	1 (0.4)		0	
Other <sup>c</sup>	16 (7.0)		9 (3.9)	
Safety Parameters	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade3-4
All-causality SAEs	96 (42.1)	65 (28.5)	71 (30.9)	46 (20.0)
Drug-related SAEs	44 (19.3)	31 (13.6)	22 (9.6)	13 (5.7)
All-causality AEs leading to DC	56 (24.6)	32 (14.0)	25 (10.9)	14 (6.1)
Drug-Related AEs leading to DC	44 (19.3)	25 (11.0)	17 (7.4)	11 (4.8)
All-Causality AEs	222 (97.4)	108 (47.4)	225 (97.8)	99 (43.0)
≥ 15% of Subjects in Any Arm, by PT				
Anemia	90 (39.5)	18 (7.9)	74 (32.2)	10 (4.3)
Constipation	73 (32.0)	1 (0.4)	64 (27.8)	1 (0.4)
Nausea	66 (28.9)	5 (2.2)	79 (34.3)	3 (1.3)
Fatigue	64 (28.1)	7 (3.1)	60 (26.1)	3 (1.3)
Alopecia	59 (25.9)	2 (0.9)	63 (27.4)	1 (0.4)
Cough	50 (21.9)	0	46 (20.0)	0

**Table 5.5.3.9-1: Safety in the Overall Treatment Period - All Treated Subjects in the Global Population**

	No. of Subjects (%)			
	Nivo+Chemo/Nivo N = 228		Placebo+Chemo/Placebo N = 230	
Safety Parameters	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade3-4
Decreased appetite	43 (18.9)	1 (0.4)	45 (19.6)	1 (0.4)
Neutrophil count decreased	37 (16.2)	24 (10.5)	20 (8.7)	15 (6.5)
Dyspnea	36 (15.8)	4 (1.8)	35 (15.2)	2 (0.9)
Diarrhea	34 (14.9)	2 (0.9)	35 (15.2)	1 (0.4)
Arthralgia	43 (18.9)	4 (1.8)	41 (17.8)	1 (0.4)
<b>Drug-related AEs</b>	203 (89.0)	74 (32.5)	200 (87.0)	58 (25.2)
≥ 15% of Subjects in Any Arm, by PT				
Anemia	57 (25.0)	8 (3.5)	51 (22.2)	8 (3.5)
Nausea	53 (23.2)	2 (0.9)	65 (28.3)	3 (1.3)
Alopecia	52 (22.8)	1 (0.4)	53 (23.0)	0
Constipation	51 (22.4)	0	39 (17.0)	1 (0.4)
Fatigue	47 (20.6)	5 (2.2)	44 (19.1)	2 (0.9)
Neutrophil count decreased	35 (15.4)	23 (10.1)	20 (8.7)	15 (6.5)
<b>All-causality Select AEs, by Category</b>				
Endocrine	42 (18.4)	2 (0.9)	13 (15.7)	0
Gastrointestinal	37 (16.2)	6 (2.6)	37 (16.1)	2 (0.9)
Hepatic	46 (20.2)	5 (2.2)	31 (13.5)	3 (1.3)
Pulmonary	17 (7.5)	4 (1.8)	8 (3.5)	5 (2.2)
Renal	34 (14.9)	3 (1.3)	18 (7.8)	1 (0.4)
Skin	71 (31.1)	3 (1.3)	53 (23.0)	0
Hypersensitivity/Infusion Reactions	15 (6.6)	2 (0.9)	14 (6.1)	3 (1.3)
<b>Drug-Related Select AEs, by Category</b>				
Endocrine	33 (14.5)	1 (0.4)	12 (5.2)	0
Gastrointestinal	28 (12.3)	5 (2.2)	20 (8.7)	1 (0.4)
Hepatic	30 (13.2)	3 (1.3)	20 (8.7)	2 (0.9)
Pulmonary	14 (6.1)	3 (1.3)	3 (1.3)	2 (0.9)
Renal	26 (11.4)	2 (0.9)	10 (4.3)	1 (0.4)
Skin	54 (23.7)	3 (1.3)	34 (14.8)	0
Hypersensitivity/Infusion Reactions	14 (6.1)	2 (0.9)	11 (4.8)	3 (1.3)

**Table 5.5.3.9-1: Safety in the Overall Treatment Period - All Treated Subjects in the Global Population**

	No. of Subjects (%)			
	Nivo+Chemo/Nivo N = 228		Placebo+Chemo/Placebo N = 230	
Safety Parameters	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade3-4
All-causality IMAEs within 100 Days of Last Dose				
Treated with Immune Modulating Medication, by Category				
Diarrhea/Colitis	5 (2.2)	2 (0.9)	2 (0.9)	0
Hepatitis	0	0	1 (0.4)	0
Pneumonitis	12 (5.3)	5 (2.2)	3 (1.3)	2 (0.9)
Nephritis/Renal Dysfunction	7 (3.1)	3 (1.3)	0	0
Rash	11 (4.8)	2 (0.9)	2 (0.9)	0
Hypersensitivity/Infusion Reactions	1 (0.4)	0	0	0
All-causality Endocrine IMAEs within 100 Days of Last Dose				
With or Without Immune Modulating Medication, by Category				
Adrenal Insufficiency	4 (1.8)	0	0	0
Hypophysitis	2 (0.9)	0	1 (0.4)	1 (0.4)
Hypothyroidism/Thyroiditis	25 (11.0)	0	4 (1.7)	0
Hyperthyroidism	11 (4.8)	1 (0.4)	5 (2.2)	0
Diabetes Mellitus	2 (0.9)	0	0	0
All-causality OESIs within 100 Days of Last Dose				
With or Without Immune Modulating Medication, by Category <sup>d</sup>				
Pancreatitis	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Myositis/Rhabdomyolysis	2 (0.9)	2 (0.9)	0	0
Guillain-Barre Syndrome	1 (0.4)	0	0	0
Myocarditis	1 (0.4)	1 (0.4)	0	0

<sup>a</sup> In both subjects, the cause of death per investigator was pneumonitis.

<sup>b</sup> The subject died at home and communication with family was unsuccessful.

<sup>c</sup> The verbatim terms reported for the 'other' reasons for were consistent with events anticipated in the study population. None were considered related to study drug (per the investigator).

<sup>d</sup> No OESIs were reported in the following categories: encephalitis, myasthenic syndrome, demyelination, uveitis, or graft versus host disease.

MedDRA version 26.0; CTCAE version 4.0.

Includes events reported between first treatment and 30 days after last treatment of study therapy including definitive surgery and radiotherapy, unless otherwise indicated.

Abbreviations: AEs - adverse events, chemo - chemotherapy, CTCAE - Common Terminology Criteria for Adverse Events, IMAEs - immune-mediated adverse events, MedDRA - Medical Dictionary for Regulatory Activities, nivo - nivolumab, OESIs - other events of special interest, SAEs - serious adverse events



### 5.5.4 Nivolumab in Other Combinations

Nivolumab in other combinations is being evaluated in subjects with NSCLC, RCC, pancreatic cancer, GBM, hematologic malignancies and the safety data are presented below.

#### 5.5.4.1 Nivolumab in Combination with Tyrosine Kinase Inhibitors

Nivolumab in combination with cabozantinib has demonstrated clinical benefit in subjects with advanced RCC and has been approved for use in this population in the US, EU (see [Appendix 2](#) [USPI] and [Appendix 3](#) [EU SmPC] for efficacy information). I-O combinations with various TKIs demonstrate that skin toxicity, pneumonitis/interstitial lung disease rates, and liver function test results can occur, but the particular toxicity associated with the combination and the magnitude of the increase can differ considerably based on the individual agents being combined. The underlying mechanisms for toxicities with these combinations are currently unknown and may be based on different kinases targeted by different compounds (beyond the primary target), or may be off-target effects, or simply be an exacerbation by the checkpoint inhibitors of a subclinical tissue damage induced by the TKI.

#### 5.5.4.2 Nivolumab in Combination with Erlotinib - CA209012 (NSCLC)

The study design and efficacy of CA209012 are discussed in [Section 5.4.1.2](#).

A summary of safety is provided in Table 5.5.4.2-1 for subjects treated with nivolumab + erlotinib in CA209012. Most deaths in CA209012 were due to disease progression. No deaths were reported due to study drug toxicity in subjects treated with nivolumab + erlotinib.

**Table 5.5.4.2-1: Summary of Safety in Subjects with Chemotherapy-naïve NSCLC Treated with Nivolumab + Erlotinib – CA209012**

Category Preferred Term	Nivolumab + Erlotinib N = 21 n (%)	
	Any Grade	Grade 3-4
AEs	21 (100.0)	16 (76.2)
Drug-related AEs	21 (100.0)	5 (23.8)
Drug-related AEs in $\geq 10\%$ of Subjects		
Rash	10 (47.6)	0
Fatigue	6 (28.6)	0
Paronychia	6 (28.6)	0
Diarrhea	5 (23.8)	2 (9.5)
Skin Fissures	5 (23.8)	0
Nausea	4 (19.0)	0
Dry Skin	4 (19.0)	0
Alopecia	3 (14.3)	0
Vomiting	3 (14.3)	0
Pruritus	3 (14.3)	0
Hypothyroidism	3 (14.3)	0
ALT Increased	3 (14.3)	1 (4.8)
AST Increased	3 (14.3)	2 (9.5)

**Table 5.5.4.2-1: Summary of Safety in Subjects with Chemotherapy-naïve NSCLC Treated with Nivolumab + Erlotinib – CA209012**

Category Preferred Term	Nivolumab + Erlotinib N = 21 n (%)	
	Any Grade	Grade 3-4
Dry Mouth	3 (14.3)	0
Nail Disorder	3 (14.3)	0
Arthralgia	1 (4.8)	0
Constipation	1 (4.8)	0
Dysgeusia	1 (4.8)	0
SAEs	13 (61.9)	11 (52.4)
Drug-related SAEs	3 (14.3)	2 (9.5)
Drug-related SAEs in > 1 Subject	0	0
AEs Leading to Discontinuation	6 (28.6)	4 (19.0)
Drug-related AEs Leading to Discontinuation	4 (19.0)	3 (14.3)
Drug-related AEs Leading to Discontinuation in > 1 Subject		
Diarrhea	2 (9.5)	2 (9.5)

Source: Preliminary data for CA209012, database lock date 28-Mar-2014

Note: Safety events were reported between the first dose and 100 days after the last dose of study drug.

#### **5.5.4.3 Nivolumab Monotherapy or in Combination with Chemotherapy - CA209370 (NSCLC)**

CA209370 is a master protocol of Phase 1/2 studies of nivolumab in NSCLC using nivolumab as maintenance after induction chemotherapy or as first-line treatment alone or in combination with standard of care therapies.<sup>175</sup> Subjects were assigned to treatment groups based on histology, ECOG PS, and mutation status to one of 5 groups (Groups: A, B, C, D, and E):

New approvals of immunotherapy agents in first and subsequent lines of therapy contributed to inadequate enrollment. Given the low enrollment rates and early discontinuations of each group, the numbers of subjects included per treatment arm were small.

A summary of safety is provided in [Table 5.5.4.3-1](#). The following were the key safety findings as of the LPLV of 15-Apr-2020.

**Group A:** A total of 132 subjects were across Cohort A (subjects were treated with single agent nivolumab, a single agent of bevacizumab or a combination of both) and Cohort B (subjects were treated with single agent nivolumab, a single agent of pemetrexed or a combination of both) following first-line treatment with the investigator's choice of chemotherapy.

- In Cohort A, the most common adverse events (AEs) in the nivolumab arm were back pain, cough, and nausea (each reported in 4 [30.8%] subjects).
- In Cohort A, the most common AEs in the nivolumab + bevacizumab arm were cough (4 [66.7%] subjects) and diarrhoea (3 [50.0%] subjects).
- In Cohort B, the most common AEs in the nivolumab arm were fatigue (16 [45.7%] subjects), diarrhoea (13 [37.1%] subjects), and dyspnoea (10 [28.6%] subjects).

- In Cohort B, the most common AEs in the pemetrexed + nivolumab arm were oedema peripheral (14 [41.2%] subjects), fatigue (13 [38.2%] subjects), and decreased appetite and anaemia (both in 11 [32.4%] subjects).
- The cause of death in 1 subject (7.7%) in the Cohort A, nivolumab arm was due to drug toxicity. There were no drug toxicity induced deaths in Cohort B.

Group B: A total of 35 subjects were administered either single-agent nivolumab or best supportive care (BSC) as maintenance following first-line treatment with the investigator's choice of chemotherapy.

- The most common AEs in the nivolumab arm were fatigue and diarrhoea (both in 5 [35.7%] subjects), and constipation (4 [28.6%] subjects).
- The most common AEs in the BSC arm were malignant neoplasm progression (5 [35.7%] subjects), and back pain, hypercalcemia, pneumonia, upper respiratory tract infection, and weight decreased (each in 3 [21.4%] subjects).
- There were no drug toxicity induced deaths in Group B.

Group C: A total of 51 subjects were administered either the investigator's choice of chemotherapy or single-agent nivolumab as first-line treatment.

- The most common AEs in the nivolumab arm were malignant neoplasm progression (9 [36.0%] subjects), nausea and fatigue (both in 8 [32.0%] subjects), and diarrhoea (7 [28.0%] subjects).
- The most common AEs in the investigator's choice of chemotherapy arm were nausea (10 [38.5%] subjects), diarrhoea (9 [34.6%] subjects), and neutropenia (8 [30.8%]).
- There were no drug toxicity induced deaths in Group C.

Group D: A total of 104 subjects were administered a first-line treatment with erlotinib monotherapy or a combination of nivolumab and erlotinib.

- The most common AEs in the nivolumab + erlotinib arm were diarrhoea (34 [69.4%] subjects), fatigue (25 [51.0%] subjects), nausea (24 [49.0%] subjects), and dermatitis acneiform (23 [46.9%] subjects).
- The most common AEs in the erlotinib arm were diarrhoea (36 [65.5%] subjects), dermatitis acneiform (29 [52.7%] subjects), fatigue (23 [41.8%] subjects), and nausea and decreased appetite (both in 21 [38.2%] subjects).
- There were no drug toxicity induced deaths in Group D.

Group E: A total of 13 subjects were administered a combination therapy of nivolumab and crizotinib as first-line treatment.

- The most common AEs were ALT increased and fatigue (both in 8 [61.5%] subjects) and AST increased (7 [53.8%] subjects).
- The cause of death in 1 subject (7.7%) in Group E, was due to drug toxicity.

**Table 5.5.4.3-1: Overall Summary of Safety - All Treated Subjects- CA209370**

	Group A Cohort A			Group A Cohort B			Group B		Group C		Group D		Group E
Category	Nivo 240 mg N=13 n (%)	Bevacizu mab + Nivo 5 mg/kg N=6 n (%)	Bevacizu mab N=9 n (%)	Nivo 240 mg N=35 n (%)	Pemetre xed + Nivo 5 mg/kg N=34 n (%)	Pemetre xed N=34 n (%)	Nivo 240 mg N=14 n (%)	Best Supporti ve Care N=14 n (%)	Nivo 240 mg N=25 n (%)	Investiga tor's Choice of Chemo N=26 n (%)	Nivo 240 mg + Erlotinib N=49 n (%)	Erlotinib N=55 n (%)	Nivo 240 mg + Crizotini b N=13 n (%)
AE's	12 (92.3)	6 (100.0)	9 (100.0)	35 (100.0)	34 (100.0)	33 (97.1)	13 (92.9)	13 (92.9)	25 (100.0)	26 (100.0)	49 (100.0)	55 (100.0)	13 (100.0)
Drug- related AEs	10 (76.9)	3 (50.0)	5 (55.6)	30 (85.7)	32 (94.1)	19 (55.9)	10 (71.4)	0	14 (56.0)	21 (80.8)	47 (95.9)	55 (100.0)	13 (100.0)
SAEs	6 (46.2)	1 (16.7)	5 (55.6)	15 (42.9)	16 (47.1)	14 (41.2)	5 (35.7)	7 (50.0)	23 (92.0)	7 (26.9)	25 (51.0)	17 (30.9)	8 (61.5)
Drug- related SAEs	2 (15.4)	0	0	3 (8.6)	7 (20.6)	4 (11.8)	0	0	7 (28.0)	2 (7.7)	13 (26.5)	1 (1.8)	5 (38.5)
AEs leading to discontin uation	2 (15.4)	2 (33.3)	0	7 (20.0)	12 (35.3)	9 (26.5)	3 (21.4)	0	10 (40.0)	1 (3.8)	21 (42.9)	7 (12.7)	6 (46.2)
Drug- related AEs leading to discontin uation	1 (7.7)	1 (16.7)	0	4 (11.4)	7 (20.6)	5 (14.7)	1 (7.1)	0	4 (16.0)	1 (3.8)	16 (32.7)	2 (3.6)	5 (38.5)

Source: Final CSR CA209370. <sup>175</sup> Includes events reported between first dose and 30 days after last dose of study drug.

#### **5.5.4.4 Nivolumab Monotherapy or in Combination with Chemotherapy - CA2098HW (Colorectal Cancer)**

The study design and efficacy of CA2098HW are discussed in [Section 5.4.10.2](#).

##### **Safety Results:**

The safety profile of nivo+ipi (nivo 240 mg + ipi 1 mg/kg Q3W for 4 doses then nivo 480 mg Q4W for up to 2 years) as 1L combination therapy for subjects with MSI-H/dMMR mCRC was consistent with the established safety profile of each drug in the regimen. No new safety concerns were identified.

In 1L treated subjects, nivo+ipi combination therapy had a favorable safety profile compared with chemo despite a longer median treatment duration (13.52 vs 3.96 months).

- The frequency of deaths was lower in the nivo+ipi arm than the chemo arm (22.0% vs 42.0%).
- In addition, the following AE categories were reported in a lower proportion of subjects in the nivo+ipi arm compared with the chemo arm:
  - All-causality AEs: SAEs (45.5% vs 51.1%) and Grade 3-4 SAEs (34.5% vs 42.0%), AEs leading to discontinuation (all grades: 20.0% vs 39.8%), and Grade 3-4 AEs (48.0% vs 67.0%)
  - Drug-related AEs: AEs leading to discontinuation (all grades: 16.5% vs 31.8%), AEs (all grades: 80.0% vs 94.3%), and Grade 3-4 AEs (23.0% vs 47.7%)

The following AE categories were reported in a similar proportion of subjects in the nivo+ipi and chemo arms: drug-related SAEs (all grades: 19.0% vs 19.3%, Grade 3-4: 16.0% vs 15.9%), all-causality AEs leading to discontinuation of study therapy (any drug in the regimen: Grade 3-4: 14.5% vs 14.8%), drug related AEs leading to discontinuation of study therapy (Grade 3-4: 11.5% vs 10.2%), and all-causality AEs (all grades: 98.5% vs 97.7%).

There were 2 study drug-related deaths (per investigator) reported in the nivo+ipi arm (myocarditis and pneumonitis, 1 case each) and 1 in the chemo arm (acute myocarditis); the death in the chemo arm was reported during Crossover treatment and was considered by the investigator to be related to nivo+ipi.

As anticipated, adverse events considered to be immune mediated (such as select AEs, IMAEs, and OESIs) were more frequently reported with nivo+ipi compared with chemo, but they were mostly manageable using the established algorithms. Also as anticipated, the types of events known to be associated with chemo (such as asthenia, neutropenia, neutrophil count decreased, anemia, decreased appetite, and nausea) were reported at notably lower frequencies with nivo+ipi than chemo.

Grade 3/4 laboratory abnormalities (hematology, liver tests, kidney function tests, thyroid function tests, and electrolytes) reflected the known laboratory abnormalities associated with nivo, ipi, and chemo.

#### **5.5.4.5    *Nivolumab in Combination with Sunitinib or Pazopanib - CA209016 (RCC)***

The study design and efficacy of CA209016 are discussed in [Section 5.4.3.1](#).

Based on data from the Phase 1 study (CA209016), nivolumab in combination with VEGFR-TKIs (sunitinib and pazopanib) has an acceptable safety profile in subjects with metastatic RCC, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation (summarized in [Table 5.5.4.5-1](#)). No new safety concerns were identified with nivolumab combination therapies.

The following were the key safety findings for the subjects in CA209016:

- The most frequently reported Grade 3-4 drug-related AEs with anti-angiogenic therapy + nivolumab 2 mg/kg combination therapy were ALT increased and AST increased (28.6% each with sunitinib + nivolumab 2 mg/kg, 20% each with pazopanib + nivolumab). Hypertension and hyponatremia were the most frequently reported Grade 3-4 drug-related AEs with sunitinib + nivolumab 5 mg/kg combination therapy (19.2% each).
- The majority of deaths were reported as due to disease progression. There were no deaths attributed to study drug toxicity.

Based on the protocol-defined stopping rules for dose escalation in CA209016, the pazopanib arm was not dose-escalated due to observed toxicity (elevated liver function tests [LFTs]).

**Table 5.5.4.5-1: Safety with Nivolumab in Combination with Sunitinib or Pazopanib in Subjects with Metastatic RCC by Worst CTC Grade - CA209016**

	SUN + NIVO2 N = 7		SUN + NIVO5 N = 26		PAZ + NIVO2 N = 20	
<b>Death, n (%)</b>	3 (42.9)		9 (34.6)		13 (65.0)	
<i>Within 30 Days of Last Dose</i>	0		0		1 (5.0)	
<i>Within 100 Days of Last Dose</i>	0		1 (3.8)		2 (10.0)	
<i>Due to Study Drug Toxicity</i>	0		0		0	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<b>All-causality SAEs, n (%)</b>	3 (42.9)	1 (14.3)	16 (61.5)	14 (53.8)	13 (65.0)	10 (50.0)
<b>Drug-related SAEs, n (%)</b>	2 (28.6)	0	12 (46.2)	10 (38.5)	2 (10.0)	2 (10.0)
<b>All-causality AEs Leading to Discontinuation, n (%)</b>	3 (42.9)	2 (28.6)	10 (38.5)	9 (34.6)	5 (25.0)	4 (20.0)
<b>Drug-related AEs Leading to Discontinuation, n (%)</b>	3 (42.9)	2 (28.6)	10 (38.5)	9 (34.6)	5 (25.0)	4 (20.0)
<b>All-causality AEs, n (%)</b>	7 (100.0)	6 (85.7)	26 (100.0)	24 (92.3)	20 (100.0)	16 (80.0)
<b>Drug-related AEs, n (%)</b>	7 (100.0)	5 (71.4)	26 (100.0)	22 (84.6)	20 (100.0)	14 (70.0)
<b>All-causality Select AEs, within 30 Days of Last Dose, by Category, n (%)</b>	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<i>Endocrine</i>	3 (42.9)	0	9 (34.6)	0	5 (25.0)	2 (10.0)
<i>Gastrointestinal</i>	6 (85.7)	0	15 (57.7)	3 (11.5)	14 (70.0)	5 (25.0)
<i>Hepatic</i>	3 (42.9)	2 (28.6)	13 (50.0)	7 (26.9)	7 (35.0)	4 (20.0)
<i>Pulmonary</i>	0	0	2 (7.7)	1 (3.8)	1 (5.0)	0
<i>Renal</i>	2 (28.6)	1 (14.3)	11 (42.3)	2 (7.7)	3 (15.0)	1 (5.0)
<i>Skin</i>	7 (100.0)	1 (14.3)	19 (73.1)	3 (11.5)	13 (65.0)	0
<i>Hypersensitivity/Infusion Reactions</i>	0	0	1 (3.8)	0	2 (10.0)	1 (5.0)
<b>Drug-related Select AEs, within 30 Days of Last Dose, by Category, n (%)</b>	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<i>Endocrine</i>	3 (42.9)	0	8 (30.8)	0	5 (25.0)	2 (10.0)
<i>Gastrointestinal</i>	6 (85.7)	0	15 (57.7)	3 (11.5)	12 (60.0)	4 (20.0)
<i>Hepatic</i>	3 (42.9)	2 (28.6)	12 (46.2)	6 (23.1)	7 (35.0)	4 (20.0)
<i>Pulmonary</i>	0	0	1 (.8)	1 (3.8)	1 (5.0)	0
<i>Renal</i>	2 (28.6)	1 (14.3)	10 (38.5)	2 (7.7)	1 (5.0)	0
<i>Skin</i>	7 (100.0)	1 (14.3)	19 (73.1)	1 (3.8)	11 (55.0)	0
<i>Hypersensitivity/Infusion Reactions</i>	0	0	0	0	1 (5.0)	0
<b>All-causality Immune-mediated AEs, by Category</b>						
<b><i>Immune-mediated AEs Treated with Immune-modulating medication</i></b>	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<i>Diarrhea/Colitis</i>	0	0	0	0	1 (5.0)	1 (5.0)
<i>Hepatitis</i>	0	0	4 (15.4)	3 (11.5)	4 (20.0)	3 (15.0)
<i>Pneumonitis</i>	0	0	2 (7.7)	1 (3.8)	1 (5.0)	0
<i>Nephritis and Renal Dysfunction</i>	1 (14.3)	1 (14.3)	1 (3.8)	0	0	0
<i>Rash</i>	2 (28.6)	0	4 (15.4)	2 (7.7)	2 (10.0)	0
<i>Hypersensitivity</i>	0	0	0	0	1 (5.0)	1 (5.0)
<b><i>Immune-Mediated Endocrine AEs Treated with or without Immune-Modulating Medications</i></b>	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<i>Adrenal Insufficiency</i>	0	0	0	0	0	0
<i>Hypophysitis</i>	0	0	0	0	0	0
<i>Hypothyroidism/Thyroiditis</i>	2 (28.6)	0	8 (30.8)	0	4 (20.0)	1 (5.0)
<i>Hyperthyroidism</i>	1 (14.3)	0	4 (15.4)	0	0	0
<i>Diabetes Mellitus</i>	0	0	0	0	1 (5.0)	1 (5.0)

Source: CA209016 Final CSR<sup>125</sup>, database lock date 16-Mar-2016

Treatment: SUN=Sunitinib; PAZ=Pazopanib; NIVO=Nivolumab

#### 5.5.4.6 **Nivolumab Monotherapy or in Combination with Ipilimumab vs Placebo - CA209914 (Renal Cell Carcinoma)**

The study design and efficacy of CA209914 are discussed in [Section 5.4.3.2](#).

##### **Safety Results:**

The overall safety profile of nivo or nivo + ipi as adjuvant treatment in subjects with early stage RCC who have undergone nephrectomy surgery was acceptable and consistent with the known safety profile of nivolumab monotherapy and nivolumab and ipilimumab combination therapy. No new safety signals were identified.

##### **Part A:**

The frequency and severity of all-causality and drug-related AEs, SAEs, AEs leading to discontinuation, select AEs, and IMAEs in Part A were higher in the nivo + ipi arm compared with the placebo arm (Table 5.5.4.6-1). Although the overall frequencies of all causality and drug-related AEs were higher in the nivo + ipi arm, the majority were of low grade (Grade 1-2).

The frequency and severity of all-causality and drug-related AEs, SAEs, and AEs leading to discontinuation in Part B were generally highest in the nivo + ipi arm compared with nivo or placebo arms. The overall frequencies of all causality and drug-related AEs were higher in the nivo and nivo + ipi arms than in the placebo arm but the majority of AEs were of low grade (Grade 1-2). Select AEs and IMAEs were more frequently reported in the nivo + ipi and nivo arms than in the placebo arm. Most select AEs and IMAEs were Grade 1-2, except for adrenal insufficiency and hepatitis.

**Table 5.5.4.6-1: Summary of Safety - All Treated Part A Subjects (Data Cutoff 28-Jun-2022)**

Safety Parameters	No. of Subjects (%)			
	Nivo + ipi (N = 404)		Placebo (N =407)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<b>Deaths</b>	33 ( 8.2)		28 ( 6.9)	
Primary Reason for Death				
Disease	17 ( 4.2)		21 ( 5.2)	
Study Drug Toxicity	4 ( 1.0) <sup>a</sup>		0	
Unknown	4 ( 1.0)		1 ( 0.2)	
Other	8 ( 2.0)		6 ( 1.5)	
<b>All-causality SAEs</b>	118 ( 29.2)	99 ( 24.5)	22 ( 5.4)	13 ( 3.2)
<b>Drug-related SAEs</b>	88 ( 21.8)	72 ( 17.8)	2 ( 0.5)	0
<b>All-causality AEs leading to DC</b>	129 ( 31.9)	82 ( 20.3)	9 ( 2.2)	8 ( 2.0)
<b>Drug-Related AEs leading to DC</b>	117 ( 29.0)	74 ( 18.3)	4 ( 1.0)	4 ( 1.0)



**Table 5.5.4.6-1: Summary of Safety - All Treated Part A Subjects (Data Cutoff 28-Jun-2022)**

Safety Parameters	No. of Subjects (%)			
	Nivo + ipi (N = 404)		Placebo (N =407)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<b>All-causality AEs</b>	392 ( 97.0)	154 ( 38.1)	361 ( 88.7)	42 ( 10.3)
≥ 15% of Subjects in Any Treatment Arm				
Pruritus	128 ( 31.7)	2 ( 0.5)	69 ( 17.0)	0
Fatigue	123 ( 30.4)	3 ( 0.7)	109 ( 26.8)	1 ( 0.2)
Diarrhea	111 ( 27.5)	16 ( 4.0)	85 ( 20.9)	2 ( 0.5)
Rash	91 ( 22.5)	5 ( 1.2)	38 ( 9.3)	1 ( 0.2)
Nausea	69 ( 17.1)	2 ( 0.5)	50 ( 12.3)	0
Headache	71 ( 17.6)	2 ( 0.5)	59 ( 14.5)	0
Hyperthyroidism	66 ( 16.3)	1 ( 0.2)	5 ( 1.2)	0
Hypothyroidism	65 ( 16.1)	2 ( 0.5)	20 ( 4.9)	0
Arthralgia	65 ( 16.1)	1 ( 0.2)	55 ( 13.5)	0
<b>Drug-related AEs</b>	359 ( 88.9)	115 ( 28.5)	231 ( 56.8)	8 ( 2.0)
≥ 10 % of Subjects in Any Treatment Arm				
Pruritus	109 ( 27.0)	2 ( 0.5)	53 ( 13.0)	0
Fatigue	99 ( 24.5)	3 ( 0.7)	76 ( 18.7)	1 ( 0.2)
Diarrhea	79 ( 19.6)	15 ( 3.7)	43 ( 10.6)	0
Rash	77 ( 19.1)	4 ( 1.0)	27 ( 6.6)	1 ( 0.2)
Hyperthyroidism	64 ( 15.8)	1 ( 0.2)	3 ( 0.7)	0
Hypothyroidism	63 ( 15.6)	2 ( 0.5)	12 ( 2.9)	0
<b>All-Causality Select AEs, by Category</b>				
Endocrine	173 ( 42.8)	27 ( 6.7)	27 ( 6.6)	0
Gastrointestinal	119 ( 29.5)	26 ( 6.4)	87 ( 21.4)	2 ( 0.5)
Hepatic	79 ( 19.6)	19 ( 4.7)	28 ( 6.9)	4 ( 1.0)
Pulmonary	10 ( 2.5)	3 ( 0.7)	1 ( 0.2)	0
Renal	54 ( 13.4)	3 ( 0.7)	48 ( 11.8)	1 ( 0.2)
Skin	227 ( 56.2)	12 ( 3.0)	122 ( 30.0)	3 ( 0.7)
Hypersensitivity/Infusion Reactions	27 ( 6.7)	2 ( 0.5)	5 ( 1.2)	0
<b>Drug-Related Select AEs, by Category</b>				
Endocrine	165 ( 40.8)	24 ( 5.9)	16 ( 3.9)	0
Gastrointestinal	86 ( 21.3)	25 ( 6.2)	44 ( 10.8)	0

**Table 5.5.4.6-1: Summary of Safety - All Treated Part A Subjects (Data Cutoff 28-Jun-2022)**

Safety Parameters	No. of Subjects (%)			
	Nivo + ipi (N = 404)		Placebo (N =407)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hepatic	60 ( 14.9)	17 ( 4.2)	15 ( 3.7)	1 ( 0.2)
Pulmonary	9 ( 2.2)	3 ( 0.7)	1 ( 0.2)	0
Renal	22 ( 5.4)	3 ( 0.7)	16 ( 3.9)	1 ( 0.2)
Skin	201 ( 49.8)	11 ( 2.7)	91 ( 22.4)	3 ( 0.7)
Hypersensitivity/Infusion Reactions	26 ( 6.4)	1 ( 0.2)	5 ( 1.2)	0
<b>All-causality IMAEs within 100 Days of Last Dose</b>				
<b>Treated with Immune Modulating Medication</b>				
Rash	71 ( 17.6)	10 ( 2.5)	12 ( 2.9)	2 ( 0.5)
Pneumonitis	10 ( 2.5)	3 ( 0.7)	1 ( 0.2)	0
Diarrhea/Colitis	37 ( 9.2)	22 ( 5.4)	3 ( 0.7)	0
Hepatitis	23 ( 5.7)	14 ( 3.5)	3 ( 0.7)	2 ( 0.5)
Nephritis/Renal Dysfunction	10 ( 2.5)	5 ( 1.2)	6 ( 1.5)	1 ( 0.2)
Hypersensitivity/Infusion Reactions	10 ( 2.5)	1 ( 0.2)	0	0
<b>All-causality Endocrine IMAEs within 100 Days of Last Dose</b>				
<b>With or Without Immune Modulating Medication</b>				
Hypothyroidism	78 ( 19.3)	2 ( 0.5)	13 ( 3.2)	0
Hyperthyroidism	63 ( 15.6)	1 ( 0.2)	2 ( 0.5)	0
Adrenal Insufficiency	35 ( 8.7)	11 ( 2.7)	2 ( 0.5)	0
Thyroiditis	11 ( 2.7)	2 ( 0.5)	0	0
Diabetes Mellitus	9 ( 2.2)	8 ( 2.0)	0	0
Hypophysitis	30 ( 7.4)	12 ( 3.0)	0	0

<sup>a</sup> PTs of drug-related fatal events: cardiac arrest, immunotherapy induced diarrhoea/colitis, aortic dissection/ischemic cerebral infarction/pulmonary embolism, drug-induced myocarditis.

MedDRA version 25.0; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Abbreviations: AE, adverse event; DC, discontinuation; IMAE, immune-mediated adverse event; SAE, serious adverse event.

## Part B

The frequency and severity of all-causality and drug-related AEs, SAEs, and AEs leading to discontinuation in Part B were generally highest in the nivo + ipi arm compared with nivo or placebo arms (Table 5.5.4.6-2). The overall frequencies of all causality and drug-related AEs were

higher in the nivo and nivo + ipi arms than in the placebo arm but the majority of AEs were of low grade (Grade 1-2). Select AEs and IMAEs were more frequently reported in the nivo + ipi and nivo arms than in the placebo arm. Most select AEs and IMAEs were Grade 1-2, except for adrenal insufficiency and hepatitis.

**Table 5.5.4.6-2: Summary of Safety - All Treated Part B Subjects (Data Cutoff 28-Sep-2023)**

Safety Parameters	No. of Subjects (%)					
	Nivo (N = 408)		Placebo (N =207)		Nivo + Ipi (N = 204)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<b>Deaths</b>	19 ( 4.7)		8 ( 3.9)		8 ( 3.9)	
Primary Reason for Death						
Disease	6 ( 1.5)		7 ( 3.4)		1 ( 0.5)	
Study Drug Toxicity	0		0		0	
Unknown	5 ( 1.2)		0		1 ( 0.5)	
Other	8 ( 2.0)		1 ( 0.5)		6 ( 2.9)	
<b>All-causality SAEs</b>	36 ( 8.8)	34 ( 8.3)	12 ( 5.8)	9 ( 4.3)	41 ( 20.1)	33 ( 16.2)
<b>Drug-related SAEs</b>	19 ( 4.7)	17 ( 4.2)	0	0	31 ( 15.2)	27 ( 13.2)
<b>All-causality AEs leading to DC</b>	49 ( 12.0)	25 ( 6.1)	6 ( 2.9)	4 ( 1.9)	63 ( 30.9)	36 ( 17.6)
<b>Drug-Related AEs leading to DC</b>	39 ( 9.6)	21 ( 5.1)	2 ( 1.0)	2 ( 1.0)	58 ( 28.4)	30 ( 14.7)
<b>All-causality AEs</b>	362 ( 88.7)	70 ( 17.2)	182 ( 87.9)	31 ( 5.0)	193 ( 94.6)	59 ( 28.9)
≥ 15% of Subjects in Any Treatment Arm						
Pruritus	100 ( 24.5)	2 ( 0.5)	33 ( 15.9)	0	80 ( 39.2)	1 ( 0.5)
Fatigue	97 ( 23.8)	0	47 ( 22.7)	0	58 ( 28.4)	0
Diarrhea	73 ( 17.9)	2 ( 0.5)	34 ( 16.4)	1 ( 0.5)	59 ( 28.9)	0
Arthralgia	54 ( 13.2)	0	34 ( 16.4)	0	32 ( 15.7)	1 ( 0.5)
Hypothyroidism	47 ( 11.5)	0	6 ( 2.9)	0	45 ( 22.1)	0
Hyperthyroidism	47 ( 11.5)	0	2 ( 1.0)	0	33 ( 16.2)	0
Rash	46 ( 11.3)	1 ( 0.2)	15 ( 7.2)	0	37 ( 18.1)	1 ( 0.5)
Blood creatinine increased	40 ( 9.8)	0	19 ( 9.2)	0	33 ( 16.2)	0
<b>Drug-related AEs</b>	296 ( 72.5)	36 ( 8.8)	107 ( 51.7)	4 ( 1.9)	173 ( 84.8)	41 ( 20.1)

**Table 5.5.4.6-2: Summary of Safety - All Treated Part B Subjects (Data Cutoff 28-Sep-2023)**

Safety Parameters	No. of Subjects (%)					
	Nivo (N = 408)		Placebo (N =207)		Nivo + Ipi (N = 204)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<b>≥ 10% of Subjects in Any Treatment Arm</b>						
Pruritus	87 ( 21.3)	2 ( 0.5)	31 ( 15.0)	0	72 ( 35.3)	1 ( 0.5)
Fatigue	76 ( 18.6)	0	33 ( 15.9)	0	45 ( 22.1)	0
Diarrhea	44 ( 10.8)	2 ( 0.5)	19 ( 9.2)	0	38 ( 18.6)	0
Hypothyroidism	45 ( 11.0)	0	6 ( 2.9)	0	43 ( 21.1)	0
Hyperthyroidism	45 ( 11.0)	0	2 ( 1.0)	0	32 ( 15.7)	0
Arthralgia	32 ( 7.8)	0	16 ( 7.7)	0	23 ( 11.3)	1 ( 0.5)
Rash	39 ( 9.6)	1 ( 0.2)	12 ( 5.8)	0	35 ( 17.2)	1 ( 0.5)
Adrenal insufficiency	8 ( 2.0)	2 ( 0.5)	2 ( 1.0)	0	22 ( 10.8)	8 ( 3.9)
<b>All-Causality Select AEs, by Category</b>						
Endocrine	102 ( 25.0)	5 ( 1.2)	12 ( 5.8)	0	97 ( 47.5)	13 ( 6.4)
Gastrointestinal	77 ( 18.9)	2 ( 0.5)	34 ( 16.4)	1 ( 0.5)	61 ( 29.9)	5 ( 2.5)
Hepatic	53 ( 13.0)	10 ( 2.5)	20 ( 9.7)	3 ( 1.4)	44 ( 21.6)	9 ( 4.4)
Pulmonary	9 ( 2.2)	1 ( 0.2)	0	0	2 ( 1.0)	2 ( 1.0)
Renal	46 ( 11.3)	0	20 ( 9.7)	0	43 ( 21.1)	3 ( 1.5)
Skin	159 ( 39.0)	5 ( 1.2)	49 ( 23.7)	0	119 ( 58.3)	4 ( 2.0)
Hypersensitivity/Infusion Reactions	18 ( 4.4)	1 ( 0.2)	3 ( 1.4)	0	12 ( 5.9)	1 ( 0.5)
<b>Drug-Related Select AEs, by Category</b>						
Endocrine	95 ( 23.3)	4 ( 1.0)	11 ( 5.3)	0	91 ( 44.6)	13 ( 6.4)
Gastrointestinal	49 ( 12.0)	2 ( 0.5)	19 ( 9.2)	0	41 ( 20.1)	5 ( 2.5)
Hepatic	35 ( 8.6)	9 ( 2.2)	9 ( 4.3)	2 ( 1.0)	36 ( 17.6)	6 ( 2.9)

**Table 5.5.4.6-2: Summary of Safety - All Treated Part B Subjects (Data Cutoff 28-Sep-2023)**

Safety Parameters	No. of Subjects (%)					
	Nivo (N = 408)		Placebo (N =207)		Nivo + Ipi (N = 204)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Pulmonary	9 ( 2.2)	1 ( 0.2)	0	0	2 ( 1.0)	2 ( 1.0)
Renal	19 ( 4.7)	0	4 ( 1.9)	0	15 ( 7.4)	1 ( 0.5)
Skin	135 ( 33.1)	3 ( 0.7)	41 ( 19.8)	0	108 ( 52.9)	4 ( 2.0)
Hypersensitivity/Infusion Reactions	15 ( 3.7)	0	3 ( 1.4)	0	11 ( 5.4)	1 ( 0.5)
<b>All-causality IMAEs within 100 Days of Last Dose Treated with Immune Modulating Medication</b>						
Rash	30 ( 7.4)	3 ( 0.7)	5 ( 2.4)	0	26 ( 12.7)	4 ( 2.0)
Pneumonitis	6 ( 1.5)	2 ( 0.5)	0	0	2 ( 1.0)	2 ( 1.0)
Diarrhea/Colitis	10 ( 2.5)	1 ( 0.2)	1 ( 0.5)	1 ( 0.5)	14 ( 6.9)	6 ( 2.9)
Hepatitis	8 ( 2.0)	5 ( 1.2)	4 ( 1.9)	3 ( 1.4)	11 ( 5.4)	4 ( 2.0)
Nephritis/Renal Dysfunction	3 ( 0.7)	2 ( 0.5)	0	0	5 ( 2.5)	1 ( 0.5)
Hypersensitivity/Infusion Reactions	2 ( 0.5)	0	0	0	1 ( 0.5)	1 ( 0.5)
<b>All-causality Endocrine IMAEs within 100 Days of Last Dose With or Without Immune Modulating Medication</b>						
Hypothyroidism	52 ( 12.7)	0	6 ( 2.9)	0	49 ( 24.0)	0
Hyperthyroidism	45 ( 11.0)	0	2 ( 1.0)	0	30 ( 14.7)	0
Adrenal Insufficiency	13 ( 3.2)	3 ( 0.7)	2 ( 1.0)	0	24 ( 11.8)	10 ( 4.9)
Thyroiditis	10 ( 2.5)	0	0	0	9 ( 4.4)	0
Diabetes Mellitus	4 ( 1.0)	3 ( 0.7)	1 ( 0.5)	0	2 ( 1.0)	1 ( 0.5)
Hypophysitis	1 ( 0.2)	0	0	0	14 ( 6.9)	

MedDRA version 26.0; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.  
Abbreviations: AE, adverse event; DC, discontinuation; IMAE, immune-mediated adverse event; SAE, serious adverse event.

#### **5.5.4.7 Nivolumab in Combination with Ipilimumab and Cobimetinib - CA209032 (Pancreatic Cancer)**

The study design and efficacy of CA209032 (pancreatic cancer) are discussed in [Section 5.4.14.1](#).

Based on the data from Phase 1/2 study (CA209032), no new safety concerns were identified with nivolumab in combination with ipilimumab and cobimetinib. In the nivolumab + ipilimumab + cobimetinib arm (n=30), 22 (73.3%) subjects had died as of the 03-Aug-2018 database lock. No deaths were reported due to study drug toxicity.<sup>149</sup>

The following were key safety findings in subjects treated with nivolumab + ipilimumab + cobimetinib:

- The most frequently reported SAEs were malignant neoplasm progression (10.0%), pyrexia (10.0%), nausea (6.7%), and pleural effusion (6.7%).
- The most frequently reported drug-related SAEs were diarrhoea (3.3%), pyrexia (3.3%), adrenal insufficiency (3.3%), steatohepatitis (3.3%), and pneumonitis (3.3%).
- The most frequently reported AEs leading to discontinuation were diarrhoea (3.3%), anemia (3.3%), thrombocytopenia (3.3%), steatohepatitis (3.3%), dyspnoea (3.3%), pneumonitis (3.3%), and pruritis (3.3%).

#### **5.5.4.8 Nivolumab in Combination with Radiation Therapy - CA209498 (Glioblastoma)**

The study design and efficacy data of CA209498 are discussed in [Section 5.4.11.2](#).

Based on the data from Phase 3 study (CA209498) the overall safety profile of nivolumab + RT combination therapy in subjects with newly diagnosed GBM and MGMT promoter unmethylated was consistent with nivolumab's known safety profile in terms of the type and severity of reported events. No new safety concerns with nivolumab + RT combination therapy were identified as compared to safety observations in other nivolumab studies in other indications.

A summary of safety is provided in [Table 5.5.4.8-1](#).

**Table 5.5.4.8-1: Safety with Nivolumab in Combination with Radiation Therapy in Subjects with Glioblastoma- CA209498**

		Nivo + RT N = 278	TMZ + RT N = 275
Worst Grade		n (%)	
<b>Deaths</b>		269 (96.8%)	253 (92.0%)
Within 30 days of last dose		16 (5.8%)	9 (3.3%)
Within 100 days of last dose		63 (22.7%)	42 (15.3%)
Due to study drug toxicity		3 (1.1%)	0
<b>All Causality SAEs</b>	Any Grade	165 (59.4%)	104 (37.8%)
	Grade 3-4	117 (42.1%)	70 (25.5%)
	Grade 5	13 (4.7%)	6 (2.2%)
<b>Drug Related SAEs</b>	Any Grade	50 (18.0%)	21 (7.6%)
	Grade 3-4	38 (13.7%)	17 (6.2%)
	Grade 5	1 (0.4%)	0
<b>All Causality AEs Leading to Discontinuation</b>	Any Grade	52 (18.7%)	29 (10.5%)
	Grade 3-4	39 (14.0%)	22 (8.0%)
	Grade 5	2 (0.7%)	1 (0.4%)
<b>Drug Related AEs Leading to Discontinuation</b>	Any Grade	25 (9.0%)	16 (5.8%)
	Grade 3-4	21 (7.6%)	12 (4.4%)
	Grade 5	0	0
<b>All Causality AEs</b>	Any Grade	276 (99.3%)	272 (98.9%)
	Grade 3-4	152 (54.7%)	126 (45.8%)
	Grade 5	13 (4.7%)	6 (2.2%)
<b>Drug Related AEs</b>	Any Grade	202 (72.7%)	209 (76.0%)
	Grade 3-4	63 (22.7%)	68 (24.7%)
	Grade 5	1 (0.4%)	0

Source: Closeout CSR CA209498- database lock 04-Apr-2022.



#### **5.5.4.9    *Nivolumab in Combination with Radiation Therapy and Chemotherapy - CA209143 (Glioblastoma)***

The study design and efficacy of CA209143 are discussed in [Section 5.4.11.1](#).

The overall safety profile in Cohort 1c was consistent with nivolumab's known safety profile in terms of the type and severity of reported events. The types of select AEs and IMAEs were also similar to nivolumab's known safety profile. Safety summaries for Parts A and B are presented in and [Table 5.5.4.9-2](#), respectively.

The safety profile of nivolumab + RT was manageable.

Overall, the data indicated that select AEs and IMAEs associated with the immune-mediated mechanism of nivolumab were manageable using established safety algorithms in this population.

**Table 5.5.4.9-1: Safety with Nivolumab in Combination with Radiation Therapy and Chemotherapy in Subjects with Glioblastoma (Part A) - CA209143**

	Number (%) Subjects							
	Cohort 1c (unmethylated) N = 16		Cohort 1c (methylated or unknown) N = 15		Cohort 1c Combined N = 31		Cohort 1d N = 30	
DEATHS	14 ( 87.5)		9 ( 60.0)		23 ( 74.2)		30 (100.0)	
WITHIN 30 DAYS OF LAST DOSE	0		0		0		1 ( 3.3)	
WITHIN 100 DAYS OF LAST DOSE	1 ( 6.3)		1 ( 6.7)		2 ( 6.5)		5 ( 16.7)	
DUE TO STUDY DRUG TOXICITY	0		0		0		0	
	Number (%) Subjects							
	Cohort 1c (unmethylated) N = 16		Cohort 1c (methylated or unknown) N = 15		Cohort 1c Combined N = 31		Cohort 1d N = 30	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ALL CAUSALITY SAEs	11 ( 68.8)	10 ( 62.5)	9 ( 60.0)	9 ( 60.0)	20 ( 64.5)	19 ( 61.3)	16 ( 53.3)	10 ( 33.3)
DRUG-RELATED SAEs	5 ( 31.3)	4 ( 25.0)	6 ( 40.0)	5 ( 33.3)	11 ( 35.5)	9 ( 29.0)	6 ( 20.0)	4 ( 13.3)
ALL CAUSALITY AEs LEADING TO DC	3 ( 18.8)	3 ( 18.8)	3 ( 20.0)	2 ( 13.3)	6 ( 19.4)	5 ( 16.1)	6 ( 20.0)	3 ( 10.0)
DRUG-RELATED AEs LEADING TO DC	2 ( 12.5)	2 ( 12.5)	2 ( 13.3)	1 ( 6.7)	4 ( 12.9)	3 ( 9.7)	5 ( 16.7)	3 ( 10.0)
ALL CAUSALITY AEs	16 (100.0)	13 ( 81.3)	15 (100.0)	12 ( 80.0)	31 (100.0)	25 ( 80.6)	29 ( 96.7)	16 ( 53.3)
Most Frequent AEs (≥ 20% of Any Grade in any treatment group)								
Fatigue	11 ( 68.8)	1 ( 6.3)	12 ( 80.0)	0	23 ( 74.2)	1 ( 3.2)	16 ( 53.3)	0
Headache	8 ( 50.0)	1 ( 6.3)	8 ( 53.3)	0	16 ( 51.6)	1 ( 3.2)	13 ( 43.3)	1 ( 3.3)
Constipation	7 ( 43.8)	0	3 ( 20.0)	0	10 ( 32.3)	0	4 ( 13.3)	0
Rash	6 ( 37.5)	1 ( 6.3)	3 ( 20.0)	0	9 ( 29.0)	1 ( 3.2)	2 ( 6.7)	0
Nausea	5 ( 31.3)	0	8 ( 53.3)	0	13 ( 41.9)	0	8 ( 26.7)	0
Pyrexia	4 ( 25.0)	0	2 ( 13.3)	0	6 ( 19.4)	0	4 ( 13.3)	1 ( 3.3)
Aphasia	4 ( 25.0)	2 ( 12.5)	2 ( 13.3)	0	6 ( 19.4)	2 ( 6.5)	3 ( 10.0)	1 ( 3.3)
Diarrhoea	4 ( 25.0)	1 ( 6.3)	4 ( 26.7)	0	8 ( 25.8)	1 ( 3.2)	4 ( 13.3)	0
Dry skin	4 ( 25.0)	0	4 ( 26.7)	0	8 ( 25.8)	0	1 ( 3.3)	0
Alanine amino- transferase increased	4 ( 25.0)	1 ( 6.3)	4 ( 26.7)	1 ( 6.7)	8 ( 25.8)	2 ( 6.5)	5 ( 16.7)	2 ( 6.7)
Aspartate amino- transferase increased	4 ( 25.0)	0	5 ( 33.3)	2 ( 13.3)	9 ( 29.0)	2 ( 6.5)	3 ( 10.0)	2 ( 6.7)
Platelet count decreased	4 ( 25.0)	0	4 ( 26.7)	1 ( 6.7)	8 ( 25.8)	1 ( 3.2)	2 ( 6.7)	1 ( 3.3)
Malignant neoplasm progression	4 ( 25.0)	4 ( 25.0)	2 ( 13.3)	2 ( 13.3)	6 ( 19.4)	6 ( 19.4)	4 ( 13.3)	1 ( 3.3)
Anaemia	4 ( 25.0)	0	2 ( 13.3)	1 ( 6.7)	6 ( 19.4)	1 ( 3.2)	1 ( 3.3)	0
Cough	4 ( 25.0)	0	2 ( 13.3)	0	6 ( 19.4)	0	5 ( 16.7)	0

**Table 5.5.4.9-1: Safety with Nivolumab in Combination with Radiation Therapy and Chemotherapy in Subjects with Glioblastoma (Part A) - CA209143**

	Number (%) Subjects							
	Cohort 1c (unmethylated) N = 16		Cohort 1c (methylated or unknown) N = 15		Cohort 1c Combined N = 31		Cohort 1d N = 30	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hypertension	4 ( 25.0)	0	1 ( 6.7)	0	5 ( 16.1)	0	6 ( 20.0)	1 ( 3.3)
Lymphocyte count decreased	3 ( 18.8)	2 ( 12.5)	3 ( 20.0)	3 ( 20.0)	6 ( 19.4)	5 ( 16.1)	3 ( 10.0)	2 ( 6.7)
White blood cell count decreased	3 ( 18.8)	0	3 ( 20.0)	2 ( 13.3)	6 ( 19.4)	2 ( 6.5)	0	0
Hyperglycaemia	3 ( 18.8)	1 ( 6.3)	4 ( 26.7)	1 ( 6.7)	7 ( 22.6)	2 ( 6.5)	7 ( 23.3)	2 ( 6.7)
Seizure	3 ( 18.8)	2 ( 12.5)	3 ( 20.0)	1 ( 6.7)	6 ( 19.4)	3 ( 9.7)	9 ( 30.0)	1 ( 3.3)
Dizziness	3 ( 18.8)	0	4 ( 26.7)	0	7 ( 22.6)	0	5 ( 16.7)	0
Lipase increased	2 ( 12.5)	1 ( 6.3)	4 ( 26.7)	0	6 ( 19.4)	1 ( 3.2)	5 ( 16.7)	4 ( 13.3)
Dehydration	2 ( 12.5)	1 ( 6.3)	3 ( 20.0)	1 ( 6.7)	5 ( 16.1)	2 ( 6.5)	1 ( 3.3)	0
Vomiting	2 ( 12.5)	0	4 ( 26.7)	0	6 ( 19.4)	0	2 ( 6.7)	0
Pruritus	2 ( 12.5)	0	5 ( 33.3)	0	7 ( 22.6)	0	3 ( 10.0)	0
Back pain	2 ( 12.5)	1 ( 6.3)	3 ( 20.0)	0	5 ( 16.1)	1 ( 3.2)	2 ( 6.7)	0
Alopecia	1 ( 6.3)	0	4 ( 26.7)	0	5 ( 16.1)	0	2 ( 6.7)	0
Rash maculo-papular	1 ( 6.3)	0	4 ( 26.7)	0	5 ( 16.1)	0	4 ( 13.3)	1 ( 3.3)
Vision blurred	1 ( 6.3)	0	4 ( 26.7)	0	5 ( 16.1)	0	3 ( 10.0)	0
Musculoskeletal pain	1 ( 6.3)	0	3 ( 20.0)	0	4 ( 12.9)	0	0	0
Amylase increased	1 ( 6.3)	1 ( 6.3)	3 ( 20.0)	1 ( 6.7)	4 ( 12.9)	2 ( 6.5)	2 ( 6.7)	1 ( 3.3)
Arthralgia	0	0	5 ( 33.3)	0	5 ( 16.1)	0	3 ( 10.0)	0
Abdominal pain	0	0	4 ( 26.7)	0	4 ( 12.9)	0	3 ( 10.0)	0
Upper respiratory tract infection	0	0	4 ( 26.7)	0	4 ( 12.9)	0	0	0
<b>DRUG-RELATED AEs</b>	<b>15 ( 93.8)</b>	<b>9 ( 56.3)</b>	<b>14 ( 93.3)</b>	<b>7 ( 46.7)</b>	<b>29 ( 93.5)</b>	<b>16 ( 51.6)</b>	<b>25 ( 83.3)</b>	<b>9 ( 30.0)</b>
<b>Most Frequent AEs (≥ 15% of Any Grade in any treatment group)</b>								
Headache	5 ( 31.3)	1 ( 6.3)	7 ( 46.7)	0	12 ( 38.7)	1 ( 3.2)	4 ( 13.3)	0
Fatigue	7 ( 43.8)	1 ( 6.3)	9 ( 60.0)	0	16 ( 51.6)	1 ( 3.2)	9 ( 30.0)	0
Alanine amino-transferase increased	4 ( 25.0)	1 ( 6.3)	4 ( 26.7)	1 ( 6.7)	8 ( 25.8)	2 ( 6.5)	4 ( 13.3)	2 ( 6.7)
Aspartate amino-transferase increased	4 ( 25.0)	0	5 ( 33.3)	2 ( 13.3)	9 ( 29.0)	2 ( 6.5)	3 ( 10.0)	2 ( 6.7)
Platelet count decreased	4 ( 25.0)	0	3 ( 20.0)	0	7 ( 22.6)	0	1 ( 3.3)	0
Diarrhoea	4 ( 25.0)	1 ( 6.3)	4 ( 26.7)	0	8 ( 25.8)	1 ( 3.2)	2 ( 6.7)	0
Nausea	3 ( 18.8)	0	4 ( 26.7)	0	7 ( 22.6)	0	4 ( 13.3)	0
Rash	3 ( 18.8)	1 ( 6.3)	1 ( 6.7)	0	4 ( 12.9)	1 ( 3.2)	1 ( 3.3)	0
Lipase increased	2 ( 12.5)	1 ( 6.3)	4 ( 26.7)	0	6 ( 19.4)	1 ( 3.2)	5 ( 16.7)	4 ( 13.3)
White blood cell count decreased	2 ( 12.5)	0	3 ( 20.0)	2 ( 13.3)	5 ( 16.1)	2 ( 6.5)	1 ( 3.3)	0
Pruritus	1 ( 6.3)	0	4 ( 26.7)	0	5 ( 16.1)	0	2 ( 6.7)	0

Amylase increased 1 ( 6.3) 1 ( 6.3) 3 ( 20.0) 1 ( 6.7) 4 ( 12.9) 2 ( 6.5) 1 ( 3.3) 1 ( 3.3)  
**Table 5.5.4.9-1: Safety with Nivolumab in Combination with Radiation Therapy and Chemotherapy in Subjects with Glioblastoma (Part A) - CA209143**

	Number (%) Subjects							
	Cohort 1c (unmethylated) N = 16		Cohort 1c (methylated or unknown) N = 15		Cohort 1c Combined N = 31		Cohort 1d N = 30	
	Any Gr	Gr 3-4	Any Gr	Gr 3-4	Any Gr	Gr 3-4	Any Gr	Gr 3-4
<b>DRUG-RELATED AEs</b>	15 ( 93.8)	9 ( 56.3)	14 ( 93.3)	7 ( 46.7)	29 ( 93.5)	16 ( 51.6)	25 ( 83.3)	9 ( 30.0)
<b>Most Frequent AEs (≥ 15% of Any Grade in any treatment group)</b>								
Abdominal pain	0	0	3 ( 20.0)	0	3 ( 9.7)	0	1 ( 3.3)	0
Dry skin	2 ( 12.5)	0	3 ( 20.0)	0	5 ( 16.1)	0	0	0
Rash maculo-papular	0	0	4 ( 26.7)	0	4 ( 12.9)	0	4 ( 13.3)	1 ( 3.3)
<b>ALL CAUSALITY SELECT AEs, BY CATEGORY</b>								
SKIN	7 ( 43.8)	1 ( 6.3)	9 ( 60.0)	1 ( 6.7)	16 ( 51.6)	2 ( 6.5)	7 ( 23.3)	2 ( 6.7)
GASTROINTESTINAL	4 ( 25.0)	1 ( 6.3)	4 ( 26.7)	0	8 ( 25.8)	1 ( 3.2)	4 ( 13.3)	0
HEPATIC	5 ( 31.3)	2 ( 12.5)	6 ( 40.0)	2 ( 13.3)	11 ( 35.5)	4 ( 12.9)	8 ( 26.7)	3 ( 10.0)
ENDOCRINE	2 ( 12.5)	0	3 ( 20.0)	0	5 ( 16.1)	0	6 ( 20.0)	0
RENAL	0	0	0	0	0	0	4 ( 13.3)	3 ( 10.0)
PULMONARY	0	0	1 ( 6.7)	0	1 ( 3.2)	0	1 ( 3.3)	0
HYPERSENSITIVITY/INFUSION REACTION	0	0	1 ( 6.7)	0	1 ( 3.2)	0	1 ( 3.3)	0
<b>DRUG-RELATED SELECT AEs, BY CATEGORY</b>								
SKIN	4 ( 25.0)	1 ( 6.3)	7 ( 46.7)	0	11 ( 35.5)	1 ( 3.2)	4 ( 13.3)	2 ( 6.7)
GASTROINTESTINAL	4 ( 25.0)	1 ( 6.3)	4 ( 26.7)	0	8 ( 25.8)	1 ( 3.2)	2 ( 6.7)	0
HEPATIC	5 ( 31.3)	2 ( 12.5)	6 ( 40.0)	2 ( 13.3)	11 ( 35.5)	4 ( 12.9)	7 ( 23.3)	3 ( 10.0)
ENDOCRINE	2 ( 12.5)	0	2 ( 13.3)	0	4 ( 12.9)	0	6 ( 20.0)	0
PULMONARY	0	0	1 ( 6.7)	0	1 ( 3.2)	0	1 ( 3.3)	0
HYPERSENSITIVITY/INFUSION REACTION	0	0	0	0	0	0	1 ( 3.3)	0
RENAL	0	0	0	0	0	0	4 ( 13.3)	3 ( 10.0)

Source: CA209143 Interim CSR<sup>142</sup>; database lock date 08-Aug-2019

**Table 5.5.4.9-2: Safety with Nivolumab in Combination with Radiation Therapy and Chemotherapy in Subjects with Glioblastoma (Part B) - CA209143**

	Number (%) Subjects	
	Cohort 1c (N=28)	Cohort 1d (N=28)
<b>DEATHS</b>	24 ( 85.7)	27 ( 96.4)
WITHIN 30 DAYS OF LAST DOSE	1 ( 3.6)	1 ( 3.6)
WITHIN 100 DAYS OF LAST DOSE	4 ( 14.3)	7 ( 25.0)
DUE TO STUDY DRUG TOXICITY	0	0

	Number (%) Subjects			
	Cohort 1c (N=28)		Cohort 1d (N=28)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<b>ALL-CAUSALITY SAEs</b>	13 ( 46.4)	11 ( 39.3)	15 ( 53.6)	12 ( 42.9)
<b>DRUG-RELATED SAEs</b>	8 ( 28.6)	6 ( 21.4)	5 ( 17.9)	4 ( 14.3)
<b>ALL-CAUSALITY AEs LEADING TO DC</b>	7 ( 25.0)	5 ( 17.9)	5 ( 17.9)	5 ( 17.9)
<b>DRUG-RELATED AEs LEADING TO DC</b>	5 ( 17.9)	4 ( 14.3)	4 ( 14.3)	4 ( 14.3)
<b>ALL-CAUSALITY AEs</b>	27 ( 96.4)	17 ( 60.7)	28 (100.0)	16 ( 57.1)
<b>Most Frequent AEs (≥ 20% of Any Grade in either treatment group)</b>				
Fatigue	20 ( 71.4)	0	18 ( 64.3)	0
Headache	18 ( 64.3)	0	11 ( 39.3)	1 ( 3.6)
Nausea	15 ( 53.6)	0	7 ( 25.0)	1 ( 3.6)
Constipation	12 ( 42.9)	0	1 ( 3.6)	0
Vomiting	7 ( 25.0)	0	4 ( 14.3)	0
Decreased appetite	7 ( 25.0)	0	9 ( 32.1)	0
Seizure	6 ( 21.4)	3 ( 10.7)	11 ( 39.3)	1 ( 3.6)
Hyperglycaemia	6 ( 21.4)	1 ( 3.6)	2 ( 7.1)	1 ( 3.6)
Arthralgia	6 ( 21.4)	0	3 ( 10.7)	0
Confusional state	6 ( 21.4)	0	4 ( 14.3)	1 ( 3.6)
Insomnia	6 ( 21.4)	0	3 ( 10.7)	0
Diarrhea	3 ( 10.7)	0	8 ( 28.6)	1 ( 3.6)
Rash	2 ( 7.1)	0	7 ( 25.0)	0
<b>DRUG-RELATED AEs</b>	24 ( 85.7)	13 ( 46.4)	20 ( 71.4)	8 ( 28.6)
<b>Most Frequent Drug-related AEs (≥ 15% of Any Grade in either treatment group)</b>				
Fatigue	10 ( 35.7)	0	8 ( 28.6)	0
Headache	4 ( 14.3)	0	5 ( 17.9)	1 ( 3.6)
<b>ALL CAUSALITY SELECT AES, BY CATEGORY</b>				
ENDOCRINE	4 ( 14.3)	0	3 ( 10.7)	0
GASTROINTESTINAL	3 ( 10.7)	0	8 ( 28.6)	1 ( 3.6)
HEPATIC	5 ( 17.9)	2 ( 7.1)	3 ( 10.7)	1 ( 3.6)
PULMONARY	0	0	1 ( 3.6)	1 ( 3.6)
RENAL	3 ( 10.7)	1 ( 3.6)	2 ( 7.1)	0
SKIN	9 ( 32.1)	0	11 ( 39.3)	0
HYPERSENSITIVITY/INFUSION REACTIONS	3 ( 10.7)	0	2 ( 7.1)	0
<b>DRUG-RELATED SELECT AES, BY CATEGORY</b>				
ENDOCRINE	3 ( 10.7)	0	2 ( 7.1)	0
GASTROINTESTINAL	3 ( 10.7)	0	4 ( 14.3)	1 ( 3.6)
HEPATIC	4 ( 14.3)	1 ( 3.6)	3 ( 10.7)	1 ( 3.6)
PULMONARY	0	0	1 ( 3.6)	1 ( 3.6)
RENAL	2 ( 7.1)	1 ( 3.6)	0	0
SKIN	4 ( 14.3)	0	4 ( 14.3)	0
HYPERSENSITIVITY/INFUSION REACTIONS	3 ( 10.7)	0	1 ( 3.6)	0

Source: CA209143 Interim CSR<sup>142</sup>; database lock date 08-Aug-2019

#### **5.5.4.10 *Nivolumab in Combination with Lirilumab - CA209039 (Hematologic Malignancies)***

The study design and efficacy of CA209039 are discussed in [Section 5.4.18.1](#).

The overall safety profile of the combination of nivolumab and lirilumab is within the expected profile of both agents in subjects with relapsed/refractory hematologic malignancies.

A summary of safety is provided in [Table 5.5.4.10-1](#).

**Table 5.5.4.10-1: Safety with Nivolumab in Combination with Lirilumab in Subjects with Hematologic Malignancies - CA209039**

	<b>cHL N=21</b>	<b>MM N=10</b>	<b>BCL N=32</b>	<b>DLBL N=26</b>	<b>FBL N=6</b>	<b>TCL N=9</b>	<b>CTL N=3</b>	<b>PTL N=6</b>	<b>Total N=72</b>
<b>Deaths</b>	4 (19.0)	7 (70.0)	24 (75.0)	22 (84.6)	2 (33.3)	7 (77.8)	2 (66.7)	5 (83.3)	42 (58.3)
Disease	4 (19.0)	4 (40.0)	21 (65.6)	19 (73.1)	2 (33.3)	7 (77.8)	2 (66.7)	5 (83.3)	36 (50.0)
Study Drug Toxicity	0	0	0	0	0	0	0	0	0
Unknown	0	2 (20.0)	1 (3.1)	1 (3.8)	0	0	0	0	3 (4.2)
Other	0	1 (10.0)	2 (6.3)	2 (7.7)	0	0	0	0	3 (4.2)
<b>All-causality SAEs</b>	2 (9.5)	3 (30.0)	17 (53.1)	15 (57.7)	2 (33.3)	3 (33.3)	1 (33.3)	2 (33.3)	25 (34.7)
Grade 3-4	2 (9.5)	3 (30.0)	13 (40.6)	12 (46.2)	1 (16.7)	3 (33.3)	1 (33.3)	2 (33.3)	21 (29.2)
Grade 5	0	0	2 (6.3)	2 (7.7)	0	0	0	0	2 (2.8)
<b>Drug-related SAEs</b>	1 (4.8)	0	2 (6.3)	2 (7.7)	0	0	0	0	3 (4.2)
Grade 3-4	1 (4.8)	0	2 (6.3)	2 (7.7)	0	0	0	0	3 (4.2)
Grade 5	0	0	0	0	0	0	0	0	0
<b>All-causality AEs leading to DC</b>	0	0	5 (15.6)	5 (19.2)	0	0	0	0	5 (6.9)
<b>Drug-related AEs leading to DC</b>	0	0	0	0	0	0	0	0	0
<b>All-causality AEs</b>	21 (100.0)	10 (100.0)	31 (96.9)	25 (96.2)	6 (100.0)	9 (100.0)	3 (100.0)	6 (100.0)	71 (98.6)
Grade 3-4	7 (33.3)	7 (70.0)	15 (46.9)	14 (53.8)	1 (16.7)	4 (44.4)	1 (33.3)	3 (50.0)	33 (45.8)
Grade 5	0	0	2 (6.3)	2 (7.7)	0	0	0	0	2 (2.8)
<b>Most Frequent AEs (Total ≥ 15%)</b>									
Fatigue	8 (38.1)	4 (40.0)	14 (43.8)	13 (50.0)	1 (16.7)	3 (33.3)	1 (33.3)	2 (33.3)	29 (40.3)
Anemia	6 (28.6)	6 (60.0)	3 (9.4)	3 (11.5)	0	2 (22.2)	0	2 (33.3)	17 (23.6)
Diarrhea	6 (28.6)	3 (30.0)	8 (25.0)	6 (23.1)	2 (33.3)	2 (22.2)	0	2 (33.3)	19 (26.4)
Constipation	6 (28.6)	0	8 (25.0)	8 (30.8)	0	0	0	0	14 (19.4)
Nausea	4 (19.0)	0	8 (25.0)	7 (26.9)	1 (16.7)	2 (22.2)	1 (33.3)	1 (16.7)	14 (19.4)
Decreased appetite	2 (9.5)	2 (20.0)	6 (18.8)	5 (19.2)	1 (16.7)	4 (44.4)	0	4 (66.7)	14 (19.4)
Back pain	5 (23.8)	1 (10.0)	5 (15.6)	4 (15.4)	1 (16.7)	2 (22.2)	0	2 (33.3)	13 (18.1)
Upper respiratory tract infection	6 (28.6)	4 (40.0)	2 (6.3)	1 (3.8)	1 (16.7)	1 (11.1)	0	1 (16.7)	13 (18.1)
Infusion related reaction	6 (28.6)	1 (10.0)	4 (12.5)	4 (15.4)	0	1 (11.1)	0	1 (16.7)	12 (16.7)
Cough	4 (19.0)	0	7 (21.9)	4 (15.4)	3 (50.0)	0	0	0	11 (15.3)

**Table 5.5.4.10-1: Safety with Nivolumab in Combination with Lirilumab in Subjects with Hematologic Malignancies - CA209039**

	<b>cHL N=21</b>	<b>MM N=10</b>	<b>BCL N=32</b>	<b>DLBL N=26</b>	<b>FBL N=6</b>	<b>TCL N=9</b>	<b>CTL N=3</b>	<b>PTL N=6</b>	<b>Total N=72</b>
<b>All-causality Select Endocrine AEs</b>	2 (9.5)	0	1 (3.1)	0	1 (16.7)	1 (11.1)	0	1 (16.7)	4 (5.6)
Grade 3-4	0	0	0	0	0	1 (11.1)	0	1 (16.7)	1 (1.4)
Grade 5	0	0	0	0	0	0	0	0	0
<b>Drug-related Select Endocrine AEs</b>	2 (9.5)	0	1 (3.1)	0	1 (16.7)	0	0	0	3 (4.2)
Grade 3-4	0	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	0	0
Blood TSH increased	1 (4.8)	0	1 (3.1)	0	1 (16.7)	0	0	0	2 (2.8)
Hypothyroidism	1 (4.8)	0	0	0	0	0	0	0	1 (1.4)

Source: CA209039 Synoptic CSR<sup>176</sup>; database lock date 26-Apr-2019

MedDRA Version 21.1; CTC Version 4.0.

Notes: DLBL (N=26) and FBL (N=6) are disease subtypes of BCL (N=32), and CTL (N=3) and PTL (N=6) are disease subtypes of TCL (N=9). Includes events reported between first dose and 30 days after last dose of study therapy.

Abbreviations: AEs = adverse events; BCL = B-cell lymphoma; cHL = classic Hodgkin Lymphoma; CTL = cutaneous T-cell lymphoma; DC = discontinuation; DLBL = diffuse large B-cell lymphoma; FBL = follicular B-cell lymphoma; MM = multiple myeloma; N = total number of subjects; PTL = peripheral T-cell lymphoma; SAEs = serious adverse events; TCL = T-cell lymphoma; TSH = thyroid-stimulating hormone.



#### **5.5.4.11 Nivolumab in Combination with Palbociclib and Anastrozole - CA-2097A8 (HR + Breast Cancer)**

CA2097A8 was an open-label, randomized, non-comparative Phase 2 study assessing nivolumab plus palbociclib and anastrozole as either concurrent or phased neoadjuvant treatment for men and postmenopausal women with primary breast cancer (BC)  $\geq 2$ cm that were estrogen receptor positive (ER+) and human epidermal growth factor receptor 2-negative (HER2-). Eligible subjects included men or postmenopausal women with newly diagnosed, histologically proven ER+, HER2- primary BC  $\geq 2$ cm who were suitable to receive neoadjuvant endocrine treatment (NET) and willing to undergo standard of care breast surgery after completion of the study treatment.<sup>177</sup>

The Safety Run-in Phase was conducted in advance of the Randomized Phase to evaluate the safety and tolerability of the combination of nivolumab, with abemaciclib or palbociclib, plus anastrozole. Participants were treated and evaluated with a 3 + 3 schema in the Safety Run-in Phase in Cohort 1 (nivolumab + abemaciclib + anastrozole for 5 cycles) and Cohort 2 (nivolumab + palbociclib + anastrozole for 5 cycles).

On 06-Mar-2020, BMS decided to permanently discontinue enrollment and dosing in the nivolumab + abemaciclib + anastrozole cohorts of the CA2097A8 study. This decision was taken based on Eli Lilly's conclusion that the risk of serious interstitial lung disease (ILD)/pneumonitis in subjects receiving abemaciclib in combination with pembrolizumab was likely to be higher and more severe than reported previously for abemaciclib or pembrolizumab monotherapy based on an aggregate review of safety data.

In Cohort 2, there were two dose-limiting toxicities (DLTs) reported across both dose levels of palbociclib. However, nine participants discontinued treatment reportedly due to adverse events, with most discontinuations reported as due to Grade 3/4 hepatic adverse events after the 4-week DLT pre-specified interval. The incidence of risks observed in CA2097A8 with this combination appeared to be greater than the risk with these agents alone. BMS decided to not move forward with the randomized phase of CA209-7A8 and to close the trial after completion of the Safety Run-in.

Due to the small sample size in Cohort 1 (N=2), interpretation of safety is limited in this cohort.

In summary, in Cohort 2:

- There were no subjects who died reportedly due to study drug toxicity.
- All-causality AEs leading to discontinuation were reported in 42.9% of subjects.
- In Cohort 2 Dose Level 2 (palbociclib 100 mg in combination with nivolumab and anastrozole), 4/12 subjects discontinued treatment due to reported toxicity:
  - 3 subjects with Grade 3/4 hepatic AEs (1 Grade 3 transaminases increased, 1 Grade 4 ALT elevation, 1 Grade 4 hypertransaminasemia)
  - 1 subject with Grade 1 pneumonitis
- In Cohort 2 Dose Level 1 (palbociclib 125 mg in combination with nivolumab and anastrozole), where 5/9 subjects discontinued treatment reported due to toxicity:

- 3 subjects with Grade 3/4 hepatic AEs (2 Grade 3 ALT increased and Grade 3 AST increased, 1 Grade 4 transaminases increased)
- 1 subject with Grade 3 rash and Grade 2 immune-mediated pneumonitis
- 1 subject with Grade 3 febrile neutropenia
- Most hepatic events were reported after the 4-week DLT period.
- Hepatic events were reversible; all subjects recovered from the events after discontinuation of the study drug and concomitant steroid treatment.

#### **5.5.4.12 Nivolumab in Combination with Ipilimumab and Nivolumab in Combination with Ipilimumab and Chemotherapy -CA209568**

The study design and efficacy of CA209568 are discussed in [Section 5.4.1.8](#).

In Part 1, the overall safety profile of nivolumab + ipilimumab combination therapy was acceptable in subjects with chemotherapy-naïve stage IV or recurrent NSCLC.

- There were 209 (72.6%) subjects who died in all treated subjects with 92 (66.7%) deaths in subjects in PD-L1  $\geq 1\%$  and 95 (81.2%) in subjects with PD-L1  $<1\%$ .
- Most SAEs were Grade 1-2 in all-treated subjects. The most frequently reported Grade 5 SAE was malignant neoplasm progression (3.8%; n=11). The frequently reported Grade 3-4 SAE's were pneumonia (8.7%; n=25) and dyspnea (5.6%; n=16).
- Drug related SAEs and AEs leading to discontinuation were reported in 21.5% and 32.3% of subjects, respectively.
- In Part 2, the overall safety profile of nivolumab + ipilimumab + chemotherapy combination therapy was acceptable in subjects with chemotherapy-naïve stage IV or recurrent NSCLC.
- There were 28 (77.8%) subjects who died in all treated subjects with 10 (88.3%) deaths in subjects in PD-L1  $\geq 1\%$  and 14 (77.8%) in subjects with PD-L1  $<1\%$ .
- A Grade-3 DLT was reported in 1 subject and was determined by the investigator to be related to the study drug.
- Most select AEs and IMAEs were Grade 1-2. The most frequently reported categories of drug-related select AEs (any grade) were skin and gastrointestinal AEs
- The most frequently reported Grade 5 SAE was malignant neoplasm progression (5.6%; n=2). The most frequently reported Grade 3-4 SAE's were pyrexia (11.1%; n=4).
- Drug related SAEs and drug-related AEs leading to discontinuation were reported in 36.1% and 22.2% of subjects, respectively.

The safety profile of nivolumab + ipilimumab + chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines. No new safety concerns were identified.

#### **5.5.4.13 Nivolumab in Combination with Relatlimab-CA209142 (mCRC)**

The study design and efficacy results of Cohort 5 of study CA209142 are discussed in [Section 5.4.10.1](#).

The overall safety profile of nivolumab in combination with relatlimab in study CA209142 Cohort 5 are summarized below.

- A total of 22 (44.0%) subjects died, the majority of which were reported as due to disease (18 [36.0%] subjects). No deaths were attributed to study drug toxicity. Four (4 [8.0%]) deaths were reported as due to other or unknown reasons.
- Any-grade SAEs (regardless of causality) were reported in 24 (48.0%) subjects, with Grade 3-4 SAEs reported in 17 (34.0%) subjects. Any-grade drug-related SAEs were reported in 3 (6.0%) of subjects and Grade 3-4 drug-related SAEs were reported in 1 (2.0%) subject.
- All-causality AEs leading to discontinuation were reported in 8 (16.0%) subjects, with Grade 3-4 AEs leading to discontinuation reported in 5 (10.0%) subjects. Drug-related AEs leading to discontinuation were reported in 4 (8.0%) subjects and drug-related Grade 3-4 AEs leading to discontinuation were reported in 2 (4.0%) subjects.
- Most select AEs and IMAEs were Grade 1-2. The majority of select AEs and IMAEs resolved and were manageable using the recommended treatment guidelines for early work-up and intervention.
- Adverse events of any grade were reported in all subjects and Grade 3-4 events were reported in 25 (50.0%) subjects. Drug-related AEs were reported in 35 (70.0%) subjects. The most common (incidence  $\geq 15\%$ ) drug-related AEs were diarrhoea (12 [24.0%] subjects) and asthenia (8 [16.0%] subjects). Drug-related Grade 3-4 AEs were reported in 7 (14.0%) subjects.

The AE profile was reflective of the mechanism of action for each agent and consistent with reported data for combination nivolumab and relatlimab therapy; no new safety signals were identified.

#### **5.5.4.14 Nivolumab Monotherapy or Nivolumab in Combination with Ipilimumab or Relatlimab or Daratumumab.-CA209358**

The study design and efficacy results of CA209358 are discussed in [Section 5.4.22.1](#).

The following key safety findings were reported for all treated subjects for each cohort (total number of subjects [%]).

##### **Neoadjuvant (Nivo):**

- Total deaths: 33 (26.8%)
- Drug-related deaths: 0 (0.0%)
- Drug-related any-grade AEs (with 100 days follow-up): 70 (56.9%)
  - Drug-related any-grade select AEs (by category): skin (7.3%), hypersensitivity/infusion reaction (4.1%), gastrointestinal (3.3%), endocrine (2.4%), hepatic (2.4%)
  - Drug-related any-grade AEs leading to discontinuation: 2 (1.6%)
- Drug-related any-grade SAEs: 6 (4.9%)

**Metastatic Monotherapy (Nivo):**

- Total deaths: 76 (67.3%)
- Drug-related deaths: 1 (0.9%)
- Drug-related any-grade AEs (with 100 days follow-up): 84 (74.3%)
  - Drug-related any-grade select AEs (by category): skin (26.5%), gastrointestinal (12.4%), hepatic (11.5%), endocrine (10.6%), pulmonary (8.8%), renal (4.4%), hypersensitivity/infusion reaction (4.4%)
  - Drug-related any-grade AEs leading to discontinuation: 9 (8.0%)
- Drug-related any-grade SAEs: 8 (7.1%) subjects

**Metastatic Combo A (N3+I1):**

- Total deaths: 125 (64.1%)
- Drug-related deaths: 1 (0.5%)
- Drug-related any-grade AEs (with 100 days follow-up): 153 (78.5%)
  - Drug-related any-grade select AEs (by category): skin (41.0%), endocrine (26.7%), gastrointestinal (19.5%), hepatic (17.9%), hypersensitivity/infusion reaction (5.6%); pulmonary (5.1%), renal (3.1%)
  - Drug-related any-grade AEs leading to discontinuation: 32 (16.4%)
- Drug-related any-grade SAEs: 42 (21.5%)

**Metastatic Combo B (N1+I3):**

- Total deaths: 76 (57.1%)
- Drug-related deaths: 1 (0.8%)
- Drug-related any-grade AEs (with 100 days follow-up): 116 (87.2%)
  - Drug-related any-grade select AEs (by category): endocrine (37.6%), skin (36.8%), gastrointestinal (30.1%), hepatic (24.1%), pulmonary (11.3%), renal (4.5%), hypersensitivity/infusion reaction (3.8%)
  - Drug-related any-grade AEs leading to discontinuation: 29 (21.8%)
- Drug-related any-grade SAEs: 53 (39.8%)

**Metastatic Combo C (N+R):**

- Total deaths: 6 (75%) subjects
- Drug-related deaths and drug-related any-grade SAEs: 0 (0.0%)
- Drug-related any-grade AEs (with 100 days follow-up): 3 (37.5%)
  - Drug-related any-grade select AEs (by category): endocrine (25%), gastrointestinal (12.5%)
  - Drug-related any-grade AEs leading to discontinuation: 0 (0.0%)

### **Metastatic Combo D (N+D):**

- Total deaths: 4 (66.7%)
- Drug-related deaths and drug-related any-grade SAEs: 0 (0.0%)
- Drug-related any-grade AEs (with 100 days follow-up): 5 (83.3%)
  - Drug-related any-grade select AEs (by category): endocrine (16.7%), gastrointestinal (16.7%), skin (16.7%)
  - Drug-related any-grade AEs leading to discontinuation: 0 (0.0%)

The safety profiles of nivolumab, as a single agent or in combination with either ipilimumab, relatlimab, or daratumumab, in subjects with virus-positive or virus-negative solid tumors were manageable and consistent with previously reported the safety profiles of each individual agent as well as combination regimens. No new safety signals were identified.

#### **5.5.4.15 Nivolumab Monotherapy or Nivolumab in Combination with Ipilimumab -CA209848**

The study design and efficacy results are discussed in [Section 5.4.22.2](#).

A summary of safety results from bTMB-H subjects is provided below:

**Deaths:** A total of 80.7% of subjects in Arm A and 78.7% of subjects in Arm B died. The majority of deaths were reported as due to disease progression. One death in Arm A was reported as due to study drug toxicity (hyperglycemia)

**Other SAEs:** A total of 61.4% of subjects in Arm A and 34.0% subjects in Arm B were reported with SAEs; most were Grade 3-4. Drug-related SAEs were reported more frequently in Arm A (20.5%) than in Arm B (2.1%).

**AEs leading to discontinuation:** A total of 37.3% of subjects in Arm A and 8.5% of subjects in Arm B were reported with AEs that led to discontinuation; drug-related AEs led to discontinuation in 18.1% of subjects in Arm A and 2.1% of subjects in Arm B.

**Overall AEs:** Most subjects in both arms were reported with AEs; drug related AEs were reported in 77.1% of subjects in Arm A and 61.7% of subjects in Arm B, with diarrhea, fatigue and pruritus being the most frequently reported related AEs.

- Immune mediated AEs (IMAEs) were reported in few subjects in each arm; the most commonly reported events were rash, diarrhea/colitis and hepatitis. Common endocrine IMAEs were hypo- and hyperthyroidism in Arm A and hypothyroidism in Arm B.
- OESI were reported in few subjects in each arm: 1 subject (1.2%) with pancreatitis and 1 subject (1.2%) with myocarditis in Arm A.
- There were 4 subjects (4.8%) reported with COVID-19 related AEs in Arm A and 1 subject (1.2%) in Arm B.

A summary of safety from tTMB-H subjects is provided below:

**Deaths:** A total of 62.8% of subjects in Arm A and 78.0% of subjects in Arm B died. The majority of deaths were reported as due to disease progression. One death in Arm A was reported as due to study drug toxicity (hyperglycemia).

**Other SAEs:** A total of 48.9% of subjects in Arm A and 32.0% subjects in Arm B were reported SAE; most were Grade 3-4. Drug-related SAEs were more common in Arm A (17.0%) than in Arm B (4.0%).

**AEs leading to discontinuation:** A total of 26.6% of subjects in Arm A and 12.0% of subjects in Arm B were reported with AEs that led to discontinuation; drug-related AEs led to discontinuation in 16.0% of subjects in Arm A and 2.0% of subjects in Arm B.

**Overall AE:** Most subjects in both arms were reported with AEs; drug related AE were reported in 83.0% of subjects in Arm A and 54.0% of subjects in Arm B, with diarrhea, rash, fatigue and pruritus being the most commonly reported related AEs.

- IMAEs were reported in few subjects in each arm; the most frequently reported events were rash, diarrhea/colitis and hepatitis. Common endocrine IMAEs were hypo- or hyperthyroidism.
- OESI were reported in few subjects in each arm: 1 subject (1.1%) with myositis/rhabdomyolysis and 1 subject in Arm A (1.1%) with myocarditis.
- There were 8 subjects (8.5%) in Arm A and 1 subject (2.0%) in Arm B who were reported with COVID-19 related AEs

Safety data in this population with nivolumab+ ipilimumab or nivolumab monotherapy is consistent with known profile. As anticipated, treatment with nivolumab + ipilimumab was associated with a higher rate of AEs than nivolumab monotherapy, but the safety profile of nivolumab + ipilimumab was manageable and there were no new safety signals.

#### **5.5.4.16 Nivolumab in Combination with Lenvatinib - ONO-4538-64 (HCC)**

**Study Design:** This study was conducted in 2 parts (Part 1 and Part 2). In Part 1, the tolerability of lenvatinib in combination with nivolumab was evaluated in subjects with HCC for which no other appropriate therapy was available. The tolerability was evaluated by assessing dose limiting toxicities (DLTs) in Cycle 1 (4 weeks). Study treatment and starting dose were as follows: lenvatinib 12 mg (body weight [BW]  $\geq 60$  kg) or 8 mg (BW  $< 60$  kg) oral administration once daily (QD), and nivolumab 240 mg intravenous (IV) infusion every 2 weeks (Q2W; Days 1 and 15 of each cycle). At least 3 subjects treated with lenvatinib 12 mg (BW  $\geq 60$  kg) were to be enrolled in the 6 subjects for DLT evaluation. After the tolerability was confirmed in Part 1, additional subjects for Part 2 were enrolled. In Part 2, the safety and preliminary efficacy of the combination therapy were further evaluated in subjects with advanced or unresectable HCC who had received no prior systemic therapy. At least 5 subjects treated with lenvatinib 12 mg (BW  $\geq 60$  kg) and at least 5 subjects treated with lenvatinib 8 mg (BW  $< 60$  kg) were to be enrolled. Each part consisted of a Pretreatment Phase, a Treatment Phase, and a Follow-up Phase.

### **Safety Summary:**

- No DLTs were observed in Part 1.

The data shown in below bullets are for the overall population.

- All subjects were reported with at least 1 treatment-emergent adverse event (TEAE). The most frequently reported TEAEs ( $\geq 30\%$  of overall subjects) were diarrhea (19 subjects [63.3%]), palmar-plantar erythrodysesthesia syndrome (18 subjects [60.0%]), dysphonia (16 subjects [53.3%]), decreased appetite (15 subjects [50.0%]), proteinuria (14 subjects [46.7%]), hypertension (11 subjects [36.7%]), hypothyroidism and stomatitis (10 subjects each [33.3%]), and fatigue and malaise (9 subjects each [30.0%]).
- TEAEs with Grade 3 or above were reported in 22 (73.3%) subjects. The most frequently reported TEAE with Grade 3 or above was proteinuria (6 subjects [20.0%]). Grade 4 TEAEs included lipase increased, lymphocyte count decreased, hyponatremia, acute kidney injury, acute respiratory failure, and Stevens-Johnson syndrome (1 subject each [3.3%]).
- All subjects were reported with at least 1 treatment-related TEAE. The most frequently reported treatment-related TEAEs ( $\geq 30\%$  of overall subjects) were palmar-plantar erythrodysesthesia syndrome (18 subjects [60.0%]), dysphonia (16 subjects [53.3%]), decreased appetite (15 subjects [50.0%]), diarrhea and proteinuria (14 subjects each [46.7%]), hypertension (11 subjects [36.7%]), and hypothyroidism, stomatitis, fatigue, and malaise (9 subjects each [30.0%]).
- A total of 3 subjects were reported with fatal AEs (3 fatal AEs; bronchopulmonary aspergillosis, aortic dissection, and hepatic failure), all of which were considered to be unrelated to the study drugs by the investigator.
- Treatment-emergent SAEs were reported in 15 (50.0%) subjects. Hepatic encephalopathy occurred in 2 (6.7%) subjects, and the other SAE in 1 (3.3%) subject each.
- TEAEs leading to discontinuation of lenvatinib and discontinuation of nivolumab were reported in 5 (16.7%) subjects and 5 (16.7%) subjects, respectively. TEAEs leading to dose reduction of lenvatinib were reported in 22 (73.3%) subjects. TEAEs leading to dose interruption of lenvatinib and dose interruption of nivolumab were reported in 20 (66.7%) subjects and 8 (26.7%) subjects, respectively.
- All subjects were reported with at least 1 Select AE. Select AEs with Grade 3 or above were reported in 12 (40.0%) subjects. Treatment-related Select AEs were reported in 29 (96.7%) subjects. The most frequently reported Select AE was diarrhea (19 subjects [63.3%]), followed by palmar-plantar erythrodysesthesia syndrome (18 subjects [60.0%]), hypothyroidism (10 subjects [33.3%]), and pruritus (7 subjects [23.3%]).
- The most frequently reported treatment-emergent markedly abnormal laboratory value was high lipase (8 subjects [26.7%]), followed by high gamma-glutamyl transferase (7 subjects [23.3%]), and low lymphocytes and high aspartate aminotransferase (6 subjects each [20.0%]).

#### **5.5.4.17 Nivolumab in Combination with Ipilimumab or Chemotherapy - CA209901 (Urothelial Cancer)**

The study design and efficacy results are discussed in [Section 5.4.6.2](#).

##### **Safety Results:**

Nivo + SOC treatment in the substudy had a manageable and acceptable safety profile as demonstrated by the frequency and severity of reported AEs, proportion of subjects who discontinued due to AEs, and proportion of deaths. The safety profile of nivo + SOC is consistent with the safety profiles of each drug in the regimen and immune-related AEs were manageable using IMAE management algorithms previously established for nivolumab. The safety profile of the combination of nivo + SOC in first-line unresectable or metastatic UC is similar to approved indications across other tumor types with nivolumab in combination with chemotherapy. No new safety concerns were identified.

- Disease progression was the most frequently reported cause of death in both arms.
- The overall frequencies of SAEs (all-causality and drug-related) were numerically higher with nivo + SOC (46.7% and 24.7%, respectively) than with SOC alone (36.5% and 16.7%, respectively). The most frequently reported all causality SAEs (any grade, excluding malignant neoplasm progression) reported in  $\geq 3\%$  of subjects were:
  - Nivo + SOC: urinary tract infection (4.3%) and acute kidney injury (4.3%).
  - SOC: urinary tract infection (5.6%).
- The overall frequencies of all-causality and drug-related AEs leading to discontinuation were numerically higher in the nivo + SOC arm (29.6% and 21.1%, respectively) compared with the SOC arm (24.0% and 17.4%, respectively). The most frequently reported all-causality AEs leading to discontinuation (any grade) reported in  $\geq 2\%$  of subjects were:
  - Nivo + SOC: acute kidney injury (3.0%), blood creatinine increased (2.6%), and thrombocytopenia (2.0%).
  - SOC: anemia (2.8%), and blood creatinine increased and neutropenia (2.1% each).
- The most frequently reported drug-related AEs leading to discontinuation (any grade) reported in  $\geq 2\%$  subjects were:
  - Nivo + SOC: acute kidney injury (3.0%).
  - SOC: anemia (2.8%) and neutropenia (2.1%).
- The overall frequencies of all-causality Select AEs by category were similar between nivo + SOC and SOC alone with the exception of the endocrine, gastrointestinal, hepatic, and skin categories where there was  $> 5\%$  difference between the arms. The overall frequencies of drug-related Select AEs by category were similar between nivo + SOC and SOC alone with the exception of the endocrine, gastrointestinal, and skin categories where there was  $> 5\%$  difference between the arms. The majority of Select AEs were Grade 1-2 and most Select AEs were considered drug-related by the investigator.
- IMAEs were reported more frequently in the nivo + SOC arm than in the SOC arm. Across IMAE categories, the majority of events were manageable using the established management algorithms, with resolution reported when IMM (mostly systemic corticosteroids) were administered.



OESIs (any causality) were infrequent and reported in 9/304 (3.0%) subjects in the nivo + SOC arm and 1/288 (0.3%) subjects in the SOC arm.

### 5.5.5 Unexpected Life-threatening and/or Fatal Serious Adverse Reactions

Unexpected life-threatening and/or fatal serious adverse reactions with nivolumab monotherapy, nivolumab plus ipilimumab, and nivolumab plus other are presented below in Table 5.5.5-1, [Table 5.5.5-2](#), and [Table 5.5.5-3](#), respectively.

**Table 5.5.5-1: Life-Threatening and/or Fatal Serious Adverse Reactions with Nivolumab Monotherapy Considered Unexpected for Safety Reporting Purposes (N =17,706 subjects dosed)**

System Organ Class	Preferred Term	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
<b>Blood and Lymphatic System Disorders</b>	Anaemia	1 (0.0056)	None
	Aplasia pure red cell	1 (0.0056)	None
	Neutropenia	None	1 (0.0056)
	Pancytopenia	None	1 (0.0056)
	Thrombocytopenia	1 (0.0056)	1 (0.0056)
<b>Cardiac Disorders</b>	Atrial fibrillation	None	1 (0.0056)
	Cardiac arrest	None	1 (0.0056)
	Cardiac failure	2 (0.0113)	2 (0.0113)
	Cardiac failure acute	None	1 (0.0056)
	Cardiac failure congestive	None	1 (0.0056)
	Cardiac tamponade	1 (0.0056)	None
	Myocardial infarction	1 (0.0056)	None
	Myocardial injury	None	1 (0.0056)
	Ventricular fibrillation	None	1 (0.0056)
<b>Endocrine Disorders</b>	Adrenal insufficiency	2 (0.0113)	None
	Diabetes mellitus	1 (0.0056)	None
<b>Gastrointestinal Disorders</b>	Gastrointestinal perforation	None	1 (0.0056)
	Pancreatitis acute	None	1 (0.0056)
	Small intestinal obstruction	1 (0.0056)	None
<b>General Disorders and Administration Site Conditions</b>	Death	None	5 (0.0282)
	Multiple organ dysfunction syndrome	None	2 (0.0113)

**Table 5.5.5-1: Life-Threatening and/or Fatal Serious Adverse Reactions with Nivolumab Monotherapy Considered Unexpected for Safety Reporting Purposes (N =17,706 subjects dosed)**

System Organ Class	Preferred Term	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Sudden death	None	6 (0.0339)
<b>Hepatobiliary Disorders</b>	Autoimmune hepatitis	1 (0.0056)	1 (0.0056)
	Hepatic failure	None	3 (0.0169)
	Hepatitis	1 (0.0056)	None
	Hepatitis acute	None	1 (0.0056)
	Hepatitis fulminant	None	1 (0.0056)
	Hepatotoxicity	None	1 (0.0056)
	Vanishing bile duct syndrome	None	1 (0.0056)
<b>Immune System Disorders</b>	Anaphylactic shock	1 (0.0056)	None
<b>Infections and Infestations</b>	Pneumonia	None	5 (0.0282)
	Pneumocystis jirovecii pneumonia	1 (0.0056)	None
	Sepsis	1 (0.0056)	2 (0.0113)
	Septic shock	1 (0.0056)	2 (0.0113)
	Urosepsis	1 (0.0056)	None
<b>Investigations</b>	Lipase increased	1 (0.0056)	None
	Platelet count decreased	2 (0.0113)	None
<b>Metabolism and Nutrition Disorders</b>	Hypercalcaemia	None	1 (0.0056)
	Hypoglycaemia	None	1 (0.0056)
	Hypokalaemia	1 (0.0056)	None
	Hyponatraemia	4 (0.0226)	None
	Ketoacidosis	2 (0.0113)	None
<b>Musculoskeletal and Connective Tissue Disorders</b>	Myopathy	None	1 (0.0056)
<b>Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)</b>	Acute myeloid leukaemia	1 (0.0056)	1 (0.0056)
	Malignant neoplasm progression	None	2 (0.0113)
	Myelodysplastic syndrome	None	1 (0.0056)
	Tumour flare	1 (0.0056)	1 (0.0056)

**Table 5.5.5-1: Life-Threatening and/or Fatal Serious Adverse Reactions with Nivolumab Monotherapy Considered Unexpected for Safety Reporting Purposes (N =17,706 subjects dosed)**

System Organ Class	Preferred Term	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Tumour haemorrhage	1 (0.0056)	None
<b>Nervous System Disorders</b>	Cerebrovascular accident	None	2 (0.0113)
	Demyelinating polyneuropathy	None	1 (0.0056)
	Encephalitis toxic	None	1 (0.0056)
	Ischaemic stroke	None	1 (0.0056)
	Myasthenia gravis	None	2 (0.0113)
	Paraneoplastic neurological syndrome	None	1 (0.0056)
	Seizure	1 (0.0056)	None
	Subarachnoid haemorrhage	None	1 (0.0056)
<b>Renal and Urinary Disorders</b>	Acute kidney injury	Not Applicable <sup>a</sup>	1 (0.0056)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	Acute respiratory distress syndrome	None	2 (0.0113)
	Acute respiratory failure	2 (0.0113)	1 (0.0056)
	Dyspnoea	Not Applicable <sup>a</sup>	1 (0.0056)
	Dyspnoea exertional	None	1 (0.0056)
	Haemoptysis	None	1 (0.0056)
	Immune-mediated lung disease	None	2 (0.0113)
	Interstitial lung disease	1 (0.0056)	4 (0.0226)
	Pleural effusion	1 (0.0056)	None
	Respiratory failure	2 (0.0113)	5 (0.0282)
<b>Skin and Subcutaneous Tissue Disorders</b>	Dermatitis bullous	1 (0.0056)	None
	Erythema multiforme	None	1 (0.0056)
	Pemphigoid	None	1 (0.0056)
<b>Vascular Disorders</b>	Circulatory collapse	None	1 (0.0056)

<sup>a</sup> There are events of life-threatening SAR reported in this preferred term, however they are considered expected and are presented in [Appendix 1](#): Reference Safety Information Tables for Assessment of Expectedness of Serious Adverse Reactions

**Table 5.5.5-2: Life-Threatening and/or Fatal Serious Adverse Reactions with Nivolumab plus Ipilimumab Considered Unexpected for Safety Reporting Purposes (N = 11,701 subjects dosed)**

System Organ Class	Preferred Term	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
<b>Blood and Lymphatic System Disorders</b>	Anaemia	1 (0.0085)	None
	Aplastic anaemia	None	2 (0.0171)
	Disseminated intravascular coagulation	None	1 (0.0085)
	Febrile neutropenia	1 (0.0085)	None
	Immune thrombocytopenia	1 (0.0085)	None
	Pancytopenia	None	1 (0.0085)
	Thrombocytopenia	1 (0.0085)	None
<b>Cardiac Disorders</b>	Acute coronary syndrome	1 (0.0085)	None
	Arrhythmia	None	1 (0.0085)
	Atrioventricular block complete	1 (0.0085)	None
	Cardiac arrest	None	1 (0.0085)
	Cardiac failure	None	3 (0.0256)
	Cardiac failure acute	None	1 (0.0085)
	Cardiac tamponade	None	1 (0.0085)
	Cardiomyopathy	None	1 (0.0085)
	Cardio-respiratory distress	None	1 (0.0085)
	Myocardial infarction	None	1 (0.0085)
	Pericardial effusion	1 (0.0085)	None
	Pericarditis	1 (0.0085)	None
	Ventricular arrhythmia	None	1 (0.0085)
<b>Endocrine Disorders</b>	Adrenal insufficiency	Not Applicable <sup>a</sup>	2 (0.0171)
	Adrenocortical insufficiency acute	None	1 (0.0085)
	Hyperthyroidism	None	1 (0.0085)
	Hypophysitis	1 (0.0085)	2 (0.0171)
	Hypopituitarism	None	1 (0.0085)
	Lymphocytic hypophysitis	1 (0.0085)	None
<b>Gastrointestinal Disorders</b>	Autoimmune colitis	None	1 (0.0085)
	Colitis Ischaemic	1 (0.0085)	None
	Colitis ulcerative	1 (0.0085)	None
	Diarrhoea	3 (0.0256)	None

**Table 5.5.5-2: Life-Threatening and/or Fatal Serious Adverse Reactions with Nivolumab plus Ipilimumab Considered Unexpected for Safety Reporting Purposes (N = 11,701 subjects dosed)**

System Organ Class	Preferred Term	Occurrence of Life-Threatening SARs	Occurrence of Fatal SARs
		N (%)	N (%)
	Diverticular perforation	None	1 (0.0085)
	Duodenitis	1 (0.0085)	None
	Gastritis	1 (0.0085)	None
	Gastrointestinal motility disorder	None	1 (0.0085)
	Gastrointestinal perforation	None	1 (0.0085)
	Immune-mediated enterocolitis	1 (0.0085)	3 (0.0256)
	Intestinal obstruction	None	1 (0.0085)
	Large intestine perforation	2 (0.0171)	None
	Lower gastrointestinal haemorrhage	None	1 (0.0085)
	Oesophageal stenosis	1 (0.0085)	None
	Oesophagitis	None	1 (0.0085)
	Pancreatitis	1 (0.0085)	None
	Pancreatitis acute	1 (0.0085)	None
	Upper gastrointestinal haemorrhage	1 (0.0085)	1 (0.0085)
<b>General Disorders and Administration Site Conditions</b>	Pyrexia	1 (0.0085)	None
	General physical health deterioration	None	2 (0.0171)
	Multiple organ dysfunction syndrome	None	2 (0.0171)
	Sudden death	None	4 (0.0342)
<b>Hepatobiliary Disorders</b>	Acute hepatic failure	None	1 (0.0085)
	Autoimmune hepatitis	2 (0.0171)	5 (0.0427)
	Drug-induced liver injury	1 (0.0085)	2 (0.0171)
	Hepatic cytolysis	1 (0.0085)	None
	Hepatic failure	2 (0.0171)	5 (0.0427)
	Hepatic function abnormal	None	1 (0.0085)
	Hepatic necrosis	None	1 (0.0085)
	Hepatitis	None	1 (0.0085)
	Hepatotoxicity	2 (0.0171)	1 (0.0085)
	Hypertransaminasaemia	1 (0.0085)	None
	Immune-mediated hepatitis	None	1 (0.0085)
	Autoimmune endocrine disorder	None	1 (0.0085)

**Table 5.5.5-2: Life-Threatening and/or Fatal Serious Adverse Reactions with Nivolumab plus Ipilimumab Considered Unexpected for Safety Reporting Purposes (N = 11,701 subjects dosed)**

System Organ Class	Preferred Term	Occurrence of Life-Threatening SARs	Occurrence of Fatal SARs
		N (%)	N (%)
<b>Immune System Disorders</b>	Cytokine release syndrome	None	1 (0.0085)
	Haemophagocytic lymphohistiocytosis	None	1 (0.0085)
<b>Infections and Infestations</b>	Bacteraemia	1 (0.0085)	None
	Colonic abscess	None	1 (0.0085)
	Enterococcal sepsis	None	1 (0.0085)
	Herpes simplex reactivation	None	1 (0.0085)
	Peritonitis	None	1 (0.0085)
	Pneumonia	None	2 (0.0171)
	Sepsis	4 (0.0342)	1 (0.0085)
	Septic shock	2 (0.0171)	5 (0.0427)
	Skin infection	1 (0.0085)	None
	Staphylococcal sepsis	1 (0.0085)	None
	Urosepsis	1 (0.0085)	None
<b>Injury, Poisoning and Procedural Complications</b>	Recall phenomenon	1 (0.0085)	None
	Subdural haematoma	1 (0.0085)	None
<b>Investigations</b>	Alanine aminotransferase increased	1 (0.0085)	None
	Aspartate aminotransferase increased	1 (0.0085)	None
	Blood bilirubin increased	None	1 (0.0085)
	Hepatic enzyme increased	1 (0.0085)	None
	Platelet count decreased	1 (0.0085)	None
	Transaminases increased	1 (0.0085)	None
<b>Metabolism and Nutrition Disorders</b>	Diabetes mellitus	1 (0.0085)	None
	Hyperglycaemia	None	1 (0.0034)
	Hyperkalaemia	2 (0.0171)	None
	Hypoglycaemia	1 (0.0085)	None
	Hyponatraemia	1 (0.0085)	None
	Ketoacidosis	3 (0.0256)	None
	Type 1 diabetes mellitus	2 (0.0171)	None

**Table 5.5.5-2: Life-Threatening and/or Fatal Serious Adverse Reactions with Nivolumab plus Ipilimumab Considered Unexpected for Safety Reporting Purposes (N = 11,701 subjects dosed)**

System Organ Class	Preferred Term	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Tumour lysis syndrome	None	2 (0.0171)
<b>Musculoskeletal and Connective Tissue Disorders</b>	Polymyositis	1 (0.0085)	1 (0.0085)
<b>Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)</b>	Malignant neoplasm progression	None	3 (0.0256)
<b>Nervous System Disorders</b>	Diabetic coma	1 (0.0085)	None
	Diabetic hyperosmolar coma	1 (0.0085)	None
	Encephalitis autoimmune	None	2 (0.0171)
	Encephalopathy	2 (0.0171)	None
	Guillain-Barre syndrome	None	1 (0.0085)
	Immune-mediated encephalitis	1 (0.0085)	None
	Ischaemic cerebral infarction	None	1 (0.0085)
	Meningoradiculitis	None	1 (0.0085)
	Myasthenia gravis	2 (0.0171)	4 (0.0342)
	Myasthenic syndrome	1 (0.0085)	1 (0.0085)
	Status epilepticus	1 (0.0085)	None
<b>Renal and Urinary Disorders</b>	Autoimmune nephritis	1 (0.0085)	None
	Renal failure	1 (0.0085)	None
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	Acute respiratory failure	1 (0.0085)	None
	Autoimmune lung disease	None	1 (0.0085)
	Bronchitis chronic	1 (0.0085)	None
	Dyspnoea	1 (0.0085)	None
	Hypoxia	None	1 (0.0085)
	Immune-mediated lung disease	None	4 (0.0342)
	Interstitial lung disease	1 (0.0085)	3 (0.0256)

**Table 5.5.5-2: Life-Threatening and/or Fatal Serious Adverse Reactions with Nivolumab plus Ipilimumab Considered Unexpected for Safety Reporting Purposes (N = 11,701 subjects dosed)**

System Organ Class	Preferred Term	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Pulmonary embolism	1 (0.0085)	2 (0.0171)
	Pulmonary haemorrhage	None	1 (0.0085)
	Respiratory failure	None	3 (0.0256)
<b>Skin and Subcutaneous Tissue Disorders</b>	Drug reaction with eosinophilia and systemic symptoms	2 (0.0171)	None
	Stevens-Johnson syndrome	2 (0.0171)	None
<b>Vascular Disorders</b>	Aortic dissection	None	1 (0.0085)
	Capillary leak syndrome	1 (0.0085)	None
	Hypotension	1 (0.0085)	None
	Internal haemorrhage	None	1 (0.0085)
	Shock	2 (0.0171)	1 (0.0085)

<sup>a</sup> There are events of life-threatening SAR reported in this preferred term, however they are considered expected and are presented in [Appendix 1](#): Reference Safety Information Tables for Assessment of Expectedness of Serious Adverse Reactions.



**Table 5.5.5-3: Life-Threatening and/or Fatal Serious Adverse Reactions with Nivolumab plus Other Considered Unexpected for Safety Reporting Purposes (*N* = 3,201 subjects dosed)**

System Organ Class	Preferred Term	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
<b>Blood and Lymphatic System Disorders</b>	Anaemia	1 (0.0312)	None
	Neutropenia	1 (0.0312)	None
	Pancytopenia	2 (0.0625)	1 (0.0312)
	Thrombocytopenia	1 (0.0312)	None
<b>Cardiac Disorders</b>	Myocarditis	1 (0.0312)	1 (0.0312)
	Pericardial effusion	1 (0.0312)	None
<b>Gastrointestinal Disorders</b>	Colitis ulcerative	1 (0.0312)	None
	Small intestinal perforation	None	1 (0.0312)
<b>General Disorders and Administration Site Conditions</b>	General physical health deterioration	None	1 (0.0312)
	Sudden death	None	1 (0.0312)
<b>Hepatobiliary Disorders</b>	Acute hepatic failure	1 (0.0312)	None
	Autoimmune hepatitis	1 (0.0312)	None
	Portal vein thrombosis	1 (0.0312)	None
<b>Infections and Infestations</b>	Appendicitis	1 (0.0312)	None
	Brain abscess	1 (0.0312)	None
	Diverticulitis intestinal perforated	1 (0.0312)	None
	Pneumocystis jirovecii pneumonia	None	1 (0.0312)
	Pneumonia aspiration	None	1 (0.0312)
	Pneumonia necrotising	1 (0.0312)	None
	Pneumonia pseudomonal	1 (0.0312)	None
	Post procedural sepsis	1 (0.0312)	None
	Sepsis	None	2 (0.0625)
<b>Injury, Poisoning and Procedural Complications</b>	Infusion related reaction	1 (0.0312)	None
<b>Investigations</b>	Neutrophil count decreased	1 (0.0312)	None
	Platelet count decreased	1 (0.0312)	None
	White blood cell count decreased	1 (0.0312)	None
	Decreased appetite	1 (0.0312)	None

**Table 5.5.5-3: Life-Threatening and/or Fatal Serious Adverse Reactions with Nivolumab plus Other Considered Unexpected for Safety Reporting Purposes (*N* = 3,201 subjects dosed)**

System Organ Class	Preferred Term	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
<b>Metabolism and Nutrition Disorders</b>	Hyperglycaemia	2 (0.0625)	None
	Hyponatraemia	1 (0.0312)	None
<b>Musculoskeletal and Connective Tissue Disorders</b>	Myositis	1 (0.0312)	None
<b>Nervous System Disorders</b>	Cerebrovascular accident	None	1 (0.0312)
	Hydrocephalus	1 (0.0312)	None
	Seizure	1 (0.0312)	None
	Vasogenic cerebral oedema	None	1 (0.0312)
<b>Renal and Urinary Disorders</b>	Renal failure	1 (0.0312)	None
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	Acute pulmonary oedema	None	1 (0.0312)
	Acute respiratory failure	None	1 (0.0312)
	Lung disorder	1 (0.0312)	None
	Pneumonitis	4 (0.125)	5 (0.1562)
	Pulmonary embolism	3 (0.0937)	None
	Respiratory distress	None	1 (0.0312)
	Respiratory failure	1 (0.0312)	2 (0.0625)
<b>Skin and Subcutaneous Tissue Disorders</b>	Stevens-Johnson syndrome	None	1 (0.0312)
<b>Vascular disorders</b>	Bleeding varicose vein	1 (0.0312)	None
	Hypertension	1 (0.0312)	None

## 5.6 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The effect of development of nivolumab ADA and neutralizing antibodies on efficacy and safety have been well-studied, and the incidence rates of nivolumab ADA were low across tumor types and have not been found to impact the safety or efficacy profile of nivolumab when administered as monotherapy or in combination with cytotoxic chemotherapy. The immunogenicity of nivolumab and ipilimumab when administered in combination has been well characterized with each submission/indication with no dose adjustments recommended, as there was no evidence of any effects on efficacy, altered toxicity profile, or clinically relevant changes in PK due to increased immunogenicity incidence requiring dose adjustment.

Of 3,874 subjects with cancer who were treated with nivolumab monotherapy (3 mg/kg Q2W, 240 mg Q2W, or 480 mg Q4W) and evaluable for the presence of anti-nivolumab antibodies, 373 subjects (9.6%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay, and 21 subjects (0.5%) had neutralizing antibodies against nivolumab.<sup>178</sup>

Co-administration with chemotherapy did not affect nivolumab immunogenicity. Of the 276 subjects who were treated with nivolumab 240 mg Q2W in combination with chemotherapy and evaluable for the presence of ADA in the CA209648 study, 12 subjects (4.3%) tested positive for treatment-emergent anti-product-antibodies with 3 subjects (1.1%) testing positive for neutralizing antibodies.<sup>179</sup> Additionally, of the 198 perioperative NSCLC subjects who received nivo+chemo/nivo, 10 (5.1%) subjects were nivolumab ADA positive at baseline and 24 (12.1%) subjects were nivolumab ADA positive after start of treatment. 1 of the 198 ADA positive subjects (0.5%) was neutralizing ADA positive.<sup>120</sup>

Of the subjects who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies ranged from 13.2% to 56.3% and neutralizing antibodies against nivolumab ranged from 0% to 22.9% in RCC, NSCLC, MPM, ESCC, melanoma, CRC and HCC.<sup>63, 180, 181, 182, 183, 184, 185</sup>

Of the subjects with NSCLC who were treated with nivolumab 360 mg Q3W in combination with ipilimumab 1 mg/kg Q6W and platinum-based chemotherapy and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 33.8% and the incidence of neutralizing antibodies against nivolumab was 2.6%.<sup>186</sup>

The immunogenicity of [REDACTED] nivolumab Process D and Process C was assessed in study CA2098FC.<sup>86</sup> The results demonstrated that the incidence of nivolumab ADA was low for both processes and consistent with that observed across the nivolumab monotherapy clinical program. No subject developed neutralizing antibodies against nivolumab.

When administered as monotherapy or in combination with ipilimumab, the CL of nivolumab increased by 20% in the presence of anti-nivolumab antibodies.<sup>180</sup> However, there was no evidence

of loss of efficacy or altered safety profile in the presence of nivolumab antibodies based on the PPK and E-R analyses for both monotherapy and combination with ipilimumab.

## 5.7 QT Prolongation Potential

An intensive QT substudy was conducted to determine whether nivolumab has QT prolongation potential in CA209010. Nivolumab within the range of doses studied up to 10 mg/kg did not affect the QTc interval. There was no dose-response for QTcF,  $\Delta$ QTcF, or change from baseline in heart rate, PR interval, or QRS interval after either first dose or seventh dose. No subject had a QTcF interval > 470 msec or a  $\Delta$ QTcF > 45 msec. In addition, there was no relationship between QTcF change from baseline and nivolumab serum concentration. After careful examination of events of seizure/convulsion, syncope/presyncope, QTc prolongation, and tachycardia, no event was determined to be associated with an abnormal ECG finding potentially related to proarrhythmia. Overall, nivolumab does not have QT prolongation potential in the studied dose range.<sup>187</sup>

## 5.8 Opportunistic Infections Due to Immunosuppression

Some subjects may require prolonged treatment with high-dose corticosteroids or alternative immunosuppressants for the treatment of nivolumab-related AEs. Rare cases of opportunistic infections have occurred in subjects treated with immunosuppression.

One subject with NSCLC developed steroid-responsive pneumonitis while receiving treatment with nivolumab in combination with chemotherapy. Soon after completing corticosteroid treatment, ■ developed recurrent pulmonary symptoms. A subsequent lung biopsy identified invasive aspergillosis without evidence of pulmonary inflammation (pneumonitis). The subject died 1 week later of invasive *Aspergillus*. A second subject with NSCLC developed steroid-responsive pneumonitis after being treated with nivolumab monotherapy for over 24 weeks. ■ subsequently developed recurrent pulmonary symptoms, and a lung biopsy identified *Aspergillus* pneumonia without pulmonary inflammation (pneumonitis). ■ received antifungal therapy and recovered from this infection. A third subject with RCC developed steroid-responsive pneumonitis while receiving nivolumab treatment in combination with pazopanib. ■ was treated with high-dose corticosteroids that were tapered over 2 months and subsequently developed recurrent pulmonary symptoms. A bronchoscopic sample identified *Pneumocystis jiroveci* pneumonia. ■ was treated with antimicrobials and had a complete recovery.

One subject with NSCLC developed Grade 3 interstitial pneumonia on Day 27 after receiving one dose of nivolumab monotherapy. ■ was treated with steroid pulse therapy (methylprednisolone 1 g/day) and subsequently presented with pneumocystis pneumonia. Steroid therapy was discontinued, and sulfamethoxazole treatment was initiated. The event was improving but ongoing at the time of the subject's death (due to malignant neoplasm progression). Another subject with malignant melanoma was receiving steroids for treatment of brain metastases prior to initiating nivolumab and presented with pneumocystis pneumonia 9 days after the first nivolumab dose. The subject was hospitalized, and sulfamethoxazole and trimethoprim were administered for treatment. When pneumocystis pneumonia did not improve, antibiotic micafungin and ganciclovir were

added. The condition continued to worsen, and the subject died due to pneumocystis pneumonia and disseminated intravascular coagulation.

A [REDACTED] subject-initiated study therapy with IV nivolumab (240 mg), oral pomalidomide therapy, and oral dexamethasone for multiple myeloma. The subject was hospitalized due to pneumonitis and pneumocystis jirovecii pneumonia approximately three months after receiving a single dose of nivolumab, and the same day as administration of pomalidomide and dexamethasone. The subject was treated with trimethoprim/sulfamethoxazole and high dose steroids, but [REDACTED] condition continued to decline, and [REDACTED] died 9 days later. At the time of death multiple myeloma was rapidly progressing and pneumocystis pneumonia was ongoing.

A [REDACTED] initiated study therapy with nivolumab, ipilimumab, oxaliplatin and capecitabine for gastric cancer. Approximately 3 months after initiation of study therapy, the patient was reported to have red spots with blisters on [REDACTED] body, palms, and soles and was later diagnosed with Stevens-Johnson syndrome (SJS). The subject was treated with steroids (dexamethasone, methylprednisolone, topical methylprednisolone aceponate cream) as well as anti-histaminic treatment and pain medication. About 1 month later, the patient was reported with pneumocystis carinii pneumonia which was attributed to steroid administration to treat SJS. The event of pneumocystis carinii pneumonia was treated with antibiotics (IV followed by oral) and reported as resolved.

## 5.9 Drug-induced Liver Injury

Hepatotoxicity, such as transaminase elevations and hepatitis, has been identified as an important risk for nivolumab. A hepatic AE management algorithm that has been established ([Appendix 4](#)) and applied across the nivolumab program remains appropriate for managing drug-induced liver injury (DILI) cases. The experience to date shows that hepatic AEs, including possible DILI cases, were manageable using the established management algorithm and thus do not meaningfully alter the benefit/risk of nivolumab in the advanced malignancy populations.

Experience in the clinical program so far suggests that nivolumab in combination with ipilimumab or nivolumab followed sequentially by ipilimumab may have a higher frequency of hepatotoxicity as exhibited by transaminase elevations and hepatitis than nivolumab alone. Also, drugs with a predisposition to hepatotoxicity should be used with caution in subjects treated with a nivolumab-containing regimen.

## 6 MARKETING EXPERIENCE

Nivolumab (OPDIVO™) was first approved on 04-Jul-2014 in Japan for unresectable melanoma. Nivolumab has since been approved as a monotherapy and in combination with other agents for several indications in multiple countries. Refer to [Table 5-1](#) for the complete list of approved indication of nivolumab in the US and EU.

Qualitative and quantitative safety information received as of 12-Apr-2024 has been consistent with the established safety profile as observed in clinical trials.

## **7 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR**

### **7.1 Summary of Safety**

The monitoring of subject safety during and after a clinical study with nivolumab, including any special monitoring precautions, tests, or observations, and the proper means of recording and reporting adverse safety information (ie, AEs and abnormal laboratory values) will follow the procedures outlined in the specific study protocol. Potential safety concerns and recommended management guidelines regarding pulmonary toxicities, GI toxicities, hepatotoxicities, endocrinopathies, dermatologic toxicities, and other toxicities of concern are summarized below and described in detail in [Appendix 4](#).

The safety experience from clinical trials with nivolumab is based on experience in approximately 32,608 subjects as either monotherapy or in combination with other therapeutics in unblinded clinical trials. In general, for monotherapy, the safety profile is similar across tumor types. The exception is pulmonary inflammation AEs and hepatic AEs, which is numerically greater in subjects with NSCLC and HCC, respectively, however, it may be difficult to distinguish between nivolumab-related and unrelated causes. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade. A comprehensive listing of related AEs can be found in [Appendix 6](#).

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. A variety of preferred terms (PTs) have been used to describe similar kinds of organ-related AEs, with the result being that AE frequency tables organized by PTs can lead to underestimation of the frequency of similar kinds of organ-related AEs. To address this issue, select AE categories were created (see [Section 5.5](#)). Select AE categories group together the most common and impactful PTs by organ category. These categories include the following: pulmonary, GI, hepatic, skin, endocrine, hypersensitivity/infusion reaction, and renal AEs. The frequency of select AE categories is provided in the sub-sections for individual indications under [Section 5.5](#). It is also useful to consider the management of nivolumab-related AEs by organ category as the diagnostic work-up often requires excluding other potential diagnoses and, when appropriate, instituting specific management principles as outlined in the subsequent subsections and [Appendix 4](#).

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. As referenced in [Section 5.4](#), in select tumors combinations containing nivolumab + ipilimumab, nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy, nivolumab + cabozantinib, and nivolumab + fluoropyrimidine + platinum-containing chemotherapy have been approved in the US and/or EU. The combination of nivolumab+ipilimumab results in a safety profile with similar types of AEs compared to each agent alone, but in some cases, with a greater frequency. The optimal doses for nivolumab + ipilimumab combination continue to be evaluated and may vary by tumor type. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and

severity of AEs were greater than that observed with either agent alone. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve.

In general, the approach to suspected nivolumab-related AEs is similar across any involved organ system. Safety management algorithms for organ-specific AEs are found in [Appendix 4](#). Subjects should have a thorough diagnostic work-up to evaluate potential drug- and non-drug-related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized. Once the AE has begun to improve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE). The management of AEs considered related to any combination treatment is similar to the management of AEs caused by either agent alone and utilizes the same safety management algorithms.

As described in [Section 5.8](#), it is rare for a patient receiving immunosuppression for nivolumab-related AEs to develop an opportunistic infection. Subjects with inflammatory events of any organ category expected to require more than 4 weeks of corticosteroid or other immunosuppressive agents to manage the AE should be considered for antimicrobial/antifungal prophylaxis, per institutional guidelines, to prevent opportunistic infections such as *P. jiroveci* (formerly *P. carinii*) and fungal infections. Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate. In addition, a concomitant opportunistic infection should be considered in the differential diagnosis if a patient develops recurrent AEs in the setting of ongoing or prior immunosuppressive use. Nivolumab should not be used in subjects with active autoimmune disease given the mechanism of action of the antibody.

Please refer to [Appendix 1](#) for additional information regarding serious adverse reactions (SARs) causally associated with BMS-936558 and considered to be expected for regulatory reporting.

### **7.1.1 Pulmonary Adverse Events**

Pulmonary AEs have been observed following treatment with nivolumab. The frequency of pulmonary AEs is greater with nivolumab combination therapies than with nivolumab monotherapy. The majority of cases reported were Grade 1 or 2, and subjects were reported with either asymptomatic radiographic changes (eg, focal ground-glass opacities and patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3 or 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. Pulmonary AEs have been reported in subjects with a variety of tumor types; however, there have been numerically more cases in subjects with NSCLC. It is not clear whether the underlying NSCLC is a distinct risk factor, or if subjects with NSCLC are more likely to develop radiographic changes and symptoms for which it is difficult to distinguish between nivolumab-related and unrelated causes. At this time, no other underlying risk factor, including prior radiotherapy, presence of lung metastases, or underlying pulmonary medical history, has yet to be identified.



Asymptomatic subjects were typically managed with dose delay. Subjects with Grade 2 pneumonitis were managed with dose delay, treated with corticosteroids, and had resolution of pneumonitis within days to weeks. In cases where nivolumab treatment was restarted, recurrence of pneumonitis was infrequently reported across the nivolumab program. In a few cases, subjects who did not initially respond to corticosteroids were administered anti-tumor necrosis factor therapy (infliximab) and/or cyclophosphamide. In some of these cases, pneumonitis began to resolve following the use of these additional therapies.

Guidelines on the recommended management of pneumonitis and other pulmonary AEs are found in [Appendix 4](#). Early recognition and treatment of pneumonitis is critical to its management. Subjects should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms. As respiratory symptoms are common in subjects with cancer (eg, NSCLC), it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection or progression of disease) and a possible drug-related pulmonary toxicity as the management of these events can be quite different. For symptomatic nivolumab-related pneumonitis, the principal treatment is corticosteroids ([Appendix 4](#)). All subjects with Grade 3-4 pneumonitis should discontinue nivolumab and initiate treatment with high doses of corticosteroids.

### **7.1.2 Hepatic Adverse Events**

Hepatic AEs, including elevated LFTs and, infrequently, DILI, have been observed following treatment with nivolumab and nivolumab in combination with ipilimumab ([Section 5.5](#)). Most cases were of low or moderate grade. Higher-grade hepatic AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved.

Hepatic AEs have been reported in subjects with a variety of tumor types; however, there have been numerically more cases in subjects with HCC. It is not clear whether the underlying HCC is a distinct risk factor, or if subjects with HCC are more likely to develop LFT abnormalities and symptoms for which it is difficult to distinguish between nivolumab-related and unrelated causes. At this time, no other underlying risk factor, including prior treatment, presence of liver metastases, or underlying hepatic medical history, has yet to be identified.

The recommended management of hepatic AEs is provided in [Appendix 4](#). Early recognition and treatment of elevated LFTs and DILI are critical to their management. Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each nivolumab treatment. As LFT abnormalities are common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection, progression of disease, concomitant medications, or alcohol) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade hepatic AEs is corticosteroids ([Appendix 4](#)).



### **7.1.3      *Gastrointestinal Adverse Events***

Gastrointestinal AEs have been observed following treatment with nivolumab ([Section 5.5](#)). Most cases of diarrhea were of low grade (Grade 1-2). Colitis occurred less frequently than diarrhea. High-grade cases of diarrhea and colitis were managed with corticosteroids and, in all cases, the events resolved.

The recommended management of GI AEs is provided in [Appendix 4](#). Early recognition and treatment of diarrhea and colitis are critical to their management. Subjects should be advised to seek medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. As GI symptoms are common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade GI AEs is corticosteroids ([Appendix 4](#)). Caution should be taken in the use of narcotics in subjects with diarrhea, colitis, or abdominal pain as pain medicines may mask the signs of colonic perforation.

## **Diverticular Perforation**

The prevalence of diverticulosis in the general population is common and increases with age from 10% under 40 years of age to approximately 50% over 60 years of age. Approximately 10% to 25% of subjects with diverticulosis develop diverticulitis. Perforation occurs in 50% to 70% of instances of complicated diverticulitis.<sup>188,189</sup> Corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics are known risk factors for diverticular perforation.<sup>190</sup> Given the high prevalence of diverticulosis and diverticulitis in the general population, it is expected that some nivolumab-treated subjects will have these conditions concurrently with their malignancy. Cases of diverticular perforation while on concomitant corticosteroids (6 cases) or NSAID (1 case) were observed in the nivolumab program. While there is insufficient evidence to suggest that diverticulosis or diverticulitis is a predisposing factor for GI perforation following nivolumab administration, clinical caution should be exercised, as appropriate, for subjects on concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, be vigilant for signs and symptoms of potential perforation, especially in subjects with known diverticular disease.

### **7.1.4 Endocrinopathies**

Endocrinopathies have been observed following treatment with nivolumab (Section 5.5). Most cases were of low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (eg, TSH) or as part of a work-up for associated symptoms (eg, fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (eg, hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Moderate- to high-grade cases were managed with hormone replacement therapy and, in some cases, with the addition of corticosteroids. In some cases, nivolumab treatment was held until adequate hormone replacement was provided.

Guidelines on the recommended management of endocrinopathies are provided in Appendix 4. Early recognition and treatment of endocrinopathies are critical to its management. Subjects should be advised to seek medical evaluation if they notice new-onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens. As fatigue is common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, progression of disease, anemia, concomitant medications, or depression) and a possible drug-related AE as the management can be quite different. The principal management of endocrinopathies is hormone replacement therapy. For subjects with moderate- or high-grade events, corticosteroids may also be used (Appendix 4).

### **7.1.5 Skin Adverse Events**

Rash and pruritus were the most common skin AEs observed following treatment with either nivolumab or nivolumab + ipilimumab (Section 5.5). The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical

corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids.

Subjects should be advised to seek medical evaluation if they notice new-onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash, or if there is any unusual appearance or clinical feature associated with it. Other drugs that may cause rash should be considered in the differential and, if possible, discontinued. In addition, careful evaluation of potential benefit-risk is necessary when considering the use of nivolumab or ipilimumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior immune-stimulating therapy.

Guidelines on the recommended management of skin AEs are provided in [Appendix 4](#). The principal treatment for skin AEs, such as rash and pruritus, consists of symptomatic management. Topical corticosteroids can be used for low- to moderate-grade focal rash. Systemic corticosteroids should be used for diffuse and high-grade rash.

Rare cases of SJS and toxic epidermal necrolysis (TEN), some with fatal outcome, have been observed. If symptoms or signs of SJS or TEN appear, nivolumab or nivolumab in combination with ipilimumab should be withheld and the patient referred for specialized care for assessment and treatment. If the patient has confirmed SJS or TEN, permanent discontinuation of nivolumab or nivolumab in combination with ipilimumab is recommended.

#### **7.1.6 Renal Adverse Events**

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. The frequency of renal AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. Most cases were Grade 2 or 3 and based on creatinine elevation. Subjects with a history of RCC or prior nephrectomy did not appear to be at higher risk. Events were managed with corticosteroids and, in all cases, renal function partially or fully improved.

The recommended management of renal AEs is provided in [Appendix 4](#). Physicians should monitor creatinine regularly. As creatinine abnormalities are common in subjects with cancer and other comorbidities, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, dehydration, concomitant medications, hypotension, or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for renal AEs is corticosteroids ([Appendix 4](#)).

#### **7.1.7 Neurologic Adverse Events**

Neurologic AEs have been uncommonly observed following treatment with nivolumab ([Section 5.5](#)). The frequency of neurologic AEs may be greater with nivolumab + ipilimumab combination therapies than with nivolumab monotherapy or other nivolumab combinations. Neurologic AEs can manifest as central abnormalities (eg, aseptic meningitis, encephalopathy, or encephalitis) or peripheral sensory/motor neuropathies (eg, Guillain-Barre Syndrome, myasthenia gravis complicated with sepsis and fatality). The onset has been observed as early as after a single treatment with the nivolumab + ipilimumab combination. Approximately half of the reported

events of encephalitis events have observed to have resolved, with 50% of resolutions occurring within 2 weeks of onset.<sup>191</sup>

The recommended management of neurologic AEs is provided in [Appendix 4](#). Early recognition and treatment of neurologic AEs is critical to its management. Subjects should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible CNS abnormalities such as new headache or mental status changes. As neurologic symptoms can be common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, progression of disease, concomitant medications, or infection) and a possible drug-related AE as the management can be quite different. The principal treatments for neurologic toxicity are dose delay, corticosteroids, and IV immunoglobulin as outlined in the safety algorithm ([Appendix 4](#)). For high-grade related neurological AEs, nivolumab should be discontinued.

### **7.1.8      *Infusion Reactions***

Infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon. Investigators are advised to monitor for fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty in breathing during and immediately after administration of nivolumab. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) guidelines. Treatment recommendations are provided in study protocols and may be modified based on local treatment standards and guidelines, as appropriate.

### **7.1.9      *Lipase/Amylase Elevations***

Asymptomatic elevations in lipase and amylase have been reported. In monotherapy studies, lipase and amylase levels were not systematically monitored, so an estimate of the frequency of asymptomatic lipase/amylase elevations is unknown. In studies evaluating the safety of the nivolumab + ipilimumab combination in multiple tumor types, lipase and amylase levels were systematically monitored, and elevations in any grade of lipase/amylase were consistently noted in approximately 10% to 30% of subjects. Very few subjects reported associated symptoms (eg, abdominal pain) or radiographic findings (eg, stranding) consistent with pancreatitis. Thus, there does not seem to be of clinical significance to the elevated laboratory values.

As lipase/amylase abnormalities are not uncommon in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, progression of disease, concomitant medications, or alcohol) and a possible drug-related cause as the management can be quite different. The recommended management of nivolumab-related elevated lipase/amylase values centers around close observation. Physicians should ensure that subjects have no associated symptoms consistent with pancreatitis, such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low grade over the course of weeks, whether or not subjects receive corticosteroids. Asymptomatic elevations should be monitored

approximately on a weekly basis, and nivolumab should be held per protocol instructions. For subjects with elevated lipase/amylase and symptoms consistent with possible pancreatitis, nivolumab should be discontinued, and consultation with a gastroenterologist should be considered.

### **7.1.10 Uveitis and Visual Complaints**

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (eg, uveitis) is an uncommon, but clinically important, event. Uveitis may occur more frequently with nivolumab + ipilimumab combination therapy than with nivolumab monotherapy or nivolumab in combination with other therapies. An ophthalmologist should evaluate visual complaints with an examination of the conjunctiva, anterior and posterior chambers, and retina. Topical corticosteroids may be used to manage low-grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause (Section 7.1.3).

Vogt-Koyanagi-Harada syndrome (VKH) is a T-cell mediated autoimmune attack on melanocytes. VKH manifests as a multi-system disorder characterized by granulomatous panuveitis with exudative retinal detachments, often associated with neurologic and cutaneous manifestations. Rare cases have been observed in post-marketing use of nivolumab. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued, and corticosteroids administered accordingly.

### **7.1.11 Other Immune-mediated Adverse Events**

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued, and corticosteroids administered accordingly. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If there is a recurrence of any Grade 3 or 4 immune-related adverse reactions or life-threatening immune-related adverse reactions, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. Diagnosis of myocarditis requires a high index of suspicion and in some cases can be asymptomatic. Therefore, any cases with cardiac or cardio-pulmonary symptoms should undergo prompt diagnostic work-up to evaluate for myocarditis with close monitoring. Troponin is a sensitive but not diagnostic marker of myocarditis. If suspected, prompt initiation of high dose of steroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d) and cardiology consultation with diagnostic workup with ECG, troponin and echocardiogram. Additional testing as guided by the cardiologist and may include cardiac MRI. Once a diagnosis is confirmed, nivolumab or nivolumab in combination with ipilimumab should be withheld. For grade 3 myocarditis, nivolumab or nivolumab in combination

with ipilimumab should be permanently discontinued. The recommended management of myocarditis is provided in [Appendix 4](#).

The following events have been identified during post-approval use of nivolumab or nivolumab in combination with ipilimumab. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

- Solid organ and tissue transplant rejection has been reported in subjects who have previously undergone transplantation and who were subsequently treated with PD-1/PD-L1 inhibitors, including nivolumab. Treatment with nivolumab may increase the risk of rejection in solid organ or tissue transplant recipients.
- Rapid-onset and severe graft-versus-host disease (GVHD), some with fatal outcome, has been reported in subjects who had undergone prior allogeneic hematopoietic stem cell transplantation (HSCT) and subsequently received PD-1/PD-L1 inhibitors. Subjects should be screened to determine whether they have undergone a prior allogeneic HSCT prior to participating in nivolumab clinical trials.
- Complications of allogeneic HSCT after treatment with PD-1/PD-L1 inhibitors including nivolumab, administered before allogeneic HSCT, may be associated with an increased risk of transplant-related complications, including GVHD. Fatal cases have been reported in clinical studies. Subjects should be monitored closely for early evidence of transplant-related complications.
- Hemophagocytic lymphohistiocytosis.
- Autoimmune hemolytic anemia.
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome).

## **7.2 Overdose, Warnings, and Precautions**

There is no available information concerning overdose with nivolumab. Depending on the symptoms and/or signs leading to the suspicion of overdose, supportive medical management should be provided. There is no specific antidote.

### **7.2.1 Precautions for Women of Childbearing Potential**

The nonclinical findings of increased late-stage pregnancy loss and early infant deaths/euthanasia in nivolumab-exposed pregnant monkeys (additional details in [Section 4.3](#)) suggest a potential risk to human pregnancy with nivolumab treatment during pregnancy. Given the potential risk suggested by preliminary data from nonclinical and clinical data, dosing during pregnancy will continue to be prohibited.

Therefore, women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of study drug. These durations have been calculated using the upper limit of the half-life for nivolumab (~25 days) and are based on the recommendation that WOCBP use contraception for 5 half-lives after the last dose of a potentially fetotoxic, non-genotoxic therapy. Females should not breastfeed while receiving nivolumab and for any subsequent protocol-specified period. For ONO studies, refer to individual study protocols for the duration of WOCBP contraception use.

In addition, based on the evidence cited above, given that nivolumab is not a genotoxic agent, and that relevant systemic concentrations sufficient to produce a risk of fetal toxicity are not expected in WOCBP partners from exposure to a male participant's seminal fluid, male study participants will not be required to use contraceptive measures and/or a latex or other synthetic condom during sexual activity with a WOCBP.

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- <sup>133</sup> Interim Clinical Study Report: Study No. CA209901. A Phase 3, Open-label, Randomized Study of Nivolumab Combined with Ipilimumab, or with Standard of Care Chemotherapy, versus Standard of Care Chemotherapy in Participants with Previously Untreated Unresectable or Metastatic Urothelial Cancer. Bristol-Myers Squibb Company; 2023. Document Control No. 930210902
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- <sup>136</sup> Closeout Clinical Study Report: Study No. CA209331. Phase 3, open-label, randomized study of nivolumab or chemotherapy in subjects with relapsed small-cell lung cancer after platinum-based first line chemotherapy. Bristol-Myers Squibb Company; 2023. Document Control No. 930201251

- <sup>137</sup> Final Clinical Study Report for Study CA209451. A Randomized, Multicenter, Double-Blind, Phase 3 Study of Nivolumab, Nivolumab in Combination with Ipilimumab, or Placebo as Maintenance Therapy in Subjects with Extensive Stage Disease -Small Cell Lung Cancer after Completion of Platinum-based First-line Chemotherapy. Bristol-Myers Squibb Company; 2019. Document Control No. 930143946
- <sup>138</sup> Interim Clinical Study Report: Study No. CA209032. A Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors. Bristol-Myers Squibb Company; 2016. Document Control No. 930103271.
- <sup>139</sup> Final Clinical Study Report for Study CA209459. A Randomized, Multi-center Phase 3 Study of Nivolumab versus Sorafenib as First-Line Treatment in Patients with Advanced Hepatocellular Carcinoma. Bristol-Myers Squibb Company; 2020. Document Control No. 930151289.
- <sup>140</sup> Primary Clinical Study Report for Cohort 5 : Study No. CA209142. A Phase 2 Clinical Trial of Nivolumab, or Nivolumab Combinations, in Recurrent and Metastatic Microsatellite Instability High (MSI-H) and non-MSI-H Colon Cancer. Bristol-Myers Squibb Company; 2022. Document Control No 930190161
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- <sup>146</sup> Clinical Study Report: Study No. ONO-4538-39. ONO-4538 Phase II Study A multicenter, open-label, non-controlled study in patients with uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma ONO Pharmaceutical Co., Ltd.; 2021.
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- <sup>148</sup> Closeout Clinical Study Report for Study CA209627. An Open-label Phase 2 Multi-cohort Trial of Nivolumab in Advanced or Metastatic Malignancies. Bristol-Myers Squibb Company; 2021. Document Control No. 930177589.
- <sup>149</sup> CA209032 Interim Pancreatic Cancer Clinical Study Report: Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors. Bristol-Myers Squibb Company; 2019. Document Control No. 930138022.
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- <sup>151</sup> Interim Clinical Study Report: Study No. CA209650 A phase 2 trial of nivolumab plus ipilimumab, ipilimumab alone, or cabazitaxel in men with metastatic Castration-resistant prostate cancer. Bristol-Myers Squibb Company; 2023. Document Control No. 930198290.
- <sup>152</sup> Clinical Study Report: Study No. CA2099KD. A Phase 2 Study of Nivolumab in Combination with Either Rucaparib, Docetaxel, or Enzalutamide in Men with Castration-resistant Metastatic Prostate Cancer (CheckMate 9KD: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 9KD). Bristol-Myers Squibb Company; 2022. Document Control No. 930164097
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- <sup>154</sup> Final Clinical Study Report: Study No. CA209039. A Phase 1 dose escalation study to investigate the safety, pharmacokinetics, immunoregulatory activity, and preliminary antitumor activity of anti-Programmed-Death (PD-1) antibody (nivolumab, BMS-936558) and the combinations of nivolumab and ipilimumab or nivolumab and lirilumab in subjects with relapsed or refractory hematologic malignancy. Bristol-Myers Squibb Company; 2020. Document Control No. 930149133.
- <sup>155</sup> Clinical Study Report: Study No. CA209602. An Open-Label, Randomized Phase 3 Trial of Combinations of Nivolumab, Pomalidomide and Dexamethasone in Relapsed and Refractory Multiple Myeloma (CheckMate 602: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 602). Bristol-Myers Squibb Company; 2022. Document Control No. 930195715
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- <sup>158</sup> CA209032 Final Clinical Study Report: A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors. Bristol-Myers Squibb Company; 2020. Document Control No. 930149021.
- <sup>159</sup> Clinical Study Report: Study No. ONO-4538-23. ONO-4538 Phase III Study: A Multicenter, Randomized, Open-Label Study in Ovarian Cancer Patients. ONO Pharmaceutical Co., Ltd.; 2021.
- <sup>160</sup> CA209032 Interim Clinical Study Report: A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors. Bristol-Myers Squibb Company; 2020. Document Control No. 930149101.

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- <sup>162</sup> Primary Clinical Study Report: Study No. CA209358. Non-Comparative, Open-Label, Multiple Cohort, Phase 1/2 Study of Nivolumab Monotherapy and Nivolumab Combination Therapy in Subjects with Virus-Positive and Virus-Negative Solid Tumors. Bristol-Myers Squibb Company; 2022. Document Control No 930184495
- <sup>163</sup> Final Clinical Study Report: Study No. CA209848. A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination with Ipilimumab or Nivolumab Monotherapy in Participants with Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H). Bristol-Myers Squibb Company; 2023. Document Control No 930215342
- <sup>164</sup> Primary Clinical Study report: Study No. CA209672. A Phase 1/2 Study Of Nivolumab (BMS-936558) in combination with Ipilimumab (BMS-734016) in Chinese Subjects with Previously Treated Metastatic or Recurrent Solid Tumors. Bristol-Myers Squibb Company; 2023. Document Control No. 930203399.
- <sup>165</sup> Ad Hoc Interim Report: Study No. CA209153. A Phase 3b/4 safety trial of nivolumab (BMS-936558) in subjects with advanced or metastatic non-small cell lung cancer who have progressed during or after receiving at least one prior systemic regimen. Bristol-Myers Squibb Company; 2017. Document Control No. 930107706.
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- <sup>170</sup> Interim Synoptic Study Report: Study No. CA209817. A Phase IIIb/IV safety and efficacy trial of flat dose nivolumab in combination with ipilimumab in participants with non-small cell lung cancer. Bristol-Myers Squibb Company; 2018. Document Control No. 930126486.
- <sup>171</sup> Synoptic Clinical Study Report: Study No. CA209743. A Phase 3, Randomized, Open Label Trial of Nivolumab in Combination with Ipilimumab versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma. Bristol-Myers Squibb Company; 2023. Document Control No. 930214693.
- <sup>172</sup> Closeout Clinical Study Report: Study No. CA209205 Non-Comparative, Multi-Cohort, Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Classical Hodgkin Lymphoma (cHL) Subjects Bristol-Myers Squibb Company; 2023 Document Control No. 930212110.
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- <sup>174</sup> Final Clinical Study Report: Study No. CA2099TM. A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Of Nivolumab Or Nivolumab Plus Cisplatin, In Combination With Radiotherapy In Participants With Cisplatin Ineligible And Cisplatin Eligible Locally Advanced SCCN. Bristol-Myers Squibb Company; 2020. Document Control No. 930152731.
- <sup>175</sup> Clinical Study Report: Study No. CA209370 A Master Protocol of Phase 1/2 Studies of Nivolumab in Advanced NSCLC Using Nivolumab as Maintenance after Induction Chemotherapy or as First-line Treatment Alone or in Combination with Standard of Care Therapies. Bristol-Myers Squibb Company; 2020. Document Control No. 930162260.

- <sup>176</sup> Final Synoptic Clinical Study Report: Study No. CA209039. Multiple Phase 1/2 cohorts of nivolumab monotherapy or nivolumab combination regimens across relapsed/refractory hematologic malignancies. Bristol-Myers Squibb Company; 2019. Document Control No. 930146768.
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- <sup>179</sup> Clinical Study Report. Study No CA209648. A randomized phase 3 study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated esophageal squamous cell carcinoma Bristol-MyeSquibb Company; June 2021. Document Control Number 930170066.
- <sup>180</sup> Summary of Clinical Pharmacology: Metastatic Renal Cell Carcinoma. Bristol-Myers Squibb Company; 2017. Document Control No. 930109556.
- <sup>181</sup> Summary of Clinical Pharmacology: Previously Untreated Advanced Melanoma. Bristol-Myers Squibb Company; 2015. Document Control No. 930091000.
- <sup>182</sup> Final Clinical Study Report Study No CA209040. A Phase 1/2, Dose-Escalation, Open-Label Study of Nivolumab or Nivolumab in Combination with Other Agents in Advanced Hepatocellular Carcinoma Subjects with or without Chronic Viral Hepatitis. Bristol-Myers Squibb Company; 2019. Document Control No. 930140342.
- <sup>183</sup> Final Part 1 Clinical Study Report Study No CA209227. An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer. Bristol-Myers Squibb Company; 2019. Document Control No. 930142967.
- <sup>184</sup> Summary of Clinical Safety- Nivolumab in Combination with Ipilimumab. Unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC). Bristol-Myers Squibb Company; 2021. Document Control No. 930171368

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- <sup>186</sup> Final Clinical Study Report- Study No CA2099LA. A Phase 3, Randomized Study of Nivolumab plus Ipilimumab in Combination with Chemotherapy vs Chemotherapy alone as First Line Therapy in Stage IV Non-Small Cell Lung Cancer (NSCLC). Bristol-Myers Squibb Company; 2019. Document Control No. 930148183.
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- <sup>190</sup> Morris CR, Harvey IM, Stebbings WS, et al. Anti-inflammatory drugs, analgesics and the risk of perforated colonic diverticular disease. *Br J of Surg* 2003;90:1267-72.
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## **Appendix 1: Reference Safety Information**

25 page(s) excluding cover page

## APPENDIX 1      REFERENCE SAFETY INFORMATION FOR ASSESSMENT OF EXPECTEDNESS OF SERIOUS ADVERSE REACTIONS

The Reference Safety Information (RSI) describes expected Serious Adverse Reactions (SARs) for the investigational product. The information within the RSI does not present a comprehensive overview of the safety profile of nivolumab (BMS-936558). Additional information is available in [Section 5.5](#) Clinical Safety and [Section 7](#) Summary of Data and Guidance for the Investigator.

This section describes expected SARs for regulatory reporting purposes. The Sponsor consults this section when determining reporting requirements for Suspected Unexpected Serious Adverse Reactions (SUSARs) from clinical studies in accordance with regional and/or local regulations.

To identify expected SARs from clinical studies, the Sponsor performed a cumulative review of reported adverse reactions from completed and ongoing studies as well as post marketing data for nivolumab. SARs were identified by the Sponsor based on the nature and frequency of observed events and, after thorough assessment, reasonable evidence of causal association with nivolumab.

Those events that the Sponsor identified with sufficient evidence to classify as SARs for the investigational product are listed by System Organ Class in [Table 1](#) and [Table 2](#). If a SAR is included in the tables but is not life-threatening or fatal (indicated by “N/A”) then the Sponsor would not consider a life-threatening or fatal occurrence to be expected. If a SAR is expected to be fatal, SARs of lesser severity (i.e. life-threatening) are also expected. The frequency of “All SARs” includes reported serious occurrences (including any life-threatening and fatal SARs that were observed in clinical studies).

Fatal outcomes are only included if described as such in Section 4.8 of the European SmPC for nivolumab and are expected only when indicated in the tables below.

The justification of newly added SARs, single occurrences, and expected fatal and/or life-threatening- SARs is provided following the SAR tables in this Appendix.

Frequency is defined using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

### NIVOLUMAB MONOTHERAPY

[Table 1](#) lists expected SARs for nivolumab monotherapy. The PTs and frequencies for all SARs in [Table 1](#) reflect only those observed with administration of nivolumab monotherapy. The total number of subjects (N) includes those who received nivolumab monotherapy.

**Table 1: Serious Adverse Reactions in Adult Patients Treated with Nivolumab Monotherapy Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 17,706)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
<b>Blood and lymphatic system disorders</b>	Autoimmune haemolytic anaemia <sup>a</sup>	Rare 2 (0.0113)	N/A	N/A
	Myocarditis	Rare 9 (0.0508)	3 (0.0169)	2 (0.0113)
<b>Cardiac disorders</b>	Pericardial effusion	Rare 7 (0.0395)	N/A	N/A
	Pericarditis	Rare 6 (0.0339)	N/A	N/A
	Atrial fibrillation	Rare 3 (0.0169)	N/A	N/A
	Arrhythmia	Rare 2 (0.0113)	N/A	N/A
	Immune-mediated myocarditis	Very Rare 1 (0.0056)	N/A	1 (0.0056)
	Ventricular arrhythmia	Very rare 1 (0.0056)	N/A	N/A
<b>Endocrine disorders</b>	Adrenal insufficiency	Uncommon 58 (0.3276)	N/A	N/A
	Hypophysitis	Uncommon 37 (0.209)	N/A	N/A
	Hyperglycaemia	Uncommon 36 (0.2033)	3 (0.0169)	N/A
	Hypothyroidism	Uncommon 25 (0.1412)	N/A	N/A
	Diabetic ketoacidosis	Uncommon 18 (0.1017)	4 (0.0226)	N/A
	Type 1 diabetes mellitus	Rare 14 (0.0791)	N/A	N/A
	Hyperthyroidism	Rare 13 (0.0734)	N/A	N/A
	Diabetes mellitus	Rare 12 (0.0678)	N/A	N/A



**Table 1: Serious Adverse Reactions in Adult Patients Treated with Nivolumab Monotherapy Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 17,706)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Hypopituitarism	Rare 12 (0.0678)	N/A	N/A
	Fulminant type 1 diabetes mellitus	Rare 4 (0.0226)	N/A	N/A
	Adrenocortical insufficiency acute	Rare 2 (0.0113)	N/A	N/A
	Autoimmune thyroiditis	Rare 2 (0.0113)	N/A	N/A
	Thyroiditis	Rare 2 (0.0113)	N/A	N/A
	Autoimmune hypothyroidism	Very rare 1 (0.0056)	N/A	N/A
	Immune-mediated hyperthyroidism	Very rare 1 (0.0056)	N/A	N/A
<b>Eye disorders</b>	Uveitis	Rare 5 (0.0282)	N/A	N/A
	Iridocyclitis	Rare 2 (0.0113)	N/A	N/A
	Orbital myositis <sup>a</sup>	Rare 2 (0.0113)	N/A	N/A
<b>Gastrointestinal disorders</b>	Colitis	Uncommon 102 (0.5761)	N/A	N/A
	Diarrhoea	Uncommon 100 (0.5648)	N/A	N/A
	Pancreatitis	Uncommon 28 (0.1581)	N/A	N/A
	Nausea	Uncommon 20 (0.113)	N/A	N/A
	Immune-mediated enterocolitis	Uncommon 19 (0.1073)	N/A	N/A
	Vomiting	Uncommon 19 (0.1073)	N/A	N/A
	Gastritis	Rare	N/A	N/A

**Table 1: Serious Adverse Reactions in Adult Patients Treated with Nivolumab Monotherapy Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 17,706)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
Gastrointestinal disorders	Stomatitis	14 (0.0791) Rare 10 (0.0565)	N/A	N/A
	Autoimmune colitis	Rare 9 (0.0508)	N/A	N/A
	Abdominal pain	Rare 8 (0.0452)	N/A	N/A
	Enteritis	Rare 6 (0.0339)	N/A	N/A
	Autoimmune pancreatitis	Rare 4 (0.0226)	N/A	N/A
	Enterocolitis	Rare 4 (0.0226)	N/A	N/A
	Pancreatitis acute	Rare 4 (0.0226)	N/A	N/A
	Colitis microscopic	Rare 3 (0.0169)	N/A	N/A
	Duodenitis	Rare 2 (0.0113)	N/A	N/A
	Gastroenteritis <sup>a</sup>	Rare 2 (0.0113)	N/A	N/A
	Constipation	Very rare 1 (0.0056)	N/A	N/A
	Immune-mediated pancreatitis	Very rare 1 (0.0056)	N/A	N/A
General disorders and administration site conditions	Pyrexia	Uncommon 53 (0.2993)	N/A	N/A
	Fatigue	Uncommon 31 (0.1751)	N/A	N/A
	Asthenia	Rare 10 (0.0565)	N/A	N/A
	Mucosal inflammation	Rare 5 (0.0282)	N/A	N/A

**Table 1: Serious Adverse Reactions in Adult Patients Treated with Nivolumab Monotherapy Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 17,706)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Chills	Rare 4 (0.0226)	N/A	N/A
	Oedema peripheral	Rare 3 (0.0169)	1 (0.0056)	N/A
<b>Hepatobiliary disorders</b>	Autoimmune hepatitis	Uncommon 24 (0.1355)	N/A	N/A
	Hepatitis	Uncommon 21 (0.1186)	N/A	N/A
	Immune-mediated hepatitis	Rare 14 (0.0791)	N/A	N/A
	Hypertransaminasemia	Rare 11 (0.0621)	N/A	N/A
	Drug-induced liver injury	Rare 10 (0.0565)	N/A	N/A
	Hepatitis acute	Rare 6 (0.0339)	N/A	N/A
	Hyperbilirubinaemia	Rare 2 (0.0113)	N/A	N/A
<b>Immune system disorders</b>	Infusion related reaction	Uncommon 35 (0.1977)	2 (0.0113)	N/A
	Hypersensitivity	Rare 7 (0.0395)	N/A	N/A
	Anaphylactic reaction	Rare 4 (0.0226)	1 (0.0056)	N/A
	Drug hypersensitivity	Rare 2 (0.0113)	N/A	N/A
	Sarcoidosis	Rare 2 (0.0113)	N/A	N/A
<b>Infections and infestations</b>	Bronchitis	Rare 2 (0.0113)	N/A	N/A
	Upper respiratory tract infection	Very rare 1 (0.0056)	N/A	N/A

**Table 1: Serious Adverse Reactions in Adult Patients Treated with Nivolumab Monotherapy Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 17,706)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
<b>Investigations</b>	Alanine aminotransferase increased	Uncommon 45 (0.2542)	N/A	N/A
	Aspartate aminotransferase increased	Uncommon 38 (0.2146)	N/A	N/A
	Lipase increased	Rare 15 (0.0847)	N/A	N/A
	Liver function test increased	Rare 8 (0.0452)	N/A	N/A
	Amylase increased	Rare 7 (0.0395)	N/A	N/A
	Blood bilirubin increased	Rare 7 (0.0395)	N/A	N/A
	Blood creatinine increased	Rare 6 (0.0339)	N/A	N/A
	Hepatic enzyme increased	Rare 6 (0.0339)	N/A	N/A
	Transaminases increased	Rare 6 (0.0339)	N/A	N/A
	Gamma-glutamyltransferase increased	Rare 5 (0.0282)	N/A	N/A
	Blood creatine phosphokinase increased	Rare 4 (0.0226)	N/A	N/A
	Blood alkaline phosphatase increased	Rare 2 (0.0113)	N/A	N/A
	Blood glucose increased	Rare 2 (0.0113)	N/A	N/A
<b>Metabolism and nutrition disorders</b>	Hyponatraemia	Uncommon 33 (0.1864)	N/A	N/A
	Dehydration	Rare 13 (0.0734)	N/A	N/A

**Table 1: Serious Adverse Reactions in Adult Patients Treated with Nivolumab Monotherapy Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 17,706)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Decreased appetite	Rare 8 (0.0452)	N/A	N/A
	Hyperglycaemic hyperosmolar nonketotic syndrome	Rare 2 (0.0113)	N/A	N/A
<b>Musculoskeletal and connective tissue disorders</b>	Myositis	Rare 16 (0.0904)	1 (0.0056)	2 (0.0113)
	Arthritis	Rare 7 (0.0395)	N/A	N/A
	Polyarthrititis	Rare 7 (0.0395)	N/A	N/A
	Arthralgia	Rare 6 (0.0339)	N/A	N/A
	Myalgia	Rare 3 (0.0169)	N/A	N/A
	Rhabdomyolysis	Rare 3 (0.0169)	N/A	2 (0.0113)
	Polymyalgia rheumatica	Rare 2 (0.0113)	N/A	N/A
	Polymyositis	Rare 2 (0.0113)	N/A	N/A
<b>Nervous system disorders</b>	Encephalitis	Rare 8 (0.0452)	N/A	2 (0.0113)
	Headache	Rare 7 (0.0395)	N/A	N/A
	Myasthenia gravis	Rare 5 (0.0282)	N/A	N/A
	Guillain-Barre syndrome	Rare 4 (0.0226)	N/A	N/A
	Dizziness	Rare 3 (0.0169)	N/A	N/A
	Myasthenic syndrome	Rare 3 (0.0169)	N/A	N/A

**Table 1: Serious Adverse Reactions in Adult Patients Treated with Nivolumab Monotherapy Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 17,706)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Neuropathy peripheral	Rare 3 (0.0169)	N/A	N/A
	Peripheral motor neuropathy	Rare 3 (0.0169)	N/A	N/A
	Polyneuropathy	Rare 3 (0.0169)	N/A	N/A
	Demyelination	Rare 2 (0.0113)	N/A	N/A
	Encephalitis autoimmune <sup>a</sup>	Rare 2 (0.0113)	N/A	N/A
	Peripheral sensory neuropathy	Rare 2 (0.0113)	N/A	N/A
	Immune-mediated encephalitis <sup>a</sup>	Very rare 1 (0.0056)	N/A	N/A
<b>Renal and urinary disorders</b>	Acute kidney injury	Uncommon 37 (0.209)	3 (0.0169)	N/A
	Tubulointerstitial nephritis	Rare 15 (0.0847)	N/A	N/A
	Nephritis	Rare 5 (0.0282)	N/A	N/A
	Renal failure	Rare 5 (0.0282)	N/A	N/A
	Autoimmune nephritis	Rare 4 (0.0226)	N/A	N/A
	Immune-mediated nephritis	Rare 2 (0.0113)	N/A	N/A
<b>Respiratory, thoracic and mediastinal disorders</b>	Pneumonitis	Common 259 (1.4628)	13 (0.0734)	19 (0.1073)
	Interstitial lung disease	Uncommon 66 (0.3728)	N/A	N/A
	Dyspnoea	Uncommon 33 (0.1864)	1 (0.0056)	N/A

**Table 1: Serious Adverse Reactions in Adult Patients Treated with Nivolumab Monotherapy Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 17,706)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
Skin and subcutaneous tissue disorders	Immune-mediated lung disease	Rare 13 (0.0734)	N/A	N/A
	Respiratory failure	Rare 11 (0.0621)	N/A	N/A
	Organising pneumonia	Rare 5 (0.0282)	N/A	N/A
	Cough	Rare 4 (0.0226)	N/A	N/A
	Pemphigoid	Rare 11 (0.0621)	N/A	N/A
	Rash maculo-papular	Rare 9 (0.0508)	N/A	N/A
	Psoriasis	Rare 5 (0.0282)	N/A	N/A
	Stevens-Johnson syndrome	Rare 5 (0.0282)	N/A	N/A
	Dermatitis	Rare 4 (0.0226)	N/A	N/A
	Erythema multiforme	Rare 4 (0.0226)	N/A	N/A
	Drug eruption	Rare 3 (0.0169)	N/A	N/A
	Pruritus	Rare 3 (0.0169)	N/A	N/A
	Rash papular	Rare 2 (0.0113)	N/A	N/A
	Rash pustular	Rare 2 (0.0113)	N/A	N/A
	Toxic epidermal necrolysis	Rare 2 (0.0113)	1 (0.0056)	1 (0.0056)
	Rash macular	Very rare 1 (0.0056)	N/A	N/A

**Table 1:** Serious Adverse Reactions in Adult Patients Treated with Nivolumab Monotherapy Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 17,706)

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Rash pruritic	Very rare 1 (0.0056)	N/A	N/A
<b>Vascular disorders</b>	Hypotension	Rare 7 (0.0395)	N/A	N/A

<sup>a</sup> SAR not included in previous IB version 22.

## NIVOLUMAB IN COMBINATION WITH IPILIMUMAB

Table 2 lists expected SARs for nivolumab in combination with ipilimumab. Expected SARs for nivolumab (as described in Table 1) are expected for the combination as a causal relationship between the component drug of the combination and the SAR has been established. Therefore, the PTs and frequencies for all SARs in Table 2 reflect those observed with administration of nivolumab alone and those in combination with ipilimumab. The total number of subjects (N) includes those who received nivolumab alone as well as those who received combination therapy with nivolumab and ipilimumab.

**Table 2:** Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
<b>Blood and lymphatic system disorders</b>	Immune thrombocytopenia <sup>a</sup>	Rare 7 (0.0237)	N/A	N/A
	Autoimmune haemolytic anaemia	Rare 4 (0.0135)	N/A	N/A
	Haemophagocytic lymphohistiocytosis	Rare 4 (0.0135)	N/A	N/A
<b>Cardiac disorders</b>	Myocarditis	Uncommon 38 (0.1285)	8 (0.0271)	15 (0.0507)
	Atrial fibrillation	Rare	N/A	N/A



**Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Pericardial effusion	14 (0.0473) Rare 12 (0.0406)	N/A	N/A
	Pericarditis	Rare 10 (0.0338)	N/A	N/A
	Immune-mediated myocarditis	Rare 6 (0.0203)	N/A	3 (0.0101)
	Arrhythmia	Rare 3 (0.0101)	N/A	N/A
	Ventricular arrhythmia	Very rare 2 (0.0068)	N/A	N/A
<b>Endocrine disorders</b>	Adrenal insufficiency	Uncommon 245 (0.8285)	7 (0.0237)	N/A
	Hypophysitis	Uncommon 209 (0.7067)	N/A	N/A
	Hyperthyroidism	Uncommon 77 (0.2604)	N/A	N/A
	Hyperglycaemia	Uncommon 74 (0.2502)	6 (0.0203)	N/A
	Hypopituitarism	Uncommon 58 (0.1961)	N/A	N/A
	Type 1 diabetes mellitus	Uncommon 58 (0.1961)	N/A	N/A
	Hypothyroidism	Uncommon 57 (0.1927)	N/A	N/A
	Diabetic ketoacidosis	Uncommon 45 (0.1522)	10 (0.0338)	N/A
	Diabetes mellitus	Rare 29 (0.0981)	N/A	N/A
	Thyroiditis	Rare 26 (0.0879)	N/A	N/A
	Autoimmune thyroiditis	Rare 14 (0.0473)	N/A	N/A

**Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Adrenocortical insufficiency acute	Rare 11 (0.0372)	N/A	N/A
	Fulminant type 1 diabetes mellitus	Rare 7 (0.0237)	N/A	N/A
	Immune-mediated hypophysitis	Rare 6 (0.0203)	N/A	N/A
	Immune-mediated adrenal insufficiency	Rare 3 (0.0101)	N/A	N/A
	Immune-mediated hyperthyroidism	Rare 3 (0.0101)	N/A	N/A
	Autoimmune hypothyroidism	Very rare 2 (0.0068)	N/A	N/A
	Hyperglycaemic hyperosmolar nonketotic syndrome	Very rare 2 (0.0068)	N/A	N/A
<b>Eye disorders</b>	Uveitis	Rare 12 (0.0406)	N/A	N/A
	Diplopia	Rare 5 (0.0169)	N/A	N/A
	Orbital myositis	Rare 4 (0.0135)	N/A	N/A
	Iridocyclitis	Very rare 2 (0.0068)	N/A	N/A
	Vision blurred	Very rare 2 (0.0068)	N/A	N/A
<b>Gastrointestinal disorders</b>	Colitis	Common 568 (1.9207)	10 (0.0338)	4 (0.0135)
	Diarrhoea	Common 531 (1.7956)	N/A	N/A
	Immune-mediated enterocolitis	Uncommon 120 (0.4058)	N/A	N/A
	Vomiting	Uncommon 107 (0.3618)	N/A	N/A

**Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Pancreatitis	Uncommon 85 (0.2874)	N/A	N/A
	Nausea	Uncommon 76 (0.257)	N/A	N/A
	Autoimmune colitis	Uncommon 60 (0.2029)	N/A	N/A
	Gastritis	Uncommon 40 (0.1353)	N/A	N/A
	Enterocolitis	Uncommon 32 (0.1082)	N/A	N/A
	Abdominal pain	Rare 27 (0.0913)	N/A	N/A
	Enteritis	Rare 27 (0.0913)	N/A	N/A
	Stomatitis	Rare 15 (0.0507)	N/A	N/A
	Gastroenteritis <sup>a</sup>	Rare 10 (0.0338)	N/A	N/A
	Pancreatitis acute	Rare 10 (0.0338)	N/A	N/A
	Autoimmune pancreatitis	Rare 8 (0.0271)	N/A	N/A
	Colitis microscopic	Rare 5 (0.0169)	N/A	N/A
	Constipation	Rare 5 (0.0169)	N/A	N/A
	Duodenitis	Rare 5 (0.0169)	N/A	N/A
	Immune-mediated gastritis	Rare 4 (0.0135)	N/A	N/A
	Immune-mediated pancreatitis	Rare 4 (0.0135)	N/A	N/A
	Intestinal perforation	Rare	N/A	N/A

**Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
		4 (0.0135)		
<b>General disorders and administration site conditions</b>	Pyrexia	Uncommon 220 (0.7439)	N/A	N/A
	Fatigue	Uncommon 91 (0.3077)	N/A	N/A
	Asthenia	Rare 28 (0.0947)	N/A	N/A
	Mucosal inflammation	Rare 9 (0.0304)	N/A	N/A
	Chills	Rare 8 (0.0271)	N/A	N/A
	Oedema peripheral	Rare 7 (0.0237)	N/A	N/A
<b>Hepatobiliary disorders</b>	Autoimmune hepatitis	Uncommon 134 (0.4531)	N/A	N/A
	Hepatitis	Uncommon 107 (0.3618)	N/A	N/A
	Immune-mediated hepatitis	Uncommon 88 (0.2976)	N/A	N/A
	Hypertransaminasaemia	Uncommon 51 (0.1725)	N/A	N/A
	Drug-induced liver injury	Uncommon 38 (0.1285)	N/A	N/A
	Hepatitis acute	Rare 16 (0.0541)	N/A	N/A
	Hyperbilirubinaemia	Rare 6 (0.0203)	N/A	N/A
<b>Immune system disorders</b>	Infusion related reaction	Uncommon 64 (0.2164)	N/A	N/A
	Sarcoidosis	Rare 15 (0.0507)	N/A	N/A
	Hypersensitivity	Rare 10 (0.0338)	N/A	N/A

**Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Autoimmune disorder	Rare 7 (0.0237)	N/A	N/A
	Anaphylactic reaction	Rare 6 (0.0203)	N/A	N/A
	Drug hypersensitivity	Rare 4 (0.0135)	N/A	N/A
	Infusion related hypersensitivity reaction	Very rare 2 (0.0068)	N/A	N/A
<b>Infections and infestations</b>	Upper respiratory tract infection	Rare 4 (0.0135)	N/A	N/A
	Bronchitis	Rare 3 (0.0101)	N/A	N/A
<b>Investigations</b>	Alanine aminotransferase increased	Uncommon 165 (0.5579)	N/A	N/A
	Aspartate aminotransferase increased	Uncommon 125 (0.4227)	N/A	N/A
	Lipase increased	Uncommon 51 (0.1725)	N/A	N/A
	Blood creatinine increased	Uncommon 31 (0.1048)	N/A	N/A
	Liver function test increased	Rare 25 (0.0845)	N/A	N/A
	Amylase increased	Rare 22 (0.0744)	N/A	N/A
	Transaminases increased	Rare 22 (0.0744)	N/A	N/A
	Blood bilirubin increased	Rare 21 (0.071)	N/A	N/A
	Hepatic enzyme increased	Rare 20 (0.0676)	N/A	N/A

**Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Blood alkaline phosphatase increased	Rare 8 (0.0271)	N/A	N/A
	Gamma-glutamyltransferase increased	Rare 8 (0.0271)	N/A	N/A
	Blood creatine phosphokinase increased	Rare 7 (0.0237)	N/A	N/A
	Blood glucose increased	Very rare 2 (0.0068)	N/A	N/A
<b>Metabolism and nutrition disorders</b>	Hyponatraemia	Uncommon 94 (0.3179)	N/A	N/A
	Dehydration	Uncommon 51 (0.1725)	N/A	N/A
	Decreased appetite	Rare 25 (0.0845)	N/A	N/A
	Tumour lysis syndrome <sup>a</sup>	Rare 3 (0.0101)	N/A	N/A
<b>Musculoskeletal and connective tissue disorders</b>	Myositis	Uncommon 43 (0.1454)	2 (0.0068)	3 (0.0101)
	Arthralgia	Rare 22 (0.0744)	N/A	N/A
	Arthritis	Rare 21 (0.071)	N/A	N/A
	Rhabdomyolysis	Rare 15 (0.0507)	3 (0.0101)	5 (0.0169)
	Myalgia	Rare 11 (0.0372)	N/A	N/A
	Polyarthritis	Rare 11 (0.0372)	N/A	N/A
	Polymyalgia rheumatica	Rare 5 (0.0169)	N/A	N/A

**Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Pain in extremity	Rare 4 (0.0135)	N/A	N/A
	Polymyositis	Rare 4 (0.0135)	N/A	N/A
	Autoimmune arthritis	Rare 3 (0.0101)	N/A	N/A
	Back pain	Rare 3 (0.0101)	N/A	N/A
	Immune-mediated myositis	Rare 3 (0.0101)	N/A	N/A
	Autoimmune myositis	Very rare 2 (0.0068)	N/A	N/A
	Immune-mediated arthritis	Very rare 2 (0.0068)	N/A	N/A
<b>Nervous system disorders</b>	Encephalitis	Uncommon 35 (0.1184)	1 (0.0034)	6 (0.0203)
	Headache	Uncommon 34 (0.115)	N/A	N/A
	Myasthenia gravis	Rare 17 (0.0575)	N/A	N/A
	Encephalitis autoimmune	Rare 14 (0.0473)	N/A	N/A
	Guillain-Barre syndrome	Rare 14 (0.0473)	N/A	N/A
	Meningitis aseptic	Rare 13 (0.044)	N/A	N/A
	Peripheral sensory neuropathy	Rare 13 (0.044)	N/A	N/A
	Neuropathy peripheral	Rare 10 (0.0338)	N/A	N/A
	Polyneuropathy	Rare 9 (0.0304)	N/A	N/A

**Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
	Immune-mediated encephalitis	Rare 8 (0.0271)	N/A	N/A
	Myasthenic syndrome	Rare 7 (0.0237)	N/A	N/A
	Peripheral motor neuropathy	Rare 7 (0.0237)	N/A	N/A
	Dizziness	Rare 6 (0.0203)	N/A	N/A
	Meningitis	Rare 5 (0.0169)	N/A	N/A
	Autoimmune neuropathy	Rare 3 (0.0101)	N/A	N/A
	Demyelination	Very rare 2 (0.0068)	N/A	N/A
	Myelitis <sup>a</sup>	Very rare 2 (0.0068)	N/A	N/A
	Myelitis transverse <sup>a</sup>	Very rare 2 (0.0068)	N/A	N/A
<b>Renal and urinary disorders</b>	Acute kidney injury	Uncommon 123 (0.4159)	7 (0.0237)	5 (0.0169)
	Tubulointerstitial nephritis	Rare 28 (0.0947)	N/A	N/A
	Renal failure	Rare 25 (0.0845)	N/A	N/A
	Nephritis	Rare 15 (0.0507)	N/A	N/A
	Autoimmune nephritis	Rare 12 (0.0406)	N/A	N/A
	Immune-mediated nephritis	Rare 5 (0.0169)	N/A	N/A
<b>Respiratory, thoracic and</b>	Pneumonitis	Common 588 (1.9883)	21 (0.071)	43 (0.1454)



**Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
<b>mediastinal disorders</b>	Interstitial lung disease	Uncommon 102 (0.3449)	N/A	N/A
	Dyspnoea	Uncommon 75 (0.2536)	N/A	N/A
	Immune-mediated lung disease	Uncommon 31 (0.1048)	N/A	N/A
	Respiratory failure	Rare 17 (0.0575)	N/A	N/A
	Cough	Rare 8 (0.0271)	N/A	N/A
	Organising pneumonia	Rare 7 (0.0237)	N/A	N/A
<b>Skin and subcutaneous tissue disorders</b>	Rash maculo-papular	Uncommon 41 (0.1386)	N/A	N/A
	Pemphigoid	Rare 19 (0.0642)	N/A	N/A
	Drug eruption	Rare 9 (0.0304)	N/A	N/A
	Pruritus	Rare 9 (0.0304)	N/A	N/A
	Psoriasis	Rare 9 (0.0304)	N/A	N/A
	Stevens-Johnson syndrome	Rare 8 (0.0271)	N/A	N/A
	Dermatitis	Rare 7 (0.0237)	N/A	N/A
	Erythema multiforme	Rare 6 (0.0203)	N/A	N/A
	Toxic epidermal necrolysis	Rare 4 (0.0135)	1 (0.0034)	2 (0.0068)
	Rash pustular	Rare 3 (0.0101)	N/A	N/A
	Rash macular	Very rare	N/A	N/A

**Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purposes (Number of Subjects Dosed = 29,573)**

System Organ Class	Preferred Term	Frequency of All SARs N (%)	Occurrence of Life-Threatening SARs N (%)	Occurrence of Fatal SARs N (%)
		2 (0.0068) Very rare		
	Rash papular	2 (0.0068)	N/A	N/A
	Rash pruritic	Very rare 2 (0.0068)	N/A	N/A
<b>Vascular disorders</b>	Hypotension	Rare 24 (0.0812)	N/A	N/A

<sup>a</sup> SAR not included in previous IB version 22.

## NIVOLUMAB IN PEDIATRIC SUBJECTS

Any SARs reported from ongoing pediatric studies will be considered as unexpected for expedited reporting purposes.

## EXPLANATION OF CHANGES TO THE REFERENCE SAFETY INFORMATION

This section describes the changes to the RSI since the last update of nivolumab IB version 22. SARs that have been newly added to IB version 23 are denoted with an 'a' in [Table 1](#) and [Table 2](#).

As described in the prior IB version 22, the Opdivo EU SmPC was updated and no longer includes footnotes designating "life-threatening" ADRs in Section 4.8. The life-threatening SARs as described in [Table 1](#) and [Table 2](#) above are consistent with IB version 22 and with the Company's assessment based on clinical trial experience, nivolumab mechanism of action, and safety evaluations.

A detailed description of new SARs, removed SARs, SARs with a single occurrence or changed SARs (eg, due to frequency, severity, MedDRA versioning) and fatal SARs is provided below.

### **Table 1: Serious Adverse Reactions in Adults Treated with Nivolumab Considered Expected for Safety Reporting Purposes**

The following SARs were added to Table 1 for nivolumab monotherapy:

Autoimmune haemolytic anaemia (AHA) is a rare blood cell disorder that develops when the immune system makes antibodies that attack and destroy the red blood cells. Information reported in the scientific literature reflects the severity of AHA and complete resolution in most cases after red blood cell transfusion, corticosteroid treatment, and, when necessary, treatment with additional immunosuppressive therapy such as rituximab. Autoimmune hemolytic anemia has been reported in patients treated with nivolumab and nivolumab in combination with ipilimumab. Based on a

comprehensive evaluation of individual cases retrieved from the safety database, scientific literature review, and biological plausibility, BMS has concluded that AHA is an adverse drug reaction (ADR) with nivolumab and nivolumab in combination with ipilimumab and is listed in Section 4.8 Undesirable effects of the Opdivo SmPC. Autoimmune haemolytic anaemia has been added as a SAR for nivolumab monotherapy in [Table 1](#) based on this evaluation and a frequency of 2 (0.0113%) in pooled clinical trials.

Orbital myositis is consistent with muscular inflammation and the existing expected SAR Myositis. Literature reports showed extraocular muscles can be selectively involved in autoimmune processes as part of immune checkpoint inhibitor irAEs, suggesting that isolated ocular myositis during treatment represents a subgroup of generalized immune related myositis with predominant ocular symptoms.<sup>1</sup> Orbital myositis has been included in [Table 2](#) as a SAR for nivolumab in combination with ipilimumab in prior versions of the IB. Based on a frequency of 2 (0.0113%) in pooled clinical trials, it is also being added as a SAR in [Table 1](#).

The PT Gastroenteritis is added as a new SAR as it is consistent with other expected SARs describing mucosal inflammation (including gastritis and enteritis) and reflects the known immune-mediated inflammation caused by nivolumab in the gastrointestinal tract.

The PTs Encephalitis autoimmune and Immune-mediated encephalitis have been added as SARs as they are consistent with the existing SAR encephalitis (which is described in the nivolumab CCDS and other reference documents) and represent a more specific description of the immune-mediated mechanism by which nivolumab is causally associated with the event. Immune-mediated encephalitis has been included despite the low frequency of this SAR as it is consistent with existing SARs and the known immune-mediated mechanism by which nivolumab is causally associated with the event.

The following single occurrence SARs have been included in prior versions of the nivolumab IB RSI based on mechanism of action, known class effects, scientific literature, and/or clinical trial experience:

Ventricular arrhythmia is a Very rare SAR for nivolumab monotherapy and for nivolumab in combination with ipilimumab. The Opdivo SmPC lists “Arrhythmia (including ventricular arrhythmia)” in Section 4.8 as adverse reactions with nivolumab monotherapy and with nivolumab in combination with ipilimumab, which was supported by a pooled data analysis across several completed nivolumab clinical trials across multiple tumor types. Therefore, ventricular arrhythmia, which was present as a SAR in nivolumab IB version 21, remains as a SAR in nivolumab IB version 22 despite the low frequency.

Immune-mediated myocarditis is consistent with PTs describing the SAR of myocarditis which is an established immune-mediated reaction associated with nivolumab and is described in the Opdivo SmPC Section 4.4 Special warnings and precautions for use, and Section 4.8 Undesirable effects and with existing SARs.

Autoimmune hypothyroidism is one of the known endocrinopathies observed with administration of nivolumab. Hypothyroidism has previously been included as a SAR for

nivolumab alone and with nivolumab in combination with ipilimumab. The Opdivo SmPC describes hypothyroidism in Section 4.4 and Section 4.8 for both nivolumab alone and nivolumab in combination with ipilimumab. In addition, the PTs “Hypothyroidism” and “Autoimmune hypothyroidism” map to the same High-Level Term (HLT) of Thyroid hypofunction disorders. Therefore, based on the mechanism by which nivolumab is causally associated with the event of hypothyroidism as well as the MedDRA structure, the terms are considered to be synonyms, and Autoimmune hypothyroidism is considered an expected SAR despite the low frequency.

Immune-mediated hyperthyroidism is one of the known endocrinopathies observed with administration of nivolumab. Hyperthyroidism has previously been included as a SAR for nivolumab alone and in combination with ipilimumab. The Opdivo SmPC describes hyperthyroidism in Section 4.4 and Section 4.8 for both nivolumab alone and nivolumab in combination with ipilimumab. In addition, the PTs “Hyperthyroidism” and “Autoimmune hyperthyroidism” map to the same High-Level Term (HLT) of Thyroid hyperfunction disorders. Therefore, based on the mechanism by which nivolumab is causally associated with the event of hyperthyroidism as well as the MedDRA structure, the terms are considered to be synonyms, and Immune-mediated hyperthyroidism is considered an expected SAR despite the low frequency.

Constipation is listed in Section 4.8 of the Opdivo SmPC as an ADR for nivolumab alone and in combination with ipilimumab. Constipation is a gastrointestinal disorder, which is established as an adverse drug reaction (ADR) for both nivolumab and ipilimumab. Constipation is also described in Section 5 of this nivolumab IB version 22.

Immune-mediated pancreatitis, despite low frequency, is consistent with known immune-mediated reactions associated with nivolumab as described in the Opdivo SmPC Section 4.4 Special warnings and precautions for use, and Section 4.8 Undesirable effects and with existing SARs (eg Pancreatitis, Pancreatitis autoimmune).

Rash macular and rash pruritic are immune-related skin adverse reactions which are part of the known safety profile of nivolumab. Serious skin reactions, including various forms of rash, are well described throughout the nivolumab product information (labels, risk management plan, etc.). Section 4.8 of the Opdivo SmPC includes both PTs as ADRs for nivolumab alone and nivolumab in combination with nivolumab. Therefore, despite the low frequency in pooled data from nivolumab clinical trials, these events are considered expected for expedited safety reporting purposes.

Upper respiratory tract infection was a SAR in IB version 21 with a frequency of 2 (0.0125%) in nivolumab monotherapy. Due to changes in clinical data reporting and MedDRA, the frequency changed to 1. This event is described in other sections of this IB as well as in Section 4.8 of the Opdivo SmPC as an ADR.

Fatal outcomes are only included if described as such in Section 4.8 of the Opdivo SmPC and are expected only when indicated by a frequency in the respective column in the tables above. Life-threatening Toxic epidermal necrolysis (TEN) is expected (n=1). TEN with a fatal outcome is

included in the Opdivo SmPC for both nivolumab monotherapy and nivolumab in combination with ipilimumab. Encephalitis with a fatal outcome is described in the SmPC for nivolumab monotherapy, and thus fatal outcomes have been included in [Table 1](#).

Myocarditis with a fatal outcome is described within the nivolumab SmPC Section 4.8 and was included in prior RSI tables for nivolumab monotherapy and in combination with ipilimumab. The additional specifier “immune-mediated” is consistent with the already described myocarditis since it is a known immune-mediated reaction associated with nivolumab monotherapy and nivolumab in combination with ipilimumab. Therefore immune-mediated myocarditis with a fatal outcome has been included in the nivolumab monotherapy table (n=1).

## **Table 2: Serious Adverse Reactions in Adults Treated with Nivolumab and Nivolumab in Combination with Ipilimumab Considered Expected for Safety Reporting Purpose**

All events established as SARs for nivolumab monotherapy (as reflected in [Table 1](#)) are expected for nivolumab in combination with ipilimumab. Therefore, SARs listed in [Table 2](#) reflect those that have been observed in patients who received nivolumab monotherapy and in patients who received ipilimumab in combination with nivolumab.

The following SARs were added to [Table 2](#) for nivolumab in combination with ipilimumab:

Immune thrombocytopenia was added as a SAR and describes autoimmune mechanism by which nivolumab may be associated with thrombocytopenia (as described in Section 4.8 of the EU SmPC).

As described above, the PT Gastroenteritis is added as a new SAR in Table 2 as it is consistent with other expected SARS describing mucosal inflammation (including enteritis) and reflects the known immune-mediated inflammation caused by nivolumab in combination with ipilimumab in the gastrointestinal tract.

Myelitis and Myelitis transverse are rare neurologic immune-mediated reactions and were added as SARs for nivolumab in combination with following a comprehensive analysis of diagnostic details, clinical presentation, response to immunomodulators, and any potentially confounding factors. Based on the review of the data and given the biological plausibility of ICI therapy to be associated with myelitis and myelitis transverse, these terms were added to Section 4.4 Special warnings and precautions for use, and Section 4.8 Undesirable effects of the Opdivo SmPC.

Tumour lysis syndrome (TLS) describes the range of metabolic complications caused by the rapid and extensive release of cellular constituents upon the lysis of malignant cells. Although a specific mechanism by which nivolumab causes TLS has not been elucidated, TLS has been observed with cytotoxic therapies, including ICIs. TLS is listed in Section 4.8 Undesirable effects of the Opdivo SmPC as well as the Yervoy SmPC and has been added as a SAR to Table 2 based on observed events in clinical trial subjects receiving nivolumab in combination with ipilimumab.

Fatal outcomes are only included if described as such in Section 4.8 of the Opdivo SmPC and are expected only when indicated by a frequency in the respective column in the tables above. Life-

threatening Toxic epidermal necrolysis (TEN) is included in [Table 2](#) nivolumab in combination with ipilimumab. TEN with a fatal outcome is included in the Opdivo SmPC for both nivolumab monotherapy and nivolumab in combination with ipilimumab.

## REFERENCES

- <sup>1</sup> Garibaldi M, Calabrò F, Merlonghi G, et al. Immune checkpoint inhibitors (ICIs)-related ocular myositis. *Neuromuscul Disord* 2020; 30(5): 420-423.

## **Appendix 2: US Product Information**

54 page(s) excluding cover page



## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OPDIVO safely and effectively. See full prescribing information for OPDIVO.

### OPDIVO® (nivolumab) injection, for intravenous use

Initial U.S. Approval: 2014

#### RECENT MAJOR CHANGES

Indications and Usage (1)	3/2024
Dosage and Administration (2)	3/2024
Warnings and Precautions (5.1)	3/2024

#### INDICATIONS AND USAGE

OPDIVO is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of:

##### Melanoma

- adult and pediatric (12 years and older) patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab. (1.1)
- for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma. (1.2)

##### Non-Small Cell Lung Cancer (NSCLC)

- adult patients with resectable (tumors  $\geq 4$  cm or node positive) non-small cell lung cancer in the neoadjuvant setting, in combination with platinum-doublet chemotherapy. (1.3)
- adult patients with metastatic non-small cell lung cancer expressing PD-L1 ( $\geq 1\%$ ) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab. (1.4)
- adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy. (1.4)
- adult patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. (1.4)

##### Malignant Pleural Mesothelioma

- adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab. (1.5)

##### Renal Cell Carcinoma (RCC)

- adult patients with intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment in combination with ipilimumab. (1.6)
- adult patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib. (1.6)
- adult patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.6)

##### Classical Hodgkin Lymphoma (cHL)

- adult patients with classical Hodgkin lymphoma that has relapsed or progressed after<sup>a</sup>: (1.7)
  - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy that includes autologous HSCT.

##### Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy. (1.8)

##### Urothelial Carcinoma

- adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC. (1.9)
- adult patients with unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine. (1.9)
- adult patients with locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy.
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.9)

##### Colorectal Cancer

- adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.<sup>a</sup> (1.10)

##### Hepatocellular Carcinoma (HCC)

- adult patients with hepatocellular carcinoma who have been previously treated with sorafenib in combination with ipilimumab.<sup>a</sup> (1.11)

##### Esophageal Cancer

- adult patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT). (1.12)
- adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy. (1.12)
- adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with ipilimumab. (1.12)

- adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy. (1.12)

##### Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy. (1.13)

<sup>a</sup> This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

#### DOSAGE AND ADMINISTRATION

- Administer by intravenous infusion after dilution based upon recommended infusion rate for each indication. (2)
- Unresectable or metastatic melanoma
  - Adult and pediatric patients weighing 40 kg or greater: 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - Pediatric patients weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. (2.2)
  - Adult and pediatric patients weighing 40 kg or greater: 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - Pediatric patients weighing less than 40 kg: 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. (2.2)
- Adjuvant treatment of melanoma
  - Adult and pediatric patients weighing 40 kg or greater: 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - Pediatric patients weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks (2.2)
- Neoadjuvant treatment of resectable (tumors  $\geq 4$  cm or node positive) non-small cell lung cancer
  - 360 mg with platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles. (2.2)
- Metastatic non-small cell lung cancer
  - 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks. (2.2)
  - 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy. (2.2)
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Malignant pleural mesothelioma
  - 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks. (2.2)
- Advanced renal cell carcinoma
  - 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - 240 mg every 2 weeks or 480 mg every 4 weeks administered in combination with cabozantinib 40 mg once daily without food. (2.2)
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Classical Hodgkin lymphoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Recurrent or metastatic squamous cell carcinoma of the head and neck
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Adjuvant treatment of urothelial carcinoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- First-line unresectable or metastatic urothelial carcinoma
  - 360 mg every 3 weeks with cisplatin and gemcitabine on the same day for up to 6 cycles, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Previously treated locally advanced or metastatic urothelial carcinoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
  - Adult and pediatric patients weighing 40 kg or greater: 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - Pediatric patients weighing less than 40 kg: 3 mg/kg every 2 weeks. (2.2)
  - Adult and pediatric patients weighing 40 kg or greater: 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Hepatocellular carcinoma
  - 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Adjuvant treatment of resected esophageal or gastroesophageal cancer
  - 240 mg every 2 weeks or 480 mg every 4 weeks for total treatment duration of 1 year. (2.2)
- Esophageal squamous cell carcinoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks in combination with chemotherapy regimen of fluoropyrimidine- and platinum-containing chemotherapy. (2.2)

(Continued)

## HIGHLIGHTS OF PRESCRIBING INFORMATION (Continued)

- 3 mg/kg every 2 weeks or 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks. (2.2)
- 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC, GEJC, or EAC)
  - 360 mg every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks. (2.2)
  - 240 mg every 2 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks. (2.2)
- See full Prescribing Information for preparation and administration instructions and dosage modifications for adverse reactions.

### DOSAGE FORMS AND STRENGTHS

- Injection: 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), 120 mg/12 mL (10 mg/mL), and 240 mg/24 mL (10 mg/mL) solution in a single-dose vial. (3)

### CONTRAINDICATIONS

- None. (4)

### WARNINGS AND PRECAUTIONS

- Immune-Mediated Adverse Reactions: (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis and hepatotoxicity, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, and immune-mediated nephritis and renal dysfunction.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue based on severity and type of reaction. (2.3)
- Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue OPDIVO (nivolumab) based on severity of reaction. (5.2)
- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patient who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)

- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.5)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq 20\%$ ) in patients were:

- As a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, vomiting, and urinary tract infection. (6.1)
- In combination with ipilimumab: fatigue, diarrhea, rash, pruritus, nausea, musculoskeletal pain, pyrexia, cough, decreased appetite, vomiting, abdominal pain, dyspnea, upper respiratory tract infection, arthralgia, headache, hypothyroidism, constipation, decreased weight, and dizziness. (6.1)
- In combination with platinum-doublet chemotherapy: nausea, fatigue, musculoskeletal pain, constipation, decreased appetite, rash, vomiting, and peripheral neuropathy. (6.1)
- In combination with ipilimumab and platinum-doublet chemotherapy: fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus. (6.1)
- In combination with cabozantinib: diarrhea, fatigue, hepatotoxicity, palmar-plantar erythrodysesthesia syndrome, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection. (6.1)
- In combination with fluoropyrimidine- and platinum-containing chemotherapy: nausea, peripheral neuropathy, decreased appetite, fatigue, constipation, stomatitis, diarrhea, vomiting, abdominal pain, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2024

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\*Sections or subsections omitted from the full prescribing information are not listed.

**1 INDICATIONS AND USAGE****1.1 Unresectable or Metastatic Melanoma**

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

**1.2 Adjuvant Treatment of Melanoma**

OPDIVO is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

**1.3 Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer**

OPDIVO, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors  $\geq 4$  cm or node positive) non-small cell lung cancer (NSCLC).

**1.4 Metastatic Non-Small Cell Lung Cancer**

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 ( $\geq 1\%$ ) as determined by an FDA-approved test [see *Dosage and Administration* (2.1)], with no EGFR or ALK genomic tumor aberrations.
- OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.
- OPDIVO is indicated for the treatment of adult patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

**1.5 Malignant Pleural Mesothelioma**

OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

**1.6 Advanced Renal Cell Carcinoma**

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced RCC.
- OPDIVO, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced RCC.
- OPDIVO as a single agent is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

**1.7 Classical Hodgkin Lymphoma**

OPDIVO is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:

- autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- 3 or more lines of systemic therapy that includes autologous HSCT.

This indication is approved under accelerated approval based on overall response rate [see *Clinical Studies* (14.7)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**1.8 Squamous Cell Carcinoma of the Head and Neck**

OPDIVO is indicated for the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

**1.9 Urothelial Carcinoma**

OPDIVO is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC [see *Clinical Studies* (14.9)].

OPDIVO, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

OPDIVO is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy.
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

**1.10 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer**

OPDIVO, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on overall response rate and duration of response [see *Clinical Studies* (14.10)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**1.11 Hepatocellular Carcinoma**

OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall response rate and duration of response [see *Clinical Studies* (14.11)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

**1.12 Esophageal Cancer**

- OPDIVO is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).
- OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
- OPDIVO is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

**1.13 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma**

OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

**2 DOSAGE AND ADMINISTRATION****2.1 Patient Selection**

Select patients with metastatic NSCLC for treatment with OPDIVO in combination with ipilimumab based on PD-L1 expression [see *Clinical Studies* (14.4)].

Information on FDA-approved tests for the determination of PD-L1 expression in NSCLC is available at: <http://www.fda.gov/CompanionDiagnostics>.

**2.2 Recommended Dosage**

The recommended dosages of OPDIVO as a single agent are presented in Table 1.

**Table 1: Recommended Dosages for OPDIVO as a Single Agent**

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Metastatic non-small cell lung cancer	240 mg every 2 weeks* or 480 mg every 4 weeks*	Until disease progression or unacceptable toxicity
Advanced renal cell carcinoma		
Classical Hodgkin lymphoma		
Squamous cell carcinoma of the head and neck		
Locally advanced or metastatic urothelial carcinoma		
Esophageal squamous cell carcinoma		
Unresectable or metastatic melanoma	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks* or 480 mg every 4 weeks*	Until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks* or 6 mg/kg every 4 weeks*	

(Continued)

**Table 1: Recommended Dosages for OPDIVO as a Single Agent**  
(Continued)

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Adjuvant treatment of melanoma	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks*  or 480 mg every 4 weeks*	Until disease recurrence or unacceptable toxicity for up to 1 year
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks*  or 6 mg/kg every 4 weeks*	
Adjuvant treatment of urothelial carcinoma (UC)	240 mg every 2 weeks*  or 480 mg every 4 weeks*	Until disease recurrence or unacceptable toxicity for up to 1 year
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks*  or 480 mg every 4 weeks*	Until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks*	
Adjuvant treatment of resected esophageal or gastroesophageal junction cancer	240 mg every 2 weeks*  or 480 mg every 4 weeks*	Until disease progression or unacceptable toxicity for a total treatment duration of 1 year

\* 30-minute intravenous infusion.

The recommended dosages of OPDIVO in combination with other therapeutic agents are presented in Table 2. Refer to the respective Prescribing Information for each therapeutic agent administered in combination with OPDIVO for the recommended dosage information, as appropriate.

**Table 2: Recommended Dosages of OPDIVO in Combination with Other Therapeutic Agents**

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Unresectable or metastatic melanoma	1 mg/kg every 3 weeks* with ipilimumab 3 mg/kg intravenously*	In combination with ipilimumab for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier
	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks*  or 480 mg every 4 weeks*	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks*  or 6 mg/kg every 4 weeks*	
Neoadjuvant treatment of resectable non-small cell lung cancer	360 mg every 3 weeks* with platinum-doublet chemotherapy on the same day every 3 weeks	In combination with platinum-doublet chemotherapy for 3 cycles

(Continued)

**Table 2: Recommended Dosages of OPDIVO in Combination with Other Therapeutic Agents**  
(Continued)

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Metastatic non-small cell lung cancer expressing PD-L1	360 mg every 3 weeks* with ipilimumab 1 mg/kg every 6 weeks*	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
Metastatic or recurrent non-small cell lung cancer	360 mg every 3 weeks* with ipilimumab 1 mg/kg every 6 weeks* and histology-based platinum doublet chemotherapy every 3 weeks	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression  <b>2 cycles of histology-based platinum-doublet chemotherapy</b>
Malignant pleural mesothelioma	360 mg every 3 weeks* with ipilimumab 1 mg/kg every 6 weeks*	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
Advanced renal cell carcinoma	3 mg/kg every 3 weeks* with ipilimumab 1 mg/kg intravenously*	In combination with ipilimumab for 4 doses
	240 mg every 2 weeks*  or 480 mg every 4 weeks*	OPDIVO: Until disease progression, unacceptable toxicity, or up to 2 years
	Administer OPDIVO in combination with cabozantinib 40 mg orally once daily without food	Cabozantinib: Until disease progression or unacceptable toxicity
	240 mg every 2 weeks*  or 480 mg every 4 weeks*	After completing 4 doses of combination therapy with ipilimumab, administer as single agent until disease progression or unacceptable toxicity
First-line unresectable or metastatic urothelial carcinoma	360 mg every 3 weeks*  Administer OPDIVO in combination with cisplatin and gemcitabine on the same day every 3 weeks	In combination with cisplatin and gemcitabine for up to 6 cycles
	240 mg every 2 weeks*  or 480 mg every 4 weeks*	After completing up to 6 cycles of combination therapy, administer as single agent until disease progression, unacceptable toxicity, or up to 2 years from first dose
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	3 mg/kg every 3 weeks* with ipilimumab 1 mg/kg intravenously*	In combination with ipilimumab for 4 doses
	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks*  or 480 mg every 4 weeks*	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks*	

(Continued)



**Table 2: Recommended Dosages of OPDIVO in Combination with Other Therapeutic Agents**

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Hepatocellular carcinoma	1 mg/kg every 3 weeks* with ipilimumab 3 mg/kg intravenously*	In combination with ipilimumab for 4 doses
	240 mg every 2 weeks* or 480 mg every 4 weeks*	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
Esophageal squamous cell carcinoma	240 mg every 2 weeks* or 480 mg every 4 weeks* Administer OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy	OPDIVO: Until disease progression, unacceptable toxicity, or up to 2 years Chemotherapy: Until disease progression or unacceptable toxicity
	3 mg/kg every 2 weeks* or 360 mg every 3 weeks* with ipilimumab 1 mg/kg every 6 weeks*	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years
Gastric cancer, Gastroesophageal junction cancer, and Esophageal adenocarcinoma	240 mg every 2 weeks* with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks or 360 mg every 3 weeks* with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks	Until disease progression, unacceptable toxicity, or up to 2 years

\* 30-minute intravenous infusion on the same day.

### 2.3 Dose Modifications

No dose reduction for OPDIVO is recommended. In general, withhold OPDIVO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue OPDIVO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for OPDIVO or OPDIVO in combination for adverse reactions that require management different from these general guidelines are summarized in Table 3 and Table 4.

When OPDIVO is administered in combination with ipilimumab, withhold or permanently discontinue both ipilimumab and OPDIVO for an adverse reaction meeting these dose modification guidelines.

**Table 3: Recommended Dosage Modifications for Adverse Reactions**

Adverse Reaction	Severity	Dosage Modification
<b>Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]</b>		
Pneumonitis	Grade 2	Withhold <sup>a</sup>
	Grades 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold <sup>a</sup>
For colitis in patients treated with combination therapy with ipilimumab, see Table 4.	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST/ALT increases to >3 and ≤8 times ULN or Total bilirubin increases to >1.5 and ≤3 times ULN.	Withhold <sup>a</sup>
For liver enzyme elevations in patients treated with combination therapy with ipilimumab, see Table 4.	AST or ALT increases to >8 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue

(Continued)

**Table 3: Recommended Dosage Modifications for Adverse Reactions (Continued)**

Adverse Reaction	Severity	Dosage Modification
<b>Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]</b>		
Hepatitis with tumor involvement of the liver <sup>b</sup>  For liver enzyme elevations in patients treated with combination therapy with ipilimumab, see Table 4.	Baseline AST/ALT is >1 and ≤3 times ULN and increases to >5 and ≤10 times ULN or Baseline AST/ALT is >3 and ≤5 times ULN and increases to >8 and ≤10 times ULN.  AST/ALT increases to >10 times ULN or Total bilirubin increases to >3 times ULN.	Withhold <sup>a</sup>  Permanently discontinue
Endocrinopathies <sup>c</sup>	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold <sup>a</sup>
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold <sup>a</sup>
	Grade 3 or 4	Permanently discontinue
<b>Other Adverse Reactions</b>		
Infusion-Related Reactions [see Warnings and Precautions (5.2)]	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

<sup>a</sup> Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

<sup>b</sup> If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue OPDIVO based on recommendations for hepatitis with no liver involvement.

<sup>c</sup> Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

**Table 4: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with Combination Therapy**

Treatment	Adverse Reaction	Severity	Dosage Modification
OPDIVO in combination with ipilimumab	Colitis	Grade 2	Withhold <sup>a</sup>
		Grade 3 or 4	Permanently discontinue
	Hepatitis with no tumor involvement of the liver or Hepatitis with tumor involvement of the liver/non-HCC	AST/ALT increases to >3 times ULN and ≤5 times ULN or Total bilirubin increases to ≥1.5 and ≤3 times ULN.	Withhold <sup>a</sup>
		AST or ALT >5 times ULN or Total bilirubin >3 times ULN.	Permanently discontinue
	Hepatitis with tumor involvement of the liver <sup>b</sup> /HCC	Baseline AST/ALT is >1 and ≤3 times ULN and increases to >5 and ≤10 times ULN or Baseline AST/ALT is >3 and ≤5 times ULN and increases to >8 and ≤10 times ULN.	Withhold <sup>a</sup>
		AST/ALT increases to >10 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue
OPDIVO in combination with cabozantinib	Liver enzyme elevations	ALT or AST >3 times ULN but ≤10 times ULN with concurrent total bilirubin <2 times ULN	Withhold <sup>c</sup> both OPDIVO and cabozantinib until adverse reactions recover <sup>d</sup> to Grades 0-1
		ALT or AST >10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN	Permanently discontinue <sup>e</sup> both OPDIVO and cabozantinib

<sup>a</sup> Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

<sup>b</sup> If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue OPDIVO in combination with ipilimumab based on recommendations for hepatitis with no liver involvement.

<sup>c</sup> Consider corticosteroid therapy for hepatic adverse reactions if OPDIVO is withheld or discontinued when administered in combination with cabozantinib.

<sup>d</sup> After recovery, rechallenge with one or both of OPDIVO and cabozantinib may be considered. If rechallenging with cabozantinib with or without OPDIVO, refer to cabozantinib Prescribing Information.

## 2.4 Preparation and Administration

Visually inspect for particulate matter and discoloration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard if cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake.

### Preparation

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL.
  - For adult and pediatric patients with body weight 40 kg or greater, do not exceed a total volume of infusion of 160 mL.
  - For adult and pediatric patients with body weight less than 40 kg, do not exceed a total volume of infusion of 4 mL/kg of body weight.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.
- The product does not contain a preservative.

- After preparation, store the diluted solution either:

- at room temperature and room light for no more than 8 hours from the time of preparation to end of the infusion. Discard diluted solution if not used within 8 hours from the time of preparation; or
- under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light for no more than 7 days from the time of preparation to end of infusion. Discard diluted solution if not used within 7 days from the time of preparation.

- Do not freeze.

### Administration

- Administer the infusion, after dilution, over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).
- Administer OPDIVO in combination with other therapeutic agents as follows:
  - With ipilimumab: administer OPDIVO first followed by ipilimumab on the same day.
  - With platinum-doublet chemotherapy: administer OPDIVO first followed by platinum-doublet chemotherapy on the same day.
  - With ipilimumab and platinum-doublet chemotherapy: administer OPDIVO first followed by ipilimumab and then platinum-doublet chemotherapy on the same day.
  - With fluoropyrimidine- and platinum-containing chemotherapy: administer OPDIVO first followed by fluoropyrimidine- and platinum-containing chemotherapy on the same day.
- Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.
- Do not co-administer other drugs through the same intravenous line.

## 3 DOSAGE FORMS AND STRENGTHS

Injection: 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), 120 mg/12 mL (10 mg/mL), and 240 mg/24 mL (10 mg/mL) clear to opalescent, colorless to pale-yellow solution in a single-dose vial.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Severe and Fatal Immune-Mediated Adverse Reactions

OPDIVO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO depending on severity [see *Dosage and Administration* (2.3)]. In general, if OPDIVO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

### Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis, which is defined as requiring use of steroids and no clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

*OPDIVO as a Single Agent*

Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%) adverse reactions. Pneumonitis led to permanent discontinuation of OPDIVO in 1.1% and withholding of OPDIVO in 0.8% of patients.

Systemic corticosteroids were required in 100% (61/61) of patients with pneumonitis. Pneumonitis resolved in 84% of the 61 patients. Of the 15 patients in whom OPDIVO was withheld for pneumonitis, 14 reinitiated OPDIVO after symptom improvement; of these, 4 (29%) had recurrence of pneumonitis.

*OPDIVO with Ipilimumab*

**OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg:** In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO with ipilimumab in 5% of patients and withholding of OPDIVO with ipilimumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after reinitiation of OPDIVO with ipilimumab.

*Immune-Mediated Colitis*

OPDIVO can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

*OPDIVO as a Single Agent*

Immune-mediated colitis occurred in 2.9% (58/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (1.7%) and Grade 2 (1%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 0.9% of patients.

Systemic corticosteroids were required in 100% (58/58) of patients with colitis. Four patients required addition of infliximab to high-dose corticosteroids. Colitis resolved in 86% of the 58 patients. Of the 18 patients in whom OPDIVO was withheld for colitis, 16 reinitiated OPDIVO after symptom improvement; of these, 12 (75%) had recurrence of colitis.

*OPDIVO with Ipilimumab*

**OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg:** Immune-mediated colitis occurred in 25% (115/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (0.4%), Grade 3 (14%), and Grade 2 (8%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO with ipilimumab in 14% and withholding of OPDIVO with ipilimumab in 4.4% of patients.

Systemic corticosteroids were required in 100% (115/115) of patients with colitis. Approximately 23% of patients required addition of infliximab to high-dose corticosteroids. Colitis resolved in 93% of the 115 patients. Of the 20 patients in whom OPDIVO with ipilimumab was withheld for colitis, 16 reinitiated treatment after symptom improvement; of these, 9 (56%) had recurrence of colitis.

**OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg:** Immune-mediated colitis occurred in 9% (60/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (4.4%) and Grade 2 (3.7%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.2% and withholding of OPDIVO with ipilimumab in 2.7% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (60/60) of patients with colitis. Approximately 23% of patients with immune-mediated colitis required addition of infliximab to high-dose corticosteroids. Colitis resolved in 95% of the 60 patients. Of the 18 patients in whom OPDIVO with ipilimumab was withheld for colitis, 16 reinitiated treatment after symptom improvement; of these, 10 (63%) had recurrence of colitis.

*Immune-Mediated Hepatitis and Hepatotoxicity*

OPDIVO can cause immune-mediated hepatitis, defined as requiring the use of corticosteroids and no clear alternate etiology.

*OPDIVO as a Single Agent*

Immune-mediated hepatitis occurred in 1.8% (35/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%) adverse reactions. Hepatitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 0.6% of patients.

Systemic corticosteroids were required in 100% (35/35) of patients with hepatitis. Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 35 patients. Of the 12 patients in whom OPDIVO was withheld for hepatitis, 11 reinitiated OPDIVO after symptom improvement; of these, 9 (82%) had recurrence of hepatitis.

*OPDIVO with Ipilimumab*

**OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg:** Immune-mediated hepatitis occurred in 15% (70/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 8% or withholding of OPDIVO with ipilimumab in 3.5% of patients.

Systemic corticosteroids were required in 100% (70/70) of patients with hepatitis. Approximately 9% of patients with immune-mediated hepatitis required the addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 70 patients. Of the 16 patients in whom OPDIVO with ipilimumab was withheld for hepatitis, 14 reinitiated treatment after symptom improvement; of these, 8 (57%) had recurrence of hepatitis.

**OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg:** Immune-mediated hepatitis occurred in 7% (48/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.6% and withholding of OPDIVO with ipilimumab in 2.6% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (48/48) of patients with hepatitis. Approximately 19% of patients with immune-mediated hepatitis required addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 88% of the 48 patients. Of the 17 patients in whom OPDIVO with ipilimumab was withheld for hepatitis, 14 reinitiated treatment after symptom improvement; of these, 10 (71%) had recurrence of hepatitis.

*OPDIVO with Cabozantinib*

OPDIVO in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to OPDIVO alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt OPDIVO and cabozantinib and consider administering corticosteroids [see *Dosage and Administration* (2.3)].

With the combination of OPDIVO and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% of patients [see *Adverse Reactions* (6.1)]. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either OPDIVO (n=11) or cabozantinib (n=9) administered as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving OPDIVO, 2 patients receiving cabozantinib, and 7 patients receiving both OPDIVO and cabozantinib.

*Immune-Mediated Endocrinopathies**Adrenal Insufficiency*

OPDIVO can cause primary or secondary adrenal insufficiency. For grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold OPDIVO depending on severity [see *Dosage and Administration* (2.3)].

*OPDIVO as a Single Agent*

Adrenal insufficiency occurred in 1% (20/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.4%) and Grade 2 (0.6%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.4% of patients.

Approximately 85% of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 90% (18/20) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 35% of the 20 patients. Of the 8 patients in whom OPDIVO was withheld for adrenal insufficiency, 4 reinitiated OPDIVO after symptom improvement and all required hormone replacement therapy for their ongoing adrenal insufficiency.

*OPDIVO with Ipilimumab*

**OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg:** Adrenal insufficiency occurred in 8% (35/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO with ipilimumab in 0.4% and withholding of OPDIVO with ipilimumab in 2.0% of patients.

Approximately 71% (25/35) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 37% of the 35 patients. Of the 9 patients in whom OPDIVO with ipilimumab was withheld for adrenal insufficiency, 7 reinitiated treatment after symptom improvement and all required hormone replacement therapy for their ongoing adrenal insufficiency.

**OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg:** Adrenal insufficiency occurred in 7% (48/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO with ipilimumab in 1.2% and withholding of OPDIVO with ipilimumab in 2.1% of patients with RCC or CRC.



Approximately 94% (45/48) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 29% of the 48 patients. Of the 14 patients in whom OPDIVO with ipilimumab was withheld for adrenal insufficiency, 11 reinitiated treatment after symptom improvement; of these, all received hormone replacement therapy and 2 (18%) had recurrence of adrenal insufficiency.

#### *OPDIVO with Cabozantinib*

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received OPDIVO with cabozantinib, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO and cabozantinib in 0.9% and withholding of OPDIVO and cabozantinib in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom OPDIVO with cabozantinib was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

#### *Hypophysitis*

OPDIVO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue OPDIVO depending on severity [see *Dosage and Administration* (2.3)].

#### *OPDIVO as a Single Agent*

Hypophysitis occurred in 0.6% (12/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.2%) and Grade 2 (0.3%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO in <0.1% and withholding of OPDIVO in 0.2% of patients.

Approximately 67% (8/12) of patients with hypophysitis received hormone replacement therapy, including systemic corticosteroids. Hypophysitis resolved in 42% of the 12 patients. Of the 3 patients in whom OPDIVO was withheld for hypophysitis, 2 reinitiated OPDIVO after symptom improvement; of these, none had recurrence of hypophysitis.

#### *OPDIVO with Ipilimumab*

*OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg:* Hypophysitis occurred in 9% (42/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (2.4%) and Grade 2 (6%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO with ipilimumab in 0.9% and withholding of OPDIVO with ipilimumab in 4.2% of patients.

Approximately 86% of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 88% (37/42) of patients with hypophysitis. Hypophysitis resolved in 38% of the 42 patients. Of the 19 patients in whom OPDIVO with ipilimumab was withheld for hypophysitis, 9 reinitiated treatment after symptom improvement; of these, 1 (11%) had recurrence of hypophysitis.

*OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg:* Hypophysitis occurred in 4.4% (29/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO with ipilimumab in 1.2% and withholding of OPDIVO with ipilimumab in 2.1% of patients with RCC or CRC.

Approximately 72% (21/29) of patients with hypophysitis received hormone replacement therapy, including systemic corticosteroids. Hypophysitis resolved in 59% of the 29 patients. Of the 14 patients in whom OPDIVO with ipilimumab was withheld for hypophysitis, 11 reinitiated treatment after symptom improvement; of these, 2 (18%) had recurrence of hypophysitis.

#### *Thyroid Disorders*

OPDIVO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management as clinically indicated. Withhold or permanently discontinue OPDIVO depending on severity [see *Dosage and Administration* (2.3)].

#### *Thyroiditis*

#### *OPDIVO as a Single Agent*

Thyroiditis occurred in 0.6% (12/1994) of patients receiving OPDIVO as a single agent, including Grade 2 (0.2%) adverse reactions. Thyroiditis led to permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.2% of patients.

Systemic corticosteroids were required in 17% (2/12) of patients with thyroiditis. Thyroiditis resolved in 58% of the 12 patients. Of the 3 patients in whom OPDIVO was withheld for thyroiditis, 1 reinitiated OPDIVO after symptom improvement without recurrence of thyroiditis.

#### *Hyperthyroidism*

#### *OPDIVO as a Single Agent*

Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (<0.1%) and Grade 2 (1.2%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.4% of patients.

Approximately 19% of patients with hyperthyroidism received methimazole, 7% received carbimazole, and 4% received propylthiouracil. Systemic corticosteroids were required in 9% (5/54) of patients. Hyperthyroidism resolved in 76% of the 54 patients. Of the 7 patients in whom OPDIVO was withheld for hyperthyroidism, 4 reinitiated OPDIVO after symptom improvement; of these, none had recurrence of hyperthyroidism.

#### *OPDIVO with Ipilimumab*

*OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg:* Hyperthyroidism occurred in 9% (42/456) of patients with melanoma or HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (0.9%) and Grade 2 (4.2%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of OPDIVO with ipilimumab in no patients and withholding of OPDIVO with ipilimumab in 2.4% of patients.

Approximately 26% of patients with hyperthyroidism received methimazole and 21% received carbimazole. Systemic corticosteroids were required in 17% (7/42) of patients. Hyperthyroidism resolved in 91% of the 42 patients. Of the 11 patients in whom OPDIVO with ipilimumab was withheld for hyperthyroidism, 8 reinitiated treatment after symptom improvement; of these, 1 (13%) had recurrence of hyperthyroidism.

*OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg:* Hyperthyroidism occurred in 12% (80/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (0.6%) and Grade 2 (4.5%) adverse reactions. Hyperthyroidism led to permanent discontinuation of OPDIVO with ipilimumab in no patients and withholding of OPDIVO with ipilimumab in 2.3% of patients with RCC or CRC.

Of the 80 patients with RCC or CRC who developed hyperthyroidism, approximately 16% received methimazole and 3% received carbimazole. Systemic corticosteroids were required in 20% (16/80) of patients with hyperthyroidism. Hyperthyroidism resolved in 85% of the 80 patients. Of the 15 patients in whom OPDIVO with ipilimumab was withheld for hyperthyroidism, 11 reinitiated treatment after symptom improvement; of these, 3 (27%) had recurrence of hyperthyroidism.

#### *Hypothyroidism*

#### *OPDIVO as a Single Agent*

Hypothyroidism occurred in 8% (163/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.2%) and Grade 2 (4.8%) adverse reactions. Hypothyroidism led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.5% of patients.

Approximately 79% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 3.1% (5/163) of patients with hypothyroidism. Hypothyroidism resolved in 35% of the 163 patients. Of the 9 patients in whom OPDIVO was withheld for hypothyroidism, 3 reinitiated OPDIVO after symptom improvement; of these, 1 (33%) had recurrence of hypothyroidism.

#### *OPDIVO with Ipilimumab*

*OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg:* Hypothyroidism occurred in 20% (91/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (0.4%) and Grade 2 (11%) adverse reactions. Hypothyroidism led to the permanent discontinuation of OPDIVO with ipilimumab in 0.9% and withholding of OPDIVO with ipilimumab in 0.9% of patients.

Approximately 89% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 2.2% (2/91) of patients with hypothyroidism. Hypothyroidism resolved in 41% of the 91 patients. Of the 4 patients in whom OPDIVO with ipilimumab was withheld for hypothyroidism, 2 reinitiated treatment after symptom improvement; of these, none had recurrence of hypothyroidism.

*OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg:* Hypothyroidism occurred in 18% (122/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (0.6%) and Grade 2 (11%) adverse reactions. Hypothyroidism led to permanent discontinuation of OPDIVO with ipilimumab in 0.2% and withholding of OPDIVO with ipilimumab in 1.4% of patients with RCC or CRC.

Of the 122 patients with RCC or CRC who developed hypothyroidism, approximately 82% received levothyroxine. Systemic corticosteroids were required in 7% (9/122) of patients with hypothyroidism. Hypothyroidism resolved in 27% of the 122 patients. Of the 9 patients in whom OPDIVO with ipilimumab was withheld for hypothyroidism, 5 reinitiated treatment after symptom improvement; of these, 1 (20%) had recurrence of hypothyroidism.

#### *Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis*

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold OPDIVO depending on severity [see *Dosage and Administration* (2.3)].



*OPDIVO as a Single Agent*

Diabetes occurred in 0.9% (17/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.4%) and Grade 2 (0.3%) adverse reactions, and two cases of diabetic ketoacidosis. Diabetes led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.1% of patients.

No patients (0/17) with diabetes required systemic corticosteroids. Diabetes resolved in 29% of the 17 patients. Of the 2 patients in whom OPDIVO was withheld for diabetes, both reinitiated OPDIVO after symptom improvement; of these, neither had recurrence of diabetes.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear alternate etiology.

*OPDIVO as a Single Agent*

Immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%) adverse reactions. Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.4% of patients.

Systemic corticosteroids were required in 100% (23/23) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 78% of the 23 patients. Of the 7 patients in whom OPDIVO was withheld for nephritis or renal dysfunction, 7 reinitiated OPDIVO after symptom improvement; of these, 1 (14%) had recurrence of nephritis or renal dysfunction.

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis, defined as requiring the use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue OPDIVO depending on severity [see *Dosage and Administration* (2.3)].

*OPDIVO as a Single Agent*

Immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.5% of patients.

Systemic corticosteroids were required in 100% (171/171) of patients with immune-mediated rash. Rash resolved in 72% of the 171 patients. Of the 10 patients in whom OPDIVO was withheld for immune-mediated rash, 9 reinitiated OPDIVO after symptom improvement; of these, 3 (33%) had recurrence of immune-mediated rash.

*OPDIVO with Ipilimumab*

**OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg:** Immune-mediated rash occurred in 28% (127/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (4.8%) and Grade 2 (10%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO with ipilimumab in 0.4% and withholding of OPDIVO with ipilimumab in 3.9% of patients.

Systemic corticosteroids were required in 100% (127/127) of patients with immune-mediated rash. Rash resolved in 84% of the 127 patients. Of the 18 patients in whom OPDIVO with ipilimumab was withheld for immune-mediated rash, 15 reinitiated treatment after symptom improvement; of these, 8 (53%) had recurrence of immune-mediated rash.

**OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg:** Immune-mediated rash occurred in 16% (108/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (3.5%) and Grade 2 (4.2%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO with ipilimumab in 0.5% of patients and withholding of OPDIVO with ipilimumab in 2.0% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (108/108) of patients with immune-mediated rash. Rash resolved in 75% of the 108 patients. Of the 13 patients in whom OPDIVO with ipilimumab was withheld for immune-mediated rash, 11 reinitiated treatment after symptom improvement; of these, 5 (46%) had recurrence of immune-mediated rash.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO or OPDIVO in combination with ipilimumab, or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

**Cardiac/Vascular:** Myocarditis, pericarditis, vasculitis

**Nervous System:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

**Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss

**Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis

**Musculoskeletal and Connective Tissue:** Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatic

**Endocrine:** Hypoparathyroidism

**Other (Hematologic/Immune):** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection

**5.2 Infusion-Related Reactions**

OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions [see *Dosage and Administration* (2.3)].

OPDIVO as a Single Agent

In patients who received OPDIVO as a 60-minute intravenous infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients.

In a trial assessing the pharmacokinetics and safety of a more rapid infusion, in which patients received OPDIVO as a 60-minute intravenous infusion or a 30-minute intravenous infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation, or withholding of OPDIVO.

OPDIVO with Ipilimumab*OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg*

Infusion-related reactions occurred in 2.5% (10/407) of patients with melanoma and in 8% (4/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks.

*OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg*

Infusion-related reactions occurred in 5.1% (28/547) of patients with RCC and 4.2% (5/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, respectively. Infusion-related reactions occurred in 12% (37/300) of patients with malignant pleural mesothelioma who received OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks.

**5.3 Complications of Allogeneic Hematopoietic Stem Cell Transplantation**

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1 receptor blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause) [see *Adverse Reactions* (6.1)]. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody prior to or after an allogeneic HSCT.

**5.4 Embryo-Fetal Toxicity**

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for 5 months after the last dose [see *Use in Specific Populations* (8.1, 8.3)].

**5.5 Increased Mortality in Patients with Multiple Myeloma when OPDIVO Is Added to a Thalidomide Analogue and Dexamethasone**

In randomized clinical trials in patients with multiple myeloma, the addition of a PD-1 blocking antibody, including OPDIVO, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]
- Infusion-Related Reactions [see Warnings and Precautions (5.2)]
- Complications of Allogeneic HSCT [see Warnings and Precautions (5.3)]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in WARNINGS AND PRECAUTIONS reflect exposure to OPDIVO as a single agent in 1994 patients enrolled in CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 or a single-arm trial in NSCLC (n=117); OPDIVO 1 mg/kg with ipilimumab 3 mg/kg in patients enrolled in CHECKMATE-067 (n=313), CHECKMATE-040 (n=49), or another randomized trial (n=94); OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg (n=666) in patients enrolled in CHECKMATE-214 or CHECKMATE-142; OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in patients enrolled in CHECKMATE-227 (n=576) or CHECKMATE-743 (n=300); OPDIVO 360 mg with ipilimumab 1 mg/kg and 2 cycles of platinum-doublet chemotherapy in CHECKMATE-9LA (n=361); and OPDIVO 240 mg with cabozantinib 40 mg in patients enrolled in CHECKMATE-9ER (n=320).

#### Unresectable or Metastatic Melanoma

##### Previously Treated Metastatic Melanoma

The safety of OPDIVO was evaluated in CHECKMATE-037, a randomized, open-label trial in 370 patients with unresectable or metastatic melanoma [see Clinical Studies (14.1)]. Patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102): dacarbazine 1000 mg/m<sup>2</sup> intravenously every 3 weeks or carboplatin AUC 6 mg/mL/min and paclitaxel 175 mg/m<sup>2</sup> intravenously every 3 weeks. The median duration of exposure was 5.3 months (range: 1 day to 13.8+ months) in OPDIVO-treated patients and was 2 months (range: 1 day to 9.6+ months) in chemotherapy-treated patients. In this ongoing trial, 24% of patients received OPDIVO for >6 months and 3% of patients received OPDIVO for >1 year.

The population characteristics in the OPDIVO group and the chemotherapy group were similar: 66% male, median age 59.5 years, 98% White, baseline Eastern Cooperative Oncology Group (ECOG) performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. There were more patients in the OPDIVO group with elevated lactate dehydrogenase (LDH) at baseline (51% vs. 38%).

Serious adverse reactions occurred in 41% of patients receiving OPDIVO. OPDIVO was discontinued for adverse reactions in 9% of patients. Twenty-six percent of patients receiving OPDIVO had a dose interruption for an adverse reaction. Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. The most common adverse reaction (reported in ≥20% of patients) was rash.

Tables 5 and 6 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-037.

**Table 5: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-037**

Adverse Reaction	OPDIVO (n=268)		Chemotherapy (n=102)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>a</sup>	21	0.4	7	0
Pruritus	19	0	3.9	0
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough	17	0	6	0

(Continued)

**Table 5: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-037**

Adverse Reaction	OPDIVO (n=268)		Chemotherapy (n=102)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Infections</b>				
Upper respiratory tract infection <sup>b</sup>	11	0	2	0
<b>General</b>				
Peripheral edema	10	0	5	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, and acneiform dermatitis.

<sup>b</sup> Includes rhinitis, pharyngitis, and nasopharyngitis.

Clinically important adverse reactions in <10% of patients who received OPDIVO were:

*Cardiac Disorders:* ventricular arrhythmia

*Eye Disorders:* iridocyclitis

*General Disorders and Administration Site Conditions:* infusion-related reactions

*Investigations:* increased amylase, increased lipase

*Nervous System Disorders:* dizziness, peripheral and sensory neuropathy

*Skin and Subcutaneous Tissue Disorders:* exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis

**Table 6: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-037**

Laboratory Abnormality	OPDIVO		Chemotherapy	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased AST	28	2.4	12	1
Hyponatremia	25	5	18	1.1
Increased alkaline phosphatase	22	2.4	13	1.1
Increased ALT	16	1.6	5	0
Hyperkalemia	15	2	6	0

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 252 to 256 patients) and chemotherapy group (range: 94 to 96 patients).

#### Previously Untreated Metastatic Melanoma

##### CHECKMATE-066

The safety of OPDIVO was also evaluated in CHECKMATE-066, a randomized, double-blind, active-controlled trial in 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma [see Clinical Studies (14.1)]. The trial excluded patients with autoimmune disease and patients requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=206) or dacarbazine 1000 mg/m<sup>2</sup> intravenously every 3 weeks (n=205). The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. In this trial, 47% of patients received OPDIVO for >6 months and 12% of patients received OPDIVO for >1 year.

The trial population characteristics in the OPDIVO group and dacarbazine group: 59% male, median age 65 years, 99.5% White, 61% with M1c stage disease, 74% with cutaneous melanoma, 11% with mucosal melanoma, 4% with brain metastasis, and 37% with elevated LDH at baseline. There were more patients in the OPDIVO group with ECOG performance status 0 (71% vs. 59%).

Serious adverse reactions occurred in 36% of patients receiving OPDIVO. Adverse reactions led to permanent discontinuation of OPDIVO in 7% of patients and dose interruption in 26% of patients; no single type of adverse reaction accounted for the majority of OPDIVO discontinuations. Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO.

The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were increased gamma-glutamyl transferase (3.9%) and diarrhea (3.4%). The most common adverse reactions (reported in ≥20% of patients and at a higher incidence than in the dacarbazine arm) were fatigue, musculoskeletal pain, rash, and pruritus.

Tables 7 and 8 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-066.

**Table 7: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-066**

Adverse Reaction	OPDIVO (n=206)		Dacarbazine (n=205)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>General</b>				
Fatigue	49	1.9	39	3.4
Edema <sup>a</sup>	12	1.5	4.9	0
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>b</sup>	32	2.9	25	2.4
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>c</sup>	28	1.5	12	0
Pruritus	23	0.5	12	0
Vitiligo	11	0	0.5	0
Erythema	10	0	2.9	0
<b>Infections</b>				
Upper respiratory tract infection <sup>d</sup>	17	0	6	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes periorbital edema, face edema, generalized edema, gravitational edema, localized edema, peripheral edema, pulmonary edema, and lymphedema.

<sup>b</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, pain in jaw, and spinal pain.

<sup>c</sup> Includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, dermatitis, allergic dermatitis, exfoliative dermatitis, acneiform dermatitis, drug eruption, and skin reaction.

<sup>d</sup> Includes rhinitis, viral rhinitis, pharyngitis, and nasopharyngitis.

Clinically important adverse reactions in <10% of patients who received OPDIVO were:

*Nervous System Disorders:* peripheral neuropathy

**Table 8: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-066**

Laboratory Abnormality	OPDIVO		Dacarbazine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased ALT	25	3	19	0.5
Increased AST	24	3.6	19	0.5
Increased alkaline phosphatase	21	2.6	14	1.6
Increased bilirubin	13	3.1	6	0

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 194 to 197 patients) and dacarbazine group (range: 186 to 193 patients).

#### CHECKMATE-067

The safety of OPDIVO, administered with ipilimumab or as a single agent, was evaluated in CHECKMATE-067, a randomized (1:1:1), double-blind trial in 937 patients with previously untreated, unresectable or metastatic melanoma [see *Clinical Studies* (14.1)]. The trial excluded patients with autoimmune disease, a medical condition requiring systemic treatment with corticosteroids (more than 10 mg daily prednisone equivalent) or other immunosuppressive medication within 14 days of the start of study therapy, a positive test result for hepatitis B or C, or a history of HIV.

Patients were randomized to receive:

- OPDIVO 1 mg/kg over 60 minutes with ipilimumab 3 mg/kg by intravenous infusion every 3 weeks for 4 doses followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (OPDIVO and ipilimumab arm; n=313), or
- OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (OPDIVO arm; n=313), or
- Ipilimumab 3 mg/kg by intravenous infusion every 3 weeks for up to 4 doses (ipilimumab arm; n=311).

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

The population characteristics were: 65% male, median age 61 years, 97% White, baseline ECOG performance status 0 (73%) or 1 (27%), 93% with American Joint Committee on Cancer (AJCC) Stage IV disease, 58% with M1c stage disease; 36% with elevated LDH at baseline, 4% with a history of brain metastasis, and 22% had received adjuvant therapy.

Serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO and ipilimumab arm relative to the OPDIVO arm.

The most frequent (≥10%) serious adverse reactions in the OPDIVO and ipilimumab arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). The most frequent adverse reactions leading to discontinuation of both drugs in the OPDIVO and ipilimumab arm and of OPDIVO in the OPDIVO arm, respectively, were colitis (10% and 0.6%), diarrhea (8% and 2.2%), increased ALT (4.8% and 1.0%), increased AST (4.5% and 0.6%), and pneumonitis (1.9% and 0.3%).

The most common (≥20%) adverse reactions in the OPDIVO and ipilimumab arm were fatigue, diarrhea, rash, nausea, pyrexia, pruritus, musculoskeletal pain, vomiting, decreased appetite, cough, headache, dyspnea, upper respiratory tract infection, arthralgia, and increased transaminases. The most common (≥20%) adverse reactions in the OPDIVO arm were fatigue, rash, musculoskeletal pain, diarrhea, nausea, cough, pruritus, upper respiratory tract infection, decreased appetite, headache, constipation, arthralgia, and vomiting.

Tables 9 and 10 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-067.

**Table 9: Adverse Reactions Occurring in ≥10% of Patients on the OPDIVO and Ipilimumab Arm or the OPDIVO Arm and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067**

Adverse Reaction	OPDIVO and Ipilimumab (n=313)		OPDIVO (n=313)		Ipilimumab (n=311)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>General</b>						
Fatigue <sup>a</sup>	62	7	59	1.6	51	4.2
Pyrexia	40	1.6	16	0	18	0.6
<b>Gastrointestinal</b>						
Diarrhea	54	11	36	5	47	7
Nausea	44	3.8	30	0.6	31	1.9
Vomiting	31	3.8	20	1	17	1.6
<b>Skin and Subcutaneous Tissue</b>						
Rash <sup>b</sup>	53	6	40	1.9	42	3.5
Vitiligo	9	0	10	0.3	5	0
<b>Musculoskeletal and Connective Tissue</b>						
Musculoskeletal pain <sup>c</sup>	32	2.6	42	3.8	36	1.9
Arthralgia	21	0.3	21	1	16	0.3
<b>Metabolism and Nutrition</b>						
Decreased appetite	29	1.9	22	0	24	1.3
<b>Respiratory, Thoracic and Mediastinal</b>						
Cough/productive cough	27	0.3	28	0.6	22	0
Dyspnea/exertional dyspnea	24	2.9	18	1.3	17	0.6
<b>Infections</b>						
Upper respiratory tract infection <sup>d</sup>	23	0	22	0.3	17	0
<b>Endocrine</b>						
Hypothyroidism	19	0.6	11	0	5	0
Hyperthyroidism	11	1.3	6	0	1	0
<b>Investigations</b>						
Decreased weight	12	0	7	0	7	0.3
<b>Vascular</b>						
Hypertension <sup>e</sup>	7	2.2	11	5	9	2.3

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes asthenia and fatigue.

<sup>b</sup> Includes pustular rash, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, exfoliative dermatitis, psoriasisform dermatitis, drug eruption, morbilliform rash, erythematous rash, generalized rash, macular rash, maculopapular rash, and pruritic rash.

<sup>c</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

<sup>d</sup> Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis.

<sup>e</sup> Includes hypertension and blood pressure increased.



Clinically important adverse reactions in <10% of patients who received OPDIVO with ipilimumab or OPDIVO as a single agent were:

*Gastrointestinal Disorders:* stomatitis, intestinal perforation

*Skin and Subcutaneous Tissue Disorders:* vitiligo

*Musculoskeletal and Connective Tissue Disorders:* myopathy, Sjogren's syndrome, spondyloarthritis, myositis (including polymyositis)

*Nervous System Disorders:* neuritis, peroneal nerve palsy

**Table 10: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥20% of Patients Treated with OPDIVO with Ipilimumab or Single-Agent OPDIVO and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067**

Laboratory Abnormality	OPDIVO and Ipilimumab		OPDIVO		Ipilimumab	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
<b>Chemistry</b>						
Increased ALT	55	16	25	3	29	2.7
Hyperglycemia	53	5.3	46	7	26	0
Increased AST	52	13	29	3.7	29	1.7
Hyponatremia	45	10	22	3.3	26	7
Increased lipase	43	22	32	12	24	7
Increased alkaline phosphatase	41	6	27	2	23	2
Hypocalcemia	31	1.1	15	0.7	20	0.7
Increased amylase	27	10	19	2.7	15	1.6
Increased creatinine	26	2.7	19	0.7	17	1.3
<b>Hematology</b>						
Anemia	52	2.7	41	2.6	41	6
Lymphopenia	39	5	41	4.9	29	4

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab (range: 75 to 297); OPDIVO (range: 81 to 306); ipilimumab (range: 61 to 301).

*Adjuvant Treatment of Melanoma*

*CHECKMATE-76K*

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-76K, a randomized (2:1), double-blind trial in 788 patients with completely resected Stage IIB/C melanoma who received OPDIVO 480 mg by intravenous infusion over 30 minutes every 4 weeks (n=524) or placebo by intravenous infusion over 30 minutes every 4 weeks (n=264) for up to 1 year [see *Clinical Studies* (14.2)]. The median duration of exposure was 11 months in patients treated with OPDIVO and 11 months in patients treated with placebo.

Serious adverse reactions occurred in 18% of patients treated with OPDIVO. A fatal adverse reaction occurred in 1 (0.2%) patient (heart failure and acute kidney injury). Permanent discontinuation of OPDIVO due to an adverse reaction occurred in 17% of patients. Adverse reactions which resulted in permanent discontinuation of OPDIVO in >1% of patients included diarrhea (1.1%), arthralgia (1.7%), and rash (1.7%).

Dosage interruptions of OPDIVO due to an adverse reaction occurred in 25% of patients. Adverse reactions which required dosage interruption in >1% of patients included COVID-19 infection, infusion related reaction, diarrhea, arthralgia, and increased ALT.

The most common adverse reactions (reported in ≥20% of patients) were fatigue, musculoskeletal pain, rash, diarrhea, and pruritus.

Tables 11 and 12 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-76K.

**Table 11: Adverse Reactions Occurring in ≥10% of Patients Treated with OPDIVO - CHECKMATE-76K**

Adverse Reaction	OPDIVO (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>General</b>				
Fatigue <sup>a</sup>	36	0.4	34	0.4
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>b</sup>	30	0.4	26	0.4

(Continued)

**Table 11: Adverse Reactions Occurring in ≥10% of Patients Treated with OPDIVO - CHECKMATE-76K**  
(Continued)

Adverse Reaction	OPDIVO (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>c</sup>	28	1.1	15	0.4
Pruritus	20	0.2	11	0
<b>Gastrointestinal</b>				
Diarrhea <sup>d</sup>	23	1.3	16	0
Nausea	14	0	11	0
<b>Endocrine</b>				
Hypothyroidism <sup>e</sup>	14	0	2.3	0
<b>Nervous System</b>				
Headache <sup>f</sup>	12	0.2	14	0.8

Toxicity was graded per NCI CTCAE v5.

<sup>a</sup> Includes asthenia.

<sup>b</sup> Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, spinal pain, pain in extremity.

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

<sup>d</sup> Includes autoimmune colitis, colitis, diarrhea, enteritis, enterocolitis

<sup>e</sup> Includes autoimmune hypothyroidism, blood thyroid stimulating hormone increased.

<sup>f</sup> Includes cluster headache, migraine.

**Table 12: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-76K**

Laboratory Abnormality	OPDIVO (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Hematology</b>				
Anemia	19	0	14	0
Lymphopenia	17	1.1	17	1.7
Neutropenia	10	0	10	0.4
<b>Chemistry</b>				
AST Increased	25	2.2	16	0.4
Lipase Increased	22	2.9	21	2.3
ALT Increased	20	2.1	15	0.4
Amylase Increased	17	0.4	9	0
Creatinine Increased	15	0.4	13	0
Sodium decreased	13	0.6	11	0.4
Potassium increased	13	1	15	1.1

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

*CHECKMATE-238*

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-238, a randomized (1:1), double-blind trial in 905 patients with completely resected Stage IIIB/C or Stage IV melanoma received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=452) or ipilimumab 10 mg/kg by intravenous infusion every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year (n=453) [see *Clinical Studies* (14.2)]. The median duration of exposure was 11.5 months in OPDIVO-treated patients and was 2.7 months in ipilimumab-treated patients. In this ongoing trial, 74% of patients received OPDIVO for >6 months.

Serious adverse reactions occurred in 18% of OPDIVO-treated patients. Study therapy was discontinued for adverse reactions in 9% of OPDIVO-treated patients and 42% of ipilimumab-treated patients. Twenty-eight percent of OPDIVO-treated patients had at least one omitted dose for an adverse reaction. Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients.

The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. The most common adverse reactions (at least 20%) were fatigue, diarrhea, rash, musculoskeletal pain, pruritus, headache, nausea, upper respiratory infection, and abdominal pain. The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%).

Tables 13 and 14 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-238.

**Table 13: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-238**

Adverse Reaction	OPDIVO (n=452)		Ipilimumab 10 mg/kg (n=453)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>General</b>				
Fatigue <sup>a</sup>	57	0.9	55	2.4
<b>Gastrointestinal</b>				
Diarrhea	37	2.4	55	11
Nausea	23	0.2	28	0
Abdominal pain <sup>b</sup>	21	0.2	23	0.9
Constipation	10	0	9	0
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>c</sup>	35	1.1	47	5.3
Pruritus	28	0	37	1.1
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>d</sup>	32	0.4	27	0.4
Arthralgia	19	0.4	13	0.4
<b>Nervous System</b>				
Headache	23	0.4	31	2
Dizziness <sup>e</sup>	11	0	8	0
<b>Infections</b>				
Upper respiratory tract infection <sup>f</sup>	22	0	15	0.2
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough/productive cough	19	0	19	0
Dyspnea/exertional dyspnea	10	0.4	10	0.2
<b>Endocrine</b>				
Hypothyroidism <sup>g</sup>	12	0.2	7.5	0.4

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes asthenia.<sup>b</sup> Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness.<sup>c</sup> Includes dermatitis described as acneiform, allergic, bullous, or exfoliative and rash described as generalized, erythematous, macular, papular, maculopapular, pruritic, pustular, vesicular, or butterfly, and drug eruption.<sup>d</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, spinal pain, and pain in extremity.<sup>e</sup> Includes postural dizziness and vertigo.<sup>f</sup> Includes upper respiratory tract infection including viral respiratory tract infection, lower respiratory tract infection, rhinitis, pharyngitis, and nasopharyngitis.<sup>g</sup> Includes secondary hypothyroidism and autoimmune hypothyroidism.**Table 14: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-238**

Laboratory Abnormality	OPDIVO		Ipilimumab 10 mg/kg	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Hematology</b>				
Lymphopenia	27	0.4	12	0.9
Anemia	26	0	34	0.5
Leukopenia	14	0	2.7	0.2
Neutropenia	13	0	6	0.5
<b>Chemistry</b>				
Increased Lipase	25	7	23	9
Increased ALT	25	1.8	40	12
Increased AST	24	1.3	33	9
Increased Amylase	17	3.3	13	3.1
Hyponatremia	16	1.1	22	3.2
Hyperkalemia	12	0.2	9	0.5
Increased Creatinine	12	0	13	0
Hypocalcemia	10	0.7	16	0.5

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 400 to 447 patients) and ipilimumab 10 mg/kg group (range: 392 to 443 patients).**Neoadjuvant Treatment of Resectable (Tumors ≥4 cm or Node Positive) Non-Small Cell Lung Cancer**

The safety of OPDIVO in combination with platinum-doublet chemotherapy was evaluated in CHECKMATE-816, a randomized, open-label, multicenter trial in patients with resectable NSCLC [see *Clinical Studies* (14.3)]. Patients received either OPDIVO 360 mg administered in combination with platinum-doublet chemotherapy administered every 3 weeks for 3 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 3 cycles.

The median age of patients who received OPDIVO in combination with platinum-doublet chemotherapy or platinum-doublet chemotherapy was 65 years (range: 34 – 84); 72% male; 47% White, 50% Asian, and 2% Black/African-American.

Serious adverse reactions occurred in 30% of patients who were treated with OPDIVO in combination with platinum-doublet chemotherapy. Serious adverse reactions in >2% included pneumonia and vomiting. No fatal adverse reactions occurred in patients who received OPDIVO in combination with platinum-doublet chemotherapy.

Study therapy with OPDIVO in combination with platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 10% of patients and 30% had at least one treatment withheld for an adverse reaction. The most common adverse reactions (≥1%) resulting in permanent discontinuation of OPDIVO in combination with platinum-doublet chemotherapy were anaphylactic reaction (1.7%), acute kidney injury (1.1%), rash (1.1%), and fatigue (1.1%).

The most common (>20%) adverse reactions were nausea, constipation, fatigue, decreased appetite, and rash. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were neutropenia, hyperglycemia, leukopenia, lymphopenia, increased amylase, anemia, thrombocytopenia, and hyponatremia.

Tables 15 and 16 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-816.

**Table 15: Adverse Reactions in >10% of Patients with Early-Stage NSCLC Receiving Neoadjuvant OPDIVO and Platinum-Doublet Chemotherapy in CHECKMATE-816**

Adverse Reaction	OPDIVO and Platinum-Doublet Chemotherapy (n=176)		Platinum-Doublet Chemotherapy (n=176)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
<b>Gastrointestinal</b>				
Nausea	38	0.6	45	1.1
Constipation	34	0	32	1.1
Vomiting	11	1.1	13	0.6
<b>General</b>				
Fatigue <sup>a</sup>	26	2.3	23	1.1
Malaise	15	0.6	14	0.6
<b>Metabolism and Nutrition</b>				
Decreased appetite	20	1.1	23	2.3
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>b</sup>	20	2.3	7	0
Alopecia	11	0	15	0
<b>Nervous System</b>				
Peripheral neuropathy <sup>c</sup>	13	0	6	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes fatigue and asthenia.<sup>b</sup> Includes rash, dermatitis, acneiform dermatitis, atopic dermatitis, bullous dermatitis, drug eruption, maculopapular rash, and pruritic rash.<sup>c</sup> Includes peripheral neuropathy, dysesthesia, hypoesthesia, peripheral motor neuropathy, peripheral sensory neuropathy.

**Table 16: Select Laboratory Values Worsening from Baseline<sup>a</sup> Occurring in >20% of Patients with Early-Stage NSCLC Receiving Neoadjuvant OPDIVO and Platinum-Doublet Chemotherapy in CHECKMATE-816**

Laboratory Abnormality	OPDIVO and Platinum-Doublet Chemotherapy <sup>a</sup>		Platinum-Doublet Chemotherapy <sup>a</sup>	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
<b>Hematology</b>				
Anemia	63	3.5	70	6
Neutropenia	58	22	58	27
Leukopenia	53	5	51	11
Lymphopenia	38	4.7	31	1.8
Thrombocytopenia	24	2.9	22	3
<b>Chemistry</b>				
Hyperglycemia	37	6	35	2.9
Hypomagnesemia	25	1.2	29	1.2
Hyponatremia	25	2.4	28	1.8
Increased amylase	23	3.6	13	1.8
Increased ALT	23	0	20	1.2

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and platinum-doublet chemotherapy group (range: 73 to 171 patients) and platinum-doublet chemotherapy group (range: 68 to 171 patients).

#### Metastatic Non-Small Cell Lung Cancer

##### First-line Treatment of Metastatic NSCLC: In Combination with Ipilimumab

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations [see Clinical Studies (14.4)]. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received OPDIVO 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks and ipilimumab 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO and ipilimumab-treated patients was 4.2 months (range: 1 day to 25.5 months); 39% of patients received OPDIVO and ipilimumab for >6 months and 23% of patients received OPDIVO and ipilimumab for >1 year. The population characteristics were: median age 64 years (range: 26 to 87); 48% were ≥65 years of age, 76% White, and 67% male. Baseline ECOG performance status was 0 (35%) or 1 (65%), 85% were former/current smokers, 11% had brain metastases, 28% had squamous histology and 72% had non-squamous histology.

Serious adverse reactions occurred in 58% of patients. OPDIVO and ipilimumab were discontinued for adverse reactions in 24% of patients and 53% had at least one dose withheld for an adverse reaction.

The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. The most common (≥20%) adverse reactions were fatigue, rash, decreased appetite, musculoskeletal pain, diarrhea/colitis, dyspnea, cough, hepatitis, nausea, and pruritus.

Tables 17 and 18 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

**Table 17: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-227**

Adverse Reaction	OPDIVO and Ipilimumab (n=576)		Platinum-Doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>General</b>				
Fatigue <sup>a</sup>	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema <sup>b</sup>	14	0.2	12	0.5
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>c</sup>	34	4.7	10	0.4
Pruritus <sup>d</sup>	21	0.5	3.3	0
<b>Metabolism and Nutrition</b>				
Decreased appetite	31	2.3	26	1.4

(Continued)

**Table 17: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-227**

Adverse Reaction	OPDIVO and Ipilimumab (n=576)		Platinum-Doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>e</sup>	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
<b>Gastrointestinal</b>				
Diarrhea/colitis <sup>f</sup>	26	3.6	16	0.9
Nausea	21	1	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1	18	2.3
Abdominal pain <sup>g</sup>	10	0.2	9	0.7
<b>Respiratory, Thoracic, and Mediastinal</b>				
Dyspnea <sup>h</sup>	26	4.3	16	2.1
Cough <sup>i</sup>	23	0.2	13	0
<b>Hepatobiliary</b>				
Hepatitis <sup>j</sup>	21	9	10	1.2
<b>Endocrine</b>				
Hypothyroidism <sup>k</sup>	16	0.5	1.2	0
Hyperthyroidism <sup>l</sup>	10	0	0.5	0
<b>Infections and Infestations</b>				
Pneumonia <sup>m</sup>	13	7	8	4
<b>Nervous System</b>				
Headache	11	0.5	6	0

<sup>a</sup> Includes fatigue and asthenia.

<sup>b</sup> Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.

<sup>c</sup> Includes autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.

<sup>d</sup> Includes pruritus and pruritus generalized.

<sup>e</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.

<sup>f</sup> Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.

<sup>g</sup> Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.

<sup>h</sup> Includes dyspnea and dyspnea exertional.

<sup>i</sup> Includes cough and productive cough.

<sup>j</sup> Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased.

<sup>k</sup> Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.

<sup>l</sup> Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.

<sup>m</sup> Includes lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral, atypical pneumonia, organizing pneumonia.

Other clinically important adverse reactions in CHECKMATE-227 were:

**Skin and Subcutaneous Tissue:** urticaria, alopecia, erythema multiforme, vitiligo

**Gastrointestinal:** stomatitis, pancreatitis, gastritis

**Musculoskeletal and Connective Tissue:** arthritis, polymyalgia rheumatica, rhabdomyolysis

**Nervous System:** peripheral neuropathy, autoimmune encephalitis

**Blood and Lymphatic System:** eosinophilia

**Eye Disorders:** blurred vision, uveitis

**Cardiac:** atrial fibrillation, myocarditis

**Table 18: Laboratory Values Worsening from Baseline<sup>a</sup> Occurring in ≥20% of Patients on OPDIVO and Ipilimumab - CHECKMATE-227**

Laboratory Abnormality	OPDIVO and Ipilimumab		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Hematology</b>				
Anemia	46	3.6	78	14
Lymphopenia	46	5	60	15
<b>Chemistry</b>				
Hyponatremia	41	12	26	4.9
Increased AST	39	5	26	0.4
Increased ALT	36	7	27	0.7
Increased lipase	35	14	14	3.4
Increased alkaline phosphatase	34	3.8	20	0.2
Increased amylase	28	9	18	1.9
Hypocalcemia	28	1.7	17	1.3
Hyperkalemia	27	3.4	22	0.4
Increased creatinine	22	0.9	17	0.2

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 494 to 556 patients) and chemotherapy group (range: 469 to 542 patients).

*First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Ipilimumab and Platinum-Doublet Chemotherapy*

The safety of OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA [see *Clinical Studies (14.4)*]. Patients received either OPDIVO 360 mg administered every 3 weeks in combination with ipilimumab 1 mg/kg administered every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months); 50% of patients received OPDIVO and ipilimumab for >6 months and 13% of patients received OPDIVO and ipilimumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy. The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Study therapy with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Tables 19 and 20 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

**Table 19: Adverse Reactions in >10% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA**

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>General</b>				
Fatigue <sup>a</sup>	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>b</sup>	39	4.5	27	2
<b>Gastrointestinal</b>				
Nausea	32	1.7	41	0.9
Diarrhea <sup>c</sup>	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2	17	1.4
Abdominal pain <sup>d</sup>	12	0.6	11	0.9
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>e</sup>	30	4.7	10	0.3
Pruritus <sup>f</sup>	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
<b>Metabolism and Nutrition</b>				
Decreased appetite	28	2	22	1.7
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough <sup>g</sup>	19	0.6	15	0.9
Dyspnea <sup>h</sup>	18	4.7	14	3.2
<b>Endocrine</b>				
Hypothyroidism <sup>i</sup>	19	0.3	3.4	0
<b>Nervous System</b>				
Headache	11	0.6	7	0
Dizziness <sup>j</sup>	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes fatigue and asthenia

<sup>b</sup> Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis

<sup>c</sup> Includes colitis, ulcerative colitis, diarrhea, and enterocolitis

<sup>d</sup> Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain

<sup>e</sup> Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blennorrhagica, palmar-plantar erythrodysesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria

<sup>f</sup> Includes pruritus and generalized pruritus

<sup>g</sup> Includes cough, productive cough, and upper-airway cough syndrome

<sup>h</sup> Includes dyspnea, dyspnea at rest, and exertional dyspnea

<sup>i</sup> Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine

<sup>j</sup> Includes dizziness, vertigo and positional vertigo



**Table 20: Laboratory Values Worsening from Baseline<sup>a</sup> Occurring in >20% of Patients on OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA**

Laboratory Abnormality	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Hematology</b>				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9
Thrombocytopenia	23	4.3	24	5
<b>Chemistry</b>				
Hyperglycemia	45	7	42	2.6
Hyponatremia	37	10	27	7
Increased ALT	34	4.3	24	1.2
Increased lipase	31	12	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	7	19	1.3
Increased AST	30	3.5	22	0.3
Hypomagnesemia	29	1.2	33	0.6
Hypocalcemia	26	1.4	22	1.8
Increased creatinine	26	1.2	23	0.6
Hyperkalemia	22	1.7	21	2.1

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

#### Second-line Treatment of Metastatic NSCLC

The safety of OPDIVO was evaluated in CHECKMATE-017, a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen and in CHECKMATE-057, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen [see *Clinical Studies* (14.4)]. These trials excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. Patients received OPDIVO 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks or docetaxel 75 mg/m<sup>2</sup> intravenously every 3 weeks. The median duration of therapy in OPDIVO-treated patients in CHECKMATE-017 was 3.3 months (range: 1 day to 21.7+ months) and in CHECKMATE-057 was 2.6 months (range: 0 to 24.0+ months). In CHECKMATE-017, 36% of patients received OPDIVO for at least 6 months and 18% of patients received OPDIVO for at least 1 year and in CHECKMATE-057, 30% of patients received OPDIVO for >6 months and 20% of patients received OPDIVO for >1 year.

Across both trials, the median age of OPDIVO-treated patients was 61 years (range: 37 to 85); 38% were ≥65 years of age, 61% were male, and 91% were White. Ten percent of patients had brain metastases and ECOG performance status was 0 (26%) or 1 (74%).

In CHECKMATE-057, in the OPDIVO arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis. Serious adverse reactions occurred in 46% of patients receiving OPDIVO. OPDIVO was discontinued in 11% of patients and was delayed in 28% of patients for an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. Across both trials, the most common adverse reactions (≥20%) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

Tables 21 and 22 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-057.

**Table 21: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-017 and CHECKMATE-057**

Adverse Reaction	OPDIVO (n=418)		Docetaxel (n=397)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough	31	0.7	24	0
<b>Metabolism and Nutrition</b>				
Decreased appetite	28	1.4	23	1.5
<b>Skin and Subcutaneous Tissue</b>				
Pruritus	10	0.2	2	0

Toxicity was graded per NCI CTCAE v4.

Other clinically important adverse reactions observed in OPDIVO-treated patients and which occurred at a similar incidence in docetaxel-treated patients and not listed elsewhere in section 6 include: fatigue/asthenia (48% all Grades, 5% Grade 3-4), musculoskeletal pain (33% all Grades), pleural effusion (4.5% all Grades), pulmonary embolism (3.3% all Grades).

**Table 22: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of OPDIVO-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-017 and CHECKMATE-057**

Laboratory Abnormality	OPDIVO		Docetaxel	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Chemistry</b>				
Hyponatremia	35	7	34	4.9
Increased AST	27	1.9	13	0.8
Increased alkaline phosphatase	26	0.7	18	0.8
Increased ALT	22	1.7	17	0.5
Increased creatinine	18	0	12	0.5
Increased TSH <sup>b</sup>	14	N/A	6	N/A

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 405 to 417 patients) and docetaxel group (range: 372 to 390 patients), except for TSH: OPDIVO group n=314 and docetaxel group n=297.

<sup>b</sup> Not graded per NCI CTCAE v4.

#### Malignant Pleural Mesothelioma

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-743, a randomized, open-label trial in patients with previously untreated unresectable malignant pleural mesothelioma [see *Clinical Studies* (14.5)]. Patients received either OPDIVO 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks and ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years; or platinum-doublet chemotherapy for up to 6 cycles. The median duration of therapy in OPDIVO and ipilimumab-treated patients was 5.6 months (range: 0 to 26.2 months); 48% of patients received OPDIVO and ipilimumab for >6 months and 24% of patients received OPDIVO and ipilimumab for >1 year.

Serious adverse reactions occurred in 54% of patients who were treated with OPDIVO in combination with ipilimumab. The most frequent (≥2%) serious adverse reactions were pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.3%) patients and included pneumonitis, acute heart failure, sepsis and encephalitis.

Both OPDIVO and ipilimumab were permanently discontinued due to adverse reactions in 23% of patients and 52% had at least one dose withheld due to an adverse reaction.

The most common (≥20%) adverse reactions were fatigue, musculoskeletal pain, rash, diarrhea, dyspnea, nausea, decreased appetite, cough, and pruritus.

Tables 23 and 24 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-743.



**Table 23: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-743**

Adverse Reaction	OPDIVO and Ipilimumab (n=300)		Chemotherapy (n=284)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>General</b>				
Fatigue <sup>a</sup>	43	4.3	45	6
Pyrexia <sup>b</sup>	18	1.3	4.6	0.7
Edema <sup>c</sup>	17	0	8	0
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>d</sup>	38	3.3	17	1.1
Arthralgia	13	1	1.1	0
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>e</sup>	34	2.7	11	0.4
Pruritus <sup>f</sup>	21	1	1.4	0
<b>Gastrointestinal</b>				
Diarrhea <sup>g</sup>	32	6	12	1.1
Nausea	24	0.7	43	2.5
Constipation	19	0.3	30	0.7
Abdominal pain <sup>h</sup>	15	1	10	0.7
Vomiting	14	0	18	2.1
<b>Respiratory, Thoracic, and Mediastinal</b>				
Dyspnea <sup>i</sup>	27	2.3	16	3.2
Cough <sup>j</sup>	23	0.7	9	0
<b>Metabolism and Nutrition</b>				
Decreased appetite	24	1	25	1.4
<b>Endocrine</b>				
Hypothyroidism <sup>k</sup>	15	0	1.4	0
<b>Infections and Infestations</b>				
Upper respiratory tract infection <sup>l</sup>	12	0.3	7	0
Pneumonia <sup>m</sup>	10	4	4.2	2.1

<sup>a</sup> Includes fatigue and asthenia.<sup>b</sup> Includes pyrexia and tumor-associated fever.<sup>c</sup> Includes edema, generalized edema, peripheral edema, and peripheral swelling.<sup>d</sup> Includes musculoskeletal pain, back pain, bone pain, flank pain, involuntary muscle contractions, muscle spasms, muscle twitching, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, polymyalgia rheumatica, and spinal pain.<sup>e</sup> Includes rash, acne, acneiform dermatitis, allergic dermatitis, atopic dermatitis, autoimmune dermatitis, bullous dermatitis, contact dermatitis, dermatitis, drug eruption, dyshidrotic eczema, eczema, erythematous rash, exfoliative rash, generalized exfoliative dermatitis, generalized rash, granulomatous dermatitis, keratoderma blennorrhagica, macular rash, maculopapular rash, morbilliform rash, nodular rash, papular rash, psoriasiform dermatitis, pruritic rash, pustular rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, toxic skin eruption, and urticaria.<sup>f</sup> Includes pruritus, allergic pruritus, and generalized pruritus.<sup>g</sup> Includes diarrhea, colitis, enteritis, infectious enteritis, enterocolitis, infectious enterocolitis, microscopic colitis, ulcerative colitis, and viral enterocolitis.<sup>h</sup> Includes abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain, lower abdominal pain, and upper abdominal pain.<sup>i</sup> Includes dyspnea, dyspnea at rest, and exertional dyspnea.<sup>j</sup> Includes cough, productive cough, and upper-airway cough syndrome.<sup>k</sup> Includes hypothyroidism, autoimmune thyroiditis, decreased free tri-iodothyronine, increased blood thyroid stimulating hormone, primary hypothyroidism, thyroiditis, and autoimmune hypothyroidism.<sup>l</sup> Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis.<sup>m</sup> Includes pneumonia, lower respiratory tract infection, lung infection, aspiration pneumonia, and *Pneumocystis jirovecii* pneumonia.**Table 24: Laboratory Values Worsening from Baseline<sup>a</sup> Occurring in ≥20% of Patients on OPDIVO and Ipilimumab - CHECKMATE-743**

Laboratory Abnormality	OPDIVO and Ipilimumab		Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Chemistry</b>				
Hyperglycemia	53	3.7	34	1.1
Increased AST	38	7	17	0
Increased ALT	37	7	15	0.4
Increased lipase	34	13	9	0.8
Hyponatremia	32	8	21	2.9
Increased alkaline phosphatase	31	3.1	12	0
Hyperkalemia	30	4.1	16	0.7
Hypocalcemia	28	0	16	0
Increased amylase	26	5	13	0.9
Increased creatinine	20	0.3	20	0.4
<b>Hematology</b>				
Lymphopenia	43	8	57	14
Anemia	43	2.4	75	15

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 109 to 297 patients) and chemotherapy group (range: 90 to 276 patients).**Advanced Renal Cell Carcinoma****First-line Renal Cell Carcinoma****CHECKMATE-214**

The safety of OPDIVO with ipilimumab was evaluated in CHECKMATE-214, a randomized open-label trial in 1082 patients with previously untreated advanced RCC received OPDIVO 3 mg/kg over 60 minutes with ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (n=547) or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (n=535) [see *Clinical Studies* (14.6)]. The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in OPDIVO and ipilimumab-treated patients and 7.8 months (range: 1 day to 20.2+ months) in sunitinib-treated patients. In this trial, 57% of patients in the OPDIVO and ipilimumab arm were exposed to treatment for >6 months and 38% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 59% of patients receiving OPDIVO and ipilimumab. Study therapy was discontinued for adverse reactions in 31% of OPDIVO and ipilimumab patients. Fifty-four percent (54%) of patients receiving OPDIVO and ipilimumab had a dose interruption for an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO and ipilimumab were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea. The most common adverse reactions (reported in ≥20% of patients) were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, and decreased appetite. The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of OPDIVO and ipilimumab-treated patients include increased lipase, anemia, increased creatinine, increased ALT, increased AST, hyponatremia, increased amylase, and lymphopenia.

Tables 25 and 26 summarize adverse reactions and laboratory abnormalities, respectively, that occurred in >15% of OPDIVO and ipilimumab-treated patients in CHECKMATE-214.

**Table 25: Adverse Reactions in >15% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-214**

Adverse Reaction	OPDIVO and Ipilimumab (n=547)		Sunitinib (n=535)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Adverse Reaction General</b>	99	65	99	76
Fatigue <sup>a</sup>	58	8	69	13
Pyrexia	25	0.7	17	0.6
Edema <sup>b</sup>	16	0.5	17	0.6
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>c</sup>	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
<b>Gastrointestinal</b>				
Diarrhea	38	4.6	58	6
Nausea	30	2	43	1.5
Vomiting	20	0.9	28	2.1
Abdominal pain	19	1.6	24	1.9
Constipation	17	0.4	18	0
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>d</sup>	37	4	40	2.6
Arthralgia	23	1.3	16	0
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
<b>Metabolism and Nutrition</b>				
Decreased appetite	21	1.8	29	0.9
<b>Nervous System</b>				
Headache	19	0.9	23	0.9
<b>Endocrine</b>				
Hypothyroidism	18	0.4	27	0.2

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes asthenia.<sup>b</sup> Includes peripheral edema, peripheral swelling.<sup>c</sup> Includes dermatitis described as acneiform, bullous, and exfoliative, drug eruption, rash described as exfoliative, erythematous, follicular, generalized, macular, maculopapular, papular, pruritic, and pustular, fixed-drug eruption.<sup>d</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.**Table 26: Laboratory Values Worsening from Baseline<sup>a</sup> Occurring in >15% of Patients on OPDIVO and Ipilimumab - CHECKMATE-214**

Laboratory Abnormality	OPDIVO and Ipilimumab		Sunitinib	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Chemistry</b>				
Increased lipase	48	20	51	20
Increased creatinine	42	2.1	46	1.7
Increased ALT	41	7	44	2.7
Increased AST	40	4.8	60	2.1
Increased amylase	39	12	33	7
Hyponatremia	39	10	36	7
Increased alkaline phosphatase	29	2	32	1
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	21	0.4	35	0.6
Hypomagnesemia	16	0.4	26	1.6
<b>Hematology</b>				
Anemia	43	3	64	9
Lymphopenia	36	5	63	14

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab group (range: 490 to 538 patients) and sunitinib group (range: 485 to 523 patients).

In addition, among patients with TSH ≤ULN at baseline, a lower proportion of patients experienced a treatment-emergent elevation of TSH &gt; ULN in the OPDIVO and ipilimumab group compared to the sunitinib group (31% and 61%, respectively).

**CHECKMATE-9ER**

The safety of OPDIVO with cabozantinib was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received OPDIVO 240 mg over 30 minutes every 2 weeks with cabozantinib 40 mg orally once daily (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320) [see *Clinical Studies* (14.6)]. Cabozantinib could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in OPDIVO and cabozantinib-treated patients. In this trial, 82% of patients in the OPDIVO and cabozantinib arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving OPDIVO and cabozantinib. The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either OPDIVO or cabozantinib occurred in 20% of patients: 7% OPDIVO only, 8% cabozantinib only, and 6% both drugs due to same adverse reaction at the same time. Adverse reaction leading to dose interruption or reduction of either OPDIVO or cabozantinib occurred in 83% of patients: 3% OPDIVO only, 46% cabozantinib only, and 21% both drugs due to same adverse reaction at the same time, and 6% both drugs sequentially.

The most common adverse reactions reported in ≥20% of patients treated with OPDIVO and cabozantinib were diarrhea, fatigue, hepatotoxicity, palmar-plantar erythrodysesthesia syndrome, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Tables 27 and 28 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9ER.

**Table 27: Adverse Reactions in >15% of Patients Receiving OPDIVO and Cabozantinib - CHECKMATE-9ER**

Adverse Reaction	OPDIVO and Cabozantinib (n=320)		Sunitinib (n=320)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Gastrointestinal</b>				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal pain <sup>a</sup>	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia <sup>b</sup>	15	0	22	0.3
<b>General</b>				
Fatigue <sup>c</sup>	51	8	50	8
<b>Hepatobiliary</b>				
Hepatotoxicity <sup>d</sup>	44	11	26	5
<b>Skin and Subcutaneous Tissue</b>				
Palmar-plantar erythrodysesthesia syndrome	40	8	41	8
Stomatitis <sup>e</sup>	37	3.4	46	4.4
Rash <sup>f</sup>	36	3.1	14	0
Pruritus	19	0.3	4.4	0
<b>Vascular</b>				
Hypertension <sup>g</sup>	36	13	39	14
<b>Endocrine</b>				
Hypothyroidism <sup>h</sup>	34	0.3	30	0.3
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>i</sup>	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
<b>Metabolism and Nutrition</b>				
Decreased appetite	28	1.9	20	1.3
<b>Nervous System</b>				
Dysgeusia	24	0	22	0
Headache	16	0	12	0.6
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough <sup>j</sup>	20	0.3	17	0
Dysphonia	17	0.3	3.4	0
<b>Infections and Infestations</b>				
Upper respiratory tract infection <sup>k</sup>	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.<sup>b</sup> Includes gastroesophageal reflux disease.<sup>c</sup> Includes asthenia.

(Continued)

**Table 27: Adverse Reactions in >15% of Patients Receiving OPDIVO and Cabozantinib - CHECKMATE-9ER**  
(Continued)

<sup>d</sup> Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.

<sup>e</sup> Includes mucosal inflammation, aphthous ulcer, mouth ulceration.

<sup>f</sup> Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.

<sup>g</sup> Includes blood pressure increased, blood pressure systolic increased.

<sup>h</sup> Includes primary hypothyroidism.

<sup>i</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

<sup>j</sup> Includes productive cough.

<sup>k</sup> Includes nasopharyngitis, pharyngitis, rhinitis.

**Table 28: Laboratory Values Worsening from Baseline<sup>a</sup> Occurring in >20% of Patients on OPDIVO and Cabozantinib - CHECKMATE-9ER**

Laboratory Abnormality	OPDIVO and Cabozantinib		Sunitinib	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Chemistry</b>				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
<b>Hematology</b>				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.5	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and cabozantinib group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

#### Previously Treated Renal Cell Carcinoma

##### CHECKMATE-025

The safety of OPDIVO was evaluated in CHECKMATE-025, a randomized open-label trial in 803 patients with advanced RCC who had experienced disease progression during or after at least one anti-angiogenic treatment regimen received OPDIVO 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks (n=406) or everolimus 10 mg daily (n=397) [see Clinical Studies (14.6)]. The median duration of treatment was 5.5 months (range: 1 day to 29.6+ months) in OPDIVO-treated patients and 3.7 months (range: 6 days to 25.7+ months) in everolimus-treated patients.

Rate of death on treatment or within 30 days of the last dose was 4.7% on the OPDIVO arm. Serious adverse reactions occurred in 47% of patients receiving OPDIVO. Study therapy was discontinued for adverse reactions in 16% of OPDIVO patients. Forty-four percent (44%) of patients receiving OPDIVO had a dose interruption for an adverse reaction.

The most frequent serious adverse reactions in at least 2% of patients were: acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. The most common adverse reactions (≥20%) were fatigue, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia. The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of patients include increased creatinine, lymphopenia, anemia, increased AST, increased alkaline phosphatase, hyponatremia, increased triglycerides, and hyperkalemia. In addition, among patients with TSH < ULN at baseline, a greater proportion of patients experienced a treatment-emergent elevation of TSH >ULN in the OPDIVO group compared to the everolimus group (26% and 14%, respectively).

Tables 29 and 30 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-025.

**Table 29: Adverse Reactions in >15% of Patients Receiving OPDIVO - CHECKMATE-025**

Adverse Reaction	OPDIVO (n=406)		Everolimus (n=397)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Adverse Reaction</b>	98	56	96	62
<b>General</b>				
Fatigue <sup>a</sup>	56	6	57	7
Pyrexia	17	0.7	20	0.8
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough/productive cough	34	0	38	0.5
Dyspnea/exertional dyspnea	27	3	31	2
Upper respiratory infection <sup>b</sup>	18	0	11	0
<b>Gastrointestinal</b>				
Nausea	28	0.5	29	1
Diarrhea <sup>c</sup>	25	2.2	32	1.8
Constipation	23	0.5	18	0.5
Vomiting	16	0.5	16	0.5
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>d</sup>	28	1.5	36	1
Pruritus/generalized pruritus	19	0	14	0
<b>Metabolism and Nutrition</b>				
Decreased appetite	23	1.2	30	1.5
<b>Musculoskeletal and Connective Tissue</b>				
Arthralgia	20	1	14	0.5
Back pain	21	3.4	16	2.8

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes asthenia, decreased activity, fatigue, and malaise.

<sup>b</sup> Includes nasopharyngitis, pharyngitis, rhinitis, and viral upper respiratory infection (URI).

<sup>c</sup> Includes colitis, enterocolitis, and gastroenteritis.

<sup>d</sup> Includes dermatitis, acneiform dermatitis, erythematous rash, generalized rash, macular rash, maculopapular rash, papular rash, pruritic rash, erythema multiforme, and erythema.

Other clinically important adverse reactions in CHECKMATE-025 were:

*General Disorders and Administration Site Conditions:* peripheral edema/edema

*Gastrointestinal Disorders:* abdominal pain/discomfort

*Musculoskeletal and Connective Tissue Disorders:* extremity pain, musculoskeletal pain

*Nervous System Disorders:* headache/migraine, peripheral neuropathy

*Investigations:* weight decreased

*Skin Disorders:* palmar-plantar erythrodysesthesia

**Table 30: Laboratory Values Worsening from Baseline<sup>a</sup> Occurring in >15% of Patients on OPDIVO - CHECKMATE-025**

Laboratory Abnormality	OPDIVO		Everolimus	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Hematology</b>				
Lymphopenia	42	6	53	11
Anemia	39	8	69	16
<b>Chemistry</b>				
Increased creatinine	42	2	45	1.6
Increased AST	33	2.8	39	1.6
Increased alkaline phosphatase	32	2.3	32	0.8
Hyponatremia	32	7	26	6
Hyperkalemia	30	4	20	2.1
Hypocalcemia	23	0.9	26	1.3
Increased ALT	22	3.2	31	0.8
Hypercalcemia	19	3.2	6	0.3
<b>Lipids</b>				
Increased triglycerides	32	1.5	67	11
Increased cholesterol	21	0.3	55	1.4

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 259 to 401 patients) and everolimus group (range: 257 to 376 patients).

## Classical Hodgkin Lymphoma

The safety of OPDIVO was evaluated in 266 adult patients with cHL (243 patients in the CHECKMATE-205 and 23 patients in the CHECKMATE-039 trials) [see *Clinical Studies* (14.7)]. Patients received OPDIVO 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity.

The median age was 34 years (range: 18 to 72), 98% of patients had received autologous HSCT, none had received allogeneic HSCT, and 74% had received brentuximab vedotin. The median number of prior systemic regimens was 4 (range: 2 to 15). Patients received a median of 23 doses (cycles) of OPDIVO (range: 1 to 48), with a median duration of therapy of 11 months (range: 0 to 23 months).

Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last nivolumab dose, 2 from infection 8 to 9 months after completing nivolumab, and 6 from complications of allogeneic HSCT. Serious adverse reactions occurred in 26% of patients. Dose delay for an adverse reaction occurred in 34% of patients. OPDIVO was discontinued due to adverse reactions in 7% of patients.

The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. The most common adverse reactions (≥20%) among all patients were upper respiratory tract infection, fatigue, cough, diarrhea, pyrexia, musculoskeletal pain, rash, nausea, and pruritus.

Tables 31 and 32 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-205 and CHECKMATE-039.

**Table 31: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039**

Adverse Reaction <sup>a</sup>	OPDIVO (n=266)	
	All Grades (%)	Grades 3-4 (%)
<b>Infections</b>		
Upper respiratory tract infection <sup>b</sup>	44	0.8
Pneumonia/bronchopneumonia <sup>c</sup>	13	3.8
Nasal congestion	11	0
<b>General</b>		
Fatigue <sup>d</sup>	39	1.9
Pyrexia	29	<1
<b>Respiratory, Thoracic and Mediastinal</b>		
Cough/productive cough	36	0
Dyspnea/exertional dyspnea	15	1.5
<b>Gastrointestinal</b>		
Diarrhea <sup>e</sup>	33	1.5
Nausea	20	0
Vomiting	19	<1
Abdominal pain <sup>f</sup>	16	<1
Constipation	14	0.4
<b>Musculoskeletal and Connective Tissue</b>		
Musculoskeletal pain <sup>g</sup>	26	1.1
Arthralgia	16	<1
<b>Skin and Subcutaneous Tissue</b>		
Rash <sup>h</sup>	24	1.5
Pruritus	20	0
<b>Nervous System</b>		
Headache	17	<1
Neuropathy peripheral <sup>i</sup>	12	<1
<b>Injury, Poisoning and Procedural Complications</b>		
Infusion-related reaction	14	<1
<b>Endocrine</b>		
Hypothyroidism/thyroiditis	12	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes events occurring up to 30 days after last nivolumab dose, regardless of causality. After an immune-mediated adverse reaction, reactions following nivolumab rechallenge were included if they occurred up to 30 days after completing the initial nivolumab course.

<sup>b</sup> Includes nasopharyngitis, pharyngitis, rhinitis, and sinusitis.

<sup>c</sup> Includes pneumonia bacterial, pneumonia mycoplasmal, pneumocystis jirovecii pneumonia.

<sup>d</sup> Includes asthenia.

<sup>e</sup> Includes colitis.

<sup>f</sup> Includes abdominal discomfort and upper abdominal pain.

<sup>g</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, and pain in extremity.

<sup>h</sup> Includes dermatitis, dermatitis acneiform, dermatitis exfoliative, and rash described as macular, papular, maculopapular, pruritic, exfoliative, or acneiform.

<sup>i</sup> Includes hyperesthesia, hypoesthesia, paresthesia, dysesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy. These numbers are specific to treatment-emergent events.

Additional information regarding clinically important adverse reactions:

**Immune-mediated pneumonitis:** In CHECKMATE-205 and CHECKMATE-039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO (one Grade 3 and 12 Grade 2). The median time to onset was 4.5 months (range: 5 days to 12 months). All 13 patients received systemic corticosteroids, with resolution in 12. Four patients permanently discontinued OPDIVO due to pneumonitis. Eight patients continued OPDIVO (three after dose delay), of whom two had recurrence of pneumonitis.

**Peripheral neuropathy:** Treatment-emergent peripheral neuropathy was reported in 12% (31/266) of all patients receiving OPDIVO. Twenty-eight patients (11%) had new-onset peripheral neuropathy and 3 patients had worsening of neuropathy from baseline. The median time to onset was 50 (range: 1 to 309) days.

**Complications of allogeneic HSCT after OPDIVO:** Of 17 patients with cHL from the CHECKMATE-205 and CHECKMATE-039 trials who underwent allogeneic HSCT after treatment with OPDIVO, 6 patients (35%) died from transplant-related complications. Five deaths occurred in the setting of severe (Grade 3 to 4) or refractory GVHD. Hyperacute GVHD occurred in 2 patients (12%) and Grade 3 or higher GVHD was reported in 5 patients (29%). Hepatic VOD occurred in 1 patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure.

Table 32 summarizes laboratory abnormalities in patients with cHL. The most common (≥20%) treatment-emergent laboratory abnormalities included cytopenias, liver function abnormalities, and increased lipase. Other common findings (≥10%) included increased creatinine, electrolyte abnormalities, and increased amylase.

**Table 32: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039**

Laboratory Abnormality	OPDIVO <sup>a</sup> (n=266)	
	All Grades (%) <sup>b</sup>	Grades 3-4 (%) <sup>b</sup>
<b>Hematology</b>		
Leukopenia	38	4.5
Neutropenia	37	5
Thrombocytopenia	37	3
Lymphopenia	32	11
Anemia	26	2.6
<b>Chemistry<sup>c</sup></b>		
Increased AST	33	2.6
Increased ALT	31	3.4
Increased lipase	22	9
Increased alkaline phosphatase	20	1.5
Hyponatremia	20	1.1
Hypokalemia	16	1.9
Increased creatinine	16	<1
Hypocalcemia	15	<1
Hyperkalemia	15	1.5
Hypomagnesemia	14	<1
Increased amylase	13	1.5
Increased bilirubin	11	1.5

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement: range: 203 to 266 patients.

<sup>b</sup> Includes events occurring up to 30 days after last nivolumab dose. After an immune-mediated adverse reaction, reactions following nivolumab rechallenge were included if they occurred within 30 days of completing the initial nivolumab course.

<sup>c</sup> In addition, in the safety population, fasting hyperglycemia (all grade 1-2) was reported in 27 of 69 (39%) evaluable patients and fasting hypoglycemia (all grade 1-2) in 11 of 69 (16%).

## Squamous Cell Carcinoma of the Head and Neck

The safety of OPDIVO was evaluated in CHECKMATE-141, a randomized, active-controlled, open-label, multicenter trial in patients with recurrent or metastatic SCCN with progression during or within 6 months of receiving prior platinum-based therapy [see *Clinical Studies* (14.8)]. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma). Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=236) or investigator's choice of either cetuximab (400 mg/m<sup>2</sup> initial dose intravenously followed by 250 mg/m<sup>2</sup> weekly), or methotrexate (40 to 60 mg/m<sup>2</sup> intravenously weekly), or docetaxel (30 to 40 mg/m<sup>2</sup> intravenously weekly). The median duration of exposure to nivolumab was 1.9 months (range: 1 day to 16.1+ months) in OPDIVO-treated patients. In this trial, 18% of patients received OPDIVO for >6 months and 2.5% of patients received OPDIVO for >1 year.



The median age of all randomized patients was 60 years (range: 28 to 83); 28% of patients in the OPDIVO group were ≥65 years of age and 37% in the comparator group were ≥65 years of age, 83% were male and 83% were White, 12% were Asian, and 4% were Black. Baseline ECOG performance status was 0 (20%) or 1 (78%), 45% of patients received only one prior line of systemic therapy, the remaining 55% of patients had two or more prior lines of therapy, and 90% had prior radiation therapy.

Serious adverse reactions occurred in 49% of patients receiving OPDIVO. OPDIVO was discontinued in 14% of patients and was delayed in 24% of patients for an adverse reaction. Adverse reactions and laboratory abnormalities occurring in patients with SCCHN were generally similar to those occurring in patients with melanoma and NSCLC.

The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. The most common adverse reactions occurring in ≥10% of OPDIVO-treated patients and at a higher incidence than investigator's choice were cough and dyspnea. The most common laboratory abnormalities occurring in ≥10% of OPDIVO-treated patients and at a higher incidence than investigator's choice were increased alkaline phosphatase, increased amylase, hypercalcemia, hyperkalemia, and increased TSH.

#### Adjuvant Treatment of Urothelial Carcinoma (UC)

The safety of OPDIVO was evaluated in CHECKMATE-274, a randomized, double-blind, multicenter trial of adjuvant OPDIVO versus placebo in adult patients who had undergone radical resection of UC originating in the bladder or upper urinary tract (renal pelvis or ureter) and were at high risk of recurrence [see *Clinical Studies* (14.9)]. Patients received OPDIVO 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=351) or placebo (n=348) until recurrence or unacceptable toxicity for a maximum of 1 year. The median duration of OPDIVO treatment was 8.8 months (range: 0 to 12.5).

Serious adverse reactions occurred in 30% of OPDIVO patients. The most frequent serious adverse reaction reported in ≥2% of patients was urinary tract infection. Fatal adverse reactions occurred in 1% of patients; these included events of pneumonitis (0.6%). OPDIVO was discontinued for adverse reactions in 18% of patients. OPDIVO was delayed for adverse reaction in 33% of patients.

The most common adverse reactions (reported in ≥20% of patients) were rash, fatigue, diarrhea, pruritus, musculoskeletal pain, and urinary tract infection.

Tables 33 and 34 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-274.

**Table 33: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-274**

Adverse Reaction	OPDIVO (n=351)		Placebo (n=348)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>a</sup>	36	1.7	19	0.3
Pruritus	30	0	16	0
<b>General</b>				
Fatigue/Asthenia	36	1.1	32	0.3
Pyrexia	10	0.3	10	0.3
<b>Gastrointestinal</b>				
Diarrhea <sup>b</sup>	30	2.8	27	1.7
Nausea	16	0.6	13	0
Abdominal pain <sup>c</sup>	15	0.9	15	0.6
Constipation	13	0.3	15	0.3
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>d</sup>	28	0.6	24	0.9
Arthralgia	11	0.3	13	0
<b>Infections</b>				
Urinary tract infection <sup>e</sup>	22	6	23	9
Upper respiratory tract infection <sup>f</sup>	16	0.3	16	0.6
<b>Endocrine</b>				
Hyperthyroidism	11	0	1.1	0
Hypothyroidism	11	0	2.3	0
<b>Renal and Urinary Disorders</b>				
Renal dysfunction <sup>g</sup>	17	1.7	16	0.9
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough <sup>h</sup>	14	0	11	0
Dyspnea <sup>i</sup>	11	0.3	6	0.3
<b>Metabolism and Nutrition</b>				
Decreased appetite	13	0.9	7	0.3
<b>Nervous System Disorders</b>				
Dizziness <sup>j</sup>	11	0.3	9	0
<b>Hepatobiliary</b>				
Hepatitis <sup>k</sup>	11	4	8	0.6

(Continued)

**Table 33: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-274 (Continued)**

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes acne, blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis contact, eczema, eczema asteatotic, eczema nummular, erythema, erythema multiforme, lichen sclerosus, lichenoid keratosis, pemphigoid, photosensitivity reaction, pigmentation disorder, psoriasis, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rosacea, skin exfoliation, skin lesion, skin reaction, toxic skin eruption, and urticaria.

<sup>b</sup> Includes colitis, colitis microscopic, diarrhea, duodenitis, enteritis, immune-mediated enterocolitis.

<sup>c</sup> Includes abdominal pain, abdominal discomfort, abdominal tenderness, lower and upper abdominal pain.

<sup>d</sup> Includes musculoskeletal pain, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain.

<sup>e</sup> Includes cystitis, escherichia urinary tract infection, pyelonephritis, pyelonephritis acute, pyelonephritis chronic, urethritis, urinary tract infection, urinary tract infection bacterial, urinary tract infection staphylococcal, and urosepsis.

<sup>f</sup> Includes upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis.

<sup>g</sup> Includes acute kidney injury, autoimmune nephritis, blood creatinine increased, glomerular filtration rate decreased, immune-mediated nephritis, nephritis, renal failure, and renal impairment.

<sup>h</sup> Includes cough, productive cough, and upper-airway cough syndrome.

<sup>i</sup> Includes dyspnea and exertional dyspnea.

<sup>j</sup> Includes dizziness, postural dizziness and vertigo.

<sup>k</sup> Includes aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, cholangitis, drug-induced liver injury, hepatic failure, hepatic function abnormal, hepatitis, hepatocellular injury, hyperbilirubinemia, gamma-glutamyl transferase increased, liver injury, and transaminases increased.

**Table 34: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of Patients - CHECKMATE-274**

Laboratory Abnormality	OPDIVO (n=351)		Placebo (n=348)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Chemistry</b>				
Increased creatinine	36	1.7	36	2.6
Increased amylase	34	8	23	3.2
Increased lipase	33	12	31	10
Hyperkalemia	32	5	30	6
Increased alkaline phosphatase	24	2.3	15	0.6
Increased AST	24	3.5	16	0.9
Increased ALT	23	2.9	15	0.6
Hyponatremia	22	4.1	17	1.8
Hypocalcemia	17	1.2	11	0.9
Hypomagnesemia	16	0	9	0
Hypercalcemia	12	0.3	8	0.3
<b>Hematology</b>				
Lymphopenia	33	2.9	27	1.5
Anemia	30	1.4	28	0.9
Neutropenia	11	0.6	10	0.3

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 322 to 348 patients) and placebo group (range: 312 to 341 patients).

#### First-line Treatment of Unresectable or Metastatic UC

The safety of OPDIVO was evaluated in CHECKMATE-901, a randomized, open-label trial in cisplatin-eligible patients with unresectable or metastatic UC [see *Clinical Studies* (14.9)]. Patients received either OPDIVO 360 mg with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by single-agent OPDIVO 480 mg every 4 weeks up to 2 years (n=304), or cisplatin and gemcitabine chemotherapy every 3 weeks for up to 6 cycles (n=288). Patients discontinuing cisplatin alone were permitted to switch to carboplatin.

Among patients who received OPDIVO with chemotherapy, the median duration of OPDIVO exposure was 7.4 months (range: 0.03 to 47.9 months). Serious adverse reactions occurred in 48% of patients receiving OPDIVO in combination with chemotherapy. The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with chemotherapy were urinary tract infection (4.9%), acute kidney injury (4.3%), anemia (3%), pulmonary embolism (2.6%), sepsis (2.3%), and platelet count decreased (2.3%). The most common adverse reactions (reported in ≥20% of patients) were nausea, fatigue, musculoskeletal pain, constipation, decreased appetite, rash, vomiting, and peripheral neuropathy.

Fatal adverse reactions occurred in 3.6% of patients who received OPDIVO in combination with chemotherapy; these included sepsis (1%).

OPDIVO and/or chemotherapy were discontinued in 30% of patients and were delayed in 67% of patients for an adverse reaction.

Tables 35 and 36 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-901.

**Table 35: Adverse Reactions Occurring in ≥10% of Treated Patients - CHECKMATE-901**

Adverse Reaction	OPDIVO and Platinum-Doublet Chemotherapy (n=304)		Platinum-Doublet Chemotherapy (n=288)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Gastrointestinal disorders</b>				
Nausea	52	0.3	53	1
Constipation	30	0	28	0.7
Vomiting	23	1.3	19	2.1
Diarrhea <sup>a</sup>	19	2	14	0
Abdominal pain <sup>b</sup>	14	0.3	9	0.3
<b>General</b>				
Fatigue <sup>c</sup>	48	3.9	43	4.2
Edema <sup>d</sup>	18	0	9	0.3
Pyrexia <sup>e</sup>	14	1	14	0
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>f</sup>	33	3	21	0.3
<b>Metabolism and Nutrition</b>				
Decreased appetite	30	1.6	19	1
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>g</sup>	25	2.3	7	0.3
Pruritus	17	0.7	3.5	0
<b>Nervous System Disorders</b>				
Peripheral neuropathy <sup>h</sup>	20	0.7	14	0
Headache <sup>i</sup>	11	0	5	0
<b>Infections</b>				
Urinary tract infection <sup>j</sup>	19	8	18	8
<b>Endocrine disorders</b>				
Hyperthyroidism <sup>k</sup>	17	0	0.3	0
<b>Renal and Urinary Disorders</b>				
Renal dysfunction <sup>l</sup>	14	6	11	1.7
Hematuria	11	1	7	1.4
<b>Investigations</b>				
Weight decreased	11	0.3	6	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes colitis, immune-mediated enterocolitis.

<sup>b</sup> Includes upper abdominal pain, lower abdominal pain, abdominal discomfort, epigastric discomfort, gastrointestinal pain, and hepatic pain.

<sup>c</sup> Includes asthenia.

<sup>d</sup> Includes peripheral edema, swelling, peripheral swelling, localized edema, swelling, face edema, testicular edema, gravitational edema, and edema genital.

<sup>e</sup> Includes hyperthermia, body temperature increased and hyperpyrexia.

<sup>f</sup> Includes back pain, arthralgia, bone pain, arthritis, musculoskeletal chest pain, non-cardiac chest pain, myalgia, neck pain, pain in extremity, and spinal pain.

<sup>g</sup> Includes maculopapular rash, erythematous rash, macular rash, papular rash, pustular rash, acneiform dermatitis, dermatitis, allergic dermatitis, atopic dermatitis, exfoliative rash, eczema asteatotic, erythema multiforme, palmar-plantar erythrodysesthesia syndrome, eczema, dermatitis exfoliative generalized, and skin exfoliation.

<sup>h</sup> Includes paresthesia, peripheral sensory neuropathy, hypoesthesia, dysesthesia, neuralgia, hyperesthesia, peripheral motor neuropathy, polyneuropathy.

<sup>i</sup> Includes occipital neuralgia.

<sup>j</sup> Includes urosepsis, cystitis, pyelonephritis, pyelonephritis acute, urinary tract infection enterococcal, escherichia urinary tract infection.

<sup>k</sup> Includes blood stimulating hormone increased.

<sup>l</sup> Includes acute kidney injury, renal failure, renal impairment, glomerular filtration rate decreased, anuria, azotemia.

**Table 36: Selected Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥20% of Patients - CHECKMATE-901**

Laboratory Abnormality	OPDIVO and Platinum-Doublet Chemotherapy (n=304)		Platinum-Doublet Chemotherapy (n=288)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Hematology</b>				
Anemia	88	21	80	21
Neutropenia	82	35	76	28
Lymphopenia	71	17	56	13
Thrombocytopenia	60	13	51	8
<b>Chemistry</b>				
Increased creatinine	53	2.4	42	1.1
Hypomagnesemia	48	3.8	39	1.5
Hyponatremia	43	13	39	8
Hyperglycemia	41	3.9	37	3.2
Hypocalcemia	36	2.1	24	1.1
Hyperkalemia	33	3.0	32	1.1
Increased amylase	32	4.2	23	3.6
Increased AST	31	2.4	17	0.7
Increased ALT	29	2.4	19	0.7

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 289-301 patients) and chemotherapy group (range: 265-281 patients).

#### Previously Treated Advanced or Metastatic UC

The safety of OPDIVO was evaluated in CHECKMATE-275, a single arm trial in which 270 patients with locally advanced or metastatic UC had disease progression during or following platinum-containing chemotherapy or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy [see *Clinical Studies* (14.9)]. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 3.3 months (range: 0 to 13.4+). Forty-six percent (46%) of patients had a dose interruption for an adverse reaction.

Fourteen patients (5.2%) died from causes other than disease progression. This includes 4 patients (1.5%) who died from pneumonitis or cardiovascular failure which was attributed to treatment with OPDIVO. Serious adverse reactions occurred in 54% of patients. OPDIVO was discontinued for adverse reactions in 17% of patients.

The most frequent serious adverse reactions reported in ≥2% of patients were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. The most common adverse reactions (reported in ≥20% of patients) were fatigue, musculoskeletal pain, nausea, and decreased appetite.

Tables 37 and 38 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-275.

**Table 37: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275**

Adverse Reaction	OPDIVO (n=270)	
	All Grades (%)	Grades 3-4 (%)
<b>Adverse Reaction</b>		
	99	51
<b>General</b>		
Asthenia/fatigue/malaise	46	7
Pyrexia/tumor associated fever	17	0.4
Edema/peripheral edema/peripheral swelling	13	0.4
<b>Musculoskeletal and Connective Tissue</b>		
Musculoskeletal pain <sup>a</sup>	30	2.6
Arthralgia	10	0.7
<b>Metabolism and Nutrition</b>		
Decreased appetite	22	2.2
<b>Gastrointestinal</b>		
Nausea	22	0.7
Diarrhea	17	2.6
Constipation	16	0.4
Abdominal pain <sup>b</sup>	13	1.5
Vomiting	12	1.9

(Continued)

**Table 37: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275 (Continued)**

Adverse Reaction	OPDIVO (n=270)	
	All Grades (%)	Grades 3-4 (%)
<b>Respiratory, Thoracic and Mediastinal</b>		
Cough/productive cough	18	0
Dyspnea/exertional dyspnea	14	3.3
<b>Infections</b>		
Urinary tract infection/escherichia/fungal urinary tract infection	17	7
<b>Skin and Subcutaneous Tissue</b>		
Rash <sup>c</sup>	16	1.5
Pruritus	12	0
<b>Endocrine</b>		
Thyroid disorders <sup>d</sup>	15	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain.

<sup>b</sup> Includes abdominal discomfort, lower and upper abdominal pain.

<sup>c</sup> Includes dermatitis, dermatitis acneiform, dermatitis bullous, and rash described as generalized, macular, maculopapular, or pruritic.

<sup>d</sup> Includes autoimmune thyroiditis, blood TSH decrease, blood TSH increase, hyperthyroidism, hypothyroidism, thyroiditis, thyroxine decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine free increased, tri-iodothyronine increased.

**Table 38: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients - CHECKMATE-275**

Laboratory Abnormality	OPDIVO <sup>a</sup>	
	All Grades (%)	Grades 3-4 (%)
<b>Chemistry</b>		
Hyperglycemia	42	2.4
Hyponatremia	41	11
Increased creatinine	39	2
Increased alkaline phosphatase	33	5.5
Hypocalcemia	26	0.8
Increased AST	24	3.5
Increased lipase	20	7
Hyperkalemia	19	1.2
Increased ALT	18	1.2
Increased amylase	18	4.4
Hypomagnesemia	16	0
<b>Hematology</b>		
Lymphopenia	42	9
Anemia	40	7
Thrombocytopenia	15	2.4
Leukopenia	11	0

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: range: 84 to 256 patients.

#### MSI-H or dMMR Metastatic Colorectal Cancer

The safety of OPDIVO administered as a single agent or in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, open-label trial [see *Clinical Studies* (14.10)]. In CHECKMATE-142, 74 patients with mCRC received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or until intolerable toxicity and 119 patients with mCRC received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks until disease progression or until unacceptable toxicity.

In the OPDIVO with ipilimumab cohort, serious adverse reactions occurred in 47% of patients. Treatment was discontinued in 13% of patients and delayed in 45% of patients for an adverse reaction. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. The most common adverse reactions (reported in ≥20% of patients) were fatigue, diarrhea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, decreased appetite, and vomiting.

Tables 39 and 40 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-142. Based on the design of CHECKMATE-142, the data below cannot be used to identify statistically significant differences between the two cohorts summarized below for any adverse reaction.

**Table 39: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-142**

Adverse Reaction	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>General</b>				
Fatigue <sup>a</sup>	54	5	49	6
Pyrexia	24	0	36	0
Edema <sup>b</sup>	12	0	7	0
<b>Gastrointestinal</b>				
Diarrhea	43	2.7	45	3.4
Abdominal pain <sup>c</sup>	34	2.7	30	5
Nausea	34	1.4	26	0.8
Vomiting	28	4.1	20	1.7
Constipation	20	0	15	0
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>d</sup>	28	1.4	36	3.4
Arthralgia	19	0	14	0.8
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough	26	0	19	0.8
Dyspnea	8	1	13	1.7
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>e</sup>	23	1.4	25	4.2
Pruritus	19	0	28	1.7
Dry Skin	7	0	11	0
<b>Infections</b>				
Upper respiratory tract infection <sup>f</sup>	20	0	9	0
<b>Endocrine</b>				
Hyperglycemia	19	2.7	6	1
Hypothyroidism	5	0	14	0.8
Hyperthyroidism	4	0	12	0
<b>Nervous System</b>				
Headache	16	0	17	1.7
Dizziness	14	0	11	0
<b>Metabolism and Nutrition</b>				
Decreased appetite	14	1.4	20	1.7
<b>Psychiatric</b>				
Insomnia	9	0	13	0.8
<b>Investigations</b>				
Weight decreased	8	0	10	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes asthenia.

<sup>b</sup> Includes peripheral edema and peripheral swelling.

<sup>c</sup> Includes upper abdominal pain, lower abdominal pain, and abdominal discomfort.

<sup>d</sup> Includes back pain, pain in extremity, myalgia, neck pain, and bone pain.

<sup>e</sup> Includes dermatitis, dermatitis acneiform, and rash described as maculo-papular, erythematous, and generalized.

<sup>f</sup> Includes nasopharyngitis and rhinitis.

Clinically important adverse reactions reported in <10% of patients receiving OPDIVO with ipilimumab were encephalitis (0.8%), necrotizing myositis (0.8%), and uveitis (0.8%).

**Table 40: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of Patients - CHECKMATE-142**

Laboratory Abnormality	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Hematology</b>				
Anemia	50	7	42	9
Lymphopenia	36	7	25	6
Neutropenia	20	4.3	18	0
Thrombocytopenia	16	1.4	26	0.9

(Continued)

**Table 40: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of Patients - CHECKMATE-142**  
(Continued)

Laboratory Abnormality	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Chemistry</b>				
Increased alkaline phosphatase	37	2.8	28	5
Increased lipase	33	19	39	12
Increased ALT	32	2.8	33	12
Increased AST	31	1.4	40	12
Hyponatremia	27	4.3	26	5
Hypocalcemia	19	0	16	0
Hypomagnesemia	17	0	18	0
Increased amylase	16	4.8	36	3.4
Increased bilirubin	14	4.2	21	5
Hypokalemia	14	0	15	1.8
Increased creatinine	12	0	25	3.6
Hyperkalemia	11	0	23	0.9

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. Number of evaluable patients ranges from 62 to 71 for the OPDIVO cohort and from 87 to 114 for the OPDIVO and ipilimumab cohort.

#### Hepatocellular Carcinoma

The safety of OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg was evaluated in a subgroup comprising 49 patients with HCC and Child-Pugh Class A cirrhosis enrolled in Cohort 4 of CHECKMATE-040, a multicenter, multiple-cohort, open-label trial [see *Clinical Studies* (14.11)] who progressed on or were intolerant to sorafenib. OPDIVO and ipilimumab were administered every 3 weeks for 4 doses, followed by single-agent OPDIVO 240 mg every 2 weeks until disease progression or unacceptable toxicity. During the OPDIVO and ipilimumab combination period, 33 of 49 (67%) patients received all 4 planned doses of OPDIVO and ipilimumab. During the entire treatment period, the median duration of exposure to OPDIVO was 5.1 months (range: 0 to 35+ months) and to ipilimumab was 2.1 months (range: 0 to 4.5 months). Forty-seven percent of patients were exposed to treatment for >6 months, and 35% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 59% of patients. Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.

The most frequent serious adverse reactions (reported in ≥4% of patients) were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis.

Tables 41 and 42 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-040.

**Table 41: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 of CHECKMATE-040**

Adverse Reaction	OPDIVO and Ipilimumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
<b>Skin and Subcutaneous Tissue</b>		
Rash	53	8
Pruritus	53	4
<b>Musculoskeletal and Connective Tissue</b>		
Musculoskeletal pain	41	2
Arthralgia	10	0
<b>Gastrointestinal</b>		
Diarrhea	39	4
Abdominal pain	22	6
Nausea	20	0
Ascites	14	6
Constipation	14	0
Dry mouth	12	0
Dyspepsia	12	2
Vomiting	12	2
Stomatitis	10	0

(Continued)

**Table 41: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 of CHECKMATE-040**  
(Continued)

Adverse Reaction	OPDIVO and Ipilimumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
<b>Respiratory, Thoracic and Mediastinal</b>		
Cough	37	0
Dyspnea	14	0
Pneumonitis	10	2
<b>Metabolism and Nutrition</b>		
Decreased appetite	35	2
<b>General</b>		
Fatigue	27	2
Pyrexia	27	0
Malaise	18	2
Edema	16	2
Influenza-like illness	14	0
Chills	10	0
<b>Nervous System</b>		
Headache	22	0
Dizziness	20	0
<b>Endocrine</b>		
Hypothyroidism	20	0
Adrenal insufficiency	18	4
<b>Investigations</b>		
Weight decreased	20	0
<b>Psychiatric</b>		
Insomnia	18	0
<b>Blood and Lymphatic System</b>		
Anemia	10	4
<b>Infections</b>		
Influenza	10	2
<b>Vascular</b>		
Hypotension	10	0

Clinically important adverse reactions reported in <10% of patients who received OPDIVO with ipilimumab were hyperglycemia (8%), colitis (4%), and increased blood creatine phosphokinase (2%).

**Table 42: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 of CHECKMATE-040**

Laboratory Abnormality	OPDIVO and Ipilimumab (n=47)	
	All Grades (%)	Grades 3-4 (%)
<b>Hematology</b>		
Lymphopenia	53	13
Anemia	43	4.3
Neutropenia	43	9
Leukopenia	40	2.1
Thrombocytopenia	34	4.3
<b>Chemistry</b>		
Increased AST	66	40
Increased ALT	66	21
Increased bilirubin	55	11
Increased lipase	51	26
Hyponatremia	49	32
Hypocalcemia	47	0
Increased alkaline phosphatase	40	4.3
Increased amylase	38	15
Hypokalemia	26	2.1
Hyperkalemia	23	4.3
Increased creatinine	21	0
Hypomagnesemia	11	0

In patients who received OPDIVO with ipilimumab, virologic breakthrough occurred in 4 of 28 (14%) patients and 2 of 4 (50%) patients with active HBV or HCV at baseline, respectively. HBV virologic breakthrough was defined as at least a 1 log increase in HBV



DNA for those patients with detectable HBV DNA at baseline. HCV virologic breakthrough was defined as a 1 log increase in HCV RNA from baseline.

#### Esophageal Cancer

##### Adjuvant Treatment of Resected Esophageal or Gastroesophageal Junction Cancer

The safety of OPDIVO was evaluated in CHECKMATE-577, a randomized, placebo-controlled, double-blinded, multicenter trial in 792 treated patients with completely resected (negative margins) esophageal or gastroesophageal junction cancer who had residual pathologic disease following chemoradiotherapy (CRT) [see *Clinical Studies* (14.12)]. The trial excluded patients who did not receive concurrent CRT prior to surgery, had stage IV resectable disease, autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications. Patients received either OPDIVO 240 mg or placebo by intravenous infusion over 30 minutes every 2 weeks for 16 weeks followed by 480 mg or placebo by intravenous infusion over 30 minutes every 4 weeks beginning at week 17. Patients were treated until disease recurrence, unacceptable toxicity, or for up to 1-year total duration. The median duration of exposure was 10.1 months (range: <0.1 to 14 months) in OPDIVO-treated patients and 9 months (range: <0.1 to 15 months) in placebo-treated patients. Among patients who received OPDIVO, 61% were exposed for >6 months and 54% were exposed for >9 months.

Serious adverse reactions occurred in 33% of patients receiving OPDIVO. A serious adverse reaction reported in ≥2% of patients who received OPDIVO was pneumonitis. A fatal adverse reaction of myocardial infarction occurred in one patient who received OPDIVO.

OPDIVO was discontinued in 12% of patients and was delayed in 28% of patients for an adverse reaction.

Tables 43 and 44 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-577.

**Table 43: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO - CHECKMATE-577**

Adverse Reaction	OPDIVO (n=532)		Placebo (n=260)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Adverse Reaction</b>	96	34	93	32
<b>Gastrointestinal</b>				
Diarrhea	29	0.9	29	0.8
Nausea	23	0.8	21	0
Abdominal Pain <sup>a</sup>	17	0.8	20	1.5
Vomiting	15	0.6	16	1.2
Dysphagia	13	0.8	17	3.5
Dyspepsia <sup>b</sup>	12	0.2	16	0.4
Constipation	11	0	12	0
<b>General</b>				
Fatigue <sup>c</sup>	34	1.3	29	1.5
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough <sup>d</sup>	20	0.2	21	0.4
Dyspnea <sup>e</sup>	12	0.8	12	0.4
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>f</sup>	21	0.9	10	0.4
Pruritus	13	0.4	6	0
<b>Investigations</b>				
Weight decreased	13	0.4	9	0
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>g</sup>	21	0.6	20	0.8
Arthralgia	10	0.2	8	0
<b>Metabolism and Nutrition</b>				
Decreased appetite	15	0.9	10	0.8
<b>Endocrine</b>				
Hypothyroidism	11	0	1.5	0

<sup>a</sup> Includes upper abdominal pain, lower abdominal pain, and abdominal discomfort.

<sup>b</sup> Includes gastroesophageal reflux.

<sup>c</sup> Includes asthenia.

<sup>d</sup> Includes productive cough.

<sup>e</sup> Includes dyspnea exertional.

<sup>f</sup> Includes rash pustular, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, exfoliative rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic.

<sup>g</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, spinal pain.

**Table 44: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of Patients - CHECKMATE-577**

Laboratory Abnormality	OPDIVO (n=532)		Placebo (n=260)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Chemistry</b>				
Increased AST	27	2.1	22	0.8
Increased alkaline phosphatase	25	0.8	18	0.8
Increased albumin	21	0.2	18	0
Increased ALT	20	1.9	16	1.2
Increased amylase	20	3.9	13	1.3
Hyponatremia	19	1.7	12	1.2
Hyperkalemia	17	0.8	15	1.6
Hypokalemia	12	1	11	1.2
Transaminases increased <sup>b</sup>	11	1.5	6	1.2
<b>Hematology</b>				
Lymphopenia	44	17	35	12
Anemia	27	0.8	21	0.4
Neutropenia	24	1.5	23	0.4

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 163 to 526 patients) and Placebo group (range: 86 to 256 patients).

<sup>b</sup> Includes alanine aminotransferase increased, aspartate aminotransferase increased.

#### First-line Treatment of Unresectable Advanced or Metastatic ESCC

The safety of OPDIVO in combination with chemotherapy or in combination with ipilimumab was evaluated in CHECKMATE-648, a randomized, active-controlled, multicenter, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic ESCC [see *Clinical Studies* (14.12)]. Patients received one of the following treatments:

- OPDIVO 240 mg on days 1 and 15, 5-FU (fluorouracil) 800 mg/m<sup>2</sup>/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m<sup>2</sup> intravenously on day 1 (of a 4-week cycle).
- OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks.
- 5-FU (fluorouracil) 800 mg/m<sup>2</sup>/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m<sup>2</sup> intravenously on day 1 (of a 4-week cycle).

Among patients who received OPDIVO with chemotherapy, the median duration of exposure was 5.7 months (range: 0.1 to 30.6 months). Among patients who received OPDIVO and ipilimumab, the median duration of exposure was 2.8 months (range: 0 to 24 months).

Serious adverse reactions occurred in 62% of patients receiving OPDIVO in combination with chemotherapy and in 69% of patients receiving OPDIVO in combination with ipilimumab. The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with chemotherapy were pneumonia (11%), dysphagia (7%), esophageal stenosis (2.9%), acute kidney injury (2.9%), and pyrexia (2.3%). The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with ipilimumab were pneumonia (10%), pyrexia (4.3%), pneumonitis (4%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%).

Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with chemotherapy; these included pneumonitis, pneumatosis intestinalis, pneumonia, and acute kidney injury and in 5 (1.6%) patients who received OPDIVO in combination with ipilimumab; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome.

OPDIVO and/or chemotherapy were discontinued in 39% of patients and were delayed in 71% of patients for an adverse reaction. OPDIVO and/or ipilimumab were discontinued in 23% of patients and were delayed in 46% of patients for an adverse reaction.

The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with chemotherapy were nausea, decreased appetite, fatigue, constipation, stomatitis, diarrhea, and vomiting. The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with ipilimumab were rash, fatigue, pyrexia, nausea, diarrhea, and constipation.

Tables 45 and 46 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-648.

Table 45: Adverse Reactions in ≥10% of Patients - CHECKMATE-648

Adverse Reaction	OPDIVO with Cisplatin and 5-FU (n=310)		OPDIVO and Ipilimumab (n=322)		Cisplatin and 5-FU (n=304)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Gastrointestinal</b>						
Nausea	65	4.2	22	0.6	56	2.6
Constipation	44	1	20	0.3	43	1
Stomatitis <sup>a</sup>	44	9	11	0.6	35	3
Diarrhea	29	2.9	22	1.9	20	2
Vomiting	23	2.3	15	1.6	19	3
Dysphagia	14	7	12	5	12	4.9
Abdominal pain <sup>b</sup>	13	1.9	10	0.9	11	0.7
<b>Metabolism and Nutrition</b>						
Decreased appetite	51	7	17	4	50	6
<b>General</b>						
Fatigue <sup>c</sup>	47	3.5	28	2.5	41	4.9
Pyrexia <sup>d</sup>	19	0.3	23	0.9	12	0.3
Edema <sup>e</sup>	16	0	7	0	13	0
<b>Nervous System</b>						
Peripheral neuropathy <sup>f</sup>	18	1.3	2.8	0	13	1
<b>Psychiatric</b>						
Insomnia	16	0	8	0	10	0.3
<b>Skin and Subcutaneous Tissue</b>						
Rash <sup>g</sup>	16	0.6	31	3.1	7	0
Pruritus	11	0	17	0.9	3.6	0
Alopecia	10	0			11	0
<b>Respiratory, Thoracic and Mediastinal</b>						
Cough <sup>h</sup>	16	0.3	13	0.3	13	0.3
<b>Infections and Infestations</b>						
Pneumonia <sup>i</sup>	13	5	14	8	10	2.6
<b>Endocrine</b>						
Hypothyroidism	7	0	14	0	0.3	0
<b>Investigations</b>						
Weight decreased	12	0.6	12	1.9	11	1
<b>Musculoskeletal and Connective Tissue</b>						
Musculoskeletal pain <sup>j</sup>	11	0.3	14	0.6	8	0.3

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes aphthous ulcer, mouth ulceration, and mucosal inflammation.

<sup>b</sup> Includes abdominal discomfort, abdominal pain lower, and abdominal pain upper.

<sup>c</sup> Includes asthenia and malaise.

<sup>d</sup> Includes tumor associated fever.

<sup>e</sup> Includes swelling, generalized edema, edema peripheral, and peripheral swelling.

<sup>f</sup> Includes hyperesthesia, hypoesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.

<sup>g</sup> Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculopapular, rash papular, and rash pruritic.

<sup>h</sup> Includes productive cough.

<sup>i</sup> Includes organizing pneumonia, pneumonia bacterial, and pneumonia pseudomonal.

<sup>j</sup> Includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, and spinal pain.

Table 46: Laboratory Values Worsening from Baseline<sup>a</sup> Occurring in ≥10% of Patients - CHECKMATE-648

Laboratory Abnormality	OPDIVO with Cisplatin and 5-FU (n=310)		OPDIVO and Ipilimumab (n=322)		Cisplatin and 5-FU (n=304)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Hematology</b>						
Anemia	81	21	52	7	66	14
Lymphopenia	67	23	50	13	44	8
Neutropenia	61	18	13	1.3	48	13
Leukopenia	53	11			39	5
Thrombocytopenia	43	3.3	12	1	29	2.8
<b>Chemistry</b>						
Hyponatremia	52	15	45	11	40	8
Hypocalcemia	43	3	32	0	23	0.7
Increased creatinine	41	2.3	15	0.7	31	0.7
Hypomagnesemia	35	1.7	15	0	25	1.8
Hyperglycemia	34	0	43	4.3	36	0.8
Hyperkalemia	33	2.3	23	1.6	24	0.7
Hypokalemia	29	9	19	5	17	6
Increased alkaline phosphatase	26	1.3	31	3.3	15	0
Increased AST	23	3.3	39	6	11	1.4
Increased ALT	23	2.3	33	6	8	0.7
Hypoglycemia	18	0.4	15	1.2	7	0
Hypercalcemia	11	2.6	15	2	8	0

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO with cisplatin and 5-FU group (range: 60 to 305 patients), OPDIVO and ipilimumab group (range: 59 to 307 patients) or cisplatin and 5-FU group (range: 56 to 283 patients).

#### Previously-Treated Unresectable Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

The safety of OPDIVO was evaluated in ATTRACTION-3, a randomized, active-controlled, open-label, multicenter trial in 209 patients with unresectable advanced, recurrent or metastatic ESCC refractory or intolerant to at least one fluoropyrimidine- and platinum-based chemotherapy [see *Clinical Studies* (14.12)]. The trial excluded patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had autoimmune disease, used systemic corticosteroids or immunosuppressants, had apparent tumor invasion of organs adjacent to the esophageal tumor or had stents in the esophagus or respiratory tract. Patients received OPDIVO 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=209) or investigator's choice: docetaxel 75 mg/m<sup>2</sup> intravenously every 3 weeks (n=65) or paclitaxel 100 mg/m<sup>2</sup> intravenously once a week for 6 weeks followed by 1 week off (n=143). Patients were treated until disease progression or unacceptable toxicity. The median duration of exposure was 2.6 months (range: 0 to 29.2 months) in OPDIVO-treated patients and 2.6 months (range: 0 to 21.4 months) in docetaxel- or paclitaxel-treated patients. Among patients who received OPDIVO, 26% were exposed for >6 months and 10% were exposed for >1 year.

Serious adverse reactions occurred in 38% of patients receiving OPDIVO. Serious adverse reactions reported in ≥2% of patients who received OPDIVO were pneumonia, esophageal fistula, interstitial lung disease and pyrexia. The following fatal adverse reactions occurred in patients who received OPDIVO: interstitial lung disease or pneumonitis (1.4%), pneumonia (1.0%), septic shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death (0.5%).

OPDIVO was discontinued in 13% of patients and was delayed in 27% of patients for an adverse reaction.

Tables 47 and 48 summarize the adverse reactions and laboratory abnormalities, respectively, in ATTRACTION-3.

**Table 47: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO - ATTRACTION-3**

Adverse Reaction	OPDIVO (n=209)		Docetaxel or Paclitaxel (n=208)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>a</sup>	22	1.9	28	1
Pruritus	12	0	7	0
<b>Metabolism and Nutrition</b>				
Decreased appetite <sup>b</sup>	21	1.9	35	5
<b>Gastrointestinal</b>				
Diarrhea <sup>c</sup>	18	1.9	17	1.4
Constipation	17	0	19	0
Nausea	11	0	20	0.5
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>d</sup>	17	0	26	1.4
<b>Infections</b>				
Upper respiratory tract infection <sup>e</sup>	17	1	14	0
Pneumonia <sup>f</sup>	13	5	19	9
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough <sup>g</sup>	16	0	14	0.5
<b>General</b>				
Pyrexia <sup>h</sup>	16	0.5	19	0.5
Fatigue <sup>i</sup>	12	1.4	27	4.8
<b>Blood and Lymphatic System</b>				
Anemia <sup>j</sup>	13	8	30	13
<b>Endocrine</b>				
Hypothyroidism <sup>k</sup>	11	0	1.4	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes urticaria, drug eruption, eczema, eczema asteatotic, eczema nummular, palmar-plantar erythrodysesthesia syndrome, erythema, erythema multiforme, blister, skin exfoliation, Stevens-Johnson syndrome, dermatitis, dermatitis described as acneiform, bullous, or contact, and rash described as maculo-papular, generalized, or pustular.

<sup>b</sup> Includes hypophagia, and food aversion.

<sup>c</sup> Includes colitis.

<sup>d</sup> Includes spondylolisthesis, periarthritis, musculoskeletal chest pain, neck pain, arthralgia, back pain, myalgia, pain in extremity, arthritis, bone pain, and periarthritis calcarea.

<sup>e</sup> Includes influenza, influenza like illness, pharyngitis, nasopharyngitis, tracheitis, and bronchitis and upper respiratory infection with bronchitis.

<sup>f</sup> Includes pneumonia aspiration, pneumonia bacterial, and lung infection. Two patients (1.0%) died of pneumonia in the OPDIVO treatment arm. Two patients (1.0%) died of pneumonia in the chemotherapy treatment arm; these deaths occurred with paclitaxel only.

<sup>g</sup> Includes productive cough.

<sup>h</sup> Includes tumor-associated fever.

<sup>i</sup> Includes asthenia.

<sup>j</sup> Includes hemoglobin decreased, and iron deficiency anemia.

<sup>k</sup> Includes blood thyroid stimulating hormone increased.

**Table 48: Laboratory Abnormalities Worsening from Baseline<sup>a</sup> Occurring in ≥10% of Patients - ATTRACTION-3**

Laboratory Abnormality	OPDIVO (n=209)		Docetaxel or Paclitaxel (n=208)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Chemistry</b>				
Increased creatinine	78	0.5	68	0.5
Hyperglycemia	52	5	62	5
Hyponatremia	42	11	50	12
Increased AST	40	6	30	1
Increased alkaline phosphatase	33	4.8	24	1
Increased ALT	31	5	22	1.9
Hypercalcemia	22	6	14	2.9
Hyperkalemia	22	0.5	31	1
Hypoglycemia	14	1.4	14	0.5
Hypokalemia	11	2.9	13	3.4
<b>Hematology</b>				
Lymphopenia	46	19	72	43
Anemia	42	9	71	17
Leukopenia	11	0.5	79	45

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (209 patients) and Docetaxel or Paclitaxel group (range: 207 to 208 patients).

#### Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

The safety of OPDIVO in combination with chemotherapy was evaluated in CHECKMATE-649, a randomized, multicenter, open-label trial in patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma [see *Clinical Studies* (14.13)]. The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive or had untreated central nervous system (CNS) metastases. Patients were randomized to receive OPDIVO in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

- OPDIVO 240 mg in combination with mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or mFOLFOX6 every 2 weeks.
- OPDIVO 360 mg in combination with CapeOX (capecitabine and oxaliplatin) every 3 weeks or CapeOX every 3 weeks.

Patients were treated with OPDIVO in combination with chemotherapy or chemotherapy until disease progression, unacceptable toxicity, or up to 2 years. The median duration of exposure was 6.8 months (range: 0 to 33.5 months) in OPDIVO and chemotherapy-treated patients. Among patients who received OPDIVO and chemotherapy, 54% were exposed for >6 months and 28% were exposed for >1 year.

Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation. Serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy. OPDIVO and/or chemotherapy were discontinued in 44% of patients and at least one dose was withheld in 76% of patients due to an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with chemotherapy were peripheral neuropathy, nausea, fatigue, diarrhea, vomiting, decreased appetite, abdominal pain, constipation, and musculoskeletal pain.

Tables 49 and 50 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-649.

**Table 49: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Chemotherapy - CHECKMATE-649**

Adverse Reaction	OPDIVO and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Adverse Reaction</b>	99	69	98	59
<b>Nervous System</b>				
Peripheral neuropathy <sup>a</sup>	53	7	46	4.8
Headache	11	0.8	6	0.3
<b>Gastrointestinal</b>				
Nausea	48	3.2	44	3.7
Diarrhea	39	5	34	3.7
Vomiting	31	4.2	29	4.2
Abdominal pain <sup>b</sup>	27	2.8	24	2.6
Constipation	25	0.6	21	0.4
Stomatitis <sup>c</sup>	17	1.8	13	0.8
<b>General</b>				
Fatigue <sup>d</sup>	44	7	40	5
Pyrexia <sup>e</sup>	19	1	11	0.4
Edema <sup>f</sup>	12	0.5	8	0.1
<b>Metabolism and Nutrition</b>				
Decreased appetite	29	3.6	26	2.5
Hypoalbuminemia <sup>g</sup>	14	0.3	9	0.3
<b>Investigations</b>				
Weight decreased	17	1.3	15	0.7
Increased lipase	14	7	8	3.7
Increased amylase	12	3.1	5	0.4
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>h</sup>	20	1.3	14	2
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>i</sup>	18	1.7	4.4	0.1
Palmar-plantar erythrodysesthesia syndrome	13	1.5	12	0.8
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough <sup>j</sup>	13	0.1	9	0
<b>Infections and Infestations</b>				
Upper respiratory tract infection <sup>k</sup>	10	0.1	7	0.1

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes dysesthesia, hypoesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.

<sup>b</sup> Includes abdominal discomfort, abdominal pain lower, and abdominal pain upper.

<sup>c</sup> Includes aphthous ulcer, mouth ulceration, and mucosal inflammation.

<sup>d</sup> Includes asthenia.

<sup>e</sup> Includes tumor associated fever.

<sup>f</sup> Includes swelling, generalized edema, edema peripheral, and peripheral swelling.

<sup>g</sup> Includes blood albumin decreased.

<sup>h</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

<sup>i</sup> Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, nodular rash, rash erythematous, rash macular, rash maculopapular, rash papular, rash pruritic, and rash vesicular.

<sup>j</sup> Includes productive cough.

<sup>k</sup> Includes nasopharyngitis, pharyngitis, and rhinitis.

**Table 50: Laboratory Values Worsening from Baseline<sup>a</sup> Occurring in ≥10% of Patients - CHECKMATE-649**

Laboratory Abnormality	OPDIVO and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
<b>Hematology</b>				
Neutropenia	73	29	62	23
Leukopenia	69	12	59	9
Thrombocytopenia	68	7	63	4.4
Anemia	59	14	60	10
Lymphopenia	59	12	49	9
<b>Chemistry</b>				
Increased AST	52	4.6	47	1.9
Hypocalcemia	42	1.6	37	1
Hyperglycemia	41	3.9	38	2.7
Increased ALT	37	3.4	30	1.9
Hyponatremia	34	6	24	5
Hypokalemia	27	7	24	4.8
Hyperbilirubinemia	24	2.8	21	2
Increased creatinine	15	1	9	0.5
Hyperkalemia	14	1.4	11	0.7
Hypoglycemia	12	0.7	9	0.2
Hypernatremia	11	0.5	7.1	0

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and mFOLFOX6 or CapeOX group (407 to 767 patients) or mFOLFOX6 or CapeOX group (range: 405 to 735 patients).

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of OPDIVO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Eye:* Vogt-Koyanagi-Harada (VKH) syndrome

*Complications of OPDIVO Treatment After Allogeneic HSCT:* Treatment refractory, severe acute and chronic GVHD

*Blood and lymphatic system disorders:* Hemophagocytic lymphohistiocytosis (HLH) (including fatal cases), autoimmune hemolytic anemia (including fatal cases)

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on data from animal studies and its mechanism of action [see *Clinical Pharmacology* (12.1)], OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death (see *Data*). Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available data on OPDIVO use in pregnant women to evaluate a drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

#### Data

##### Animal Data

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.



## 8.2 Lactation

### Risk Summary

There are no data on the presence of nivolumab in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment and for 5 months after the last dose of OPDIVO.

## 8.3 Females and Males of Reproductive Potential

### Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating OPDIVO [see Use in Specific Populations (8.1)].

### Contraception

OPDIVO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for 5 months following the last dose.

## 8.4 Pediatric Use

The safety and effectiveness of OPDIVO have been established in pediatric patients aged 12 years and older for the following indications: as a single agent and in combination with ipilimumab for the treatment of unresectable or metastatic melanoma, as a single agent for the adjuvant treatment of completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma and, as a single agent or in combination with ipilimumab for the treatment of MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of OPDIVO for these indications is supported by evidence from adequate and well-controlled studies in adults with melanoma or MSI-H or dMMR mCRC and additional pharmacokinetic data in pediatric patients. Nivolumab exposure in pediatric patients 12 years and older is comparable to that of adults and the courses of melanoma and MSI-H or dMMR mCRC are similar in pediatric patients aged 12 years and older to that of adults to allow extrapolation of safety and efficacy [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1, 14.10)].

The safety and effectiveness of OPDIVO have not been established for pediatric patients younger than 12 years old with melanoma or MSI-H or dMMR mCRC.

The safety and effectiveness of OPDIVO have not been established in pediatric patients with non-small cell lung cancer, malignant pleural mesothelioma, advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, hepatocellular carcinoma, esophageal cancer, gastric cancer, gastroesophageal cancer and esophageal adenocarcinoma.

## 8.5 Geriatric Use

### Single Agent

Of 3569 patients with melanoma, NSCLC, renal cell carcinoma, urothelial carcinoma, ESCC, and esophageal or gastroesophageal junction cancer who were randomized to single agent OPDIVO in clinical studies, 41% were 65 years and over and 10% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients [see Clinical Studies (14.1, 14.2, 14.4, 14.6, 14.9, 14.12)].

In patients with cHL, recurrent head and neck SCC, or dMMR or MSI-H metastatic CRC (mCRC) who were treated with single agent OPDIVO in clinical studies did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients [see Clinical Studies (14.7, 14.8, 14.10)].

### In Combination with Ipilimumab

Of the 314 patients with melanoma who were randomized to OPDIVO in combination with ipilimumab, 41% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients [see Clinical Studies (14.1)].

Of the 576 patients with NSCLC who were randomized to OPDIVO in combination with ipilimumab, 48% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29%) relative to all patients who received OPDIVO with ipilimumab (18%). Of the 396 patients in the primary efficacy population (PD-L1  $\geq 1\%$ ) randomized to OPDIVO in combination with ipilimumab, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older [see Clinical Studies (14.3)].

Of the 303 patients with malignant pleural mesothelioma who were randomized to OPDIVO in combination with ipilimumab, 77% were 65 years old or older and 26% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (68% and 35%, respectively) relative to all patients who received OPDIVO with ipilimumab (54% and 28%, respectively). For patients aged 75 years or older who received chemotherapy, the rate of serious adverse reactions was 34% and the discontinuation rate due to adverse reactions was 26% relative to 28% and 19% respectively for all patients. The hazard ratio for overall survival was 0.76 (95% CI: 0.52, 1.11) in the 71 patients younger than 65 years compared to 0.74 (95% CI: 0.59, 0.93) in the 232 patients 65 years or older randomized to OPDIVO in combination with ipilimumab [see Clinical Studies (14.5)].

Of the 550 patients with renal cell carcinoma who were randomized to OPDIVO in combination with ipilimumab, 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients. In elderly patients with intermediate or poor risk, no overall difference in effectiveness was reported [see Clinical Studies (14.6)].

Of the 49 patients with hepatocellular carcinoma who were treated with OPDIVO in combination with ipilimumab, 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of OPDIVO in combination with ipilimumab did not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients [see Clinical Studies (14.11)].

Of the 325 patients with ESCC who were randomized to OPDIVO in combination with ipilimumab, 43% were 65 years old or older and 7% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (38%) relative to all patients who received OPDIVO with ipilimumab (23%). For patients aged 75 years or older who received chemotherapy, the discontinuation rate due to adverse reactions was 33% relative to 23% for all patients [see Clinical Studies (14.12)].

### In Combination with Platinum-Containing Chemotherapy

Of the 179 patients with NSCLC who were randomized to OPDIVO in combination with platinum-doublet chemotherapy, 48% were 65 years old or older and 6% were 75 years old or older. No overall differences in safety or effectiveness were reported between patients older and younger than 65 years [see Clinical Studies (14.3)].

Of the 1,110 patients with ESCC, GC, GEJC, or EAC who were randomized to OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy, 42% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients [see Clinical Studies (14.12, 14.13)].

Of the 304 patients with UC who were treated with OPDIVO in combination with gemcitabine and platinum-doublet chemotherapy, 40% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years of age and over and younger patients. Clinical studies of OPDIVO with platinum-doublet chemotherapy did not include sufficient numbers of patients aged 75 years and over to determine whether safety and effectiveness differs compared to younger patients. [see Clinical Studies (14.9)].

### In Combination with Ipilimumab and Platinum-Doublet Chemotherapy

Of the 361 patients with NSCLC who were randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy, 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received OPDIVO with ipilimumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older [see Clinical Studies (14.4)].

### In Combination with Cabozantinib

Of the 320 patients with renal cell carcinoma who were treated with OPDIVO in combination with cabozantinib, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients [see Clinical Studies (14.6)].

## 11 DESCRIPTION

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line.

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles.

OPDIVO (nivolumab) injection for intravenous use is supplied in single-dose vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), penicetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response,

including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

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, and results in improved anti-tumor responses in metastatic melanoma and advanced RCC. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity.

## 12.2 Pharmacodynamics

There are no clinically significant exposure-response relationships for efficacy or safety for nivolumab monotherapy across the approved dosing regimens, regardless of cancer type.

## 12.3 Pharmacokinetics

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single agent OPDIVO and OPDIVO with ipilimumab. The PK of nivolumab was studied in patients over a dose range of 0.1 mg/kg to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO as a 60-minute intravenous infusion every 2 or 3 weeks. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion. Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold.

### Distribution

The geometric mean volume of distribution at steady state (V<sub>ss</sub>) and coefficient of variation (CV%) is 6.8 L (27.3%).

### Elimination

Nivolumab clearance (CL) decreases over time, with a mean maximal reduction from baseline values (CV%) of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CL<sub>ss</sub>) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CL<sub>ss</sub> is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state.

The geometric mean elimination half-life (t<sub>1/2</sub>) is 25 days (77.5%).

### Specific Populations

The following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), sex, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment (eGFR ≥15 mL/min/1.73 m<sup>2</sup>), and mild (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). Nivolumab has not been studied in patients with severe hepatic impairment (TB greater than 3 times ULN and any AST).

### Pediatric Patients

The exposures of nivolumab in pediatric patients 12 years of age or older are comparable to those in adults at the recommended dosage [see *Dosage and Administration* (2.2)].

### Drug Interaction Studies

When OPDIVO 3 mg/kg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 3 weeks, the CL of nivolumab and ipilimumab were unchanged compared to nivolumab or ipilimumab administered alone.

When OPDIVO 1 mg/kg every 3 weeks was administered in combination with ipilimumab 3 mg/kg every 3 weeks, the CL of nivolumab was increased by 29% compared to OPDIVO administered alone and the CL of ipilimumab was unchanged compared to ipilimumab administered alone.

When OPDIVO 3 mg/kg every 2 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks, the CL of nivolumab was unchanged compared to OPDIVO administered alone and the CL of ipilimumab was increased by 30% compared to ipilimumab administered alone.

When OPDIVO 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy, the CL of nivolumab was unchanged compared to OPDIVO administered alone and the CL of ipilimumab increased by 22% compared to ipilimumab administered alone.

## 12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of OPDIVO or of other nivolumab products.

Anti-drug antibody and neutralizing antibody responses were monitored throughout the treatment period where the benefit to risk ratio was assessed. Incidence of anti-drug antibodies and neutralizing antibodies are presented in Table 51.

**Table 51: OPDIVO Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) Incidence**

Treatment Regimen <sup>a</sup>	Indication(s)	ADA	NAb <sup>b</sup>
OPDIVO as a single agent	Multiple <sup>c</sup>	11% (229/2,085)	7% (15/229)
OPDIVO with ipilimumab for 4 doses followed by OPDIVO as a single agent	Melanoma	38% (149/394)	12% (18/149)
	HCC	56% (27/48)	41% (11/27)
	RCC and CRC	26% (132/516)	3% (4/132)
OPDIVO with ipilimumab	Malignant Pleural Mesothelioma	26% (69/269)	2.9% (2/69)
	NSCLC	37% (180/491)	3.9% (7/180)
OPDIVO with ipilimumab and 2 cycles of platinum-doublet chemotherapy	NSCLC	34% (104/308)	8% (8/104)

<sup>a</sup> Details of each treatment regimen are described in Section 14 [see *Clinical Studies* (14)].

<sup>b</sup> NAb incidence is reported among the subset of patients positive for ADA.

<sup>c</sup> Includes unresectable or metastatic melanoma, metastatic NSCLC, advanced RCC, cHL, recurrent or metastatic SCCHN, and UC indications.

ADA = treatment-emergent anti-nivolumab antibodies, NAb = neutralizing antibodies, HCC = hepatocellular carcinoma, RCC = renal cell carcinoma, CRC = colorectal cancer, NSCLC = non-small cell lung cancer.

## Effects of Anti-Drug Antibodies

Presence of treatment-emergent anti-nivolumab antibodies increased nivolumab clearance by up to 20% after administration of nivolumab as monotherapy or in combination with ipilimumab. These anti-drug antibody-associated pharmacokinetic changes were not considered to be clinically significant. There was no identified clinically significant effect of anti-drug antibodies on incidence of infusion-related reactions. The effects of anti-drug antibodies on effectiveness have not been fully characterized.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

### 13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

## 14 CLINICAL STUDIES

### 14.1 Unresectable or Metastatic Melanoma

#### Previously Treated Metastatic Melanoma

CHECKMATE-037 (NCT01721746) was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive OPDIVO 3 mg/kg intravenously every 2 weeks or investigator's choice of chemotherapy, either single-agent dacarbazine 1000 mg/m<sup>2</sup> every 3 weeks or the combination of carboplatin AUC 6 intravenously every 3 weeks and paclitaxel 175 mg/m<sup>2</sup> intravenously every 3 weeks. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

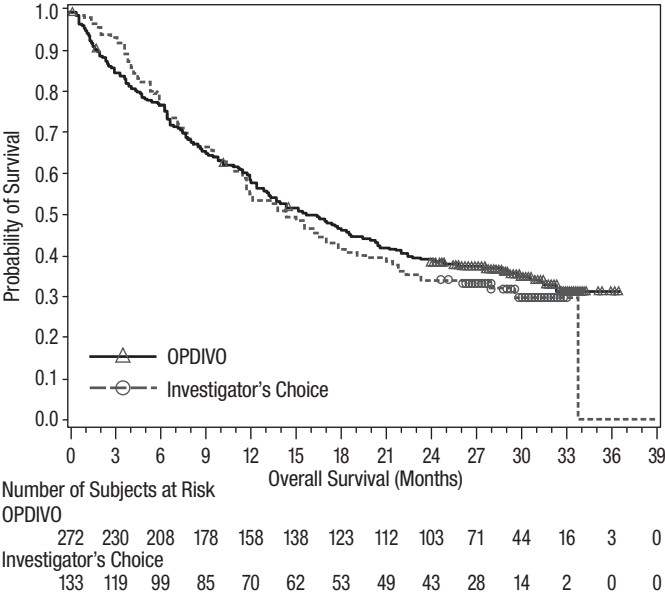
Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in CHECKMATE-037 and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed overall response rate (ORR) as measured by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response.

Among the 120 patients treated with OPDIVO, the median age was 58 years (range: 25 to 88), 65% of patients were male, 98% were White, and the ECOG performance score was 0 (58%) or 1 (42%). Disease characteristics were M1c disease (76%), BRAF V600 mutation positive (22%), elevated LDH (56%), history of brain metastases (18%), and two or more prior systemic therapies for metastatic disease (68%).

The ORR was 32% (95% confidence interval [CI]: 23, 41), consisting of 4 complete responses and 34 partial responses in OPDIVO-treated patients. Of 38 patients with responses, 87% had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer.

There were responses in patients with and without BRAF V600 mutation-positive melanoma. A total of 405 patients were randomized and the median duration of OS was 15.7 months (95% CI: 12.9, 19.9) in OPDIVO-treated patients compared to 14.4 months (95% CI: 11.7, 18.2) (HR 0.95; 95.54% CI: 0.73, 1.24) in patients assigned to investigator's choice of treatment. Figure 1 summarizes the OS results.

Figure 1: Overall Survival - CHECKMATE-037\*



\* The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies, and differences in baseline factors.

Previously Untreated Metastatic Melanoma  
CHECKMATE-066

CHECKMATE-066 (NCT01721772) was a multicenter, double-blind, randomized (1:1) trial in 418 patients with BRAF V600 wild-type unresectable or metastatic melanoma. Patients were randomized to receive either OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or dacarbazine 1000 mg/m<sup>2</sup> intravenously every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (≥5% of tumor cell membrane staining by immunohistochemistry vs. <5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). Key eligibility criteria included histologically confirmed, unresectable or metastatic, cutaneous, mucosal, or acral melanoma; no prior therapy for metastatic disease; completion of prior adjuvant or neoadjuvant therapy at least 6 weeks prior to randomization; ECOG performance status 0 or 1; absence of autoimmune disease; and absence of active brain or leptomeningeal metastases. The trial excluded patients with ocular melanoma. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year and then every 12 weeks thereafter. The major efficacy outcome measure was overall survival (OS). Additional outcome measures included investigator-assessed progression-free survival (PFS) and ORR per RECIST v1.1.

The trial population characteristics were: median age was 65 years (range: 18 to 87), 59% were male, and 99.5% were White. Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma (11%), elevated LDH level (37%), PD-L1 ≥5% tumor cell membrane expression (35%), and history of brain metastasis (4%). More patients in the OPDIVO arm had an ECOG performance status of 0 (71% vs. 58%).

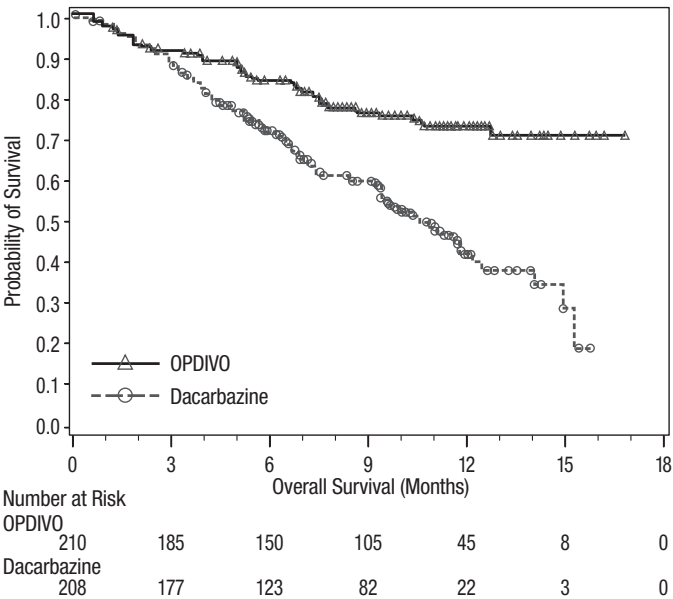
CHECKMATE-066 demonstrated a statistically significant improvement in OS for the OPDIVO arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. At the time of analysis, 88% (63/72) of OPDIVO-treated patients had ongoing responses, which included 43 patients with ongoing response of 6 months or longer. Efficacy results are shown in Table 52 and Figure 2.

Table 52: Efficacy Results - CHECKMATE-066

	OPDIVO (n=210)	Dacarbazine (n=208)
<b>Overall Survival</b>		
Deaths (%)	50 (24)	96 (46)
Median (months) (95% CI)	NR <sup>a</sup>	10.8 (9.3, 12.1)
Hazard ratio (95% CI) <sup>b</sup>	0.42 (0.30, 0.60)	
p-value <sup>c,d</sup>	<0.0001	
<b>Progression-free Survival</b>		
Disease progression or death (%)	108 (51)	163 (78)
Median (months) (95% CI)	5.1 (3.5, 10.8)	2.2 (2.1, 2.4)
Hazard ratio (95% CI) <sup>b</sup>	0.43 (0.34, 0.56)	
p-value <sup>c,d</sup>	<0.0001	
<b>Overall Response Rate</b>		
(95% CI)	34% (28, 41)	9% (5, 13)
Complete response rate	4%	1%
Partial response rate	30%	8%

<sup>a</sup> Not Reached  
<sup>b</sup> Based on a stratified proportional hazards model.  
<sup>c</sup> Based on stratified log-rank test.  
<sup>d</sup> p-value is compared with the allocated alpha of 0.0021 for this interim analysis.

Figure 2: Overall Survival - CHECKMATE-066



CHECKMATE-067

CHECKMATE-067 (NCT01844505) was a multicenter, randomized (1:1:1), double-blind trial in 945 patients with previously untreated, unresectable or metastatic melanoma to one of the following arms: OPDIVO and ipilimumab, OPDIVO, or ipilimumab. Patients were required to have completed adjuvant or neoadjuvant treatment at least 6 weeks prior to randomization and have no prior treatment with anti-CTLA-4 antibody and no evidence of active brain metastasis, ocular melanoma, autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients were randomized to receive:

- OPDIVO 1 mg/kg with ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (OPDIVO and ipilimumab arm),
- OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (OPDIVO arm), or
- Ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by placebo every 2 weeks (ipilimumab arm).

Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the AJCC staging system (M0, M1a, M1b vs. M1c). Tumor assessments were conducted 12 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter. The major efficacy outcome measures were investigator-assessed PFS per RECIST v1.1 and OS. Additional efficacy outcome measures were confirmed ORR and duration of response.

The trial population characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were:



AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥5% tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%).

CHECKMATE-067 demonstrated statistically significant improvements in OS and PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. The trial was not designed to assess whether adding ipilimumab to OPDIVO improves PFS or OS compared to OPDIVO as a single agent. Efficacy results are shown in Table 53 and Figure 3.

**Table 53: Efficacy Results - CHECKMATE-067**

	OPDIVO and Ipilimumab (n=314)	OPDIVO (n=316)	Ipilimumab (n=315)
<b>Overall Survival<sup>a</sup></b>			
Deaths (%)	128 (41)	142 (45)	197 (63)
Hazard ratio <sup>b</sup> (vs. ipilimumab)	0.55	0.63	
(95% CI)	(0.44, 0.69)	(0.50, 0.78)	
p-value <sup>c,d</sup>	<0.0001	<0.0001	
<b>Progression-free Survival<sup>a</sup></b>			
Disease progression or death	151 (48%)	174 (55%)	234 (74%)
Median (months)	11.5	6.9	2.9
(95% CI)	(8.9, 16.7)	(4.3, 9.5)	(2.8, 3.4)
Hazard ratio <sup>b</sup> (vs. ipilimumab)	0.42	0.57	
(95% CI)	(0.34, 0.51)	(0.47, 0.69)	
p-value <sup>c,e</sup>	<0.0001	<0.0001	
<b>Confirmed Overall Response Rate<sup>a</sup></b>			
(95% CI)	50% (44, 55)	40% (34, 46)	14% (10, 18)
p-value <sup>f</sup>	<0.0001	<0.0001	
Complete response	8.9%	8.5%	1.9%
Partial response	41%	31%	12%
<b>Duration of Response</b>			
Proportion ≥6 months in duration	76%	74%	63%
Range (months)	1.2+ to 15.8+	1.3+ to 14.6+	1.0+ to 13.8+

<sup>a</sup> OS results are based on final OS analysis with 28 months of minimum follow-up; PFS (co-primary endpoint) and ORR (secondary endpoint) results were based on primary analysis with 9 months of minimum follow-up.

<sup>b</sup> Based on a stratified proportional hazards model.

<sup>c</sup> Based on stratified log-rank test.

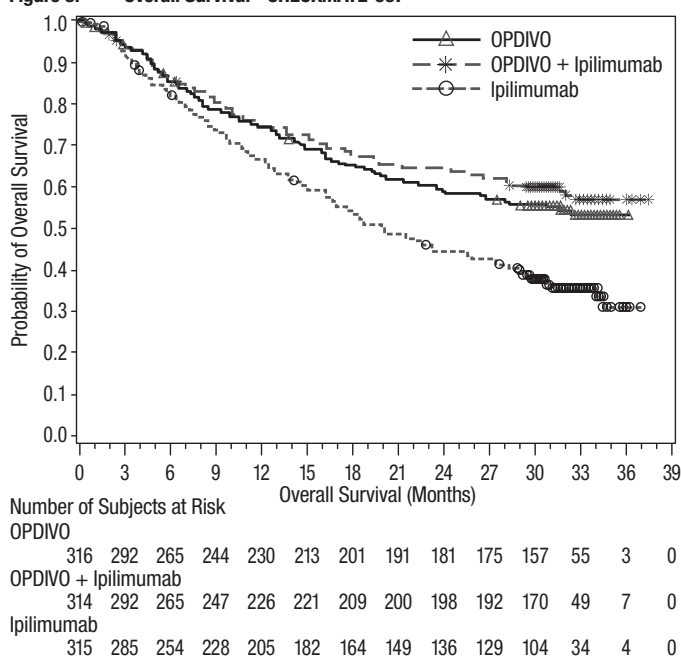
<sup>d</sup> If the maximum of the two OS p-values is less than 0.04 (a significance level assigned by the Hochberg procedure), then both p-values are considered significant.

<sup>e</sup> p-value is compared with .005 of the allocated alpha for final PFS treatment comparisons.

<sup>f</sup> Based on the stratified Cochran-Mantel-Haenszel test.

+ Censored observation

**Figure 3: Overall Survival - CHECKMATE-067**



Based on a minimum follow-up of 48 months, the median OS was not reached (95% CI: 38.2, NR) in the OPDIVO and ipilimumab arm. The median OS was 36.9 months (95% CI: 28.3, NR) in the OPDIVO arm and 19.9 months (95% CI: 16.9, 24.6) in the ipilimumab arm.

Based on a minimum follow-up of 28 months, the median PFS was 11.7 months (95% CI: 8.9, 21.9) in the OPDIVO and ipilimumab arm, 6.9 months (95% CI: 4.3, 9.5) in the OPDIVO arm, and 2.9 months (95% CI: 2.8, 3.2) in the ipilimumab arm. Based on a minimum follow-up of 28 months, the proportion of responses lasting ≥24 months was 55% in the OPDIVO and ipilimumab arm, 56% in the OPDIVO arm, and 39% in the ipilimumab arm.

## 14.2 Adjuvant Treatment of Melanoma

### CHECKMATE-76K

CHECKMATE-76K (NCT04099251) was a randomized, double-blind trial in 790 patients with completely resected Stage IIB/C melanoma. Patients were randomized (2:1) to receive OPDIVO 480 mg or placebo by intravenous infusion every 4 weeks for up to 1 year or until disease recurrence or unacceptable toxicity. Enrollment required complete resection of the primary melanoma with negative margins and a negative sentinel lymph node within 12 weeks prior to randomization, and ECOG performance status of 0 or 1. The trial excluded patients with ocular/uveal or mucosal melanoma, autoimmune disease, any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery. Randomization was stratified by AJCC 8th staging system edition (T3b vs. T4a vs. T4b). The major efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, from any cause, whichever occurred first and as assessed by the investigator. Tumor assessments were conducted every 26 weeks during years 1-3 and every 52 weeks thereafter until year 5.

The trial population characteristics were: median age 62 years (range: 19 to 92), 61% were male, 98% were White, 0.4% Black or African American, 0.1% Asian, and 1.1% race unknown, 2.2% Hispanic or Latino, 58% Not Hispanic or Latino, 40% ethnicity unknown, and 94% had an ECOG performance status of 0. Sixty one percent had stage IIB and 39% had stage IIC melanoma.

CHECKMATE-76K demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the placebo arm. Efficacy results are shown in Table 54 and Figure 4.

**Table 54: Efficacy Results - CHECKMATE-76K**

	OPDIVO N=526	Placebo N=264
<b>Recurrence-free Survival</b>		
Number of events, n (%)	66 (13%)	69 (26%)
Median (months) <sup>b</sup>	NR <sup>a</sup>	NR <sup>a</sup>
(95% CI)	(28.5, NR)	(21.6, NR)
Hazard ratio <sup>c</sup>		0.42
(95% CI)		(0.30, 0.59)
p-value <sup>d</sup>		p<0.0001

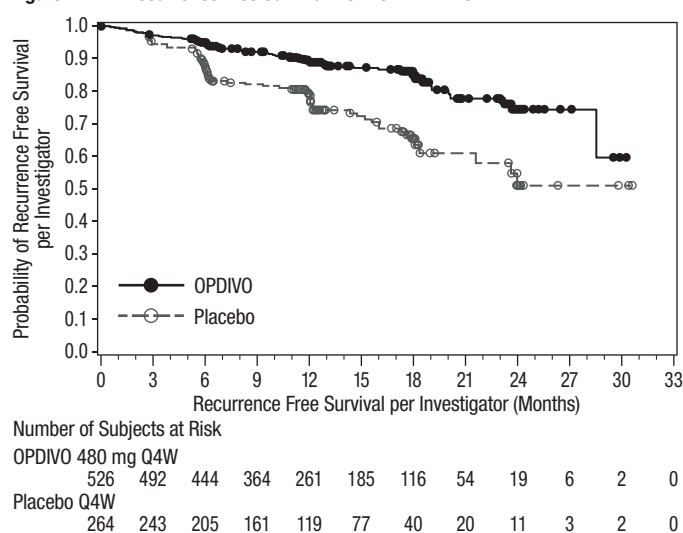
<sup>a</sup> Not reached.

<sup>b</sup> Based on Kaplan-Meier estimates.

<sup>c</sup> Hazard Ratio is OPDIVO over placebo based on a stratified Cox proportional hazard model.

<sup>d</sup> Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value <0.033.

**Figure 4: Recurrence-free Survival - CHECKMATE-76K**





## CHECKMATE-238

CHECKMATE-238 (NCT02388906) was a randomized, double-blind trial in 906 patients with completely resected Stage IIIB/C or Stage IV melanoma. Patients were randomized (1:1) to receive OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or ipilimumab 10 mg/kg intravenously every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year. Enrollment required complete resection of melanoma with margins negative for disease within 12 weeks prior to randomization. The trial excluded patients with a history of ocular/uveal melanoma, autoimmune disease, and any condition requiring systemic treatment with either corticosteroids ( $\geq 10$  mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed  $\geq 6$  months prior to randomization. Randomization was stratified by PD-L1 status (positive [based on 5% level] vs. negative/indeterminate) and AJCC stage (Stage IIIB/C vs. Stage IV M1a-M1b vs. Stage IV M1c). The major efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, from any cause, whichever occurs first and as assessed by the investigator. Patients underwent imaging for tumor recurrence every 12 weeks for the first 2 years then every 6 months thereafter.

The trial population characteristics were: median age was 55 years (range: 18 to 86), 58% were male, 95% were White, and 90% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIB (34%), Stage IIIC (47%), Stage IV (19%), M1a-b (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1  $\geq 5\%$  tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%).

CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the ipilimumab 10 mg/kg arm. Efficacy results are shown in Table 55 and Figure 5.

Table 55: Efficacy Results - CHECKMATE-238

	OPDIVO N=453	Ipilimumab 10 mg/kg N=453
<b>Recurrence-free Survival</b>		
Number of events, n (%)	154 (34%)	206 (45%)
Median (months) (95% CI)	NR <sup>a</sup>	NR <sup>a</sup> (16.56, NR <sup>a</sup> )
Hazard ratio <sup>b</sup> (95% CI)		0.65 (0.53, 0.80)
p-value <sup>c,d</sup>		p<0.0001
<b>Overall Survival</b>		
Number of events, n (%) <sup>e</sup>	100 (22%)	111 (25%)
Median (months) (95% CI)	NR <sup>a</sup>	NR <sup>a</sup>
Hazard ratio <sup>b</sup> (95% CI)		0.87 (0.67, 1.14)
p-value		0.3148

<sup>a</sup> Not reached.

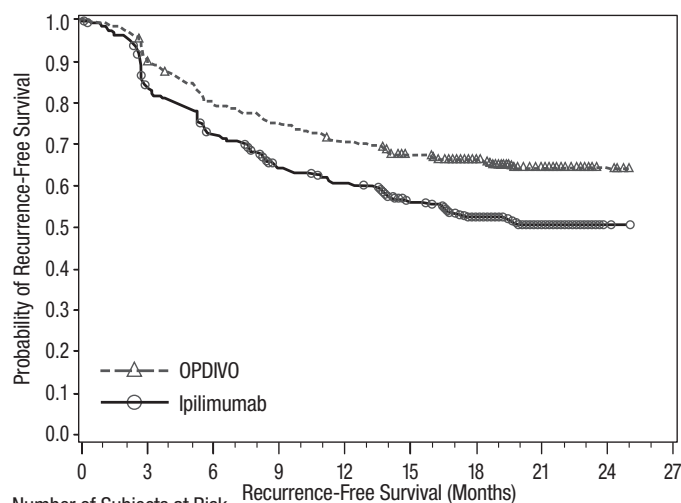
<sup>b</sup> Based on a stratified proportional hazards model.

<sup>c</sup> Based on a stratified log-rank test.

<sup>d</sup> p-value is compared with 0.0244 of the allocated alpha for this analysis.

<sup>e</sup> At the time of the final OS analysis, fewer overall survival events were observed than originally anticipated (approximately 302).

Figure 5: Recurrence-free Survival - CHECKMATE-238

14.3 Neoadjuvant Treatment of Resectable (Tumors  $\geq 4$  cm or Node Positive) Non-Small Cell Lung Cancer

CHECKMATE-816 (NCT02998528) was a randomized, open label trial in patients with resectable NSCLC. The trial included patients with resectable, histologically confirmed Stage IB ( $\geq 4$  cm), II, or IIIA NSCLC (per the 7th edition American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging criteria), ECOG performance status 0 or 1, and measurable disease (per RECIST version 1.1). Patients with unresectable or metastatic NSCLC, known EGFR mutations or ALK translocations, Grade 2 or greater peripheral neuropathy, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

Patients were randomized to receive either:

- OPDIVO 360 mg administered intravenously over 30 minutes and platinum-doublet chemotherapy administered intravenously every 3 weeks for up to 3 cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for up to 3 cycles.

Platinum-doublet chemotherapy consisted of paclitaxel 175 mg/m<sup>2</sup> or 200 mg/m<sup>2</sup> and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> (non-squamous histology); or gemcitabine 1000 mg/m<sup>2</sup> or 1250 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> (squamous histology). In the platinum-doublet chemotherapy arm, two additional treatment regimen options included vinorelbine 25 mg/m<sup>2</sup> or 30 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup>; or docetaxel 60 mg/m<sup>2</sup> or 75 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> (any histology).

Stratification factors for randomization were tumor PD-L1 expression level ( $\geq 1\%$  versus  $<1\%$  or non-quantifiable), disease stage (IB/II versus IIIA), and sex (male versus female). Tumor assessments were performed at baseline, within 14 days of surgery, every 12 weeks after surgery for 2 years, then every 6 months for 3 years, and every year for 5 years until disease recurrence or progression. The major efficacy outcome measures were event-free survival (EFS) based on blinded independent central review (BICR) assessment and pathologic complete response (pCR) as evaluated by blinded independent pathology review (BIPR). Additional efficacy outcome measures included OS.

A total of 358 patients were randomized to receive either OPDIVO in combination with platinum-doublet chemotherapy (n=179) or platinum-doublet chemotherapy (n=179). The median age was 65 years (range: 34 to 84) with 51% of patients  $\geq 65$  years and 7% of patients  $\geq 75$  years, 50% were Asian, 47% were White, 2% were Black, and 71% were male. Baseline ECOG performance status was 0 (67%) or 1 (33%); 50% had tumors with PD-L1 expression  $\geq 1\%$ ; 35% had stage IB/II and 64% had stage IIIA disease; 51% had tumors with squamous histology and 49% had tumors with non-squamous histology; and 89% were former/current smokers.

Eighty-three percent of patients in the OPDIVO in combination with platinum-doublet chemotherapy arm had definitive surgery compared to 75% of patients in the platinum-doublet chemotherapy arm.

The study demonstrated statistically significant improvements in EFS and pCR. Efficacy results are presented in Table 56 and Figure 6.

**Table 56: Efficacy Results - CHECKMATE-816**

	OPDIVO and Platinum-Doublet Chemotherapy (n=179)	Platinum-Doublet Chemotherapy (n=179)
<b>Event-free Survival (EFS) per BICR</b>		
Events (%)	64 (35.8)	87 (48.6)
Median (months) <sup>a</sup>	31.6	20.8
(95% CI)	(30.2, NR)	(14.0, 26.7)
Hazard Ratio <sup>b</sup>		0.63
(95% CI)		(0.45, 0.87)
Stratified log-rank p-value <sup>c</sup>		0.0052
<b>Pathologic Complete Response (pCR) per BIPR</b>		
Number of patients with pCR	43	4
pCR Rate (%), (95% CI) <sup>d</sup>	24.0 (18.0, 31.0)	2.2 (0.6, 5.6)
Estimated treatment difference (95% CI) <sup>e</sup>		21.6 (15.1, 28.2)
p-value <sup>f</sup>		<0.0001

Minimum follow-up for EFS was 21 months.

<sup>a</sup> Kaplan-Meier estimate.

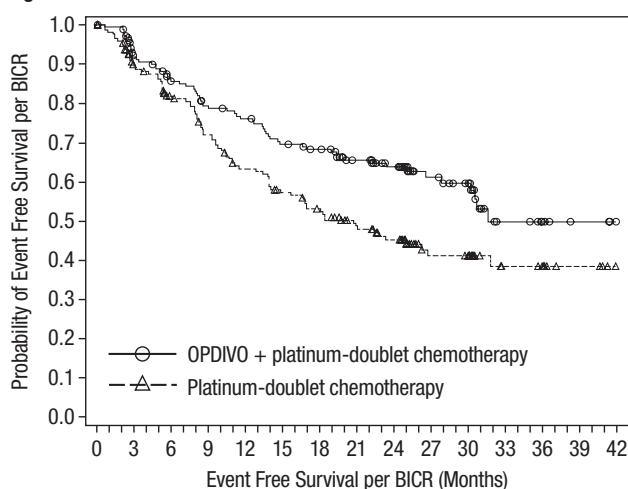
<sup>b</sup> Based on a stratified Cox proportional hazard model.

<sup>c</sup> Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0262.

<sup>d</sup> Based on Clopper and Pearson method.

<sup>e</sup> Strata-adjusted difference based on Cochran-Mantel-Haenszel method of weighting.

<sup>f</sup> From stratified CMH test.

**Figure 6: Event-Free Survival - CHECKMATE-816**

Number of Subjects at Risk

OPDIVO + platinum-doublet chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Platinum-doublet chemotherapy	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

At the time of the EFS analysis, 26% of the patients had died. A prespecified interim analysis for OS resulted in a HR of 0.57 (95% CI: 0.38, 0.87), which did not cross the boundary for statistical significance.

#### 14.4 Metastatic Non-Small Cell Lung Cancer

##### First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Ipilimumab

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [IASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression ≥1%. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Randomization was stratified by tumor histology (non-squamous versus squamous). The evaluation of efficacy relied on the comparison between:

- OPDIVO 3 mg/kg administered intravenously over 30 minutes every 2 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks; or
- Platinum-doublet chemotherapy

Chemotherapy regimens consisted of pemetrexed (500 mg/m<sup>2</sup>) and cisplatin (75 mg/m<sup>2</sup>) or pemetrexed (500 mg/m<sup>2</sup>) and carboplatin (AUC 5 or 6) for non-squamous NSCLC or gemcitabine (1000 or 1250 mg/m<sup>2</sup>) and cisplatin (75 mg/m<sup>2</sup>) or gemcitabine (1000 mg/m<sup>2</sup>) and carboplatin (AUC 5) (gemcitabine was administered on Days 1 and 8 of each cycle) for squamous NSCLC.

Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment continued beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to ipilimumab were permitted to continue OPDIVO as a single agent. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

In Part 1a, a total of 793 patients were randomized to receive either OPDIVO in combination with ipilimumab (n=396) or platinum-doublet chemotherapy (n=397). The median age was 64 years (range: 26 to 87) with 49% of patients ≥65 years and 10% of patients ≥75 years, 76% White, and 65% male. Baseline ECOG performance status was 0 (34%) or 1 (65%), 50% with PD-L1 ≥50%, 29% with squamous and 71% with non-squamous histology, 10% had brain metastases, and 85% were former/current smokers.

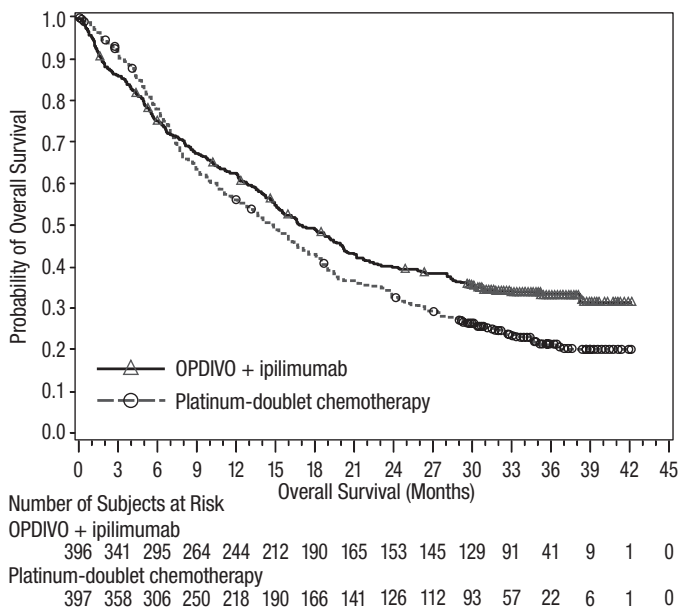
The study demonstrated a statistically significant improvement in OS for PD-L1 ≥1% patients randomized to the OPDIVO and ipilimumab arm compared with the platinum-doublet chemotherapy arm. The OS results are presented in Table 57 and Figure 7.

**Table 57: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a**

	OPDIVO and Ipilimumab (n=396)	Platinum-Doublet Chemotherapy (n=397)
<b>Overall Survival</b>		
Events (%)	258 (65%)	298 (75%)
Median (months) <sup>a</sup>	17.1	14.9
(95% CI)	(15, 20.1)	(12.7, 16.7)
Hazard ratio (95% CI) <sup>b</sup>		0.79 (0.67, 0.94)
Stratified log-rank p-value		0.0066

<sup>a</sup> Kaplan-Meier estimate.

<sup>b</sup> Based on a stratified Cox proportional hazard model.

**Figure 7: Overall Survival (PD-L1 ≥1%) - CHECKMATE-227**

BICR-assessed PFS showed a HR of 0.82 (95% CI: 0.69, 0.97), with a median PFS of 5.1 months (95% CI: 4.1, 6.3) in the OPDIVO and ipilimumab arm and 5.6 months (95% CI: 4.6, 5.8) in the platinum-doublet chemotherapy arm. The BICR-assessed confirmed ORR was 36% (95% CI: 31, 41) in the OPDIVO and ipilimumab arm and 30% (95% CI: 26, 35) in the platinum-doublet chemotherapy arm. Median duration of response observed in the OPDIVO and ipilimumab arm was 23.2 months and 6.2 months in the platinum-doublet chemotherapy arm.

#### First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Ipilimumab and Platinum-Doublet Chemotherapy

CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with stable brain metastases were eligible for enrollment.

Patients were randomized 1:1 to receive either:

- OPDIVO 360 mg administered intravenously over 30 minutes every 3 weeks, ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks, and platinum-doublet chemotherapy administered intravenously every 3 weeks for 2 cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for 4 cycles.

Platinum-doublet chemotherapy consisted of either carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m<sup>2</sup>, or cisplatin 75 mg/m<sup>2</sup> and pemetrexed 500 mg/m<sup>2</sup> for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m<sup>2</sup> for squamous NSCLC. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Treatment could continue beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent as part of the study. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

A total of 719 patients were randomized to receive either OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients ≥65 years and 10% of patients ≥75 years. The majority of patients were White (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% had tumors with PD-L1 expression ≥1% and 37% had tumors with PD-L1 expression that was <1%, 32% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 86% were former or current smokers.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR. Efficacy results from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) are presented in Table 58.

**Table 58: Efficacy Results - CHECKMATE-9LA**

	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=361)	Platinum-Doublet Chemotherapy (n=358)
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)
Median (months)	14.1	10.7
(95% CI)	(13.2, 16.2)	(9.5, 12.5)
Hazard ratio (96.71% CI) <sup>a</sup>	0.69 (0.55, 0.87)	
Stratified log-rank p-value <sup>b</sup>	0.0006	
Progression-free Survival per BICR		
Events (%)	232 (64.3)	249 (69.6)
Hazard ratio (97.48% CI) <sup>a</sup>	0.70 (0.57, 0.86)	
Stratified log-rank p-value <sup>c</sup>	0.0001	
Median (months) <sup>d</sup>	6.8	5.0
(95% CI)	(5.6, 7.7)	(4.3, 5.6)
Overall Response Rate per BICR (%)		
(95% CI) <sup>e</sup>	38	25
	(33, 43)	(21, 30)
Stratified CMH test p-value <sup>f</sup>	0.0003	
Duration of Response per BICR		
Median (months)	10.0	5.1
(95% CI) <sup>d</sup>	(8.2, 13.0)	(4.3, 7.0)

<sup>a</sup> Based on a stratified Cox proportional hazard model.

<sup>b</sup> p-value is compared with the allocated alpha of 0.033 for this interim analysis.

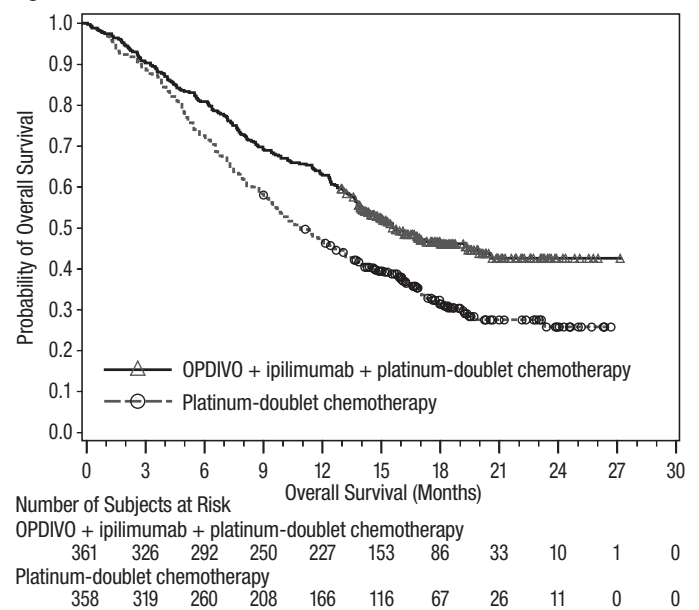
<sup>c</sup> p-value is compared with the allocated alpha of 0.0252 for this interim analysis.

<sup>d</sup> Kaplan-Meier estimate.

<sup>e</sup> Confidence interval based on the Clopper and Pearson Method.

<sup>f</sup> p-value is compared with the allocated alpha of 0.025 for this interim analysis.

With an additional 4.6 months of follow-up, the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving OPDIVO and ipilimumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 8).

**Figure 8: Overall Survival - CHECKMATE-9LA**

#### Second-line Treatment of Metastatic Squamous NSCLC

CHECKMATE-017 (NCT01642004) was a randomized (1:1), open-label trial in 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=135) or docetaxel 75 mg/m<sup>2</sup> intravenously every 3 weeks (n=137). Randomization was stratified by prior paclitaxel vs. other prior treatment and region (US/Canada vs. Europe vs. Rest of World). This trial included patients regardless of their PD-L1 status. The trial

excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS.

The trial population characteristics were: median age was 63 years (range: 39 to 85) with 44% ≥65 years of age and 11% ≥75 years of age. The majority of patients were White (93%) and male (76%); the majority of patients were enrolled in Europe (57%) with the remainder in US/Canada (32%) and the rest of the world (11%). Baseline ECOG performance status was 0 (24%) or 1 (76%) and 92% were former/current smokers. Baseline disease characteristics of the population as reported by investigators were Stage IIIb (19%), Stage IV (80%), and brain metastases (6%). All patients received prior therapy with a platinum-doublet regimen and 99% of patients had tumors of squamous-cell histology.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 199 events were observed (86% of the planned number of events for final analysis). Efficacy results are shown in Table 59 and Figure 9.

**Table 59: Efficacy Results - CHECKMATE-017**

	OPDIVO (n=135)	Docetaxel (n=137)
<b>Overall Survival</b>		
Deaths (%)	86 (64%)	113 (82%)
Median (months) (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
Hazard ratio (95% CI) <sup>a</sup>	0.59 (0.44, 0.79)	
p-value <sup>b,c</sup>	0.0002	
<b>Overall Response Rate</b>		
(95% CI)	27 (20%) (14, 28)	12 (9%) (5, 15)
p-value <sup>d</sup>	0.0083	
Complete response	1 (0.7%)	0
Median duration of response (months) (95% CI)	NR <sup>e</sup> (9.8, NR <sup>e</sup> )	8.4 (3.6, 10.8)
<b>Progression-free Survival</b>		
Disease progression or death (%)	105 (78%)	122 (89%)
Median (months)	3.5	2.8
Hazard ratio (95% CI) <sup>a</sup>	0.62 (0.47, 0.81)	
p-value <sup>b</sup>	0.0004	

<sup>a</sup> Based on a stratified proportional hazards model.

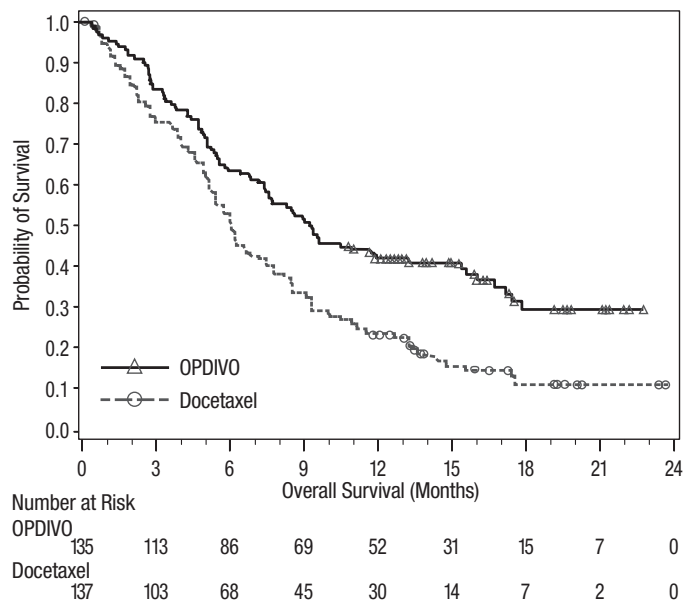
<sup>b</sup> Based on stratified log-rank test.

<sup>c</sup> p-value is compared with .0315 of the allocated alpha for this interim analysis.

<sup>d</sup> Based on the stratified Cochran-Mantel-Haenszel test.

<sup>e</sup> Not Reached

**Figure 9: Overall Survival - CHECKMATE-017**



Archival tumor specimens were retrospectively evaluated for PD-L1 expression. Across the trial population, 17% of 272 patients had non-quantifiable results. Among the 225 patients with quantifiable results, 47% had PD-L1 negative squamous NSCLC, defined as <1% of tumor cells expressing PD-L1 and 53% had PD-L1 positive squamous NSCLC defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratios for survival were 0.58 (95% CI: 0.37, 0.92) in the PD-L1 negative subgroup and 0.69 (95% CI: 0.45, 1.05) in the PD-L1 positive subgroup.

#### Second-line Treatment of Metastatic Non-Squamous NSCLC

CHECKMATE-057 (NCT01673867) was a randomized (1:1), open-label trial in 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy in patients with known sensitizing EGFR mutation or ALK translocation was allowed. Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=292) or docetaxel 75 mg/m<sup>2</sup> intravenously every 3 weeks (n=290). Randomization was stratified by prior maintenance therapy (yes vs. no) and number of prior therapies (1 vs. 2). The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression.

The trial population characteristics: median age was 62 years (range: 21 to 85) with 42% of patients ≥65 years and 7% of patients ≥75 years. The majority of patients were White (92%) and male (55%); the majority of patients were enrolled in Europe (46%) followed by the US/Canada (37%) and the rest of the world (17%). Baseline ECOG performance status was 0 (31%) or 1 (69%), 79% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. Prior therapy included platinum-doublet regimen (100%) and 40% received maintenance therapy as part of the first-line regimen. Histologic subtypes included adenocarcinoma (93%), large cell (2.4%), and bronchoalveolar (0.9%).

CHECKMATE-057 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 60 and Figure 10.

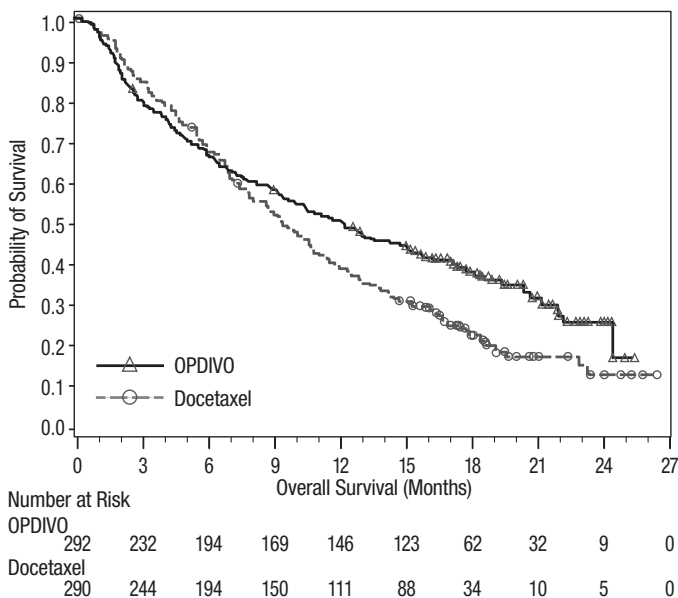


Table 60: Efficacy Results - CHECKMATE-057

	OPDIVO (n=292)	Docetaxel (n=290)
<b>Overall Survival</b>		
Deaths (%)	190 (65%)	223 (77%)
Median (months)	12.2	9.4
(95% CI)	(9.7, 15.0)	(8.0, 10.7)
Hazard ratio (95% CI) <sup>a</sup>	0.73 (0.60, 0.89)	
p-value <sup>b,c</sup>	0.0015	
<b>Overall Response Rate</b>		
(95% CI)	56 (19%) (15, 24)	36 (12%) (9, 17)
p-value <sup>d</sup>	0.02	
Complete response	4 (1.4%)	1 (0.3%)
Median duration of response (months)	17	6
(95% CI)	(8.4, NR <sup>e</sup> )	(4.4, 7.0)
<b>Progression-free Survival</b>		
Disease progression or death (%)	234 (80%)	245 (84%)
Median (months)	2.3	4.2
Hazard ratio (95% CI) <sup>a</sup>	0.92 (0.77, 1.11)	
p-value <sup>b</sup>	0.39	

<sup>a</sup> Based on a stratified proportional hazards model.<sup>b</sup> Based on stratified log-rank test.<sup>c</sup> p-value is compared with .0408 of the allocated alpha for this interim analysis.<sup>d</sup> Based on the stratified Cochran-Mantel-Haenszel test.<sup>e</sup> Not Reached.

Figure 10: Overall Survival - CHECKMATE-057



Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the trial population, 22% of 582 patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% PD-L1 negative, defined as <1% of tumor cells expressing PD-L1 and 54% had PD-L1 expression, defined as ≥1% of tumor cells expressing PD-L1. Among the 246 patients with tumors expressing PD-L1, 26% had ≥1% but <5% tumor cells with positive staining, 7% had ≥5% but <10% tumor cells with positive staining, and 67% had ≥10% tumor cells with positive staining. Figures 11 and 12 summarize the results of prespecified analyses of OS and PFS in subgroups determined by percentage of tumor cells expressing PD-L1.

Figure 11: Forest Plot: OS Based on PD-L1 Expression - CHECKMATE-057

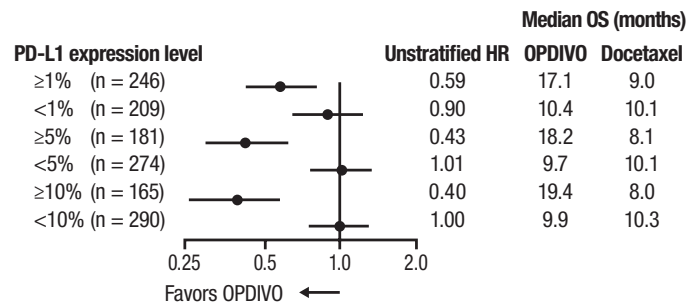
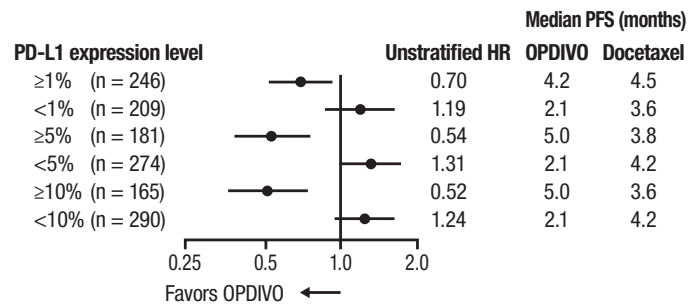


Figure 12: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



#### 14.5 Malignant Pleural Mesothelioma

CHECKMATE-743 (NCT02899299) was a randomized, open-label trial in patients with unresectable malignant pleural mesothelioma. The trial included patients with histologically confirmed and previously untreated malignant pleural mesothelioma with no palliative radiotherapy within 14 days of initiation of therapy. Patients with interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, or active brain metastasis were excluded from the trial.

Patients were randomized 1:1 to receive either:

- OPDIVO 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks and ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years, or
- cisplatin 75 mg/m<sup>2</sup> and pemetrexed 500 mg/m<sup>2</sup>, or carboplatin 5 AUC and pemetrexed 500 mg/m<sup>2</sup> administered every 3 weeks for 6 cycles.

Stratification factors for randomization were tumor histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and sex (male vs. female). Study treatment continued for up to 2 years, or until disease progression or unacceptable toxicity. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent. Treatment could continue beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR utilizing modified RECIST criteria.

A total of 605 patients were randomized to receive either OPDIVO in combination with ipilimumab (n=303) or chemotherapy (n=302). The median age was 69 years (range: 25 to 89), with 72% of patients ≥65 years and 26% ≥75 years; 85% were White, 11% were Asian, and 77% were male. Baseline ECOG performance status was 0 (40%) or 1 (60%), 35% had Stage III and 51% had Stage IV disease, 75% had epithelioid and 25% had non-epithelioid histology, 75% had tumors with PD-L1 expression ≥1%, and 22% had tumors with PD-L1 expression <1%.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO in combination with ipilimumab compared to chemotherapy. Efficacy results from the prespecified interim analysis are presented in Table 61 and Figure 13.

**Table 61: Efficacy Results - CHECKMATE-743**

	OPDIVO and Ipilimumab (n=303)	Chemotherapy (n=302)
<b>Overall Survival<sup>a</sup></b>		
Events (%)	200 (66)	219 (73)
Median (months) <sup>b</sup> (95% CI)	18.1 (16.8, 21.5)	14.1 (12.5, 16.2)
Hazard ratio (95% CI) <sup>c</sup>	0.74 (0.61, 0.89)	
Stratified log-rank p-value <sup>d</sup>	0.002	
<b>Progression-free Survival</b>		
Events (%)	218 (72)	209 (69)
Hazard ratio (95% CI) <sup>c</sup>	1.0 (0.82, 1.21)	
Median (months) <sup>b</sup> (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)
<b>Overall Response Rate<sup>e</sup></b>	40%	43%
(95% CI)	(34, 45)	(37, 49)
<b>Duration of Response</b>		
Median (months) <sup>b</sup> (95% CI)	11.0 (8.1, 16.5)	6.7 (5.3, 7.1)

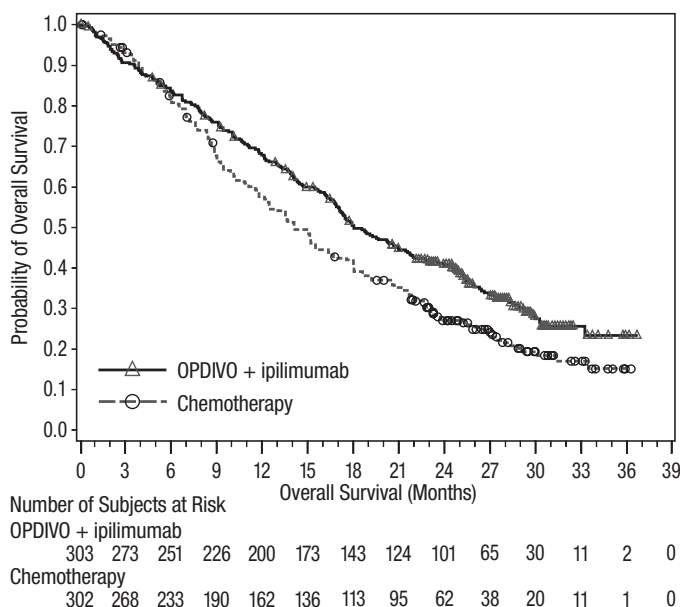
<sup>a</sup> At the time of the interim analysis, 419 deaths (89% of the deaths needed for the final analysis) had occurred.

<sup>b</sup> Kaplan-Meier estimate.

<sup>c</sup> Stratified Cox proportional hazard model.

<sup>d</sup> p-value is compared with the allocated alpha of 0.0345 for this interim analysis.

<sup>e</sup> Based on confirmed response by BICR.

**Figure 13: Overall Survival - CHECKMATE-743**

In a prespecified exploratory analysis based on histology, in the subgroup of patients with epithelioid histology, the hazard ratio (HR) for OS was 0.85 (95% CI: 0.68, 1.06), with median OS of 18.7 months in the OPDIVO and ipilimumab arm and 16.2 months in the chemotherapy arm. In the subgroup of patients with non-epithelioid histology, the HR for OS was 0.46 (95% CI: 0.31, 0.70), with median OS of 16.9 months in the OPDIVO and ipilimumab arm and 8.8 months in the chemotherapy arm.

## 14.6 Advanced Renal Cell Carcinoma

### First-line Renal Cell Carcinoma

#### CHECKMATE-214

CHECKMATE-214 (NCT02231749) was a randomized (1:1), open-label trial in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region.

Efficacy was evaluated in intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status <80%,

hemoglobin less than the lower limit of normal, corrected calcium of >10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal).

Patients were randomized to OPDIVO 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by OPDIVO 3 mg/kg intravenously every two weeks (n=425), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (n=422). Treatment continued until disease progression or unacceptable toxicity.

The trial population characteristics were: median age was 61 years (range: 21 to 85) with 38% ≥65 years of age and 8% ≥75 years of age. The majority of patients were male (73%) and White (87%) and 26% and 74% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively.

The major efficacy outcome measures were OS, PFS (independent radiographic review committee [IRRC]-assessed) and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. In this population, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to OPDIVO and ipilimumab as compared with sunitinib (Table 62 and Figure 14). OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS. Efficacy results are shown in Table 62 and Figure 14.

**Table 62: Efficacy Results - CHECKMATE-214**

	Intermediate/Poor-Risk	
	OPDIVO and Ipilimumab (n=425)	Sunitinib (n=422)
<b>Overall Survival</b>		
Deaths (%)	140 (32.9)	188 (44.5)
Median survival (months)	NR <sup>a</sup>	25.9
Hazard ratio (99.8% CI) <sup>b</sup>	0.63 (0.44, 0.89)	
p-value <sup>c,d</sup>	<0.0001	
<b>Confirmed Overall Response Rate (95% CI)</b>	41.6% (36.9, 46.5)	26.5% (22.4, 31.0)
p-value <sup>e,f</sup>	<0.0001	
Complete response (CR)	40 (9.4)	5 (1.2)
Partial response (PR)	137 (32.2)	107 (25.4)
Median duration of response (months) (95% CI)	NR <sup>a</sup> (21.8, NR <sup>a</sup> )	18.2 (14.8, NR <sup>a</sup> )
<b>Progression-free Survival</b>		
Disease progression or death (%)	228 (53.6)	228 (54.0)
Median (months)	11.6	8.4
Hazard ratio (99.1% CI) <sup>a</sup>	0.82 (0.64, 1.05)	
p-value <sup>c</sup>	NS <sup>g</sup>	

<sup>a</sup> Not Reached

<sup>b</sup> Based on a stratified proportional hazards model.

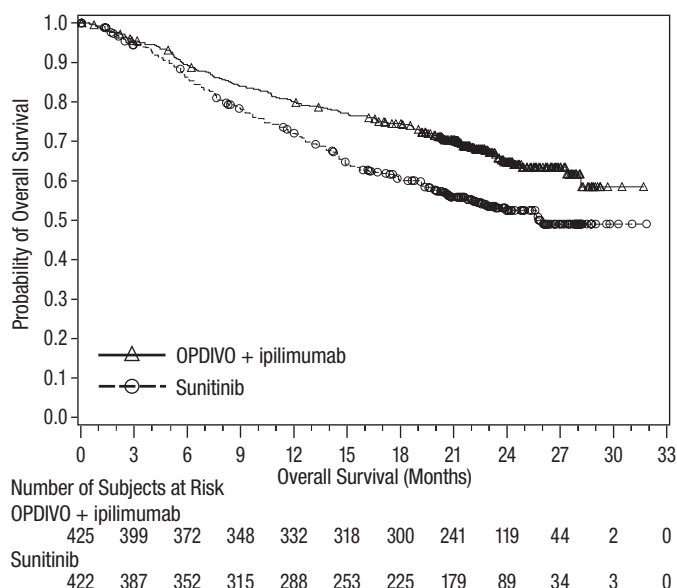
<sup>c</sup> Based on a stratified log-rank test.

<sup>d</sup> p-value is compared to alpha 0.002 in order to achieve statistical significance.

<sup>e</sup> Based on the stratified DerSimonian-Laird test.

<sup>f</sup> p-value is compared to alpha 0.001 in order to achieve statistical significance.

<sup>g</sup> Not Significant at alpha level of 0.009.

**Figure 14: Overall Survival (Intermediate/Poor Risk Population) - CHECKMATE-214**

CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to OPDIVO and ipilimumab (n=125) or to sunitinib (n=124). These patients were not evaluated as part of the efficacy analysis population. OS in favorable risk patients receiving OPDIVO and ipilimumab compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of OPDIVO and ipilimumab in previously untreated renal cell carcinoma with favorable-risk disease has not been established.

#### CHECKMATE-9ER

CHECKMATE-9ER (NCT03141177) was a randomized, open-label study of OPDIVO combined with cabozantinib versus sunitinib in patients with previously untreated advanced RCC. CHECKMATE-9ER excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression. Patients were stratified by IMDC prognostic score (favorable vs. intermediate vs. poor), PD-L1 tumor expression ( $\geq 1\%$  vs.  $< 1\%$  or indeterminate), and region (US/Canada/Western Europe/Northern Europe vs. Rest of World).

Patients were randomized to OPDIVO 240 mg intravenously every 2 weeks and cabozantinib 40 mg orally daily (n=323), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (4 weeks on treatment followed by 2 weeks off) (n=328). Treatment continued until disease progression per RECIST v1.1 or unacceptable toxicity. Treatment beyond RECIST-defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at Week 12, then every 6 weeks until Week 60, and then every 12 weeks thereafter.

The trial population characteristics were: median age 61 years (range: 28 to 90) with 38%  $\geq 65$  years of age and 10%  $\geq 75$  years of age. The majority of patients were male (74%) and White (82%) and 23% and 77% of patients had a baseline KPS of 70% to 80% and 80% to 100%, respectively. Patient distribution by IMDC risk categories was 22% favorable, 58% intermediate, and 20% poor.

The major efficacy outcome measure was PFS (BICR assessed). Additional efficacy outcome measures were OS and ORR (BICR assessed). The trial demonstrated a statistically significant improvement in PFS, OS, and ORR for patients randomized to OPDIVO and cabozantinib compared with sunitinib. Consistent results for PFS were observed across pre-specified subgroups of IMDC risk categories and PD-L1 tumor expression status. An updated OS analysis was conducted when 271 deaths were observed based on the pre-specified number of deaths for the pre-planned final analysis of OS. Efficacy results are shown in Table 63 and Figures 15 and 16.

**Table 63: Efficacy Results - CHECKMATE-9ER**

	OPDIVO and Cabozantinib (n=323)	Sunitinib (n=328)
<b>Progression-free Survival</b>		
Disease progression or death (%)	144 (45)	191 (58)
Median PFS (months) <sup>a</sup> (95% CI)	16.6 (12.5, 24.9)	8.3 (7.0, 9.7)
Hazard ratio (95% CI) <sup>b</sup>	0.51 (0.41, 0.64)	
p-value <sup>c,d</sup>	<0.0001	
<b>Overall Survival</b>		
Deaths (%)	67 (21)	99 (30)
Median OS (months) <sup>a</sup> (95% CI)	NR <sup>e</sup>	NR (22.6, NR <sup>e</sup> )
Hazard ratio (98.89% CI) <sup>b</sup>	0.60 (0.40, 0.89)	
p-value <sup>c,d,f</sup>	0.0010	
<b>Updated Overall Survival</b>		
Deaths (%)	121 (37)	150 (46)
Median OS (months) <sup>a</sup> (95% CI)	37.7 (35.5, NR)	34.3 (29.0, NR)
Hazard ratio (95% CI) <sup>b</sup>	0.70 (0.55, 0.90)	
<b>Confirmed Objective Response Rate (95% CI)<sup>g</sup></b>		
	55.7% (50.1, 61.2)	27.1% (22.4, 32.3)
p-value <sup>h</sup>	<0.0001	
Complete Response	26 (8%)	15 (4.6%)
Partial Response	154 (48%)	74 (23%)
Median duration of response in months (95% CI) <sup>a</sup>	20.2 (17.3, NR <sup>e</sup> )	11.5 (8.3, 18.4)

<sup>a</sup> Based on Kaplan-Meier estimates.

<sup>b</sup> Stratified Cox proportional hazards model.

<sup>c</sup> Based on stratified log-rank test

<sup>d</sup> 2-sided p-values from stratified log-rank test.

<sup>e</sup> Not Reached

<sup>f</sup> p-value is compared with the allocated alpha of 0.0111 for this interim analysis

<sup>g</sup> CI based on the Clopper-Pearson method.

<sup>h</sup> 2-sided p-value from Cochran-Mantel-Haenszel test.

<sup>a</sup> Based on Kaplan-Meier estimates.

<sup>b</sup> Stratified Cox proportional hazards model.

<sup>c</sup> Based on stratified log-rank test

<sup>d</sup> 2-sided p-values from stratified log-rank test.

<sup>e</sup> Not Reached

<sup>f</sup> p-value is compared with the allocated alpha of 0.0111 for this interim analysis

<sup>g</sup> CI based on the Clopper-Pearson method.

<sup>h</sup> 2-sided p-value from Cochran-Mantel-Haenszel test.

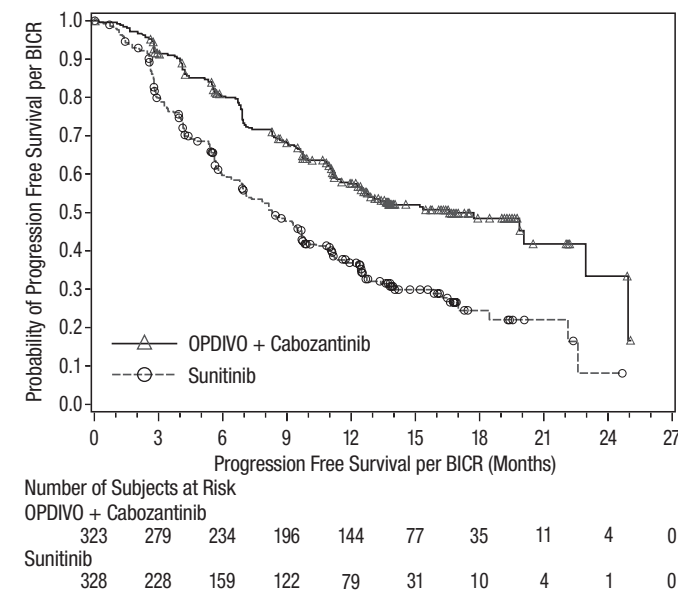
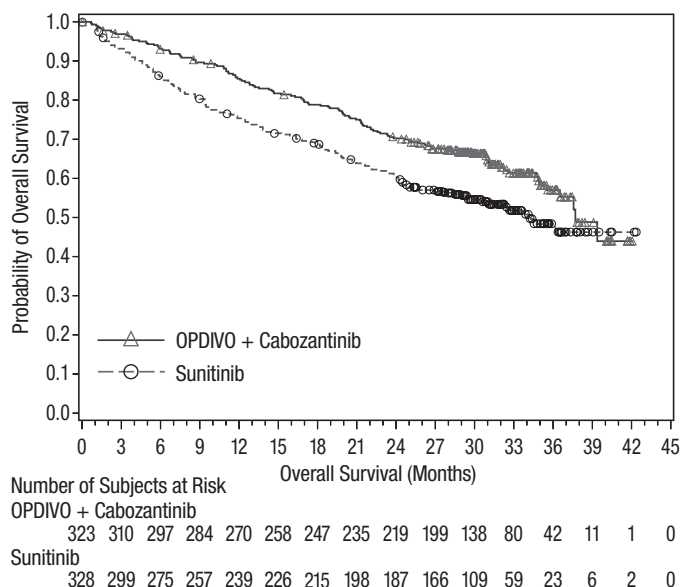
**Figure 15: Progression-free Survival - CHECKMATE-9ER**

Figure 16: Updated Overall Survival - CHECKMATE-9ER



In an exploratory analysis, the updated analysis of OS in patients with IMDC favorable, intermediate, intermediate/poor, and poor risk demonstrated a HR (95% CI) of 1.03 (0.55, 1.92), 0.74 (0.54, 1.01), 0.65 (0.50, 0.85), and 0.49 (0.31, 0.79), respectively.

#### Previously Treated Renal Cell Carcinoma

##### CHECKMATE-025

CHECKMATE-025 (NCT01668784) was a randomized (1:1), open-label trial in patients with advanced RCC who had experienced disease progression during or after one or two prior anti-angiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS)  $\geq 70\%$  and patients were included regardless of their PD-L1 status. The trial excluded patients with any history of or concurrent brain metastases, prior treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by region, Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group and the number of prior anti-angiogenic therapies. Patients were randomized OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=410) or everolimus 10 mg orally daily (n=411). The first tumor assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. The major efficacy outcome measure was overall survival (OS).

The trial population characteristics were: median age was 62 years (range: 18 to 88) with 40%  $\geq 65$  years of age and 9%  $\geq 75$  years of age. The majority of patients were male (75%) and White (88%) and 34% and 66% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. The majority of patients (77%) were treated with one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 34% favorable, 47% intermediate, and 19% poor.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis). OS benefit was observed regardless of PD-L1 expression level. Efficacy results are shown in Table 64 and Figure 17.

Table 64: Efficacy Results - CHECKMATE-025

	OPDIVO (n=410)	Everolimus (n=411)
<b>Overall Survival</b>		
Deaths (%)	183 (45)	215 (52)
Median survival (months) (95% CI)	25.0 (21.7, NR <sup>a</sup> )	19.6 (17.6, 23.1)
Hazard ratio (95% CI) <sup>b</sup>	0.73 (0.60, 0.89)	
p-value <sup>c,d</sup>	0.0018	
<b>Confirmed Overall Response Rate (95% CI)</b>		
	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median duration of response (months) (95% CI)	23.0 (12.0, NR <sup>a</sup> )	13.7 (8.3, 21.9)
Median time to onset of confirmed response (months) (min, max)	3.0 (1.4, 13.0)	3.7 (1.5, 11.2)

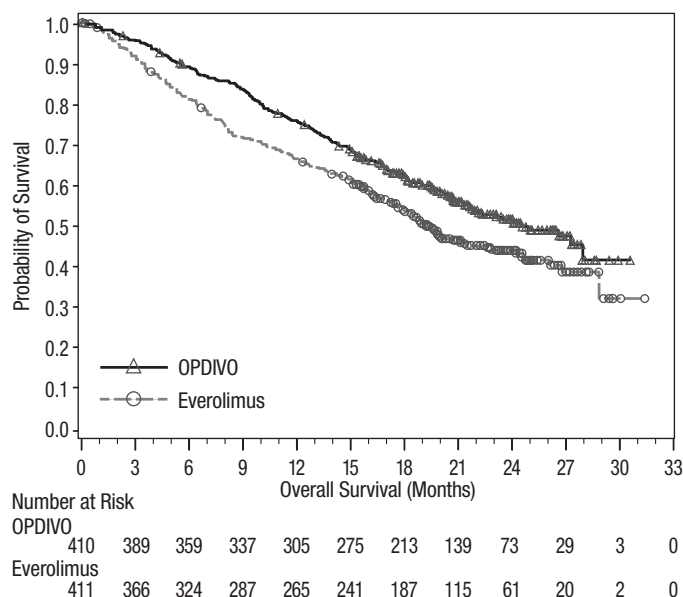
<sup>a</sup> Not Reached

<sup>b</sup> Based on a stratified proportional hazards model.

<sup>c</sup> Based on a stratified log-rank test.

<sup>d</sup> p-value is compared with 0.0148 of the allocated alpha for this interim analysis.

Figure 17: Overall Survival - CHECKMATE-025



#### 14.7 Classical Hodgkin Lymphoma

Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with cHL after failure of autologous HSCT.

CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort trial in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation trial that included cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance  $< 40$  mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. In addition, both studies required an adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) of over 60% in patients with prior pulmonary toxicity.

Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity. A cycle consisted of one dose. Dose reduction was not permitted.

Efficacy was evaluated by ORR as determined by an IRRC. Additional outcome measures included duration of response (DOR).

Efficacy was evaluated in 95 patients in CHECKMATE-205 and CHECKMATE-039 combined who had failure of autologous HSCT and post-transplantation brentuximab vedotin. The median age was 37 years (range: 18 to 72). The majority were male (64%) and White (87%). Patients had received a median of 5 prior systemic regimens (range: 2 to 15). They received a median of 27 doses of OPDIVO (range: 3 to 48), with a median duration of therapy of 14 months (range: 1 to 23 months). Efficacy results are shown in Table 65.



**Table 65: Efficacy in cHL after Autologous HSCT and Post-transplantation Brentuximab Vedotin**

	CHECKMATE-205 and CHECKMATE-039 (n=95)
<b>Overall Response Rate, n (%)<sup>a</sup></b>	63 (66%)
(95% CI)	(56, 76)
Complete remission rate	6 (6%)
(95% CI)	(2, 13)
Partial remission rate	57 (60%)
(95% CI)	(49, 70)
<b>Duration of Response (months)</b>	
Median <sup>b</sup>	13.1
(95% CI)	(9.5, NR <sup>d</sup> )
Range <sup>c</sup>	0+, 23.1+
<b>Time to Response (months)</b>	
Median	2.0
Range	0.7, 11.1

<sup>a</sup> Per 2007 revised International Working Group criteria.<sup>b</sup> Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 9.9 months.<sup>c</sup> A + sign indicates a censored value.<sup>d</sup> Not Reached

Efficacy was also evaluated in 258 patients in CHECKMATE-205 and CHECKMATE-039 combined who had relapsed or progressive cHL after autologous HSCT. The analysis included the group described above. The median age was 34 years (range: 18 to 72). The majority were male (59%) and White (86%). Patients had a median of 4 prior systemic regimens (range: 2 to 15), with 85% having 3 or more prior systemic regimens and 76% having prior brentuximab vedotin. Of the 195 patients having prior brentuximab vedotin, 17% received it only before autologous HSCT, 78% received it only after HSCT, and 5% received it both before and after HSCT. Patients received a median of 21 doses of OPDIVO (range: 1 to 48), with a median duration of therapy of 10 months (range: 0 to 23 months). Efficacy results are shown in Table 66.

**Table 66: Efficacy in cHL after Autologous HSCT**

	CHECKMATE-205 and CHECKMATE-039 (n=258)
<b>Overall Response Rate, n (%)</b>	179 (69%)
(95% CI)	(63, 75)
Complete remission rate	37 (14%)
(95% CI)	(10, 19)
Partial remission rate	142 (55%)
(95% CI)	(49, 61)
<b>Duration of Response (months)</b>	
Median <sup>a,b</sup>	NR <sup>c</sup>
(95% CI)	(12.0, NR <sup>c</sup> )
Range	0+, 23.1+
<b>Time to Response (months)</b>	
Median	2.0
Range	0.7, 11.1

<sup>a</sup> Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 6.7 months.<sup>b</sup> The estimated median duration of PR was 13.1 months (95% CI, 9.5, NE). The median duration of CR was not reached.<sup>c</sup> Not Reached

#### 14.8 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

CHECKMATE-141 (NCT02105636) was a randomized (2:1), active-controlled, open-label trial enrolling patients with metastatic or recurrent SCCHN who had experienced disease progression during or within 6 months of receiving platinum-based therapy administered in either the adjuvant, neo-adjuvant, primary (unresectable locally advanced) or metastatic setting. The trial excluded patients with autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. Patients were randomized to receive OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or investigator's choice of cetuximab (400 mg/m<sup>2</sup> initial dose intravenously followed by 250 mg/m<sup>2</sup> weekly), or methotrexate (40 to 60 mg/m<sup>2</sup> intravenously weekly), or docetaxel (30 to 40 mg/m<sup>2</sup> intravenously weekly).

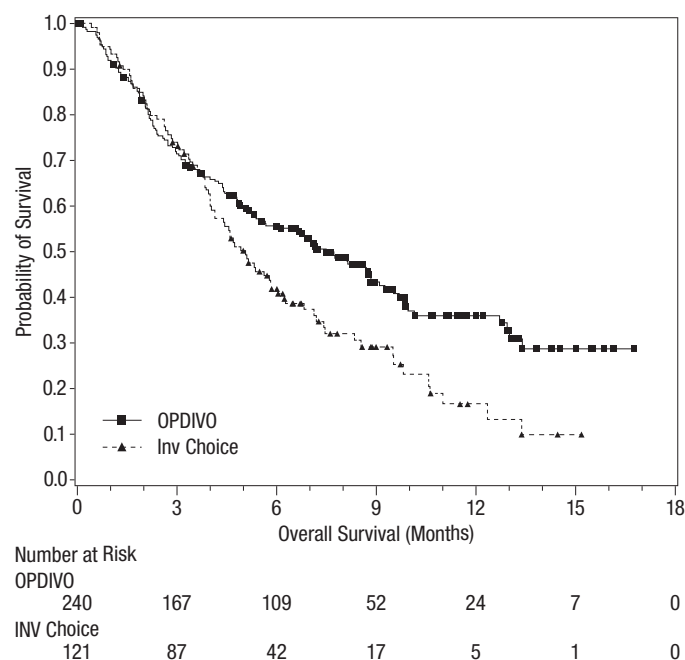
Randomization was stratified by prior cetuximab treatment (yes/no). The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS and ORR.

A total of 361 patients were randomized; 240 patients to the OPDIVO arm and 121 patients to the investigator's choice arm (docetaxel: 45%; methotrexate: 43%; and cetuximab: 12%). The trial population characteristics were: median age was 60 years (range: 28 to 83) with 31% ≥65 years of age, 83% were White, 12% Asian, and 4% were Black, and 83% male. Baseline ECOG performance status was 0 (20%) or 1 (78%), 76% were former/current smokers, 90% had Stage IV disease, 45% of patients received only one prior line of systemic therapy, the remaining 55% received two or more prior lines of systemic therapy, and 25% had HPV p16-positive tumors, 24% had HPV p16-negative tumors, and 51% had unknown status.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). There were no statistically significant differences between the two arms for PFS (HR=0.89; 95% CI: 0.70, 1.13) or ORR (13.3% [95% CI: 9.3, 18.3] vs. 5.8% [95% CI: 2.4, 11.6] for nivolumab and investigator's choice, respectively). Efficacy results are shown in Table 67 and Figure 18.

**Table 67: Overall Survival - CHECKMATE-141**

	OPDIVO (n=240)	Cetuximab, Methotrexate or Docetaxel (n=121)
<b>Overall Survival</b>		
Deaths (%)	133 (55%)	85 (70%)
Median (months)	7.5	5.1
(95% CI)	(5.5, 9.1)	(4.0, 6.0)
Hazard ratio (95% CI) <sup>a</sup>	0.70 (0.53, 0.92)	
p-value <sup>b,c</sup>	0.0101	

<sup>a</sup> Based on stratified proportional hazards model.<sup>b</sup> Based on stratified log-rank test.<sup>c</sup> p-value is compared with 0.0227 of the allocated alpha for this interim analysis.**Figure 18: Overall Survival - CHECKMATE-141**

Archival tumor specimens were retrospectively evaluated for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx assay. Across the trial population, 28% (101/361) of patients had non-quantifiable results. Among the 260 patients with quantifiable results, 43% (111/260) had PD-L1 negative SCCHN, defined as <1% of tumor cells expressing PD-L1, and 57% (149/260) had PD-L1 positive SCCHN, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratio for survival was 0.89 (95% CI: 0.54, 1.45) with median survivals of 5.7 and 5.8 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 negative subgroup. The HR for survival was 0.55 (95% CI: 0.36, 0.83) with median survivals of 8.7 and 4.6 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 positive SCCHN subgroup.

## 14.9 Urothelial Carcinoma

### Adjuvant Treatment of UC at High Risk of Recurrence

CHECKMATE-274 (NCT02632409) was a randomized, double-blind, placebo-controlled study of adjuvant OPDIVO in patients who were within 120 days of radical resection (R0) of UC of the bladder or upper urinary tract (renal pelvis or ureter) at high risk of recurrence. High risk of recurrence was defined as either 1) ypT2-ypT4a or ypN<sup>+</sup> for patients who received neoadjuvant cisplatin or 2) pT3-pT4a or pN<sup>+</sup> for patients who did not receive neoadjuvant cisplatin and who also either were ineligible for or refused adjuvant cisplatin. Patients were randomized 1:1 to receive OPDIVO 240 mg or placebo by intravenous infusion every 2 weeks until recurrence or until unacceptable toxicity for a maximum treatment duration of 1 year. Patients were stratified by pathologic nodal status (N+ vs. N0/x with <10 nodes removed vs. N0 with ≥10 nodes removed), tumor cells expressing PD-L1 (≥1% vs. <1%/indeterminate as determined by the central lab using the PD-L1 IHC 28-8 pharmDx assay), and use of neoadjuvant cisplatin (yes vs. no).

The trial population characteristics were: median age of 67 years (range: 30 to 92); 76% male; 76% White, 22% Asian, 0.7% Black, and 0.1% American Indian or Alaska Native. Of the 335 (47%) of patients with node-positive UC, 44 (6%) had non-muscle-invasive (<pT2) primary tumors. ECOG performance status was 0 (63%), 1 (35%), or 2 (2%). Prior neoadjuvant cisplatin had been given to 43% of patients; of the 57% who did not receive prior neoadjuvant cisplatin, reasons listed were ineligibility (22%), patient preference (33%), and other/not reported (2%). Tumor PD-L1 expression was ≥1% in 40% of patients, and 21% of patients had upper tract UC.

The major efficacy outcome measures were investigator-assessed DFS in all randomized patients and in patients with tumors expressing PD-L1 ≥1%. DFS was defined as time to first recurrence (local urothelial tract, local non-urothelial tract, or distant metastasis), or death. Additional efficacy outcome measures included OS.

At the pre-specified interim analysis, CHECKMATE-274 demonstrated a statistically significant improvement in DFS for patients randomized to OPDIVO vs. placebo in the all randomized patient population, as well as in the subpopulation of patients with PD-L1 ≥1%, as shown in Table 68 and Figure 19.

In exploratory subgroup analyses in patients with upper tract UC (n=149), no improvement in DFS was observed in the nivolumab arm compared to the placebo arm. The unstratified DFS hazard ratio estimate was 1.15 (95% CI: 0.74, 1.80).

In an exploratory subgroup analysis in patients with PD-L1 expression of <1% (n=414), the unstratified DFS hazard ratio estimate was 0.83 (95% CI: 0.64, 1.08).

OS data is immature with 33% of deaths in the overall randomized population. In the UTUC subpopulation, 37 deaths occurred (20 in the nivolumab arm, 17 in the placebo arm).

**Table 68: Efficacy Results – CHECKMATE-274**

	All Randomized		PD-L1 ≥1%	
	OPDIVO (n=353)	Placebo (n=356)	OPDIVO (n=140)	Placebo (n=142)
<b>Disease-free Survival</b>				
Events <sup>a</sup> , n (%)	170 (48)	204 (57)	55 (39)	81 (57)
Local recurrence	47 (13)	64 (18)	10 (7)	24 (17)
Distant recurrence	108 (31)	127 (36)	40 (29)	52 (37)
Death	14 (4)	10 (3)	5 (4)	5 (4)
Median DFS (months) <sup>b</sup>	20.8	10.8	N.R.	8.4
(95% CI)	(16.5, 27.6)	(8.3, 13.9)	(21.2, N.E.)	(5.6, 21.2)
Hazard ratio <sup>c</sup>	0.70		0.55	
(95% CI)	(0.57, 0.86)		(0.39, 0.77)	
p-value	0.0008 <sup>d</sup>		0.0005 <sup>e</sup>	

N.R. Not reached, N.E. Not estimable

<sup>a</sup> Includes disease at baseline events (protocol deviations): n=1 in OPDIVO arm and n=3 in placebo arm.

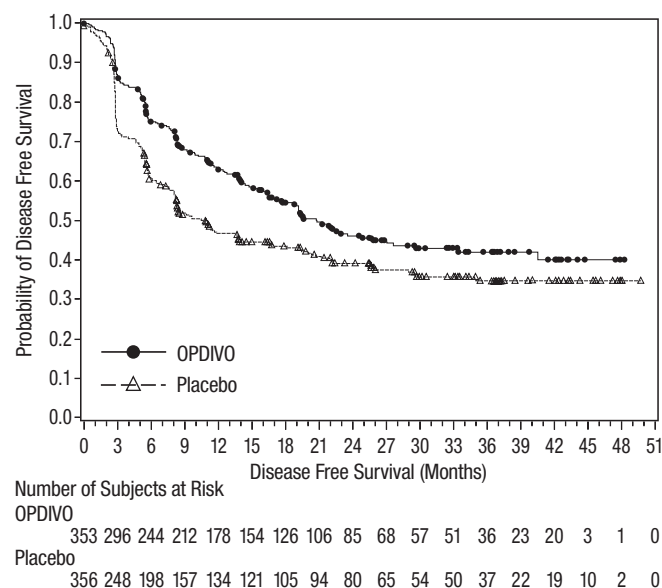
<sup>b</sup> Based on Kaplan-Meier estimates.

<sup>c</sup> Stratified Cox proportional hazard model. Hazard ratio is OPDIVO over placebo.

<sup>d</sup> Log-rank test stratified by prior neoadjuvant cisplatin, pathological nodal status, PD-L1 status (≥1% vs <1%/indeterminate). Boundary for statistical significance in all randomized patients: p-value <0.01784.

<sup>e</sup> Log-rank test stratified by prior neoadjuvant cisplatin, pathological nodal status. Boundary for statistical significance in all randomized patients with PD-L1 ≥1%: p-value <0.01282.

**Figure 19: Disease-free Survival in All Randomized Patients - CHECKMATE-274**



### First-line Treatment of Unresectable or Metastatic UC

CHECKMATE-901 (NCT 03036098) was a randomized, open-label study in patients with previously untreated unresectable or metastatic UC. Prior neoadjuvant or adjuvant chemotherapy were permitted as long as the disease recurrence took place ≥12 months from completion of therapy. Patients who were ineligible for cisplatin and those with active CNS metastases were excluded. Stratification factors for randomization were PD-L1 status (≥1% vs. <1% or indeterminate) and liver metastasis. Patients were randomized 1:1 to receive either:

- OPDIVO 360 mg and cisplatin 70 mg/m<sup>2</sup> on Day 1 and gemcitabine 1000 mg/m<sup>2</sup> on Days 1 and 8 of a 21-day cycle for up to 6 cycles followed by single-agent OPDIVO 480 mg every 4 weeks until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, OPDIVO was continued for up to 2 years from first dose.
- Cisplatin 70 mg/m<sup>2</sup> on Day 1 and gemcitabine 1000 mg/m<sup>2</sup> on Days 1 and 8 of a 21-day cycle for up to 6 cycles, until disease progression or unacceptable toxicity.

The major efficacy outcome measures were OS and PFS as assessed by BICR using RECIST v1.1. Additional efficacy outcome measures included ORR as assessed by BICR.

The median age was 65 years of age (range: 32 to 86) with 51% of patients ≥65 years of age and 12% of patients ≥75 years of age, 23% were Asian, 72% were White, 0.3% were Black, 0.3% were American Indian or Alaska Native, 4.9% were Other, 12% were Hispanic or Latino, and 77% were male. Baseline ECOG performance status was 0 (53%) or 1 (46%). At baseline, 87% of patients had metastatic UC, including 20% with liver metastases, 11% had locally advanced UC, and 51% had UC histologic variants. Forty-nine (16%) in the OPDIVO in combination with cisplatin-based chemotherapy arm and 43 (14%) in the cisplatin-based chemotherapy arm switched from cisplatin to carboplatin after at least one cycle of cisplatin.

Efficacy results are presented in Table 69 and Figures 20 and 21.

Table 69: Efficacy Results - CHECKMATE 901

	OPDIVO and Cisplatin and Gemcitabine (n=304)	Cisplatin and Gemcitabine (n=304)
<b>Overall Survival (OS)</b>		
Events, n (%)	172 (56.6)	193 (63.5)
Median (months)	21.7	18.9
(95% CI) <sup>a</sup>	(18.6, 26.4)	(14.7, 22.4)
Hazard ratio (95% CI) <sup>b</sup>	0.78 (0.63, 0.96)	
p-value <sup>c</sup>	0.0171	
<b>Progression-free Survival (PFS)<sup>d</sup></b>		
Events, n (%)	211 (69.4)	191 (62.8)
Median (months)	7.9	7.6
(95% CI) <sup>a</sup>	(7.6, 9.5)	(6.0, 7.8)
Hazard ratio (95% CI) <sup>b</sup>	0.72 (0.59, 0.88)	
p-value <sup>c</sup>	0.0012	
<b>Objective Response Rate (ORR)<sup>d</sup></b>		
Response rate, n (%)	175 (57.6%)	131 (43.1%)
(95% CI)	(51.8, 63.2)	(37.5, 48.9)
Complete response rate, n (%)	66 (22%)	36 (12%)
Partial response rate, n (%)	109 (36%)	95 (31%)
<b>Duration of Response (DoR)</b>		
Median (months)	9.5	7.3
(95% CI) <sup>a</sup>	(7.6, 15.1)	(5.7, 8.9)

<sup>a</sup> Based on Kaplan-Meier Estimates<sup>b</sup> Stratified Cox proportional hazard model.<sup>c</sup> 2 sided p values from stratified log-rank test.<sup>d</sup> Assessed by BICR.

Figure 20: Overall Survival - CHECKMATE-901

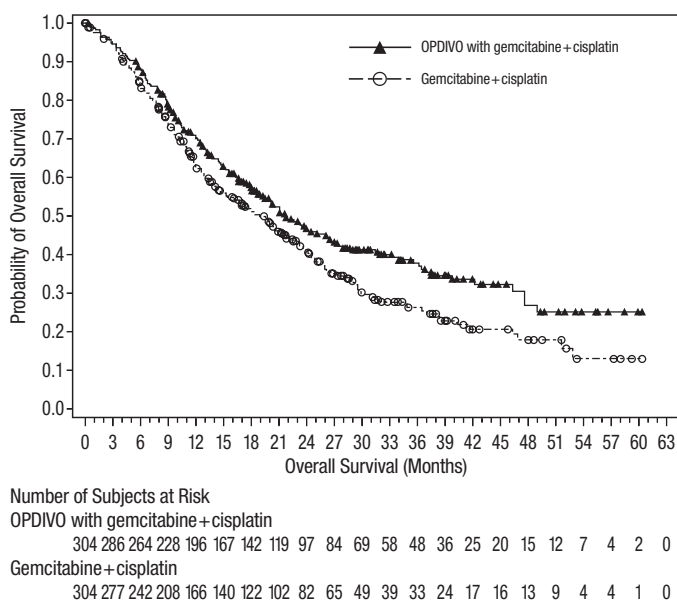
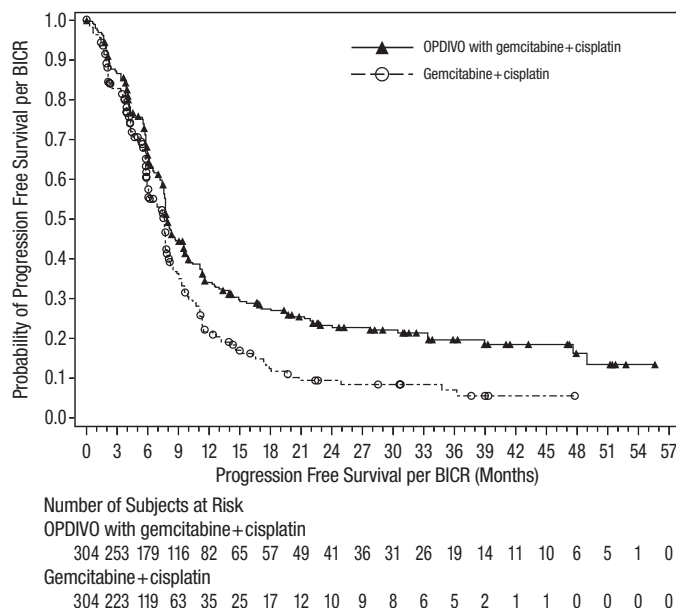


Figure 21: Progression-free Survival - CHECKMATE-901



## Previously Treated Advanced or Metastatic UC

CHECKMATE-275 (NCT02387996) was a single-arm trial in 270 patients with locally advanced or metastatic UC who had disease progression during or following platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Patients were excluded for active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, and ECOG performance status >1. Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 8 weeks for the first 48 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed ORR as assessed by IRR using RECIST v1.1 and DOR.

The median age was 66 years (range: 38 to 90), 78% were male, 86% were White. Twenty-seven percent had non-bladder urothelial carcinoma and 84% had visceral metastases. Thirty-four percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy. Twenty-nine percent of patients had received ≥2 prior systemic regimens in the metastatic setting. Thirty-six percent of patients received prior cisplatin only, 23% received prior carboplatin only, and 7% were treated with both cisplatin and carboplatin in the metastatic setting. Forty-six percent of patients had an ECOG performance status of 1. Eighteen percent of patients had a hemoglobin <10 g/dL, and twenty-eight percent of patients had liver metastases at baseline. Patients were included regardless of their PD-L1 status.

Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are shown in Table 70. Median time to response was 1.9 months (range: 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%).

Table 70: Efficacy Results - CHECKMATE-275

	All Patients N=270	PD-L1 <1% N=146	PD-L1 ≥1% N=124
<b>Confirmed Overall Response Rate, n (%)</b>	53 (19.6%)	22 (15.1%)	31 (25.0%)
(95% CI)	(15.1, 24.9)	(9.7, 21.9)	(17.7, 33.6)
Complete response rate	7 (2.6%)	1 (0.7%)	6 (4.8%)
Partial response rate	46 (17.0%)	21 (14.4%)	25 (20.2%)
<b>Median Duration of Response<sup>a</sup> (months)</b>	10.3	7.6	NR <sup>b</sup>
(range)	(1.9+, 12.0+)	(3.7, 12.0+)	(1.9+, 12.0+)

<sup>a</sup> Estimated from the Kaplan-Meier Curve<sup>b</sup> Not Reached



#### 14.10 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

CHECKMATE-142 (NCT02060188) was a multicenter, non-randomized, multiple parallel-cohort, open-label trial conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG performance status 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients enrolled in the single agent OPDIVO MSI-H mCRC cohort received OPDIVO 3 mg/kg by intravenous infusion (IV) every 2 weeks. Patients enrolled in the OPDIVO and ipilimumab MSI-H mCRC cohort received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses, followed by OPDIVO as a single agent at a dose of 3 mg/kg as intravenous infusion every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression.

Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures included ORR and DOR as assessed by BICR using RECIST v1.1.

A total of 74 patients were enrolled in the single-agent MSI-H mCRC OPDIVO cohort. The median age was 53 years (range: 26 to 79) with 23% ≥65 years of age and 5% ≥75 years of age; 59% were male and 88% were White. Baseline ECOG performance status was 0 (43%), 1 (55%), or 3 (1.4%) and 36% were reported to have Lynch Syndrome. Across the 74 patients, 72% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 7%, 30%, 28%, 19%, and 16% received 0, 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 42% of patients had received an anti-EGFR antibody.

A total of 119 patients were enrolled in the OPDIVO and ipilimumab MSI-H mCRC cohort. The median age was 58 years (range: 21 to 88), with 32% ≥65 years of age and 9% ≥75 years of age; 59% were male and 92% were White. Baseline ECOG performance status was 0 (45%) and 1 (55%), and 29% were reported to have Lynch Syndrome. Across the 119 patients, 69% had received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 10%, 40%, 24%, and 15% received 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 29% had received an anti-EGFR antibody.

Efficacy results for each of these single-arm cohorts are shown in Table 71.

**Table 71: Efficacy Results – CHECKMATE-142**

	OPDIVO <sup>a</sup> MSI-H/dMMR Cohort		OPDIVO and Ipilimumab <sup>b</sup> MSI-H/dMMR Cohort	
	All Patients (n=74)	Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=53)	All Patients (n=119)	Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)
<b>Overall Response Rate per BICR; n (%)</b>	28 (38%)	17 (32%)	71 (60%)	46 (56%)
(95% CI) <sup>c</sup>	(27, 50)	(20, 46)	(50, 69)	(45, 67)
Complete Response (%)	8 (11%)	5 (9%)	17 (14%)	11 (13%)
Partial Response (%)	20 (27%)	12 (23%)	54 (45%)	35 (43%)
<b>Duration of Response</b>				
Proportion of responders with ≥6 months response duration	86%	94%	89%	87%
Proportion of responders with ≥12 months response duration	82%	88%	77%	74%

<sup>a</sup> Minimum follow-up 33.7 months for all patients treated with OPDIVO (n=74).

<sup>b</sup> Minimum follow-up 27.5 months for all patients treated with OPDIVO and ipilimumab (n=119).

<sup>c</sup> Estimated using the Clopper-Pearson method.

#### 14.11 Hepatocellular Carcinoma

CHECKMATE-040 (NCT01658878) was a multicenter, multiple cohort, open-label trial that evaluated the efficacy of OPDIVO as a single agent and in combination with ipilimumab in patients with hepatocellular carcinoma (HCC) who progressed on or were intolerant to sorafenib. Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible.

Tumor assessments were conducted every 6 weeks for 48 weeks and then every 12 weeks thereafter. The major efficacy outcome measure was confirmed overall

response rate as assessed by BICR using RECIST v1.1 and modified RECIST (mRECIST) for HCC. Duration of response was also assessed.

The efficacy of OPDIVO in combination with ipilimumab was evaluated in 49 patients (Cohort 4) who received OPDIVO 1 mg/kg and ipilimumab 3 mg/kg administered every 3 weeks for 4 doses, followed by single-agent OPDIVO at 240 mg every 2 weeks until disease progression or unacceptable toxicity. The median age was 60 years (range: 18 to 80); 88% were male, 74% were Asian, and 25% were White. Baseline ECOG performance status was 0 (61%) or 1 (39%). Fifty-seven (57%) percent of patients had active HBV infection, 8% had active HCV infection, and 35% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 16% and non-alcoholic fatty liver disease in 6% of patients. Child-Pugh class and score was A5 for 82% and A6 for 18%; 80% of patients had extrahepatic spread; 35% had vascular invasion; and 51% had AFP levels ≥400 µg/L. Prior cancer treatment history included surgery (74%), radiotherapy (29%), or local treatment (59%). All patients had received prior sorafenib, of whom 10% were unable to tolerate sorafenib; 29% of patients had received 2 or more prior systemic therapies.

Efficacy results are shown in Table 72. The results for OPDIVO in combination with ipilimumab in Cohort 4 are based on a minimum follow-up of 28 months.

**Table 72: Efficacy Results - Cohort 4 of CHECKMATE-040**

	OPDIVO and Ipilimumab (Cohort 4) (n=49)
<b>Overall Response Rate per BICR,<sup>a</sup> n (%), RECIST v1.1</b>	16 (33%)
(95% CI) <sup>b</sup>	(20, 48)
Complete response	4 (8%)
Partial response	12 (24%)
<b>Duration of Response per BICR,<sup>a</sup> RECIST v1.1</b>	n=16
Range (months)	4.6, 30.5+
Percent with duration ≥6 months	88%
Percent with duration ≥12 months	56%
Percent with duration ≥24 months	31%
<b>Overall Response Rate per BICR,<sup>a</sup> n (%), mRECIST</b>	17 (35%)
(95% CI) <sup>b</sup>	(22, 50)
Complete response	6 (12%)
Partial response	11 (22%)

<sup>a</sup> Confirmed by BICR.

<sup>b</sup> Confidence interval is based on the Clopper and Pearson method.

#### 14.12 Esophageal Cancer

##### Adjuvant Treatment of Resected Esophageal or Gastroesophageal Junction Cancer

CHECKMATE-577 (NCT02743494) was a randomized, multicenter, double-blind trial in 794 patients with completely resected (negative margins) esophageal or gastroesophageal junction cancer who had residual pathologic disease following concurrent chemoradiotherapy (CRT). Patients were randomized (2:1) to receive either OPDIVO 240 mg or placebo by intravenous infusion over 30 minutes every 2 weeks for 16 weeks followed by 480 mg or placebo by intravenous infusion over 30 minutes every 4 weeks beginning at week 17. Treatment was until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. Enrollment required complete resection within 4 to 16 weeks prior to randomization. The trial excluded patients who did not receive CRT prior to surgery, had stage IV resectable disease, autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications. Randomization was stratified by tumor PD-L1 status (≥1% vs. <1% or indeterminate or non-evaluable), pathologic lymph node status (positive ≥ypN1 vs. negative ypN0), and histology (squamous vs. adenocarcinoma). The major efficacy outcome measure was disease-free survival (DFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant from the primary resected site) or death, from any cause, whichever occurred first as assessed by the investigator prior to subsequent anti-cancer therapy. Patients on treatment underwent imaging for tumor recurrence every 12 weeks for 2 years, and a minimum of one scan every 6 to 12 months for years 3 to 5.

The trial population characteristics were: median age 62 years (range: 26 to 86), 36% were ≥65 years of age, 85% were male, 15% were Asian, 82% were White, and 1.1% were Black. Disease characteristics were AJCC Stage II (35%) or Stage III (65%) at initial diagnosis carcinoma, EC (60%) or GEJC (40%) at initial diagnosis, with pathologic positive lymph node status (58%) at study entry and histological confirmation of predominant adenocarcinoma (71%) or squamous cell carcinoma (29%). The baseline Tumor PD-L1 status ≥1% was positive for 16% of patients and negative for 72% of patients. Baseline ECOG performance status was 0 (58%) or 1 (42%).

CHECKMATE-577 demonstrated a statistically significant improvement in DFS for patients randomized to the OPDIVO arm as compared with the placebo arm. DFS benefit was observed regardless of tumor PD-L1 expression and histology.

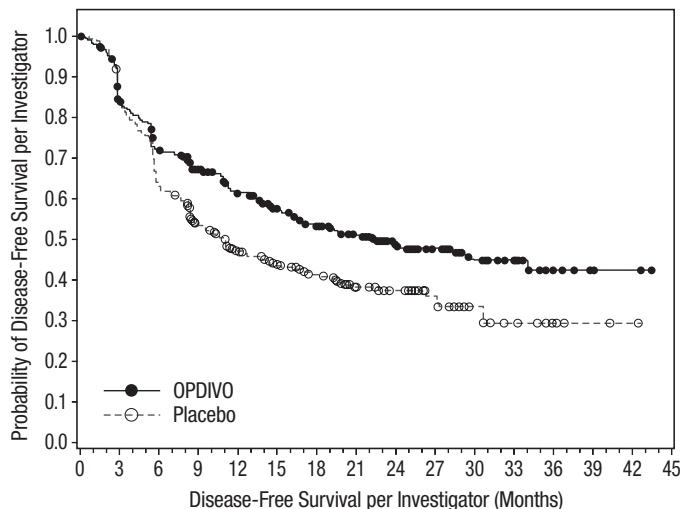
Efficacy results are shown in Table 73 and Figure 22.

Table 73: Efficacy Results - CHECKMATE-577

	OPDIVO (n=532)	Placebo (n=262)
<b>Disease-free Survival</b>		
Number of events, n (%)	241 (45%)	155 (59%)
Median (months) (95% CI)	22.4 (16.6, 34.0)	11.0 (8.3, 14.3)
Hazard ratio <sup>a</sup> (95% CI)	0.69 (0.56, 0.85)	
p-value <sup>b</sup>	0.0003	

<sup>a</sup> Based on a stratified proportional hazards model.<sup>b</sup> Based on a stratified log-rank test.

Figure 22: Disease-free Survival - CHECKMATE-577



OPDIVO	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

Table 74: Efficacy Results - CHECKMATE-648

	OPDIVO with Cisplatin and Fluorouracil (n=321)	OPDIVO and Ipilimumab (n=325)	Cisplatin and Fluorouracil (n=324)	OPDIVO with Cisplatin and Fluorouracil (n=158)	OPDIVO and Ipilimumab (n=158)	Cisplatin and Fluorouracil (n=157)
	All Patients			TC PD-L1 expression ≥1%		
<b>Overall Survival</b>						
Deaths (%)	209 (65)	216 (66)	232 (72)	98 (62)	106 (67)	121 (77)
Median (months) (95% CI)	13.2 (11.1, 15.7)	12.8 (11.3, 15.5)	10.7 (9.4, 11.9)	15.4 (11.9, 19.5)	13.7 (11.2, 17.0)	9.1 (7.7, 10)
Hazard ratio (95% CI) <sup>b</sup>	0.74 (0.61, 0.90)	0.78 (0.65, 0.95)	-	0.54 (0.41, 0.71)	0.64 (0.49, 0.84)	-
p-value <sup>c</sup>	0.0021 <sup>S1</sup>	0.0110 <sup>S2</sup>	-	<0.0001 <sup>S3</sup>	0.0010 <sup>S4</sup>	-
<b>Progression-free Survival<sup>a</sup></b>						
Disease progression or death (%)	235 (73)	258 (79)	210 (65)	117 (74)	123 (78)	100 (64)
Median (months) (95% CI)	5.8 (5.6, 7.0)	2.9 (2.7, 4.2)	5.6 (4.3, 5.9)	6.9 (5.7, 8.3)	4.0 (2.4, 4.9)	4.4 (2.9, 5.8)
Hazard ratio (95% CI) <sup>b</sup>	0.81 (0.67, 0.99)	1.26 (1.04, 1.52)	-	0.65 (0.49, 0.86)	1.02 (0.78, 1.34)	-
p-value <sup>c</sup>	NS	NT	-	0.0023 <sup>S5</sup>	NS	-
<b>Overall Response Rate, n (%)<sup>a,NT</sup></b>	152 (47.4)	90 (27.7)	87 (26.9)	84 (53.2)	56 (35.4)	31 (19.7)
(95% CI)	(41.8, 53.0)	(22.9, 32.9)	(22.1, 32.0)	(45.1, 61.1)	(28.0, 43.4)	(13.8, 26.8)
Complete response (%)	43 (13.4)	36 (11.1)	20 (6.2)	26 (16.5)	28 (17.7)	8 (5.1)
Partial response (%)	109 (34.0)	54 (16.6)	67 (20.7)	58 (36.7)	28 (17.7)	23 (14.6)
<b>Duration of Response (months)<sup>a</sup></b>						
Median (95% CI)	8.2 (6.9, 9.7)	11.1 (8.3, 14.0)	7.1 (5.7, 8.2)	8.4 (6.9, 12.4)	11.8 (7.1, 27.4)	5.7 (4.4, 8.7)
Range	1.4+, 35.9+	1.4+, 34.5+	1.4+, 31.8+	1.4+, 34.6+	1.4+, 34.5+	1.4+, 31.8+

<sup>a</sup> Assessed by BICR.<sup>b</sup> Based on stratified Cox proportional hazard model. Hazard ratios are reported for each OPDIVO containing arm compared to chemotherapy within each analysis population.<sup>c</sup> Based on a stratified 2-sided log-rank test.<sup>S1, S2, S3, S4, S5</sup> Significant p-value compared to stopping boundary of 0.009, 0.018, 0.005, 0.014, and 0.015 respectively.

NS: Not Statistically significant, NT: Not evaluated for statistical significance as per pre-specified hierarchical testing procedure

## First-line Treatment of Unresectable Advanced or Metastatic ESCC

CHECKMATE-648 (NCT03143153) was a randomized, active-controlled, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic ESCC (squamous or adenocarcinoma histology). The trial enrolled patients whose tumor was evaluable for tumor cell (TC) PD-L1 expression [also called PD-L1 tumor proportion score (TPS)], which was evaluated using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. A retrospective scoring of a patient's tumor PD-L1 status using Combined Positive Score (CPS), was also conducted using the PD-L1-stained tumor specimens used for randomization. Patients were not amenable to chemoradiation or surgery with curative intent. Prior treatment with curative intent was allowed if completed more than six months prior to trial enrollment. The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumor to organs adjacent to the esophageal tumor. Patients were randomized to receive one of the following treatments:

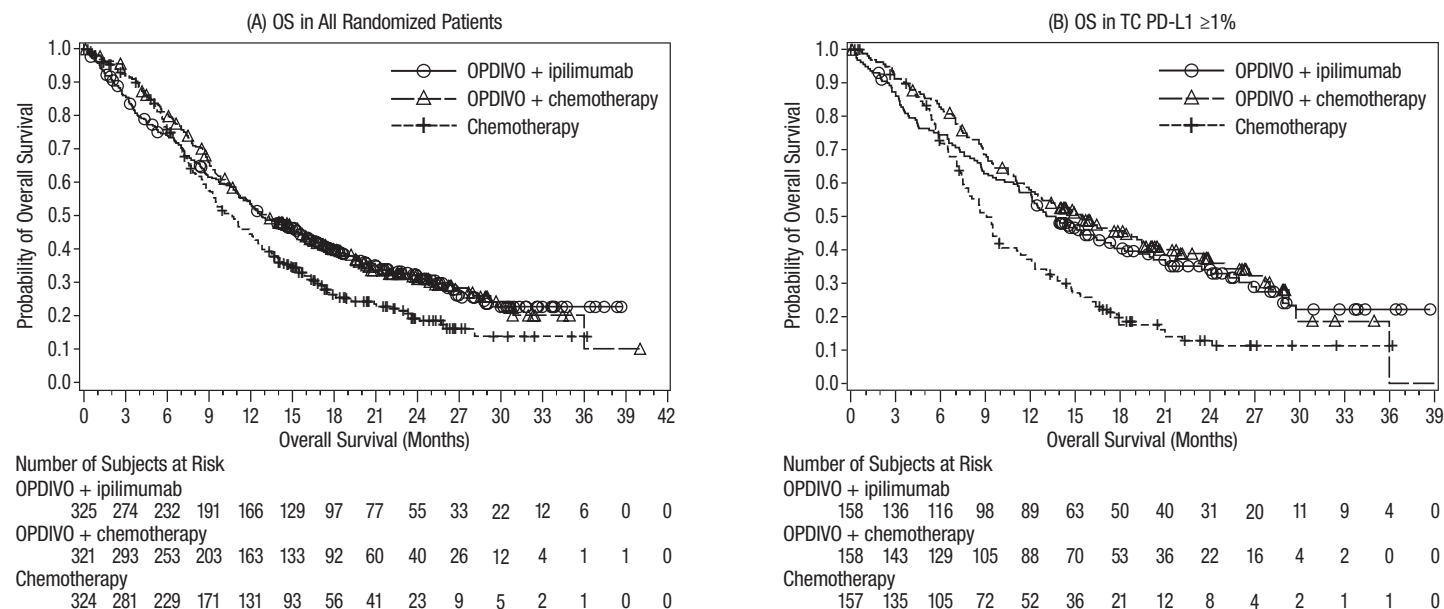
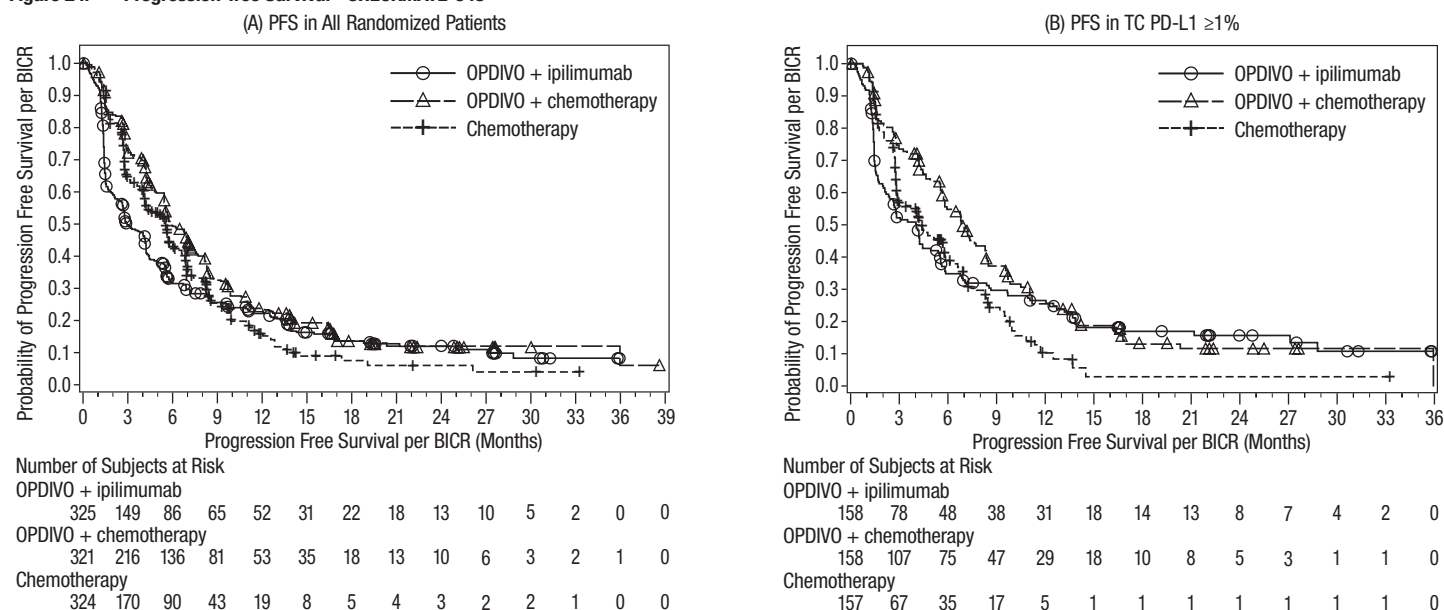
- OPDIVO 240 mg on days 1 and 15, fluorouracil 800 mg/m<sup>2</sup>/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m<sup>2</sup> intravenously on day 1 (of a 4-week cycle).
- OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks.
- Fluorouracil 800 mg/m<sup>2</sup>/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m<sup>2</sup> intravenously on day 1 (of a 4-week cycle).

Patients received OPDIVO until disease progression, unacceptable toxicity, or up to 2 years. In patients who received OPDIVO in combination with chemotherapy and in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent.

Randomization was stratified by TC PD-L1 expression (≥1% vs. <1% or indeterminate), region (East Asia vs. Rest of Asia vs. Rest of World), ECOG performance status (0 vs. 1), and number of organs with metastases (≤1 vs. ≥2). The major efficacy outcome measures were OS and BICR-assessed PFS in patients with TC PD-L1 expression ≥1%. Additional efficacy measures included OS in all randomized patients, BICR-assessed PFS in all randomized patients, and ORR assessed by BICR in TC PD-L1 expression ≥1% and in all randomized patients. The tumor assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

A total of 970 patients were randomized in CHECKMATE-648 study among whom 965 and 906 patients had quantifiable TC PD-L1 expression and CPS at baseline, respectively. The trial population characteristics for all randomized patients were median age 64 years (range: 26 to 90), 47% were ≥65 years of age, 82% were male, 71% were Asian, 26% were White, and 1.1% were Black. Patients had histological confirmation of squamous cell carcinoma (98%) or adenocarcinoma cell carcinoma (1.9%) in the esophagus. Baseline ECOG performance status was 0 (47.0%) or 1 (53%).

Efficacy results are shown in Table 74 and Figure 23 and 24.

**Figure 23: Overall Survival – CHECKMATE-648****Figure 24: Progression-free Survival – CHECKMATE-648**

Exploratory subgroup analyses of patients with TC PD-L1 expression  $<1\%$  (n=492) were conducted. OS results for each OPDIVO containing arm compared to chemotherapy were:

- OPDIVO with Chemotherapy (n=163) vs. Chemotherapy (n=165): unstratified OS HR was 0.99 (95% CI: 0.76, 1.29) with median OS of 12 months (95% CI: 9.9, 15.5) on the OPDIVO with Chemotherapy arm and 12.2 months (95% CI: 10.7, 14) on the Chemotherapy arm.
- OPDIVO with Ipilimumab (n=164) vs. Chemotherapy (n=165): unstratified OS HR was 0.97 (95% CI: 0.74, 1.26) with median OS of 12 months (95% CI: 10.1, 16.0) on the OPDIVO with Ipilimumab arm and 12.2 months (95% CI: 10.7, 14) on the Chemotherapy arm.

Exploratory subgroup analyses were also conducted by PD-L1 status per CPS ( $\geq 1$  and  $<1$ ) for each OPDIVO containing arm compared to chemotherapy. Among the 906 patients with quantifiable PD-L1 CPS at baseline, 278 in the OPDIVO with chemotherapy arm, 266 in the OPDIVO with Ipilimumab arm, and 280 in the chemotherapy arm had PD-L1 CPS  $\geq 1$ . A total of 27 patients in the OPDIVO with chemotherapy arm, 31 patients in the OPDIVO with Ipilimumab arm, and 24 patients in the chemotherapy arm had PD-L1 CPS  $<1$ .

OS results for each comparison by PD-L1 CPS status were:

- OPDIVO with Chemotherapy vs. Chemotherapy: unstratified OS HR was 0.69 (95% CI: 0.56, 0.84) for PD-L1 CPS  $\geq 1$  subgroup and 0.98 (95% CI: 0.50, 1.95) for PD-L1 CPS  $<1$  subgroup.

- OPDIVO with Ipilimumab vs. Chemotherapy: unstratified OS HR was 0.76 (95% CI: 0.62, 0.93) for PD-L1 CPS  $\geq 1$  subgroup and 1.0 (95% CI: 0.52, 1.94) for PD-L1 CPS  $<1$  subgroup.

#### Previously Treated Unresectable Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

ATTRACTION-3 (NCT02569242) was a multicenter, randomized (1:1), active-controlled, open-label trial in patients with unresectable advanced, recurrent, or metastatic ESCC, who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen. The trial enrolled patients regardless of PD-L1 status, but tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had autoimmune disease, used systemic corticosteroids or immunosuppressants, or had apparent tumor invasion of organs adjacent to the esophageal tumor or had stents in the esophagus or respiratory tract. Patients were randomized to receive OPDIVO 240 mg by intravenous infusion over 30 minutes every 2 weeks or investigator's choice of taxane chemotherapy consisting of docetaxel (75 mg/m<sup>2</sup> intravenously every 3 weeks) or paclitaxel (100 mg/m<sup>2</sup> intravenously once a week for 6 weeks followed by 1 week off).

Randomization was stratified by region (Japan vs. Rest of World), number of organs with metastases ( $\leq 1$  vs.  $\geq 2$ ), and PD-L1 status ( $\geq 1\%$  vs.  $<1\%$  or indeterminate). Patients were treated until disease progression, assessed by the investigator per RECIST v1.1, or unacceptable toxicity. The tumor assessments were conducted every 6 weeks for 1 year,



and every 12 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were ORR and PFS as assessed by the investigator using RECIST v1.1 and DOR.

A total of 419 patients were randomized; 210 to the OPDIVO arm and 209 to the investigator's choice arm (docetaxel: 31%, paclitaxel: 69%). The trial population characteristics were: median age 65 years (range: 33 to 87), 53% were ≥65 years of age, 87% were male, 96% were Asian and 4% were White. Sixty-seven percent of patients had received one prior systemic therapy regimen and 26% had received two prior systemic therapy regimens prior to enrolling in ATTRACTION-3. Baseline ECOG performance status was 0 (50%) or 1 (50%).

ATTRACTION-3 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice of taxane chemotherapy. OS benefit was observed regardless of PD-L1 expression level. The minimum follow-up was 17.6 months. Efficacy results are shown in Table 75 and Figure 25.

**Table 75: Efficacy Results - ATTRACTION-3**

	OPDIVO (n=210)	Docetaxel or Paclitaxel (n=209)
<b>Overall Survival<sup>a</sup></b>		
Deaths (%)	160 (76%)	173 (83%)
Median (months)	10.9	8.4
(95% CI)	(9.2, 13.3)	(7.2, 9.9)
Hazard ratio (95% CI) <sup>b</sup>	0.77 (0.62, 0.96)	
p-value <sup>c</sup>	0.0189	
<b>Overall Response Rate<sup>d</sup></b>		
(95% CI)	33 (19.3) (13.7, 26.0)	34 (21.5) (15.4, 28.8)
Complete response (%)	1 (0.6)	2 (1.3)
Partial response (%)	32 (18.7)	32 (20.3)
Median duration of response (months)	6.9	3.9
(95% CI)	(5.4, 11.1)	(2.8, 4.2)
p-value <sup>e</sup>	0.6323	
<b>Progression-free Survival<sup>a,f</sup></b>		
Disease progression or death (%)	187 (89)	176 (84)
Median (months)	1.7	3.4
(95% CI)	(1.5, 2.7)	(3.0, 4.2)
Hazard ratio (95% CI) <sup>b</sup>	1.1 (0.9, 1.3)	

<sup>a</sup> Based on ITT analysis

<sup>b</sup> Based on a stratified proportional hazards model.

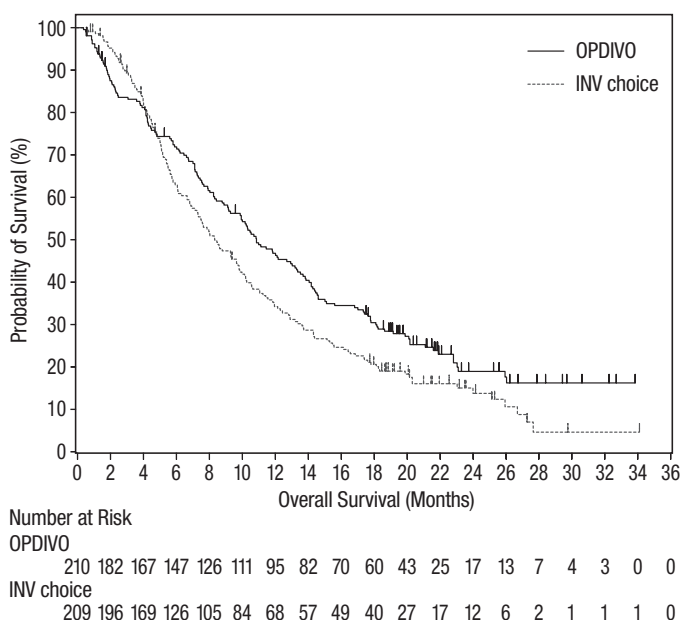
<sup>c</sup> Based on a stratified log-rank test.

<sup>d</sup> Based on Response Evaluable Set (RES) analysis, n=171 in OPDIVO group and n=158 in investigator's choice group.

<sup>e</sup> Based on stratified Cochran-Mantel-Haenszel test; p-value not significant.

<sup>f</sup> PFS not tested due to pre-specified hierarchical testing strategy.

**Figure 25: Overall Survival - ATTRACTION-3**



Of the 419 patients, 48% had PD-L1 positive ESCC, defined as ≥1% of tumor cells expressing PD-L1. The remaining 52% had PD-L1 negative ESCC defined as <1% of tumor cells expressing PD-L1.

In a pre-specified exploratory analysis by PD-L1 status, the hazard ratio (HR) for OS was 0.69 (95% CI: 0.51, 0.94) with median survivals of 10.9 and 8.1 months for the OPDIVO and investigator's choice arms, respectively, in the PD-L1 positive subgroup. In the PD-L1 negative subgroup, the HR for OS was 0.84 (95% CI: 0.62, 1.14) with median survivals of 10.9 and 9.3 months for the OPDIVO and investigator's choice arms, respectively.

#### 14.13 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

CHECKMATE-649 (NCT02872116) was a randomized, multicenter, open-label trial in patients (n=1581) with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. The trial enrolled patients regardless of PD-L1 status, and tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive, or had untreated CNS metastases. Patients were randomized to receive OPDIVO in combination with chemotherapy (n=789) or chemotherapy (n=792). Patients received one of the following treatments:

- OPDIVO 240 mg in combination with mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or mFOLFOX6 every 2 weeks.
- OPDIVO 360 mg in combination with CapeOX (capecitabine and oxaliplatin) every 3 weeks or CapeOX every 3 weeks.

Patients were treated until disease progression, unacceptable toxicity, or up to 2 years. In patients who received OPDIVO in combination with chemotherapy and in whom chemotherapy was discontinued, OPDIVO monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks up to 2 years after treatment initiation.

Randomization was stratified by tumor cell PD-L1 status (≥1% vs. <1% or indeterminate), region (Asia vs. US vs. Rest of World), ECOG performance status (0 vs. 1), and chemotherapy regimen (mFOLFOX6 vs. CapeOX). The major efficacy outcome measures, assessed in patients with PD-L1 CPS ≥5, were PFS assessed by BICR and OS. Additional efficacy outcome measures included OS and PFS in patients with PD-L1 CPS ≥1 and in all randomized patients, and ORR and DOR as assessed by BICR in patients with PD-L1 CPS ≥1 and ≥5, and in all randomized patients. Tumor assessments were conducted per RECIST v1.1 every 6 weeks up to and including week 48, then every 12 weeks thereafter.

The trial population characteristics were: median age 61 years (range: 18 to 90), 39% were ≥65 years of age, 70% were male, 24% were Asian, and 69% were White, and 1% were Black. Baseline ECOG performance status was 0 (42%) or 1 (58%). Seventy percent of patients had adenocarcinoma tumors in the stomach, 16% in the gastroesophageal junction, and 13% in the esophagus.

CHECKMATE-649 demonstrated a statistically significant improvement in OS and PFS for patients with PD-L1 CPS ≥5. Statistically significant improvement in OS was also demonstrated for all randomized patients. The minimum follow-up was 12.1 months. Efficacy results are shown in Table 76 and Figures 26, 27, and 28.

Table 76: Efficacy Results - CHECKMATE-649

	OPDIVO and mFOLFOX6 or CapeOX (n=789)	mFOLFOX6 or CapeOX (n=792)	OPDIVO and mFOLFOX6 or CapeOX (n=641)	mFOLFOX6 or CapeOX (n=655)	OPDIVO and mFOLFOX6 or CapeOX (n=473)	mFOLFOX6 or CapeOX (n=482)
	All Patients		PD-L1 CPS ≥1		PD-L1 CPS ≥5	
Overall Survival						
Deaths (%)	544 (69)	591 (75)	434 (68)	492 (75)	309 (65)	362 (75)
Median (months) (95% CI)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)	14.0 (12.6, 15.0)	11.3 (10.6, 12.3)	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)
Hazard ratio (95% CI) <sup>a</sup>	0.80 (0.71, 0.90)		0.77 (0.68, 0.88)		0.71 (0.61, 0.83)	
p-value <sup>b</sup>	0.0002		<0.0001		<0.0001	
Progression-free Survival <sup>c</sup>						
Disease progression or death (%)	559 (70.8)	557 (70.3)	454 (70.8)	472 (72.1)	328 (69.3)	350 (72.6)
Median (months) (95% CI)	7.7 (7.1, 8.5)	6.9 (6.6, 7.1)	7.5 (7.0, 8.4)	6.9 (6.1, 7.0)	7.7 (7.0, 9.2)	6.0 (5.6, 6.9)
Hazard ratio (95% CI) <sup>a</sup>	0.77 (0.68, 0.87)		0.74 (0.65, 0.85)		0.68 (0.58, 0.79)	
p-value <sup>b</sup>	- <sup>e</sup>		- <sup>e</sup>		<0.0001	
Overall Response Rate, n (%) <sup>c,d</sup>						
(95% CI)	370 (47) (43, 50)	293 (37) (34, 40)	314 (49) (45, 53)	249 (38) (34, 42)	237 (50) (46, 55)	184 (38) (34, 43)
Complete response (%)	78 (10)	52 (7)	65 (10)	42 (6)	55 (12)	34 (7)
Partial response (%)	292 (37)	241 (30)	249 (39)	207 (32)	182 (38)	150 (31)
Duration of Response (months) <sup>c,d</sup>						
Median (95% CI)	8.5 (7.2, 9.9)	6.9 (5.8, 7.2)	8.5 (7.7, 10.3)	6.9 (5.8, 7.6)	9.5 (8.1, 11.9)	6.9 (5.6, 7.9)
Range	1.0+, 29.6+	1.2+, 30.8+	1.1+, 29.6+	1.2+, 30.8+	1.1+, 29.6+	1.2+, 30.8+

<sup>a</sup> Based on stratified Cox proportional hazard model.<sup>b</sup> Based on stratified log-rank test.<sup>c</sup> Assessed by BICR.<sup>d</sup> Based on confirmed response.<sup>e</sup> Not evaluated for statistical significance.

In an exploratory analysis in patients with PD-L1 CPS <1 (n=265), the median OS was 13.1 months (95% CI: 9.8, 16.7) for the OPDIVO and chemotherapy arm and 12.5 months (95% CI: 10.1, 13.8) for the chemotherapy arm, with a stratified HR of 0.85 (95% CI: 0.63, 1.15).

In an exploratory analysis in patients with PD-L1 CPS <5 (n=606), the median OS was 12.4 months (95% CI: 10.6, 14.3) for the OPDIVO and chemotherapy arm and 12.3 months (95% CI: 11.0, 13.2) for the chemotherapy arm, with a stratified HR of 0.94 (95% CI: 0.78, 1.14).

Figure 26: Overall Survival (All Patients) - CHECKMATE-649

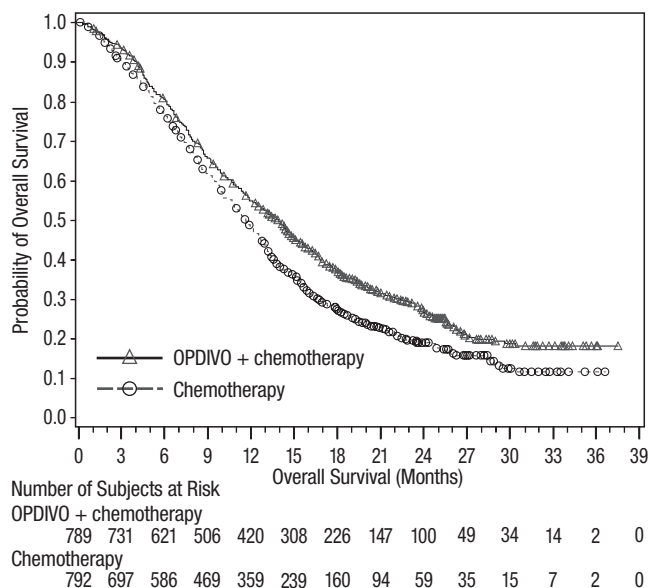


Figure 27: Overall Survival (PD-L1 CPS ≥1) - CHECKMATE-649

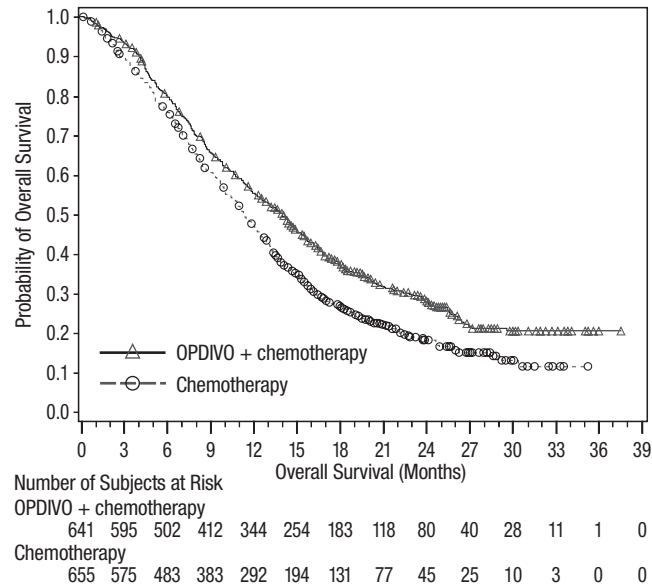
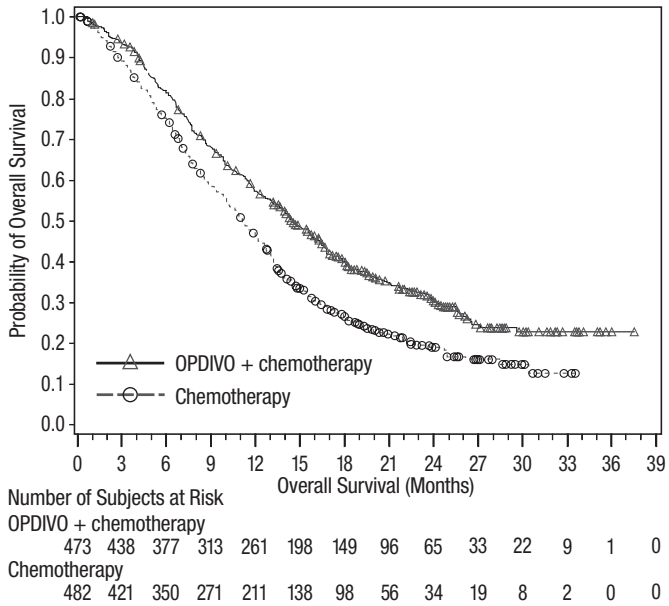




Figure 28: Overall Survival (PD-L1 CPS ≥5) - CHECKMATE-649



16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) Injection is a clear to opalescent, colorless to pale-yellow solution in a single-dose vial available as follows:

Carton Contents	NDC
40 mg/4 mL (10 mg/mL) single-dose vial	0003-3772-11
100 mg/10 mL (10 mg/mL) single-dose vial	0003-3774-12
120 mg/12 mL (10 mg/mL) single-dose vial	0003-3756-14
240 mg/24 mL (10 mg/mL) single-dose vial	0003-3734-13

Store under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the original package until time of use. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation of OPDIVO, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see Warnings and Precautions (5.1)].
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [see Warnings and Precautions (5.1)].
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see Warnings and Precautions (5.1)].
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus [see Warnings and Precautions (5.1)].
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction [see Warnings and Precautions (5.1)].
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash [see Warnings and Precautions (5.1)].

Infusion-Related Reactions

- Advise patients of the potential risk of infusion-related reactions [see Warnings and Precautions (5.2)].

Complications of Allogeneic HSCT

- Advise patients of potential risk of post-transplant complications [see Warnings and Precautions (5.3)].

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.4), Use in Specific Populations (8.1)].
- Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose [see Use in Specific Populations (8.3)].

Lactation

- Advise women not to breastfeed during treatment with OPDIVO and for 5 months after the last dose [see Use in Specific Populations (8.2)].

Manufactured by:  
Bristol-Myers Squibb Company  
Princeton, NJ 08543 USA

U.S. License No. 1713

**MEDICATION GUIDE**  
**OPDIVO® (op-DEE-voh)**  
**(nivolumab)**  
**injection**

Read this Medication Guide before you start receiving OPDIVO and before each infusion. There may be new information. If your healthcare provider prescribes OPDIVO in combination with ipilimumab, also read the Medication Guide that comes with ipilimumab. If your healthcare provider prescribes OPDIVO in combination with cabozantinib, also read the Patient Information that comes with cabozantinib. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is the most important information I should know about OPDIVO?**

OPDIVO is a medicine that may treat certain cancers by working with your immune system. OPDIVO can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or can lead to death. These problems may happen anytime during treatment or even after your treatment has ended. You may have more than one of these problems at the same time. Some of these problems may happen more often when OPDIVO is used in combination with another therapy.

**Call or see your healthcare provider right away if you develop any new or worse signs or symptoms, including:**

**Lung problems.**

- new or worsening cough
- shortness of breath
- chest pain

**Intestinal problems.**

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdominal) pain or tenderness

**Liver problems.**

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

**Hormone gland problems.**

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

**Kidney problems.**

- decrease in your amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

**Skin problems.**

- rash
- itching
- skin blistering or peeling
- painful sore or ulcers in mouth or nose, throat, or genital area

**Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with OPDIVO. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:**

- Chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- Confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- Double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- Persistent or severe muscle pain or weakness, muscle cramps
- Low red blood cells, bruising

**Getting medical treatment right away may help keep these problems from becoming more serious.** Your healthcare provider will check you for these problems during treatment with OPDIVO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with OPDIVO, if you have severe side effects.

### **What is OPDIVO?**

OPDIVO is a prescription medicine used to treat:

- **adults and children 12 years of age and older with a type of skin cancer called melanoma:**
  - OPDIVO may be used alone or in combination with ipilimumab to treat melanoma that has spread or cannot be removed by surgery (advanced melanoma), **or**
  - OPDIVO may be used alone to help prevent Stage IIB, Stage IIC, Stage III or Stage IV melanoma from coming back after it has been completely removed by surgery.
- **adults with a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - OPDIVO may be used in combination with chemotherapy that contains platinum and another chemotherapy medicine before you have surgery for early-stage NSCLC.
  - OPDIVO may be used in combination with ipilimumab as your first treatment for NSCLC:
    - when your lung cancer has spread to other parts of your body (metastatic), **and**
    - your tumors are positive for PD-L1, but do not have an abnormal EGFR or ALK gene.
  - OPDIVO may be used in combination with ipilimumab and 2 cycles of chemotherapy that contains platinum and another chemotherapy medicine, as the first treatment of your NSCLC when your lung cancer:
    - has spread or grown, or comes back, **and**
    - your tumor does not have an abnormal EGFR or ALK gene.
  - OPDIVO may be used when your lung cancer:
    - has spread or grown, **and**
    - you have tried chemotherapy that contains platinum, **and** it did not work or is no longer working.
    - If your tumor has an abnormal EGFR or ALK gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, **and** it did not work or is no longer working.
- **adults with a type of cancer that affects the lining of the lungs and chest wall called malignant pleural mesothelioma.**
  - OPDIVO may be used in combination with ipilimumab as your first treatment for malignant pleural mesothelioma that cannot be removed by surgery.
- **adults with kidney cancer (renal cell carcinoma).**
  - OPDIVO may be used in combination with ipilimumab in certain adults when their cancer has spread (advanced RCC), and you have not already had treatment for your advanced RCC.
  - OPDIVO may be used in combination with cabozantinib when your cancer has spread (advanced RCC), and you have not already had treatment for your advanced RCC.
  - OPDIVO may be used alone when your cancer has spread or grown after treatment with other cancer medicines.
- **adults with a type of blood cancer called classical Hodgkin lymphoma.**
  - **OPDIVO may be used if:**
    - your cancer has come back or spread after a type of stem cell transplant that uses your own stem cells (autologous), **and**
    - you used the medicine brentuximab vedotin before or after your stem cell transplant, **or**
    - you received at least 3 kinds of treatment including a stem cell transplant that uses your own stem cells (autologous).
- **adults with head and neck cancer (squamous cell carcinoma).**
  - **OPDIVO may be used when your head and neck cancer:**
    - has come back or spread, **and**
    - you have tried chemotherapy that contains platinum and it did not work or is no longer working.
- **adults with cancer of the lining of the urinary tract (urothelial carcinoma).**
  - **OPDIVO may be used to help prevent cancer of the urinary tract from coming back after it was removed by surgery.**
  - **OPDIVO may be used in combination with chemotherapy medicines cisplatin and gemcitabine as your first treatment when your urinary tract cancer has spread (metastatic) or cannot be removed by surgery.**
  - **OPDIVO may be used when your urinary tract cancer has spread or grown (locally advanced or metastatic), and:**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working, **or**
    - your cancer worsened within 12 months of treatment with chemotherapy that contains platinum, either before or after surgery to remove your cancer.

- **adults and children 12 years of age and older, with a type of colon or rectal cancer (colorectal cancer).**
  - OPDIVO may be used alone or in combination with ipilimumab when your colon or rectal cancer:
    - has spread to other parts of the body (metastatic),
    - is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), **and**
    - you have tried treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, and it did not work or is no longer working.
- **adults with liver cancer (hepatocellular carcinoma).**
  - OPDIVO may be used in combination with ipilimumab if you have previously received treatment with sorafenib.
- **adults with cancer of the tube that connects your throat to your stomach (esophageal cancer).**
  - OPDIVO may be used to help prevent your esophageal or gastroesophageal junction cancer from coming back when:
    - your esophageal or gastroesophageal junction cancer has been treated with chemoradiation followed by surgery to completely remove the cancer, **but**
    - some cancer cells were still present in the removed tumor or lymph nodes.
  - OPDIVO may be used in combination with chemotherapy that contains fluoropyrimidine and platinum when your esophageal cancer:
    - is a type called squamous cell carcinoma, **and**
    - cannot be removed with surgery (advanced), or has spread to other parts of the body (metastatic), **and**
    - you have not already had treatment for your advanced or metastatic esophageal cancer.
  - OPDIVO may be used in combination with ipilimumab when your esophageal cancer:
    - is a type called squamous cell carcinoma, **and**
    - cannot be removed with surgery (advanced), or has spread to other parts of the body (metastatic), **and**
    - you have not already had treatment for your advanced or metastatic esophageal cancer.
  - OPDIVO may be used alone when your esophageal cancer:
    - is a type called squamous cell carcinoma, **and**
    - cannot be removed with surgery, **and**
    - has come back or spread to other parts of the body after you have received chemotherapy that contains fluoropyrimidine and platinum.
- **adults with cancer of the stomach (gastric cancer), cancer where the esophagus joins the stomach (gastroesophageal junction cancer), and in adults with esophageal adenocarcinoma.**
  - OPDIVO may be used in combination with chemotherapy that contains fluoropyrimidine and platinum when your gastric, gastroesophageal junction, or esophageal cancer:
    - cannot be removed with surgery, **or**
    - has spread to other parts of the body.

It is not known if OPDIVO is safe and effective in children younger than 12 years of age with melanoma or MSI-H or dMMR metastatic colorectal cancer.

It is not known if OPDIVO is safe and effective in children for the treatment of any other cancers.

**Before receiving OPDIVO, tell your healthcare provider about all of your medical conditions, including if you:**

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area in the past and have received other medicines that are like OPDIVO
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. OPDIVO can harm your unborn baby.

**Females who are able to become pregnant:**

- Your healthcare provider should do a pregnancy test before you start receiving OPDIVO.
- You should use an effective method of birth control during treatment and for 5 months after your last dose of OPDIVO. Talk to your healthcare provider about birth control methods that you can use during this time.
- Tell your healthcare provider right away if you become pregnant during treatment with OPDIVO.
- are breastfeeding or plan to breastfeed. It is not known if OPDIVO passes into your breast milk. Do not breastfeed during treatment and for 5 months after your last dose of OPDIVO.

**Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.**

**How will I receive OPDIVO?**

- Your healthcare provider will give you OPDIVO into your vein through an intravenous (IV) line over 30 minutes.

- When OPDIVO is used alone, it is usually given every 2 weeks or 4 weeks depending on the dose you are receiving.
- When OPDIVO is used in combination with ipilimumab (except for treating NSCLC), OPDIVO is usually given every 3 weeks, for a total of 4 doses. Ipilimumab will be given on the same day. After that, OPDIVO will be given alone every 2 weeks or 4 weeks depending on the dose you are receiving.
- For NSCLC before you have surgery, OPDIVO is given in combination with chemotherapy every 3 weeks for 3 cycles.
- For NSCLC that has spread to other parts of your body, when OPDIVO is used in combination with ipilimumab, OPDIVO is given every 3 weeks, and ipilimumab is given every 6 weeks for up to 2 years. Your healthcare provider will determine if you will also need to receive chemotherapy every 3 weeks for 2 cycles.
- For malignant pleural mesothelioma, OPDIVO is given every 3 weeks and ipilimumab is given every 6 weeks for up to 2 years.
- For RCC, when used in combination with cabozantinib, OPDIVO is usually given every 2 weeks or 4 weeks depending on the dose you are receiving. Cabozantinib is given once daily by mouth.
- For UC that has spread to other parts of your body or cannot be removed by surgery, when OPDIVO is used in combination with chemotherapy medicines cisplatin and gemcitabine, OPDIVO is given every 3 weeks for up to 6 cycles. Chemotherapy will be given on the same day. After that, OPDIVO will be given alone every 2 weeks or 4 weeks depending on the dose you are receiving.
- When OPDIVO is used in combination with chemotherapy for treating esophageal squamous cell carcinoma (ESCC), OPDIVO is given either every 2 weeks or every 4 weeks, for up to 2 years.
- When OPDIVO is used in combination with ipilimumab for esophageal squamous cell carcinoma, OPDIVO is given every 2 weeks or 3 weeks and ipilimumab is given every 6 weeks for up to 2 years.
- For gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma, when used in combination with fluoropyrimidine and platinum-containing chemotherapy, OPDIVO is given every 2 weeks or 3 weeks depending on the dose you are receiving, for up to 2 years. Chemotherapy will be given on the same day.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

**What are the possible side effects of OPDIVO?****OPDIVO can cause serious side effects, including:**

- **See “What is the most important information I should know about OPDIVO?”**
- **Severe infusion reactions.** Tell your healthcare provider or nurse right away if you get these symptoms during an infusion of OPDIVO:
  - chills or shaking
  - itching or rash
  - flushing
  - shortness of breath or wheezing
  - dizziness
  - feel like passing out
  - fever
  - back or neck pain
- **Complications of stem cell transplant that uses donor stem cells (allogeneic).** These complications can be severe and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with OPDIVO. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

**The most common side effects of OPDIVO when used alone include:**

- |                                      |                                     |
|--------------------------------------|-------------------------------------|
| • feeling tired                      | • shortness of breath               |
| • rash                               | • constipation                      |
| • pain in muscles, bones, and joints | • decreased appetite                |
| • itchy skin                         | • back pain                         |
| • diarrhea                           | • upper respiratory tract infection |
| • nausea                             | • fever                             |
| • weakness                           | • headache                          |
| • cough                              | • stomach-area (abdominal) pain     |
| • vomiting                           | • urinary tract infection           |

**The most common side effects of OPDIVO when used in combination with ipilimumab include:**

- |                 |                                     |
|-----------------|-------------------------------------|
| • feeling tired | • vomiting                          |
| • diarrhea      | • stomach-area (abdominal) pain     |
| • rash          | • shortness of breath               |
| • itching       | • upper respiratory tract infection |



- nausea
- pain in muscles, bones, and joints
- fever
- cough
- decreased appetite

**The most common side effects of OPDIVO when used in combination with chemotherapy include:**

- nausea
- feeling tired
- pain in muscles, bones, and joints
- constipation

- headache
- low thyroid hormone levels (hypothyroidism)
- constipation
- decreased weight
- dizziness

- decreased appetite
- rash
- vomiting
- numbness, pain, tingling, or burning in your hands and feet

**The most common side effects of OPDIVO when used in combination with ipilimumab and chemotherapy include:**

- feeling tired
- pain in muscles, bones, and joints
- nausea
- diarrhea

- rash
- decreased appetite
- constipation
- itching

**The most common side effects of OPDIVO when used in combination with cabozantinib include:**

- diarrhea
- feeling tired or weak
- liver problems. See “What is the most important information I should know about OPDIVO?”
- rash, redness, pain, swelling or blisters on the palms of your hands or soles of your feet
- mouth sores
- rash

- high blood pressure
- low thyroid hormone levels
- pain in muscles, bones, and joints
- decreased appetite
- nausea
- change in the sense of taste
- stomach-area (abdominal) pain
- cough
- upper respiratory tract infection

**The most common side effects of OPDIVO when used in combination with fluoropyrimidine and platinum-containing chemotherapy include:**

- nausea
- numbness, pain, tingling, or burning in your hands or feet
- decreased appetite
- feeling tired
- constipation

- mouth sores
- diarrhea
- vomiting
- stomach-area (abdominal) pain
- pain in muscles, bones, and joints

These are not all the possible side effects of OPDIVO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of OPDIVO.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about OPDIVO that is written for health professionals.

**What are the ingredients in OPDIVO?**

**Active ingredient:** nivolumab

**Inactive ingredients:** mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and Water for Injection. May contain hydrochloric acid and/or sodium hydroxide.

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For more information, call 1-855-673-4861 or go to [www.OPDIVO.com](http://www.OPDIVO.com).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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## **Appendix 3: EU Summary of Product Characteristics**

148 page(s) excluding cover page

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**



## 1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL concentrate for solution for infusion.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.

One vial of 4 mL contains 40 mg of nivolumab.

One vial of 10 mL contains 100 mg of nivolumab.

One vial of 12 mL contains 120 mg of nivolumab.

One vial of 24 mL contains 240 mg of nivolumab.

Nivolumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

### Excipient with known effect

Each mL of concentrate contains 0.1 mmol (or 2.5 mg) sodium.

For the full list of excipients, see [section 6.1](#).

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to pale yellow liquid that may contain few light particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### Melanoma

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older.

Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (see [sections 4.4](#) and [5.1](#)).

#### Adjuvant treatment of melanoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see [section 5.1](#)).

#### Non-small cell lung cancer (NSCLC)

OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

### Neoadjuvant treatment of NSCLC

OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression  $\geq 1\%$  (see [section 5.1](#) for selection criteria).

### Malignant pleural mesothelioma (MPM)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

### Renal cell carcinoma (RCC)

OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (see section 5.1).

OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (see section 5.1).

### Classical Hodgkin lymphoma (cHL)

OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

### Squamous cell cancer of the head and neck (SCCHN)

OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1).

### Urothelial carcinoma

OPDIVO in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

### Adjuvant treatment of urothelial carcinoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression  $\geq 1\%$ , who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1).

### Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)

OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy (see section 5.1).

### Oesophageal squamous cell carcinoma (OSCC)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression  $\geq 1\%$ .

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression  $\geq 1\%$ .

OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

### Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC)

OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (see [section 5.1](#)).

### Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS)  $\geq 5$ .

## **4.2 Posology and method of administration**

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

### PD-L1 testing

If specified in the indication, patient selection for treatment with OPDIVO based on the tumour expression of PD-L1 should be confirmed by a validated test (see [sections 4.1, 4.4, and 5.1](#)).

### Posology

#### *OPDIVO as monotherapy*

The recommended dose of OPDIVO is either nivolumab 240 mg every 2 weeks **or** 480 mg every 4 weeks depending on the indication and population (see [sections 5.1 and 5.2](#)), as presented in [Table 1](#).

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

Indication*	Recommended dose and infusion time
Melanoma (advanced or adjuvant treatment)	Adults and adolescents (12 years of age and older and weighing at least 50 kg): 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes or over 30 minutes (adjuvant melanoma, see <a href="#">section 5.1</a> )
	Adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes
Renal cell carcinoma Muscle invasive urothelial carcinoma (MIUC) (adjuvant treatment)	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Oesophageal or gastro-oesophageal junction cancer (adjuvant treatment)	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks, followed by 480 mg every 4 weeks over 30 minutes
Non-small cell lung cancer Classical Hodgkin lymphoma Squamous cell cancer of the head and neck Urothelial carcinoma Oesophageal squamous cell carcinoma	240 mg every 2 weeks over 30 minutes

\*As per monotherapy indication in [section 4.1](#).

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

#### *OPDIVO in combination with ipilimumab*

##### Melanoma

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

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

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

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

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

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

**Malignant pleural mesothelioma**

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

**Renal cell carcinoma and dMMR or MSI-H colorectal cancer**

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

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

**Table 3: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for RCC and dMMR or MSI-H CRC**

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

**Oesophageal squamous cell carcinoma**

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

*OPDIVO in combination with cabozantinib*

**Renal cell carcinoma**

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

**Table 4: Recommended doses and infusion times for intravenous administration of nivolumab in combination with oral administration of cabozantinib for RCC**

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

*OPDIVO in combination with ipilimumab and chemotherapy*

*Non-small cell lung cancer*

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.

*OPDIVO in combination with chemotherapy*

*Neoadjuvant treatment of non-small cell lung cancer*

The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for 3 cycles (see [section 5.1](#)).

*Oesophageal squamous cell carcinoma*

The recommended dose of nivolumab is 240 mg every 2 weeks or 480 mg every 4 weeks administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy (see [section 5.1](#)). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

*Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma*

The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 3 weeks **or** 240 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 2 weeks (see [section 5.1](#)). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

*First-line treatment of unresectable or metastatic urothelial carcinoma*

The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks over 30 minutes **or** at 480 mg every 4 weeks over 30 minutes (see [section 5.1](#)). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months from first dose, whichever comes first.

*Duration of treatment*

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

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

For OPDIVO in combination with cabozantinib, OPDIVO should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Cabozantinib should be continued until disease progression or unacceptable toxicity. Refer to the Summary of Product Characteristics (SmPC) for cabozantinib.

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 nivolumab or nivolumab in combination with ipilimumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Dose escalation or reduction is not recommended for OPDIVO as monotherapy or in combination with other therapeutic agents. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 5. Detailed guidelines for the management of immune-related adverse reactions are described in [section 4.4](#). When nivolumab is administered in combination with other therapeutic agents, refer to the SmPC of these other combination therapeutic agents regarding dosing.

**Table 5: Recommended treatment modifications for OPDIVO or OPDIVO in combination**

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	- OPDIVO monotherapy	
	- OPDIVO+ipilimumab <sup>a</sup>	Permanently discontinue treatment
Immune-related hepatitis	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment

**NOTE:** for RCC patients treated with **OPDIVO in combination with cabozantinib** with liver enzyme elevations, see dosing guidelines following this table.

Immune-related adverse reaction	Severity	Treatment modification
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy <sup>b</sup> as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see <a href="#">section 4.4</a> )
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete <sup>c</sup>
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

<sup>a</sup> During administration of the second phase of treatment (nivolumab monotherapy) following combination treatment, permanently discontinue treatment if Grade 3 diarrhoea or colitis occurs.

<sup>b</sup> Recommendation for the use of hormone replacement therapy is provided in section 4.4.

<sup>c</sup> The safety of re-initiating nivolumab or nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known.

OPDIVO as monotherapy or in combination with other therapeutic agents should be permanently discontinued for:

- Grade 4 or recurrent Grade 3 adverse reactions;
- Persistent Grade 2 or 3 adverse reactions despite management.

Patients treated with OPDIVO must be given the patient alert card and be informed about the risks of OPDIVO (see also [package leaflet](#)).

When OPDIVO is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or OPDIVO monotherapy could be resumed based on the evaluation of the individual patient.

When OPDIVO is administered in combination with chemotherapy, refer to the SmPC of the other combination therapy agents regarding dosing. If any agents are withheld, the other agents may be continued. If dosing is resumed after a delay, either the combination treatment, OPDIVO monotherapy or chemotherapy alone could be resumed based on the evaluation of the individual patient.



#### *OPDIVO in combination with cabozantinib in RCC*

When OPDIVO is used in combination with cabozantinib, the above treatment modifications in [Table 5](#) also apply to the OPDIVO component. In addition, for liver enzyme elevations, in patients with RCC being treated with OPDIVO in combination with cabozantinib:

- If ALT or AST > 3 times ULN but ≤ 10 times ULN without concurrent total bilirubin ≥ 2 times ULN, both OPDIVO and cabozantinib should be withheld until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or rechallenge with both medicines after recovery may be considered. If rechallenging with cabozantinib, refer to cabozantinib SmPC.
- If ALT or AST > 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both OPDIVO and cabozantinib should be permanently discontinued and corticosteroid therapy may be considered.

#### *Special populations*

##### Paediatric population

The safety and efficacy of OPDIVO in children below 18 years of age have not been established except in adolescents 12 years of age and older with melanoma. Currently available data of OPDIVO as monotherapy or in combination with ipilimumab are described in [sections 4.2, 4.8, 5.1 and 5.2](#).

##### Elderly

No dose adjustment is required for elderly patients (≥ 65 years) (see section 5.2).

##### Renal impairment

Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

##### Hepatic impairment

Based on the population PK results, no dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. OPDIVO must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment.

#### Method of administration

OPDIVO is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30 or 60 minutes depending on the dose (see [Tables 1, 2, 3 and 4](#)). The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm.

OPDIVO must not be administered as an intravenous push or bolus injection.

The total dose of OPDIVO required can be infused directly as a 10 mg/mL solution or can be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection (see [section 6.6](#)).

When administered in combination with ipilimumab and/or chemotherapy, OPDIVO should be given first followed by ipilimumab (if applicable) and then by chemotherapy on the same day. Use separate infusion bags and filters for each infusion.

For instructions on the preparation and handling of the medicinal product before administration, see section 6.6.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in [section 6.1](#).

### 4.4 Special warnings and precautions for use

#### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

#### Assessment of PD-L1 status

When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is used.

#### Immune-related adverse reactions

When nivolumab is administered in combination, refer to the SmPC of the other combination therapy agents prior to initiation of treatment. Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Immune-related adverse reactions have occurred at similar frequencies when OPDIVO was administered in combination with cabozantinib relative to nivolumab monotherapy. Therefore, the guidance below for immune-related adverse reactions applies to the OPDIVO component of the combination, except where specifically noted. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see [section 4.2](#)).

Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Cardiac and pulmonary adverse reactions including pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions (see [section 4.2](#)).

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

Nivolumab or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

#### *Immune-related pneumonitis*

Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see [section 4.8](#)). Patients

should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy infiltrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 pneumonitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

For Grade 2 (symptomatic) pneumonitis, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

#### *Immune-related colitis*

Severe diarrhoea or colitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see [section 4.8](#)). Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Infectious and other aetiologies of diarrhoea should be ruled out, therefore appropriate laboratory tests and additional examinations must be performed. If diagnosis of corticosteroid-refractory immune-related colitis is confirmed addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered.

For Grade 4 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Nivolumab monotherapy should be withheld for Grade 3 diarrhoea or colitis, and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab monotherapy may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab monotherapy must be permanently discontinued. Grade 3 diarrhoea or colitis observed with nivolumab in combination with ipilimumab requires permanent discontinuation of treatment and initiation of corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent diarrhoea or colitis should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

#### *Immune-related hepatitis*

Severe hepatitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see [section 4.8](#)). Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 transaminase or total bilirubin elevation, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 transaminase or total bilirubin elevation, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

#### *Immune-related nephritis and renal dysfunction*

Severe nephritis and renal dysfunction have been observed with monotherapy treatment or nivolumab in combination with ipilimumab (see [section 4.8](#)). Patients should be monitored for signs and symptoms of nephritis or renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.

For Grade 4 serum creatinine elevation, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 or 3 serum creatinine elevation, nivolumab or nivolumab in combination with ipilimumab should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

#### *Immune-related endocrinopathies*

Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), diabetes mellitus, and diabetic ketoacidosis have been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see [section 4.8](#)).

Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycaemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate aetiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.

For symptomatic hypothyroidism, nivolumab or nivolumab in combination with ipilimumab should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, nivolumab or nivolumab in combination with ipilimumab should be withheld and antithyroid medication should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening hyperthyroidism or hypothyroidism.

For symptomatic Grade 2 adrenal insufficiency, nivolumab or nivolumab in combination with ipilimumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised.

For symptomatic Grade 2 or 3 hypophysitis, nivolumab or nivolumab in combination with ipilimumab should be withheld, and hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the pituitary gland is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening (Grade 4) hypophysitis. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.

For symptomatic diabetes, nivolumab or nivolumab in combination with ipilimumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening diabetes.

#### *Immune-related skin adverse reactions*

Severe rash has been observed with nivolumab in combination with ipilimumab and, less commonly, with nivolumab as monotherapy (see [section 4.8](#)). Nivolumab or nivolumab in combination with ipilimumab should be withheld for Grade 3 rash and discontinued for Grade 4 rash. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Rare cases of SJS and TEN some of them with fatal outcome have been observed. If symptoms or signs of SJS or TEN appear, treatment with nivolumab or nivolumab in combination with ipilimumab should be discontinued and the patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab or nivolumab in combination with ipilimumab, permanent discontinuation of treatment is recommended (see [section 4.2](#)).

Caution should be used when considering the use of nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

#### *Other immune-related adverse reactions*

The following immune-related adverse reactions were reported in less than 1% of patients treated with nivolumab monotherapy or nivolumab in combination with ipilimumab in clinical trials across doses and tumour types: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenia gravis, myasthenic syndrome, aseptic meningitis, encephalitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, rhabdomyolysis, and myelitis. Cases of Vogt-Koyanagi-Harada syndrome, hypoparathyroidism, and cystitis noninfective have been reported post-marketing (see [sections 4.2 and 4.8](#)).

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued (see [section 4.2](#)), and appropriate treatment instituted.

The diagnosis of myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected,

prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, nivolumab or nivolumab in combination with ipilimumab should be withheld or permanently discontinued (see [section 4.2](#)).

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients.

Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab as monotherapy and nivolumab in combination with ipilimumab. Caution should be taken when nivolumab is administered as monotherapy or in combination with ipilimumab. If HLH is confirmed, administration of nivolumab or nivolumab in combination with ipilimumab should be discontinued and treatment for HLH initiated.

#### Infusion reactions

Severe infusion reactions have been reported in clinical trials of nivolumab or nivolumab in combination with ipilimumab (see [section 4.8](#)). In case of a severe or life-threatening infusion reaction, the nivolumab or nivolumab in combination with ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab or nivolumab in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

#### Disease-specific precautions

##### *Advanced melanoma*

Patients with a baseline performance score  $\geq 2$ , active brain metastases or leptomeningeal metastases, autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of nivolumab or nivolumab in combination with ipilimumab (see [sections 4.5](#) and [5.1](#)). Patients with ocular/uveal melanoma were excluded from pivotal clinical trials of melanoma. In addition, CA209037 excluded patients who have had a Grade 4 adverse reaction that was related to anti-CTLA-4 therapy (see [section 5.1](#)). Patients with baseline performance score of 2, treated leptomeningeal metastases, ocular/uveal melanoma, autoimmune disease and patients who have had a Grade 3-4 adverse reaction that was related to prior anti-CTLA-4 therapy were included in study CA209172 (see [section 5.1](#)). In the absence of data for patients who had been receiving systemic immunosuppressants prior to study entry, and for patients with active brain or leptomeningeal metastases, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Relative to nivolumab monotherapy, an increase in PFS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. The improvement in OS was similar between nivolumab in combination with ipilimumab and nivolumab monotherapy in patients with high tumour PD-L1 expression (PD-L1  $\geq 1\%$ ). Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy (see [sections 4.8](#) and [5.1](#)).

##### Use of nivolumab in melanoma patients with rapidly progressing disease

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with rapidly progressing disease (see [section 5.1](#)).



### *Adjuvant treatment of melanoma*

There are no data on adjuvant treatment in patients with melanoma with the following risk factors (see sections 4.5 and 5.1):

- patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids ( $\geq 10$  mg daily prednisone or equivalent) or other immunosuppressive medications,
- patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed  $\geq 6$  months prior to randomisation),
- patients treated with prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways),
- subjects under the age of 18 years.

In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

### *Non-small cell lung cancer*

#### *First-line treatment of NSCLC*

Patients with active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, active (untreated) brain metastasis, who received prior systemic treatment for advanced disease, or who had sensitising EGFR mutations or ALK translocations were excluded from the pivotal trial in first-line treatment of NSCLC (see sections 4.5 and 5.1). Limited data are available in elderly patients ( $\geq 75$  years) (see section 5.1). In these patients, nivolumab in combination with ipilimumab and chemotherapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

#### *Treatment of NSCLC after prior chemotherapy*

Patients with a baseline performance score  $\geq 2$ , active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of NSCLC (see sections 4.5 and 5.1). Patients with baseline performance score of 2 were included in study CA209171 (see section 5.1). In the absence of data for patients with autoimmune disease, symptomatic interstitial lung disease, active brain metastases and patients who had been receiving systemic immunosuppressants prior to study entry, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In non-squamous NSCLC, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumour PD-L1 expression (see section 5.1).

#### *Neoadjuvant treatment of NSCLC*

Patients with a baseline performance score  $\geq 2$ , active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, unresectable or metastatic disease, who received prior anti-cancer treatment for resectable disease, or who had known EGFR mutations or ALK translocations were excluded from the pivotal trial in neoadjuvant treatment of resectable NSCLC (see section 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

### *Malignant pleural mesothelioma*

Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the pivotal trial in first-line treatment of MPM (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with



ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

#### *Renal cell carcinoma*

##### *Nivolumab or nivolumab in combination with ipilimumab*

Patients with any history of concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of nivolumab or nivolumab in combination with ipilimumab (see [sections 4.5](#) and [5.1](#)). In the absence of data, nivolumab or nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

##### *Nivolumab in combination with cabozantinib*

Patients with any active brain metastases, autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of nivolumab in combination with cabozantinib (see [sections 4.5](#) and [5.1](#)). In the absence of data, nivolumab in combination with cabozantinib should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

When nivolumab is given with cabozantinib, higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported relative to nivolumab monotherapy in patients with advanced RCC (see [section 4.8](#)). Liver enzymes should be monitored before initiation of and periodically throughout treatment. Medical management guidelines for both medicines should be followed (see [section 4.2](#) and refer to the SmPC for cabozantinib).

#### *Classical Hodgkin lymphoma*

Patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL (see [section 5.1](#)). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

##### *Complications of allogeneic haematopoietic stem cell transplant (HSCT) in classical Hodgkin lymphoma*

Cases of acute graft-versus-host disease (GVHD) and transplant related mortality (TRM) have been observed from the follow-up of patients with cHL undergoing allogeneic HSCT after previous exposure to nivolumab. Careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications should be made case-by-case (see [section 4.8](#)).

In patients treated with nivolumab after allogeneic HSCT, rapid-onset and severe GVHD, some with fatal outcome, have been reported in the post-marketing setting. Treatment with nivolumab may increase the risk of severe GVHD and death in patients who have had prior allogeneic HSCT, mainly in those with prior history of GVHD. The benefit of treatment with nivolumab versus the possible risk should be considered in these patients (see [section 4.8](#)).

#### *Head and neck cancer*

Patients with a baseline performance score  $\geq 2$ , active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or carcinoma of the nasopharynx or salivary gland as the primary tumour sites were excluded from the SCCHN clinical trial (see [sections 4.5](#) and [5.1](#)). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In head and neck cancer, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were ECOG performance status, fast progressive disease on prior platinum therapy and high tumour burden.

### *Urothelial carcinoma*

#### *Treatment of advanced urothelial carcinoma*

Patients with a baseline performance score  $\geq 2$ , active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of urothelial carcinoma (see [sections 4.5](#) and [5.1](#)). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

#### *Adjuvant treatment of urothelial carcinoma*

Patients with a baseline performance score of  $\geq 2$  (except patients with a baseline performance score of 2 who have not received cisplatin based neoadjuvant chemotherapy and are considered ineligible for cisplatin adjuvant chemotherapy), evidence of disease after surgery, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trial of adjuvant treatment of urothelial carcinoma (see [sections 4.5](#) and [5.1](#)). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

### *dMMR or MSI-H colorectal cancer*

Patients with a baseline performance score  $\geq 2$ , active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trial in dMMR or MSI-H metastatic CRC (see [sections 4.5](#) and [5.1](#)). In the absence of data, nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

### *Oesophageal squamous cell carcinoma*

#### *First-line treatment of OSCC*

Patients with a baseline performance score  $\geq 2$ , any history of concurrent brain metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the clinical trial in OSCC (see [sections 4.5](#) and [5.1](#)). In the absence of data, nivolumab in combination with ipilimumab or chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

In the first-line OSCC trial, a higher number of deaths within 4 months was observed with nivolumab in combination with ipilimumab compared to chemotherapy. Physicians should consider the delayed onset of effect of nivolumab in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease (see [section 5.1](#)).

#### *Treatment of OSCC after prior first-line chemotherapy*

The majority of clinical data available in oesophageal squamous cell carcinoma are in patients of Asian origin (see [section 5.1](#)).

Patients with a baseline performance score  $\geq 2$ , brain metastases that were symptomatic or required treatment, apparent tumour invasion in organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in OSCC (see [sections 4.5](#) and [5.1](#)). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with OSCC. A higher number of deaths within 2.5 months after randomisation was observed with nivolumab compared to chemotherapy. No specific factor(s) associated with early deaths could be identified (see [section 5.1](#)).

#### *Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer*

Patients with a baseline performance score  $\geq 2$ , who did not receive concurrent chemoradiotherapy (CRT) prior to surgery, with stage IV resectable disease, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in

oesophageal and gastro-oesophageal junction cancer (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

#### *Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma*

Patients who had baseline ECOG performance score  $\geq 2$ , untreated central nervous system metastases, active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in gastric, GEJ or oesophageal adenocarcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Study CA209649 excluded patients with known HER2-positive status. Patients with undetermined status were allowed in the study and represented 40.3% of patients (see section 5.1).

#### Patients on controlled sodium diet

Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. This medicinal product contains 10 mg sodium per 4 mL vial, 25 mg sodium per 10 mL vial, 30 mg sodium per 12 mL vial or 60 mg sodium per 24 mL vial, which is equivalent to 0.5%, 1.25%, 1.5% or 3% respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult.

#### Patient alert card

All prescribers of OPDIVO must be familiar with the physician information and management guidelines. The prescriber must discuss the risks of OPDIVO therapy with the patient. The patient will be provided with the patient alert card with each prescription.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Nivolumab is a human monoclonal antibody, as such pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab.

#### Other forms of interaction

##### *Systemic immunosuppression*

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions. The preliminary results show that systemic immunosuppression after starting nivolumab treatment does not appear to preclude the response on nivolumab.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no data from the use of nivolumab in pregnant women. Studies in animals have shown embryofetal toxicity (see section 5.3). Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore, nivolumab has the potential to be transmitted from the mother to the developing foetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab.

#### Breast-feeding

It is unknown whether nivolumab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from

nivolumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

#### Fertility

Studies to evaluate the effect of nivolumab on fertility have not been performed. Thus, the effect of nivolumab on male and female fertility is unknown.

### **4.7 Effects on ability to drive and use machines**

Nivolumab or nivolumab in combination with ipilimumab may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as fatigue (see section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that nivolumab does not adversely affect them.

### **4.8 Undesirable effects**

#### Nivolumab as monotherapy (see [section 4.2](#))

##### *Summary of the safety profile*

In the pooled dataset of nivolumab as monotherapy across tumour types (n = 4646) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions ( $\geq 10\%$ ) were fatigue (44%), musculoskeletal pain (28%), diarrhoea (26%), rash (24%), cough (22%), nausea (22%), pruritus (19%), decreased appetite (17%), arthralgia (17%), constipation (16%), dyspnoea (16%), abdominal pain (15%), upper respiratory tract infection (15%), pyrexia (13%), headache (13%), anaemia (13%) and vomiting (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). The incidence of Grade 3-5 adverse reactions was 44%, with 0.3% fatal adverse reactions attributed to study drug. With a minimum of 63 months follow-up in NSCLC, no new safety signals were identified.

##### *Tabulated summary of adverse reactions*

Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 4646) are presented in Table 6. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

**Table 6: Adverse reactions with nivolumab monotherapy**

	Nivolumab monotherapy
<b>Infections and infestations</b>	
Very common	upper respiratory tract infection
Common	pneumonia <sup>a</sup> , bronchitis
Rare	aseptic meningitis
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
<b>Blood and lymphatic system disorders</b>	
Very common	lymphopaenia <sup>b</sup> , anaemia <sup>b,i</sup> , leucopenia <sup>b</sup> , neutropaenia <sup>a,b</sup> , thrombocytopaenia <sup>b</sup>
Uncommon	eosinophilia
Not known	haemophagocytic lymphohistiocytosis
<b>Immune system disorders</b>	
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity (including anaphylactic reaction)
Uncommon	sarcoidosis
Not known	solid organ transplant rejection <sup>f</sup>

	<b>Nivolumab monotherapy</b>
<b>Endocrine disorders</b>	
Common	hypothyroidism, hyperthyroidism, thyroiditis
Uncommon	adrenal insufficiency <sup>j</sup> , hypopituitarism, hypophysitis, diabetes mellitus
Rare	diabetic ketoacidosis, hypoparathyroidism
<b>Metabolism and nutrition disorders</b>	
Very common	decreased appetite, hyperglycaemia <sup>b</sup>
Common	dehydration, weight decreased, hypoglycaemia <sup>b</sup>
Uncommon	metabolic acidosis
Not known	tumour lysis syndrome <sup>g</sup>
<b>Nervous system disorders</b>	
Very common	headache
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis <sup>a,k</sup>
Not known	myelitis (including transverse myelitis)
<b>Eye disorders</b>	
Common	blurred vision, dry eye
Uncommon	uveitis
Not known	Vogt-Koyanagi-Harada syndrome <sup>f</sup>
<b>Cardiac disorders</b>	
Common	tachycardia, atrial fibrillation
Uncommon	myocarditis <sup>a</sup> , pericardial disorders <sup>h</sup> , arrhythmia (including ventricular arrhythmia)
<b>Vascular disorders</b>	
Common	hypertension
Rare	vasculitis
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very common	dyspnoea <sup>a</sup> , cough
Common	pneumonitis <sup>a</sup> , pleural effusion
Uncommon	lung infiltration
<b>Gastrointestinal disorders</b>	
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation
Common	colitis <sup>a</sup> , stomatitis, dry mouth
Uncommon	pancreatitis, gastritis
Rare	duodenal ulcer
<b>Hepatobiliary disorders</b>	
Uncommon	hepatitis, cholestasis
<b>Skin and subcutaneous tissue disorders</b>	
Very common	rash <sup>c</sup> , pruritus
Common	vitiligo, dry skin, erythema, alopecia
Uncommon	psoriasis, rosacea, erythema multiforme, urticaria
Rare	toxic epidermal necrolysis <sup>a, d</sup> , Stevens-Johnson syndrome <sup>a</sup>
Not known	lichen sclerosus <sup>e</sup> , other lichen disorders

	<b>Nivolumab monotherapy</b>
<b>Musculoskeletal and connective tissue disorders</b>	
Very common	musculoskeletal pain <sup>e</sup> , arthralgia
Common	arthritis
Uncommon	polymyalgia rheumatica
Rare	Sjogren's syndrome, myopathy, myositis (including polymyositis) <sup>a</sup> , rhabdomyolysis <sup>a,d</sup>
<b>Renal and urinary disorders</b>	
Common	renal failure (including acute kidney injury) <sup>a</sup>
Rare	tubulointerstitial nephritis, cystitis noninfective
<b>General disorders and administration site conditions</b>	
Very common	fatigue, pyrexia
Common	pain, chest pain, oedema <sup>l</sup>
<b>Investigations<sup>b</sup></b>	
Very common	increased AST, hyponatraemia, hypoalbuminaemia, increased alkaline phosphatase, increased creatinine, increased ALT, increased lipase, hyperkalaemia, increased amylase, hypocalcaemia, hypomagnesaemia, hypokalaemia, hypercalcaemia
Common	increased total bilirubin, hypernatraemia, hypermagnesaemia

Adverse reaction frequencies presented in [Table 6](#) may not be fully attributable to nivolumab alone but may contain contributions from the underlying disease.

<sup>a</sup> Fatal cases have been reported in completed or ongoing clinical studies.

<sup>b</sup> Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.

<sup>c</sup> Rash is a composite term which includes rash maculopapular, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash vesicular, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.

<sup>d</sup> Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

<sup>e</sup> Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, and spinal pain.

<sup>f</sup> Post-marketing event (also see [section 4.4](#)).

<sup>g</sup> Reported in clinical studies and in the post-marketing setting.

<sup>h</sup> Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.

<sup>i</sup> Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia, haemoglobin decreased, iron deficiency anaemia and red blood cell count decreased.

<sup>j</sup> Includes adrenal insufficiency, adrenocortical insufficiency acute, and secondary adrenocortical insufficiency.

<sup>k</sup> Includes encephalitis and limbic encephalitis.

<sup>l</sup> Oedema is a composite term which includes generalised oedema, oedema peripheral, peripheral swelling and swelling.

## Nivolumab in combination with other therapeutic agents (see [section 4.2](#))

### *Summary of the safety profile*

When nivolumab is administered in combination, refer to the SmPC for the other therapeutic agents for additional information on the safety profile, prior to initiation of treatment.

### Nivolumab in combination with ipilimumab (with or without chemotherapy)

In the pooled dataset of nivolumab administered in combination with ipilimumab (with or without chemotherapy) across tumour types (n = 2094) with minimum follow-up ranging from 6 to 47 months, the most frequent adverse reactions ( $\geq 10\%$ ) were fatigue (50%), rash (38%), diarrhoea (37%), nausea (31%), pruritus (29%), musculoskeletal pain (28%), pyrexia (25%), cough (24%), decreased appetite (23%), vomiting (20%), dyspnoea (19%), constipation (19%), arthralgia (19%), abdominal pain (18%), hypothyroidism (16%), headache (16%), upper respiratory tract infection (15%), oedema (13%), and dizziness (11%). The incidence of Grade 3-5 adverse reactions was 67% for nivolumab in combination with ipilimumab (with or without chemotherapy), with 0.7% fatal adverse reactions attributed to study drug. Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, fatigue (62%), rash (57%), diarrhoea (52%), nausea (42%), pruritus (40%),

pyrexia (36%), and headache (26%) were reported at an incidence rate  $\geq 10\%$  higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate. Among patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy, anaemia (32%) and neutropaenia (15%) were reported at an incidence rate  $\geq 10\%$  higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate.

#### Nivolumab in combination with chemotherapy

In the pooled dataset of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy across tumour types (n = 1572), with a minimum follow-up ranging from 7.4 to 20 months for gastric, GEJ or oesophageal adenocarcinoma, OSCC, or urothelial carcinoma, or following 3 cycles of treatment for resectable NSCLC, the most frequent adverse reactions ( $\geq 10\%$ ) were nausea (51%), fatigue (41%), peripheral neuropathy (34%), decreased appetite (32%), constipation (31%), diarrhoea (30%), vomiting (26%), stomatitis (19%), abdominal pain (19%), rash (19%), musculoskeletal pain (18%), pyrexia (17%), oedema (including peripheral oedema) (13%), cough (12%), pruritus (11%), and hypoalbuminaemia (10%). Incidences of Grade 3-5 adverse reactions were 72% for nivolumab in combination with chemotherapy, with 1.3% fatal adverse reactions attributed to nivolumab in combination with chemotherapy. Median duration of therapy was 6.44 months (95% CI: 5.95, 6.80) for nivolumab in combination with chemotherapy, 4.34 months (95% CI: 4.04, 4.70) for chemotherapy for gastric, GEJ or oesophageal adenocarcinoma, or OSCC and 7.39 months (95% CI: 7.06, 8.38) for urothelial carcinoma. For resectable NSCLC, ninety-three percent (93%) of patients received 3 cycles of nivolumab in combination with chemotherapy.

#### Nivolumab in combination with cabozantinib

In the dataset of nivolumab 240 mg every 2 weeks in combination with cabozantinib 40 mg once daily in RCC (n = 320), with a minimum follow-up of 16.0 months, the most frequent adverse reactions ( $\geq 10\%$ ) were diarrhoea (64.7%), fatigue (51.3%), -palmar plantar erythrodysesthesia syndrome (40.0%), stomatitis (38.8%), musculoskeletal pain (37.5%), hypertension (37.2%), rash (36.3%), hypothyroidism (35.6%), decreased appetite (30.3%), nausea (28.8%), abdominal pain (25.0%), dysgeusia (23.8%), upper respiratory tract infection (20.6%), cough (20.6%), pruritus (20.6%), arthralgia (19.4%), vomiting (18.4%), dysphonia (17.8%), headache (16.3%), dyspepsia (15.9%), dizziness (14.1%), constipation (14.1%), pyrexia (14.1%), oedema (13.4%), muscle spasm (12.2%), dyspnoea (11.6%), proteinuria (10.9%) and hyperthyroidism (10.0%). The incidence of Grade 3-5 adverse reactions was 78%, with 0.3% fatal adverse reactions attributed to study drug.

#### *Tabulated summary of adverse reactions*

Adverse reactions reported in the pooled dataset for patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy) (n = 2094), nivolumab in combination with chemotherapy (n = 1572), and nivolumab in combination with cabozantinib (n = 320) are presented in Table 7. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

**Table 7: Adverse reactions with nivolumab in combination with other therapeutic agents**

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
<b>Infections and infestations</b>			
Very common	upper respiratory tract infection		upper respiratory tract infection
Common	pneumonia, bronchitis, conjunctivitis	upper respiratory tract infection, pneumonia <sup>a</sup>	pneumonia
Rare	aseptic meningitis		



	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
<b>Blood and lymphatic system disorders</b>			
Very common	anaemia <sup>b,i</sup> , thrombocytopaenia <sup>b</sup> , leucopenia <sup>b</sup> , lymphopaenia <sup>b</sup> , neutropaenia <sup>b</sup>	neutropaenia <sup>b</sup> , anaemia <sup>b,i</sup> , leucopenia <sup>b</sup> , lymphopaenia <sup>b</sup> , thrombocytopaenia <sup>b</sup>	anaemia <sup>b</sup> , thrombocytopaenia <sup>b</sup> , leucopenia <sup>b</sup> , lymphopaenia <sup>b</sup> , neutropaenia <sup>b</sup>
Common	eosinophilia	febrile neutropaenia <sup>a</sup>	eosinophilia
Uncommon	febrile neutropaenia	eosinophilia	
Not known	haemophagocytic lymphohistiocytosis		
<b>Immune system disorders</b>			
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity	hypersensitivity, infusion related reaction (including cytokine release syndrome)	hypersensitivity (including anaphylactic reaction)
Uncommon			infusion related hypersensitivity reaction
Rare	sarcoidosis		
Not known	solid organ transplant rejection <sup>f</sup>		
<b>Endocrine disorders</b>			
Very common	hypothyroidism		hypothyroidism, hyperthyroidism
Common	hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, hypopituitarism, diabetes mellitus	hypothyroidism, hyperthyroidism, diabetes mellitus	adrenal insufficiency
Uncommon	diabetic ketoacidosis	adrenal insufficiency, thyroiditis, hypopituitarism, hypophysitis	hypophysitis, thyroiditis
Rare	hypoparathyroidism		
<b>Metabolism and nutrition disorders</b>			
Very common	decreased appetite, hyperglycaemia <sup>b</sup> , hypoglycaemia <sup>b</sup>	decreased appetite, hypoalbuminaemia, hyperglycaemia <sup>b</sup> , hypoglycaemia <sup>b</sup>	decreased appetite, hypoglycaemia <sup>b</sup> , hyperglycaemia <sup>b</sup> , weight decreased
Common	dehydration, hypoalbuminaemia, hypophosphataemia, weight decreased	hypophosphataemia	dehydration
Uncommon	metabolic acidosis		
Rare		tumour lysis syndrome	
Not known	tumour lysis syndrome <sup>g</sup>		

	<b>Combination with ipilimumab (with or without chemotherapy)</b>	<b>Combination with chemotherapy</b>	<b>Combination with cabozantinib</b>
<b>Nervous system disorders</b>			
Very common	headache, dizziness	peripheral neuropathy	dysgeusia, dizziness, headache
Common	peripheral neuropathy	paraesthesia, dizziness, headache	peripheral neuropathy
Uncommon	polyneuropathy, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis, myasthenia gravis		encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Rare	Guillain-Barré syndrome, neuritis, myelitis (including transverse myelitis)	Guillain Barré syndrome, encephalitis	
Not known		myelitis (including transverse myelitis)	
<b>Ear and labyrinth disorders</b>			
Common			tinnitus
<b>Eye disorders</b>			
Common	blurred vision, dry eye	dry eye, blurred vision	dry eye, blurred vision
Uncommon	uveitis, episcleritis	uveitis	uveitis
Rare	Vogt Koyanagi Harada syndrome		
<b>Cardiac disorders</b>			
Common	tachycardia, atrial fibrillation	tachycardia, atrial fibrillation	atrial fibrillation, tachycardia
Uncommon	myocarditis <sup>a</sup> , arrhythmia (including ventricular arrhythmia) <sup>a</sup> , bradycardia	myocarditis	myocarditis
Not known	pericardial disorders <sup>h</sup>		
<b>Vascular disorders</b>			
Very common			hypertension
Common	hypertension	thrombosis <sup>a,j</sup> , hypertension, vasculitis	thrombosis <sup>j</sup>
<b>Respiratory, thoracic and mediastinal disorders</b>			
Very common	cough, dyspnoea	cough	dysphonia, dyspnoea, cough
Common	pneumonitis <sup>a</sup> , pulmonary embolism <sup>a</sup> , pleural effusion	pneumonitis <sup>a</sup> , dyspnoea	pneumonitis, pulmonary embolism, pleural effusion, epistaxis
<b>Gastrointestinal disorders</b>			
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation	diarrhoea <sup>a</sup> , stomatitis, vomiting, nausea, abdominal pain, constipation	diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia
Common	colitis <sup>a</sup> , pancreatitis, stomatitis, gastritis, dry mouth	colitis, dry mouth	colitis, gastritis, oral pain, dry mouth, haemorrhoids
Uncommon	duodenitis	pancreatitis	pancreatitis, small intestine perforation <sup>a</sup> , glossodynia
Rare	intestinal perforation <sup>a</sup>		

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
<b>Hepatobiliary disorders</b>			
Common	hepatitis		hepatitis
Uncommon		hepatitis	
<b>Skin and subcutaneous tissue disorders</b>			
Very common	rash <sup>c</sup> , pruritus	rash <sup>c</sup> , pruritus	palmar-plantar erythrodysesthesia syndrome, rash <sup>c</sup> , pruritus
Common	alopecia, vitiligo, urticaria, dry skin, erythema,	palmar-plantar erythrodysesthesia syndrome, skin hyperpigmentation, alopecia, dry skin, erythema	alopecia, dry skin, erythema, hair colour change
Uncommon	Stevens-Johnson syndrome, erythema multiforme, psoriasis		psoriasis, urticaria
Rare	toxic epidermal necrolysis <sup>a,d</sup> , lichen sclerosus, other lichen disorders		
Not known			lichen sclerosus, other lichen disorders
<b>Musculoskeletal and connective tissue disorders</b>			
Very common	musculoskeletal pain <sup>e</sup> , arthralgia	musculoskeletal pain <sup>e</sup>	musculoskeletal pain <sup>e</sup> , arthralgia, muscle spasm
Common	muscle spasms, muscular weakness, arthritis	arthralgia, muscular weakness	arthritis
Uncommon	polymyalgia rheumatica, myopathy, myositis (including polymyositis) <sup>a</sup>		myopathy, osteonecrosis of the jaw, fistula
Rare	spondyloarthropathy, Sjogren's syndrome, rhabdomyolysis <sup>a</sup>		
<b>Renal and urinary disorders</b>			
Very common			proteinuria
Common	renal failure (including acute kidney injury) <sup>a</sup>	renal failure <sup>a</sup>	renal failure, acute kidney injury
Uncommon	tubulointerstitial nephritis, nephritis	cystitis noninfective, nephritis	nephritis
Rare	cystitis noninfective		cystitis noninfective <sup>g</sup>
<b>General disorders and administration site conditions</b>			
Very common	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema
Common	chest pain, pain, chills	malaise	pain, chest pain

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
<b>Investigations</b>			
Very common	increased alkaline phosphatase <sup>b</sup> , increased AST <sup>b</sup> , increased ALT <sup>b</sup> , increased total bilirubin <sup>b</sup> , increased creatinine <sup>b</sup> , increased amylase <sup>b</sup> , increased lipase <sup>b</sup> , hyponatraemia <sup>b</sup> , hyperkalaemia <sup>b</sup> , hypokalaemia <sup>b</sup> , hypercalcaemia <sup>b</sup> , hypocalcaemia <sup>b</sup>	hypocalcaemia <sup>b</sup> , increased AST <sup>b</sup> , increased ALT <sup>b</sup> , hyponatraemia <sup>b</sup> , increased amylase <sup>b</sup> , hypomagnesaemia <sup>b</sup> , increased alkaline phosphatase <sup>b</sup> , hypokalaemia <sup>b</sup> , increased creatinine <sup>b</sup> , increased lipase <sup>b</sup> , hyperkalaemia <sup>b</sup> , increased total bilirubin <sup>b</sup>	increased alkaline phosphatase <sup>b</sup> , increased ALT <sup>b</sup> , increased AST <sup>b</sup> , increased total bilirubin <sup>b</sup> , increased creatinine <sup>b</sup> , increased amylase <sup>b</sup> , increased lipase <sup>b</sup> , hypokalaemia <sup>b</sup> , hypomagnesaemia <sup>b</sup> , hyponatraemia <sup>b</sup> , hypocalcaemia <sup>b</sup> , hypercalcaemia <sup>b</sup> , hypophosphataemia <sup>b</sup> , hyperkalaemia <sup>b</sup> , hypermagnesaemia <sup>b</sup> , hypernatraemia <sup>b</sup>
Common	hypernatraemia <sup>b</sup> , hypermagnesaemia <sup>b</sup> , increased thyroid stimulating hormone, increased gamma-glutamyltransferase	hypernatraemia <sup>b</sup> , hypercalcaemia <sup>b</sup> , hypermagnesaemia <sup>b</sup>	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 7 may not be fully attributable to nivolumab alone or in combination with other therapeutic agents, but may contain contributions from the underlying disease or from medicinal product used in combination.

<sup>a</sup> Fatal cases have been reported in completed or ongoing clinical studies.

<sup>b</sup> Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See “Description of selected adverse reactions; laboratory abnormalities” below.

<sup>c</sup> Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption, nodular rash, and pemphigoid.

<sup>d</sup> Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

<sup>e</sup> Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, and spinal pain.

<sup>f</sup> Post-marketing event (also see section 4.4).

<sup>g</sup> Reported in clinical studies and in the post-marketing setting.

<sup>h</sup> Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler’s syndrome.

<sup>i</sup> Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia, haemoglobin decreased, iron deficiency anaemia and red blood cell count decreased.

<sup>j</sup> Thrombosis is a composite term which includes portal vein thrombosis, pulmonary vein thrombosis, pulmonary thrombosis, aortic thrombosis, arterial thrombosis, deep vein thrombosis, pelvic vein thrombosis, vena cava thrombosis, venous thrombosis, limb venous thrombosis.

#### Description of selected adverse reactions

Nivolumab or nivolumab in combination with other therapeutic agents is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment generally was required in a greater proportion of patients receiving nivolumab in combination with other agents than in those receiving nivolumab monotherapy. Table 8 presents the percentage of patients with immune-related adverse reactions who were permanently discontinued from treatment by dosing regimen. Additionally, for patients who experienced an event, Table 8 presents the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents) by dosing regimen. The management guidelines for these adverse reactions are described in section 4.4.

**Table 8: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab monotherapy, nivolumab in combination with ipilimumab (with or without chemotherapy),**

**nivolumab in combination with chemotherapy, or nivolumab in combination with cabozantinib)**

	Nivolumab monotherapy %	Nivolumab in combination with ipilimumab (with or without chemotherapy) %	Nivolumab in combination with chemotherapy %	Nivolumab in combination with cabozantinib %
<b>Immune-related adverse reaction leading to permanent discontinuation</b>				
Pneumonitis	1.4	2.5	1.8	2.5
Colitis	1.2	6	1.8	2.5
Hepatitis	1.1	5	0.8	4.1
Nephritis and renal dysfunction	0.3	1.2	3.3	0.6
Endocrinopathies	0.5	2.0	0.6	1.3
Skin	0.8	1.0	1.0	2.2
Hypersensitivity/Infusion reaction	0.1	0.3	1.8	0
<b>Immune-related adverse reaction requiring high-dose corticosteroids<sup>a,b</sup></b>				
Pneumonitis	65	59	58	56
Colitis	14	32	8	8
Hepatitis	21	37	8	23
Nephritis and renal dysfunction	22	27	7	9
Endocrinopathies	5	20	5	4.2
Skin	3.3	8	6	8
Hypersensitivity/Infusion reaction	18	16	22	0

<sup>a</sup> at least 40 mg daily prednisone equivalents

<sup>b</sup> frequency is based on the number of patients who experienced the immune-related adverse reaction

*Immune-related pneumonitis*

In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.3% (155/4646). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (42/4646) and 1.7% (77/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (33/4646) and <0.1% (1/4646) of patients respectively. Six patients (0.1%) had a fatal outcome. Median time to onset was 15.1 weeks (range: 0.7-85.1). Resolution occurred in 107 patients (69.0%) with a median time to resolution of 6.7 weeks (range: 0.1<sup>+</sup>-109.1<sup>+</sup>); <sup>+</sup> denotes a censored observation.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of pneumonitis including interstitial lung disease, was 6.9% (145/2094). Grade 2, Grade 3, and Grade 4 cases were reported in 3.5% (73/2094), 1.1% (24/2094), and 0.4% (8/2094) of patients, respectively. Four patients (0.2%) had a fatal outcome. Median time to onset was 2.7 months (range: 0.1-56.8). Resolution occurred in 119 patients (82.1%) with a median time to resolution of 6.1 weeks (range: 0.3-149.3<sup>+</sup>).

In patients treated with nivolumab in combination with chemotherapy, the incidence of pneumonitis including interstitial lung disease was 4.3% (67/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 2.1% (33/1572), 0.9% (14/1572), and 0.2% (3/1572), of patients, respectively. Two patients (0.1%) had a fatal outcome. Median time to onset was 25 weeks (range: 1.6-96.9). Resolution occurred in 48 patients (71.6%) with a median time to resolution of 10.4 weeks (range: 0.3<sup>+</sup>-121.3<sup>+</sup>).

In patients treated with nivolumab in combination with cabozantinib, the incidence of pneumonitis including interstitial lung disease was 5.6% (18/320). Grade 2 and Grade 3 cases were reported in

1.9% (6/320) and 1.6% (5/320) of patients, respectively. Median time to onset was 26.9 weeks (range: 12.3-74.3 weeks). Resolution occurred in 14 patients (77.8%) with a median time to resolution of 7.5 weeks (range: 2.1-60.7<sup>+</sup> weeks).

#### *Immune-related colitis*

In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 15.4% (716/4646). The majority of cases were Grade 1 or 2 in severity reported in 9.9% (462/4646) and 4.0% (186/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.4% (67/4646) and <0.1% (1/4646) of patients respectively. Median time to onset was 8.3 weeks (range: 0.1-115.6). Resolution occurred in 639 patients (90.3%) with a median time to resolution of 2.9 weeks (range: 0.1-124.4<sup>+</sup>).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of diarrhoea or colitis was 27.7% (580/2094). Grade 2, Grade 3, and Grade 4 cases were reported in 8.8% (184/2094), 6.8% (142/2094), and 0.1% (3/2094), of patients, respectively. One patient (<0.1%) had a fatal outcome. Median time to onset was 1.4 months (range: 0.0-48.9). Resolution occurred in 577 patients (90.8%) with a median time to resolution of 2.7 weeks (range: 0.1-159.4<sup>+</sup>). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of diarrhoea or colitis was 46.7%, including Grade 2 (13.6%), Grade 3 (15.8%), and Grade 4 (0.4%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of diarrhoea or colitis was 24.0% (377/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 7.3% (115/1572), 3.2% (51/1572), and 0.4% (6/1572) of patients, respectively. One patient (< 0.1%) had a fatal outcome. Median time to onset was 4.4 weeks (range: 0.1-93.6). Resolution occurred in 329 patients (87.7%) with a median time to resolution of 1.6 weeks (range: 0.1-212.3<sup>+</sup>).

In patients treated with nivolumab in combination with cabozantinib, the incidence of diarrhoea, colitis, frequent bowel movements or enteritis was 59.1% (189/320). Grade 2 and Grade 3 cases were reported in 25.6% (82/320) and 6.3% (20/320) of patients, respectively. Grade 4 were reported in 0.6% (2/320). Median time to onset was 12.9 weeks (range: 0.3-110.9 weeks). Resolution occurred in 143 patients (76.1%) with a median time to resolution of 12.9 weeks (range: 0.1-139.7<sup>+</sup> weeks).

#### *Immune-related hepatitis*

In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 8.0% (371/4646). The majority of cases were Grade 1 or 2 in severity reported in 4.3% (200/4646) and 1.8% (82/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.6% (74/4646) and 0.3% (15/4646) of patients, respectively. Median time to onset was 10.6 weeks (range: 0.1-132.0). Resolution occurred in 298 patients (81.4%) with a median time to resolution of 6.1 weeks (range: 0.1-126.4<sup>+</sup>).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of liver function test abnormalities was 19.2% (402/2094). Grade 2, Grade 3, and Grade 4 cases were reported in 4.2% (88/2094), 7.8% (163/2094), and 1.2% (25/2094) of patients, respectively. Median time to onset was 1.9 months (range: 0.0-36.6). Resolution occurred in 351 patients (87.8%) with a median time to resolution of 5.3 weeks (range: 0.1-175.9<sup>+</sup>). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of liver function test abnormalities was 30.1% including Grade 2 (6.9%), Grade 3 (15.8%), and Grade 4 (1.8%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of liver function test abnormalities was 18.6% (293/1572). Grade 2, Grade 3 and Grade 4 cases were reported in 5.6% (88/1572), 2.9% (45/1572) and < 0.1% (1/1572) of patients, respectively. Median time to onset was 7.7 weeks (range: 0.1-99.0). Resolution occurred in 231 patients (79.9%) with a median time to resolution of 7.4 weeks (range: 0.4-240.0<sup>+</sup>).

In patients treated with nivolumab in combination with cabozantinib, the incidence of liver function test abnormalities was 41.6% (133/320). Grade 2, Grade 3, and Grade 4 cases were reported in 14.7% (47/320), 10.3% (33/320), and 0.6% (2/320) of patients, respectively. Median time to onset was 8.3 weeks (range: 0.1-107.9 weeks). Resolution occurred in 101 patients (75.9%) with a median time to resolution of 9.6 weeks (range: 0.1-89.3<sup>+</sup> weeks).

#### *Immune-related nephritis and renal dysfunction*

In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.6% (121/4646). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (69/4646) and 0.7% (32/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (18/4646) and <0.1% (2/4646) of patients, respectively. Median time to onset was 12.1 weeks (range: 0.1-79.1). Resolution occurred in 80 patients (69.0%) with a median time to resolution of 8.0 weeks (range: 0.3-79.1<sup>+</sup>).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of nephritis or renal dysfunction was 6.1% (128/2094). Grade 2, Grade 3, and Grade 4 cases were reported in 2.3% (49/2094), 1.0% (20/2094), and 0.5% (10/2094) of patients, respectively. Two patients (< 0.1%) had a fatal outcome. Median time to onset was 2.5 months (range: 0.0-34.8). Resolution occurred in 97 patients (75.8%) with a median time to resolution of 6.3 weeks (range: 0.1-172.1<sup>+</sup>).

In patients treated with nivolumab in combination with chemotherapy, the incidence of nephritis or renal dysfunction was 10.8% (170/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 4.1% (64/1572), 1.5% (24/1572), and 0.1% (2/1572) of patients, respectively. Two patients (0.1%) had a fatal outcome. Median time to onset was 6.9 weeks (range: 0.1-60.7). Resolution occurred in 111 patients (65.3%) with a median time to resolution of 11.6 weeks (range: 0.1-226.0<sup>+</sup>).

In patients treated with nivolumab in combination with cabozantinib, the incidence of nephritis, immune mediated nephritis, renal failure, acute kidney injury, blood creatinine increased or blood urea increased was 10.0% (32/320). Grade 2 and Grade 3 cases were reported in 3.4% (11/320), and 1.3% (4/320) of patients, respectively. Median time to onset was 14.2 weeks (range: 2.1-87.1 weeks). Resolution occurred in 18 patients (58.1%) with a median time to resolution of 10.1 weeks (range: 0.6-90.9<sup>+</sup> weeks).

#### *Immune-related endocrinopathies*

In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 13.0% (603/4646). The majority of cases were Grade 1 or 2 in severity reported in 6.6% (305/4646) and 6.2% (290/4646) of patients, respectively. Grade 3 thyroid disorders were reported in 0.2% (8/4646) of patients. Hypophysitis (3 Grade 1, 7 Grade 2, 9 Grade 3, and 1 Grade 4), hypopituitarism (6 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute and blood corticotrophin decreased) (2 Grade 1, 23 Grade 2, and 11 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) (1 Grade 1, 3 Grade 2 and 8 Grade 3 and 2 Grade 4), were reported. Median time to onset of these endocrinopathies was 11.1 weeks (range: 0.1-126.7). Resolution occurred in 323 patients (48.7%). Median time to resolution was 48.6 weeks (range: 0.4-204.4<sup>+</sup>).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of thyroid disorders was 22.9% (479/2094). Grade 2 and Grade 3 thyroid disorders were reported in 12.5% (261/2094) and 1.0% (21/2094) of patients, respectively. Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 2.0% (42/2094) and 1.6% (33/2094) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.8% ((16/2094)) and 0.5% ((11/2094)) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 2.3% (49/2094), 1.5% (32/2094) and 0.2% (4/2094) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus occurred in 0.1% (1/2094), 0.2% (4/2094), < 0.1% (1/2094), and 0.1 (3/2094) of patients, respectively, and Grade 4 diabetic ketoacidosis was reported in < 0.1% (2/2094) of patients.



Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-28.1). Resolution occurred in 201 patients (40.7%). Time to resolution ranged from 0.3 to 257.1<sup>+</sup> weeks.

In patients treated with nivolumab in combination with chemotherapy, the incidence of thyroid disorders was 12.7% (199/1572). Grade 2 thyroid disorder was reported in 6.2% (97/1572) patients. Grade 3 hypophysitis occurred in 0.1% (2/1572) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (3/1572) and 0.3% (4/1572) of patients, respectively. Grade 2, Grade 3 and Grade 4 adrenal insufficiency occurred in 0.6% (9/1572), 0.2% (3/1572) and <0.1% (1/1572) of patients, respectively. One patient (<0.1%) had a fatal outcome due to adrenal insufficiency. Diabetes mellitus including Type 1 diabetes mellitus, fulminant Type 1 diabetes mellitus and diabetic ketoacidosis (3 Grade 2, 2 Grade 3 and 1 Grade 4) were reported. Median time to onset of these endocrinopathies was 14.7 weeks (range: 1.1-124.3). Resolution occurred in 81 patients (37.2%). Time to resolution ranged from 0.4 to 233.6<sup>+</sup> weeks.

In patients treated with nivolumab in combination with cabozantinib, the incidence of thyroid disorders was 43.1% (138/320). Grade 2 and Grade 3 thyroid disorders were reported in 23.1% (74/320) and 0.9% (3/320) of patients, respectively. Hypophysitis occurred in 0.6% (2/320) of patients, all Grade 2. Adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 4.7% (15/320) of patients. Grade 2 and Grade 3 adrenal insufficiency cases were reported in 2.2% (7/320) and 1.9% (6/320) of patients, respectively. Median time to onset of these endocrinopathies was 12.3 weeks (range: 2.0-89.7 weeks). Resolution occurred in 50 patients (35.2%). Time to resolution ranged from 0.9 to 132.0<sup>+</sup> weeks.

#### *Immune-related skin adverse reactions*

In patients treated with nivolumab monotherapy, the incidence of rash was 30.0% (1396/4646). The majority of cases were Grade 1 in severity reported in 22.8% (1060/4646) of patients. Grade 2 and Grade 3 cases were reported in 5.9% (274/4646) and 1.3% (62/4646) of patients respectively. Median time to onset was 6.7 weeks (range: 0.1-121.1). Resolution occurred in 896 patients (64.6%) with a median time to resolution of 20.1 weeks (0.1-192.7<sup>+</sup>).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of rash was 46.2% (968/2094). Grade 2, Grade 3, and Grade 4 cases were reported in 14.1% (296/2094), 4.6% (97/2094), and < 0.1% (2/2094) of patients, respectively. Median time to onset was 0.7 months (range: 0.0-33.8). Resolution occurred in 671 patients (69.6%) with a median time to resolution of 11.1 weeks (range: 0.1-268.7<sup>+</sup>). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of rash was 65.2%, including Grade 2 (20.3%) and Grade 3 (7.8%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of rash was 25.6% (402/1572). Grade 2 and Grade 3 cases were reported in 6.2% (97/1572), and 2.5% (39/1572) of patients, respectively. Median time to onset was 7.0 weeks (range: 0.1-97.4). Resolution occurred in 273 patients (68.1%) with a median time to resolution of 12.3 weeks (range: 0.1-258.7<sup>+</sup>).

In patients treated with nivolumab in combination with cabozantinib, the incidence of rash was 62.8% (201/320). Grade 2 and Grade 3 cases were reported in 23.1% (74/320) and 10.6% (34/320) of patients, respectively. Median time to onset was 6.14 weeks (range: 0.1-104.4 weeks). Resolution occurred in 137 patients (68.2%) with a median time to resolution of 18.1 weeks (range: 0.1-130.6<sup>+</sup> weeks).

Rare cases of SJS and TEN some of them with fatal outcome have been observed (see [sections 4.2](#) and [4.4](#)).

#### *Infusion reactions*

In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 4.0% (188/4646), including 9 Grade 3 and 3 Grade 4 cases.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of hypersensitivity/infusion reactions was 4.9% (103/2094). Grade 1, Grade 2, Grade 3, and Grade 4 cases were reported in 2.1% (44/2094), 2.5% (53/2094), 0.2% (5/2094), and < 0.1% (1/2094) of patients, respectively. Among patients with MPM treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg, the incidence of hypersensitivity/infusion reactions was 12%.

In patients treated with nivolumab in combination with chemotherapy, the incidence of hypersensitivity/infusion reactions was 8.5% (134/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (76/1572), 1.1% (18/1572) and 0.2% (3/1572) of patients, respectively.

In patients treated with nivolumab in combination with cabozantinib, the incidence of hypersensitivity/infusion reactions was 2.5% (8/320). All 8 patients were Grade 1 or 2 in severity. Grade 2 cases were reported in 0.3% (1/320) of patients.

#### *Complications of allogeneic HSCT in classical Hodgkin lymphoma*

Rapid onset of GVHD has been reported with nivolumab use before and after allogeneic HSCT (see [section 4.4](#)).

In 62 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 17/62 patients (27.4%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in four patients (6%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (12%) within the first 6 weeks post-transplantation. Steroids were used in four patients and three patients responded to steroids. Hepatic veno-occlusive disease occurred in two patients, one of whom died of GVHD and multi-organ failure. Nineteen of 62 patients (30.6%) died from complications of allogeneic HSCT after nivolumab. The 62 patients had a median follow-up from subsequent allogeneic HSCT of 38.5 months (range: 0-68 months).

#### *Elevated liver enzymes when nivolumab is combined with cabozantinib in RCC*

In a clinical study of previously untreated patients with RCC receiving nivolumab in combination with cabozantinib, a higher incidence of Grades 3 and 4 ALT increased (10.1%) and AST increased (8.2%) were observed relative to nivolumab monotherapy in patients with advanced RCC. In patients with Grade  $\geq 2$  increased ALT or AST (n=85): median time to onset was 10.1 weeks (range: 2.0 to 106.6 weeks), 26% received corticosteroids for median duration of 1.4 weeks (range: 0.9 to 75.3 weeks), and resolution to Grades 0-1 occurred in 91% with median time to resolution of 2.3 weeks (range: 0.4 to 108.1<sup>+</sup> weeks). Among the 45 patients with Grade  $\geq 2$  increased ALT or AST who were rechallenged with either nivolumab (n=10) or cabozantinib (n=10) administered as a single agent or with both (n=25), recurrence of Grade  $\geq 2$  increased ALT or AST was observed in 3 patients receiving OPDIVO, 4 patients receiving cabozantinib, and 8 patients receiving both OPDIVO and cabozantinib.

#### *Laboratory abnormalities*

In patients treated with nivolumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.4% for anaemia (all Grade 3), 0.7% for thrombocytopaenia, 0.7% for leucopenia, 8.7% for lymphopaenia, 0.9% for neutropaenia, 1.7% for increased alkaline phosphatase, 2.6% for increased AST, 2.3% for increased ALT, 0.8% for increased total bilirubin, 0.7% for increased creatinine, 2.0% for hyperglycaemia, 0.7% for hypoglycaemia, 3.8% for increased amylase, 6.9% for increased lipase, 4.7% for hyponatraemia, 1.6% for hyperkalaemia, 1.3% for hypokalaemia, 1.1% for hypercalcaemia, 0.6% for hypermagnesaemia, 0.4% for hypomagnesaemia, 0.6% for hypocalcaemia, 0.6% for hypoalbuminaemia, and <0.1% for hypernatraemia.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.9% for anaemia, 1.5% for thrombocytopaenia, 2.3% for leucopenia, 7.3% for lymphopaenia, 3.4% for neutropaenia, 2.9% for increased alkaline phosphatase, 7.3% for increased AST, 8.4% for increased ALT, 1.2% for increased total bilirubin, 1.6% for increased creatinine, 5.8% for hyperglycaemia, 0.9% for hypoglycaemia, 8.4% for increased amylase, 16.7% for

increased lipase, 0.8% for hypocalcaemia, 0.2% for hypernatraemia, 1.0% for hypercalcaemia, 1.9% for hyperkalaemia, 0.5% for hypermagnesaemia, 3.4% for hypokalaemia, and 9.8% for hyponatraemia.

Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, a higher proportion of patients experienced a worsening from baseline to Grade 3 or 4 increased ALT (15.3%).

In patients treated with nivolumab in combination with chemotherapy, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 15.8% for anaemia, 6.9% for thrombocytopenia, 12.2% leukopenia, 14.6% for lymphopenia, 27.6% neutropenia, 2.4% for increased alkaline phosphatase, 3.4% for increased AST, 2.6% for increased ALT, 2.0% for increased bilirubin, 1.4% for increased creatinine, 4.5% for increased amylase, 5.2% for increased lipase, 0.5% for hypernatraemia, 8.8% for hyponatraemia, 1.9% for hyperkalaemia, 5.6% for hypokalaemia, 0.8% for hypercalcaemia, 1.9% for hypocalcaemia, 1.5% for hypermagnesaemia, 2.9% for hypomagnesaemia, 3.5% for hyperglycaemia, and 0.7% for hypoglycaemia.

In patients treated with nivolumab in combination with cabozantinib, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.5% for anaemia (all Grade 3), 0.3% for thrombocytopenia, 0.3% for leucopenia, 7.5% for lymphopenia, 3.5% for neutropenia, 3.2% for increased alkaline phosphatase, 8.2% for increased AST, 10.1% for increased ALT, 1.3% for increased total bilirubin, 1.3% for increased creatinine, 11.9% for increased amylase, 15.6% for increased lipase, 3.5% for hyperglycaemia, 0.8% for hypoglycaemia, 2.2% for hypocalcaemia, 0.3% for hypercalcaemia, 5.4% for hyperkalaemia, 4.2% for hypermagnesaemia, 1.9% for hypomagnesaemia 3.2% for hypokalaemia, 12.3% for hyponatraemia, and 21.2% for hypophosphataemia.

#### *Immunogenicity*

Of the 3529 patients who were treated with nivolumab monotherapy 3 mg/kg or 240 mg every 2 weeks and evaluable for the presence of anti-product-antibodies, 328 patients (9.3%) tested positive for treatment-emergent anti-product-antibodies with 21 patients (0.6%) testing positive for neutralising antibodies.

Co-administration with chemotherapy did not affect nivolumab immunogenicity. Of the patients who were treated with nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of anti-product-antibodies, 7.5% tested positive for treatment emergent anti-product-antibodies with 0.5% tested positive for neutralising antibodies.

Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26.0% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 24.9% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralising antibodies against nivolumab was 0.8% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 1.5% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 13.7% and neutralising antibodies against ipilimumab ranged from 0 to 0.4%.

Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-nivolumab antibodies or neutralising antibodies against nivolumab, the incidence of anti-nivolumab antibodies was 33.8% and the incidence of neutralising antibodies was 2.6%. Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-ipilimumab antibodies or neutralising antibodies against ipilimumab, the incidence of anti-ipilimumab antibodies was 7.5%, and the neutralising antibodies was 1.6%.

Although the clearance of nivolumab was increased by 20% when anti-nivolumab-antibodies were present, there was no evidence of loss of efficacy or altered toxicity profile in the presence of

nivolumab antibodies based on the pharmacokinetic and exposure-response analyses for both monotherapy and combination.

#### Paediatric population

The safety of nivolumab as monotherapy (3 mg/kg every 2 weeks) and in combination with ipilimumab (nivolumab 1 mg/kg or 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks) was evaluated in 97 paediatric patients aged  $\geq 1$  year to  $< 18$  years (including 53 patients 12 to  $< 18$  years) with recurrent or refractory solid or haematological tumours, including advanced melanoma, in clinical study CA209070. The safety profile in paediatric patients was generally similar to that seen in adults treated with nivolumab as monotherapy or in combination with ipilimumab. No new safety signals were observed. Long-term safety data is unavailable on the use of nivolumab in adolescents 12 years of age and older.

The most common adverse reactions (reported in at least 20% of paediatric patients) treated with nivolumab monotherapy were fatigue (35.9%) and decreased appetite (21.9%). The majority of adverse reactions reported for nivolumab monotherapy were Grade 1 or 2 in severity. Twenty-one patients (33%) had one or more Grades 3 to 4 adverse reactions.

The most common adverse reactions (reported in at least 20% of paediatric patients) treated with nivolumab in combination with ipilimumab were fatigue (33.3%) and rash maculo-papular (21.2%). The majority of adverse reactions reported for nivolumab in combination with ipilimumab were Grade 1 or 2 in severity. Ten patients (30%) had one or more Grades 3 to 4 adverse reactions.

No new safety signals were observed in clinical study CA209908 of 151 paediatric patients with high-grade primary central nervous system (CNS) malignancies (see [section 5.1](#)), relative to data available in adult studies across indications.

#### Elderly

No overall differences in safety were reported between elderly ( $\geq 65$  years) and younger patients ( $< 65$  years). Data from SCCHN, adjuvant melanoma, and adjuvant OC or GEJC patients 75 years of age or older are too limited to draw conclusions on this population (see [section 5.1](#)). Data from dMMR or MSI-H CRC patients 75 years of age or older are limited (see [section 5.1](#)). Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population (see [section 5.1](#)). In MPM patients, there was a higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older (68% and 35%, respectively) relative to all patients who received nivolumab in combination with ipilimumab (54% and 28%, respectively). For patients treated with nivolumab in combination with cabozantinib, data from RCC patients 75 years of age or older are too limited to draw conclusions on this population (see [section 5.1](#)).

#### Hepatic or renal impairment

In the non-squamous NSCLC study (CA209057), the safety profile in patients with baseline renal or hepatic impairment was comparable to that in the overall population. These results should be interpreted with caution due to the small sample size within the subgroups.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in \[Appendix V\]\(#\)](#).

### **4.9 Overdose**

No cases of overdose have been reported in clinical trials. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PDL-1 (Programmed cell death protein 1/ death ligand 1) inhibitors. ATC code: L01FF01.

#### Mechanism of action

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.

#### Clinical efficacy and safety

Based on modelling of dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between a nivolumab dose of 240 mg every 2 weeks or 3 mg/kg every 2 weeks. Additionally, based on these relationships, there were no clinically significant differences between a nivolumab dose of 480 mg every 4 weeks or 3 mg/kg every 2 weeks in adjuvant treatment of melanoma, advanced melanoma and advanced RCC.

#### *Melanoma*

##### Treatment of advanced melanoma

##### Randomised phase 3 study vs. dacarbazine (CA209066)

The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209066). The study included adult patients (18 years or older) with confirmed, treatment-naïve, Stage III or IV BRAF wild-type melanoma and an ECOG performance-status score of 0 or 1. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

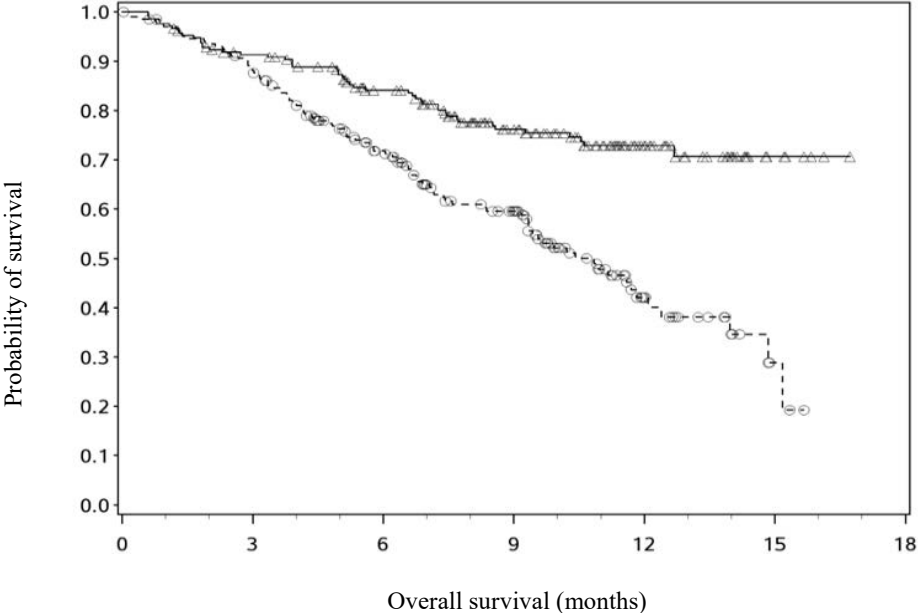
A total of 418 patients were randomised to receive either nivolumab (n = 210) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine (n = 208) at 1000 mg/m<sup>2</sup> every 3 weeks. Randomisation was stratified by tumour PD-L1 status and M stage (M0/M1a/M1b versus M1c). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse events with the study drug, as determined by the investigator. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and objective response rate (ORR).

Baseline characteristics were balanced between the two groups. The median age was 65 years (range: 18-87), 59% were men, and 99.5% were white. Most patients had ECOG performance score of 0 (64%) or 1 (34%). Sixty-one percent of patients had M1c stage disease at study entry. Seventy-four

percent of patients had cutaneous melanoma, and 11% had mucosal melanoma; 35% of patients had PD-L1 positive melanoma ( $\geq 5\%$  tumour cell membrane expression). Sixteen percent of patients had received prior adjuvant therapy; the most common adjuvant treatment was interferon (9%). Four percent of patients had a history of brain metastasis, and 37% of patients had a baseline LDH level greater than ULN at study entry.

The Kaplan-Meier curves for OS are shown in Figure 1.

**Figure 1:** Kaplan-Meier curves of OS (CA209066)



Number of subjects at risk

Nivolumab						
210	185	150	105	45	8	0
Dacarbazine						
208	177	123	82	22	3	0

—△— Nivolumab (events: 50/210), median and 95% CI: N.A.  
---○--- Dacarbazine (events: 96/208), median and 95% CI: 10.84 (9.33, 12.09)

The observed OS benefit was consistently demonstrated across subgroups of patients including baseline ECOG performance status, M stage, history of brain metastases, and baseline LDH level. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 5% or 10%).

Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Efficacy results are shown in [Table 9](#).

**Table 9: Efficacy results (CA209066)**

	nivolumab (n = 210)	dacarbazine (n = 208)
<b>Overall survival</b>		
Events	50 (23.8%)	96 (46.2%)
Hazard ratio		0.42
99.79% CI		(0.25, 0.73)
95% CI		(0.30, 0.60)
p-value		< 0.0001
Median (95% CI)	Not reached	10.8 (9.33, 12.09)
Rate (95% CI)		
At 6 months	84.1 (78.3, 88.5)	71.8 (64.9, 77.6)
At 12 months	72.9 (65.5, 78.9)	42.1 (33.0, 50.9)
<b>Progression-free survival</b>		
Events	108 (51.4%)	163 (78.4%)
Hazard ratio		0.43
95% CI		(0.34, 0.56)
p-value		< 0.0001
Median (95% CI)	5.1 (3.48, 10.81)	2.2 (2.10, 2.40)
Rate (95% CI)		
At 6 months	48.0 (40.8, 54.9)	18.5 (13.1, 24.6)
At 12 months	41.8 (34.0, 49.3)	NA
<b>Objective response</b>		
	84 (40.0%)	29 (13.9%)
(95% CI)	(33.3, 47.0)	(9.5, 19.4)
Odds ratio (95% CI)		4.06 (2.52, 6.54)
p-value		< 0.0001
Complete response (CR)	16 (7.6%)	2 (1.0%)
Partial response (PR)	68 (32.4%)	27 (13.0%)
Stable disease (SD)	35 (16.7%)	46 (22.1%)
<b>Median duration of response</b>		
Months (range)	Not reached (0 <sup>+</sup> -12.5 <sup>+</sup> )	6.0 (1.1-10.0 <sup>+</sup> )
<b>Median time to response</b>		
Months (range)	2.1 (1.2-7.6)	2.1 (1.8-3.6)

“+” denotes a censored observation.

#### Randomised phase 3 study vs. chemotherapy (CA209037)

The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, open-label study (CA209037). The study included adult patients who had progressed on or after ipilimumab and if BRAF V600 mutation positive had also progressed on or after BRAF kinase inhibitor therapy. Patients with active autoimmune disease, ocular melanoma, active brain or leptomeningeal metastases or a known history of prior ipilimumab-related high-grade (Grade 4 per CTCAE v4.0) adverse reactions, except for resolved nausea, fatigue, infusion reactions, or endocrinopathies, were excluded from the study.



A total of 405 patients were randomised to receive either nivolumab (n = 272) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or chemotherapy (n = 133) which consisted of the investigator's choice of either dacarbazine (1000 mg/m<sup>2</sup> every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m<sup>2</sup> every 3 weeks). Randomisation was stratified by BRAF and tumour PD-L1 status and best response to prior ipilimumab.

The co-primary efficacy outcome measures were confirmed ORR in the first 120 patients treated with nivolumab, as measured by independent radiology review committee (IRRC) using RECIST, version 1.1, and comparison of OS of nivolumab to chemotherapy. Additional outcome measures included duration and timing of response.

The median age was 60 years (range: 23-88). Sixty-four percent of patients were men and 98% were white. ECOG performance scores were 0 for 61% of patients and 1 for 39% of patients. The majority (75%) of patients had M1c stage disease at study entry. Seventy-three percent of patients had cutaneous melanoma and 10% had mucosal melanoma. The number of prior systemic regimen received was 1 for 27% of patients, 2 for 51% of patients, and > 2 for 21% of patients. Twenty-two percent of patients had tumours that tested BRAF mutation positive and 50% of patients had tumours that were considered PD-L1 positive. Sixty-four percent of patients had no prior clinical benefit (CR/PR or SD) on ipilimumab. Baseline characteristics were balanced between groups except for the proportions of patients who had a history of brain metastasis (19% and 13% in the nivolumab group and chemotherapy group, respectively) and patients with LDH greater than ULN at baseline (51% and 35%, respectively).

At the time of this final ORR analysis, results from 120 nivolumab-treated patients and 47 chemotherapy-treated patients who had a minimum of 6 months of follow-up were analysed. Efficacy results are presented in Table 10.

**Table 10: Best overall response, time and duration of response (CA209037)**

	<b>nivolumab (n = 120)</b>	<b>chemotherapy (n = 47)</b>
<b>Confirmed objective response (IRRC)</b> (95% CI)	38 (31.7%) (23.5, 40.8)	5 (10.6%) (3.5, 23.1)
Complete response (CR)	4 (3.3%)	0
Partial response (PR)	34 (28.3%)	5 (10.6%)
Stable disease (SD)	28 (23.3%)	16 (34.0%)
<b>Median duration of response</b>		
Months (range)	Not reached	3.6 (Not available)
<b>Median time to response</b>		
Months (range)	2.1 (1.6-7.4)	3.5 (2.1-6.1)

Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

#### Updated analysis (24-month follow-up)

Among all randomised patients, the ORR was 27.2% (95% CI: 22.0, 32.9) in the nivolumab group and 9.8% (95% CI: 5.3, 16.1) in the chemotherapy group. Median durations of response were 31.9 months (range: 1.4<sup>+</sup>-31.9) and 12.8 months (range: 1.3<sup>+</sup>-13.6<sup>+</sup>), respectively. The PFS HR for nivolumab vs. chemotherapy was 1.03 (95% CI: 0.78, 1.36). The ORR and PFS were assessed by IRRC per RECIST version 1.1.

There was no statistically significant difference between nivolumab and chemotherapy in the final OS analysis. The primary OS analysis was not adjusted to account for subsequent therapies, with

54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies and differences in baseline factors. More patients in the nivolumab arm had poor prognostic factors (elevated LDH and brain metastases) than in the chemotherapy arm.

***Efficacy by BRAF status:*** Objective responses to nivolumab (according to the definition of the co-primary endpoint) were observed in patients with or without BRAF mutation-positive melanoma. The ORRs in the BRAF mutation-positive subgroup were 17% (95% CI: 8.4, 29.0) for nivolumab and 11% (95% CI: 2.4, 29.2) for chemotherapy, and in the BRAF wild-type subgroup were 30% (95% CI: 24.0, 36.7) and 9% (95% CI: 4.6, 16.7), respectively.

The PFS HRs for nivolumab vs. chemotherapy were 1.58 (95% CI: 0.87, 2.87) for BRAF mutation-positive patients and 0.82 (95% CI: 0.60, 1.12) for BRAF wild-type patients. The OS HRs for nivolumab vs. chemotherapy were 1.32 (95% CI: 0.75, 2.32) for BRAF mutation-positive patients and 0.83 (95% CI: 0.62, 1.11) for BRAF wild-type patients.

***Efficacy by tumour PD-L1 expression:*** Objective responses to nivolumab were observed regardless of tumour PD-L1 expression. However, the role of this biomarker (tumour PD-L1 expression) has not been fully elucidated.

In patients with tumour PD-L1 expression  $\geq 1\%$ , ORR was 33.5% for nivolumab (n = 179; 95% CI: 26.7, 40.9) and 13.5% for chemotherapy (n = 74; 95% CI: 6.7, 23.5). In patients with tumour PD-L1 expression  $<1\%$ , ORR per IRRC was 13.0% (n = 69; 95% CI: 6.1, 23.3) and 12.0% (n = 25; 95% CI: 2.5, 31.2), respectively.

The PFS HRs for nivolumab vs. chemotherapy were 0.76 (95% CI: 0.54, 1.07) in patients with tumour PD-L1 expression  $\geq 1\%$  and 1.92 (95% CI: 1.05, 3.5) in patients with tumour PD-L1 expression  $<1\%$ .

The OS HRs for nivolumab vs. chemotherapy were 0.69 (95% CI: 0.49, 0.96) in patients with tumour PD-L1 expression  $\geq 1\%$  and 1.52 (95% CI: 0.89, 2.57) in patients with tumour PD-L1 expression  $<1\%$ .

These subgroup analyses should be interpreted with caution given the small size of the subgroups and lack of statistically significant difference in OS in the all randomised population.

#### ***Open-label phase 1 dose-escalation study (MDX1106-03)***

The safety and tolerability of nivolumab were investigated in a phase 1, open-label dose-escalation study in various tumour types, including malignant melanoma. Of the 306 previously treated patients enrolled in the study, 107 had melanoma and received nivolumab at a dose of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg for a maximum of 2 years. In this patient population, objective response was reported in 33 patients (31%) with a median duration of response of 22.9 months (95% CI: 17.0, NR). The median PFS was 3.7 months (95% CI: 1.9, 9.3). The median OS was 17.3 months (95% CI: 12.5, 37.8), and the estimated OS rates were 42% (95% CI: 32, 51) at 3 years, 35% (95% CI: 26, 44) at 4 years, and 34% (95% CI: 25, 43) at 5 years (minimum follow-up of 45 months).

#### ***Single-arm phase 2 study (CA209172)***

Study CA209172 was a single-arm, open label study of nivolumab monotherapy in patients with stage III (unresectable) or stage IV metastatic melanoma after prior treatment containing an anti-CTLA-4 monoclonal antibody. Safety was the primary endpoint and efficacy was a secondary endpoint. Of the 1008 treated patients, 103 (10%) had ocular/uveal melanoma, 66 (7%) had an ECOG performance score of 2, 165 (16%) had asymptomatic treated and untreated CNS metastases, 13 (1.3%) had treated leptomeningeal metastases, 25 (2%) had autoimmune disease, and 84 (8%) had Grade 3-4 immune-related AEs with prior anti-CTLA-4 therapy. No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. Efficacy results based on investigator-assessed response rates at week 12 are presented in [Table 11](#) below.

**Table 11: Response rate at week 12 - all response evaluable patients and by subgroup (CA209172)**

	Total	Ocular/ Uveal melanoma	ECOG PS 2	CNS metastasis	Autoimmune disease	Grade 3-4 irAEs with anti-CTLA-4
N	161/588	4/61	4/20	20/73	3/16	13/46
(%) <sup>a</sup>	(27.4)	(6.6)	(20.0)	(27.4)	(18.8)	(28.3)

<sup>a</sup> Responses were assessed per RECIST 1.1 for 588/1008 (58.3%) of patients who continued treatment through week 12 and had a follow-up scan at week 12.

*Randomised phase 3 study of nivolumab in combination with ipilimumab or nivolumab as monotherapy vs. ipilimumab as monotherapy (CA209067)*

The safety and efficacy of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg or nivolumab 3 mg/kg vs. ipilimumab 3 mg/kg monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209067). The differences between the two nivolumab-containing groups were evaluated descriptively. The study included adult patients with confirmed unresectable Stage III or Stage IV melanoma. Patients were to have ECOG performance status score of 0 or 1. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled. Prior adjuvant or neoadjuvant therapy was allowed if it was completed at least 6 weeks prior to randomisation. Patients with active autoimmune disease, ocular/uveal melanoma, or active brain or leptomeningeal metastases were excluded from the study.

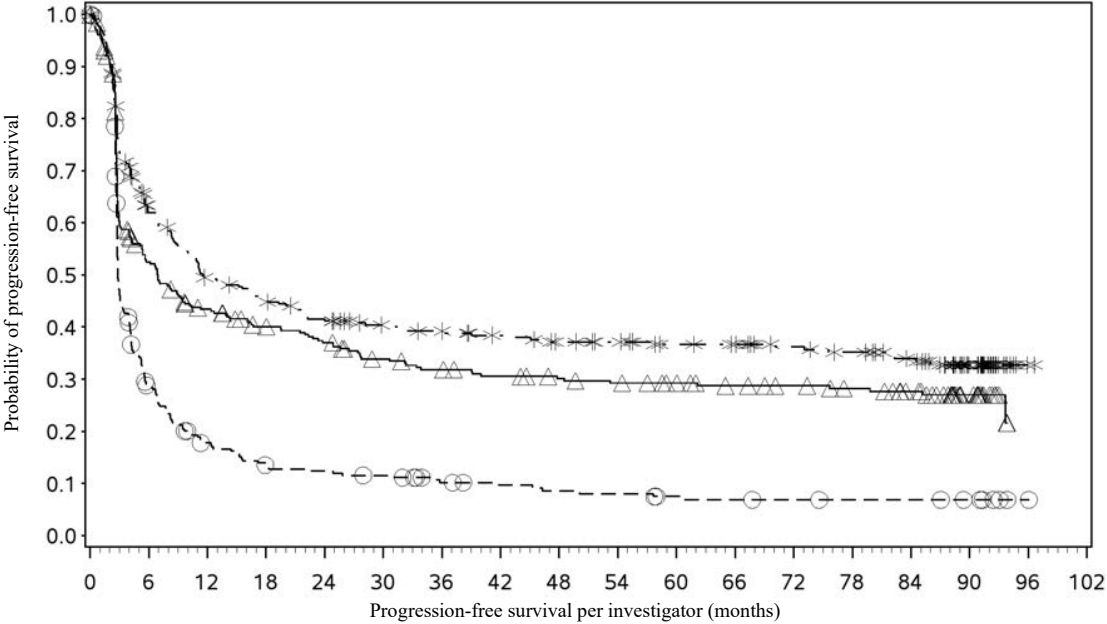
A total of 945 patients were randomised to receive nivolumab in combination with ipilimumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks. Patients in the nivolumab monotherapy arm received nivolumab 3 mg/kg every 2 weeks. Patients in the comparator arm received ipilimumab 3 mg/kg and nivolumab-matched placebo intravenously every 3 weeks for 4 doses followed by placebo every 2 weeks. Randomisation was stratified by PD-L1 expression ( $\geq 5\%$  vs.  $< 5\%$  tumour cell membrane expression), BRAF status, and M stage per the American Joint Committee on Cancer (AJCC) staging system. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments were conducted 12 weeks after randomisation then every 6 weeks for the first year, and every 12 weeks thereafter. The primary outcome measures were progression-free survival and OS. ORR and the duration of response were also assessed.

Baseline characteristics were balanced across the three treatment groups. The median age was 61 years (range: 18 to 90 years), 65% of patients were men, and 97% were white. ECOG performance status score was 0 (73%) or 1 (27%). The majority of the patients had AJCC Stage IV disease (93%); 58% had M1c disease at study entry. Twenty-two percent of patients had received prior adjuvant therapy. Thirty-two percent of patients had BRAF mutation-positive melanoma; 26.5% of patients had PD-L1  $\geq 5\%$  tumour cell membrane expression. Four percent of patients had a history of brain metastasis, and 36% of patients had a baseline LDH level greater than ULN at study entry. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the three treatment groups. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

At primary analysis (minimum follow-up 9 months) the median PFS was 6.9 months in the nivolumab group as compared with 2.9 months in the ipilimumab group (HR = 0.57, 99.5% CI: 0.43, 0.76;  $p < 0.0001$ ). The median PFS was 11.5 months in the nivolumab in combination with ipilimumab group, as compared with 2.9 months in the ipilimumab group (HR = 0.42, 99.5% CI: 0.31, 0.57;  $p < 0.0001$ ).

PFS results from descriptive analysis (with minimum follow up of 90 months) are shown in Figure 2 (all randomised population), Figure 3 (at the tumour PD-L1 5% cut off), and Figure 4 (at the tumour PD-L1 1% cut off).

**Figure 2: Progression-free survival (CA209067)**



Number of subjects at risk

Nivolumab + ipilimumab																
314	175	138	126	112	103	99	93	87	84	78	76	70	66	57	33	1
Nivolumab																
316	151	120	106	97	84	78	73	69	66	62	57	54	50	44	21	0
Ipilimumab																
315	78	46	34	31	28	21	18	16	15	12	11	10	9	9	7	1

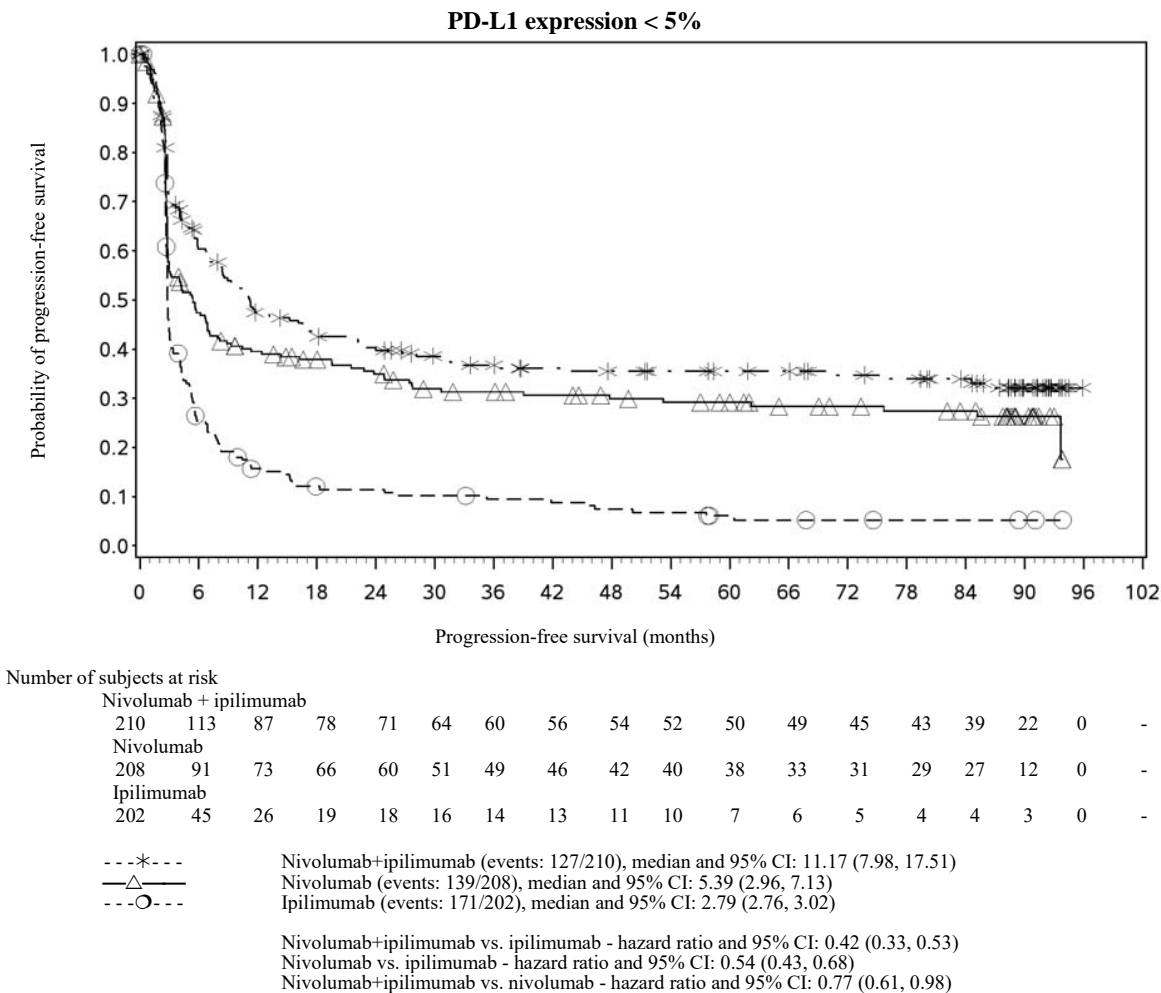
- \*--- Nivolumab+ipilimumab (events: 189/314), median and 95% CI: 11.50 (8.90, 20.04).  
PFS rate at 12 months and 95% CI: 49% (44, 55), PFS rate at 60 months and 95% CI: 36% (32, 42), PFS rate at 90 months and 95% CI: 33% (27, 39)
- △— Nivolumab (events: 208/316), median and 95% CI: 6.93 (5.13, 10.18).  
PFS rate at 12 months and 95% CI: 42% (36, 47), PFS rate at 60 months and 95% CI: 29% (24, 35), PFS rate at 90 months and 95% CI: 27% (22, 33)
- Ipilimumab (events: 261/315), median and 95% CI: 2.86 (2.79, 3.09).  
PFS rate at 12 months and 95% CI: 18% (14, 23), PFS rate at 60 months and 95% CI: 8% (5, 12), PFS rate at 90 months and 95% CI: 7% (4, 11)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.35, 0.51)

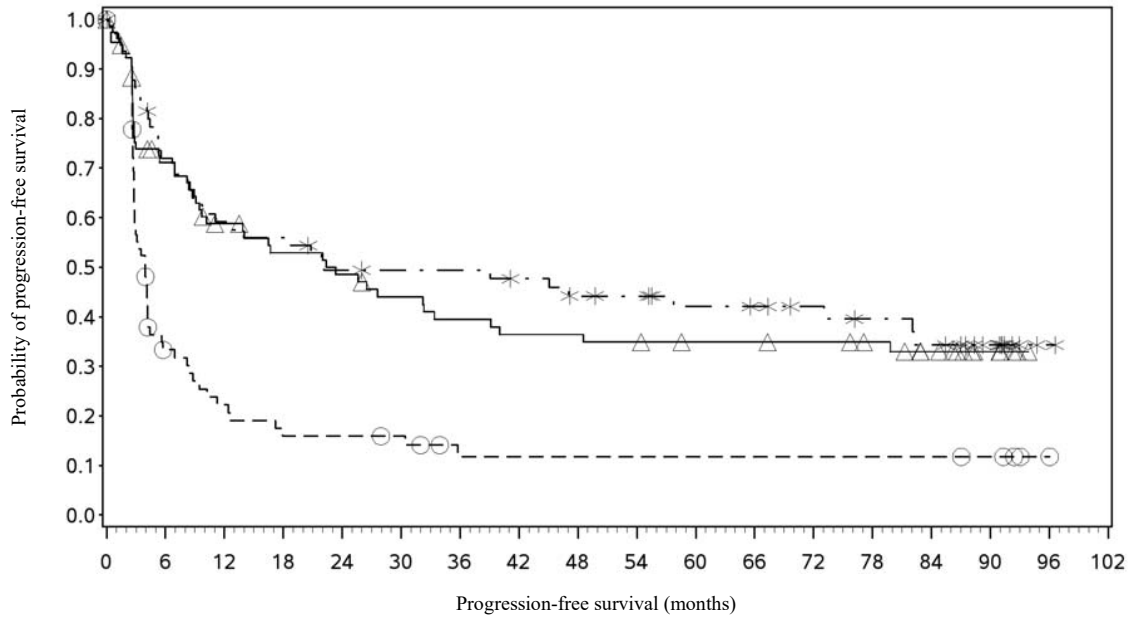
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.53 (0.44, 0.64)

Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.79 (0.65, 0.97)

**Figure 3: Progression-free survival by PD-L1 expression: 5% cut off (CA209067)**



# PD-L1 expression $\geq 5\%$



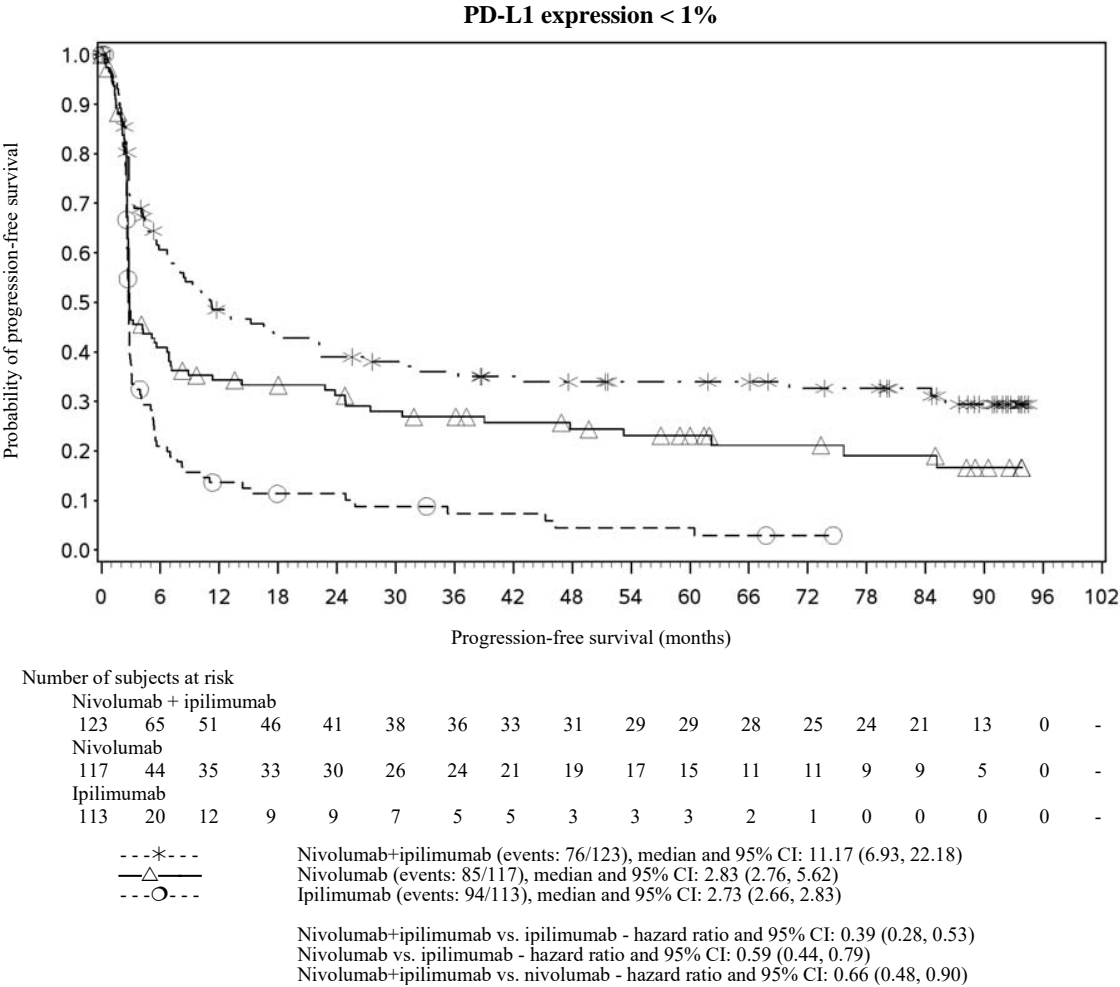
Number of subjects at risk

Nivolumab + ipilimumab																
68	45	37	35	30	29	29	27	24	23	20	19	17	15	13	8	1
Nivolumab																
80	52	41	36	33	29	26	24	24	23	21	21	20	18	14	7	0
Ipilimumab																
75	21	14	10	10	9	5	5	5	5	5	5	5	5	5	4	1

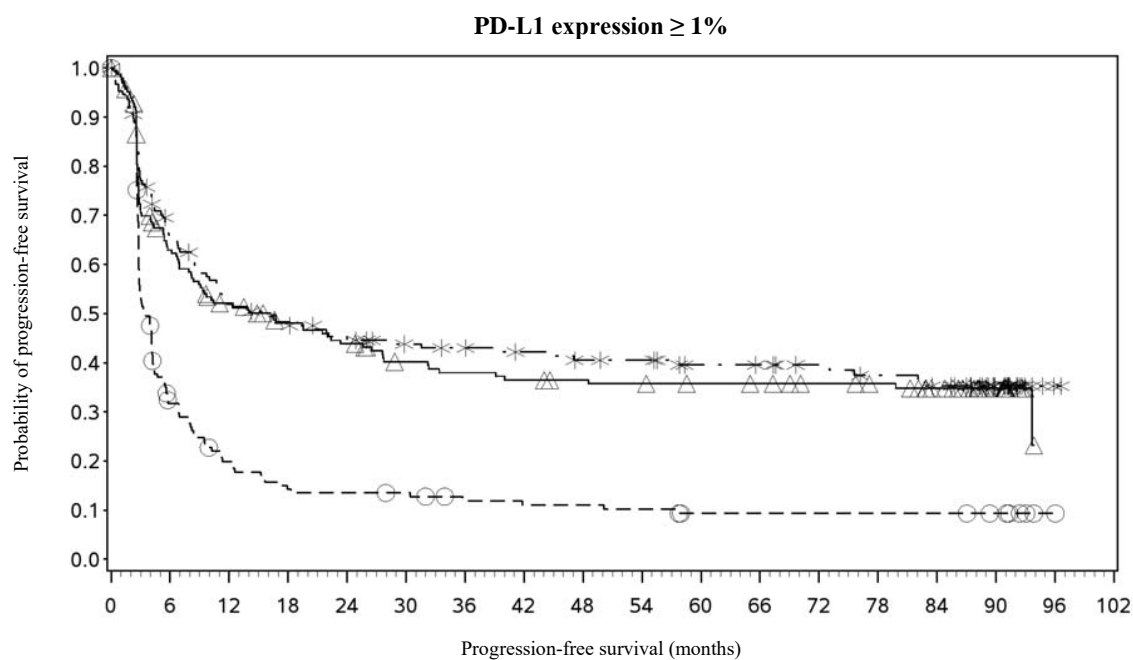
---\*--- Nivolumab+ipilimumab (events: 36/68), median and 95% CI: 22.11 (9.72, 82.07)  
 ---△--- Nivolumab (events: 48/80), median and 95% CI: 22.34 (9.46, 39.13)  
 ---○--- Ipilimumab (events: 60/75), median and 95% CI: 3.94 (2.79, 4.21)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.38 (0.25, 0.58)  
 Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.43 (0.29, 0.64)  
 Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.89 (0.58, 1.35)

**Figure 4: Progression-free survival by PD-L1 expression: 1% cut off (CA209067)**







Number of subjects at risk

Nivolumab + ipilimumab

155 93 73 67 60 55 53 50 47 46 41 40 37 34 31 17 1 -

Nivolumab

171 99 79 69 63 54 51 49 47 46 44 43 40 38 32 14 0 -

Ipilimumab

164 46 28 20 19 18 14 13 13 12 9 9 9 9 9 7 1 -

---\*---

Nivolumab+ipilimumab (events: 90/155), median and 95% CI: 16.13 (8.90, 45.08)

---△---

Nivolumab (events: 102/171), median and 95% CI: 16.20 (8.11, 27.60)

---○---

Ipilimumab (events: 137/164), median and 95% CI: 3.48 (2.83, 4.17)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.32, 0.55)

Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.45 (0.35, 0.59)

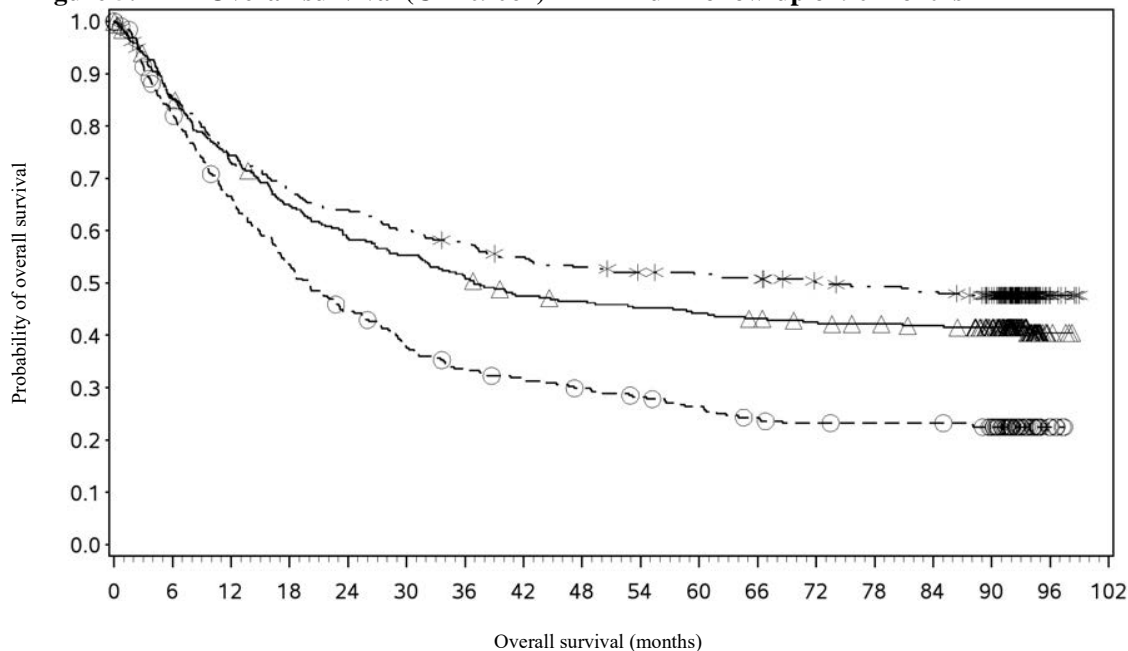
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.92 (0.69, 1.22)

The final (primary) OS analysis occurred when all patients had a minimum follow-up of 28 months. At 28 months, median OS was not reached in the nivolumab group as compared with 19.98 months in the ipilimumab group (HR = 0.63, 98% CI: 0.48, 0.81; p-value: < 0.0001). Median OS was not reached in the nivolumab in combination with ipilimumab group as compared with the ipilimumab group (HR = 0.55, 98% CI: 0.42, 0.72; p-value: < 0.0001).

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 90 months show outcomes consistent with the original primary analysis. OS results from this follow-up analysis are shown in [Figure 5](#) (all randomised), [Figure 6](#) and [7](#) (at the tumour PD-L1 5% and 1% cut off).

The OS analysis was not adjusted to account for subsequent therapies received. Subsequent systemic therapy was received by 36.0%, 49.1%, and 66.3% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively. Subsequent immunotherapy (including anti-PD1 therapy, anti-CTLA-4 antibody, or other immunotherapy) was received by 19.1%, 34.2%, and 48.3% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively.

**Figure 5: Overall survival (CA209067) - Minimum follow-up of 90 months**



Number of subjects at risk

Nivolumab+ipilimumab	314	265	227	210	199	187	179	169	163	158	156	153	147	144	141	129	7	-
Nivolumab	316	266	231	201	181	171	158	145	141	137	134	130	126	123	120	107	4	-
Ipilimumab	315	253	203	163	135	113	100	94	87	81	75	68	64	63	63	57	5	-

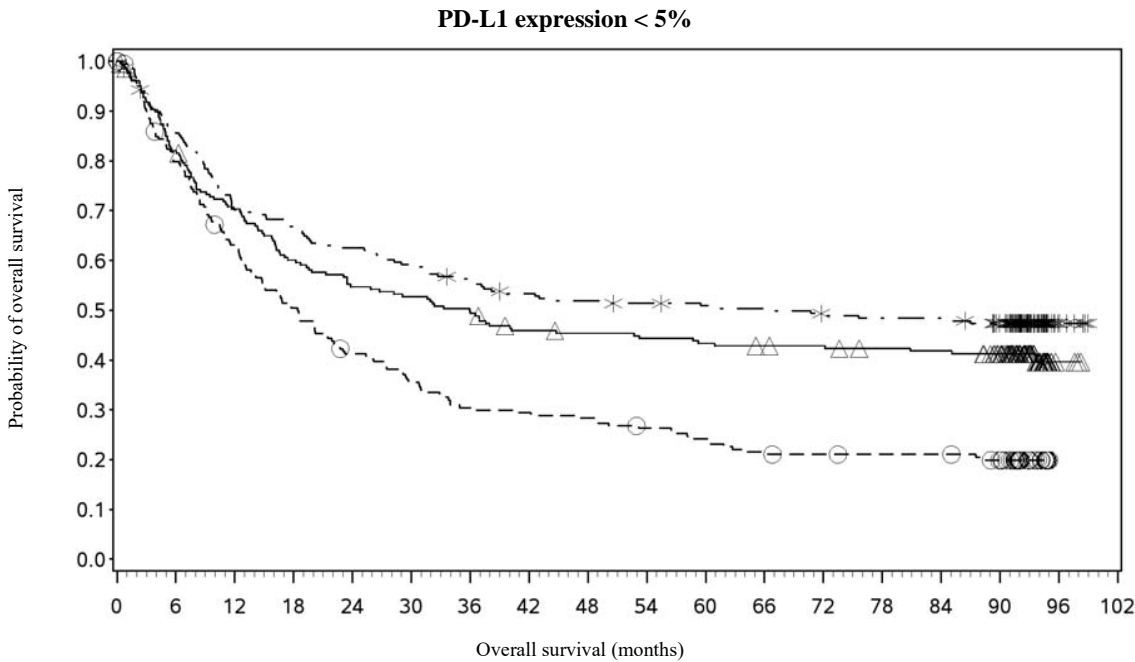
- \*--- Nivolumab+ipilimumab (events: 162/314), median and 95% CI: 72.08 (38.18, N.A.)  
OS rate and 95% CI at 12 months: 73% (68, 78), 24 months: 64% (59, 69), 36 months: 58% (52, 63), 60 months: 52% (46, 57), and 90 months: 48% (42, 53)
- △— Nivolumab (events: 182/316), median and 95% CI: 36.93 months (28.25, 58.71)  
OS rate and 95% CI at 12 months: 74% (69, 79), 24 months: 59% (53, 64), 36 months: 52% (46, 57), 60 months: 44% (39, 50), and 90 months: 42% (36, 47)
- Ipilimumab (events: 235/315), median and 95% CI: 19.94 months (16.85, 24.61)  
OS rate and 95% CI at 12 months: 67% (61, 72), 24 months: 45% (39, 50), 36 months: 34% (29, 39), 60 months: 26% (22, 31), and 90 months: 22% (18, 27)

Nivolumab+ipilimumab vs ipilimumab - HR (95% CI): 0.53 (0.44, 0.65)

Nivolumab vs ipilimumab - HR (95% CI): 0.63 (0.52, 0.77)

Nivolumab+ipilimumab vs nivolumab - HR (95% CI): 0.84 (0.68, 1.04)

**Figure 6: Overall survival by PD-L1 expression: 5% cut off (CA209067) - Minimum follow-up of 90 months**

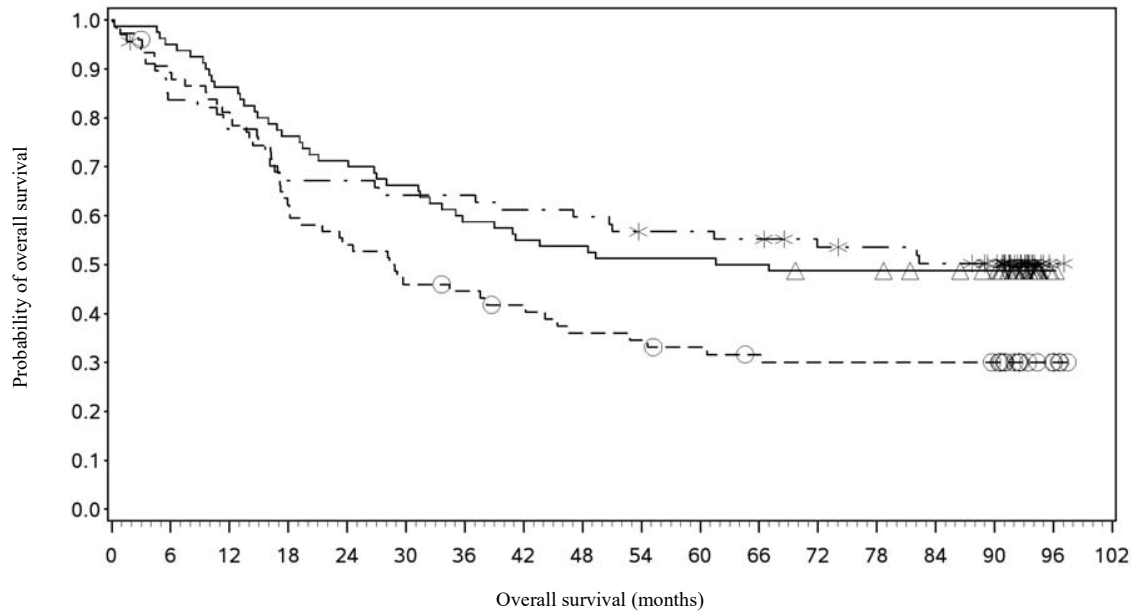


Number of subjects at risk																
Nivolumab+ipilimumab																
210	178	146	139	130	123	116	109	106	104	102	100	98	96	96	88	6
Nivolumab																
208	169	144	123	112	108	102	92	90	88	86	84	83	80	79	70	3
Ipilimumab																
202	158	124	99	80	69	59	57	55	50	46	41	39	38	38	33	0

---\*--- Nivolumab+ipilimumab (events: 109/210), median and 95% CI: 65.94 (32.72, N.A.)  
—△— Nivolumab (events: 121/208), median and 95% CI: 35.94 months (23.06, 60.91)  
---○--- Ipilimumab (events: 157/202), median and 95% CI: 18.40 months (13.70, 22.51)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.51 (0.40, 0.66)  
Nivolumab vs. ipilimumab - HR (95% CI): 0.62 (0.49, 0.79)  
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.83 (0.64, 1.07)

# PD-L1 expression $\geq 5\%$



Number of subjects at risk

Nivolumab+ipilimumab																
68	56	52	45	45	43	43	41	40	37	37	36	33	32	30	27	1
Nivolumab																
80	76	69	61	57	53	47	44	43	41	41	40	38	38	36	33	1
Ipilimumab																
75	66	60	46	40	34	32	29	25	24	22	20	19	19	19	18	4

---\*---

Nivolumab+ipilimumab (events: 33/68), median and 95% CI: N.A. (39.06, N.A.)

---△---

Nivolumab (events: 41/80), median and 95% CI: 64.28 months (33.64, N.A.)

---○---

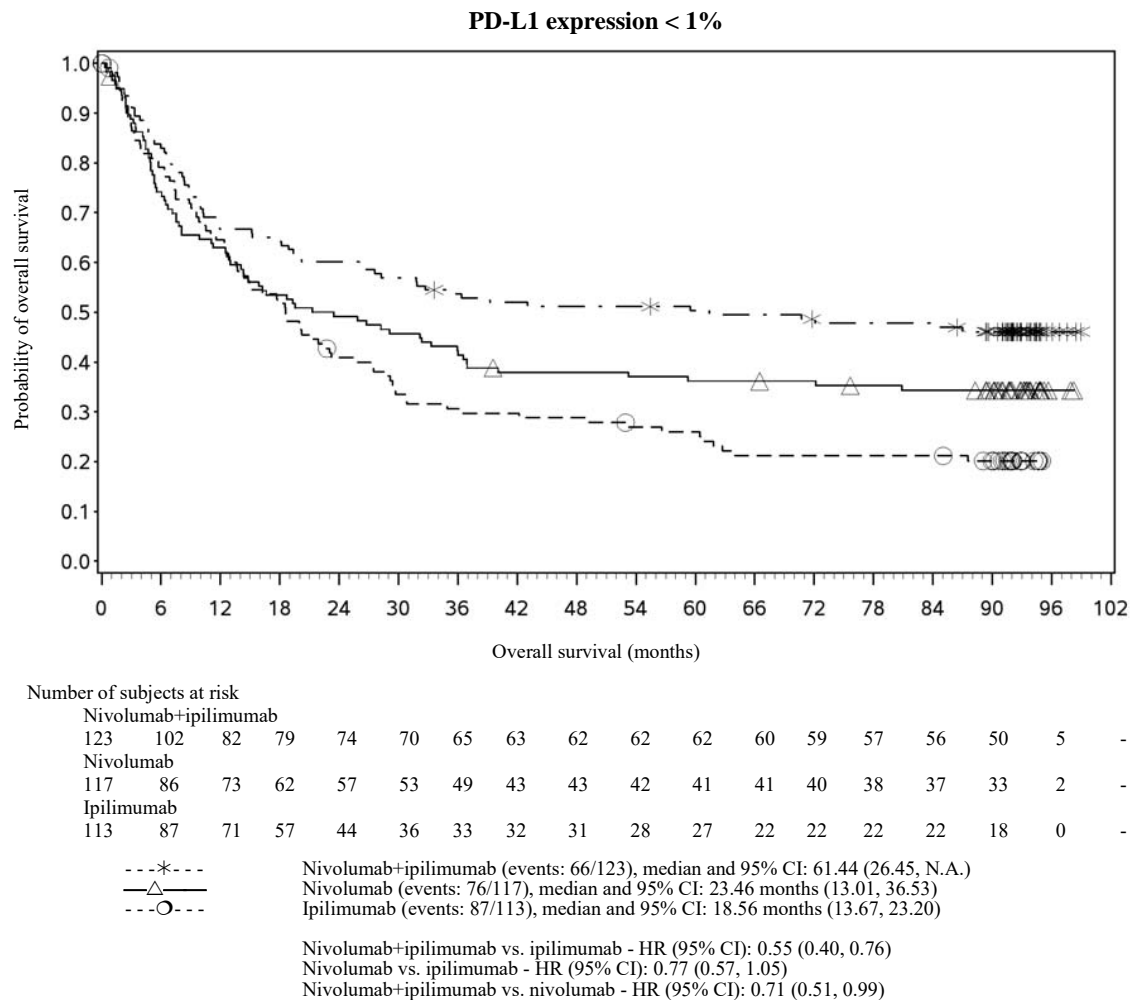
Ipilimumab (events: 51/75), median and 95% CI: 28.88 months (18.10, 44.16)

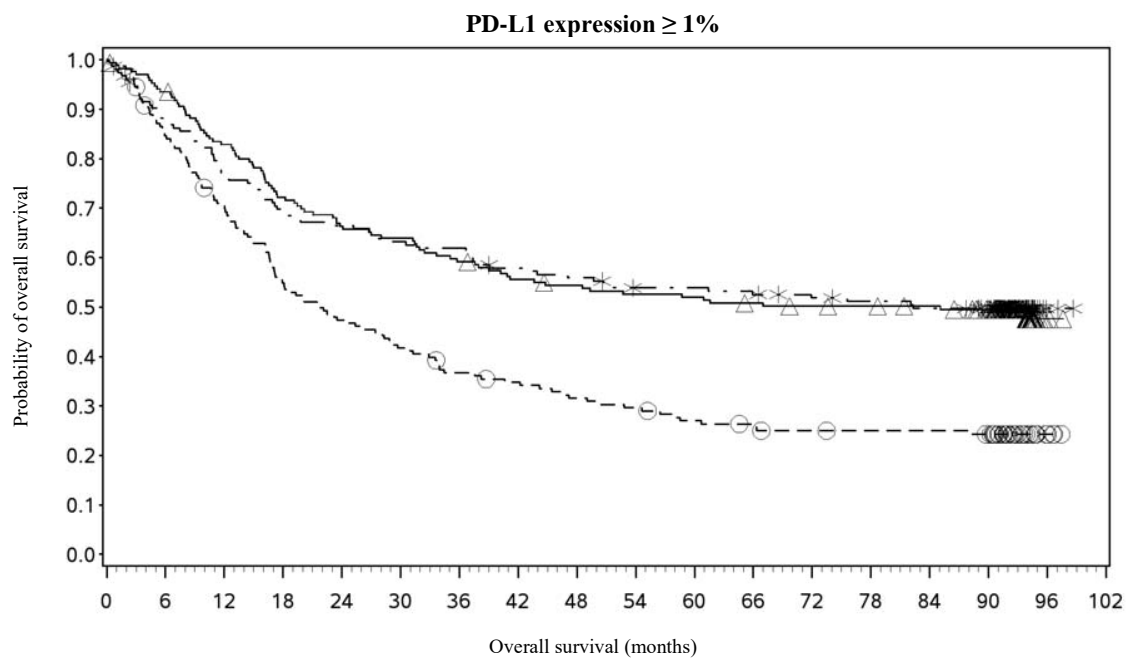
Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.61 (0.39, 0.94)

Nivolumab vs. ipilimumab - HR (95% CI): 0.61 (0.41, 0.93)

Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.99 (0.63, 1.57)

**Figure 7: Overall survival by PD-L1 expression: 1% cut off (CA209067) - Minimum follow-up of 90 months**





Number of subjects at risk

Nivolumab+ipilimumab																	
155	132	116	105	101	96	94	87	84	79	79	77	74	72	70	65	2	-
Nivolumab																	
171	159	140	122	112	108	100	93	90	87	86	83	81	80	78	70	2	-
Ipilimumab																	
164	137	113	88	76	67	58	54	49	46	41	39	36	35	35	33	4	-

---\*--- Nivolumab+ipilimumab (events: 76/155), median and 95% CI: 82.30 (39.06, N.A.)  
 ---△--- Nivolumab (events: 86/171), median and 95% CI: 85.09 months (39.00, N.A.)  
 ---○--- Ipilimumab (events: 121/164), median and 95% CI: 21.49 months (16.85, 29.08)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.52 (0.39, 0.70)  
 Nivolumab vs. ipilimumab - HR (95% CI): 0.52 (0.39, 0.69)  
 Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 1.01 (0.74, 1.37)

Minimum follow-up for the analysis of ORR was 90 months. Responses are summarised in Table 12.

**Table 12: Objective response (CA209067)**

	nivolumab + ipilimumab (n = 314)	nivolumab (n = 316)	ipilimumab (n = 315)
<b>Objective response</b>	183 (58%)	142 (45%)	60 (19%)
(95% CI)	(52.6, 63.8)	(39.4, 50.6)	(14.9, 23.8)
Odds ratio (vs. ipilimumab)	6.35	3.5	
(95% CI)	(4.38, 9.22)	(2.49, 5.16)	
Complete response (CR)	71 (23%)	59 (19%)	19 (6%)
Partial response (PR)	112 (36%)	83 (26%)	41 (13%)
Stable disease (SD)	38 (12%)	29 (9%)	69 (22%)
<b>Duration of response</b>			
Median (range), months	N.A. (69.1-N.A.)	90.8 (45.7-N.A.)	19.3 (8.8-47.4)
Proportion ≥ 12 months in duration	68%	73%	44%
Proportion ≥ 24 months in duration	58%	63%	30%
<b>ORR (95% CI) by tumour PD-L1 expression</b>			
< 5%	56% (48.7, 62.5) n = 210	43% (36, 49.8) n = 208	18% (12.8, 23.8) n = 202
≥ 5%	72% (59.9, 82.3) n = 68	59% (47.2, 69.6) n = 80	21% (12.7, 32.3) n = 75
< 1%	54% (44.4, 62.7) n = 123	36% (27.2, 45.3) n = 117	18% (11.2, 26.0) n = 113
≥ 1%	65% (56.4, 72) n = 155	55% (47.2, 62.6) n = 171	20% (13.7, 26.4) n = 164

Both nivolumab-containing arms demonstrated a significant PFS and OS benefit and greater ORR compared with ipilimumab alone. The observed PFS results at 18 months of follow-up and ORR and OS results at 28 months of follow-up were consistently demonstrated across subgroups of patients including baseline ECOG performance status, BRAF status, M stage, age, history of brain metastases, and baseline LDH level. This observation was maintained with the OS results with a minimum follow-up of 90 months.

Among 131 patients who discontinued the combination due to adverse reaction after 28 months of follow-up, the ORR was 71% (93/131) with 20% (26/131) achieving a complete response and median OS was not reached.

Both nivolumab-containing arms demonstrated greater objective response rates than ipilimumab regardless of PD-L1 expression levels. ORRs were higher for the combination of nivolumab and ipilimumab relative to nivolumab monotherapy across tumour PD-L1 expression levels (Table 12) after 90 months of follow-up, with a best overall response of complete response correlating to an improved survival rate.

After 90 months of follow-up, median durations of response for patients with tumour PD-L1 expression level ≥ 5% were 78.19 months (range: 18.07-N.A.) in the combination arm, 77.21 months (range: 26.25-N.A.) in the nivolumab monotherapy arm and 31.28 months (range: 6.08-N.A.) in the ipilimumab arm. At tumour PD-L1 expression < 5%, median durations of response were not reached (range: 61.93-N.A.) in the combination arm, were 90.84 months (range: 50.43-N.A.) in the nivolumab monotherapy arm and 19.25 months (range: 5.32-47.44) in the ipilimumab monotherapy arm.

No clear cut off for PD-L1 expression can reliably be established when considering the relevant endpoints of tumour response and PFS and OS. Results from exploratory multivariate analyses



identified patient and tumour characteristics (ECOG performance status, M stage, baseline LDH, BRAF mutation status, PD-L1 status, and gender) which might contribute to the survival outcome.

#### Efficacy by BRAF status:

After 90 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had a median PFS of 16.76 months (95% CI: 8.28, 32.0) and 11.7 months (95% CI: 7.0, 19.32), while those in the nivolumab monotherapy arm had a median PFS of 5.62 months (95% CI: 2.79, 9.46) and 8.18 months (95% CI: 5.13, 19.55), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had a median PFS of 3.09 months (95% CI: 2.79, 5.19) and 2.83 months (95% CI: 2.76, 3.06), respectively.

After 90 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had an ORR of 67.0% (95% CI: 57.0, 75.9; n = 103) and 54.0% (95% CI: 47.1, 60.9; n = 211), while those in the nivolumab monotherapy arm had an ORR of 37.87% (95% CI: 28.2, 48.1; n = 98) and 48.2% (95% CI: 41.4, 55.0; n = 218), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had an ORR of 23.0% (95% CI: 15.2, 32.5; n = 100) and 17.2% (95% CI: 12.4, 22.9; n = 215).

After 90 months of follow-up, in BRAF [V600] mutation-positive patients median OS was not reached in the combination arm and 45.5 months in the nivolumab monotherapy arm. Median OS for BRAF [V600] mutation-positive patients in the ipilimumab monotherapy arm was 24.6 months. In BRAF wild-type patients median OS was 39.06 months in the combination arm, 34.37 months in the nivolumab monotherapy arm and 18.5 months in the ipilimumab monotherapy arm. The OS HRs for nivolumab in combination with ipilimumab vs. nivolumab monotherapy were 0.66 (95% CI: 0.44, 0.98) for BRAF[V600] mutation-positive patients and 0.95 (95% CI: 0.74, 1.22) for BRAF wild-type patients.

#### Randomised phase 2 study of nivolumab in combination with ipilimumab and ipilimumab (CA209069)

Study CA209069 was a randomised, Phase 2, double-blind study comparing the combination of nivolumab and ipilimumab with ipilimumab alone in 142 patients with advanced (unresectable or metastatic) melanoma with similar inclusion criteria to study CA209067 and the primary analysis in patients with BRAF wild-type melanoma (77% of patients). Investigator assessed ORR was 61% (95% CI: 48.9, 72.4) in the combination arm (n = 72) versus 11% (95% CI: 3.0, 25.4) for the ipilimumab arm (n = 37). The estimated 2 and 3 year OS rates were 68% (95% CI: 56, 78) and 61% (95% CI: 49, 71), respectively, for the combination (n = 73) and 53% (95% CI: 36, 68) and 44% (95% CI: 28, 60), respectively, for ipilimumab (n = 37).

#### Adjuvant treatment of melanoma

##### Randomised phase 3 study of nivolumab vs. placebo (CA20976K)

The safety and efficacy of nivolumab 480 mg monotherapy for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study (CA20976K). The study included patients with an ECOG performance status score of 0 or 1 who had Stage IIB or IIC American Joint Committee on Cancer (AJCC), 8<sup>th</sup> edition, histologically confirmed melanoma that had been completely surgically resected. Enrolment required complete resection of the primary melanoma with negative margins and a negative sentinel lymph node biopsy within 12 weeks prior to randomisation. Patients were enrolled regardless of their tumour PD-L1 status. The study excluded patients with ocular/uveal or mucosal melanoma, active autoimmune disease, any condition requiring systemic treatment with either corticosteroids ( $\geq 10$  mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery.

A total of 790 patients were randomised (2:1) to receive either nivolumab (n = 526) administered intravenously over 30 minutes at 480 mg every 4 weeks or placebo (n = 264) for up to 1 year or until disease recurrence or unacceptable toxicity. Randomisation was stratified by AJCC 8<sup>th</sup> edition T-category (T3b vs. T4a vs. T4b). Tumour assessments were conducted every 26 weeks during years 1-3 and every 52 weeks from 3 years to 5 years. The primary efficacy outcome measure was

recurrence-free survival (RFS). RFS, assessed by the investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first. The secondary outcome measures included OS and distant metastasis-free survival (DMFS).

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 19-92), 61% were men, and 98% were white. Baseline ECOG performance status score was 0 (94%) or 1 (6%). Sixty percent had stage IIB and 40% had stage IIC.

At a primary pre-specified interim analysis (minimum follow-up 7.8 months) a statistically significant improvement in RFS was demonstrated with nivolumab compared to placebo with a HR of 0.42 (95% CI: 0.30, 0.59;  $p < 0.0001$ ). At an updated descriptive RFS analysis (minimum follow-up of 15.6 months), nivolumab continued to demonstrate an RFS improvement with a HR of 0.53 (95% CI: 0.40, 0.71). OS was not mature. Results reported from the analyses with minimum follow-up of 15.6 months are summarised in Table 13 and [Figure 8](#).

**Table 13: Efficacy results (CA20976K)**

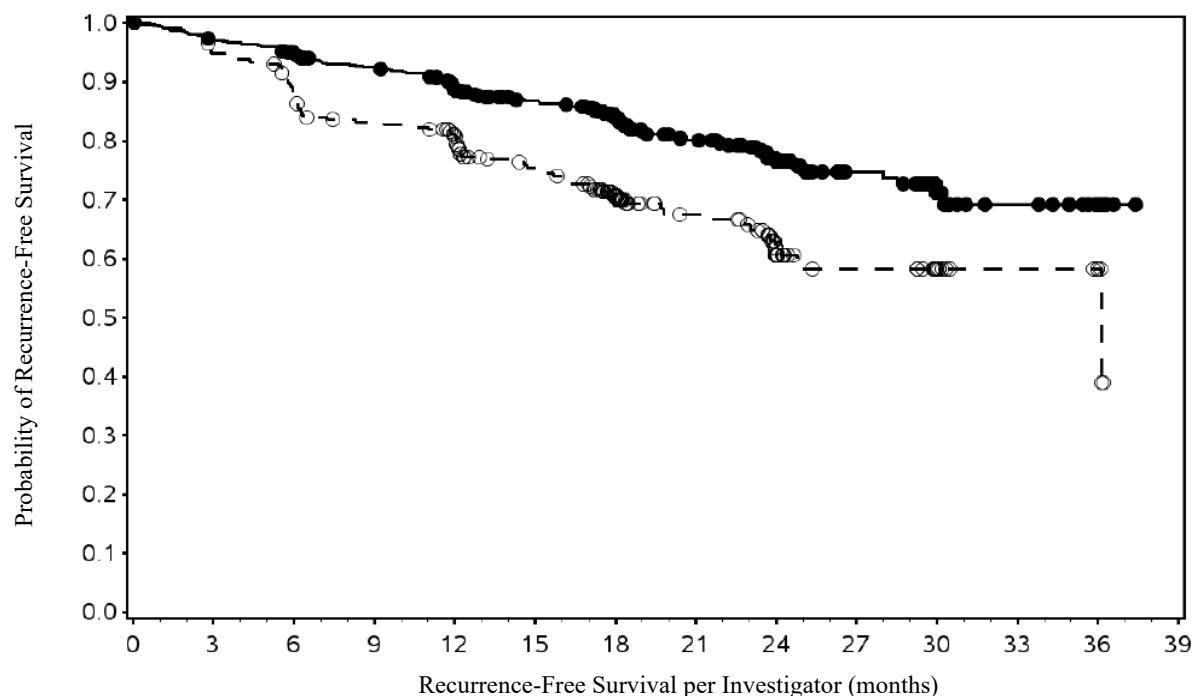
	nivolumab (n = 526)	placebo (n = 264)
<b>Recurrence-free survival with minimum follow-up 15.6 months</b>		
<b>Recurrence-free survival</b>		
Events	102 (19.4%)	84 (31.8%)
Hazard ratio <sup>a</sup>		0.53
95% CI		(0.40, 0.71)
Median (95% CI) months	NR	36.14 (24.77, NR)
Rate (95% CI) at 12 months <sup>b</sup>	88.8 (85.6, 91.2)	81.1 (75.7, 85.4)
Rate (95% CI) at 18 months <sup>b</sup>	83.9 (80.3, 86.9)	70.7 (64.5, 76.1)

<sup>a</sup> Based on stratified Cox proportional hazard model.

<sup>b</sup> Based on Kaplan-Meier estimates.

RFS benefit was consistent across key subgroups, including disease stage, T-category, and age.

**Figure 8: Recurrence-free survival (CA20976K)**



Number of subjects at risk

Nivolumab	526	492	474	456	422	386	291	210	122	74	40	22	13	0
Placebo	264	244	224	208	193	165	120	77	44	25	12	7	4	0

—●— Nivolumab (events 102/526), median and 95% CI: NR  
 ---○--- Placebo (events: 84/264), median and 95% CI: 36.14 (24.77, NR)  
 Nivolumab vs. Placebo – HR (95% CI): 0.53 (0.40, 0.71)

Based on data cut-off: 21-February-2023, minimum follow-up of 15.6 months

Tumour PD-L1 expression data were available for 302/790 (38.2%) randomised patients (36.3% and 42.0% in the nivolumab and placebo arms, respectively), as PD-L1 expression was not a stratification factor for randomisation. The exploratory RFS analyses by PD-L1 expression showed a HR for nivolumab vs placebo of 0.43 (95% CI: 0.22, 0.84) in patients (N=167) with PD-L1 expression  $\geq 1\%$ , 0.82 (95% CI: 0.44, 1.54) in patients (N=135) with PD-L1 expression  $< 1\%$ , and 0.50 (95% CI: 0.34, 0.73) in patients (N=488) with indeterminate/not reported/not evaluable PD-L1 expression.

#### Randomised phase 3 study of nivolumab vs ipilimumab 10 mg/kg (CA209238)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study (CA209238). The study included adult patients, who had an ECOG performance status score of 0 or 1, with Stage IIIB/C or Stage IV American Joint Committee on Cancer (AJCC), 7<sup>th</sup> edition, histologically confirmed melanoma that is completely surgically resected. Per the AJCC 8<sup>th</sup> edition, this corresponds to patients with lymph node involvement or metastases. Patients were enrolled regardless of their tumour PD-L1 status. Patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids ( $\geq 10$  mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed  $\geq 6$  months prior to randomisation) prior therapy with, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways), were excluded from the study.

A total of 906 patients were randomised to receive either nivolumab 3 mg/kg (n = 453) administered every 2 weeks or ipilimumab 10 mg/kg (n = 453) administered every 3 weeks for 4 doses then every 12 weeks beginning at week 24 for up to 1 year. Randomisation was stratified by tumour PD-L1 expression ( $\geq 5\%$  vs.  $< 5\%$ /indeterminate), and stage of disease per the AJCC staging system. Tumour assessments were conducted every 12 weeks for the first 2 years then every 6 months thereafter. The primary endpoint was recurrence-free survival (RFS). RFS, assessed by investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death due to any cause, whichever occurred first.

Baseline characteristics were generally balanced between the two groups. The median age was 55 years (range: 18-86), 58% were men, and 95% were white. Baseline ECOG performance status score was 0 (90%) or 1 (10%). The majority of patients had AJCC Stage III disease (81%), and 19% had Stage IV disease. Forty-eight percent of patients had macroscopic lymph nodes and 32% had tumour ulceration. Forty-two percent of patients were BRAF V600 mutation positive while 45% were BRAF wild type and 13% BRAF were status unknown. For tumour PD-L1 expression, 34% of patients had PD-L1 expression  $\geq 5\%$  and 62% had  $< 5\%$  as determined by clinical trial assay. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the treatment groups. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

At a primary pre-specified interim analysis (minimum follow-up 18 months) a statistically significant improvement in RFS with nivolumab compared to ipilimumab with HR of 0.65 (97.56% CI: 0.51, 0.83; stratified log-rank  $p < 0.0001$ ) was demonstrated. At an updated descriptive RFS analysis, with minimum follow-up of 24 months RFS improvement was confirmed with HR of 0.66 (95% CI: 0.54, 0.81;  $p < 0.0001$ ) and OS was not mature. Efficacy results with minimum follow-up of 36 months (RFS pre-specified final analysis) and 48 months (OS pre-specified final analysis) are shown in Table 14 and Figure 9 and 10 (all randomised population).

**Table 14: Efficacy results (CA209238)**

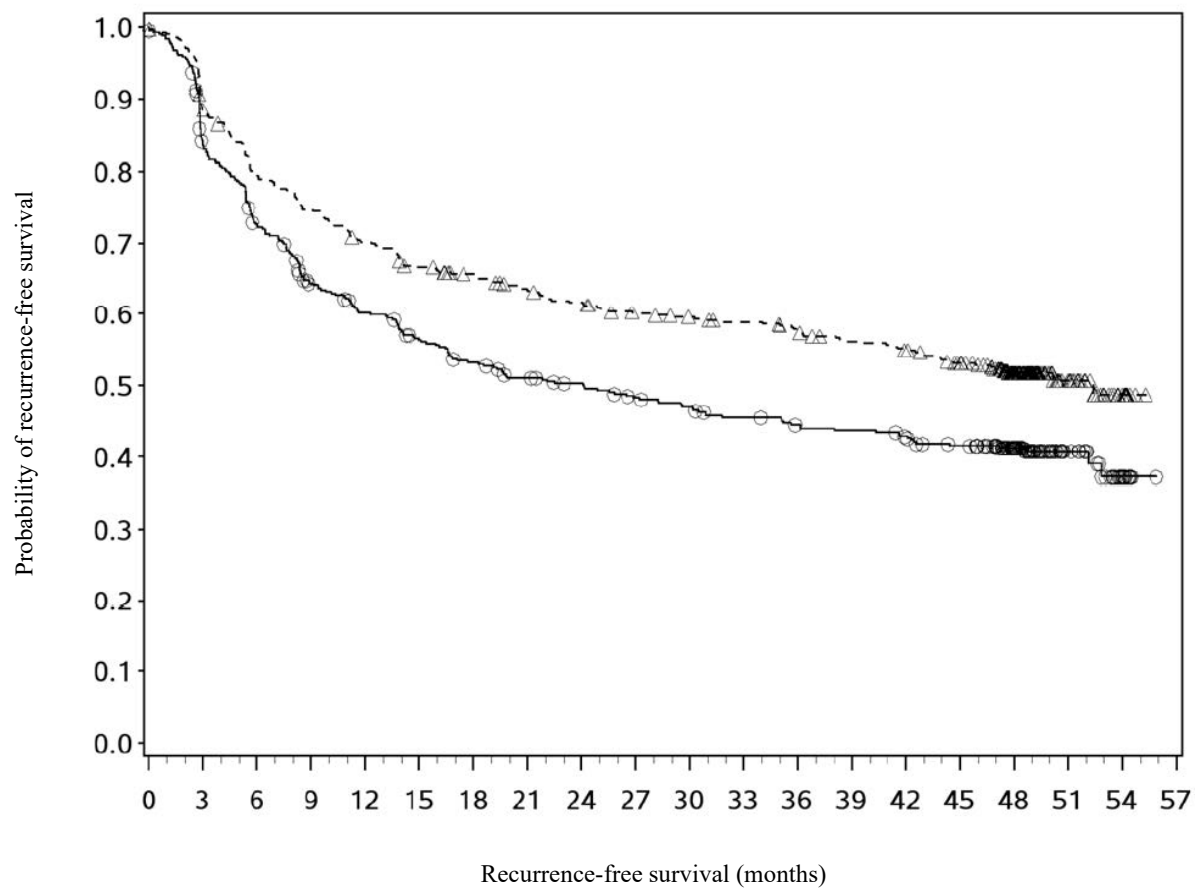
	<b>nivolumab (n = 453)</b>	<b>ipilimumab 10 mg/kg (n = 453)</b>
<b>Final pre-specified analysis</b>		
<b>Recurrence-free survival with minimum follow-up 36 months</b>		
Events	188 (41.5%)	239 (52.8%)
Hazard ratio <sup>a</sup>		0.68
95% CI		(0.56, 0.82)
p-value		$p < 0.0001$
Median (95% CI) months	NR (38.67, NR)	24.87 (16.62, 35.12)
<b>Recurrence-free survival with minimum follow-up 48 months</b>		
Events	212 (46.8%)	253 (55.8%)
Hazard ratio <sup>a</sup>		0.71
95% CI		(0.60, 0.86)
Median (95% CI) months	52.37 (42.51, NR)	24.08 (16.56, 35.09)
Rate (95% CI) at 12 months	70.4 (65.9, 74.4)	60.0 (55.2, 64.5)
Rate (95% CI) at 18 months	65.8 (61.2, 70.0)	53.0 (48.1, 57.6)
Rate (95% CI) at 24 months	62.6 (57.9, 67.0)	50.2 (45.3, 54.8)
Rate (95% CI) at 36 months	57.6 (52.8, 62.1)	44.4 (39.6, 49.1)
Rate (95% CI) at 48 months	51.7 (46.8, 56.3)	41.2 (36.4, 45.9)

	nivolumab (n = 453)	ipilimumab 10 mg/kg (n = 453)
<b>Final pre-specified analysis</b>		
<b>Overall survival with minimum follow-up 48 months</b>		
Events	100 (22.1%)	111 (24.5%)
Hazard ratio <sup>a</sup>	0.87	
95.03% CI	(0.66, 1.14)	
p-value	0.3148	
Median (95% CI) months	Not Reached	Not Reached
Rate (95% CI) at 12 months	96.2 (93.9, 97.6)	95.3 (92.8, 96.9)
Rate (95% CI) at 18 months	91.9 (88.9, 94.1)	91.8 (88.8, 94.0)
Rate (95% CI) at 24 months	88.0 (84.6, 90.7)	87.8 (84.4, 90.6)
Rate (95% CI) at 36 months	81.7 (77.8, 85.1)	81.6 (77.6, 85.0)
Rate (95% CI) at 48 months	77.9 (73.7, 81.5)	76.6 (72.2, 80.3)

<sup>a</sup> Derived from a stratified proportional hazards model.

With a minimum follow-up of 36 months, the trial demonstrated a statistically significant improvement in RFS for patients randomised to the nivolumab arm compared with the ipilimumab 10 mg/kg arm. RFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF status, and stage of disease. With a minimum follow up of 48 months, shown in [Figure 9](#), the trial continued to demonstrate improvement in RFS in the nivolumab arm compared with the ipilimumab arm. RFS benefit was sustained across all subgroups.

**Figure 9: Recurrence-free survival (CA209238)**



Number of subjects at risk

Nivolumab

453 395 354 332 311 293 283 271 262 250 245 240 233 224 218 206 147 37 11 0

Ipilimumab

453 366 316 273 253 234 220 208 201 191 185 177 171 168 163 154 113 32 10 0

---△--- Nivolumab —○— Ipilimumab

Nivolumab	453	450	447	438	427	416	405	388	383	373	366	359	350	341	337	332	324	237	45	1	0
Ipilimumab	453	447	442	430	416	407	395	382	373	363	350	345	340	333	322	316	315	218	40	0	0

With a minimum follow-up of 48 months, shown in Figure 10, median OS was not reached in either group (HR = 0.87, 95.03% CI: 0.66, 1.14; p-value: 0.3148). The overall survival data are confounded by the effects of effective subsequent anti-cancer therapies. Subsequent systemic therapy was received by 33% and 42% of patients in the nivolumab and ipilimumab arms, respectively. Subsequent immunotherapy (including anti-PD1 therapy, anti-CTLA-4 antibody, or other immunotherapy) was received by 23% and 34% of patients in the nivolumab and ipilimumab arms, respectively.

### *Non-small cell lung cancer*

*Randomised, open-label, phase 3 study of nivolumab in combination with platinum-based chemotherapy vs. platinum-based chemotherapy (CA209816)*

Approved v2400 930038243 25.0

tumours were resectable, histologically confirmed Stage IB ( $\geq 4$  cm), II, or IIIA NSCLC (per the 7<sup>th</sup> edition AJCC/Union for International Cancer Control (UICC) staging criteria).

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of a patient population with stage II-IIIa disease according to the 7<sup>th</sup> edition AJCC/UICC staging criteria: any patient with a tumour size  $\geq 5$  cm; any patient with N1 or N2 disease (regardless of primary tumour size); patients with multiple tumour nodules in either the same lobe or different ipsilateral lobes; patients with tumours that are invasive of thoracic structures (directly invade visceral pleura, parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus; or tumours that are associated with atelectasis or obstructive pneumonitis that extends to the hilar region or involves the entire lung.

The study did not include patients who had N2 status with tumours also invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

Patients with unresectable or metastatic NSCLC, known EGFR mutations or ALK translocations (testing for EGFR mutations or ALK translocations was not mandatory at study entry), Grade 2 or greater peripheral neuropathy, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Randomisation was stratified by tumour PD-L1 expression level ( $\geq 1\%$  vs.  $< 1\%$  or non-quantifiable), disease stage (IB/II vs. IIIa), and gender (male vs. female). Patients were enrolled regardless of their tumour PD-L1 status. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

A total of 358 patients were randomised to receive either nivolumab in combination with platinum-based chemotherapy (n = 179) or platinum-based chemotherapy (n = 179). Patients in the nivolumab in combination with chemotherapy arm received nivolumab 360 mg administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for up to 3 cycles. Patients in the chemotherapy arm received platinum-based chemotherapy administered every 3 weeks for up to 3 cycles. Platinum-based chemotherapy consisted of investigator's choice of paclitaxel 175 mg/m<sup>2</sup> or 200 mg/m<sup>2</sup> and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> (non-squamous histology); or gemcitabine 1000 mg/m<sup>2</sup> or 1250 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> (squamous histology). In the chemotherapy arm, two additional treatment regimen options included vinorelbine 25 mg/m<sup>2</sup> or 30 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup>; or docetaxel 60 mg/m<sup>2</sup> or 75 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> (any histology).

Tumour assessments were performed at baseline, within 14 days of surgery, every 12 weeks after surgery for 2 years, then every 6 months for 3 years, and every year for 5 years until disease recurrence or progression. The primary efficacy outcome measures were event-free survival (EFS) based on BICR assessment and pathological complete response rate (pCR) by blinded-independent pathology review (BIPR). OS was a key secondary efficacy outcome measure and exploratory endpoints included feasibility of surgery.

Baseline characteristics in the ITT population were generally balanced across treatment groups. The median age was 65 years (range: 34-84) with 51% of patients  $\geq 65$  years and 7% of patients  $\geq 75$  years; 50% of patients were Asian, 47% were white, and 71% were male. Baseline ECOG performance status was 0 (67%) or 1 (33%); 50% of patients with PD-L1  $\geq 1\%$  and 43% with PD-L1  $< 1\%$ ; 5% had Stage IB, 17% had Stage IIA, 13% had Stage IIB, and 64% had Stage IIIa disease; 51% had squamous and 49% had non-squamous histology; and 89% were former/current smokers. Definitive surgery was performed on 83% of the patients in the nivolumab in combination with chemotherapy arm and on 75% of the patients in the chemotherapy arm. Adjuvant systemic treatment was received by 14.8% of patients in the nivolumab in combination with chemotherapy arm and by 25% of patients in the chemotherapy arm.



At the final pCR analysis and pre-specified interim EFS analysis (minimum follow-up 21 months), in all randomised patients, a statistically significant improvement was demonstrated in pCR and EFS for patients randomised to nivolumab in combination with chemotherapy as compared to chemotherapy alone. The pCR response rate was 24% in the nivolumab in combination with chemotherapy arm and 2.2% in the chemotherapy arm (difference of pCR 21.6, 99% CI: 13.0, 30.3; odds ratio of pCR 13.9, 99% CI: 3.49, 55.75; stratified p-value < 0.0001). Median EFS was 31.6 months in the nivolumab in combination with chemotherapy arm and 20.8 months in the chemotherapy arm (HR = 0.63, 97.38% CI: 0.43, 0.91; stratified log-rank p-value 0.0052). The HR for OS was 0.57 (99.67% CI: 0.30, 1.07) for nivolumab in combination with chemotherapy vs. chemotherapy.

***Exploratory subgroup analysis by tumour PD-L1 expression and disease stage***

The key efficacy results for the subgroup of patients with tumour PD-L1 expression  $\geq 1\%$  and disease stage II-IIIa from an exploratory analysis with a minimum follow-up of 32.9 months are summarized in Table 15.

**Table 15: Efficacy results in patients with tumour PD-L1  $\geq 1\%$  and stage II-IIIa disease\* (CA209816)**

	nivolumab + chemotherapy (n = 81)	chemotherapy (n = 86)
<b>Event-free survival per BICR</b>		
Events	22 (27.2%)	39 (45.3%)
Hazard ratio <sup>a</sup> (95% CI)	0.49 (0.29, 0.83)	
Median (months) <sup>b</sup> (95% CI)	NR (44.42, NR)	26.71 (13.40, NR)
<b>Pathologic complete response per BIPR</b>		
Responses	26 (32.1%)	2 (2.3%)
95% CI <sup>c</sup>	(22.2, 43.4)	(0.3, 8.1)
Difference of pCR (95% CI) <sup>d</sup>	29.8% (19.0, 40.7)	

<sup>a</sup> Based on an unstratified Cox proportional hazards model.

<sup>b</sup> Kaplan-Meier estimate.

<sup>c</sup> Based on Clopper and Pearson method.

<sup>d</sup> Two-sided 95% confidence interval for unweighted difference was calculated using Newcombe method.

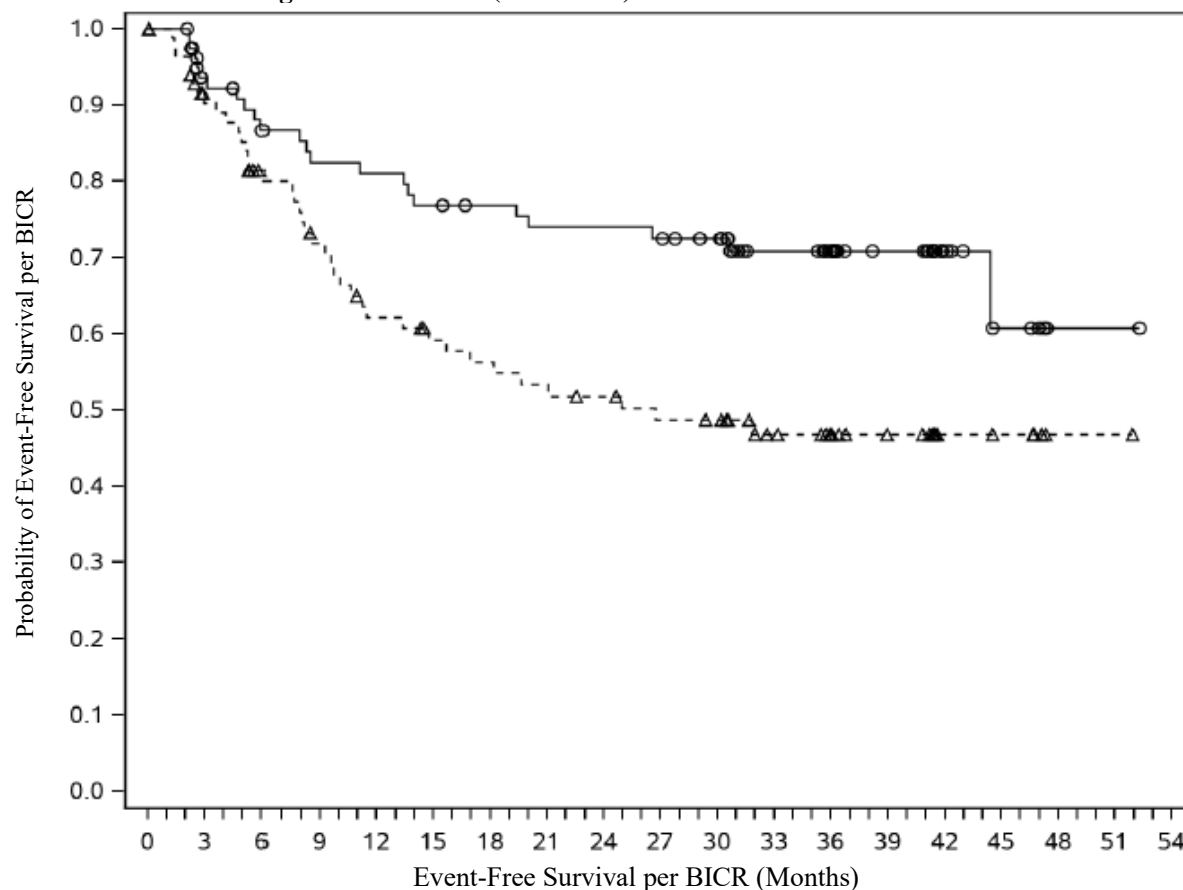
\* 7<sup>th</sup> edition AJCC/UICC staging criteria.

Minimum follow-up for EFS was 32.9 months, data cut-off: 06-Sep-2022

pCR data cut-off: 28-Jul-2020

The Kaplan-Meier curves for EFS for the subgroup of patients with tumour PD-L1 expression  $\geq 1\%$  and stage II-IIIa disease, with a minimum follow-up of 32.9 months, are shown in [Figure 11](#).

**Figure 11: Kaplan-Meier curves of EFS in patients with tumour PD-L1  $\geq 1\%$  and stage II-IIIa disease (CA209816)**



Number of Subjects at Risk

Nivolumab + chemotherapy

81 69 62 59 58 55 53 51 51 50 47 37 32 21 10 5 1 1 0

Chemotherapy

86 71 60 52 44 40 38 36 34 31 30 23 18 14 7 6 1 1 0

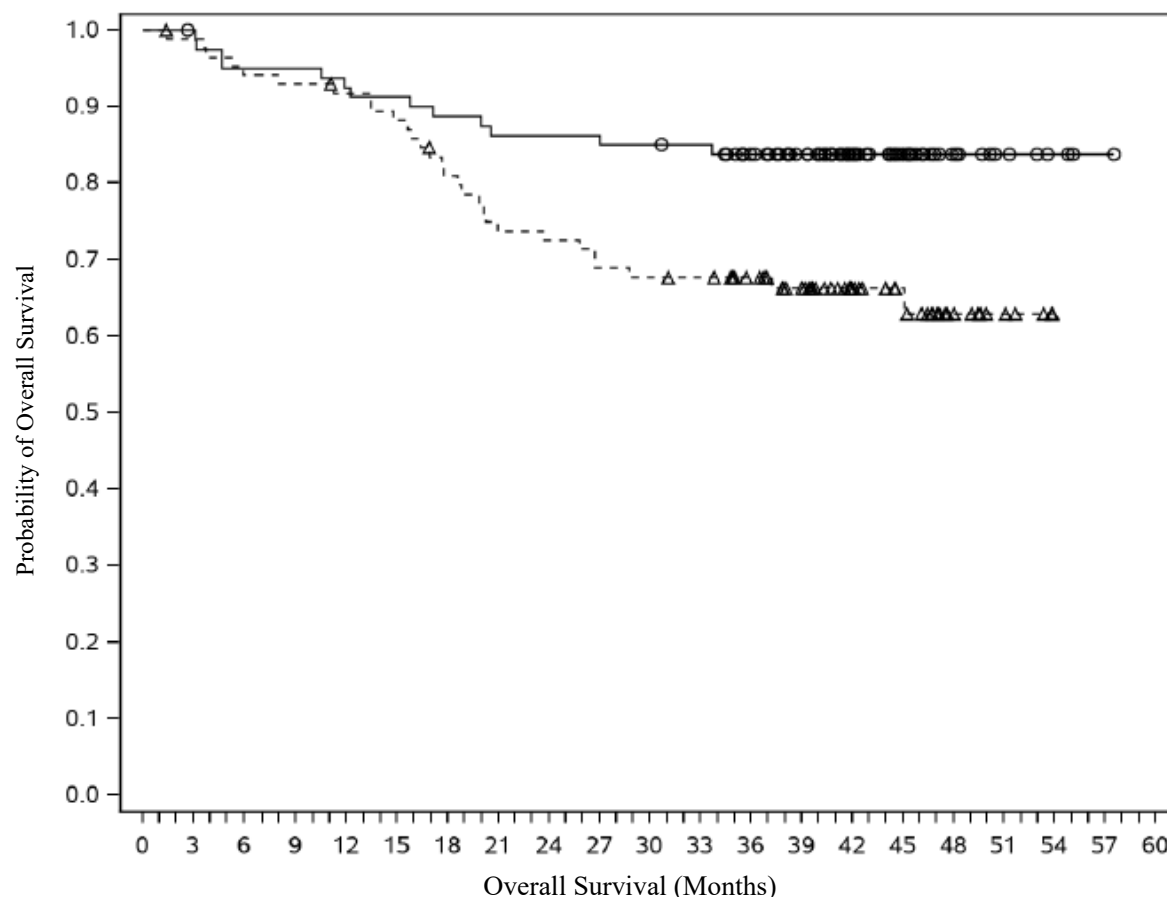
—○— Nivolumab + chemotherapy (events: 22/81), median and 95% CI: NR (44.42, NR)

---△--- Chemotherapy (events: 39/86), median and 95% CI: 26.71 (13.40, NR)

Based on data cut-off: 06-Sep-2022, minimum follow-up of 32.9 months

At the time of the updated EFS analysis, an interim analysis for OS was performed (minimum follow-up of 32.9 months). The exploratory, descriptive HR for OS in patients with tumour PD-L1 expression  $\geq 1\%$  and stage II-IIIa disease was 0.43 (95% CI: 0.22, 0.83) for nivolumab in combination with chemotherapy vs. chemotherapy. The Kaplan-Meier curves for OS for the subgroup of patients with tumour PD-L1 expression  $\geq 1\%$  and stage II-IIIa disease, with a minimum follow-up of 32.9 months, are shown in [Figure 12](#).

**Figure 12: Kaplan-Meier curves of OS in patients with tumour PD-L1  $\geq 1\%$  and stage II-IIIa disease (CA209816)**



Number of Subjects at Risk

Nivolumab + chemotherapy

81 80 76 76 74 73 71 69 69 69 68 67 59 50 33 22 11 6 3 1 0

Chemotherapy

86 84 80 79 77 74 67 61 60 57 56 55 50 41 27 20 10 5 0 0 0

—○— Nivolumab + chemotherapy (events: 13/81), median and 95% CI: NR

---△--- Chemotherapy (events: 29/86), median and 95% CI: NR

Based on data cut-off: 06-Sep-2022, minimum follow-up of 32.9 months

### First-line treatment of NSCLC

#### Randomised phase 3 study of nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy vs. 4 cycles of platinum-based chemotherapy (CA2099LA)

The safety and efficacy of nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-based chemotherapy were evaluated in a phase 3, randomised, open-label study (CA2099LA). The study included patients (18 years or older) with histologically confirmed non-squamous or squamous Stage IV or recurrent NSCLC (per the 7<sup>th</sup> International Association for the Study of Lung Cancer classification), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors). Patients were enrolled regardless of their tumour PD-L1 status.

Patients with sensitising EGFR mutations or ALK translocations, active (untreated) brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents. Randomisation was

stratified by histology (squamous vs non-squamous), tumour PD-L1 expression level ( $\geq 1\%$  vs  $< 1\%$ ), and gender (male vs female).

A total of 719 patients were randomised to receive either nivolumab in combination with ipilimumab and platinum-based chemotherapy (n = 361) or platinum-based chemotherapy (n = 358). Patients in the nivolumab in combination with ipilimumab and platinum-based chemotherapy arm received nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-based chemotherapy administered every 3 weeks for 2 cycles. Patients in the chemotherapy arm received platinum-based chemotherapy administered every 3 weeks for 4 cycles; non-squamous patients could receive optional pemetrexed maintenance therapy.

Platinum-based chemotherapy consisted of carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m<sup>2</sup>; or cisplatin 75 mg/m<sup>2</sup> and pemetrexed 500 mg/m<sup>2</sup> for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m<sup>2</sup> for squamous NSCLC.

Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to ipilimumab were permitted to continue nivolumab monotherapy. Tumour assessments were performed every 6 weeks after first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued.

CA2099LA baseline characteristics were generally balanced across all treatment groups. The median age was 65 years (range: 26-86) with 51%  $\geq 65$  years of age and 10%  $\geq 75$  years of age. The majority of patients were white (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% of patients with PD-L1  $\geq 1\%$  and 37% with PD-L1  $< 1\%$ , 31% had squamous and 69% had non-squamous histology, 17% had brain metastases, and 86% were former/current smokers. No patients received prior immunotherapy.

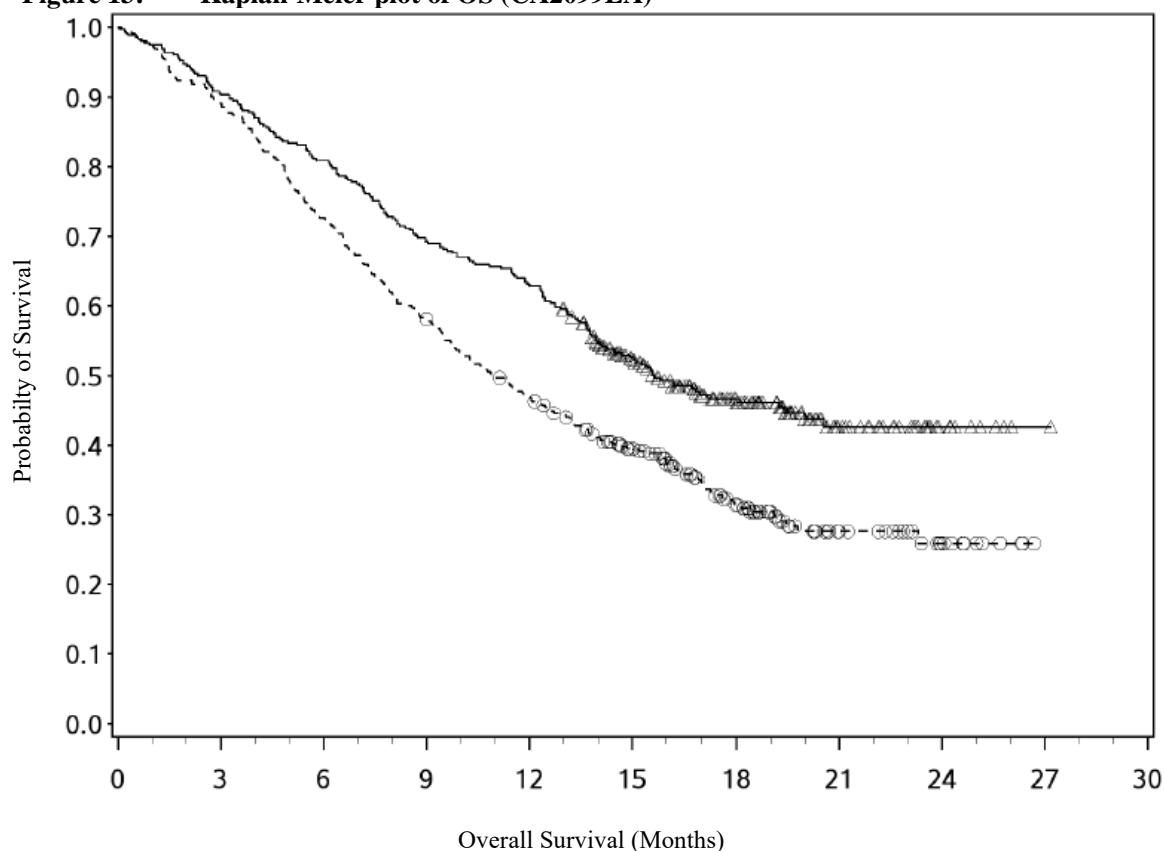
CA2099LA primary efficacy outcome measure was OS. Additional efficacy endpoints were PFS, ORR, and duration of response as assessed by BICR.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR for patients randomised to nivolumab in combination with ipilimumab and platinum-based chemotherapy as compared to platinum-based chemotherapy alone at the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis). Minimum follow-up for OS was 8.1 months.

Efficacy results are shown in [Figure 13](#) (updated OS analysis with a minimum follow-up of 12.7 months) and [Table 16](#) (primary analysis with a minimum follow-up of 8.1 months).

An updated efficacy analysis was performed when all patients had a minimum follow-up of 12.7 months (see [Figure 13](#)). At the time of this analysis, the hazard ratio for OS was 0.66 (95% CI: 0.55, 0.80) and the hazard ratio for PFS was 0.68 (95% CI: 0.57, 0.82).

**Figure 13: Kaplan-Meier plot of OS (CA2099LA)**



**Table 16: Efficacy results (CA2099LA)**

	nivolumab + ipilimumab + chemotherapy (n = 361)	chemotherapy (n = 358)
<b>Overall survival</b>		
Events	156 (43.2%)	195 (54.5%)
Hazard ratio (96.71% CI) <sup>a</sup>	0.69 (0.55, 0.87)	
Stratified log-rank p-value <sup>b</sup>	0.0006	
Median (months) (95% CI)	14.1 (13.24, 16.16)	10.7 (9.46, 12.45)
Rate (95% CI) at 6 months	80.9 (76.4,84.6)	72.3 (67.4,76.7)

	nivolumab + ipilimumab + chemotherapy (n = 361)	chemotherapy (n = 358)
<b>Progression-free survival</b>		
Events	232 (64.3%)	249 (69.6%)
Hazard ratio (97.48% CI) <sup>a</sup>	0.70 (0.57, 0.86)	
Stratified log-rank p-value <sup>c</sup>	0.0001	
Median (months) <sup>d</sup> (95% CI)	6.83 (5.55, 7.66)	4.96 (4.27, 5.55)
Rate (95% CI) at 6 months	51.7 (46.2, 56.8)	35.9 (30.5, 41.3)
<b>Overall response rate<sup>e</sup></b>		
(95% CI)	136 (37.7%) (32.7, 42.9)	90 (25.1%) (20.7, 30.0)
Stratified CMH test p-value <sup>f</sup>	0.0003	
Complete response (CR)	7 (1.9%)	3 (0.8%)
Partial response (PR)	129 (35.7%)	87 (24.3%)
<b>Duration of response</b>		
Median (months) (95% CI) <sup>d</sup>	10.02 (8.21, 13.01)	5.09 (4.34, 7.00)
% with duration ≥ 6 months <sup>g</sup>	74	41

<sup>a</sup> Based on a stratified Cox proportional hazard model.

<sup>b</sup> p-value is compared with the allocated alpha of 0.0329 for this interim analysis.

<sup>c</sup> p-value is compared with the allocated alpha of 0.0252 for this interim analysis.

<sup>d</sup> Kaplan-Meier estimate.

<sup>e</sup> Proportion with complete or partial response; CI based on the Clopper and Pearson Method.

<sup>f</sup> p-value is compared with the allocated alpha of 0.025 for this interim analysis.

<sup>g</sup> Based on Kaplan-Meier estimates of duration of response.

CMH = Cochran-Mantel-Haenszel

Subsequent systemic therapy was received by 28.8% and 41.1% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA4) was received by 3.9% and 27.9% of patients in the combination and chemotherapy arms, respectively.

In study CA2099LA, subgroup descriptive analysis relative to chemotherapy, OS benefit was shown in patients treated with nivolumab in combination with ipilimumab and chemotherapy with squamous histology (HR [95% CI] 0.65 [0.46, 0.93], n = 227) and in patients with non-squamous histology (HR [95% CI] 0.72 [0.55, 0.93], n = 492).

**Table 17** summarises efficacy results of OS, PFS, and ORR by tumour PD-L1 expression in pre-specified subgroup analyses.

**Table 17: Efficacy results by tumour PD-L1 expression (CA2099LA)**

	nivolumab + ipilimumab + chemo- therapy	chemo- therapy	nivolumab + ipilimumab + chemo- therapy	chemo- therapy	nivolumab + ipilimumab + chemo- therapy	chemo- therapy	nivolumab + ipilimumab + chemo- therapy	chemo- therapy
	PD-L1 < 1% (n = 264)		PD-L1 ≥ 1% (n = 406)		PD-L1 ≥ 1% to 49% (n = 233)		PD-L1 ≥ 50% (n = 173)	
<b>OS hazard ratio (95% CI)<sup>a</sup></b>	0.65 (0.46, 0.92)		0.67 (0.51, 0.89)		0.69 (0.48, 0.98)		0.64 (0.41, 1.02)	
<b>PFS hazard ratio (95% CI)<sup>a</sup></b>	0.77 (0.57, 1.03)		0.67 (0.53, 0.85)		0.71 (0.52, 0.97)		0.59 (0.40, 0.86)	
<b>ORR %</b>	31.1	20.9	41.9	27.6	37.8	24.5	48.7	30.9

<sup>a</sup> Hazard ratio based on unstratified Cox proportional hazards model.

A total of 70 NSCLC patients aged ≥ 75 years were enrolled in study CA2099LA (37 patients in the nivolumab in combination with ipilimumab and chemotherapy arm and 33 patients in the chemotherapy arm). A HR of 1.36 (95% CI: 0.74, 2.52) in OS and a HR of 1.12 (95% CI: 0.64, 1.96) in PFS was observed for nivolumab in combination with ipilimumab and chemotherapy vs. chemotherapy within this study subgroup. ORR was 27.0% in the nivolumab in combination with ipilimumab and chemotherapy arm and 15.2% in the chemotherapy arm. Forty-three percent of patients aged ≥ 75 years discontinued treatment with nivolumab in combination with ipilimumab and chemotherapy. Efficacy and safety data of nivolumab in combination with ipilimumab and chemotherapy are limited in this patient population.

In a subgroup analysis, a reduced survival benefit for nivolumab in combination with ipilimumab and chemotherapy compared to chemotherapy was observed in patients who were never smokers. However, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

#### Treatment of NSCLC after prior chemotherapy Squamous NSCLC

##### Randomised phase 3 study vs. docetaxel (CA209017)

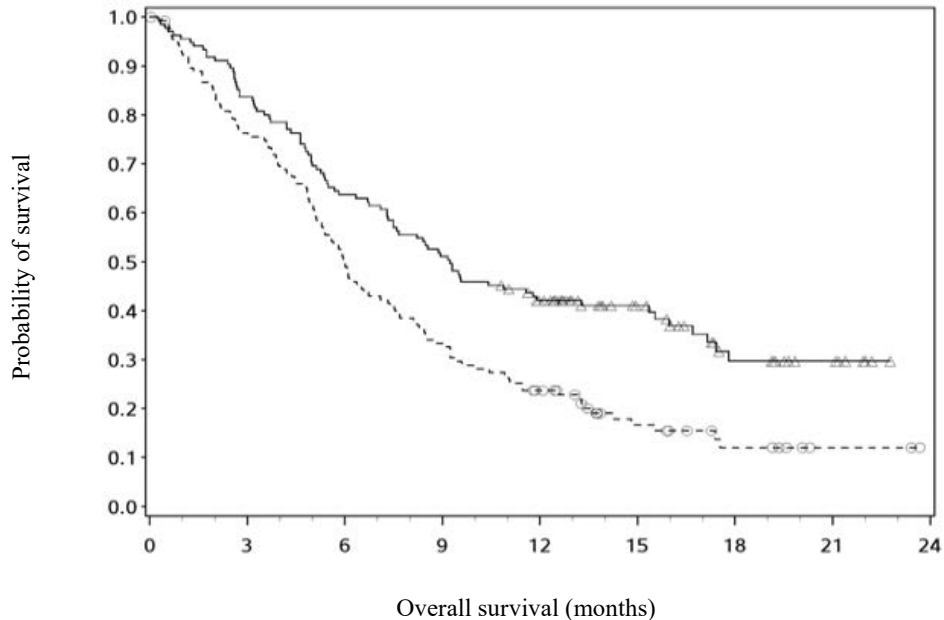
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209017). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an ECOG performance status score of 0 or 1. Patients were enrolled regardless of their tumour PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active brain metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (n = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m<sup>2</sup> every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to the RECIST, version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. In addition, symptom improvement and overall health status were assessed using the Lung cancer symptom score (LCSS) average symptom burden index and the EQ-5D Visual Analogue Scale (EQ-VAS), respectively.

Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 39-85) with 44%  $\geq$  65 years of age and 11%  $\geq$  75 years of age. The majority of patients were white (93%) and male (76%). Thirty-one percent had progressive disease reported as the best response to their most recent prior regimen and 45% received nivolumab within 3 months of completing their most recent prior regimen. Baseline ECOG performance status score was 0 (24%) or 1 (76%).

The Kaplan-Meier curves for OS are shown in Figure 14.

**Figure 14: Kaplan-Meier curves of OS (CA209017)**



Number of subjects at risk								
Nivolumab 3 mg/kg								
135	113	86	69	52	31	15	7	0
Docetaxel								
137	103	68	45	30	14	7	2	0

—△— Nivolumab 3 mg/kg (events: 86/135), median and 95% CI: 9.23 (7.33, 13.27)  
---○--- Docetaxel (events: 113/137), median and 95% CI: 6.01 (5.13, 7.33)

The observed OS benefit was consistently demonstrated across subgroups of patients. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 1%, 5% or 10%). However, the role of this biomarker (tumour PD-L1 expression) has not been fully elucidated. With a minimum of 62.6 months follow-up, OS benefit remains consistently demonstrated across subgroups.

Study CA209017 included a limited number of patients  $\geq$  75 years (11 in the nivolumab group and 18 in the docetaxel group). Nivolumab showed numerically less effect on OS (HR 1.85; 95% CI: 0.76, 4.51), PFS (HR = 1.76; 95%-CI: 0.77, 4.05) and ORR (9.1% vs. 16.7%). Because of the small sample size, no definitive conclusions can be drawn from these data.

Efficacy results are shown in [Table 18](#).



**Table 18: Efficacy results (CA209017)**

	<b>nivolumab (n = 135)</b>	<b>docetaxel (n = 137)</b>
<b>Primary analysis</b>		
Minimum follow-up: 10.6 months		
<b>Overall survival</b>		
Events	86 (63.7%)	113 (82.5%)
Hazard ratio		0.59
96.85% CI		(0.43, 0.81)
p-value		0.0002
Median (95% CI) months	9.23 (7.33, 13.27)	6.01 (5.13, 7.33)
Rate (95% CI) at 12 months	42.1 (33.7, 50.3)	23.7 (16.9, 31.1)
<b>Confirmed objective response</b>		
(95% CI)	27 (20.0%) (13.6, 27.7)	12 (8.8%) (4.6, 14.8)
Odds ratio (95% CI)		2.64 (1.27, 5.49)
p-value		0.0083
Complete response (CR)	1 (0.7%)	0
Partial response (PR)	26 (19.3%)	12 (8.8%)
Stable disease (SD)	39 (28.9%)	47 (34.3%)
<b>Median duration of response</b>		
Months (range)	Not reached (2.9-20.5 <sup>+</sup> )	8.4 (1.4 <sup>+</sup> -15.2 <sup>+</sup> )
<b>Median time to response</b>		
Months (range)	2.2 (1.6-11.8)	2.1 (1.8-9.5)
<b>Progression-free survival</b>		
Events	105 (77.8%)	122 (89.1%)
Hazard ratio		0.62
95% CI		(0.47, 0.81)
p-value		< 0.0004
Median (95% CI) (months)	3.48 (2.14, 4.86)	2.83 (2.10, 3.52)
Rate (95% CI) at 12 months	20.8 (14.0, 28.4)	6.4 (2.9, 11.8)
<b>Updated analysis</b>		
Minimum follow-up: 24.2 months		
<b>Overall survival<sup>a</sup></b>		
Events	110 (81.4%)	128 (93.4%)
Hazard ratio		0.62
95% CI		(0.47, 0.80)
Rate (95% CI) at 24 months	22.9 (16.2, 30.3)	8 (4.3, 13.3)
<b>Confirmed objective response</b>		
(95% CI)	20.0% (13.6, 27.7)	8.8% (4.6, 14.8)
<b>Median duration of response</b>		
Months (range)	25.2 (2.9-30.4)	8.4 (1.4 <sup>+</sup> -18.0 <sup>+</sup> )

	nivolumab (n = 135)	docetaxel (n = 137)
<b>Progression-free survival</b>		
Rate (95% CI) at 24 months	15.6 (9.7, 22.7)	All patients had either progressed, were censored, or lost to follow-up
<b>Updated analysis</b>		
Minimum follow-up: 62.6 months		
<b>Overall survival<sup>a</sup></b>		
Events	118 (87.4%)	133 (97.1%)
Hazard ratio		0.62
95% CI		(0.48, 0.79)
Rate (95% CI) at 60 months	12.3 (7.4, 18.5)	3.6 (1.4, 7.8)
<b>Confirmed objective response</b>		
(95% CI)	20.0% (13.6, 27.7)	8.8% (4.6, 14.8)
<b>Median duration of response</b>		
Months (range)	25.2 (2.9-70.6 <sup>+</sup> )	7.5 (0.0 <sup>+</sup> -18.0 <sup>+</sup> )
<b>Progression-free survival</b>		
Rate (95% CI) at 60 months	9.4 (4.8, 15.8)	All patients had either progressed, were censored, or lost to follow-up
<sup>a</sup> Six patients (4%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.		
<sup>++</sup> Denotes a censored observation.		

The rate of disease-related symptom improvement, as measured by LCSS, was similar between the nivolumab group (18.5%) and the docetaxel group (21.2%). The average EQ-VAS increased over time for both treatment groups, indicating better overall health status for patients remaining on treatment.

#### Single-arm phase 2 study (CA209063)

Study CA209063 was a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous NSCLC after two or more lines of therapy; otherwise similar inclusion criteria as study CA209017 were applied. Nivolumab 3 mg/kg showed an ORR of 14.5% (95% CI: 8.7,22.2%), a median OS of 8.21 months (95% CI: 6.05,10.9), and a median PFS of 1.87 months (95% CI 1.77,3.15). The PFS was measured by RECIST, version 1.1. The estimated 1-year survival rate was 41%.

#### Single-arm phase 2 study (CA209171)

Study CA209171 was a single-arm, open label study of nivolumab monotherapy in patients with previously treated advanced or metastatic squamous NSCLC. Safety was the primary endpoint and efficacy was a secondary endpoint. Of the 811 treated patients, 103 (13%) had an ECOG performance score of 2, 686 (85%) were < 75 years old and 125 (15%) were ≥ 75 years old. No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. Efficacy results based on investigator-assessed ORR are presented in Table 19 below.

**Table 19: ORR based on response evaluable patients – total and by subgroup (CA209171)**

Results	Total	ECOG PS 2	< 75 years	≥ 75 years
N responders/ N evaluable <sup>a</sup> (%)	66/671 (9.8)	1/64 (6.1)	55/568 (9.7)	11/103 (10.7)
95% CI <sup>b</sup>	(7.7, 12.3)	(0.0, 8.4)	(7.4, 12.4)	(5.5, 18.3)

<sup>a</sup> includes confirmed and unconfirmed responses, scans were mandatory only at week 8/9 and week 52.

<sup>b</sup> CR+PR, confidence interval based on the Clopper and Pearson method

## Non-squamous NSCLC

### Randomised phase 3 study vs. docetaxel (CA209057)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic non-squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209057). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen which may have included maintenance therapy and who had an ECOG performance status score of 0 or 1. An additional line of TKI therapy was allowed for patients with known EGFR mutation or ALK translocation. Patients were enrolled regardless of their tumour PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active brain metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

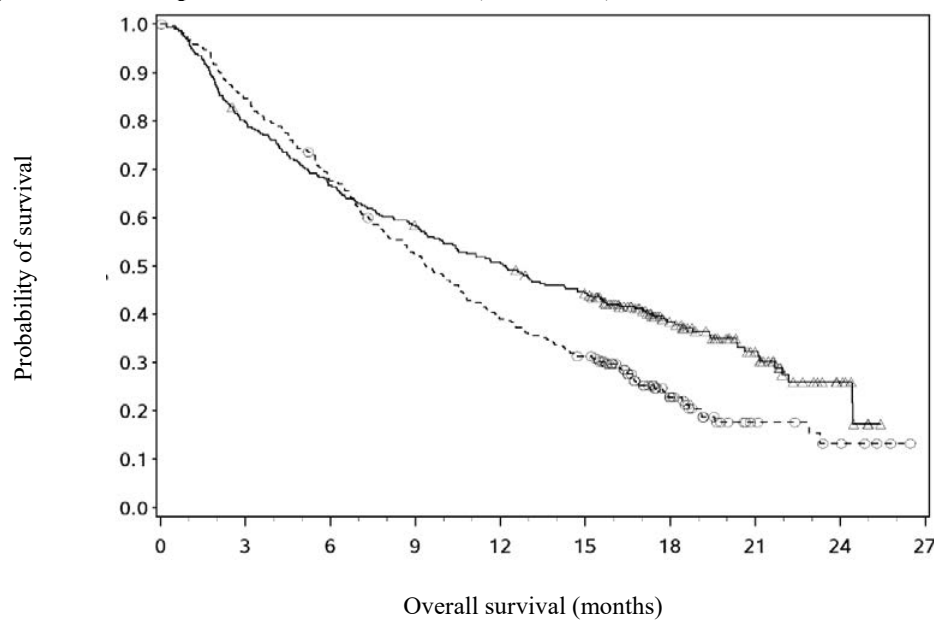
A total of 582 patients were randomised to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks (n = 292) or docetaxel 75 mg/m<sup>2</sup> every 3 weeks (n = 290). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments were conducted according to the RECIST version 1.1. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. Additional prespecified subgroup analyses were conducted to evaluate the efficacy of tumour PD-L1 expression at predefined levels of 1%, 5% and 10%. Assessment according to discrete PD-L1 expression intervals were not included in the prespecified analyses due to the small sample sizes within the intervals.

Pre-study tumour tissue specimens were systematically collected prior to randomisation in order to conduct pre-planned analyses of efficacy according to tumour PD-L1 expression. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

The median age was 62 years (range: 21 to 85) with 34% ≥ 65 years of age and 7% ≥ 75 years of age. The majority of patients were white (92%) and male (55%). Baseline ECOG performance status was 0 (31%) or 1 (69%). Seventy-nine percent of patients were former/current smokers.

The Kaplan-Meier curves for OS are shown in [Figure 15](#).

**Figure 15: Kaplan-Meier curves of OS (CA209057)**



The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 20.

**Table 20: Efficacy results (CA209057)**

	nivolumab (n = 292)	docetaxel (n = 290)
<b>Prespecified interim analysis</b>		
Minimum follow-up: 13.2 months		
<b>Overall survival</b>		
Events	190 (65.1%)	223 (76.9%)
Hazard ratio <sup>a</sup> (95.92% CI)	0.73 (0.59, 0.89)	
p-value <sup>b</sup>	0.0015	
Median (95% CI) months	12.19 (9.66, 14.98)	9.36 (8.05, 10.68)
Rate (95% CI) at 12 months	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)

	<b>nivolumab (n = 292)</b>	<b>docetaxel (n = 290)</b>
<b>Confirmed objective response</b>	56 (19.2%)	36 (12.4%)
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Odds ratio (95% CI)	1.68 (1.07, 2.64)	
p-value	0.0246	
Complete response (CR)	4 (1.4%)	1 (0.3%)
Partial response (PR)	52 (17.8%)	35 (12.1%)
Stable disease (SD)	74 (25.3%)	122 (42.1%)
<b>Median duration of response</b>		
Months (range)	17.15 (1.8-22.6 <sup>+</sup> )	5.55 (1.2 <sup>+</sup> -15.2 <sup>+</sup> )
<b>Median time to response</b>		
Months (range)	2.10 (1.2-8.6)	2.61 (1.4-6.3)
<b>Progression-free survival</b>		
Events	234 (80.1%)	245 (84.5%)
Hazard ratio	0.92	
95% CI	(0.77, 1.11)	
p-value	0.3932	
Median (95% CI) (months)	2.33 (2.17, 3.32)	4.21 (3.45, 4.86)
Rate (95% CI) at 12 months	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)
<b>Updated analysis</b>		
Minimum follow-up: 24.2 months		
<b>Overall survival<sup>c</sup></b>		
Events	228 (78.1%)	247 (85.1%)
Hazard ratio <sup>a</sup>	0.75	
(95% CI)	(0.63, 0.91)	
Rate (95% CI) at 24 months	28.7 (23.6, 34.0)	15.8 (11.9, 20.3)
<b>Confirmed objective response</b>	19.2%	12.4%
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
<b>Median duration of response</b>		
Months (range)	17.2 (1.8-33.7 <sup>+</sup> )	5.6 (1.2 <sup>+</sup> -16.8)
<b>Progression-free survival</b>		
Rate (95% CI) at 24 months	11.9 (8.3, 16.2)	1.0 (0.2, 3.3)

	nivolumab (n = 292)	docetaxel (n = 290)
<b>Updated analysis</b>		
Minimum follow-up: 62.7 months		
<b>Overall survival<sup>d</sup></b>		
Events	250 (85.6%)	279 (96.2%)
Hazard ratio <sup>a</sup> (95% CI)		0.70 (0.58, 0.83)
Rate (95% CI) at 60 months	14.0 (10.2, 18.3)	2.1 (0.9, 4.4)
<b>Confirmed objective response</b>		
(95% CI)	19.5% (15.1, 24.5)	12.4% (8.8, 16.8)
<b>Median duration of response</b>		
Months (range)	17.2 (1.8-70.4 <sup>+</sup> )	5.6 (0.0 <sup>+</sup> -33.4)
<b>Progression-free survival</b>		
Rate (95% CI) at 60 months	7.5 (4.5, 11.4)	All patients had either progressed, were censored, or lost to follow-up
<sup>a</sup>	Derived from a stratified proportional hazards model.	
<sup>b</sup>	P-value is derived from a log-rank test stratified by prior maintenance therapy and line of therapy; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0408.	
<sup>c</sup>	Sixteen patients (6%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.	
<sup>d</sup>	Seventeen patients (6%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.	
<sup>+,??</sup>	Denotes a censored observation.	

Quantifiable tumour PD-L1 expression was measured in 79% of patients in the nivolumab group and 77% of patients in the docetaxel group. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. docetaxel) at each of the predefined tumour PD-L1 expression levels of  $\geq 1\%$  (53% vs. 55%),  $\geq 5\%$  (41% vs. 38%), or  $\geq 10\%$  (37% vs. 35%).

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to docetaxel, whereas survival was similar to docetaxel in patients with low or no tumour PD-L1 expression. In terms of ORR, increasing PD-L1 expression was associated with larger ORR. Comparable to the overall population, median duration of response was increased with nivolumab vs. docetaxel for patients with no PD-L1 expression (18.3 months vs. 5.6 months) and for patients with PD-L1 expression (16.0 months vs. 5.6 months).

Table 21 summarises results of ORR and OS by tumour PD-L1 expression.

**Table 21: ORR and OS by tumour PD-L1 expression (CA209057)**

PD-L1 expression	nivolumab	docetaxel	
<b>ORR by tumour PD-L1 expression</b>			
Minimum follow-up: 13.2 months			
			<b>Odds ratio (95% CI)</b>
< 1%	10/108 (9.3%) 95% CI: 4.5, 16.4	15/101 (14.9%) 95% CI: 8.6, 23.3	0.59 (0.22, 1.48)
$\geq 1\%$	38/123 (30.9%) 95% CI: 22.9, 39.9	15/123 (12.2%) 95% CI: 7.0, 19.3	3.22 (1.60, 6.71)
$\geq 1\%$ to < 10% <sup>a</sup>	6/37 (16.2%) 95% CI: 6.2, 32.0	5/44 (11.4%) 95% CI: 3.8, 24.6	1.51 (0.35, 6.85)
$\geq 10\%$ to < 50% <sup>a</sup>	5/20 (25.0%) 95% CI: 8.7, 49.1	7/33 (21.2%) 95% CI: 9.0, 38.9	1.24 (0.26, 5.48)
$\geq 50\%$ <sup>a</sup>	27/66 (40.9%) 95% CI: 29.0, 53.7	3/46 (6.5%) 95% CI: 1.4, 17.9	9.92 (2.68, 54.09)

PD-L1 expression	nivolumab	docetaxel	
<b>OS by tumour PD-L1 expression</b>			
Minimum follow-up: 13.2 months			
	Number of events (number of patients)		Unstratified hazard ratio (95% CI)
< 1%	77 (108)	75 (101)	0.90 (0.66, 1.24)
≥ 1%	68 (123)	93 (123)	0.59 (0.43, 0.82)
≥ 1% to < 10% <sup>a</sup>	27 (37)	30 (44)	1.33 (0.79, 2.24)
≥ 10% to < 50% <sup>a</sup>	11 (20)	26 (33)	0.61 (0.30, 1.23)
≥ 50% <sup>a</sup>	30 (66)	37 (46)	0.32 (0.20, 0.53)
<b>Updated analysis</b>			
Minimum follow-up: 24.2 months			
< 1%	91 (108)	86 (101)	0.91 (0.67, 1.22)
≥ 1%	87 (123)	103 (123)	0.62 (0.47, 0.83)
<b>Updated analysis</b>			
Minimum follow-up: 62.7 months			
< 1%	100 (109)	96 (101)	0.87 (0.66, 1.16)
≥ 1%	96 (122)	119 (123)	0.55 (0.42, 0.73)

<sup>a</sup> Post-hoc analysis; results should be interpreted with caution as the subgroup samples sizes are small and, at the time of the analysis, the PD-L1 IHC 28-8 pharmDx assay was not analytically validated at the 10% or 50% expression levels.

A higher proportion of patients experienced death within the first 3 months in the nivolumab arm (59/292, 20.2%) as compared to the docetaxel arm (44/290, 15.2%). Results of a post-hoc, exploratory multivariate analysis indicated that nivolumab-treated patients with poorer prognostic features and/or aggressive disease when combined with lower (e.g., < 50%) or no tumour PD-L1 expression may be at higher risk of death within the first 3 months.

In subgroup analyses, survival benefit compared to docetaxel was not shown for patients who were never-smokers or whose tumours harboured EGFR activating mutations; however, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

### *Malignant pleural mesothelioma*

#### *Randomised phase 3 study of nivolumab in combination with ipilimumab vs. chemotherapy (CA209743)*

The safety and efficacy of nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks were evaluated in a phase 3, randomised, open-label study (CA209743). The study included patients (18 years or older) with histologically confirmed and previously untreated malignant pleural mesothelioma of epithelioid or non-epithelioid histology, ECOG performance status 0 or 1, and no palliative radiotherapy within 14 days of first study therapy. Patients were enrolled regardless of their tumour PD-L1 status.

Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the trial. Randomisation was stratified by histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and gender (male vs. female).

A total of 605 patients were randomised to receive either nivolumab in combination with ipilimumab (n = 303) or chemotherapy (n = 302). Patients in the nivolumab in combination with ipilimumab arm received nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks in combination with ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years.

Patients in the chemotherapy arm received chemotherapy for up to 6 cycles (each cycle was 21 days). Chemotherapy consisted of cisplatin 75 mg/m<sup>2</sup> and pemetrexed 500 mg/m<sup>2</sup> or carboplatin 5 AUC and pemetrexed 500 mg/m<sup>2</sup>.

Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab monotherapy. Tumour assessments were performed every 6 weeks after first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued.

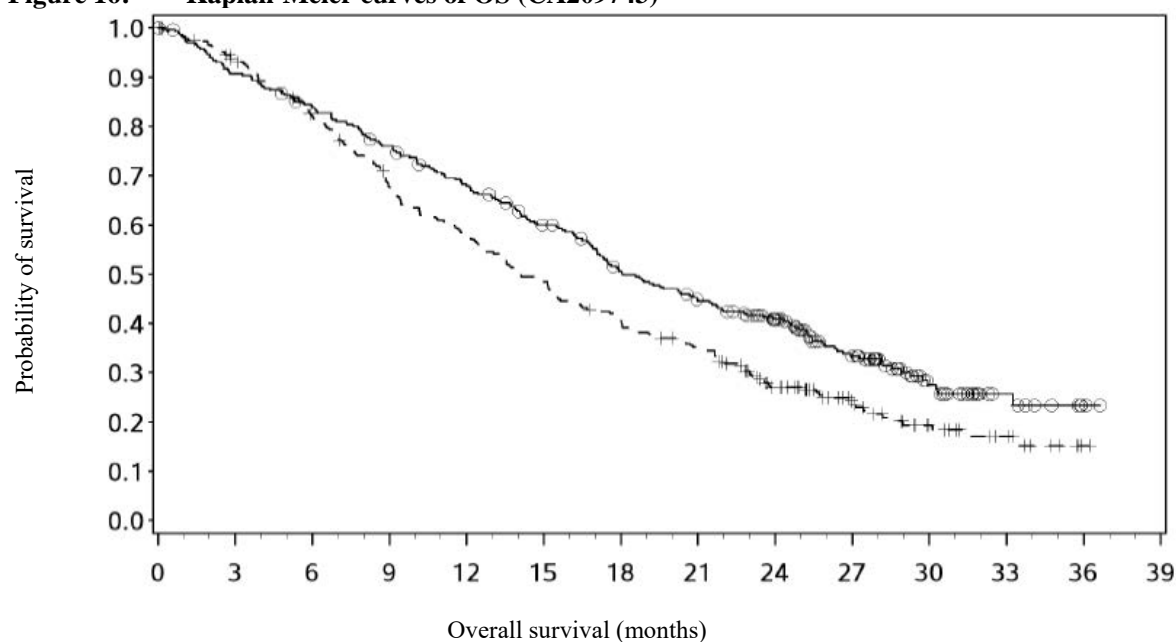
CA209743 baseline characteristics were generally balanced across all treatment groups. The median age was 69 years (range: 25-89) with 72% ≥ 65 years of age and 26% ≥ 75 years of age. The majority of patients were white (85%) and male (77%). Baseline ECOG performance status was 0 (40%) or 1 (60%), 80% of patients with PD-L1 ≥ 1% and 20% with PD-L1 < 1%, 75% had epithelioid and 25% had non-epithelioid histology.

CA209743 primary efficacy outcome measure was OS. Key secondary efficacy endpoints were PFS, ORR, and duration of response as assessed by Blinded Independent Central Review (BICR) utilising modified RECIST criteria for pleural mesothelioma. Descriptive analyses for these secondary endpoints are presented in [Table 22](#).

The study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab in combination with ipilimumab as compared to chemotherapy at the prespecified interim analysis when 419 events were observed (89% of the planned number of events for final analysis). Minimum follow-up for OS was 22 months.

Efficacy results are shown in [Figure 16](#) and [Table 22](#).



**Figure 16: Kaplan-Meier curves of OS (CA209743)****Table 22: Efficacy results (CA209743)**

	nivolumab + ipilimumab (n = 303)	chemotherapy (n = 302)
<b>Overall survival</b>		
Events	200 (66%)	219 (73%)
Hazard ratio (96.6% CI) <sup>a</sup>	0.74 (0.60, 0.91)	
Stratified log-rank p-value <sup>b</sup>	0.002	
Median (months) <sup>c</sup> (95% CI)	18.1 (16.8, 21.5)	14.1 (12.5, 16.2)
Rate (95% CI) at 24 months <sup>c</sup>	41% (35.1, 46.5)	27% (21.9, 32.4)
<b>Progression-free survival</b>		
Events	218 (72%)	209 (69%)
Hazard ratio (95% CI) <sup>a</sup>	1.0 (0.82, 1.21)	
Median (months) <sup>c</sup> (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)

	nivolumab + ipilimumab (n = 303)	chemotherapy (n = 302)
<b>Overall response rate</b>	40%	43%
(95% CI)	(34.1, 45.4)	(37.1, 48.5)
Complete response (CR)	1.7%	0
Partial response (PR)	38%	43%
<b>Duration of response</b>		
Median (months) <sup>c</sup>	11.0	6.7
(95% CI)	(8.1, 16.5)	(5.3, 7.1)

<sup>a</sup> Stratified Cox proportional hazard model.

<sup>b</sup> p-value is compared with the allocated alpha of 0.0345 for this interim analysis.

<sup>c</sup> Kaplan-Meier estimate.

Subsequent systemic therapy was received by 44.2% and 40.7% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA-4) was received by 3.3% and 20.2% of patients in the combination and chemotherapy arms, respectively.

Table 23 summarises efficacy results of OS, PFS, and ORR by histology in prespecified subgroup analyses.

**Table 23: Efficacy results by histology (CA209743)**

	Epithelioid (n = 471)		Non-epithelioid (n = 134)	
	nivolumab + ipilimumab (n = 236)	chemotherapy (n = 235)	nivolumab + ipilimumab (n = 67)	chemotherapy (n = 67)
<b>Overall survival</b>				
Events	157	164	43	55
Hazard ratio (95% CI) <sup>a</sup>	0.85 (0.68, 1.06)		0.46 (0.31, 0.70)	
Median (months) (95% CI)	18.73 (17.05, 21.72)	16.23 (14.09, 19.15)	16.89 (11.83, 25.20)	8.80 (7.62, 11.76)
Rate (95% CI) at 24 months	41.2 (34.7, 47.6)	31.8 (25.7, 38.1)	39.5 (27.5, 51.2)	9.7 (3.8, 18.9)
<b>Progression-free survival</b>				
Hazard ratio (95% CI) <sup>a</sup>	1.14 (0.92, 1.41)		0.58 (0.38, 0.90)	
Median (months) (95% CI)	6.18 (5.49, 7.03)	7.66 (7.03, 8.31)	8.31 (3.84, 11.01)	5.59 (5.13, 7.16)
<b>Overall response rate</b> (95% CI) <sup>b</sup>	38.6% (32.3, 45.1)	47.2% (40.7, 53.8)	43.3% (31.2, 56.0)	26.9% (16.8, 39.1)
<b>Duration of response</b>				
Median (months) (95% CI) <sup>c</sup>	8.44 (7.16, 14.59)	6.83 (5.59, 7.13)	24.02 (8.31, N.A.)	4.21 (2.79, 7.03)

<sup>a</sup> Hazard ratio based on unstratified Cox proportional hazards model.

<sup>b</sup> Confidence interval based on the Clopper and Pearson method

<sup>c</sup> Median computed using Kaplan-Meier method

Table 24 summarises efficacy results of OS, PFS, and ORR by baseline tumour PD-L1 expression in prespecified subgroup analyses.

**Table 24: Efficacy results by tumour PD-L1 expression (CA209743)**

	PD-L1 < 1% (n = 135)		PD-L1 ≥ 1% (n = 451)	
	nivolumab + ipilimumab (n = 57)	chemotherapy (n = 78)	nivolumab + ipilimumab (n = 232)	chemotherapy (n = 219)
<b>Overall survival</b>				
Events	40	58	150	157
Hazard ratio (95% CI) <sup>a</sup>	0.94 (0.62, 1.40)		0.69 (0.55, 0.87)	
Median (months) (95% CI) <sup>b</sup>	17.3 (10.1, 24.3)	16.5 (13.4, 20.5)	18.0 (16.8, 21.5)	13.3 (11.6, 15.4)
Rate (95% CI) at 24 months	38.7 (25.9, 51.3)	24.6 (15.5, 35.0)	40.8 (34.3, 47.2)	28.3 (22.1, 34.7)
<b>Progression-free survival</b>				
Hazard ratio (95% CI) <sup>a</sup>	1.79 (1.21, 2.64)		0.81 (0.64, 1.01)	
Median (months) (95% CI) <sup>b</sup>	4.1 (2.7, 5.6)	8.3 (7.0, 11.1)	7.0 (5.8, 8.5)	7.1 (6.2, 7.6)
<b>Overall response rate</b>				
(95% CI) <sup>c</sup>	21.1% (11.4, 33.9)	38.5% (27.7, 50.2)	43.5% (37.1, 50.2)	44.3% (37.6, 51.1)

<sup>a</sup> Hazard ratio based on unstratified Cox proportional hazards model.

<sup>b</sup> Median computed using Kaplan-Meier method.

<sup>c</sup> Confidence interval based on the Clopper and Pearson method.

A total of 157 MPM patients aged ≥ 75 years were enrolled in study CA209743 (78 in the nivolumab in combination with ipilimumab arm and 79 in the chemotherapy arm). A HR of 1.02 (95% CI: 0.70, 1.48) in OS was observed for nivolumab in combination with ipilimumab vs. chemotherapy within this study subgroup. A higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older relative to all patients who received nivolumab in combination with ipilimumab was shown (see [section 4.8](#)). However, due to the exploratory nature of this subgroup analysis, no definitive conclusions can be drawn.

### *Renal cell carcinoma*

#### Randomised phase 3 study of nivolumab as monotherapy vs. everolimus (CA209025)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced RCC with a clear cell component was evaluated in a Phase 3, randomised, open-label study (CA209025). The study included patients (18 years or older) who have experienced disease progression during or after 1 or 2 prior anti-angiogenic therapy regimens and no more than 3 total prior systemic treatment regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥ 70%. This study included patients regardless of their tumour PD-L1 status. Patients with any history of or concurrent brain metastases, prior treatment with an mammalian target of rapamycin (mTOR) inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 821 patients were randomised to receive either nivolumab 3 mg/kg (n = 410) administered intravenously over 60 minutes every 2 weeks or everolimus (n = 411) 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 8 weeks after randomisation and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after

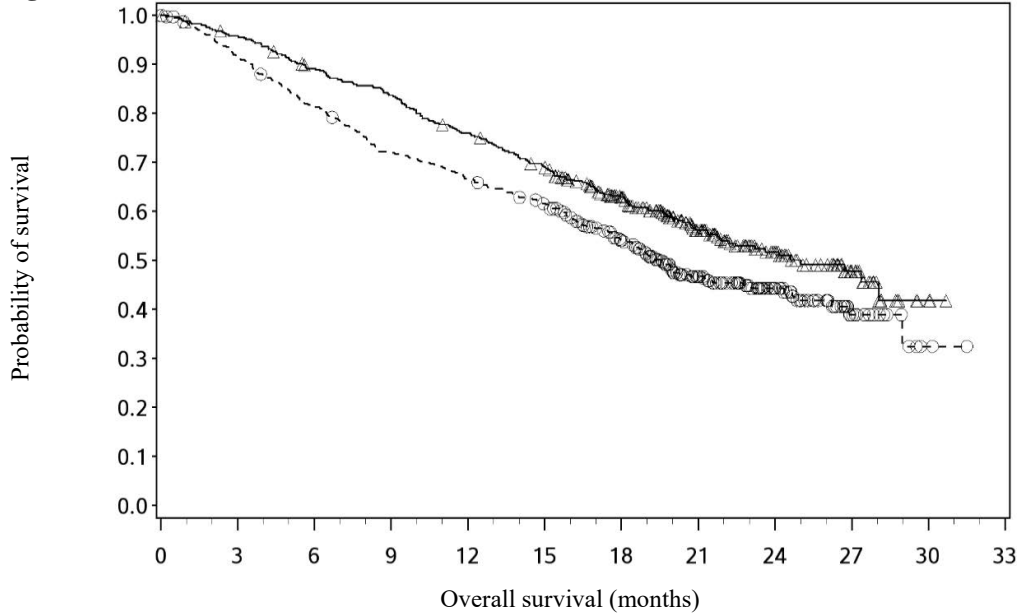
treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was OS. Secondary efficacy assessments included investigator-assessed ORR and PFS.

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40%  $\geq$  65 years of age and 9%  $\geq$  75 years of age. The majority of patients were male (75%) and white (88%), all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups were represented, and 34% and 66% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The majority of patients (72%) were treated with one prior anti-angiogenic therapy. The median duration of time from initial diagnosis to randomisation was 2.6 years in both the nivolumab and everolimus groups. The median duration of treatment was 5.5 months (range: 0-29.6+ months) in nivolumab-treated patients and was 3.7 months (range: 6 days-25.7+ months) in everolimus-treated patients.

Nivolumab was continued beyond progression in 44% of patients.

The Kaplan-Meier curves for OS are shown in Figure 17.

**Figure 17: Kaplan-Meier curves of OS (CA209025)**



Number of subjects at risk											
Nivolumab											
410	389	359	337	305	275	213	139	73	29	3	0
Everolimus											
411	366	324	287	265	241	187	115	61	20	2	0

—△— Nivolumab 3 mg/kg (events: 183/410), median and 95% CI: 25.00 (21.75, N.A.)  
---○--- Everolimus 10 mg (events: 215/411), median and 95% CI: 19.55 (17.64, 23.06)

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 25 and Figure 17). OS benefit was observed regardless of tumour PD-L1 expression level. Efficacy results are shown in Table 25.

**Table 25: Efficacy results (CA209025)**

	nivolumab (n = 410)	everolimus (n = 411)
<b>Overall survival</b>		
Events	183 (45%)	215 (52%)
Hazard ratio		0.73
98.52% CI		(0.57, 0.93)
p-value		0.0018
Median (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Rate (95% CI)		
At 6 months	89.2 (85.7, 91.8)	81.2 (77.0, 84.7)
At 12 months	76.0 (71.5, 79.9)	66.7 (61.8, 71.0)
<b>Objective response</b>		
(95% CI)	103 (25.1%) (21.0, 29.6)	22 (5.4%) (3.4, 8.0)
Odds ratio (95% CI)		5.98 (3.68, 9.72)
p-value		< 0.0001
Complete response (CR)	4 (1.0%)	2 (0.5%)
Partial response (PR)	99 (24.1%)	20 (4.9%)
Stable disease (SD)	141 (34.4%)	227 (55.2%)
<b>Median duration of response</b>		
Months (range)	11.99 (0.0-27.6 <sup>+</sup> )	11.99 (0.0 <sup>+</sup> -22.2 <sup>+</sup> )
<b>Median time to response</b>		
Months (range)	3.5 (1.4-24.8)	3.7 (1.5-11.2)
<b>Progression-free survival</b>		
Events	318 (77.6%)	322 (78.3%)
Hazard ratio		0.88
95% CI		(0.75, 1.03)
p-value		0.1135
Median (95% CI)	4.6 (3.71, 5.39)	4.4 (3.71, 5.52)

<sup>++</sup> denotes a censored observation.

NE = non-estimable

The median time to onset of objective response was 3.5 months (range: 1.4-24.8 months) after the start of nivolumab treatment. Forty-nine (47.6%) responders had ongoing responses with a duration ranging from 0.0-27.6<sup>+</sup> months.

Overall survival could be accompanied by an improvement over time in disease related symptoms and non-disease specific QoL as assessed using valid and reliable scales in the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) and the EuroQoL EQ-5D. Apparently meaningful symptom improvement (MID = 2 point change in FKSI-DRS score;  $p < 0.001$ ) and time to improvement (HR = 1.66 (1.33, 2.08),  $p < 0.001$ ) were significantly better for patients on the nivolumab arm. While both arms of the study received active therapy, the QoL data should be interpreted in the context of the open-label study design and therefore cautiously taken.

#### Phase 3b/4 safety study (CA209374)

Additional safety and descriptive efficacy data are available from study CA209374, an open-label Phase 3b/4 safety study of nivolumab monotherapy (treated with 240 mg every 2 weeks) for the

treatment of patients with advanced or metastatic RCC (n = 142), including 44 patients with non-clear cell histology.

In subjects with non-clear cell histology, at a minimum follow-up of approximately 16.7 months ORR and median duration of response were 13.6% and 10.2 months, respectively. Clinical activity was observed regardless of tumour PD-L1 expression status.

*Randomised phase 3 study of nivolumab in combination with ipilimumab vs. sunitinib (CA209214)*

The safety and efficacy of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA209214). The study included patients (18 years or older) with previously untreated, advanced or metastatic renal cell carcinoma with a clear-cell component. The primary efficacy population included those intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the International Metastatic RCC Database Consortium (IMDC) criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomisation, Karnofsky performance status <80%, haemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal). This study included patients regardless of their tumour PD-L1 status. Patients with Karnofsky performance status < 70% and patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were stratified by IMDC prognostic score and region.

A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either nivolumab 3 mg/kg (n = 425) administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks or sunitinib (n = 422) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off, every cycle. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 12 weeks after randomisation and continued every 6 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measures were OS, ORR and PFS as determined by a BICR in intermediate/poor risk patients.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 21-85) with 38% ≥ 65 years of age and 8% ≥ 75 years of age. The majority of patients were male (73%) and white (87%), and 31% and 69% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The median duration of time from initial diagnosis to randomisation was 0.4 years in both the nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg and sunitinib groups. The median duration of treatment was 7.9 months (range: 1 day-21.4+ months) in nivolumab with ipilimumab-treated patients and was 7.8 months (range: 1 days-20.2+ months) in sunitinib-treated patients. Nivolumab with ipilimumab was continued beyond progression in 29% of patients.

Efficacy results for the intermediate/poor risk patients are shown in [Table 26](#) (primary analysis with a minimum follow-up of 17.5 months and with a minimum follow-up of 60 months) and in [Figure 18](#) (minimum follow-up of 60 months).

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 60 months show outcomes consistent with the original primary analysis.

**Table 26: Efficacy results in intermediate/poor risk patients (CA209214)**

	nivolumab + ipilimumab (n = 425)	sunitinib (n = 422)
<b>Primary analysis</b> minimum follow-up: 17.5 months		
<b>Overall survival</b>		
Events	140 (33%)	188 (45%)
Hazard ratio <sup>a</sup>	0.63	
99.8% CI	(0.44, 0.89)	
p-value <sup>b, c</sup>	< 0.0001	
Median (95% CI)	NE (28.2, NE)	25.9 (22.1, NE)
Rate (95% CI)		
At 6 months	89.5 (86.1, 92.1)	86.2 (82.4, 89.1)
At 12 months	80.1 (75.9, 83.6)	72.1 (67.4, 76.2)
<b>Progression-free survival</b>		
Events	228 (53.6%)	228 (54.0%)
Hazard ratio <sup>a</sup>	0.82	
99.1% CI	(0.64, 1.05)	
p-value <sup>b, h</sup>	0.0331	
Median (95% CI)	11.6 (8.71, 15.51)	8.4 (7.03, 10.81)
<b>Confirmed objective response (BICR)</b>		
	177 (41.6%)	112 (26.5%)
(95% CI)	(36.9, 46.5)	(22.4, 31.0)
Difference in ORR (95% CI) <sup>d</sup>	16.0 (9.8, 22.2)	
p-value <sup>e, f</sup>	< 0.0001	
Complete response (CR)	40 (9.4%)	5 (1.2%)
Partial response (PR)	137 (32.2%)	107 (25.4%)
Stable disease (SD)	133 (31.3%)	188 (44.5%)
<b>Median duration of response<sup>g</sup></b>		
Months (range)	NE (1.4 <sup>+</sup> -25.5 <sup>+</sup> )	18.17 (1.3 <sup>+</sup> -23.6 <sup>+</sup> )
<b>Median time to response</b>		
Months (range)	2.8 (0.9-11.3)	3.0 (0.6-15.0)
<b>Updated analysis*</b> minimum follow-up: 60 months		
<b>Overall survival</b>		
Events	242 (57%)	282 (67%)
Hazard ratio <sup>a</sup>	0.68	
95% CI	(0.58, 0.81)	
Median (95% CI)	46.95 (35.35, 57.43)	26.64 (22.08, 33.54)
Rate (95% CI)		
At 24 months	66.3 (61.5, 70.6)	52.4 (47.4, 57.1)
At 36 months	54.6 (49.7, 59.3)	43.7 (38.7, 48.5)
At 48 months	49.9 (44.9, 54.6)	35.8 (31.1, 40.5)
At 60 months	43.0 (38.1, 47.7)	31.3 (26.8, 35.9)

	nivolumab + ipilimumab (n = 425)	sunitinib (n = 422)
<b>Progression-free survival</b>		
Events	245 (57.6%)	253 (60.0%)
Hazard ratio <sup>a</sup>	0.73	
95% CI	(0.61, 0.87)	
Median (95% CI)	11.6 (8.44, 16.63)	8.3 (7.03, 10.41)
<b>Confirmed objective response (BICR)</b>	179 (42.1%)	113 (26.8%)
(95% CI)	(37.4, 47.0)	(22.6, 31.3)
Difference in ORR (95% CI) <sup>d,e</sup>	16.2 (10.0, 22.5)	
Complete response (CR)	48 (11.3%)	9 (2.1%)
Partial response (PR)	131 (30.8%)	104 (24.6%)
Stable disease (SD)	131 (30.8%)	187 (44.3%)
<b>Median duration of response<sup>g</sup></b>		
Months (range)	NE (50.89-NE)	19.38 (15.38-25.10)
<b>Median time to response</b>		
Months (range)	2.8 (0.9-35.0)	3.1 (0.6-23.6)

<sup>a</sup> Based on a stratified proportional hazards model.

<sup>b</sup> Based on a stratified log-rank test.

<sup>c</sup> p-value is compared to alpha 0.002 in order to achieve statistical significance.

<sup>d</sup> Strata adjusted difference.

<sup>e</sup> Based on the stratified DerSimonian-Laird test.

<sup>f</sup> p-value is compared to alpha 0.001 in order to achieve statistical significance.

<sup>g</sup> Computed using Kaplan-Meier method.

<sup>h</sup> p-value is compared to alpha 0.009 in order to achieve statistical significance.

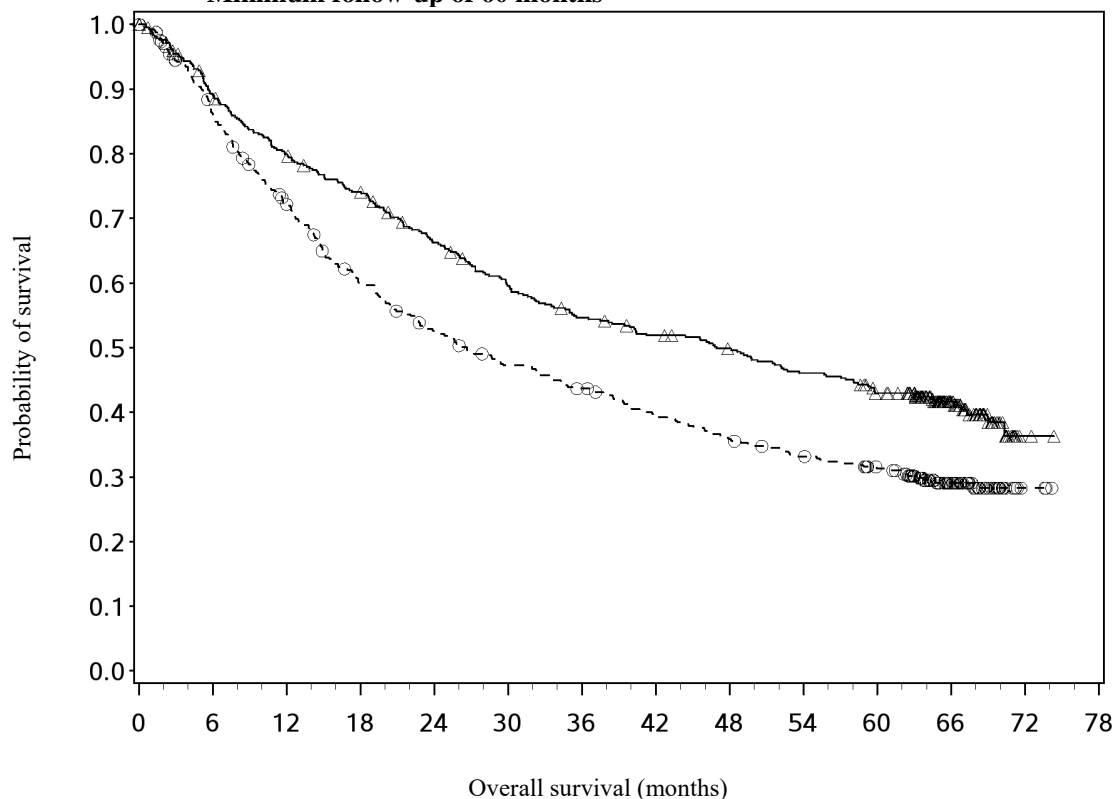
“+” denotes a censored observation.

NE = non-estimable

\* Descriptive analysis based on data cut-off: 26-Feb-2021.



**Figure 18: Kaplan-Meier curves of OS in intermediate/poor risk patients (CA209214) - Minimum follow-up of 60 months**



Number of subjects at risk

Nivolumab + ipilimumab

425 372 332 306 270 241 220 207 196 181 163 79 2 0

Sunitinib

422 353 291 237 206 184 169 151 137 125 112 58 3 0

—△— Nivolumab + ipilimumab (events: 242/425), median and 95.0% CI: 46.95 (35.35, 57.43)

---○--- Sunitinib (events: 282/422), median and 95.0% CI: 26.64 (22.08, 33.54)

An updated descriptive OS analysis was performed when all patients had a minimum follow-up of 24 months. At the time of this analysis, the hazard ratio was 0.66 (99.8% CI 0.48-0.91) with 166/425 events in the combination arm and 209/422 events in the sunitinib arm. In intermediate/poor-risk patients, OS benefit was observed in the nivolumab in combination with ipilimumab arm vs. sunitinib regardless of tumour PD-L1 expression. Median OS for tumour PD-L1 expression  $\geq 1\%$  was not reached for nivolumab in combination with ipilimumab, and was 19.61 months in the sunitinib arm (HR = 0.52; 95% CI: 0.34, 0.78). For tumour PD-L1 expression  $< 1\%$ , the median OS was 34.7 months for the nivolumab in combination with ipilimumab, and was 32.2 months in the sunitinib arm (HR = 0.70; 95% CI: 0.54, 0.92).

CA209214 also randomised 249 favourable risk patients as per IMDC criteria to nivolumab plus ipilimumab (n = 125) or to sunitinib (n = 124). These patients were not evaluated as part of the primary efficacy population. At a minimum of 24 months follow-up, OS in favourable risk patients receiving nivolumab plus ipilimumab compared to sunitinib had a hazard ratio of 1.13 (95% CI: 0.64, 1.99; p = 0.6710). With 60 months minimum follow-up, the HR for OS was 0.94 (95% CI: 0.65, 1.37).

There are no data on the use of nivolumab in combination with ipilimumab in patients with only a non clear-cell histology in first-line RCC.

Patients  $\geq 75$  years of age represented 8% of all intermediate/poor risk patients in CA209214, and the combination of nivolumab and ipilimumab showed numerically less effect on OS (HR 0.97, 95% CI: 0.48, 1.95) in this subgroup versus the overall population at a minimum follow-up of 17.5 months. Because of the small size of this subgroup, no definitive conclusions can be drawn from these data.

***Randomised phase 3 study of nivolumab in combination with cabozantinib vs. sunitinib (CA2099ER)***

The safety and efficacy of nivolumab 240 mg in combination with cabozantinib 40 mg for the first-line treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA2099ER). The study included patients (18 years or older) with advanced or metastatic RCC with a clear cell component, Karnofsky Performance Status (KPS)  $\geq 70\%$ , and measurable disease as per RECIST v1.1 regardless of their PD-L1 status or IMDC risk group. The study excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression, patients who had prior treatment with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, poorly controlled hypertension despite antihypertensive therapy, active brain metastases and uncontrolled adrenal insufficiency. Patients were stratified by IMDC prognostic score, PD-L1 tumour expression, and region.

A total of 651 patients were randomised to receive either nivolumab 240 mg (n = 323) administered intravenously every 2 weeks in combination with cabozantinib 40 mg once daily orally or sunitinib (n = 328) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off. Treatment continued until disease progression or unacceptable toxicity with nivolumab administration for up to 24 months. Treatment beyond initial investigator-assessed RECIST version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. First tumour assessment post-baseline was performed at 12 weeks ( $\pm 7$  days) following randomisation. Subsequent tumour assessments occurred at every 6 weeks ( $\pm 7$  days) until Week 60, then every 12 weeks ( $\pm 14$  days) until radiographic progression, confirmed by the BICR. The primary efficacy outcome measure was PFS as determined by a BICR. Additional efficacy measures included OS and ORR as key secondary endpoints.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 28-90) with 38.4%  $\geq 65$  years of age and 9.5%  $\geq 75$  years of age. The majority of patients were male (73.9%) and white (81.9%). Eight percent of patients were Asian, 23.2% and 76.5% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. Patient distribution by IMDC risk categories was 22.6% favourable, 57.6% intermediate, and 19.7% poor. For tumour PD-L1 expression, 72.5% of patients had PD-L1 expression  $< 1\%$  or indeterminate and 24.9% of patients had PD-L1 expression  $\geq 1\%$ . 11.5% of patients had tumours with sarcomatoid features. The median duration of treatment was 14.26 months (range: 0.2-27.3 months) in nivolumab with cabozantinib-treated patients and was 9.23 months (range: 0.8-27.6 months) in sunitinib-treated patients.

The study demonstrated a statistically significant benefit in PFS, OS, and ORR for patients randomised to nivolumab in combination with cabozantinib as compared to sunitinib. Efficacy results from the primary analysis (minimum follow-up 10.6 months; median follow-up 18.1 months) are shown in Table 27.

**Table 27: Efficacy results (CA2099ER)**

	<b>nivolumab + cabozantinib (n = 323)</b>	<b>sunitinib (n = 328)</b>
<b>Progression-free survival</b>		
Events	144 (44.6%)	191 (58.2%)
Hazard ratio <sup>a</sup>	0.51	
95% CI	(0.41, 0.64)	
p-value <sup>b, c</sup>	$< 0.0001$	
Median (95% CI) <sup>d</sup>	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)

	nivolumab + cabozantinib (n = 323)	sunitinib (n = 328)
<b>Overall survival</b>		
Events	67 (20.7%)	99 (30.2%)
Hazard ratio <sup>a</sup>	0.60	
98.89% CI	(0.40, 0.89)	
p-value <sup>b,c,e</sup>	0.0010	
Median (95% CI)	N.E.	N.E. (22.6, N.E.)
Rate (95% CI)		
At 6 months	93.1 (89.7, 95.4)	86.2 (81.9, 89.5)
<b>Confirmed objective response (BICR)</b>		
	180 (55.7%)	89 (27.1%)
(95% CI) <sup>f</sup>	(50.1, 61.2)	(22.4, 32.3)
Difference in ORR (95% CI) <sup>g</sup>	28.6 (21.7, 35.6)	
p-value <sup>h</sup>	< 0.0001	
Complete response (CR)	26 (8.0%)	15 (4.6%)
Partial response (PR)	154 (47.7%)	74 (22.6%)
Stable disease (SD)	104 (32.2%)	138 (42.1%)
<b>Median duration of response<sup>d</sup></b>		
Months (range)	20.17 (17.31, N.E.)	11.47 (8.31, 18.43)
<b>Median time to response</b>		
Months (range)	2.83 (1.0-19.4)	4.17 (1.7-12.3)
<sup>a</sup> Stratified Cox proportional hazards model. Hazard ratio is nivolumab and cabozantinib over sunitinib.		
<sup>b</sup> Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression ( $\geq 1\%$ versus $< 1\%$ or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.		
<sup>c</sup> 2-sided p-values from stratified regular log-rank test.		
<sup>d</sup> Based on Kaplan-Meier estimates.		
<sup>e</sup> Boundary for statistical significance p-value $< 0.0111$ .		
<sup>f</sup> CI based on the Clopper and Pearson method.		
<sup>g</sup> Strata adjusted difference in objective response rate (nivolumab + cabozantinib - sunitinib) based on DerSimonian and Laird.		
<sup>h</sup> 2-sided p-value from CMH test.		
NE = non-estimable		

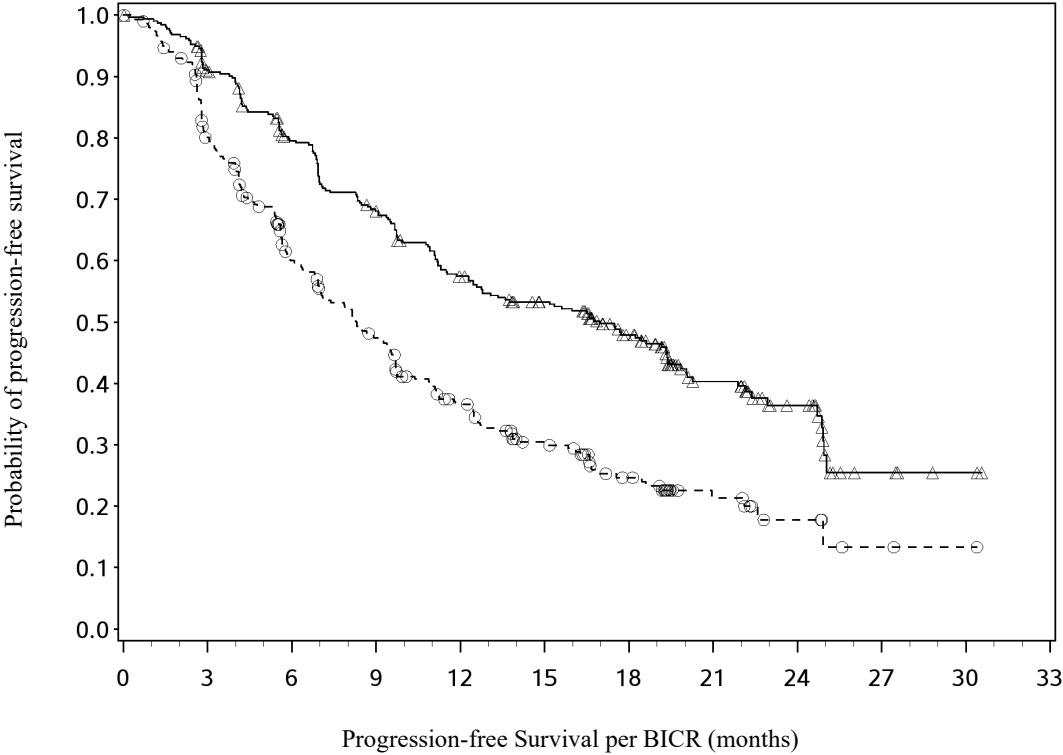
The primary analysis of PFS included censoring for new anti-cancer treatment (Table 26). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

PFS benefit was observed in the nivolumab in combination with cabozantinib arm vs. sunitinib regardless of the IMDC risk category. Median PFS for the favourable risk group was not reached for nivolumab in combination with cabozantinib, and was 12.81 months in the sunitinib arm (HR = 0.60; 95% CI: 0.37, 0.98). Median PFS for the intermediate risk group was 17.71 months for nivolumab in combination with cabozantinib and was 8.38 months in the sunitinib arm (HR = 0.54; 95% CI: 0.41, 0.73). Median PFS for the poor risk group was 12.29 months for nivolumab in combination with cabozantinib and was 4.21 months in the sunitinib arm (HR = 0.36; 95% CI: 0.23, 0.58).

PFS benefit was observed in the nivolumab in combination with cabozantinib arm vs. sunitinib regardless of tumour PD-L1 expression. Median PFS for tumour PD-L1 expression  $\geq 1\%$  was 13.08 months for nivolumab in combination with cabozantinib, and was 4.67 months in the sunitinib arm (HR = 0.45; 95% CI: 0.29, 0.68). For tumour PD-L1 expression  $< 1\%$ , the median PFS was 19.84 months for nivolumab in combination with cabozantinib, and 9.26 months in the sunitinib arm (HR = 0.50; 95% CI: 0.38, 0.65).

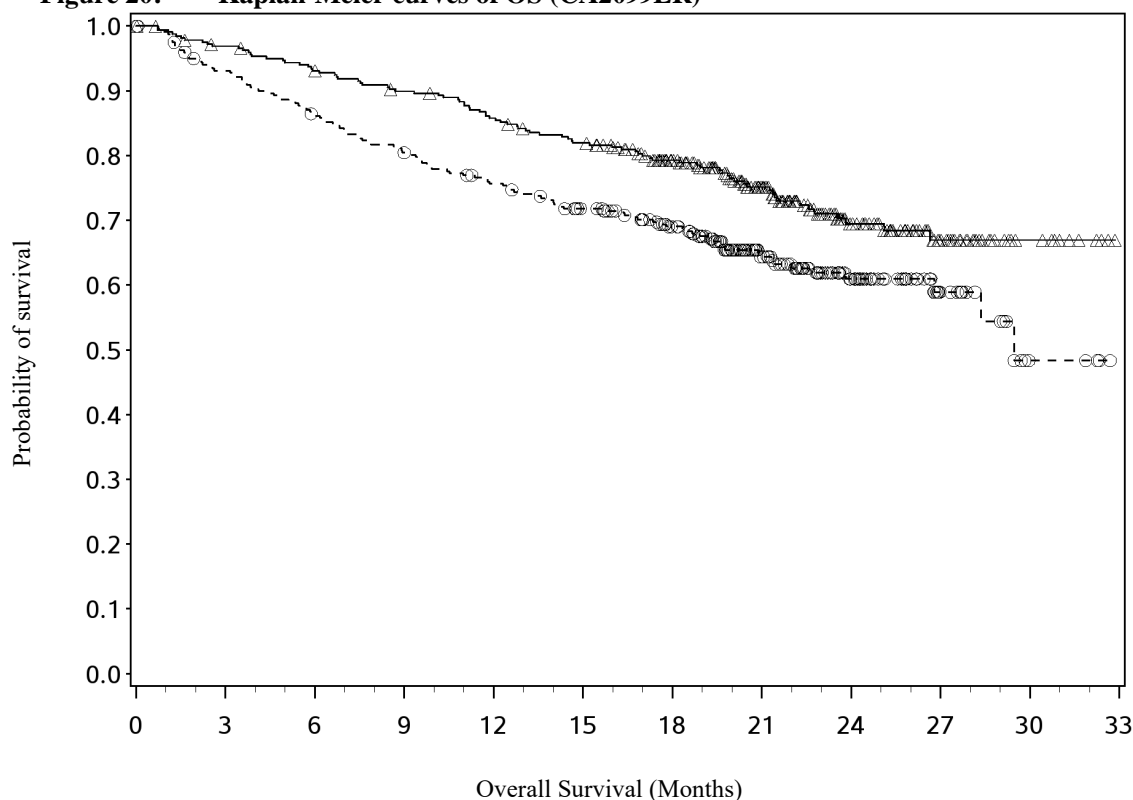
An updated PFS and OS analysis were performed when all patients had a minimum follow-up of 16.0 months and a median follow-up of 23.5 months (see Figures 19 and 20). The PFS hazard ratio was 0.52 (95% CI: 0.43, 0.64). The OS hazard ratio was 0.66 (95% CI: 0.50, 0.87). Updated efficacy data (PFS and OS) in subgroups for the IMDC risk categories and PD-L1 expression levels confirmed the original results. With the updated analysis, median PFS is reached for the favourable risk group.

**Figure 19: Kaplan-Meier curves of PFS (CA2099ER)**



Number of subjects at risk											
Nivolumab + cabozantinib											
323	280	236	201	166	145	102	56	26	5	2	0
Sunitinib											
328	230	160	122	87	61	37	17	7	2	1	0
—△— Nivolumab + cabozantinib (events: 175/323), median and 95.0% CI: 16.95 (12.58, 19.38)											
---○--- Sunitinib (events: 206/328), median and 95.0% CI: 8.31 (6.93, 9.69)											

**Figure 20: Kaplan-Meier curves of OS (CA2099ER)**



Number of subjects at risk

Nivolumab + cabozantinib

323 308 295 283 269 255 220 147 84 40 10 0

Sunitinib

328 295 272 254 236 217 189 118 62 22 4 0

—△— Nivolumab + cabozantinib (events: 86/323), median and 95% CI: NE

---○--- Sunitinib (events: 116/328), median and 95% CI: 29.47 (28.35, NE)

### *Classical Hodgkin lymphoma*

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of relapsed or refractory cHL following ASCT was evaluated in two multi-centre, open-label, single-arm studies (CA209205 and CA209039).

CA209205 is a Phase 2, open-label, multi-cohort, single-arm study of nivolumab in cHL. It includes 243 patients who had ASCT; Cohort A included 63 (26%) patients who were brentuximab vedotin naïve; Cohort B included 80 (33%) patients who had received brentuximab vedotin after ASCT failure; and Cohort C included 100 (41%) patients who had received brentuximab vedotin before and/or after ASCT out of which 33 (14%) patients received brentuximab vedotin only prior to ASCT. All patients received nivolumab 3 mg/kg monotherapy intravenously over 60 minutes every 2 weeks. The first tumour assessments were conducted 9 weeks after the start of treatment and continued thereafter until disease progression or treatment discontinuation. The primary efficacy outcome measure was ORR as determined by an IRRC. Additional efficacy measures included duration of response, PFS and OS.

CA209039 is a Phase 1b open-label, multi-centre, dose-escalation, and multidose study of nivolumab in relapsed/refractory hematologic malignancies, including 23 patients with cHL treated with nivolumab 3 mg/kg monotherapy; amongst which, 15 patients received prior brentuximab vedotin treatment as a salvage therapy following ASCT, similar to Cohort B of study CA209205. The first tumour assessments were conducted 4 weeks after the start of treatment and continued thereafter until

disease progression or treatment discontinuation. Efficacy assessments included investigator-assessed ORR, retrospectively evaluated by an IRRC, and duration of response.

Data from the 80 patients from CA209205 Cohort B and from the 15 patients from CA209039 who received prior brentuximab vedotin treatment following ASCT were integrated. Additional data from 100 patients from CA209205 Cohort C who received brentuximab before and/or after ASCT are also presented. Baseline characteristics were similar across the two studies and cohorts (see Table 28 below).

**Table 28: Baseline patient characteristics in CA209205 Cohort B, Cohort C and CA209039**

	CA209205 Cohort B and CA209039 (n = 95)	CA209205 Cohort B <sup>a</sup> (n = 80)	CA209039 (n = 15)	CA209205 Cohort C <sup>b</sup> (n = 100)
Median age, years (range)	37.0 (18–72)	37.0 (18–72)	40.0 (24–54)	32.0 (19–69)
Gender	61 (64%) M 34 (36%) F	51 (64%) M 29 (36%) F	10 (67%) M 5 (33%) F	56 (56%) M 44 (44%) F
ECOG status				
0	49 (52%)	42 (52.5%)	7 (47%)	50 (50%)
1	46 (48%)	38 (47.5%)	8 (53%)	50 (50%)
≥ 5 prior lines of systemic therapy	49 (52%)	39 (49%)	10 (67%)	30 (30%)
Prior radiation therapy	72 (76%)	59 (74%)	13 (87%)	69 (69%)
Prior ASCT				
1	87 (92%)	74 (92.5%)	13 (87%)	100 (100%)
≥ 2	8 (8%)	6 (7.5%)	2 (13%)	0 (0%)
Years from most recent transplant to first dose of study therapy, median (min-max)	3.5 (0.2–19.0)	3.4 (0.2–19.0)	5.6 (0.5–15.0)	1.7 (0.2–17.0)

<sup>a</sup> 18/80 (22.5%) of the patients in CA209205 Cohort B presented B-Symptoms at baseline.

<sup>b</sup> 25/100 (25%) of the patients in CA209205 Cohort C presented B-Symptoms at baseline.

Efficacy from both studies was evaluated by the same IRRC. Results are shown in Table 29.

**Table 29: Efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma**

	CA209205 Cohort B <sup>a</sup> and CA209039 (n = 95/12.0)	CA209205 Cohort B <sup>a</sup> (n = 80/12.0)	CA209039 (n = 15/12.0)
<b>Number (n)/ minimum follow-up (months)</b>			
<b>Objective response, n (%); (95% CI)</b>	63 (66%); (56, 76)	54 (68%); (56, 78)	9 (60%); (32, 84)
Complete remission (CR), n (%); (95% CI)	6 (6%); (2, 13)	6 (8%); (3, 16)	0 (0%); (0, 22)
Partial remission (PR), n (%); (95% CI)	57 (60%); (49, 70)	48 (60%); (48, 71)	9 (60%); (32, 84)
<b>Stable disease, n (%)</b>	22 (23)	17 (21)	5 (33)
<b>Duration of response (months)<sup>b</sup></b>			
Median (95% CI)	13.1 (9.5, NE)	13.1 (8.7, NE)	12.0 (1.8, NE)
Range	0.0 <sup>+</sup> -23.1 <sup>+</sup>	0.0 <sup>+</sup> -14.2 <sup>+</sup>	1.8-23.1 <sup>+</sup>
<b>Median time to response</b>			
Months (range)	2.0 (0.7-11.1)	2.1 (1.6-11.1)	0.8 (0.7-4.1)
<b>Median duration of follow-up</b>			
Months (range)	15.8 (1.9-27.6)	15.4 (1.9-18.5)	21.9 (11.2-27.6)
<b>Progression-free survival</b>			
Rate (95% CI) at 12 months	57 (45, 68)	55 (41, 66)	69 (37, 88)

<sup>+</sup> denotes a censored observation.

<sup>a</sup> Follow-up was ongoing at the time of data submission.

<sup>b</sup> Data unstable due to the limited duration of response for Cohort B resulting from censoring.

NE = non-estimable

Updated efficacy results from longer follow-up data of Cohort B (minimum 68.7 months) and Cohort C (minimum 61.9 months) from CA209205 are presented below in Table 30.

**Table 30: Updated efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma from longer follow-up of study CA209205**

Number (n)/ minimum follow-up (months)	CA209205 Cohort B (n = 80/68.7)	CA209205 Cohort C (n = 100/61.9) <sup>a</sup>
<b>Objective response, n (%); (95% CI)</b>	57 (71%); (60, 81)	75 (75%); (65, 83)
Complete remission (CR), n (%); (95% CI)	11 (14%); (7, 23)	21 (21%); (14, 30)
Partial remission (PR), n (%); (95% CI)	46 (58%); (46, 69)	54 (54%); (44, 64)
<b>Stable disease, n (%)</b>	14 (18%)	12 (12%)
<b>Duration of response in all responders (months)<sup>b</sup></b>		
Median (95% CI)	16.6 (9.3, 25.7)	18.2 (11.6, 30.9)
Range	0.0 <sup>+</sup> -71.0 <sup>+</sup>	0.0 <sup>+</sup> -59.8 <sup>+</sup>
<b>Duration of response in CR (months)</b>		
Median (95% CI)	30.3 (2.4, NE)	26.4 (7.1, NE)
Range	0.7 <sup>+</sup> -50.0 <sup>+</sup>	0.0 <sup>+</sup> -55.7 <sup>+</sup>
<b>Duration of response in PR (months)</b>		
Median (95% CI)	10.6 (7.5, 25.3)	14.7 (9.4, 30.4)
Range	0.0 <sup>+</sup> -67.9 <sup>+</sup>	0.0 <sup>+</sup> -55.9 <sup>+</sup>
<b>Median time to response</b>		
Months (range)	2.2 (1.6-11.1)	2.1 (0.8, 17.9)
<b>Median duration of follow-up</b>		
Months (range)	58.5 (1.9-74.3)	53.5 (1.4-70.4)
<b>Progression-free survival</b>		
Median (95% CI)	14.8 (11.0, 19.8)	15.1 (11.1, 19.1)
Rate (95% CI) at 12 months	52 (39, 63)	53 (42, 64)
Rate (95% CI) at 24 months	36 (24, 48)	37 (25, 48)
Rate (95% CI) at 60 months	16 (6, 29)	15 (6, 28)
<b>Overall survival</b>		
Median	Not reached	Not reached
Rate (95% CI) at 12 months	95 (87, 98)	90 (82, 94)
Rate (95% CI) at 24 months	87 (77, 93)	86 (77, 91)
Rate (95% CI) at 60 months	72 (60, 81)	67 (56, 75)

<sup>a</sup>“+” denotes a censored observation.

<sup>a</sup> Patients in Cohort C (n = 33) who have received brentuximab vedotin only prior to ASCT had ORR of 73% (95% CI: 55, 87), CR of 21% (95% CI: 9, 39), PR of 52% (95% CI: 34, 69). Median duration of response was 13.5 months (95% CI: 9.4, 30.9).

<sup>b</sup> Determined for subjects with CR or PR.

NE = non-estimable

B-symptoms were present in 22% (53/243) of the patients in CA209205 at baseline. Nivolumab treatment resulted in rapid resolution of B-symptoms in 88.7% (47/53) of the patients, with a median time to resolution of 1.9 months.

In a post-hoc analysis of the 80 patients in CA209205 Cohort B, 37 had no response to prior brentuximab vedotin treatment. Among these 37 patients, treatment with nivolumab resulted in an ORR of 62.2% (23/37). The median duration of response is 25.6 months (10.6, 56.5) for the 23 responders to nivolumab who had failed to achieve response with prior brentuximab vedotin treatment.

### *Squamous cell cancer of the head and neck*

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of metastatic or recurrent SCCHN were evaluated in a phase 3, randomised, open-label study (CA209141). The study included patients (18 years or older), with histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) and who have experienced disease progression during or within 6 months of receiving platinum-based therapy regimen and had an ECOG performance status score of 0 or 1. Prior platinum-based therapy was administered in either the adjuvant, neo-adjuvant, primary, recurrent, or metastatic setting. Patients were enrolled regardless of their tumour PD-L1 or human papilloma virus (HPV) status. Patients with active autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or active brain or leptomeningeal metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

A total of 361 patients were randomised to receive either nivolumab 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n = 15), 400 mg/m<sup>2</sup> loading dose followed by 250 mg/m<sup>2</sup> weekly or methotrexate (n = 52) 40 to 60 mg/m<sup>2</sup> weekly, or docetaxel (n = 54) 30 to 40 mg/m<sup>2</sup> weekly. Randomisation was stratified by prior cetuximab treatment. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to RECIST version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. Treatment beyond initial investigator-assessed RECIST version 1.1-defined progression was permitted in patients receiving nivolumab, if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and ORR. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at predefined levels of 1%, 5%, and 10%.

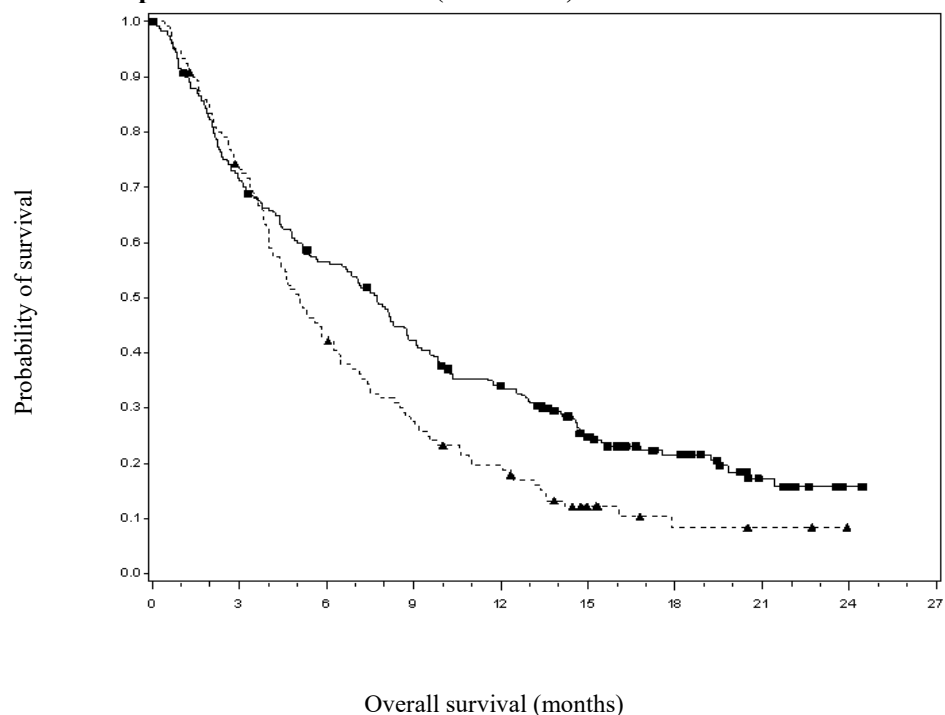
Pre-study tumour tissue specimens were systematically collected prior to randomisation in order to conduct pre-planned analyses of efficacy according to tumour PD-L1 expression. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Baseline characteristics were generally balanced between the two groups. The median age was 60 years (range: 28-83) with 31% ≥ 65 years of age and 5% ≥ 75 years of age, 83% were male, and 83% were white. Baseline ECOG performance status score was 0 (20%) or 1 (78%), 77% were former/current smokers, 90% had Stage IV disease, 66% had two or more lesions, 45%, 34% and 20% received 1, 2, or 3 or more prior lines of systemic therapy, respectively, and 25% were HPV-16 status positive.

With a minimum follow-up of 11.4 months, the trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice. The Kaplan-Meier curves for OS are shown in [Figure 21](#). Efficacy results are shown in [Table 31](#).



**Figure 21: Kaplan-Meier curves of OS (CA209141)**



Number of subjects at risk

Nivolumab								
240	169	132	98	76	45	27	12	3
Investigator's choice								
121	88	51	32	22	9	4	3	0

—■— Nivolumab 3 mg/kg (events: 184/240), median and 95% CI: 7.72 (5.68, 8.77)  
 ---▲--- Investigator's choice (events: 105/121), median and 95% CI: 5.06 (4.04, 6.24)

**Table 31: Efficacy results (CA209141)**

	nivolumab (n = 240)	investigator's choice (n = 121)
<b>Overall survival</b>		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio <sup>a</sup>		0.71
(95% CI)		(0.55, 0.90)
p-value <sup>b</sup>		0.0048
Median (95% CI) (months)	7.72 (5.68, 8.77)	5.06 (4.04, 6.24)
Rate (95% CI) at 6 months	56.5 (49.9, 62.5)	43.0 (34.0, 51.7)
Rate (95% CI) at 12 months	34.0 (28.0, 40.1)	19.7 (13.0, 27.3)
Rate (95% CI) at 18 months	21.5 (16.2, 27.4)	8.3 (3.6, 15.7)
<b>Progression-free survival</b>		
Events	204 (85.0%)	104 (86.0%)
Hazard ratio		0.87
95% CI		(0.69, 1.11)
p-value		0.2597
Median (95% CI) (months)	2.04 (1.91, 2.14)	2.33 (1.97, 3.12)
Rate (95% CI) at 6 months	21.0 (15.9, 26.6)	11.1 (5.9, 18.3)
Rate (95% CI) at 12 months	9.5 (6.0, 13.9)	2.5 (0.5, 7.8)

	nivolumab (n = 240)	investigator's choice (n = 121)
<b>Confirmed objective response<sup>c</sup></b>	32 (13.3%)	7 (5.8%)
(95% CI)	(9.3, 18.3)	(2.4, 11.6)
Odds ratio (95% CI)	2.49 (1.07, 5.82)	
Complete response (CR)	6 (2.5%)	1 (0.8%)
Partial response (PR)	26 (10.8%)	6 (5.0%)
Stable disease (SD)	55 (22.9%)	43 (35.5%)
<b>Median time to response</b>		
Months (range)	2.1 (1.8-7.4)	2.0 (1.9-4.6)
<b>Median duration of response</b>		
Months (range)	9.7 (2.8-20.3+)	4.0 (1.5+-8.5+)

<sup>a</sup> Derived from a stratified proportional hazards model.

<sup>b</sup> P-value is derived from a log-rank test stratified by prior cetuximab; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0227.

<sup>c</sup> In the nivolumab group there were two patients with CRs and seven patients with PRs who had tumour PD-L1 expression < 1%.

Quantifiable tumour PD-L1 expression was measured in 67% of patients in the nivolumab group and 82% of patients in the investigator's choice group. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. investigator's choice) at each of the predefined tumour PD-L1 expression levels of  $\geq 1\%$  (55% vs. 62%),  $\geq 5\%$  (34% vs. 43%), or  $\geq 10\%$  (27% vs. 34%).

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to investigator's choice. The magnitude of OS benefit was consistent for  $\geq 1\%$ ,  $\geq 5\%$  or  $\geq 10\%$  tumour PD-L1 expression levels (see Table 32).

**Table 32: OS by tumour PD-L1 expression (CA209141)**

PD-L1 Expression	nivolumab	investigator's choice	
OS by tumour PD-L1 expression			
	Number of events (number of patients)		Unstratified hazard ratio (95% CI)
< 1%	56 (73)	32 (38)	0.83 (0.54, 1.29)
$\geq 1\%$	66 (88)	55 (61)	0.53 (0.37, 0.77)
$\geq 5\%$	39 (54)	40 (43)	0.51 (0.32, 0.80)
$\geq 10\%$	30 (43)	31 (34)	0.57 (0.34, 0.95)

In an exploratory post-hoc analysis using a non-validated assay, both tumour cell PD-L1 expression and tumour-associated immune cell (TAIC) PD-L1 expression were analysed in relation to the magnitude of treatment effect of nivolumab compared to investigator's choice. This analysis showed that not only tumour cell PD-L1 expression but also TAIC PD-L1 expression appeared to be associated with benefit from nivolumab relative to investigator's choice (see Table 33). Due to the small numbers of patients in the subgroups, and exploratory nature of the analysis, no definitive conclusions can be drawn from these data.

**Table 33: Efficacy by tumour cell and TAIC PD-L1 expression (CA209141)**

	Median OS <sup>a</sup> (months)		Median PFS <sup>a</sup> (months)		ORR (%)	
	HR <sup>b</sup> (95% CI)		HR <sup>b</sup> (95% CI)		(95% CI) <sup>c</sup>	
	nivolumab	investigator's choice	nivolumab	investigator's choice	nivolumab	investigator's choice
<b>PD-L1 ≥ 1%, PD-L1+ TAIC abundant<sup>d</sup></b> (61 nivolumab, 47 investigator's choice)	9.10 0.43 (0.28, 0.67)	4.60	3.19 0.48 (0.31, 0.75)	1.97	19.7 (10.6, 31.8)	0 (0, 7.5)
<b>PD-L1 ≥ 1%, PD-L1+ TAIC rare<sup>d</sup></b> (27 nivolumab, 14 investigator's choice)	6.67 0.89 (0.44, 1.80)	4.93	1.99 0.93 (0.46, 1.88)	2.04	11.1 (2.4, 29.2)	7.1 (0.2, 33.9)
<b>PD-L1 &lt; 1%, PD-L1+ TAIC abundant<sup>d</sup></b> (43 nivolumab, 25 investigator's choice)	11.73 0.67 (0.38, 1.18)	6.51	2.10 0.96 (0.55, 1.67)	2.73	18.6 (8.4, 33.4)	12.0 (2.5, 31.2)
<b>PD-L1 &lt; 1%, PD-L1+ TAIC rare<sup>d</sup></b> (27 nivolumab, 10 investigator's choice)	3.71 1.09 (0.50, 2.36)	4.85	1.84 1.91 (0.84, 4.36)	2.12	3.7 (< 0.1, 19.0)	10.0 (0.3, 44.5)

<sup>a</sup> OS and PFS were estimated using Kaplan-Meier method.

<sup>b</sup> Hazard ratio in each subgroup derived from a Cox proportional hazards model with treatment as the only covariate.

<sup>c</sup> Confidence interval for ORR calculated using the Clopper-Pearson method.

<sup>d</sup> PD-L1+ TAIC in the tumour microenvironment were qualitatively assessed, and characterised as “numerous”, “intermediate”, and “rare” based on pathologist assessments. “Numerous” and “intermediate” groups were combined to define the “abundant” group.

Patients with investigator-assessed primary site of oropharyngeal cancer were tested for HPV (determined by p16 immunohistochemistry [IHC]). OS benefit was observed regardless of HPV status (HPV-positive: HR = 0.63; 95% CI: 0.38, 1.04, HPV-negative: HR = 0.64; 95% CI: 0.40, 1.03, and HPV-unknown: HR = 0.78; 95% CI: 0.55, 1.10).

Patient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30, EORTC QLQ-H&N35, and 3-level EQ-5D. Over 15 weeks of follow-up, patients treated with nivolumab exhibited stable PROs, while those assigned to investigator's choice therapy exhibited significant declines in functioning (e.g., physical, role, social) and health status as well as increased symptomatology (e.g., fatigue, dyspnoea, appetite loss, pain, sensory problems, social contact problems). The PRO data should be interpreted in the context of the open-label study design and therefore taken cautiously.

#### *Advanced urothelial carcinoma*

##### Randomised open-label phase 3 study of nivolumab in combination with chemotherapy vs. chemotherapy (CA209901)

The safety and efficacy of nivolumab in combination with cisplatin and gemcitabine followed by nivolumab monotherapy were evaluated in a randomised open-label study CA209901 in cisplatin-eligible patients with unresectable or metastatic urothelial carcinoma. The study included subjects (18 years or older) with histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra, who were eligible for cisplatin and gemcitabine. Minor histologic variants (< 50% overall) were acceptable (TCC must have been the dominant histology). All subjects were required to have

measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria. No prior systemic anti-cancer therapy for metastatic or surgically unresectable urothelial carcinoma was permitted. Prior neoadjuvant chemotherapy or prior adjuvant platinum-based chemotherapy following radical cystectomy were permitted as long as the disease recurrence took place  $\geq 12$  months from completion of therapy. Prior intravesical therapy was permitted if completed at least 4 weeks prior to initiation of study treatment. Radiation therapy (with or without chemotherapy) with curative intent was permitted if treatment was completed  $\geq 12$  months before enrolment. Palliative radiotherapy was permitted as long as it was completed at least 2 weeks prior to therapy.

A total of 608 patients were randomised to receive either nivolumab in combination with cisplatin and gemcitabine (n = 304) or cisplatin and gemcitabine (n = 304). Randomisation was stratified by tumour PD-L1 status ( $\geq 1\%$  vs.  $< 1\%$  or indeterminate) and liver metastasis (yes vs. no). The median age was 65 years of age (range: 32 to 86) with 51% of patients  $\geq 65$  years of age and 12% of patients  $\geq 75$  years of age, 23% were Asian, 72% were White, 0.3% were Black; 77% were male, 23% were female. Baseline ECOG performance status was 0 (53%) or 1 (46%). Patients in the nivolumab in combination with cisplatin and gemcitabine arm were treated with nivolumab 360 mg every three weeks, in combination with cisplatin and gemcitabine for up to 6 cycles, after which patients received nivolumab monotherapy 480 mg every 4 weeks for a total of up to 24 months. Patients received gemcitabine dosed at 1000 mg/m<sup>2</sup> IV over 30-minutes on Days 1 and 8 of the 3 week treatment cycle and cisplatin dosed at 70 mg/m<sup>2</sup> IV over 30 to 120-minutes on Day 1 of the 3 week treatment cycle. A total of 92 patients (49 in the nivolumab in combination with cisplatin and gemcitabine arm and 43 in the cisplatin and gemcitabine arm) switched from cisplatin to carboplatin after at least one cycle of cisplatin.

The study demonstrated a statistically significant benefit in OS and PFS for patients randomised to nivolumab in combination with cisplatin and gemcitabine compared to cisplatin and gemcitabine alone. Efficacy results are presented in Table 34 and [Figures 22](#) and [23](#).

**Table 34: Efficacy Results (CA209901)**

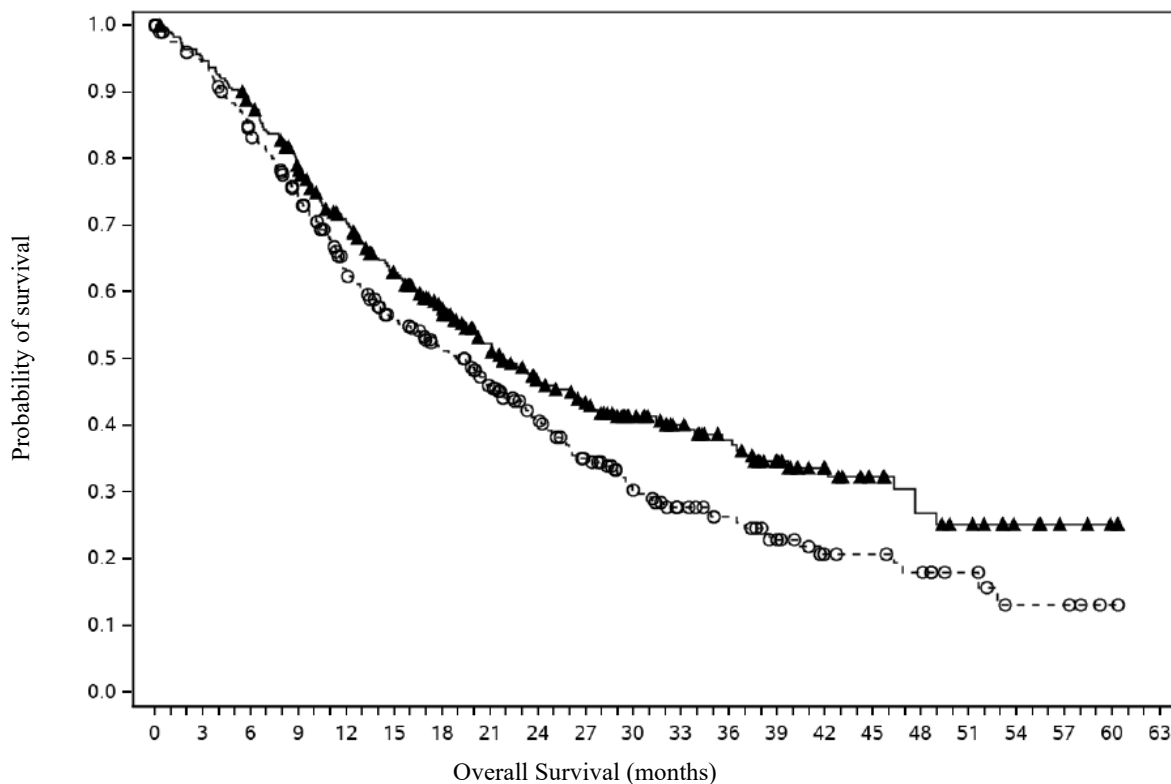
	<b>nivolumab and cisplatin-gemcitabine chemotherapy (n = 304)</b>	<b>cisplatin- gemcitabine chemotherapy (n = 304)</b>
<b>Overall Survival<sup>a</sup></b>		
Events	172 (56.6)	193 (63.5)
Median (months) (95% CI)	21.7 (18.6, 26.4)	18.9 (14.7, 22.4)
Hazard ratio (95% CI) <sup>b</sup>	0.78 (0.63, 0.96)	
p-value <sup>c</sup>	0.0171	
<b>Progression-free Survival<sup>a</sup></b>		
Events	211 (69.4)	191 (62.8)
Median (months) (95% CI)	7.92 (7.62, 9.49)	7.56 (6.05, 7.75)
Hazard ratio (95% CI) <sup>b</sup>	0.72 (0.59, 0.88)	
p-value <sup>c</sup>	0.0012	
<b>Objective Response Rate</b>		
Responders (95% CI)	175 (57.6) (51.8, 63.2)	131 (43.1) (37.5, 48.9)

<sup>a</sup> Based on Kaplan-Meier Estimates

<sup>b</sup> Stratified Cox proportional hazard model.

<sup>c</sup> 2 sided p-value from stratified log-rank test.

**Figure 22: Kaplan Meier curves of OS (CA209901)**



Number of subjects at risk

Nivolumab + gemcitabine-cisplatin chemotherapy

304 286 264 228 196 167 142 119 97 84 69 58 48 36 25 20 15 12 7 4 2 0

Gemcitabine-cisplatin chemotherapy

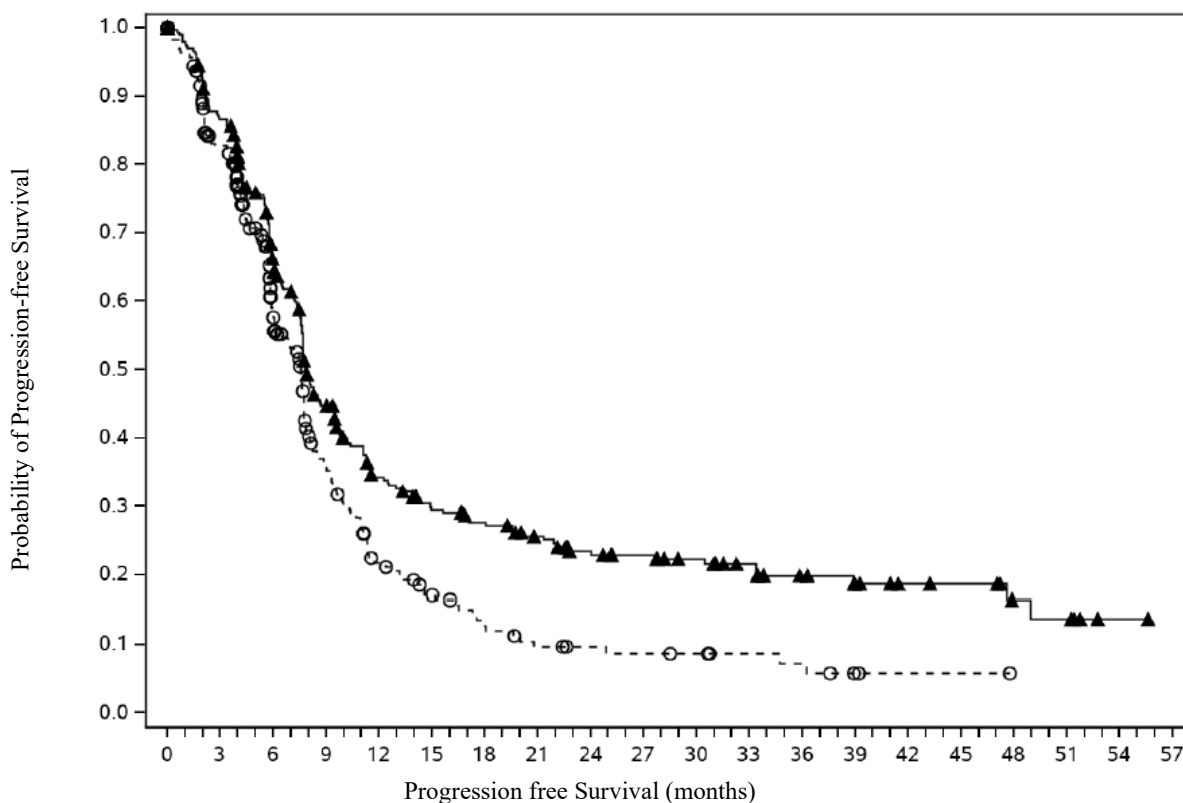
304 277 242 208 166 140 122 102 82 65 49 39 33 24 17 16 13 9 4 4 1 0

---▲--- Nivolumab + gemcitabine-cisplatin chemotherapy (events: 172/304), median and 95% CI: 21.72 (18.63, 26.38)

---○--- Gemcitabine-cisplatin chemotherapy (events: 193/304), median and 95% CI: 18.85 (14.72, 22.44)

Based on clinical data cut-off: 09-May-2023, minimum follow-up of 7.4 months

**Figure 23: Kaplan Meier curves of PFS (CA209901)**



Number of subjects at risk

Nivolumab + gemcitabine-cisplatin chemotherapy

304 253 179 116 82 65 57 49 41 36 31 26 19 14 11 10 10 6 5 1 0

Gemcitabine-cisplatin chemotherapy

304 223 119 63 35 25 17 12 12 10 9 8 6 5 2 1 1 0 0 0 0

---▲--- Nivolumab + gemcitabine-cisplatin chemotherapy (events: 211/304), median and 95% CI: 7.92 (7.62, 9.49)

---○--- Gemcitabine-cisplatin chemotherapy (events: 191/304), median and 95% CI: 7.56 (6.05, 7.75)

Based on clinical data cut-off: 09-May-2023, minimum follow-up of 7.4 months

The primary analysis of PFS included censoring for new anti-cancer treatment before disease progression (Table 34). Results for PFS with and without censoring for new anti-cancer treatment before disease progression were consistent.

#### Open-label phase 2 study (CA209275)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma was evaluated in a phase 2, multicentre, open-label, single-arm study (CA209275).

The study included patients (18 years or older) who had disease progression during or following platinum-containing chemotherapy for advanced or metastatic disease or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Patients had an ECOG performance status score of 0 or 1 and were enrolled regardless of their tumour PD-L1 status. Patients with active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients that received more than 2 prior lines of chemotherapy with liver metastases were excluded.

A total of 270 patients who received nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks with a minimum follow-up of 8.3 months were evaluable for efficacy. Treatment was

continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 8 weeks after the start of treatment and continued every 8 weeks thereafter up to 48 weeks, then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit, did not have rapid disease progression, and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was ORR as determined by BICR. Additional efficacy measures included duration of response, PFS and OS.

The median age was 66 years (range: 38 to 90) with 55%  $\geq$  65 years of age and 14%  $\geq$  75 years of age. The majority of patients were white (86%) and male (78%). Baseline ECOG performance status was 0 (54%) or 1 (46%).

**Table 35: Efficacy results (CA209275)<sup>a</sup>**

		nivolumab (n = 270)
<b>Confirmed objective response</b>		
(95% CI)		54 (20.0%) (15.4, 25.3)
Complete response (CR)		8 (3.0%)
Partial response (PR)		46 (17.0%)
Stable disease (SD)		60 (22.2%)
<b>Median duration of response<sup>b</sup></b>		
Months (range)		10.4 (1.9 <sup>+</sup> -12.0 <sup>+</sup> )
<b>Median time to response</b>		
Months (range)		1.9 (1.6, 7.2)
<b>Progression-free survival</b>		
Events (%)		216 (80)
Median (95% CI) months		2.0 (1.9, 2.6)
Rate (95% CI) at 6 months		26.1 (20.9, 31.5)
<b>Overall survival<sup>c</sup></b>		
Events (%)		154 (57)
Median (95% CI) months		8.6 (6.05, 11.27)
Rate (95% CI) at 12 months		41.0 (34.8, 47.1)
<b>Tumour PD-L1 expression level</b>		
< 1%		≥ 1%
<b>Confirmed objective response</b>		
(95% CI)		
16% (10.3, 22.7) n = 146		25% (17.7, 33.6) n = 124
<b>Median duration of response</b>		
Months (range)		
10.4 (3.7, 12.0 <sup>+</sup> )		Not Reached (1.9 <sup>+</sup> , 12.0 <sup>+</sup> )
<b>Progression-free survival</b>		
Median (95% CI) months		1.9 (1.8, 2.0) 3.6 (1.9, 3.7)
Rate (95% CI) at 6 months		22.0 (15.6, 29.2) 30.8 (22.7, 39.3)
<b>Overall survival</b>		
Median (95% CI) months		5.9 (4.37, 8.08) 11.6 (9.10, NE)
Rate (95% CI) at 12 months		34.0 (26.1, 42.1) 49.2 (39.6, 58.1)

<sup>++</sup> denotes a censored observation.

<sup>a</sup> median follow-up 11.5 months.

<sup>b</sup> Data unstable due to the limited duration of response.

<sup>c</sup> included 4 drug-related deaths: 1 pneumonitis, 1 acute respiratory failure, 1 respiratory failure, and 1 cardiovascular failure.

NE: non-estimable

Results from post-hoc, exploratory analyses indicate that in patients with low (e.g. <1%) to no tumour PD-L1 expression, other patient characteristics (e.g. liver metastases, visceral metastases, baseline haemoglobin <10g/dL and ECOG performance status = 1) might contribute to the clinical outcome.

#### Open-label phase 1/2 study (CA209032)

CA209032 was a Phase 1/2 open-label multi-cohort study which included a cohort of 78 patients (including 18 subjects who received planned crossover treatment with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg combination) with similar inclusion criteria to study CA209275 treated with nivolumab monotherapy 3 mg/kg for urothelial carcinoma. At a minimum follow-up of 9 months, investigator-assessed confirmed ORR was 24.4% (95% CI: 15.3, 35.4). The median duration of response was not reached (range: 4.4-16.6<sup>+</sup> months). The median OS was 9.7 months (95% CI: 7.26, 16.16) and the estimated OS rates were 69.2% (CI: 57.7, 78.2) at 6 months and 45.6% (CI: 34.2, 56.3) at 12 months.

#### Adjuvant treatment of urothelial carcinoma

##### Randomised phase 3 study of adjuvant nivolumab vs. placebo (CA209274)

The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of urothelial carcinoma was evaluated in a phase 3 multicentre, randomised, placebo-controlled, double-blinded study (CA209274). The study included patients (18 years or older) who have undergone radical resection of muscle invasive urothelial carcinoma (MIUC) originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence. The MIUC pathologic staging criteria that defines high risk patients was ypT2-ypT4a or ypN<sup>+</sup> for adult patients who received neoadjuvant cisplatin chemotherapy, and pT3-pT4a or pN<sup>+</sup> for adult patients who did not receive neoadjuvant cisplatin chemotherapy and were not eligible or refused adjuvant cisplatin chemotherapy. The study included patients regardless of their PD-L1 status, who had an ECOG performance status score of 0 or 1 (an ECOG PS of 2 was allowed for patients ineligible for neoadjuvant cisplatin chemotherapy). Tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. The study excluded patients with active, known or suspected autoimmune disease, patients who had treatment with any chemotherapy, radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment.

A total of 709 patients were randomised to receive either nivolumab 240 mg (n = 353) every 2 weeks or placebo (n = 356) every 2 weeks until recurrence or unacceptable toxicity for a maximum treatment duration of 1 year. Of these, 282 patients had tumour cell PD-L1 expression ≥ 1%; 140 in the nivolumab arm and 142 in the placebo arm. Randomisation was stratified by pathologic nodal status (N<sup>+</sup> vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), tumour cell PD-L1 expression (≥ 1% vs. < 1%/indeterminate), and use of cisplatin neoadjuvant chemotherapy. Tumour imaging assessments were to be performed every 12 weeks from the date of first dose to week 96, then every 16 weeks from week 96 to week 160, then every 24 weeks until non-urothelial tract recurrence or treatment was discontinued (whichever occurred later) for a maximum of 5 years. The primary efficacy outcome measures were disease-free survival (DFS) in all randomised patients and DFS in randomised patients with tumour cell PD-L1 expression ≥ 1%. DFS was defined as the time between the date of randomisation and the date of the first documented recurrence assessed by investigator (local urothelial tract, local non-urothelial tract or distant), or death (from any cause), whichever occurred first. Secondary efficacy outcome measures included overall survival (OS).

Baseline characteristics were generally balanced across treatment groups. In patients with tumour cell PD-L1 expression ≥ 1%, the median age was 66 years (range: 34 - 92 years), 76% were male and 76% were white. Eighty two percent had muscle invasive bladder cancer (MIBC), 18% had upper tract urothelial carcinoma (UTUC) (renal pelvis and ureter), 42% of patients received prior cisplatin in the neoadjuvant setting, 45% of patients were N<sup>+</sup> at radical resection, patients had ECOG performance status of 0 (61%), 1 (37%), or 2 (2%), and 7% of patients had a haemoglobin < 10 g/dL.



At the primary pre-specified interim analysis in patients with tumour cell PD-L1 expression  $\geq 1\%$  (minimum follow-up of 6.3 months and median follow-up of 22.1 months for the nivolumab arm), the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab as compared to placebo. Median DFS as determined by the investigator was not reached (95% CI: 21.19, N.R.) for nivolumab versus 8.41 months (95% CI: 5.59, 21.19) for placebo, HR 0.55 (98.72% CI: 0.35, 0.85), p-value = 0.0005. The primary analysis of DFS included censoring for new anti-cancer treatment. Results for DFS with and without censoring for new anti-cancer treatment were consistent.

In an updated descriptive DFS analysis in patients with tumour cell PD-L1 expression  $\geq 1\%$  (minimum follow-up of 11.4 months and median follow-up of 25.5 months for the nivolumab arm), DFS improvement was confirmed.

Efficacy results from this descriptive updated analysis are shown in Table 36 and [Figure 24](#).

**Table 36: Efficacy results in patients with tumour cell PD-L1  $\geq 1\%$  (CA209274)**

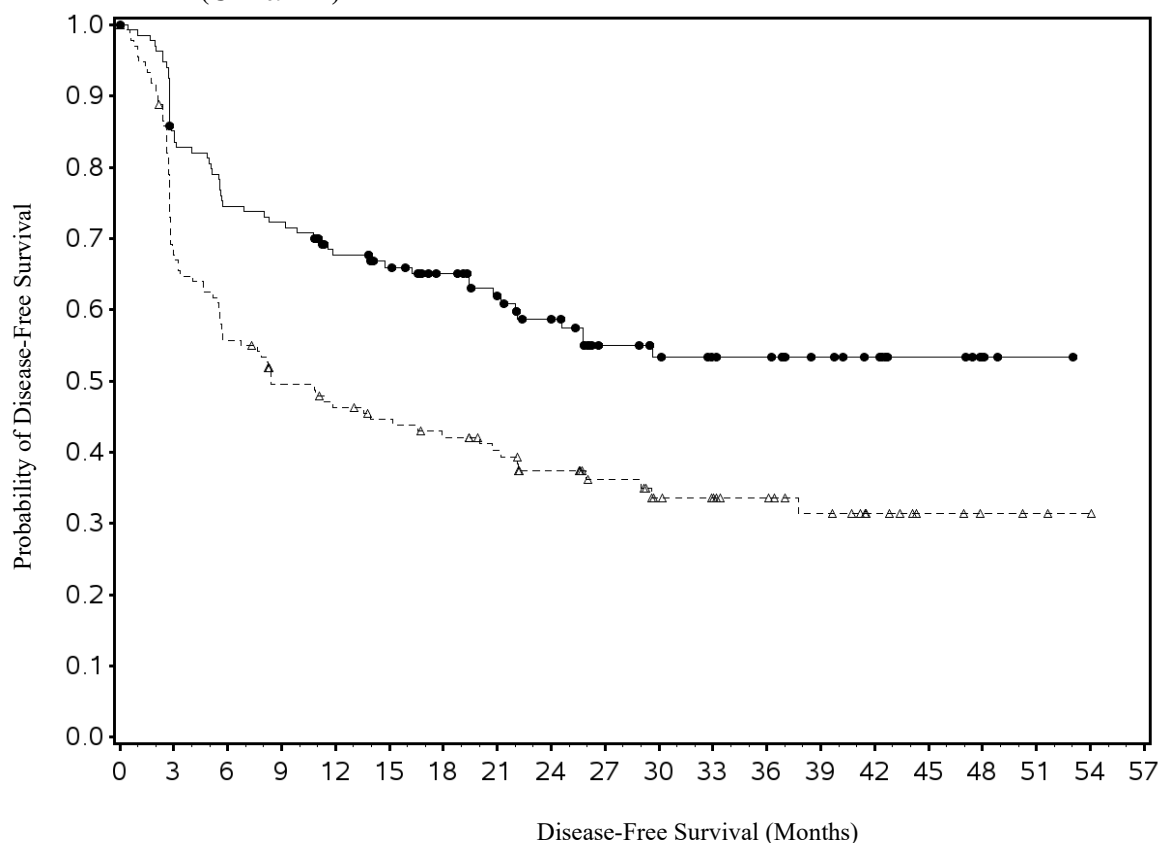
	nivolumab (n = 140)	placebo (n = 142)
<b>Disease-Free Survival</b>	Minimum follow-up 11.4 months	
Events (%)	56 (40.0)	85 (59.9)
Hazard ratio (95% CI) <sup>a</sup>	0.53 (0.38, 0.75)	
Median (95% CI) (months) <sup>b</sup>	NR (22.11, NE)	8.41 (5.59, 20.04)
Rate (95% CI) at 6 months	74.5 (66.2, 81.1)	55.7 (46.8, 63.6)
Rate (95% CI) at 12 months	67.6 (59.0, 74.9)	46.3 (37.6, 54.5)
Rate (95% CI) at 24 months	58.6 (49.3, 66.9)	37.4 (29.0, 45.8)

NR: not reached, NE: non-estimable.

<sup>a</sup> Stratified Cox proportional hazard model. Hazard Ratio is nivolumab over placebo.

<sup>b</sup> Based on Kaplan-Meier estimates.

**Figure 24: Kaplan-Meier curves of DFS in patients with tumour cell PD-L1 expression  $\geq 1\%$  (CA209274)**



Number of subjects at risk

Placebo

142 90 74 62 57 53 49 44 36 29 23 21 18 14 9 5 3 2 1 0

Nivolumab

140 113 99 96 85 75 67 58 50 38 33 30 29 22 19 8 3 1 0 0

---△--- Placebo (events: 85/142), median and 95% CI: 8.41 (5.59, 20.04)

—■— Nivolumab (events: 56/140), median and 95% CI: N.A. (22.11, N.A.)

Minimum follow-up of 11.4 months

Exploratory pre-specified subgroup descriptive analyses were performed in patients based on prior cisplatin treatment in the neoadjuvant setting.

In the subgroup of patients with tumour cell PD-L1 expression  $\geq 1\%$  who received prior cisplatin in the neoadjuvant setting (n = 118), the DFS HR was 0.37 (95% CI: 0.22, 0.64) with median DFS not reached and 8.41 months for the nivolumab and placebo arms, respectively. In the subgroup of patients with tumour cell PD-L1 expression  $\geq 1\%$  who did not receive prior cisplatin in the neoadjuvant setting (n = 164), the DFS HR was 0.69 (95% CI: 0.44, 1.08) with median DFS of 29.67 and 11.37 months for the nivolumab and placebo arms, respectively.

#### *dMMR or MSI-H colorectal cancer*

The safety and efficacy of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the treatment of dMMR or MSI-H metastatic CRC was evaluated in a Phase 2, multi-centre, open-label, single-arm study (CA209142).

The study included patients (18 years or older) with locally determined dMMR or MSI-H status, who had disease progression during, after, or were intolerant to, prior therapy with fluoropyrimidine and oxaliplatin or irinotecan. Patients who had their most recent prior treatment in the adjuvant setting should have progressed on or within 6 months of completion of adjuvant chemotherapy. Patients had

an ECOG performance status score of 0 or 1 and were enrolled regardless of their tumour PD-L1 status. Patients with active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 119 patients were treated with nivolumab 3 mg/kg administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments according to RECIST version 1.1 were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The primary outcome measure was investigator-assessed ORR. Secondary outcome measures were BICR-assessed ORR and disease control rate. Analysis of ORR included duration of and time to response. Exploratory outcome measures included PFS and OS.

The median age was 58 years (range: 21-88) with 32%  $\geq$  65 years of age and 9%  $\geq$  75 years of age, 59% were male and 92% were white. Baseline ECOG performance status was 0 (45%) or 1 (55%), 25% of patients had BRAF mutations, 37% had KRAS mutations, and 12% were unknown. Of the 119 treated patients, 109 had received prior fluoropyrimidine based chemotherapy in the metastatic setting and 9 in the adjuvant setting. Before study enrolment, of the 119 treated patients, 118 (99%) had received fluorouracil, 111 (93%) had received oxaliplatin, 87 (73%) had received irinotecan as part of prior therapies; 82 (69%) had received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Twenty three percent, 36%, 24%, and 16% received 1, 2, 3, or 4 or more prior therapies respectively, and 29% of patients had received an EGFR inhibitor.

Efficacy results (minimum follow-up 46.9 months; median follow-up 51.1 months) are shown in Table 37.

**Table 37: Efficacy results (CA209142)\***

	<b>nivolumab + ipilimumab (n = 119)</b>
<b>Confirmed objective response, n (%)</b>	77 (64.7)
(95% CI)	(55.4, 73.2)
Complete response (CR), n (%)	15 (12.6)
Partial response (PR), n (%)	62 (52.1)
Stable disease (SD), n (%)	25 (21.0)
<b>Duration of response</b>	
Median (range) months	NR (1.4, 58.0+)
<b>Median time to response</b>	
Months (range)	2.8 (1.1, 37.1)

\* per investigator assessment

“+” denotes a censored observation.

NR = not reached

The BICR-assessed ORR was 61.3% (95% CI: 52.0, 70.1), including CR rate of 20.2% (95% CI: 13.4, 28.5), PR rate of 41.2% (95% CI: 32.2, 50.6) and stable disease reported in 22.7%. BICR assessments were generally consistent with the investigator assessment. Confirmed responses were observed regardless of BRAF or KRAS mutation status, and tumour PD-L1 expression levels.

Of 119 patients 11 (9.2%) patients were  $\geq$  75 years. The investigator assessed ORR in patients  $\geq$  75 years was 45.5% (95% CI: 16.7, 76.6).

### *Oesophageal squamous cell carcinoma*

#### Randomised phase 3 study of nivolumab monotherapy in previously treated patients (ONO-4538-24/CA209473)

The safety and efficacy of nivolumab 240 mg monotherapy for the treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) was evaluated in a

phase 3 randomised active-controlled, open-label study (ONO-4538-24/CA209473). The study included adult patients (20 years or older) who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based combination regimen, and patients were enrolled regardless of tumour PD-L1 expression level. Patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had active autoimmune disease, medical conditions requiring systemic immunosuppression, and patients with apparent tumour invasion in organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), were excluded from the study.

A total of 419 patients were randomised 1:1 to receive either nivolumab 240 mg administered intravenously over 30 minutes every 2 weeks (n = 210) or investigator’s choice of taxane chemotherapy: either docetaxel (n = 65) 75 mg/m<sup>2</sup> intravenously every 3 weeks, or paclitaxel (n = 144) 100 mg/m<sup>2</sup> intravenously once a week for 6 weeks followed by 1 week off. Randomisation was stratified by location (Japan vs. rest of world), number of organs with metastases ( $\leq 1$  vs.  $\geq 2$ ) and tumour PD-L1 expression ( $\geq 1\%$  vs.  $<1\%$  or indeterminate). Treatment continued until disease progression, assessed by the investigator per RECIST version 1.1, or unacceptable toxicity. Tumour assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab with no rapid progression, investigator-assessed benefit, tolerance to treatment, stable performance status, and for whom treatment beyond progression would not delay an imminent intervention to prevent serious complications associated with disease progression (e.g. brain metastasis). The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at a predefined level of 1%. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Baseline characteristics were generally balanced between the two groups. The median age was 65 years (range: 33-87), 53% were  $\geq 65$  years of age, 10% were aged  $\geq 75$  years, 87% were male, 96% were Asian and 4% were white. Baseline ECOG performance status was 0 (50%) or 1 (50%).

With a minimum follow-up of 17.6 months, the study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator’s choice taxane chemotherapy. Efficacy results are shown in Table 38 and [Figure 25](#).

A higher proportion of patients experienced death within the first 2.5 months in the nivolumab arm (32/210, 15.2%) as compared to the chemotherapy arm (15/209, 7.2%). No specific factor(s) associated with early deaths could be identified.

**Table 38: Efficacy results (ONO-4538-24/CA209473)**

	nivolumab (n = 210)	investigator’s choice (n = 209)
<b>Overall Survival<sup>a</sup></b>		
Events	160 (76%)	173 (83%)
Hazard ratio (95% CI) <sup>b</sup>	0.77 (0.62, 0.96)	
p-value <sup>c</sup>	0.0189	
Median (95% CI) (months)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)

	nivolumab (n = 210)	investigator's choice (n = 209)
<b>Objective Response Rate<sup>d,e</sup></b>	33 (19.3%)	34 (21.5%)
(95% CI)	(13.7, 26.0)	(15.4, 28.8)
Complete response	1 (0.6%)	2 (1.3%)
Partial response	32 (18.7%)	32 (20.3%)
Stable disease	31 (18.1%)	65 (41.1%)
Median duration of response (95% CI) (months)	6.9 (5.4, 11.1)	3.9 (2.8, 4.2)
<b>Progression-Free Survival<sup>a</sup></b>		
Events	187 (89%)	176 (84%)
Median (95% CI) (months)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
Hazard ratio (95% CI) <sup>b</sup>	1.1 (0.9, 1.3)	

<sup>a</sup> Based on ITT analysis.

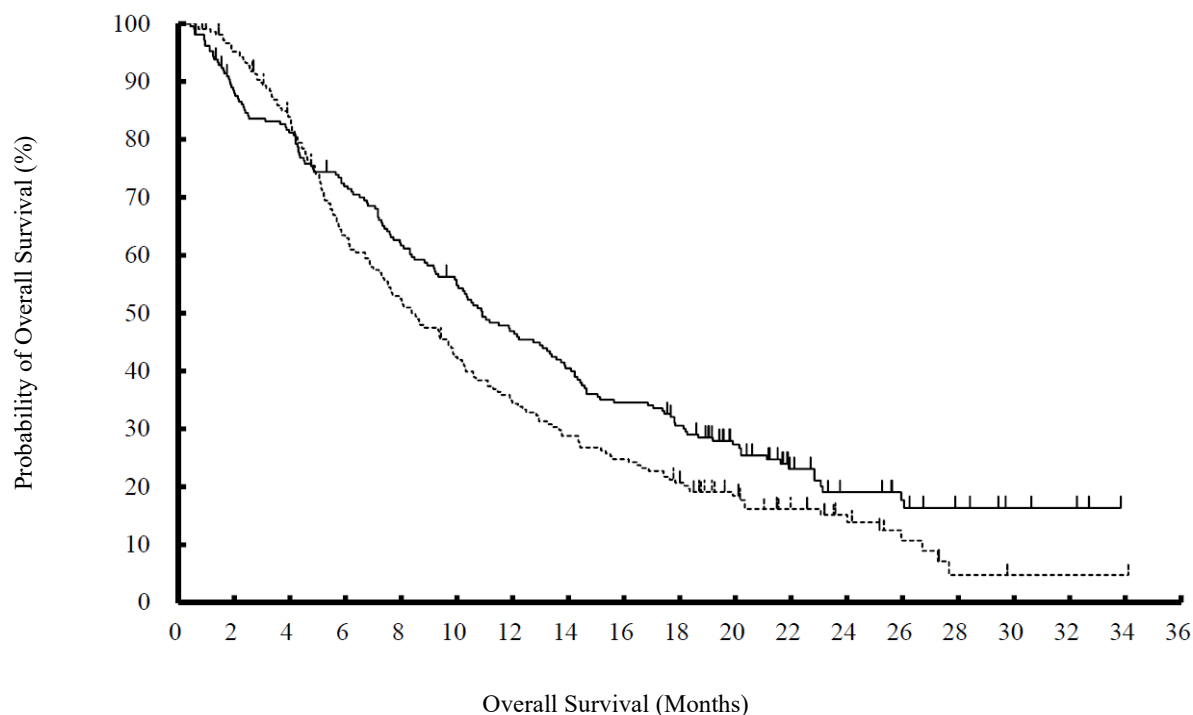
<sup>b</sup> Based on a stratified proportional hazards model.

<sup>c</sup> Based on a stratified log-rank test.

<sup>d</sup> Based on Response Evaluable Set (RES) analysis, n=171 in nivolumab group and n=158 in investigator's choice group.

<sup>e</sup> Not significant, p-value 0.6323.

**Figure 25: Kaplan-Meier curves of OS (ONO-4538-24/CA209473)**



Number of subjects at risk

Nivolumab

210 182 167 147 126 111 95 82 70 60 43 25 17 13 7 4 3 0 0

Investigator's choice

209 196 169 126 105 84 68 57 49 40 27 17 12 6 2 1 1 1 0

———— Nivolumab    - - - - - Investigator's choice

Of the 419 patients, 48% had tumour PD-L1 expression  $\geq 1\%$ . The remaining 52% of patients had tumour PD-L1 expression  $<1\%$ . The hazard ratio (HR) for OS was 0.69 (95% CI: 0.51, 0.94) with median survivals of 10.9 and 8.1 months for the nivolumab and investigator's choice taxane chemotherapy arms, respectively, in the tumour PD-L1 positive subgroup. In the tumour PD-L1

negative OSCC subgroup, the HR for OS was 0.84 (95% CI: 0.62, 1.14) with median survivals of 10.9 and 9.3 months for the nivolumab and chemotherapy arms, respectively.

*Randomised phase 3 study of nivolumab in combination with ipilimumab vs. chemotherapy and nivolumab in combination with chemotherapy vs. chemotherapy as first-line treatment (CA209648)*

The safety and efficacy of nivolumab in combination with ipilimumab and nivolumab in combination with chemotherapy were evaluated in a randomised, active-controlled, open-label study (CA209648). The study included adult patients (18 years or older) with previously untreated, unresectable advanced, recurrent or metastatic OSCC. Patients were enrolled regardless of their tumour PD-L1 status, and tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. Patients were required to have squamous cell carcinoma or adenosquamous cell carcinoma of oesophagus, not amenable to chemoradiation and/or surgery. Prior adjuvant, neoadjuvant, or definitive chemotherapy, radiotherapy or chemoradiotherapy was permitted if given as part of curative intent regimen prior to trial enrollment. Patients who had a baseline performance score  $\geq 2$ , had brain metastases that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the study. Randomisation was stratified by tumour cell PD-L1 status ( $\geq 1\%$  vs.  $< 1\%$  or indeterminate), region (East Asia vs. rest of Asia vs. rest of world), ECOG performance status (0 vs. 1), and number of organs with metastases ( $\leq 1$  vs.  $\geq 2$ ).

A total of 970 patients were randomised to receive either nivolumab in combination with ipilimumab, (n = 325), nivolumab in combination with chemotherapy (n = 321), or chemotherapy (n = 324). Of these, 473 patients had tumour cell PD-L1 expression  $\geq 1\%$ , 158 in the nivolumab plus ipilimumab arm, 158 in the nivolumab plus chemotherapy arm, and 157 in the chemotherapy arm. Patients in the nivolumab plus ipilimumab arm received nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks, and patients in the nivolumab plus chemotherapy arm received nivolumab 240 mg every 2 weeks on days 1 and 15, fluorouracil 800 mg/m<sup>2</sup>/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m<sup>2</sup> intravenously on day 1 (of a 4-week cycle). Patients in the chemotherapy arm received fluorouracil 800 mg/m<sup>2</sup>/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m<sup>2</sup> intravenously on day 1 (of a 4-week cycle). Treatment continued until disease progression, unacceptable toxicity, or up to 24 months. Patients in the nivolumab plus ipilimumab arm who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Patients in the nivolumab plus chemotherapy arm in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued.

Baseline characteristics were generally balanced across treatment groups. In patients with tumour cell PD-L1 expression  $\geq 1\%$ , the median age was 63 years (range: 26-85), 8.2% were  $\geq 75$  years of age, 81.8% were male, 73.1% were Asian, and 23.3% were white. Patients had histological confirmation of squamous cell carcinoma (98.9%) or adenosquamous cell carcinoma (1.1%) in the oesophagus. Baseline ECOG performance status was 0 (45.2%) or 1 (54.8%).

*Nivolumab in combination with ipilimumab vs. chemotherapy*

The primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with tumour cell PD-L1 expression  $\geq 1\%$ . Secondary endpoints per the pre-specified hierarchical testing included OS, PFS (by BICR), and ORR (by BICR) in all randomised patients. The tumour assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

At the primary pre-specified analysis, with a minimum follow-up of 13.1 months, the study demonstrated a statistically significant improvement in OS in patients with tumour cell PD-L1 expression  $\geq 1\%$ . Efficacy results are shown in [Table 39](#).

**Table 39: Efficacy results in patients with tumour cell PD-L1  $\geq$  1% (CA209648)**

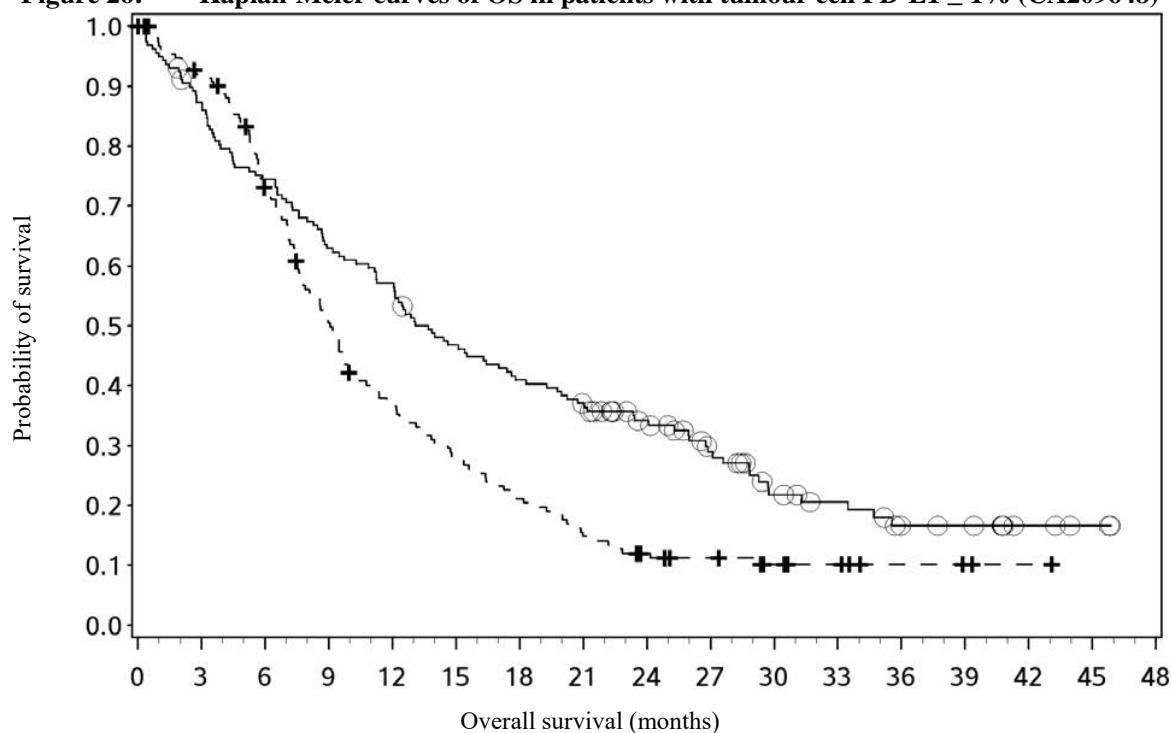
	nivolumab + ipilimumab (n = 158)	chemotherapy <sup>a</sup> (n = 157)
<b>Overall survival</b>		
Events	106 (67.1%)	121 (77.1%)
Hazard ratio (98.6% CI) <sup>b</sup>		0.64 (0.46, 0.90)
p-value <sup>c</sup>		0.0010
Median (95% CI) (months) <sup>d</sup>	13.70 (11.24, 17.02)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months <sup>d</sup>	57.1 (49.0, 64.4)	37.1 (29.2, 44.9)
<b>Progression-free survival<sup>e</sup></b>		
Events	123 (77.8%)	100 (63.7%)
Hazard ratio (98.5% CI) <sup>b</sup>		1.02 (0.73, 1.43)
p-value <sup>c</sup>		0.8958
Median (95% CI) (months) <sup>d</sup>	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)
Rate (95% CI) at 12 months <sup>d</sup>	26.4 (19.5, 33.9)	10.5 (4.7, 18.8)
<b>Overall response rate, n (%)<sup>e</sup></b>		
(95% CI)	56 (35.4) (28.0, 43.4)	31 (19.7) (13.8, 26.8)
Complete response	28 (17.7)	8 (5.1)
Partial response	28 (17.7)	23 (14.6)
<b>Duration of response<sup>e</sup></b>		
Median (95% CI) (months) <sup>d</sup>	11.83 (7.10, 27.43)	5.68 (4.40, 8.67)
Range	1.4 <sup>+</sup> , 34.5 <sup>+</sup>	1.4 <sup>+</sup> , 31.8 <sup>+</sup>

<sup>a</sup> Fluorouracil and cisplatin.<sup>b</sup> Based on stratified Cox proportional hazard model.<sup>c</sup> Based on stratified 2-sided log-rank test.<sup>d</sup> Based on Kaplan-Meier estimates.<sup>e</sup> Assessed by BICR.

At an updated descriptive analysis with a minimum follow-up of 20 months, OS improvements were consistent with the primary analysis. Median OS was 13.70 months (95% CI: 11.24, 17.41) for nivolumab plus ipilimumab vs. 9.07 months (95% CI: 7.69, 10.02) for chemotherapy (HR = 0.63; 95% CI: 0.49, 0.82). Median PFS was 4.04 months (95% CI: 2.40, 4.93) for nivolumab plus ipilimumab vs. 4.44 months (95% CI: 2.89, 5.82) for chemotherapy (HR = 1.02; 95% CI: 0.77, 1.34). The ORR was 35.4% (95% CI: 28.0, 43.4) for nivolumab plus ipilimumab vs. 19.7% (95% CI: 13.8, 26.8) for chemotherapy.

The Kaplan-Meier curves for OS with a minimum follow-up of 20 months are shown in [Figure 26](#).

**Figure 26: Kaplan-Meier curves of OS in patients with tumour cell PD-L1  $\geq 1\%$  (CA209648)**



Number of subjects at risk

Nivolumab + ipilimumab

158 136 116 98 89 72 63 55 43 31 20 16 10 9 4 2 0

Chemotherapy

157 137 107 73 53 40 30 21 15 12 8 6 3 2 1 0 0

—○— Nivolumab + ipilimumab (events: 119/158), median and 95% CI: 13.70 (11.24, 17.41)

- - - + - - - Chemotherapy (events: 130/157), median and 95% CI: 9.07 (7.69, 10.02)

Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

#### *Nivolumab in combination with chemotherapy vs. chemotherapy*

The primary efficacy outcome measures were PFS (by BICR) and OS in patients with tumour cell PD-L1 expression  $\geq 1\%$ . Secondary endpoints per the pre-specified hierarchical testing included OS, PFS (by BICR), and ORR (by BICR) in all randomised patients. The tumour assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

At the primary pre-specified analysis, with a minimum follow-up of 12.9 months the study demonstrated a statistically significant improvement in OS and PFS in patients with tumour cell PD-L1 expression  $\geq 1\%$ . Efficacy results are shown in Table 40.

**Table 40: Efficacy results in patients with tumour cell PD-L1  $\geq 1\%$  (CA209648)**

	nivolumab + chemotherapy (n = 158)	chemotherapy <sup>a</sup> (n = 157)
<b>Overall survival</b>		
Events	98 (62.0%)	121 (77.1%)
Hazard ratio (99.5% CI) <sup>b</sup>	0.54 (0.37, 0.80)	
p-value <sup>c</sup>	<0.0001	
Median (95% CI) (months) <sup>d</sup>	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months <sup>d</sup>	58.0 (49.8, 65.3)	37.1 (29.2, 44.9)



	nivolumab + chemotherapy (n = 158)	chemotherapy <sup>a</sup> (n = 157)
<b>Progression-free survival<sup>e</sup></b>		
Events	117 (74.1%)	100 (63.7%)
Hazard ratio (98.5% CI) <sup>b</sup>	0.65 (0.46, 0.92)	
p-value <sup>c</sup>	0.0023	
Median (95% CI) (months) <sup>d</sup>	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)
Rate (95% CI) at 12 months <sup>d</sup>	25.4 (18.2, 33.2)	10.5 (4.7, 18.8)
<b>Overall response rate, n (%)<sup>e</sup></b>		
(95% CI)	84 (53.2) (45.1, 61.1)	31 (19.7) (13.8, 26.8)
Complete response	26 (16.5)	8 (5.1)
Partial response	58 (36.7)	23 (14.6)
<b>Duration of response<sup>e</sup></b>		
Median (95% CI) (months) <sup>d</sup>	8.38 (6.90, 12.35)	5.68 (4.40, 8.67)
Range	1.4 <sup>+</sup> , 34.6	1.4 <sup>+</sup> , 31.8 <sup>+</sup>

<sup>a</sup> Fluorouracil and cisplatin.

<sup>b</sup> Based on stratified Cox proportional hazard model.

<sup>c</sup> Based on stratified 2-sided log-rank test.

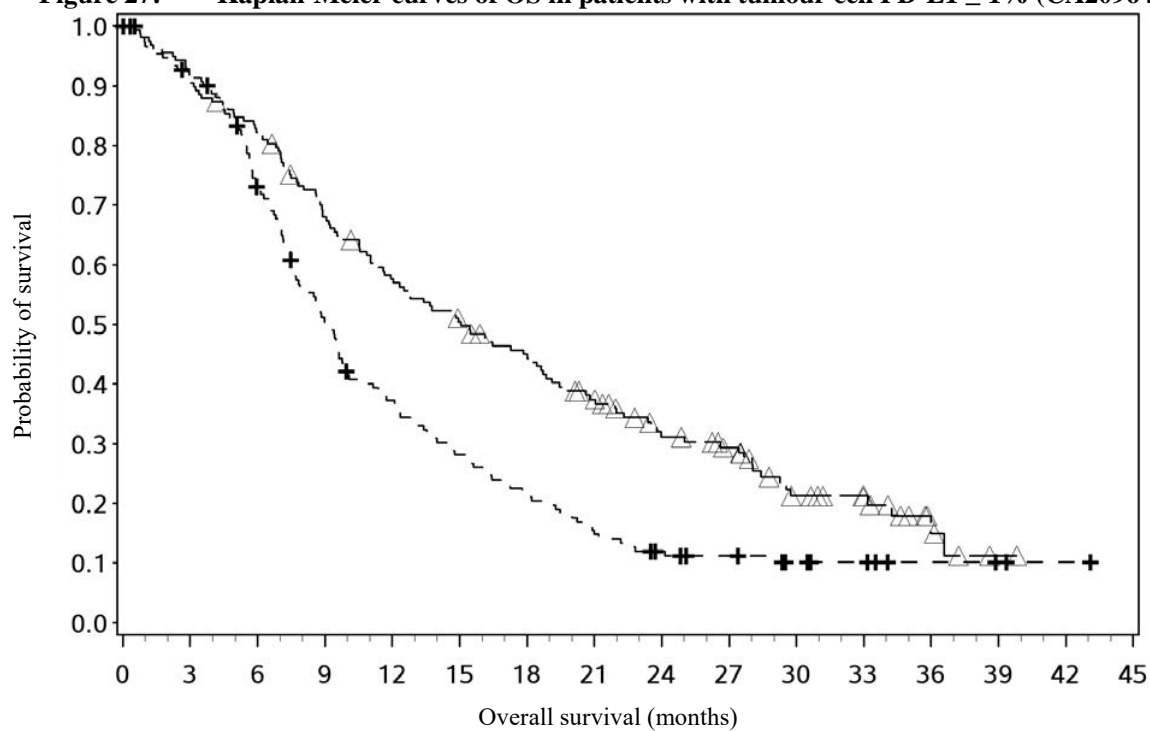
<sup>d</sup> Based on Kaplan-Meier estimates.

<sup>e</sup> Assessed by BICR.

At an updated descriptive analysis with a minimum follow-up of 20 months, OS improvements were consistent with the primary analysis. Median OS was 15.05 months (95% CI: 11.93, 18.63) for nivolumab plus chemotherapy vs. 9.07 months (95% CI: 7.69, 10.02) for chemotherapy (HR = 0.59; 95% CI: 0.46, 0.76). Median PFS was 6.93 months (95% CI: 5.68, 8.35) for nivolumab plus chemotherapy vs. 4.44 months (95% CI: 2.89, 5.82) for chemotherapy (HR = 0.66; 95% CI: 0.50, 0.87). The ORR was 53.2% (95% CI: 45.1, 61.1) for nivolumab plus chemotherapy vs. 19.7% (95% CI: 13.8, 26.8) for chemotherapy.

The Kaplan-Meier curves for OS and PFS with a minimum follow-up of 20 months are shown in [Figures 27](#) and [28](#).

**Figure 27: Kaplan-Meier curves of OS in patients with tumour cell PD-L1  $\geq 1\%$  (CA209648)**



Number of subjects at risk

Nivolumab + chemotherapy

158 143 129 105 88 76 66 52 38 32 19 15 5 1 0 0

Chemotherapy

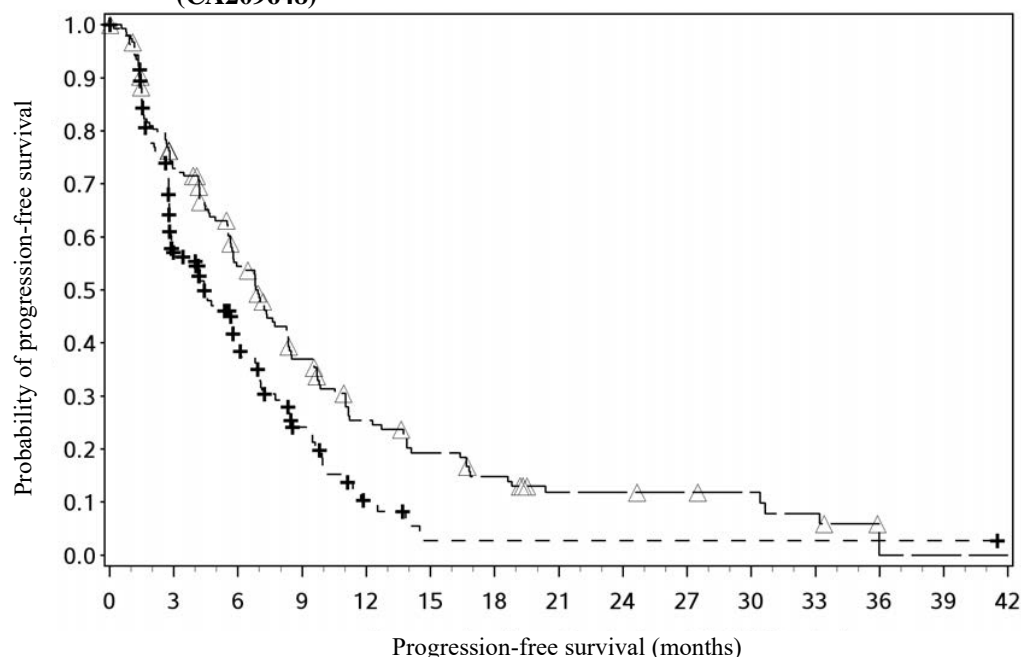
157 137 107 73 53 40 30 21 15 12 8 6 3 2 1 0

---△--- Nivolumab + chemotherapy (events: 118/158), median and 95% CI: 15.05 (11.93, 18.63)

---+--- Chemotherapy (events: 130/157), median and 95% CI: 9.07 (7.69, 10.02)

Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

**Figure 28: Kaplan-Meier curves of PFS in patients with tumour cell PD-L1  $\geq 1\%$  (CA209648)**



Number of subjects at risk

Nivolumab + chemotherapy

158 107 75 47 30 22 16 10 10 7 6 4 0 0 0

Chemotherapy

157 68 36 17 5 1 1 1 1 1 1 1 1 1 0

---△--- Nivolumab + chemotherapy (events: 123/158), median and 95% CI: 6.93 (5.65, 8.35)

---+--- Chemotherapy (events: 101/157), median and 95% CI: 4.44 (2.89, 5.82)

Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

#### *Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer*

The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer was evaluated in a phase 3 multicentre, randomised, placebo-controlled, double-blinded study (CA209577). The study included adult patients who had received CRT, followed by complete surgical resection of carcinoma within 16 weeks prior to randomisation, and who had residual pathologic disease as confirmed by the investigator, with at least ypN1 or ypT1. Patients with a baseline performance score  $\geq 2$ , who did not receive concurrent CRT prior to surgery, with stage IV resectable disease, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were enrolled regardless of tumour PD-L1 expression level.

A total of 794 patients were randomised 2:1 to receive either nivolumab 240 mg (n = 532) or placebo (n = 262). Patients were administered nivolumab intravenously over 30 minutes every 2 weeks for 16 weeks followed by 480 mg infused over 30 minutes every 4 weeks beginning at week 17. Patients were administered placebo over 30 minutes with the same dosing schedule as nivolumab. Randomisation was stratified by tumour PD-L1 status ( $\geq 1\%$  vs.  $<1\%$  or indeterminate or non-evaluable), pathologic lymph node status (positive  $\geq$  ypN1 vs. negative ypN0), and histology (squamous vs. adenocarcinoma). Treatment continued until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. The primary efficacy outcome measure was disease-free survival (DFS), as assessed by the investigator, defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant from the primary resected site) or death from any cause, whichever occurred first. Patients on treatment underwent imaging for tumour recurrence every 12 weeks for 2 years, and a minimum of one scan every 6 to 12 months for years 3 to 5.

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 26-86) with 36%  $\geq 65$  years of age and 5%  $\geq 75$  years of years. The majority of patients were white (82%) and male (85 %). Baseline ECOG performance status was 0 (58%) or 1 (42%).

At the primary pre-specified interim analysis (minimum of 6.2 months and a median of 24.4 months follow-up), the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab compared with placebo. Median DFS as determined by the investigator was 22.41 months (95% CI: 16.62, 34.00) for nivolumab versus 11.04 months (95% CI: 8.34, 14.32) for placebo, HR 0.69 (96.4% CI: 0.56, 0.86), p-value < 0.0003. The primary analysis of DFS included censoring for new anti-cancer treatment. Results for DFS with and without censoring for new anti-cancer treatment were consistent. In an updated descriptive DFS analysis with minimum of 14 months and median of 32.2 months follow-up, DFS improvement was confirmed. Efficacy results from this descriptive secondary analysis are shown in Table 41 and [Figure 29](#).

**Table 41: Efficacy results (CA209577)**

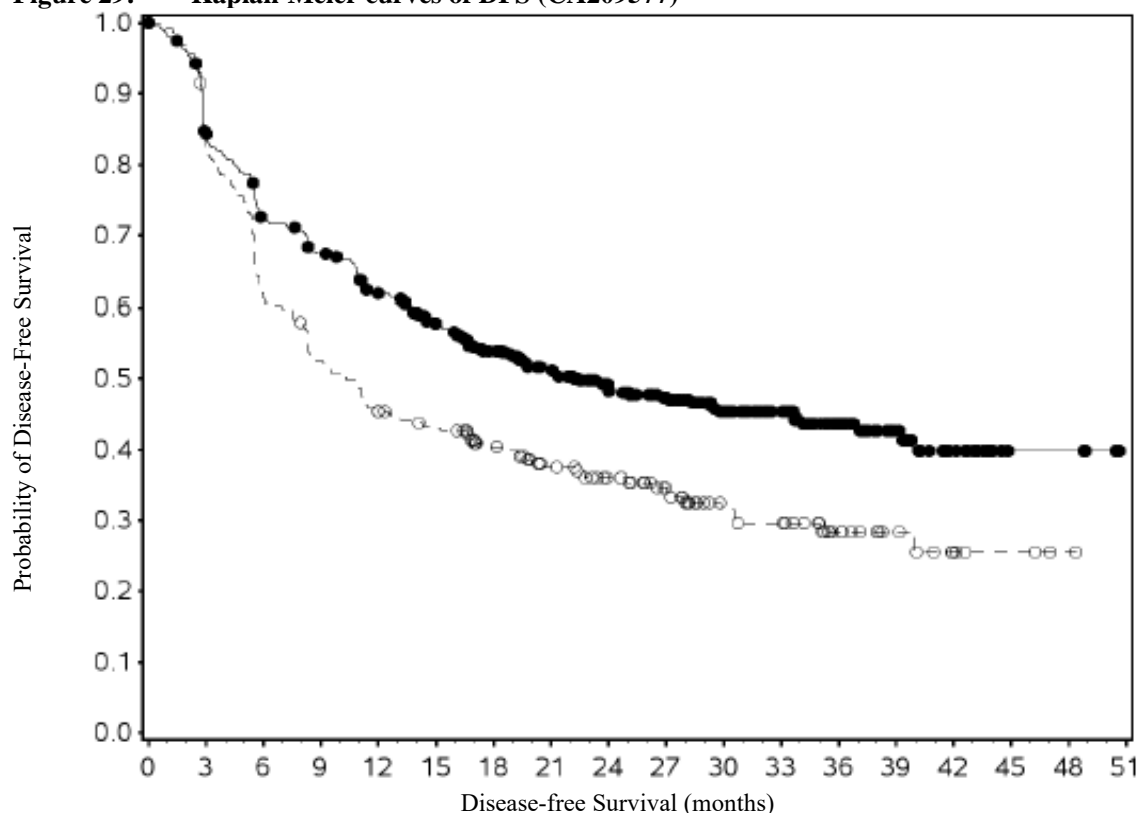
	<b>nivolumab (n = 532)</b>	<b>placebo (n = 262)</b>
<b>Disease-free Survival<sup>a</sup> with minimum follow-up 14 months<sup>c</sup></b>		
Events (%)	268 (50)	171 (65)
Hazard ratio (95% CI) <sup>b</sup>	0.67 (0.55, 0.81)	
Median (95% CI) (months)	22.4 (17.0, 33.6)	10.4 (8.3, 13.9)
Rate (95% CI) at 6 months	72.6 (68.5, 76.3)	61.5 (55.3, 67.1)
Rate (95% CI) at 12 months	61.8 (57.4, 65.8)	45.5 (39.3, 51.4)
Rate (95% CI) at 24 months	48.3 (43.7, 52.8)	36.0 (29.9, 42.0)

<sup>a</sup> Based on all randomised patients.

<sup>b</sup> Based on a stratified cox proportional hazards model.

<sup>c</sup> Descriptive analysis based on data cut-off: 18-Feb-2021.

**Figure 29: Kaplan-Meier curves of DFS (CA209577)**



Number of subjects at risk

Nivolumab	532	433	371	342	307	272	228	194	160	137	106	84	57	34	19	4	4	0
Placebo	262	211	158	134	114	107	88	73	62	50	33	30	18	11	5	3	1	0

—■— Nivolumab (events: 268/532), median and 95% CI: 22.41 (16.95, 33.64)

- - -○- - - Placebo (events: 171/262), median and 95% CI: 10.35 (8.31, 13.93)

Based on data cut-off: 18-Feb-2021, minimum follow-up of 14 months

DFS benefit was observed regardless of histology and PD-L1 expression.

#### *Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma*

The safety and efficacy of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy (dose and schedule of nivolumab selected depending on the chemotherapy regimen used, see below) was evaluated in a phase 3, randomised, open-label study (CA209649). The study included adult patients (18 years or older) with previously untreated advanced or metastatic gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma, no prior systemic treatment (including HER2 inhibitors), and ECOG performance status score 0 or 1. Patients were enrolled regardless of their tumour cell PD-L1 status, and tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. A retrospective re-scoring of a patient's tumour PD-L1 status using CPS was conducted using the PD-L1-stained tumour specimens used for randomisation. Patients with known HER2-positive tumours, who had baseline ECOG performance score  $\geq 2$ , untreated central nervous system metastases, or who had active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. A total of 643 patients with HER2-undetermined status (40.3% of the study population) were included in the study. Randomisation was stratified by tumour cell PD-L1 status ( $\geq 1\%$  vs.  $< 1\%$  or indeterminate), region (Asia vs. US vs. rest of world), ECOG performance status (0 vs. 1), and chemotherapy regimen.

Chemotherapy consisted of FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

A total of 1581 patients were randomised to receive either nivolumab in combination with chemotherapy or chemotherapy. Of these, 955 patients had PD-L1 CPS  $\geq 5$ ; 473 in the nivolumab plus chemotherapy arm and 482 in the chemotherapy arm. Patients in the nivolumab plus chemotherapy arm received either nivolumab 240 mg by intravenous infusion over 30 minutes in combination with FOLFOX (oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup> and fluorouracil 400 mg/m<sup>2</sup> intravenously on day 1 and fluorouracil 1200 mg/m<sup>2</sup> intravenously by continuous infusion over 24 hours daily or per local standard on days 1 and 2) every 2 weeks, or nivolumab 360 mg by intravenous infusion over 30 minutes in combination with CapeOX (oxaliplatin 130 mg/m<sup>2</sup> intravenously on day 1 and capecitabine 1000 mg/m<sup>2</sup> orally twice daily on days 1-14) every 3 weeks. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months for nivolumab only. In patients who received nivolumab plus chemotherapy and in whom chemotherapy was discontinued, nivolumab monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks or 480 mg every 4 weeks up to 24 months after treatment initiation. Tumour assessments were performed every 6 weeks up to and including week 48, then every 12 weeks thereafter.

Baseline characteristics were generally balanced across treatment groups. In patients with PD-L1 CPS  $\geq 5$ , the median age was 62 years (range: 18-90), 11% were  $\geq 75$  years of age, 71% were male, 25% were Asian and 69% were white. Baseline ECOG performance status was 0 (42%) or 1 (58%). Tumour locations were distributed as gastric (70%), GEJ (18%) and oesophagus (12%).

Primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with PD-L1 CPS  $\geq 5$  based on the PD-L1 IHC 28-8 pharmDX. Secondary endpoints per the pre-specified hierarchical testing were OS in patients with PD-L1 CPS  $\geq 1$  and in all randomised patients; further endpoints included ORR (BICR) in PD-L1 CPS  $\geq 5$  and all randomised patients. At the primary pre-specified analysis, with a minimum follow-up of 12.1 months, the study demonstrated a statistically significant improvement in OS and PFS in patients with PD-L1 CPS  $\geq 5$ . Median OS was 14.4 months (95% CI: 13.1, 16.2) for nivolumab in combination with chemotherapy vs. 11.1 months (95% CI: 10.0, 12.1) for chemotherapy (HR = 0.71; 98.4% CI: 0.59, 0.86; p-value <0.0001). Median PFS was 7.69 months (95% CI: 7.03, 9.17) for nivolumab in combination with chemotherapy vs. 6.05 months (95% CI: 5.55, 6.90) for chemotherapy (HR = 0.68; 98% CI: 0.56, 0.81; p-value <0.0001). The ORR was 60% (95% CI: 55, 65) for nivolumab in combination with chemotherapy vs. 45% (95% CI: 40, 50) for chemotherapy.

At an updated descriptive analysis with a minimum follow-up of 19.4 months, OS improvements were consistent with the primary analysis. Efficacy results are shown in Table 42, and [Figures 30](#), and [31](#).

**Table 42: Efficacy results in patients with PD-L1 CPS  $\geq 5$  (CA209649)**

	nivolumab + chemotherapy (n = 473)	chemotherapy (n = 482)
Minimum follow-up 19.4 months <sup>a</sup>		
<b>Overall survival</b>		
Events	344 (73%)	397 (82%)
Hazard ratio (95% CI) <sup>b</sup>	0.69 (0.60, 0.81)	
Median (95% CI) (months) <sup>c</sup>	14.4 (13.1, 16.3)	11.1 (10.0, 12.1)
Rate (95% CI) at 12 months	57.3 (52.6, 61.6)	46.4 (41.8, 50.8)
<b>Progression-free survival<sup>d</sup></b>		
Events	342 (72.3%)	366 (75.9%)
Hazard ratio (95% CI) <sup>b</sup>	0.68 (0.59, 0.79)	
Median (95% CI) (months) <sup>c</sup>	8.31 (7.03, 9.26)	6.05 (5.55, 6.90)
Rate (95% CI) at 12 months	36.3 (31.7, 41.0)	21.9 (17.8, 26.1)

	nivolumab + chemotherapy (n = 473)	chemotherapy (n = 482)
<b>Objective response rate, n<sup>d,e</sup></b>	227/378 (60%)	176/390 (45%)
(95% CI)	(54.9, 65.0)	(40.1, 50.2)
Complete response	12.2%	6.7%
Partial response	47.9%	38.5%
<b>Duration of response<sup>d,e</sup></b>		
Median (95% CI) (months) <sup>c</sup>	9.69 (8.25, 12.22)	6.97 (5.62, 7.85)

<sup>a</sup> Descriptive analysis based on data cut-off: 04-Jan-2021.

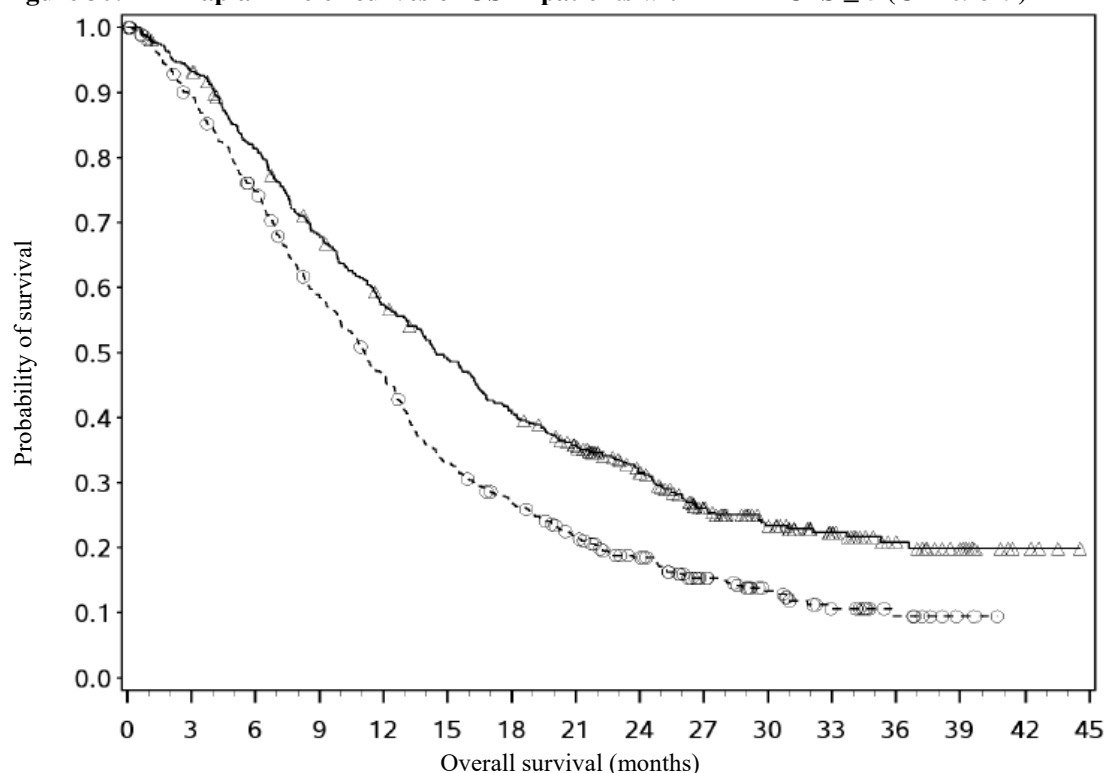
<sup>b</sup> Based on stratified long Cox proportional hazard model.

<sup>c</sup> Kaplan-Meier estimate.

<sup>d</sup> Confirmed by BICR.

<sup>e</sup> Based on patients with measurable disease at baseline.

**Figure 30: Kaplan-Meier curves of OS in patients with PD-L1 CPS  $\geq 5$  (CA209649)**



Number of subjects at risk

Nivolumab + chemotherapy

473 439 378 314 263 223 187 155 118 78 56 37 23 13 4 0

Chemotherapy

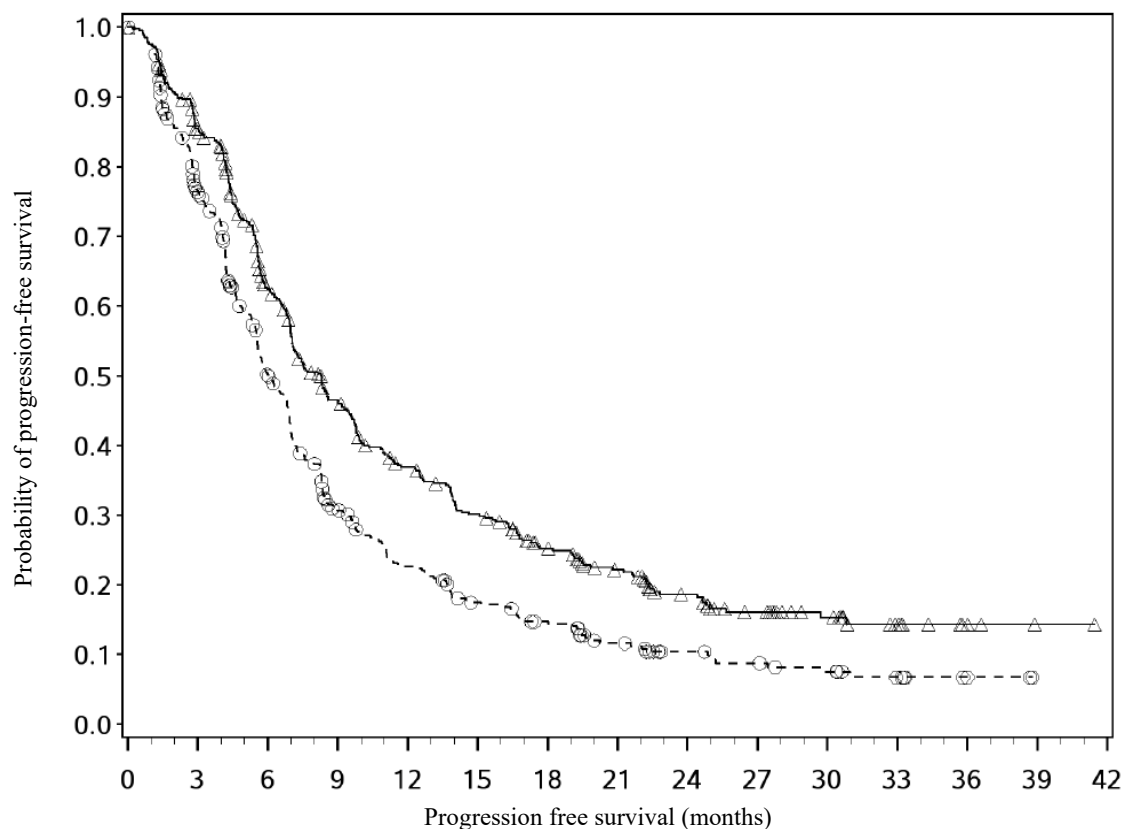
482 421 350 272 213 152 122 92 68 44 28 16 8 2 0 0

—△— Nivolumab + chemotherapy (events: 344/473), median and 95% CI: 14.42 (13.14, 16.26)

---○--- Chemotherapy (events: 397/482), median and 95% CI: 11.10 (10.02, 12.09)

Minimum follow-up of 19.4 months

**Figure 31: Kaplan-Meier curves of PFS in patients with PD-L1 CPS  $\geq 5$  (CA209649)**



Number of subjects at risk

Nivolumab + chemotherapy

473 386 259 186 143 115 88 67 47 31 20 11 4 1 0

Chemotherapy

482 328 202 114 81 58 46 30 20 16 12 7 3 0 0

—△— Nivolumab + chemotherapy (events: 342/473), median and 95% CI: 8.31 (7.03, 9.26)

---○--- Chemotherapy (events: 397/482), median and 95% CI: 6.05 (5.55, 6.90)

Minimum follow-up of 19.4 months

### Paediatric population

#### *Open label phase 1/2 study (CA209070)*

Study CA209070 was an open-label, single-arm, dose-confirmation and dose-expansion, phase 1/2 study of nivolumab as a single agent and in combination with ipilimumab in paediatric and young adult patients with recurrent or refractory solid or haematological tumours, including neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, advanced melanoma, cHL and non-Hodgkin lymphoma (NHL). Among the 126 treated patients, 97 were paediatric patients from 12 months to < 18 years of age. Of the 97 paediatric patients, 64 were treated with nivolumab monotherapy (3 mg/kg administered intravenously over 60 minutes every 2 weeks) and 33 were treated with nivolumab in combination with ipilimumab (nivolumab 1 mg/kg or 3 mg/kg administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 90 minutes every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks). Patients received either nivolumab as monotherapy for a median of 2 doses (range: 1, 89) or nivolumab in combination with ipilimumab for a median of 2 doses (range: 1, 24). The main primary outcome measures were safety, tolerability and antitumour activity as evaluated by descriptive ORR and OS.



Among the 64 paediatric patients treated with nivolumab monotherapy, 60 were response-evaluable patients (melanoma n = 1, solid tumours n = 47 and haematological tumours n = 12). In the 48 response-evaluable paediatric patients with melanoma or solid tumours, no objective responses were observed. In the 12 response-evaluable paediatric patients with haematological tumours, ORR was 25.0% (95% CI: 5.5, 57.2), including 1 complete response in cHL and 2 partial responses, one in cHL and another one in NHL. In the descriptive analyses for the 64 paediatric patients treated with nivolumab monotherapy, the median OS was 6.67 months (95% CI: 5.98, NA); 6.14 months (95% CI: 5.39, 24.67) for patients with melanoma or solid tumours, and not reached for patients with haematological tumours.

Among the 30 response-evaluable paediatric patients treated with nivolumab in combination with ipilimumab (solid tumours other than melanoma only), no objective responses were observed. For the 33 paediatric patients treated with nivolumab in combination with ipilimumab, the median OS was 8.25 months (95% CI: 5.45, 16.95) in a descriptive analysis.

#### *Open label phase 1b/2 study (CA209908)*

Study CA209908 was an open-label, sequential-arm, phase 1b/2 clinical study of nivolumab monotherapy and nivolumab in combination with ipilimumab in paediatric and young adult patients with high-grade primary CNS malignancies, including diffuse intrinsic pontine glioma (DIPG), high-grade glioma, medulloblastoma, ependymoma and other recurrent subtypes of high-grade CNS malignancy (e.g., pineoblastoma, atypical teratoid/rhabdoid tumour, and embryonal CNS tumours). Of the 151 paediatric patients (from  $\geq 6$  months to  $< 18$  years old) enrolled in the study, 77 were treated with nivolumab monotherapy (3 mg/kg every 2 weeks) and 74 were treated with nivolumab in combination with ipilimumab (3 mg/kg nivolumab followed by 1 mg/kg ipilimumab, every 3 weeks for 4 doses, followed by nivolumab monotherapy 3 mg/kg every 2 weeks). The primary efficacy outcome measures were OS in the DIPG cohort and investigator-assessed PFS, based on RANO criteria, for all other tumour types. The median OS in the DIPG cohort was 10.97 months (80% CI: 9.92, 12.16) in patients treated with nivolumab monotherapy and 10.50 months (80% CI: 9.10, 12.32) in patients treated with nivolumab in combination with ipilimumab. For all other studied CNS paediatric tumour types, the median PFS ranged from 1.23 to 2.35 months in patients treated with nivolumab monotherapy and from 1.45 to 3.09 months in patients treated with nivolumab in combination with ipilimumab. There were no objective responses observed in the study with the exception of one ependymoma patient treated with nivolumab monotherapy who had a partial response. Results for OS, PFS, and ORR observed in study CA209908 do not suggest clinically meaningful benefit over what may be expected in these patient populations.

The European Medicines Agency has deferred the obligation to submit the results of studies with nivolumab in all subsets of the paediatric population in the treatment of malignant neoplasms of lymphoid tissue (see [section 4.2](#) for information on paediatric use).

#### Safety and efficacy in elderly patients

No overall differences in safety or efficacy were reported between elderly ( $\geq 65$  years) and younger patients ( $< 65$  years). Data from SCCHN, adjuvant melanoma, and adjuvant OC or GEJC patients 75 years of age or older are too limited to draw conclusions on this population. Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population. Data from MPM patients showed a higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older (68% and 35%, respectively) relative to all patients who received nivolumab in combination with ipilimumab (54% and 28%, respectively).

## **5.2 Pharmacokinetic properties**

#### Nivolumab monotherapy

The pharmacokinetics (PK) of nivolumab is linear in the dose range of 0.1 to 10 mg/kg. The geometric mean clearance (CL), terminal half-life, and average exposure at steady state at 3 mg/kg every 2 weeks of nivolumab were 7.9 mL/h, 25.0 days, and 86.6  $\mu\text{g/mL}$ , respectively, based on a population PK analysis.

Nivolumab CL in cHL patients was approximately 32% lower relative to NSCLC. Nivolumab baseline CL in adjuvant melanoma patients was approximately 40% lower and steady state CL approximately 20% lower relative to advanced melanoma. With available safety data, these decreases in CL were not clinically meaningful.

The metabolic pathway of nivolumab has not been characterised. Nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

#### Nivolumab in combination with ipilimumab

When nivolumab 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 29% and the CL of ipilimumab was increased by 9%, which was not considered clinically relevant. When nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab was increased by 1% and the CL of ipilimumab was decreased by 1.5%, which were not considered clinically relevant.

When administered in combination with ipilimumab, the CL of nivolumab increased by 20% in the presence of anti-nivolumab antibodies and the CL of ipilimumab increased by 5.7% in the presence of anti-ipilimumab antibodies. These changes were not considered clinically relevant.

#### Nivolumab in combination with ipilimumab and chemotherapy

When nivolumab 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and with 2 cycles of chemotherapy, the CL of nivolumab decreased approximately 10% and the CL of ipilimumab increased approximately 22%, which were not considered clinically relevant.

#### Special populations

A population PK analysis suggested no difference in CL of nivolumab based on age, gender, race, solid tumour type, tumour size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful.

##### *Paediatric population*

For nivolumab monotherapy, the exposures of nivolumab in adolescents 12 years of age and older who weigh at least 50 kg are expected to be comparable to those in adult patients at the recommended dose. Body weight-based dosing is recommended for adolescents 12 years of age and older who weigh less than 50 kg.

For nivolumab in combination with ipilimumab, the exposures of nivolumab and ipilimumab in adolescents 12 years of age and older are expected to be comparable to those in adult patients at the recommended dose.

##### *Renal impairment*

The effect of renal impairment on the CL of nivolumab was evaluated in patients with mild (GFR < 90 and  $\geq 60$  mL/min/1.73 m<sup>2</sup>; n = 379), moderate (GFR < 60 and  $\geq 30$  mL/min/1.73 m<sup>2</sup>; n = 179), or severe (GFR < 30 and  $\geq 15$  mL/min/1.73 m<sup>2</sup>; n = 2) renal impairment compared to patients with normal renal function (GFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>; n = 342) in population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see [section 4.2](#)).

##### *Hepatic impairment*

The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with mild hepatic impairment (total bilirubin  $1.0 \times$  to  $1.5 \times$  ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 92) compared to patients with normal hepatic function (total bilirubin and AST  $\leq$  ULN; n = 804) in the population PK analyses. No clinically important

differences in the CL of nivolumab were found between patients with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in patients with moderate (total bilirubin  $> 1.5 \times$  to  $3 \times$  ULN and any AST) or severe hepatic impairment (total bilirubin  $> 3 \times$  ULN and any AST) (see [section 4.2](#)).

### 5.3 Preclinical safety data

Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to increase foetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels either 8 or 35 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). There was a dose-dependent increase in foetal losses and increased neonatal mortality beginning in the third trimester.

The remaining offspring of nivolumab-treated females survived to scheduled termination, with no treatment-related clinical signs, alterations to normal development, organ-weight effects, or gross and microscopic pathology changes. Results for growth indices, as well as teratogenic, neurobehavioral, immunological, and clinical pathology parameters throughout the 6-month postnatal period were comparable to the control group. However, based on its mechanism of action, foetal exposure to nivolumab may increase the risk of developing immune-related disorders or altering the normal immune response and immune-related disorders have been reported in PD-1 knockout mice.

Fertility studies have not been performed with nivolumab.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium citrate dihydrate  
Sodium chloride  
Mannitol (E421)  
Pentetic acid (diethylenetriaminepentaacetic acid)  
Polysorbate 80 (E433)  
Sodium hydroxide (for pH adjustment)  
Hydrochloric acid (for pH adjustment)  
Water for injections

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. OPDIVO should not be infused concomitantly in the same intravenous line with other medicinal products.

### 6.3 Shelf life

Unopened vial  
3 years

#### After preparation of infusion

Chemical and physical in-use stability from the time of preparation has been demonstrated as follows (times are inclusive of the administration period):

Infusion preparation	Chemical and physical in-use stability	
	Storage at 2°C to 8°C protected from light	Storage at room temperature ( $\leq 25^{\circ}\text{C}$ ) and room light
Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection	30 days	24 hours (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	7 days	8 hours (of total 7 days storage)

From a microbiological point of view the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2°C to 8°C or 8 hours (of the total 7 days of storage) at room temperature ( $\leq 25^{\circ}\text{C}$ ). Aseptic handling should be ensured during the preparation of infusion (see section 6.6).

#### **6.4 Special precautions for storage**

Store in a refrigerator (2°C-8°C).

Do not freeze.

Store in the original package in order to protect from light.

The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

For storage conditions after preparation of the infusion, see [section 6.3](#).

#### **6.5 Nature and contents of container**

4 mL of concentrate in a 10 mL vial (Type I glass) with a stopper (coated butyl rubber) and a dark blue flip-off seal (aluminium). Pack size of 1 vial.

10 mL of concentrate in a 10 mL vial (Type I glass) with a stopper (coated butyl rubber) and a grey flip-off seal (aluminium). Pack size of 1 vial.

12 mL of concentrate in a 25 mL vial (Type I glass) with a stopper (coated butyl rubber) and a blue flip-off seal (aluminium). Pack size of 1 vial.

24 mL of concentrate in a 25 mL vial (Type I glass) with a stopper (coated butyl rubber) and a red matte flip-off seal (aluminium). Pack size of 1 vial.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal and other handling**

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

#### Preparation and administration

##### *Calculating the dose*

More than one vial of OPDIVO concentrate may be needed to give the total dose for the patient.

##### Nivolumab monotherapy

The prescribed dose for the adult patient is 240 mg or 480 mg given regardless of body weight depending on indication (see [section 4.2](#)).

Melanoma (advanced or adjuvant treatment) in adolescents. The prescribed dose for adolescents 12 years of age and older weighing at least 50 kg is 240 mg or 480 mg. For adolescents 12 years of age and older and weighing less than 50 kg, the prescribed dose is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given.

- The total nivolumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The volume of OPDIVO concentrate to prepare the dose (mL) = the total nivolumab dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

#### Nivolumab in combination with ipilimumab

The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given (please see above).

#### Nivolumab in combination with ipilimumab in MPM

The prescribed dose for the patient is 360 mg given regardless of body weight.

#### Nivolumab in combination with ipilimumab in OSCC

The prescribed dose for the patient can be based on body weight (3 mg/kg) or 360 mg given regardless of body weight.

#### Nivolumab in combination with chemotherapy in resectable NSCLC

The prescribed dose for the patient is 360 mg given regardless of body weight.

#### Nivolumab in combination with chemotherapy in OSCC

The prescribed dose for the patient is 240 mg or 480 mg given regardless of body weight.

#### Nivolumab in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma

The prescribed dose for the patient is 360 mg or 240 mg given regardless of body weight.

#### Nivolumab in combination with ipilimumab and chemotherapy

The prescribed dose for the patient is 360 mg given regardless of body weight.

#### Nivolumab in combination with cabozantinib

The prescribed dose for the patient is nivolumab 240 mg or 480 mg given regardless of body weight.

#### Preparing the infusion

Take care to ensure aseptic handling when you prepare the infusion.

OPDIVO can be used for intravenous administration either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting according to the following instructions:
  - the final infusion concentration should range between 1 and 10 mg/mL
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kilogram of patient weight.

OPDIVO concentrate may be diluted with either:

- sodium chloride 9 mg/mL (0.9%) solution for injection; or
- 50 mg/mL (5%) glucose solution for injection.

#### STEP 1

- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake the vial. OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of OPDIVO concentrate using an appropriate sterile syringe.

## STEP 2

- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Gently mix the infusion by manual rotation. Do not shake.

### Administration

OPDIVO infusion must not be administered as an intravenous push or bolus injection.

Administer the OPDIVO infusion intravenously over a period of 30 or 60 minutes depending on the dose.

OPDIVO infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm).

OPDIVO infusion is compatible with PVC and polyolefin containers, glass bottles, PVC infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

After administration of the nivolumab dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

### Disposal

Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Bristol-Myers Squibb Pharma EEIG  
Plaza 254  
Blanchardstown Corporate Park 2  
Dublin 15, D15 T867  
Ireland

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1014/001  
EU/1/15/1014/002  
EU/1/15/1014/003  
EU/1/15/1014/004

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 19 June 2015  
Date of latest renewal: 23 April 2020

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**



**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND  
MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer of the biological active substance

Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics  
Cruiserath Road, Mulhuddart  
Dublin 15, D15 H6EF  
Ireland

Name and address of the manufacturer responsible for batch release

Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics  
Cruiserath Road, Mulhuddart  
Dublin 15, D15 H6EF  
Ireland

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see [Annex I](#): Summary of Product Characteristics, [section 4.2](#)).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING  
AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND  
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where OPDIVO is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use OPDIVO have access to/are provided with the patient alert card.

- **The patient alert card** shall contain the following key messages:

- That OPDIVO treatment may increase the risk of:
  - Immune-related pneumonitis
  - Immune-related colitis
  - Immune-related hepatitis
  - Immune-related nephritis and renal dysfunction
  - Immune-related endocrinopathies
  - Immune-related skin adverse reactions
  - Other immune-related ARs
- Signs or symptoms of the safety concern and when to seek attention from a HCP
- Contact details of the OPDIVO prescriber
- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
1. Post authorisation efficacy study (PAES): 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.	31 <sup>st</sup> October 2024
2. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer, the MAH should submit the OS data from the second interim analysis and the final OS analysis of the Phase III study CA209577.	By 30 <sup>th</sup> September 2024
3. Post authorisation efficacy study (PAES): In order to further characterize the efficacy of nivolumab as neoadjuvant treatment of adults with non-small cell lung cancer, the MAH should submit the OS data from the final OS analysis of the Phase 3 study CA209816.	By 30 <sup>th</sup> June 2025
4. Post authorisation efficacy study (PAES): In order to further characterize the efficacy of nivolumab as adjuvant treatment of adults with muscle invasive urothelial carcinoma, the MAH should submit the OS data from the 2 <sup>nd</sup> IA and the final OS analysis of the Phase 3 CA209274 study in the PD-L1 $\geq$ 1% population.	By 31 <sup>st</sup> December 2027
5. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or stage IIC melanoma, the MAH should submit the OS data from the first interim OS analysis of the Phase III study CA20976K.	By 31 <sup>st</sup> March 2029

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

OPDIVO 10 mg/mL concentrate for solution for infusion  
nivolumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each mL of concentrate contains 10 mg of nivolumab.  
Each vial of 4 mL contains 40 mg of nivolumab.  
Each vial of 10 mL contains 100 mg of nivolumab.  
Each vial of 12 mL contains 120 mg of nivolumab.  
Each vial of 24 mL contains 240 mg of nivolumab.

**3. LIST OF EXCIPIENTS**

Excipients: sodium citrate dihydrate, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80 (E433), sodium hydroxide, hydrochloric acid, water for injections.

See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion.

40 mg/4 mL  
100 mg/10 mL  
120 mg/12 mL  
240 mg/24 mL

1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Intravenous use.  
For single use only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bristol-Myers Squibb Pharma EEIG  
Plaza 254  
Blanchardstown Corporate Park 2  
Dublin 15, D15 T867  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1014/001 40 mg vial  
EU/1/15/1014/002 100 mg vial  
EU/1/15/1014/003 240 mg vial  
EU/1/15/1014/004 120 mg vial

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
---

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING****VIAL LABEL****1. NAME OF THE MEDICINAL PRODUCT**

OPDIVO 10 mg/mL sterile concentrate  
nivolumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each mL of concentrate contains 10 mg of nivolumab.  
Each vial of 12 mL contains 120 mg of nivolumab.  
Each vial of 24 mL contains 240 mg of nivolumab.

**3. LIST OF EXCIPIENTS**

Excipients: sodium citrate dihydrate, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80 (E433), sodium hydroxide, hydrochloric acid, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Sterile concentrate

120 mg/12 mL  
240 mg/24 mL

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
IV use  
For single use only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP



**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.  
Do not freeze.  
Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bristol-Myers Squibb Pharma EEIG  
Plaza 254  
Blanchardstown Corporate Park 2  
Dublin 15, D15 T867  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1014/003 240 mg vial  
EU/1/15/1014/004 120 mg vial

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS****VIAL LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

OPDIVO 10 mg/mL sterile concentrate  
nivolumab  
IV use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use.  
For single use only.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

40 mg/4 mL  
100 mg/10 mL

**6. OTHER**

## **B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

### OPDIVO 10 mg/mL concentrate for solution for infusion nivolumab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- It is important that you keep the alert card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See [section 4](#).

#### **What is in this leaflet**

1. What OPDIVO is and what it is used for
2. What you need to know before you use OPDIVO
3. How to use OPDIVO
4. Possible side effects
5. How to store OPDIVO
6. Contents of the pack and other information

#### **1. What OPDIVO is and what it is used for**

OPDIVO is a medicine used to treat:

- advanced melanoma (a type of skin cancer) in adults and adolescents 12 years of age and older
- melanoma after complete resection in adults and adolescents 12 years of age and older (treatment after surgery is called adjuvant therapy)
- advanced non-small cell lung cancer (a type of lung cancer) in adults
- non-small cell lung cancer (a type of lung cancer) prior to resection in adults (treatment prior to surgery is called neoadjuvant therapy)
- malignant pleural mesothelioma (a type of cancer that affects the lining of the lung) in adults
- advanced renal cell carcinoma (advanced kidney cancer) in adults
- classical Hodgkin lymphoma that has come back after or has not responded to previous therapies, including an autologous stem-cell transplant (a transplant of your own blood-producing cells) in adults
- advanced cancer of the head and neck in adults
- advanced urothelial carcinoma (bladder and urinary tract cancer) in adults
- urothelial carcinoma after complete resection in adults
- advanced colorectal cancer (colon or rectal cancer) in adults
- advanced oesophageal cancer (gullet cancer) in adults
- oesophageal (gullet) or gastro-oesophageal junction cancer with residual pathologic disease after chemoradiation followed by surgery in adults
- advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (stomach or gullet cancer) in adults.

It contains the active substance nivolumab, which is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body.

Nivolumab attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the melanoma, lung, kidney, lymphoid, head and neck, bladder, colon, rectal, stomach, oesophageal or gastro-oesophageal junction cancer cells.

OPDIVO may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflet for these other medicines. If you have any questions about these medicines, please ask your doctor.

## 2. What you need to know before you use OPDIVO

### You should not be given OPDIVO

- if you are **allergic** to nivolumab or any of the other ingredients of this medicine (listed in [section 6](#) "Contents of the pack and other information"). **Talk to your doctor** if you are not sure.

### Warnings and precautions

Talk to your doctor before using OPDIVO as it may cause:

- **Problems with your heart** such as a change in the rhythm or rate of the heartbeat or an abnormal heart rhythm.
- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Diarrhoea** (watery, loose or soft stools) or any symptoms of **inflammation of the intestines** (colitis), such as stomach pain and mucus or blood in stool.
- **Inflammation of the liver (hepatitis)**. Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, or tiredness.
- **Inflammation or problems with your kidneys**. Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.
- **Problems with your hormone producing glands** (including the pituitary, the thyroid, the parathyroid and adrenal glands) that may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache, decreased blood levels of calcium and visual disturbances.
- **Diabetes** including a serious, sometimes life-threatening problem due to acid in the blood produced from diabetes (diabetic ketoacidosis). Symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, feeling tired or having difficulty thinking clearly, breath that smells sweet or fruity, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, feeling sick or being sick, stomach pain, and deep or fast breathing.
- **Inflammation of the skin** that can lead to severe skin reaction (known as toxic epidermal necrolysis and Stevens-Johnson syndrome). Signs and symptoms of severe skin reaction may include rash, itching, and peeling of the skin (possibly fatal).
- **Inflammation of the muscles** such as myocarditis (inflammation of the heart muscle), myositis (inflammation of the muscles) and rhabdomyolysis (stiffness in muscles and joints, muscle spasm). Signs and symptoms may include muscle pain, stiffness, weakness, chest pain, or severe fatigue.
- **Solid organ transplant rejection.**
- **Graft-versus-host disease.**
- **Haemophagocytic lymphohistiocytosis**. A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

**Tell your doctor immediately** if you have any of these signs or symptoms or if they get worse. **Do not try to treat your symptoms with other medicines on your own.** Your doctor may

- give you other medicines in order to prevent complications and reduce your symptoms,
- withhold the next dose of OPDIVO,
- or stop your treatment with OPDIVO altogether.

Please note that these signs and symptoms are **sometimes delayed**, and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have **blood tests** during your treatment.

**Check with your doctor or nurse before you are given OPDIVO if:**

- you have an **autoimmune disease** (a condition where the body attacks its own cells);
- you have **melanoma of the eye**;
- you were previously given ipilimumab, another medicine for treating melanoma, and experienced **serious side effects** because of that medicine;
- you have been told that your **cancer has spread to your brain**;
- you have any history of **inflammation of the lungs**;
- you have been taken **medicines to suppress your immune system**.

**Complications of stem cell transplant that uses donor stem cells (allogeneic) after treatment with OPDIVO.** These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

**Children and adolescents**

OPDIVO should not be used in children and adolescents below 18 years of age except for adolescents 12 years of age and older with melanoma.

**Other medicines and OPDIVO**

**Before you are given OPDIVO, tell your doctor** if you are taking any medicines that suppress your immune system, such as corticosteroids, since these medicines may interfere with the effect of OPDIVO. However, once you are treated with OPDIVO, your doctor may give you corticosteroids to reduce any possible side effects that you may have during your treatment and this will not impact the effect of the medicine.

**Tell your doctor** if you are taking or have recently taken any other medicines. **Do not take any other medicines** during your treatment without talking to your doctor first.

**Pregnancy and breast-feeding**

**Tell your doctor** if you are pregnant or think you might be, if you are planning to become pregnant, or if you are breast-feeding.

**Do not use OPDIVO if you are pregnant** unless your doctor specifically tells you to. The effects of OPDIVO in pregnant women are not known, but it is possible that the active substance, nivolumab, could harm an unborn baby.

- You must use **effective contraception** while you are being treated with OPDIVO and for at least 5 months following the last dose of OPDIVO, if you are a woman who could become pregnant.
- If you become pregnant while using OPDIVO **tell your doctor**.

It is not known whether OPDIVO gets into breast milk. A risk to the breast-fed infant cannot be excluded. **Ask your doctor** if you can breast-feed during or after treatment with OPDIVO.

**Driving and using machines**

OPDIVO or OPDIVO in combination with ipilimumab may have a minor influence on the ability to drive and use machines; however, use caution when performing these activities until you are sure that OPDIVO does not adversely affect you.

**OPDIVO contains sodium**

**Tell your doctor** if you are on a low-sodium (low-salt) diet before you are given OPDIVO. This medicine contains 2.5 mg sodium (main component of cooking/table salt) in each mL of concentrate. OPDIVO contains 10 mg sodium per 4 mL vial, 25 mg sodium per 10 mL vial, 30 mg sodium per 12 mL vial or 60 mg sodium per 24 mL vial, which is equivalent to 0.5%, 1.25%, 1.5% or 3% respectively, of the recommended maximum daily dietary intake of sodium for an adult.

You will also find key messages from this package leaflet in the patient alert card you have been given by your doctor. It is important that you keep this patient alert card and show it to your partner or caregivers.

### 3. How to use OPDIVO

#### How much OPDIVO is given

When OPDIVO is given on its own, the recommended dose is either 240 mg given every 2 weeks or 480 mg given every 4 weeks depending on indication.

When OPDIVO is given on its own, for the treatment of skin cancer in adolescents 12 years of age and older and weighing at least 50 kg, the recommended dose is either 240 mg given every 2 weeks or 480 mg given every 4 weeks. For adolescents 12 years of age and older and weighing less than 50 kg, the recommended dose is either 3 mg of nivolumab per kilogram of your body weight given every 2 weeks or 6 mg of nivolumab per kilogram of your body weight given every 4 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of skin cancer in adults and adolescents 12 years of age and older, the recommended dose of OPDIVO is 1 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter the recommended dose of OPDIVO (single-agent phase) is 240 mg given every 2 weeks or 480 mg given every 4 weeks in adults and adolescents 12 years of age and older and weighing at least 50 kg or 3 mg of nivolumab per kilogram of your body weight given every 2 weeks or 6 mg of nivolumab per kilogram of your body weight given every 4 weeks for adolescents 12 years of age and older and weighing less than 50 kg.

When OPDIVO is given in combination with ipilimumab for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced colon or rectal cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter, the recommended dose of OPDIVO is 240 mg given every 2 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of malignant pleural mesothelioma, the recommended dose of OPDIVO is 360 mg every 3 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of advanced oesophageal cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight every 2 weeks or 360 mg every 3 weeks.

When OPDIVO is given in combination with chemotherapy for the neoadjuvant treatment of non-small cell lung cancer, the recommended dose of OPDIVO is 360 mg every 3 weeks.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced oesophageal cancer, the recommended dose of OPDIVO is 240 mg every 2 weeks or 480 mg every 4 weeks.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the recommended dose of OPDIVO is 360 mg every 3 weeks or 240 mg every 2 weeks.

When OPDIVO is given in combination with chemotherapy for the treatment of urothelial carcinoma, the recommended dose of OPDIVO is 360 mg nivolumab every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks.

When OPDIVO is given in combination with ipilimumab and chemotherapy for the treatment of advanced non-small cell lung cancer, the recommended dose of OPDIVO is 360 mg every 3 weeks. After completion of 2 cycles of chemotherapy, OPDIVO is given in combination with ipilimumab, the recommended dose of OPDIVO is 360 mg every 3 weeks.

When OPDIVO is given in combination with cabozantinib for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg given every 4 weeks.

Depending on your dose, the appropriate amount of OPDIVO will be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection before use. More than one vial of OPDIVO may be necessary to obtain the required dose.

### **How OPDIVO is given**

You will receive treatment with OPDIVO in a hospital or clinic, under the supervision of an experienced doctor.

OPDIVO will be given to you as an infusion (a drip) into a vein (intravenously) over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving. Your doctor will continue giving you OPDIVO for as long as you keep benefitting from it or until you no longer tolerate the treatment.

When OPDIVO is given in combination with ipilimumab for the treatment of skin, advanced kidney or advanced colon or rectal cancer, you will be given an infusion over a period of 30 minutes, every 3 weeks for the first 4 doses (combination phase). Thereafter it will be given as an infusion over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of malignant pleural mesothelioma, you will be given an infusion over a period of 30 minutes, every 3 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of advanced oesophageal cancer, you will be given an infusion over a period of 30 minutes, every 2 or 3 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with chemotherapy for the neoadjuvant treatment of non-small cell lung cancer, you will be given an infusion over a period of 30 minutes, every 3 weeks.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced oesophageal cancer, you will be given an infusion over a period of 30 minutes, every 2 or 4 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, you will be given an infusion over a period of 30 minutes every 3 weeks or every 2 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with chemotherapy for the treatment of urothelial carcinoma, you will be given an infusion over a period of 30 minutes every 2, 3 or 4 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with ipilimumab and chemotherapy for the treatment of advanced non-small cell lung cancer, you will be given an infusion over a period of 30 minutes, every 3 weeks.

When OPDIVO is given in combination with cabozantinib, you will be given an infusion over a period of 30 minutes or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving.



**If you miss a dose of OPDIVO**

It is very important for you to keep all your appointments to receive OPDIVO. If you miss an appointment, ask your doctor when to schedule your next dose.

**If you stop using OPDIVO**

Stopping your treatment may stop the effect of the medicine. Do not stop treatment with OPDIVO unless you have discussed this with your doctor.

If you have any further questions about your treatment or on the use of this medicine, ask your doctor.

When OPDIVO is given in combination with other anti-cancer medicines, you will first be given OPDIVO followed by the other medicine.

Please refer to the package leaflet of these other medicines in order to understand the use of these medicines. If you have questions about them, please ask your doctor.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

**Be aware of important symptoms of inflammation.** OPDIVO acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening and need treatment or withdrawal of OPDIVO.

The following side effects have been reported **with OPDIVO alone**:

**Very common (may affect more than 1 in 10 people)**

- Infections of the upper respiratory tract
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- Decreased appetite, high sugar levels in the blood (hyperglycaemia)
- Headache
- Shortness of breath (dyspnoea), cough
- Diarrhoea (watery, loose or soft stools), vomiting, nausea, stomach pain, constipation
- Skin rash sometimes with blisters, itching
- Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)
- Feeling tired or weak, fever

**Common (may affect up to 1 in 10 people)**

- Serious lung infection (pneumonia), bronchitis
- Reactions related to the infusion of the medicine, allergic reaction (including life-threatening allergic reaction)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss), swelling of the thyroid gland
- Dehydration, decrease in body weight, low sugar levels in the blood (hypoglycaemia)
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness
- Blurred vision, dry eyes
- Fast heart rate, abnormal heart rhythm
- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs
- Inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), dry mouth
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning

- Inflammation of the joints (arthritis)
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, oedema (swelling)

**Uncommon (may affect up to 1 in 100 people)**

- Increase in some white blood cells
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, diabetes
- Increased acid levels in the blood (metabolic acidosis)
- Damage to nerves causing numbness and weakness (polyneuropathy), inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy)
- Inflammation of the eye (which causes pain and redness)
- Inflammation of the heart muscle, inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders), changes in the rhythm or rate of the heartbeat
- Fluid in the lungs
- Inflammation of the pancreas (pancreatitis), inflammation of the stomach (gastritis)
- Inflammation of the liver (hepatitis), blockage of bile ducts (cholestasis)
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis), skin condition of the face where the nose and cheeks are unusually red (rosacea), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), hives (itchy, bumpy rash)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)

**Rare (may affect up to 1 in 1000 people)**

- A temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- A disease causing the inflammation or enlargement of a lymph node (Kikuchi lymphadenitis)
- Acid in the blood produced from diabetes (diabetic ketoacidosis), decreased function of the parathyroid gland
- A temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome), loss of the protective sheath around nerves (demyelination), a condition in which the muscles become weak and tire easily (myasthenic syndrome), inflammation of the brain
- Inflammatory disease of blood vessels
- Ulcer of the small intestines
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis or Stevens-Johnson syndrome)
- Disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), aching muscles, muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

**Other side effects that have been reported with frequency not known (cannot be estimated from the available data):**

- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection

- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus or other lichen disorders)

The following side effects have been reported **with OPDIVO in combination with other anti-cancer medicines** (the frequency and severity of side effects may vary with the combination of anti-cancer medicines received):

**Very common (may affect more than 1 in 10 people)**

- Infections of the upper respiratory tract
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite, decrease in body weight, decreased levels of albumin in the blood, high (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), headache, dizziness, altered sense of taste
- High blood pressure (hypertension)
- Shortness of breath (dyspnoea), cough, abnormal speaking sound (dysphonia)
- Diarrhoea (watery, loose or soft stools), constipation, vomiting, nausea, stomach pain, mouth ulcers and cold sores (stomatitis), indigestion (dyspepsia)
- Skin rash sometimes with blisters, itching, pain of the hands or soles of the feet: rash or redness of the skin, tingling and tenderness developing to symmetrical redness, swelling and pain primarily on the palm of the hand and sole of the foot (palmar-plantar erythrodysesthesia syndrome)
- Pain in the joints (arthralgia), pain in the muscles and bones (musculoskeletal pain), muscle spasm
- Excess protein in urine
- Feeling tired or weak, fever, oedema (swelling)

**Common (may affect up to 1 in 10 people)**

- Serious lung infection (pneumonia), bronchitis, inflammation of the eye (conjunctivitis)
- Increase in some white blood cells, decrease in neutrophils with fever
- Allergic reaction, reactions related to the infusion of the medicine
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- Dehydration, decreased levels of phosphate in the blood
- Sensations like numbness and tingling (paraesthesia)
- Hearing a persistent sound in your ear when no sound exists (tinnitus)
- Blurred vision, dry eye
- Fast heart rate, abnormal heart rhythm, inflammatory disease of blood vessels
- Formation of a blood clot within a blood vessel (thrombosis)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs, blood clots, nose bleeding
- Inflammation of the intestines (colitis), inflammation of the pancreas (pancreatitis), dry mouth, inflammation of the stomach (gastritis), oral pain, haemorrhoids (piles)
- Inflammation of the liver

- Skin colour change in patches (including vitiligo), redness of the skin, unusual hair loss or thinning, hair colour change, hives (itchy rash), discolouration or abnormal darkening of the skin (skin hyperpigmentation), dry skin
- Inflammation of the joints (arthritis), muscle weakness, aching muscles
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, chills
- Feeling generally unwell (malaise)

**Uncommon (may affect up to 1 in 100 people)**

- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- Increased acid levels in the blood
- A temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome); damage to nerves causing numbness and weakness (polyneuropathy); foot drop (peroneal nerve palsy); inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy); muscle weakness and tiredness without atrophy (myasthenia gravis or syndrome)
- Inflammation of the brain
- Inflammation of the eye (which causes pain and redness)
- Changes in the rhythm or rate of the heartbeat, slow heart rate, inflammation of the heart muscle
- Intestinal perforation, inflammation of the duodenum, burning or painful sensation in the tongue (glossodynia)
- Severe and possibly fatal peeling of the skin (Stevens-Johnson syndrome), skin disease with thickened patches of red skin, often with silvery scales (psoriasis), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme)
- Muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica), bone damage in the jaw, abnormal opening between two body parts, such as an organ or blood vessel and another structure (fistula)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

**Rare (may affect up to 1 in 1000 people)**

- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased function of the parathyroid gland
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Inflammation of the nerves
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus or other lichen disorders)
- Chronic disease of joints (spondyloarthritis), disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), muscle spasm (rhabdomyolysis)

**Other side effects that have been reported with frequency not known (cannot be estimated from the available data):**

- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)

**Tell your doctor immediately** if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

**Changes in test results**

OPDIVO alone or in combination may cause changes in the results of tests carried out by your doctor. These include:

- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- Increased or decreased amount of calcium or potassium
- Increased or decreased blood levels of magnesium or sodium
- Increased amount of thyroid stimulating hormone
- Increase in blood triglyceride levels in the blood
- Increase in cholesterol levels in the blood

**Reporting of side effects**

If you get any side effects, **talk to your doctor**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store OPDIVO**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package in order to protect from light.

The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

## **6. Contents of the pack and other information**

**What OPDIVO contains**

- The active substance is nivolumab.

Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.

Each vial contains either 40 mg (in 4 mL), 100 mg (in 10 mL), 120 mg (in 12 mL) or 240 mg (in 24 mL) of nivolumab.

- The other ingredients are sodium citrate dihydrate, sodium chloride (see [section 2](#) "OPDIVO contains sodium"), mannitol (E421), pentetic acid, polysorbate 80 (E433), sodium hydroxide, hydrochloric acid and water for injections.

### **What OPDIVO looks like and contents of the pack**

OPDIVO concentrate for solution for infusion (sterile concentrate) is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.

It is available in packs containing either 1 vial of 4 mL, 1 vial of 10 mL, 1 vial of 12 mL or 1 vial of 24 mL.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Bristol-Myers Squibb Pharma EEIG  
Plaza 254  
Blanchardstown Corporate Park 2  
Dublin 15, D15 T867  
Ireland

### **Manufacturer**

Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics  
Cruiserath Road, Mulhuddart  
Dublin 15, D15 H6EF  
Ireland

### **This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>

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**The following information is intended for healthcare professionals only:**

### **Preparation and administration of OPDIVO**

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

### **Calculating the dose**

More than one vial of OPDIVO concentrate may be needed to give the total dose for the patient.

#### **Nivolumab monotherapy**

The prescribed dose for adults is 240 mg or 480 mg given regardless of body weight depending on indication.

Melanoma (advanced or adjuvant treatment) in adolescents. The prescribed dose for adolescents 12 years of age and older weighing at least 50 kg is 240 mg or 480 mg. For adolescents 12 years of age and older and weighing less than 50 kg the prescribed dose is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given.

- The **total nivolumab dose** in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The **volume of OPDIVO concentrate** to prepare the dose (mL) = the total nivolumab dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

#### Nivolumab in combination with ipilimumab

The **prescribed dose** for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given (please see above).

#### Nivolumab in combination with ipilimumab in malignant pleural mesothelioma

The prescribed dose for the patient is 360 mg given regardless of body weight.

#### Nivolumab in combination with ipilimumab in advanced oesophageal cancer

The prescribed dose for the patient can be based on body weight (3 mg/kg) or is 360 mg given regardless of body weight.

#### Nivolumab in combination with chemotherapy in resectable non-small cell lung cancer

The prescribed dose for the patient is 360 mg given regardless of body weight.

#### Nivolumab in combination with chemotherapy in advanced oesophageal cancer

The prescribed dose for the patient is 240 mg or 480 mg given regardless of body weight.

#### Nivolumab in combination with chemotherapy in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

The prescribed dose for the patient is 360 mg or 240 mg given regardless of body weight.

#### Nivolumab in combination with ipilimumab and chemotherapy

The prescribed dose for the patient is 360 mg given regardless of body weight.

#### Nivolumab in combination with cabozantinib

The prescribed dose for the patient is nivolumab 240 mg or 480 mg given regardless of body weight.

### **Preparing the infusion**

**Take care to ensure aseptic handling** when you prepare the infusion.

OPDIVO can be used for intravenous administration either:

- **without dilution**, after transfer to an infusion container using an appropriate sterile syringe;
- or
- **after diluting** according to the following instructions:
  - the final infusion concentration should range between 1 and 10 mg/mL
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kilogram of patient weight.
- OPDIVO concentrate may be diluted with either:
  - sodium chloride 9 mg/mL (0.9%) solution for injection; or
  - 50 mg/mL (5%) glucose solution for injection.

#### **STEP 1**

- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake the vial. OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of OPDIVO concentrate using an appropriate sterile syringe.

#### **STEP 2**

- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can be transferred directly into a pre-filled bag containing the appropriate volume of

- sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Gently mix the infusion by manual rotation. Do not shake.

### Administration

OPDIVO infusion must not be administered as an intravenous push or bolus injection.

Administer the OPDIVO infusion **intravenously over a period of 30 or 60 minutes depending on the dose and the indication.**

OPDIVO infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm).

OPDIVO infusion is compatible with:

- PVC containers
- Polyolefin containers
- Glass bottles
- PVC infusion sets
- In-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

After administration of the nivolumab dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

### Storage conditions and shelf life

#### Unopened vial

OPDIVO must be **stored in a refrigerator** (2°C to 8°C). The vials must be kept in the original package in order to protect from light. OPDIVO should not be frozen.

The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

Do not use OPDIVO after the expiry date which is stated on the carton and on the vial label after EXP. The expiry date refers to the last day of that month.

#### OPDIVO infusion

Chemical and physical in-use stability from the time of preparation has been demonstrated as follows (times are inclusive of the administration period):

Infusion preparation	Chemical and physical in-use stability	
	Storage at 2°C to 8°C protected from light	Storage at room temperature (≤ 25°C) and room light
Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection	30 days	24 hours (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	7 days	8 hours (of total 7 days storage)

From a microbiological point of view the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2°C to 8°C or 8 hours (of the total 7 days of storage) at room temperature (≤ 25°C). Aseptic handling should be ensured during the preparation of infusion.



**Disposal**

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

## **Appendix 4: Management Algorithms**

18 page(s) excluding cover page

## **APPENDIX 4A MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 4.0**

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

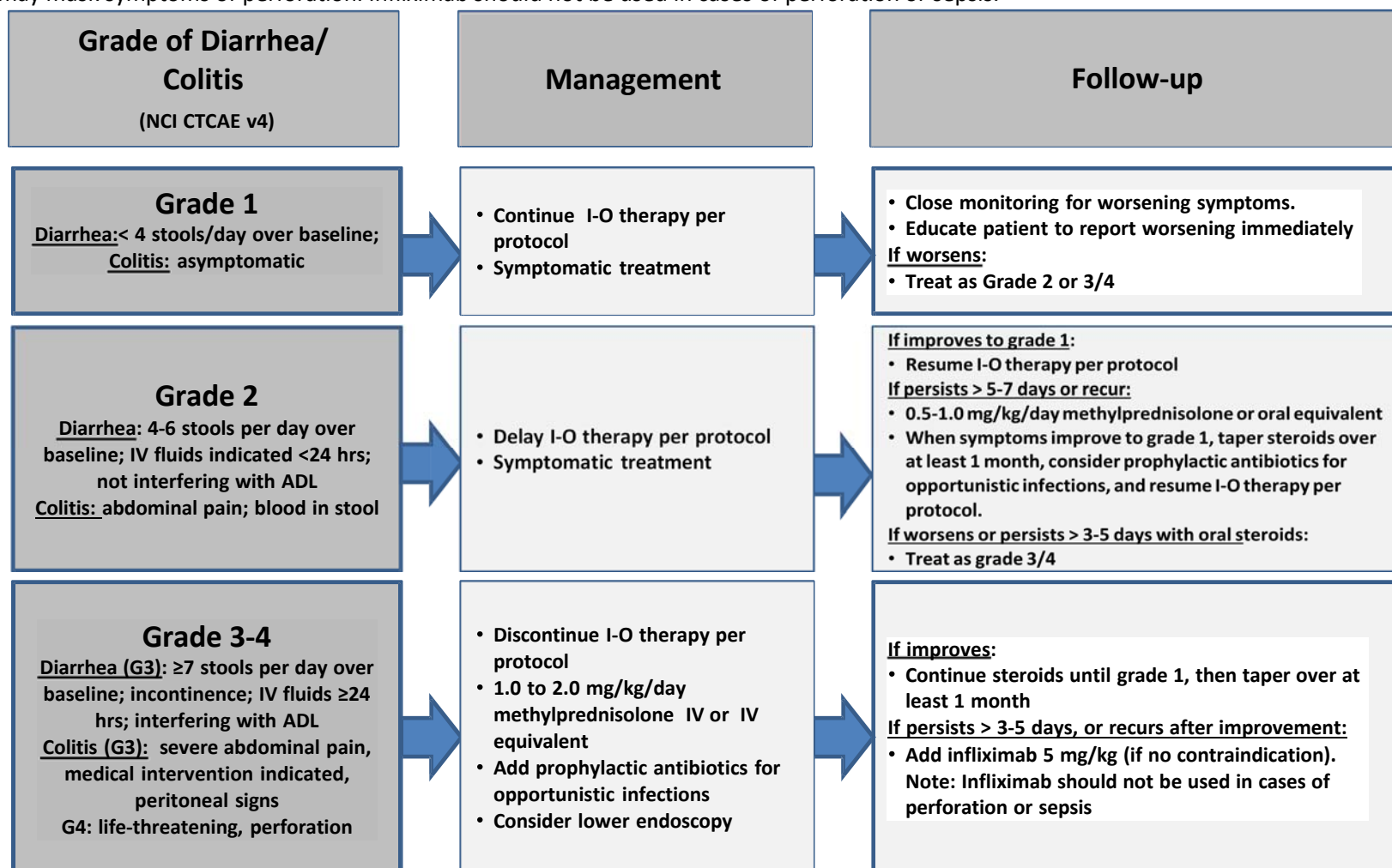
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

## GI Adverse Event Management Algorithm

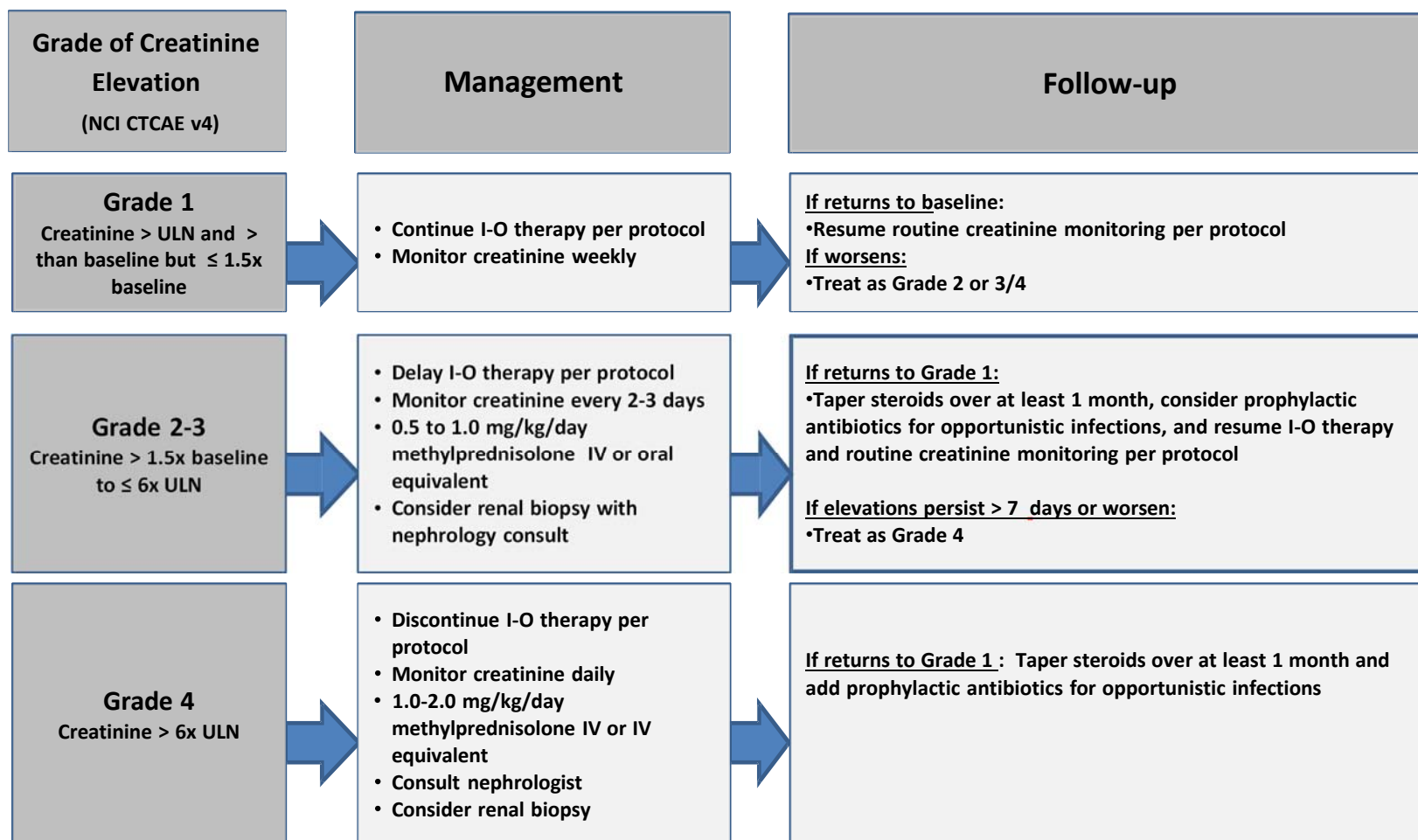
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Renal Adverse Event Management Algorithm

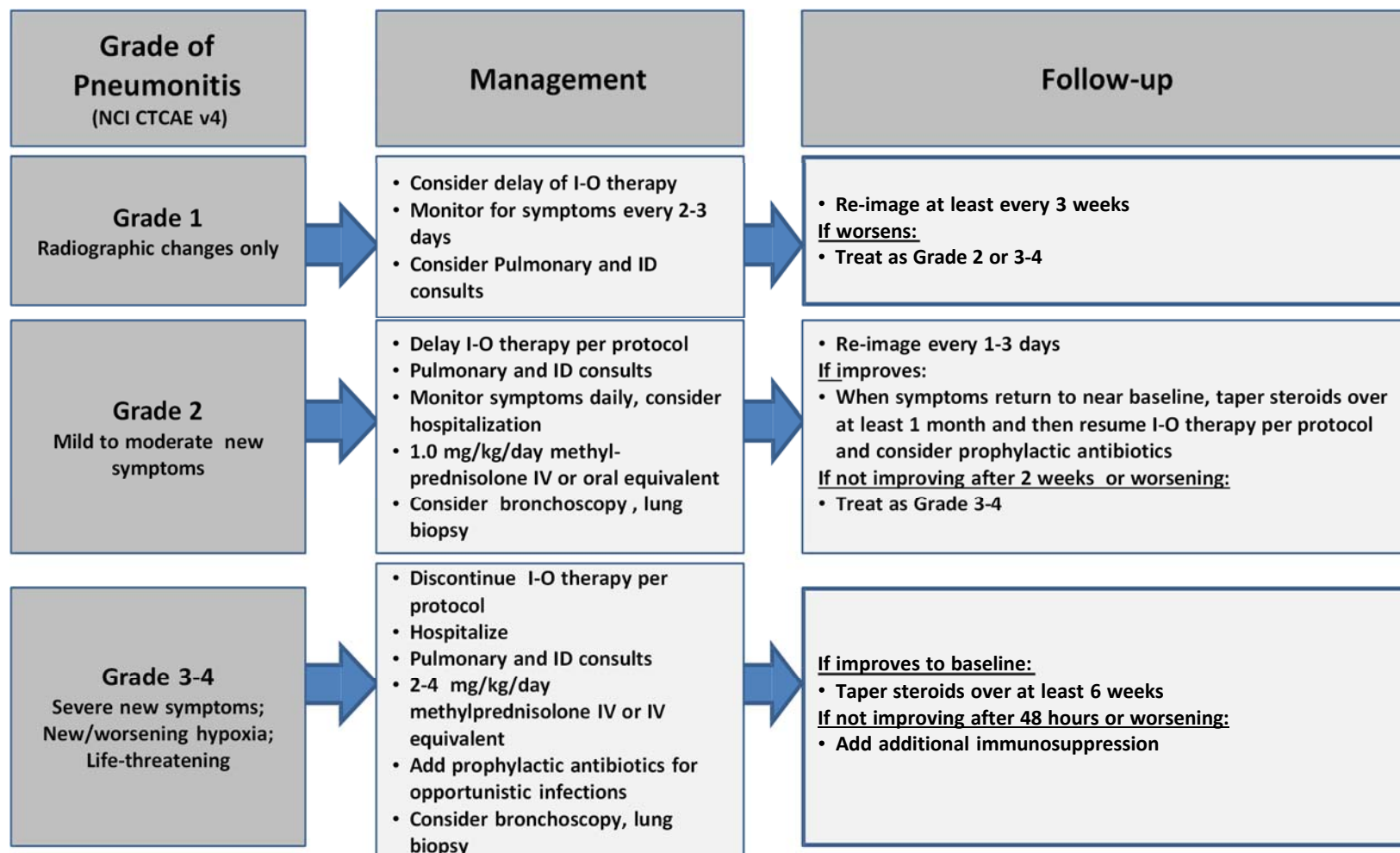
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Pulmonary Adverse Event Management Algorithm

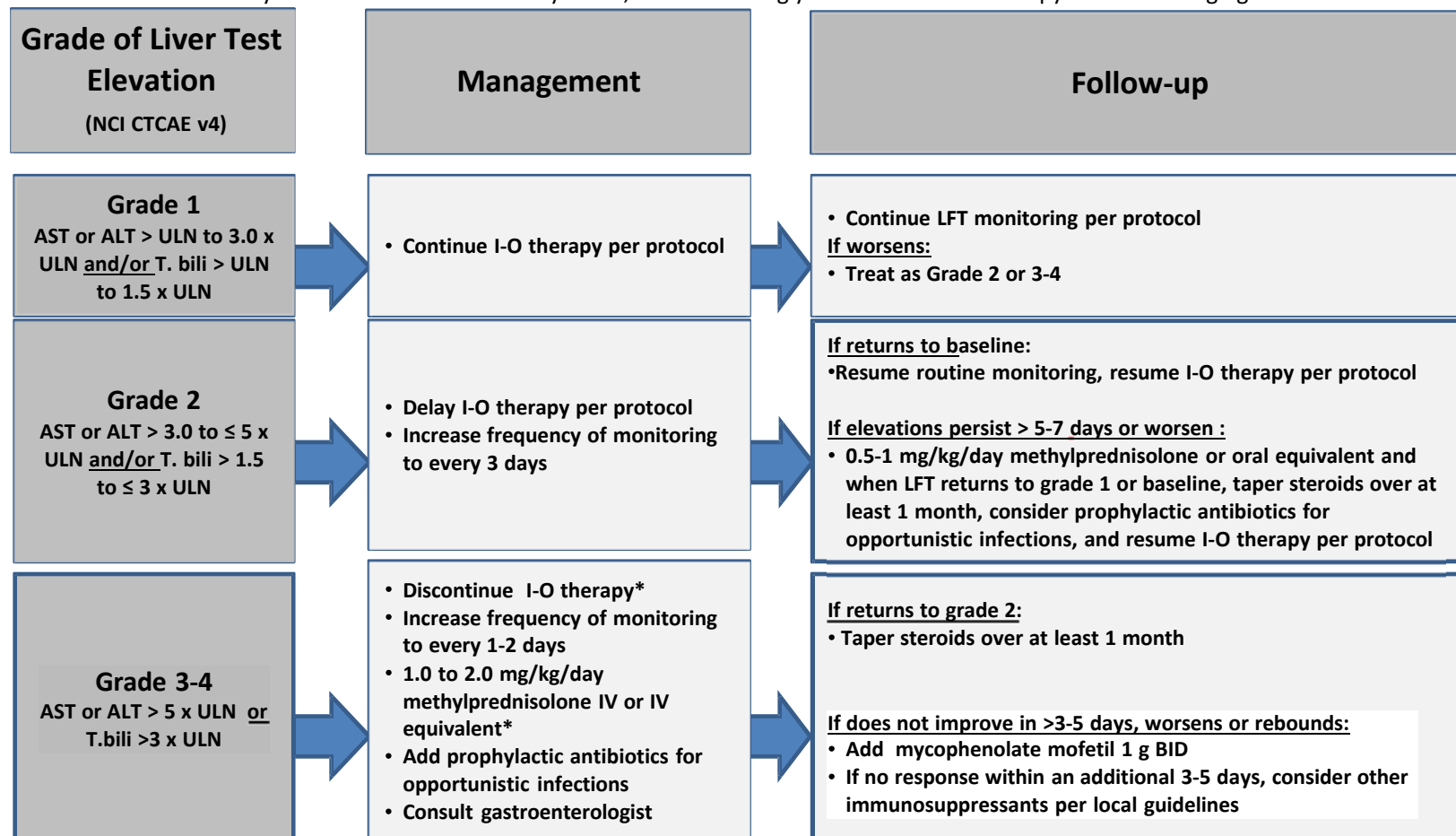
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

## Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



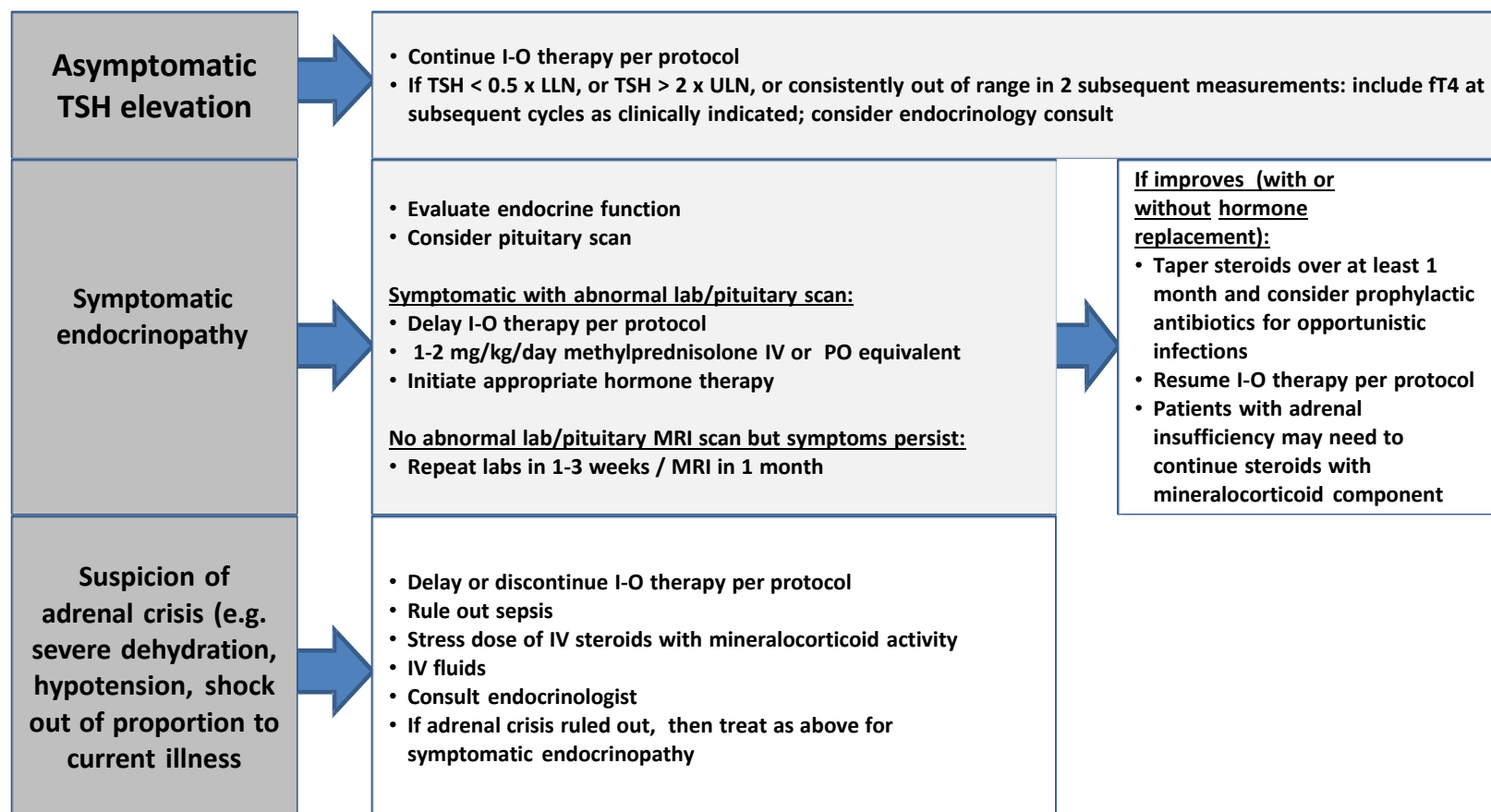
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

\*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

For subjects with HCC, please refer to the protocol for specific details.

## Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

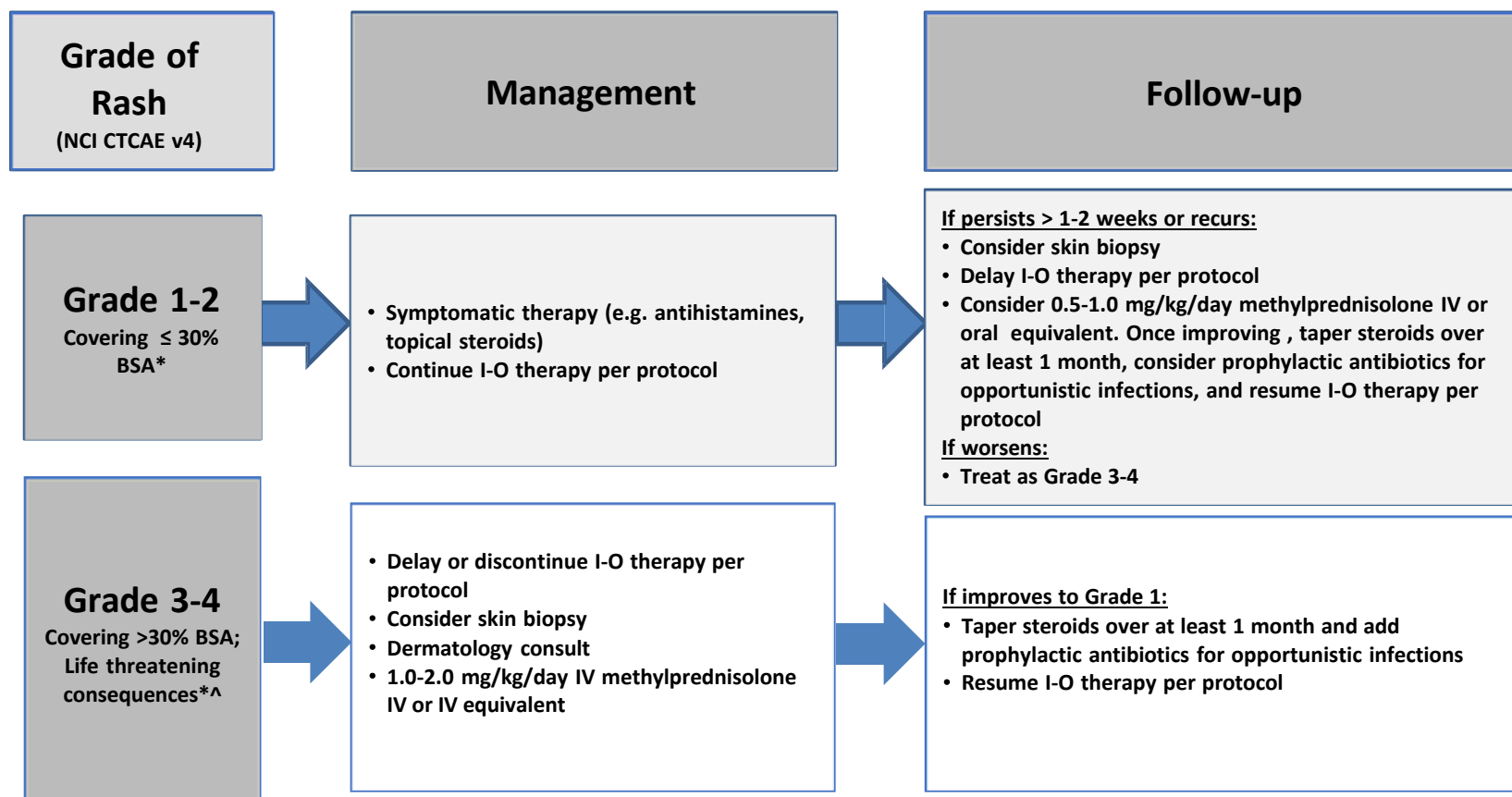


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.



## Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



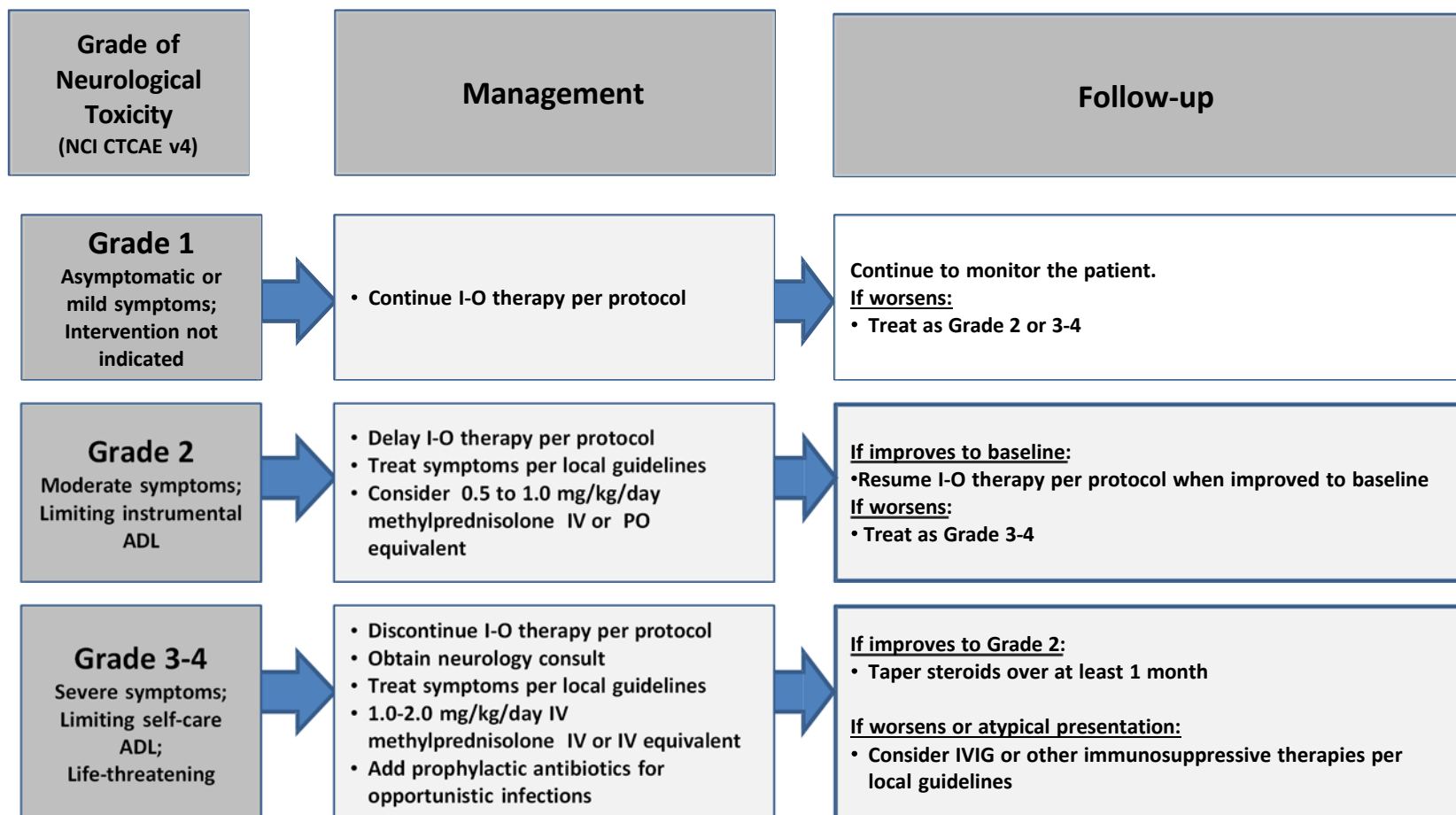
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

\*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

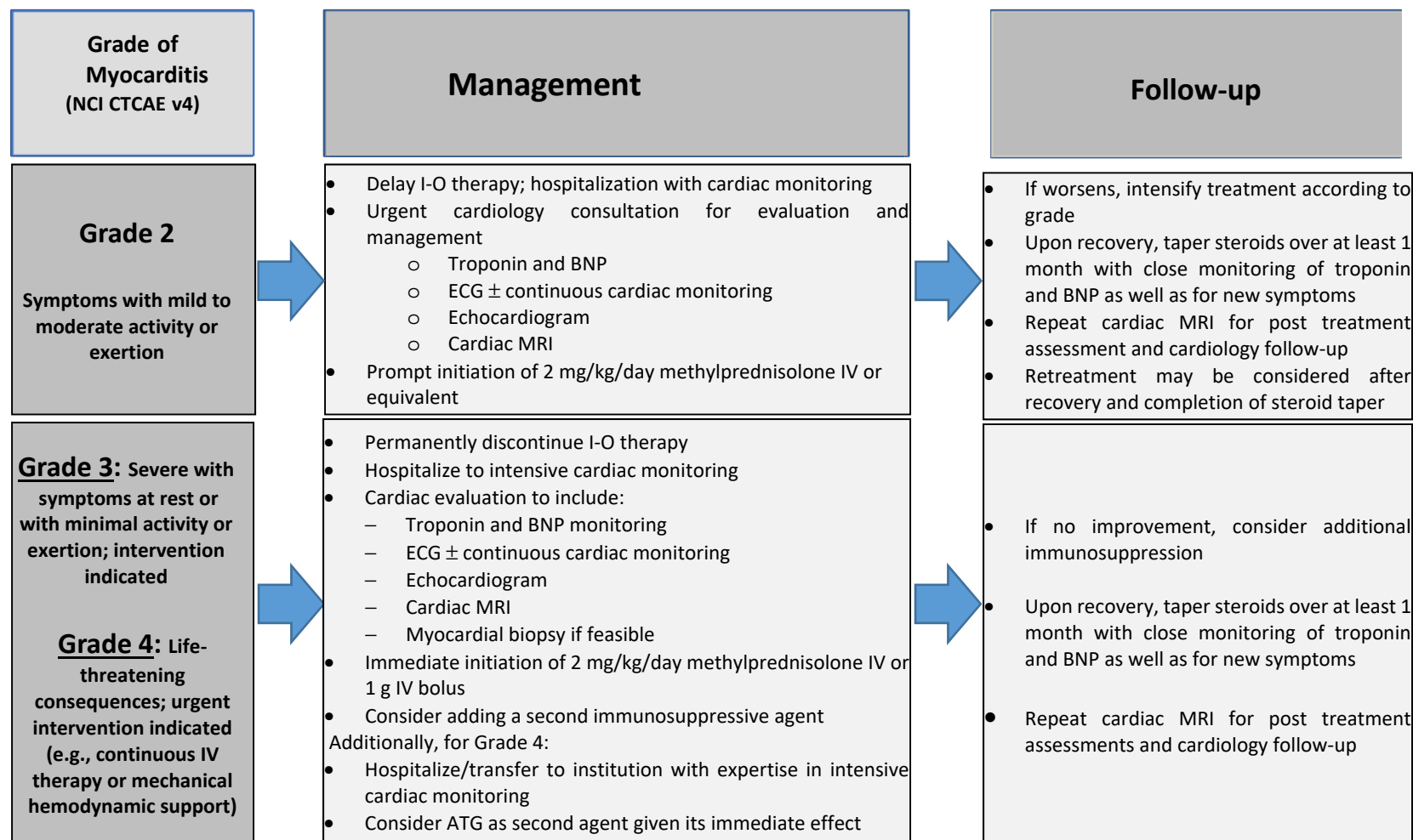
# Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

## **APPENDIX 4B: MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0**

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

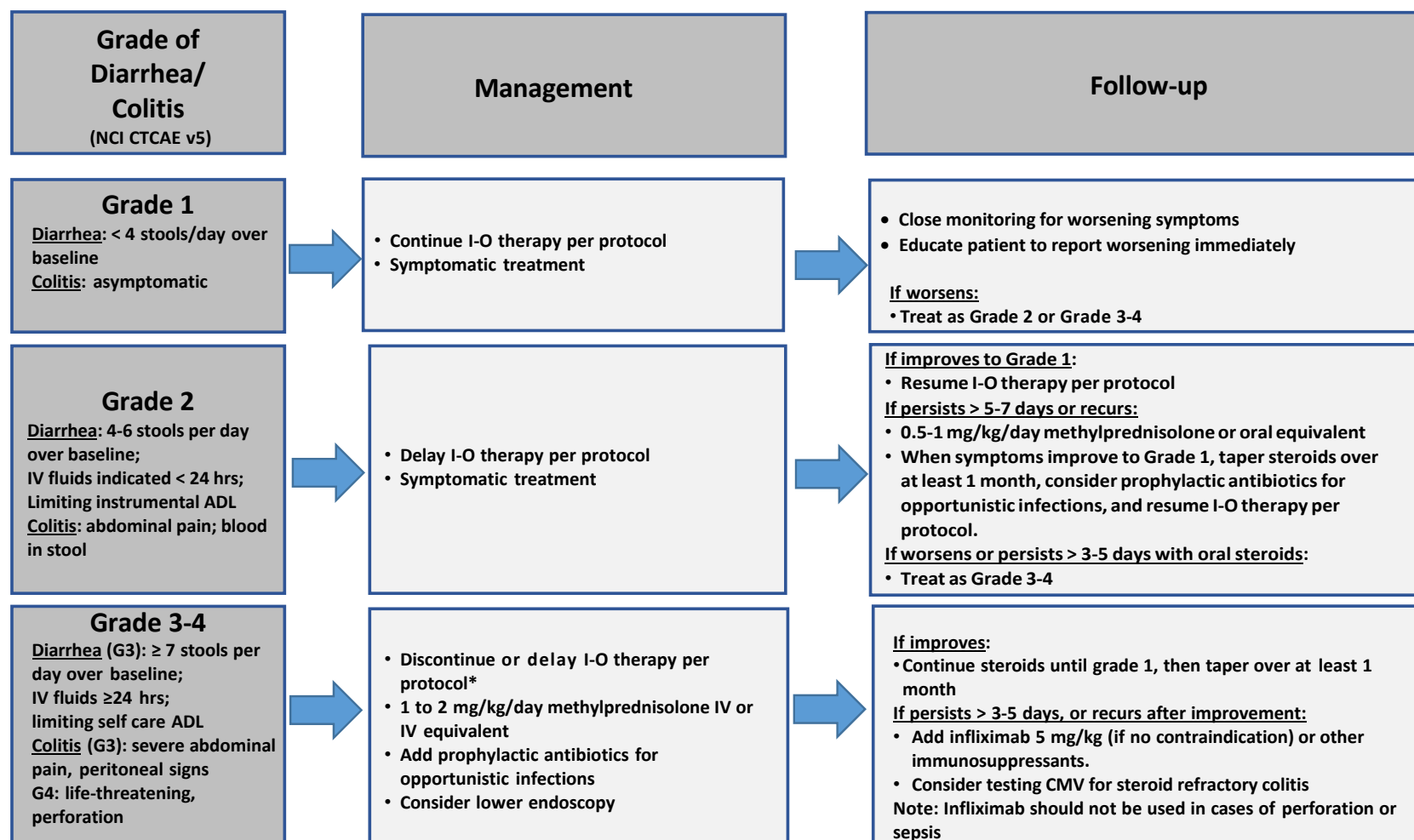
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

## GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.  
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

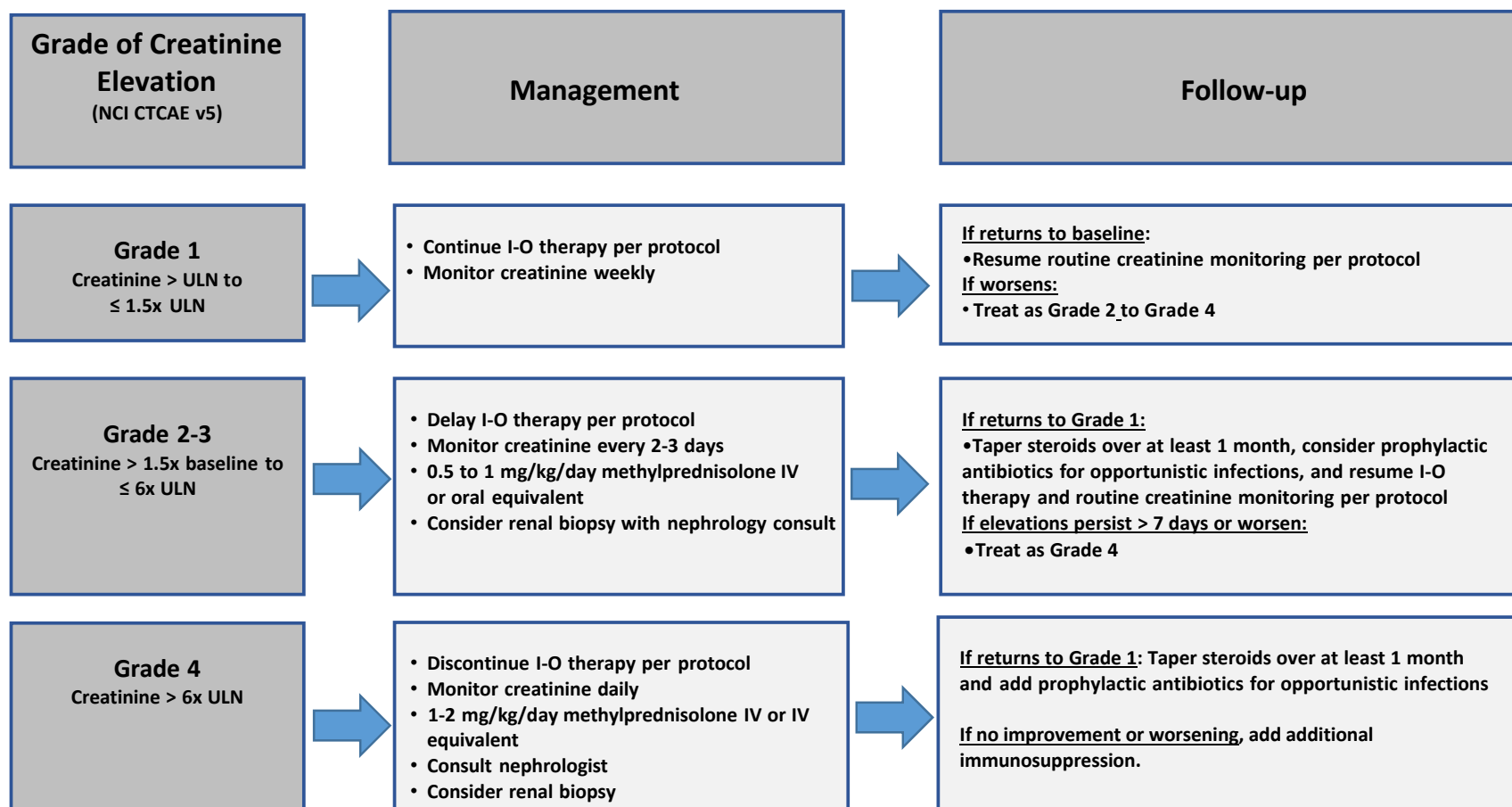


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

\* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

## Renal Adverse Event Management Algorithm

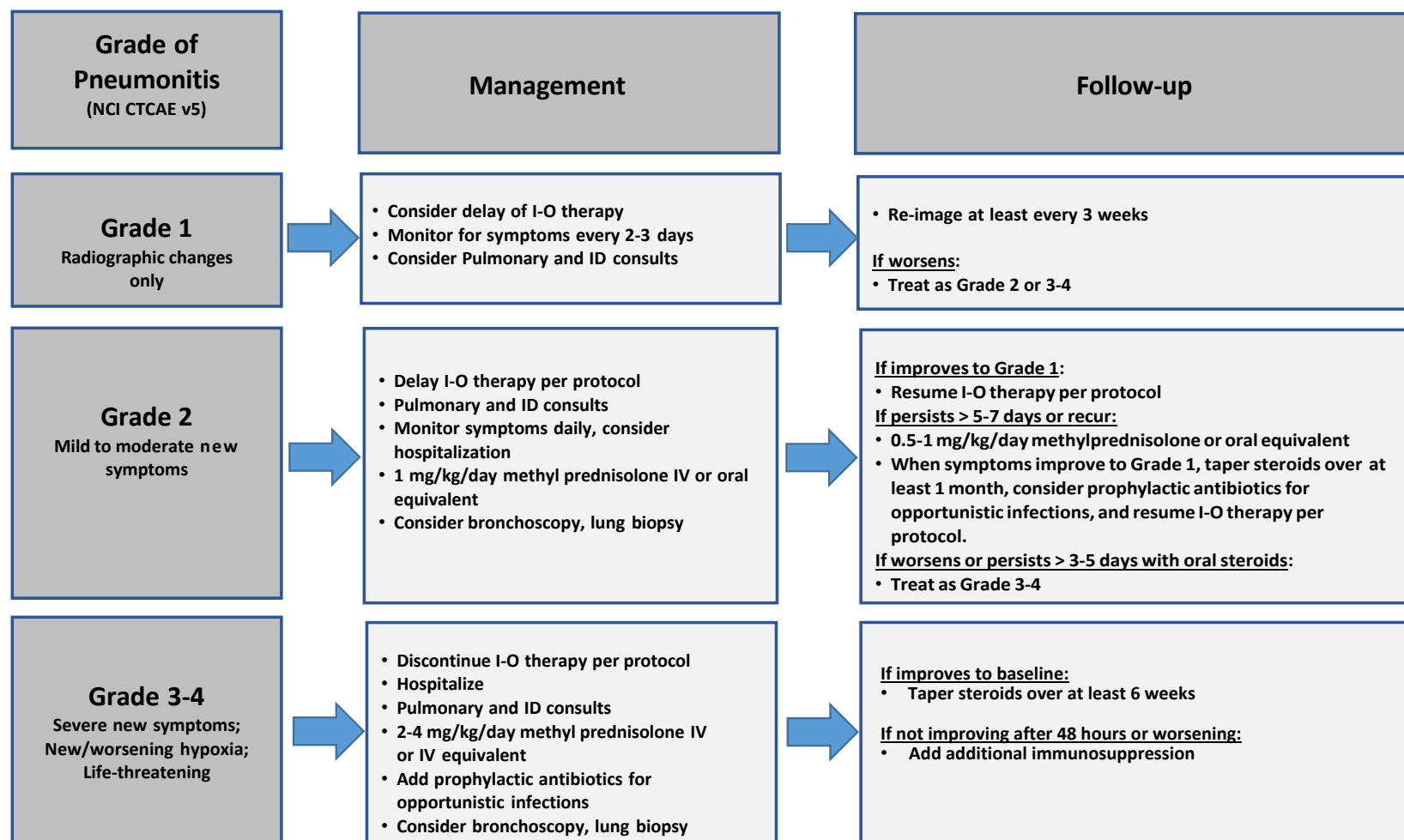
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Pulmonary Adverse Event Management Algorithm

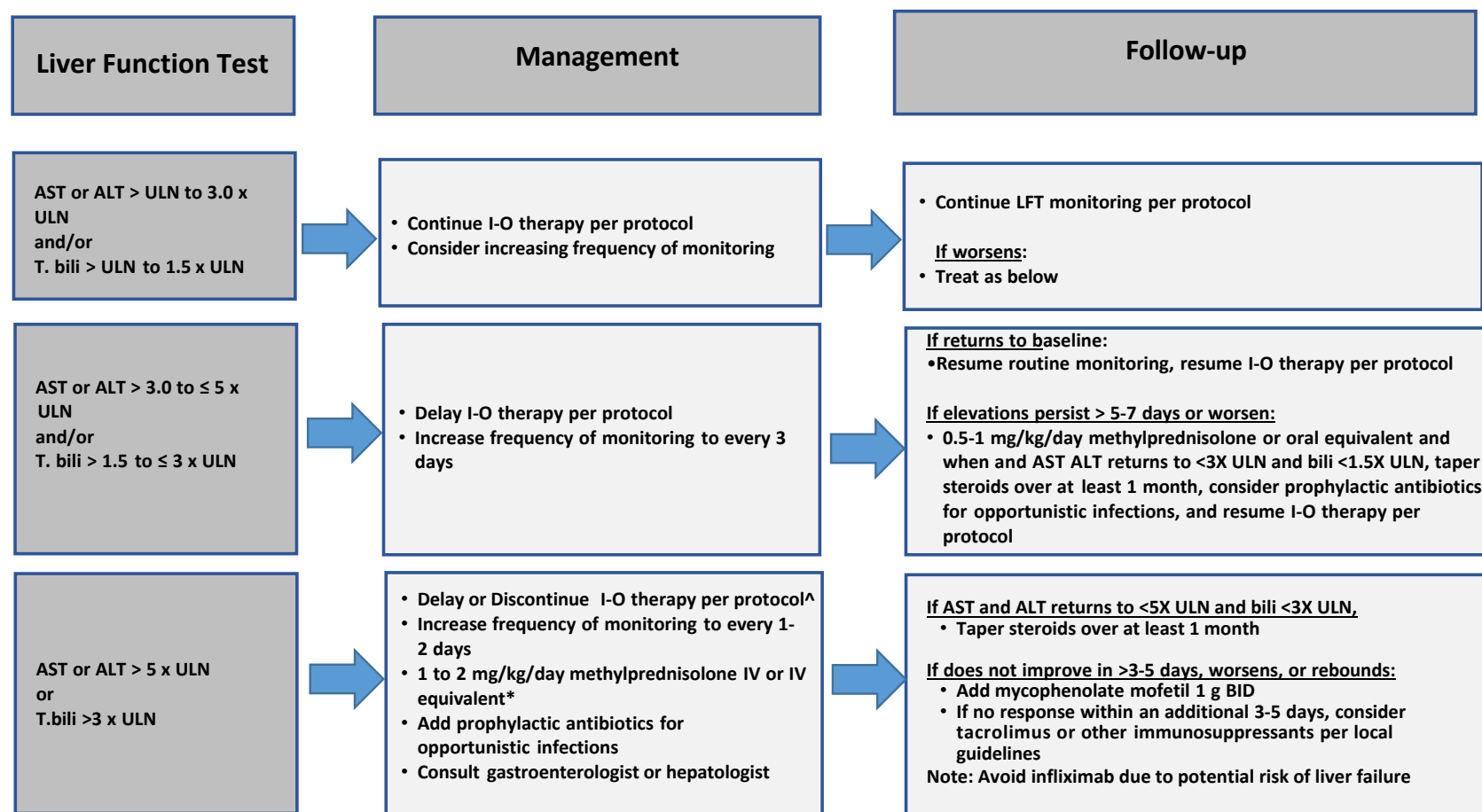
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.  
Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.  
Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

<sup>Δ</sup> Please refer to protocol dose delay and discontinue criteria for specific details.

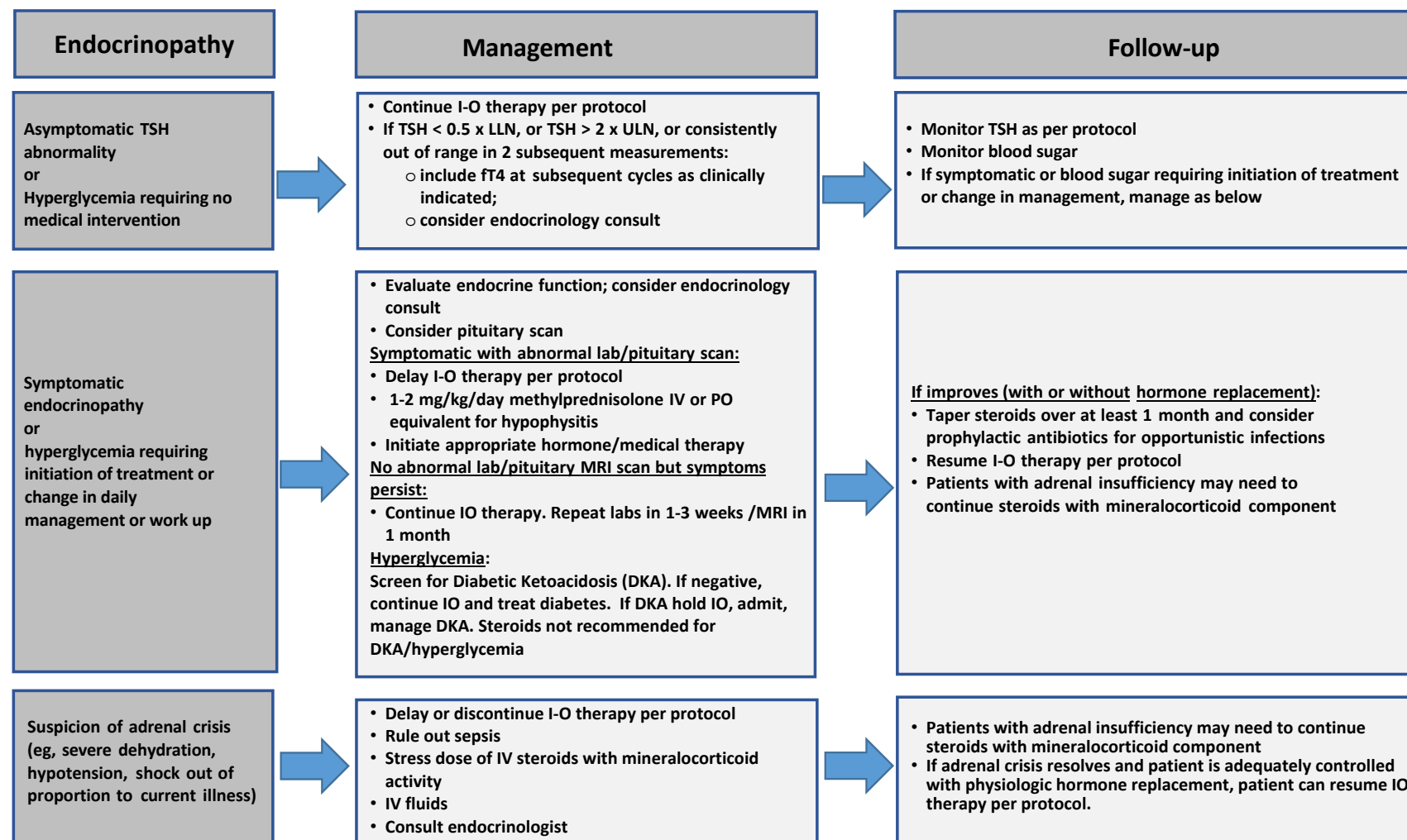
\*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

For subjects with HCC, please refer to the protocol for specific details.



## Endocrinopathy Adverse Event Management Algorithm

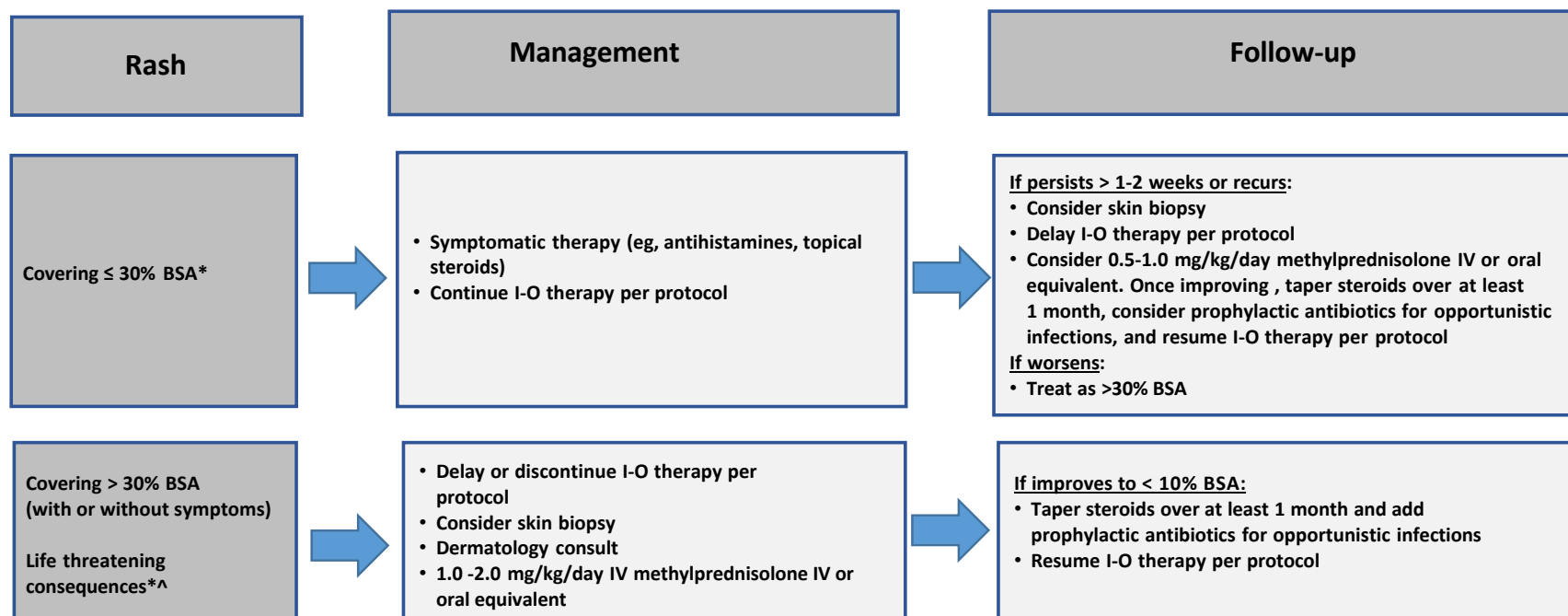
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.  
Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



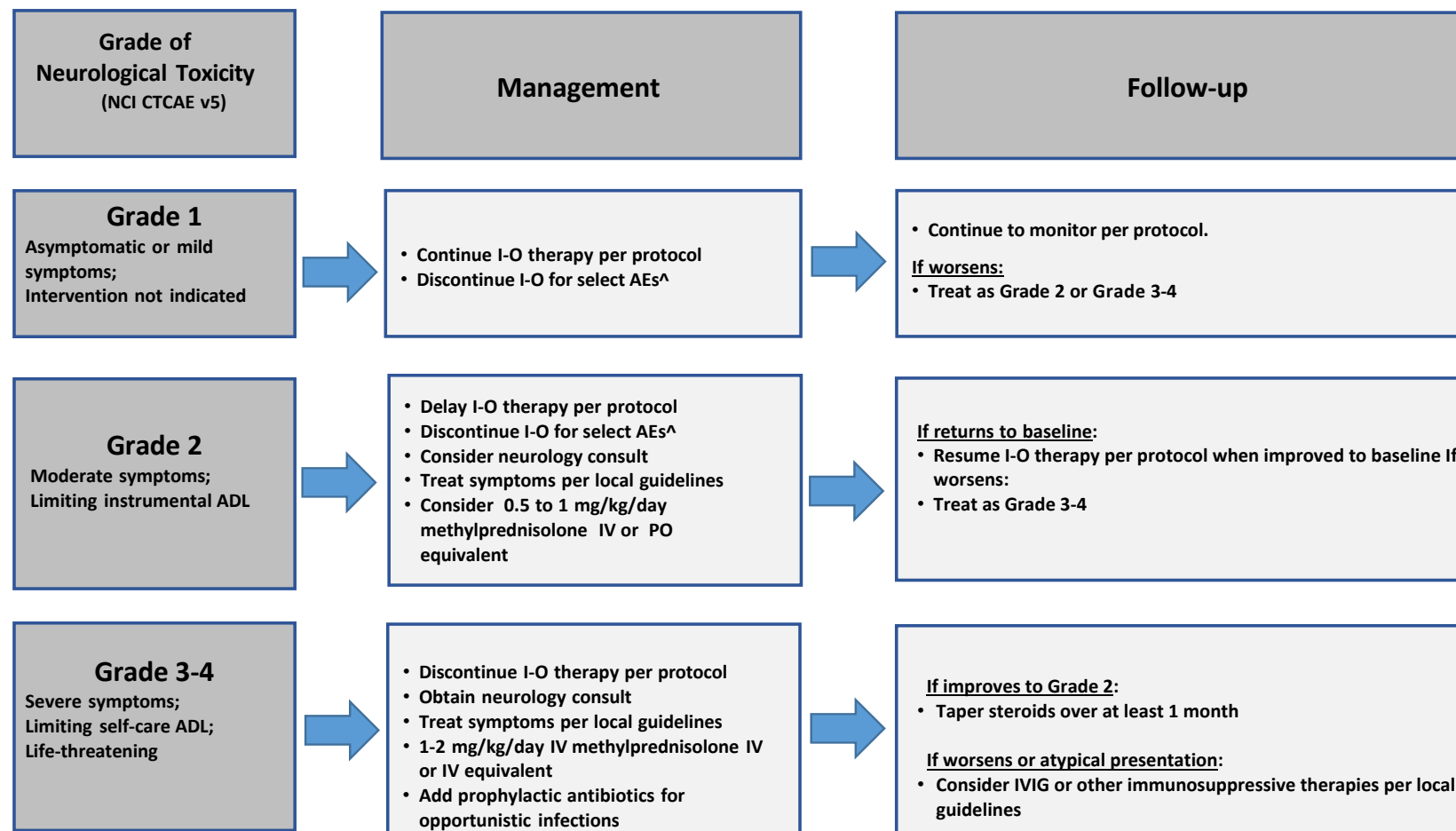
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

\*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS), toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

## Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

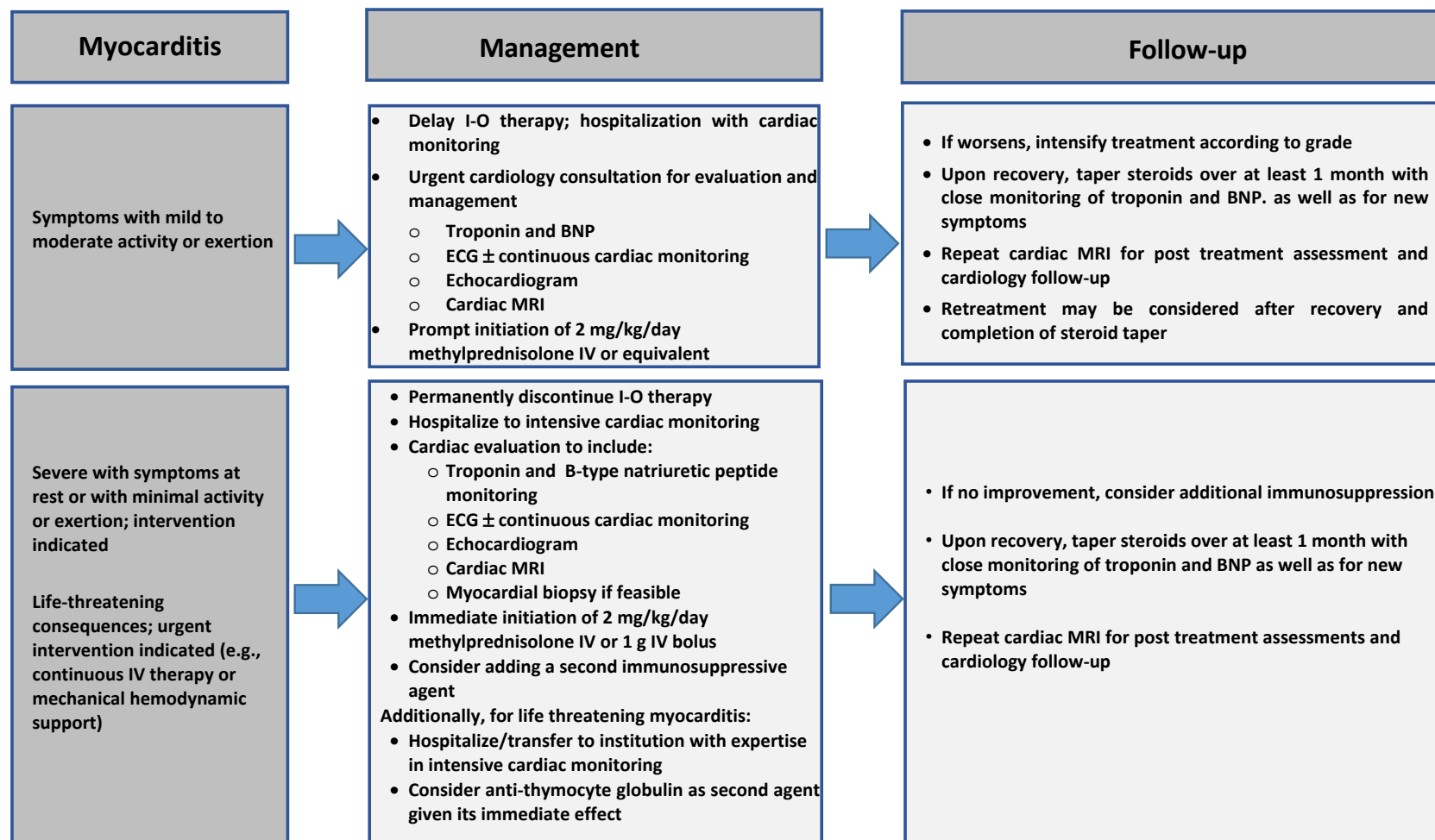


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

<sup>^</sup>Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

## Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

## **Appendix 5: List Of Studies Included In Appendix 1 (Reference Safety Information)**

13 page(s) excluding cover page

## APPENDIX 5 LIST OF STUDIES INCLUDED IN APPENDIX 1 (REFERENCE SAFETY INFORMATION)

Table 1 lists concluded, completed, and ongoing nivolumab studies with reference safety information described in [Appendix 1](#) of the Investigator Brochure.

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
Studies in Non-small Cell Lung Cancer				
CA209012	Phase 1, multi-arm safety study of nivolumab in combination with GEM/CIS, PEM/CIS, PAC/CAR, BEV maintenance, ERL, or IPI or as monotherapy in subjects with treatment-naive Stage IIIB/IV NSCLC.	√	√	√
CA209017	Phase 3, open-label, randomized, 2-arm study of nivolumab versus docetaxel in subjects with advanced metastatic squamous NSCLC previously treated with platinum-based doublet chemotherapies.	√	-	√
CA209026	Phase 3, open-label, randomized, 2-arm study of nivolumab versus investigator’s choice in subjects with Stage IV or recurrent NSCLC with strong PD-L1 positive tumor expression.	√	-	-
CA209057	Phase 3, open-label, randomized, 2-arm study of nivolumab versus docetaxel in subjects with advanced non-squamous NSCLC previously treated with platinum-based doublet chemotherapies.	√	-	-
CA209063	Phase 2, single-arm study of nivolumab in subjects with advanced or metastatic squamous NSCLC following platinum-based doublet chemotherapy and at least 1 additional systemic therapy.	√	-	-
CA209078	Phase 3, open-label, randomized, multinational study of nivolumab versus docetaxel in previously treated subjects with advanced or metastatic non-small cell lung cancer.	√	-	-
CA209153	Phase 3b/4 safety trial of nivolumab in subjects with advanced or metastatic NSCLC who have progressed during or after receiving at least 1 prior systemic regimen.	√	-	-
CA209169	Multi-center expanded access treatment protocol for patients with advanced or metastatic squamous cell non-small cell lung cancer who have received at least two prior systemic regimens.	√	-	-

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
CA209171	Phase 2, single-arm, open-label, multicenter study with nivolumab monotherapy in subjects with advanced or metastatic SQ NSCLC who have received at least two prior systemic regimens.	√	-	-
CA209370	Phase 1/2, open-label study (5 sub-studies) of nivolumab in advanced NSCLC using nivolumab as maintenance after induction chemotherapy or as first-line treatment alone or in combination with standard of care therapies.	√	-	√
CA209384	Phase IIIB/IV, dose frequency optimization study of nivolumab 240 mg every 2 weeks vs nivolumab 480 mg every 4 weeks in subjects with advanced or metastatic NSCLC.	√	-	-
CA209568	Phase 2, open-label, single arm study of nivolumab in combination with ipilimumab as first line-therapy in Stage IV non-small cell lung cancer (NSCLC).	-	√	-
CA209592	Phase 2, exploratory study of the biologic effects and biomarkers of nivolumab in combination with ipilimumab in subjects with treatment-naïve Stage IV or recurrent NSCLC.	-	√	-
CA209722	Open-Label, Randomized Trial of Nivolumab (BMS-936558) plus Pemetrexed/Platinum or Nivolumab plus Ipilimumab (BMS-734016) vs Pemetrexed plus Platinum in Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) Subjects with Epidermal Growth Factor Receptor (EGFR) Mutation Who Failed 1L or 2L EGFR Tyrosine Kinase Inhibitor (TKI) Therapy.	-	√	√
CA209817	Phase 3b/4 safety study of flat dose nivolumab in combination with ipilimumab in participants with non-small cell lung cancer.	-	√	-
CA209870	An open-label, safety study of participants with non-small lung cancer receiving second-line nivolumab monotherapy in Asia.	√	-	-
CA209907	Phase 2, open label, single arm safety study of nivolumab in participants with advanced or metastatic NSCLC who have progressed during or after receiving at least one prior systemic regimen.	√	-	-
CA2099LA	A Phase 3, Randomized Study of Nivolumab Plus Ipilimumab in Combination With Chemotherapy Vs Chemotherapy Alone as First Line Therapy in Stage IV Non-small Cell Lung Cancer (NSCLC).	-	√	√

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
Studies in Melanoma				
CA209004	Phase 1b, open-label, multicenter, multidose, dose-escalation study of nivolumab when administered concurrently or sequentially after ipilimumab in subjects with unresectable Stage III/IV malignant melanoma.	√	√	-
CA209037	Phase 3, randomized, open-label study of nivolumab versus investigator’s choice in subjects with advanced melanoma who have progressed on or after anti-CTLA-4 therapy, and if BRAF V600 mutation positive to also have progressed on or after a BRAF inhibitor.	√	-	-
CA209038	Exploratory, open-label, pharmacodynamic study of nivolumab monotherapy, ipilimumab monotherapy, and nivolumab in combination with ipilimumab treatment in subjects with advanced Stage III/IV melanoma.	√	√	-
CA209064	Phase 2, open-label, randomized study of sequential nivolumab and ipilimumab or ipilimumab and nivolumab in subjects with advanced Stage III/IV melanoma.	√	-	-
CA209066	Phase 3, randomized, double-blind study of nivolumab versus DTIC in subjects with previously untreated, unresectable or metastatic melanoma who are BRAF-WT.	√	-	-
CA209067	Phase 3, randomized, double-blind study of nivolumab monotherapy, ipilimumab monotherapy, and nivolumab combined with ipilimumab in subjects with previously untreated, unresectable or metastatic melanoma.	√	√	-
CA209069	Phase 2, randomized, double-blind study of nivolumab in combination with ipilimumab versus ipilimumab monotherapy in subjects with BRAF-WT and mutant, with untreated unresectable or metastatic melanoma.	-	√	-
CA209168	Expanded access program with nivolumab for subjects with histologically confirmed Stage III (unresectable) or Stage IV melanoma progressing after prior systemic treatment containing an anti-CTLA-4 monoclonal antibody.	√	-	-
CA209172	A single-arm, open-label, multicenter Phase II clinical trial with nivolumab (BMS-936558) for subjects with histologically confirmed Stage III (unresectable) or Stage IV melanoma progressing post prior treatment containing an anti-CTLA-4 monoclonal antibody.	√	-	-



**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
CA209204	A multi-center Phase 2 open-label study to evaluate safety and efficacy in subjects with melanoma metastatic to the brain treated with nivolumab in combination with ipilimumab followed by nivolumab monotherapy.	-	√	-
CA209218	Expanded access program with nivolumab (BMS-936558) in combination with ipilimumab (Yervoy) in subjects with unresectable or metastatic melanoma.	-	√	-
CA209238	Phase 3, double-blind study of nivolumab versus ipilimumab in subjects with complete resection of Stage IIIb/c or Stage IV melanoma.	√	-	-
CA209401	Phase 3 study of nivolumab (BMS-936558) combined with ipilimumab followed by nivolumab monotherapy as first-line therapy of subjects with histologically confirmed Stage III (unresectable) or Stage IV melanoma.	-	√	-
CA209511	Phase 3b/4, randomized, double-blind study of nivolumab 3mg/kg in combination with ipilimumab 1 mg/kg vs nivolumab 1 mg/kg in combination with ipilimumab 3mg/kg in subjects with previously untreated, unresectable or metastatic melanoma.	-	√	-
CA20976K	A Phase 3, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus placebo after complete resection of Stage IIB/C melanoma.	√	-	-
CA2098FC	A Randomized, Double-Blind, Parallel, Phase 1 Study to Compare the Pharmacokinetics of ██████████ Nivolumab Process D to Nivolumab Process C after Complete Resection of Stage IIIa/b/c/d or Stage IV Melanoma.	√	-	-
CA209915	A Phase 3 Randomized Study of Adjuvant Immunotherapy With Nivolumab Combined With Ipilimumab Versus Nivolumab Monotherapy After Complete Resection of Stage Iiib/c/d or Stage Iv Melanoma.	√	√	-
<b>Studies in Renal Cell Carcinoma</b>				
CA209009	Phase 1b, open-label, parallel-group, randomized, multidose study of nivolumab in subjects with metastatic clear-cell RCC.	√	-	-
CA209010	Phase 2, randomized, blinded, dose-ranging study of nivolumab in subjects with progressive, advanced/metastatic clear-cell RCC who received prior anti-angiogenic therapy.	√	-	-
CA209016	Phase 1, open-label, parallel-group, dose-escalation study of nivolumab in combination with VEGFR-TKIs or IPI in subjects with metastatic RCC.	-	√	√

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
CA209025 (ONO-4538-03)	Phase 3, randomized, open-label study of nivolumab versus everolimus in subjects with advanced or metastatic clear-cell RCC who have received prior anti-angiogenic therapy.	√	-	-
CA209214 (ONO-4538-16)	Phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic renal cell carcinoma.	-	√	-
CA209374	Phase 3b/4 safety trial of nivolumab (BMS-936558) in subjects with advanced or metastatic renal cell carcinoma who have progressed during or after receiving prior anti-angiogenic therapy.	√	-	-
CA20967T	A Phase 3, Open-label, Randomized, Noninferiority Trial of Subcutaneous Formulation of Nivolumab Versus Intravenous Nivolumab in Participants With Advanced or Metastatic Clear Cell Renal Cell Carcinoma Who Have Received Prior Systemic Therapy	√		
CA2097C9	A Phase 4 Study of Nivolumab in Combination with Ipilimumab in Patients with Previously Untreated Advanced Renal Cell Carcinoma and Intermediate- or Poor-risk Factors Conducted in India.	-	√	-
CA209920	Phase 3b/4 safety trial of nivolumab combined with ipilimumab in subjects with previously untreated, advanced or metastatic RCC.	-	√	-
CA2099ER	A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cabozantinib versus Sunitinib in Participants with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma.	-	-	√
<b>Studies in Lymphomas and Hematologic Malignancies</b>				
CA209039	Phase 1, dose-escalation study of nivolumab and the combinations of nivolumab and ipilimumab or nivolumab and lirilumab in subjects with relapsed or refractory hematologic malignancy.	√	√	√
CA209139	Phase 2b, single-arm, open-label study of nivolumab in subjects with relapsed or refractory diffuse large B-cell lymphoma after failure of ASCT or at least 2 prior multiagent chemotherapy regimens in subjects who are not candidates for ASCT.	√	-	-
CA209140	Phase 2b, single-arm, open-label study of nivolumab in subjects with relapsed or refractory follicular lymphoma who have failed therapy with both rituximab and an alkylating agent.	√	-	-

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
CA209205	Non-comparative, multi-cohort, single arm, open-label, Phase 2 study of nivolumab (BMS-936558) in classical Hodgkin Lymphoma (cHL) subjects after failure of autologous stem cell transplant (ASCT).	√	-	√
CA209436	Phase 1/2 study to evaluate the safety and preliminary efficacy of nivolumab in combination with brentuximab vedotin (BV) in subjects with relapsed, refractory primary mediastinal B-cell lymphoma (PMBL).	-	-	√
CA209602	An Open-Label, Randomized Phase 3 Trial of Combinations of Nivolumab, Pomalidomide and Dexamethasone in Relapsed and Refractory Multiple Myeloma.	-	-	√
CA209647 (ONO-4538-45)	Phase 2, open-label, single-arm, two-cohort study of nivolumab in relapsed/refractory primary central nervous system lymphoma or relapsed/refractory primary testicular lymphoma.	√	-	-
CA209744	Phase 2, open-label study of nivolumab + brentuximab vedotin, followed by brentuximab vedotin + bendamustine for suboptimal response, in children, adolescents, and young adults with low or standard risk relapsed/refractory cHL.	-	-	√
CA209812	A Randomized, Open-label, Phase 3 Trial of Nivolumab plus Brentuximab vedotin versus Brentuximab vedotin alone in Participants with Relapsed Refractory or Ineligible for Autologous Stem Cell Transplant (ASCT) Advanced Stage Classical Hodgkin Lymphoma.	-	-	√
<b>Studies in squamous cell carcinoma of the head and neck (SCCHN)</b>				
CA209141 (ONO-4538-11)	An open label, randomized Phase 3 clinical trial of nivolumab vs. therapy of investigator's choice in recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).	√	-	-

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
CA209651	An Open Label, Randomized, Two Arm, Phase 3 Study of Nivolumab in Combination with Ipilimumab versus EXTREME Study Regimen (Cetuximab + Cisplatin/Carboplatin + Fluorouracil) as First Line Therapy in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN).	-	√	-
CA209714	Phase 2, double-blind, randomized, two-arm study of nivolumab in combination with ipilimumab versus nivolumab in combination with placebo in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).	√	√	-
CA2099TM	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Of Nivolumab Or Nivolumab Plus Cisplatin, In Combination With Radiotherapy In Participants With Cisplatin Ineligible And Cisplatin Eligible Locally Advanced squamous cell carcinoma of the head and neck (SCCHN).	√	-	√
<b>Studies in Other Malignancies/Conditions</b>				
CA209001 (MDX1106-01)	Phase 1, open-label, dose-escalation, safety and PK study of nivolumab in subjects with pathologically verified, selected refractory or relapsed malignancies (NSCLC, CRC, MEL, cRCC, and HRPC).	√	-	-
CA209002 (MDX1106-02)	Phase 1, double-blind, placebo-controlled study of a single intravenous administration of nivolumab in subjects with active hepatitis C genotype 1 infection.	√	-	-
CA209003 (MDX1106-03)	Phase 1, multidose, dose-escalation study of nivolumab in subjects with metastatic NSCLC, CRC, melanoma, RCC, or mCRPC.	√	-	-
CA209032	Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab at different dose levels in subjects with several types of advanced or metastatic solid tumors.	√	√	-
CA209040	Phase 1/2, dose-escalation, open-label study of nivolumab or nivolumab in combination with other agents in advanced hepatocellular carcinoma subjects with or without chronic viral hepatitis.	√	√	√
CA209077	Phase 1/2, open-label study of nivolumab in Chinese subjects with previously treated advanced or recurrent solid tumors.	√	-	-

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
CA209142	Phase 2, open-label, multicenter, 2-stage Simon design stage trial of nivolumab monotherapy or in combination with ipilimumab in subjects with recurrent and metastatic MSI-H and non-MSI-H colon cancer.	√	√	-
CA209143	Randomized phase 3 open label study of nivolumab versus bevacizumab and a safety study of nivolumab or nivolumab in combination with ipilimumab in adult subjects with recurrent Glioblastoma (GBM).	√	√	-
CA209275	Phase 2 single arm clinical trial of nivolumab (BMS-936558) in subjects with metastatic or unresectable urothelial cancer who have progressed or recurred following treatment with a platinum agent.	√	-	-
CA209331	Phase 3, open-label, 2-group study of nivolumab or chemotherapy in subjects with relapsed small-cell lung cancer after platinum-based first line chemotherapy.	√	-	-
CA209358	Phase 1/2, non-comparative, two-cohort, single-arm, open-label study of nivolumab (BMS-936558) in subjects with virus-positive and virus-negative solid tumors.	√	-	-
CA209451	Phase 3, randomized, multicenter, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab as maintenance therapy in subjects with extensive stage disease SCLC (ED-SCLC) after completion of platinum-based first line chemotherapy.	√	√	-
CA209459	Phase 3, randomized, multicenter study of nivolumab versus sorafenib as first-line treatment in patients with advanced HCC.	√	-	-
CA209498	Phase 3, open-label study of nivolumab vs temozolomide, each in combination with radiation therapy in newly diagnosed adult subjects with unmethylated MGMT GBM.	-	-	√
CA209548	A Randomized Phase 3 Single Blind Study of Temozolomide plus Radiation Therapy combined with Nivolumab or Placebo in Newly Diagnosed Adult Subjects with MGMT-Methylated (tumor O6-methylguanine DNA methyltransferase) Glioblastoma.	-	-	√
CA209627	Phase 2, open-label, multi-cohort trial of nivolumab in advanced or metastatic malignancies	√		
CA209648	A Randomized Phase 3 Study of Nivolumab plus Ipilimumab or Nivolumab Combined with Fluorouracil plus Cisplatin versus Fluorouracil plus Cisplatin in Subjects with Unresectable Advanced, Recurrent or Metastatic Previously Untreated Esophageal Squamous Cell Carcinoma.	-	√	√

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
CA209649	A randomized, multicenter, open-label, Phase 3 study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine in subjects with previously untreated advanced or metastatic gastric cancer (GC) or gastroesophageal junction cancer (GEJC).	-	√	√
CA209650	Phase 2 trial of nivolumab plus ipilimumab in men with metastatic castration-resistant prostate cancer.	-	√	-
CA209672	Phase 1 trial of nivolumab in combination with ipilimumab in Chinese subjects with previously treated or recurrent solid tumors.	-	√	-
CA209743	A Phase III, Randomized, Open Label Trial of Nivolumab in Combination with Ipilimumab versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma.	-	√	-
CA20974W	A Randomized, Multi-center, Double-blinded, Placebo-controlled Phase 3 Study of Nivolumab and Ipilimumab, Nivolumab Monotherapy, or Placebo in Combination with Trans-arterial ChemoEmbolization (TACE) in Patients with Intermediate-stage Hepatocellular Carcinoma (HCC).	-	-	√
CA2097A8	Randomized, Non-comparative Neoadjuvant Phase II Study in Patients with ER+/HER2-Breast Cancer ≥ 2 cm with Safety Run-in, Assessing Nivolumab + Palbociclib + Anastrozole.	-	-	√
CA209848	A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination with Ipilimumab or Nivolumab Monotherapy in Participants with Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H).	-	√	-
CA209887	Safety Study of Nivolumab for Selected Advanced Malignancies in India.	√	-	-
CA2098TT	Pan Tumor Study for Long Term Follow-up of Cancer Survivors Who Have Participated in Trials Investigating Nivolumab	√	-	-
CA209908	Phase 1b/2 trial of nivolumab monotherapy and nivolumab in combination with ipilimumab in pediatric subjects with high grade primary CNS malignancies.	√	√	
CA2099GW	A Phase 1/2 Study to Evaluate the Safety and Preliminary Efficacy of Nivolumab Combined with Daratumumab in Participants with Advanced or Metastatic Solid Tumors.	-	-	√

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
CA2099KD	A Phase 2 Study of Nivolumab in Combination with Either Rucaparib, Docetaxel, or Enzalutamide in Men with Castration-resistant Metastatic Prostate Cancer.	-	-	√
CA2099N9	A Phase 1/2, open-label, multi-center trial of nivolumab in combination with trametinib, with or without ipilimumab for the treatment of proficient mismatch repair (pMMR)/microsatellite stable (MSS) metastatic colorectal cancer (mCRC).	-	-	√
CA2099UT	A Phase 2, Randomized, Open-label Study of Nivolumab or Nivolumab/BMS-986205 Alone or Combined with Intravesical Bacillus Calumette-Guerin (BCG) in Participants with BCG-Unresponsive, High-Risk, Non-Muscle Invasive Bladder Cancer.	√	-	√
CA2099X8	An Open-Label Exploratory Phase 2/3 Study of Nivolumab with Standard of Care Therapy vs Standard of Care Therapy for First-Line Treatment of Metastatic Colorectal Cancer.	-	-	√
<b>Studies Sponsored by ONO</b>				
ONO-4538-01	Phase 1, open-label, single dose followed by multidose dose-escalation study of nivolumab in subjects with advanced or recurrent solid tumors.	√	-	-
ONO-4538-02	Phase 2, multicenter, open-label, uncontrolled study of nivolumab in subjects with unresectable Stage III/IV or recurrent malignant melanoma.	√	-	-
ONO-4538-04	Open-label, Phase I Study To Assess Safety and PK of PD-1 in Combination with Chemotherapy in Patients with NSCLC.	-	-	√
ONO-4538-05	Phase 2, multicenter, open-label, uncontrolled study of nivolumab in subjects with Stage IIIB/IV or recurrent squamous NSCLC unsuited to radical radiotherapy and resistant to a platinum-based chemotherapeutic regimen.	√	-	-
ONO-4538-06	Phase 2, multicenter, open-label, uncontrolled study of nivolumab in subjects with Stage IIIB/IV or recurrent nonsquamous NSCLC unsuited to radical radiotherapy and resistant to a platinum-based chemotherapeutic regimen.	√	-	-
ONO-4538-07	Phase 2, multicenter, open-label, uncontrolled study of nivolumab in subjects with esophageal cancer.	√	-	-
ONO-4538-08	Phase 2, multicenter, open-label, uncontrolled study of nivolumab in subjects with previously untreated unresectable Stage III/IV or recurrent malignant melanoma.	√	-	-

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
ONO-4538-09	Phase 2 study to evaluate safety and efficacy of ONO-4538 in Stage IIIB/IV or recurrent non-small cell lung cancer patients who are unsuited to radical radiotherapy and resistance to a platinum-based chemotherapeutic regimen.	√	-	-
ONO-4538-11E	Phase 3, open label, randomized extension trial of nivolumab vs investigator's choice in recurrent or metastatic platinum-refractory SCCHN.	√	-	-
ONO-4538-12	Phase 3 multicenter, double-blind, randomized study in patients with unresectable advanced or recurrent gastric cancer.	√	-	-
ONO-4538-12E	Phase 3 multicenter, open-label, uncontrolled extension study in patients with unresectable advanced or recurrent gastric cancer.	√	-	-
ONO-4538-13	Multicenter, open-label, uncontrolled, Phase I study in solid tumor.	√	-	-
ONO-4538-14	Multicenter, open-label, uncontrolled, Phase I multiple dose study in solid tumor.	√	-	-
ONO-4538-15	Phase 2, multicenter, open-label, uncontrolled study in relapsed or refractory Hodgkin's lymphoma.	√	-	-
ONO-4538-17	Phase 2 study to evaluate efficacy and safety of combination therapy with nivolumab and ipilimumab in patients with previously untreated melanoma.	-	√	-
ONO-4538-18	Phase 1 Study of Combination Therapy of Mogamulizumab with Nivolumab in Subjects with Advanced Solid Tumors.	-	-	√
ONO-4538-19	Phase 2 study to evaluate efficacy and safety of nivolumab in patients with first recurrence of glioblastoma.	√	-	-
ONO-4538-23	Phase 3, multicenter, open label, randomized study of nivolumab vs investigator's choice in patients with ovarian cancer.	√	-	-
ONO-4538-24	Phase 3, multicenter, randomized, open-label study of nivolumab in patients with esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs.	√	-	-
ONO-4538-24E	Phase 3 extension study, multicenter, open-label, uncontrolled study of nivolumab in patients with esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs.	√	-	-



**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
ONO-4538-25	Phase 2 study to evaluate safety and efficacy of ONO-4538 (nivolumab) in Stage IIIB/IV or recurrent non-small cell lung cancer patients who are unsuited to radical radiotherapy and resistant to a platinum-based chemotherapeutic regimen.	√	-	-
ONO-4538-31	Phase 2, multicenter, open-label, randomized study of nivolumab in patients with unresectable Stage III/IV or recurrent malignant melanoma.	√	-	-
ONO-4538-32	Phase 1, open-label, multicenter study in subjects with biliary tract cancer.	√	-	√
ONO-4538-39	Phase 2, multicenter, open-label, single arm study of nivolumab in patients with uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma.	√	-	-
ONO-4538-41	Phase 2, multicenter, open-label, single arm study in malignant pleural mesothelioma.	√	-	-
ONO-4538-41E	Phase 2, extension clinical study in malignant pleural mesothelioma.	√	-	-
ONO-4538-53	Phase 1 Dose Escalation Study of ONO-4578 Given as Monotherapy and Combinations of ONO-4578 and ONO-4538 in Subjects Advanced or Metastatic Solid Tumors.	-	-	√
ONO-4538-54	Phase 1/2 study of nivolumab in Japanese subjects with sepsis or septic shock.	√	-	-
ONO-4538-64	A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma.	-	-	√
ONO-4538-67	Phase 1, multicenter, open-label, non-comparative study in patients with resectable malignancies (gastric cancer/non-small cell lung cancer).	√	-	-
ONO-4538-68	Open-label, non-comparative study of combination use of ONO-4538 and ONO-7703 in patients with advanced or metastatic solid tumors.	-	-	√
ONO-4538-83	A Multicenter, Open-Label Phase II Study in Patients with Pancreatic Cancer.	-	-	√
ONO-4538-88	A Multicenter, Open-label, Uncontrolled Study in non-small cell lung cancer and gastric cancer.	√	-	-
ONO-4538-91	A Multicenter, Open-label, Uncontrolled Study in Biliary Tract Cancer.	√	-	-
ONO-4538-98	A Multicenter, Open-label, Phase II Pan-Tumor Study in Patients Who Have Participated in Trials to Investigate Efficacy and Safety of ONO-4538 as Monotherapy or in Combination With Other Therapies and Are Continuing ONO-4538 Treatment.	-	-	√
<b>Total</b>		<b>17,709</b>	<b>11,701</b>	<b>3,201</b>

**Table 1: Summary of Nivolumab Clinical Studies with Data in the Investigator Brochure**

Study ID	Study Design (Phase)	Subjects Treated with		
		Nivo	Nivo + Ipi	Nivo + Other
Grand Total			32,608	

Abbreviations: ASCT = autologous stem cell transplant; BEV = bevacizumab; CAR = carboplatin; CIS = cisplatin; cHL = classic hodgkin's lymphoma; CNS = central nervous system; CSR = clinical study report; DTIC = dacarbazine; ERL = erlotinib; GEM = gemcitabine; HCC = hepatocellular carcinoma; HLA = human leukocyte antigen; IPI = ipilimumab; MSI-H = microsatellite instability-high; PAC = paclitaxel; PEM = pemetrexed; SCCHN = squamous cell carcinoma of the head and neck; SCLC = small cell lung cancer; TNBC = triple-negative breast cancer; WT = wild type.

## **Appendix 6: Related Adverse Event Summary by Custom Standardized MedDRA Query All Treated Subjects**

21 page(s) excluding cover page

Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
TOTAL SUBJECTS WITH AN EVENT	11544 ( 64.9)	9694 ( 82.3)
Fatigue	4471 ( 25.1)	3985 ( 33.8)
Fatigue	3375 ( 19.0)	3048 ( 25.9)
Asthenia	981 ( 5.5)	935 ( 7.9)
Malaise	231 ( 1.3)	163 ( 1.4)
Lethargy	68 ( 0.4)	61 ( 0.5)
Rash	2749 ( 15.5)	3619 ( 30.7)
Rash	1791 ( 10.1)	2172 ( 18.4)
Rash maculo-papular	594 ( 3.3)	1095 ( 9.3)
Rash pruritic	209 ( 1.2)	293 ( 2.5)
Rash macular	140 ( 0.8)	175 ( 1.5)
Rash erythematous	87 ( 0.5)	84 ( 0.7)
Dermatitis	86 ( 0.5)	80 ( 0.7)
Rash papular	76 ( 0.4)	107 ( 0.9)
Drug eruption	25 ( 0.1)	23 ( 0.2)
Dermatitis allergic	22 ( 0.1)	29 ( 0.2)
Skin irritation	9 ( <0.1)	9 ( <0.1)
Rash vesicular	7 ( <0.1)	6 ( <0.1)
Drug reaction with eosinophilia and systemic symptoms	4 ( <0.1)	2 ( <0.1)
Immune-mediated dermatitis	3 ( <0.1)	4 ( <0.1)
Autoimmune dermatitis	2 ( <0.1)	0
Rash morbilliform	2 ( <0.1)	3 ( <0.1)

MedDRA Version: 26.1

Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Anal rash	1 ( <0.1)	0
Fixed eruption	1 ( <0.1)	1 ( <0.1)
Mucocutaneous rash	1 ( <0.1)	0
Pruritus	2397 ( 13.5)	3054 ( 25.9)
Pruritus	2237 ( 12.6)	2852 ( 24.2)
Rash pruritic	209 ( 1.2)	293 ( 2.5)
Eyelids pruritus	1 ( <0.1)	6 ( <0.1)
Diarrhoea	2128 ( 12.0)	2988 ( 25.4)
Diarrhoea	2128 ( 12.0)	2988 ( 25.4)
Hypothyroidism	1789 ( 10.1)	2051 ( 17.4)
Hypothyroidism	1517 ( 8.5)	1862 ( 15.8)
Blood thyroid stimulating hormone increased	322 ( 1.8)	225 ( 1.9)
Primary hypothyroidism	11 ( <0.1)	2 ( <0.1)
Autoimmune hypothyroidism	6 ( <0.1)	11 ( <0.1)
Central hypothyroidism	2 ( <0.1)	9 ( <0.1)
Immune-mediated hypothyroidism	2 ( <0.1)	3 ( <0.1)
Myxoedema	1 ( <0.1)	0
Thyroid hormones decreased	0	2 ( <0.1)
Nausea	1518 ( 8.5)	1708 ( 14.5)
Nausea	1518 ( 8.5)	1708 ( 14.5)
Decreased appetite	1221 ( 6.9)	1310 ( 11.1)
Decreased appetite	1221 ( 6.9)	1310 ( 11.1)

MedDRA Version: 26.1

Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Musculoskeletal pain	1034 ( 5.8)	986 ( 8.4)
Myalgia	572 ( 3.2)	605 ( 5.1)
Pain in extremity	184 ( 1.0)	149 ( 1.3)
Back pain	172 ( 1.0)	160 ( 1.4)
Non-cardiac chest pain	52 ( 0.3)	31 ( 0.3)
Musculoskeletal stiffness	48 ( 0.3)	48 ( 0.4)
Neck pain	35 ( 0.2)	48 ( 0.4)
Musculoskeletal chest pain	31 ( 0.2)	21 ( 0.2)
Musculoskeletal pain	28 ( 0.2)	17 ( 0.1)
Bone pain	26 ( 0.1)	27 ( 0.2)
Musculoskeletal discomfort	12 ( <0.1)	11 ( <0.1)
Spinal pain	7 ( <0.1)	9 ( <0.1)
Limb discomfort	3 ( <0.1)	5 ( <0.1)
Tendon pain	2 ( <0.1)	1 ( <0.1)
Neuromuscular pain	1 ( <0.1)	0
Ligament pain	0	1 ( <0.1)
Alanine aminotransferase increased	902 ( 5.1)	1494 ( 12.7)
Alanine aminotransferase increased	902 ( 5.1)	1494 ( 12.7)
Aspartate aminotransferase increased	892 ( 5.0)	1439 ( 12.2)
Aspartate aminotransferase increased	892 ( 5.0)	1439 ( 12.2)
Hyperthyroidism	800 ( 4.5)	1358 ( 11.5)
Hyperthyroidism	663 ( 3.7)	1185 ( 10.1)

MedDRA Version: 26.1

Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Blood thyroid stimulating hormone decreased	120 ( 0.7)	165 ( 1.4)
Thyroxine increased	17 ( <0.1)	22 ( 0.2)
Tri-iodothyronine increased	15 ( <0.1)	14 ( 0.1)
Immune-mediated hyperthyroidism	2 ( <0.1)	4 ( <0.1)
Primary hyperthyroidism	2 ( <0.1)	0
Graves' disease	1 ( <0.1)	7 ( <0.1)
Thyroid hormones increased	1 ( <0.1)	3 ( <0.1)
Hypersensitivity	716 ( 4.0)	677 ( 5.7)
Infusion related reaction	434 ( 2.4)	404 ( 3.4)
Hypersensitivity	142 ( 0.8)	116 ( 1.0)
Eye pruritus	27 ( 0.2)	28 ( 0.2)
Face oedema	25 ( 0.1)	38 ( 0.3)
Infusion related hypersensitivity reaction	21 ( 0.1)	24 ( 0.2)
Swelling face	14 ( <0.1)	12 ( 0.1)
Drug hypersensitivity	13 ( <0.1)	13 ( 0.1)
Bronchospasm	12 ( <0.1)	6 ( <0.1)
Eyelid oedema	12 ( <0.1)	8 ( <0.1)
Lip oedema	8 ( <0.1)	4 ( <0.1)
Periorbital oedema	8 ( <0.1)	21 ( 0.2)
Eye swelling	6 ( <0.1)	3 ( <0.1)
Eye oedema	5 ( <0.1)	1 ( <0.1)
Angioedema	4 ( <0.1)	5 ( <0.1)

MedDRA Version: 26.1

Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Laryngeal oedema	4 ( <0.1)	1 ( <0.1)
Lip swelling	4 ( <0.1)	7 ( <0.1)
Periorbital swelling	4 ( <0.1)	3 ( <0.1)
Pruritus allergic	4 ( <0.1)	1 ( <0.1)
Circumoral oedema	3 ( <0.1)	0
Swollen tongue	3 ( <0.1)	2 ( <0.1)
Conjunctivitis allergic	2 ( <0.1)	2 ( <0.1)
Pharyngeal swelling	2 ( <0.1)	1 ( <0.1)
Swelling of eyelid	2 ( <0.1)	4 ( <0.1)
Conjunctival oedema	1 ( <0.1)	1 ( <0.1)
Mouth swelling	1 ( <0.1)	1 ( <0.1)
Pharyngeal oedema	1 ( <0.1)	1 ( <0.1)
Hypersensitivity pneumonitis	0	3 ( <0.1)
Oropharyngeal spasm	0	1 ( <0.1)
Pneumonitis	703 ( 4.0)	768 ( 6.5)
Pneumonitis	578 ( 3.2)	681 ( 5.8)
Interstitial lung disease	106 ( 0.6)	62 ( 0.5)
Immune-mediated lung disease	21 ( 0.1)	27 ( 0.2)
Organising pneumonia	9 ( <0.1)	6 ( <0.1)
Granulomatous pneumonitis	1 ( <0.1)	1 ( <0.1)
Hypersensitivity pneumonitis	0	3 ( <0.1)
Pyrexia	667 ( 3.7)	1144 ( 9.7)

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Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Pyrexia	655 ( 3.7)	1119 ( 9.5)
Body temperature increased	7 ( <0.1)	9 ( <0.1)
Hyperthermia	4 ( <0.1)	17 ( 0.1)
Hyperpyrexia	2 ( <0.1)	2 ( <0.1)
Anaemia	611 ( 3.4)	543 ( 4.6)
Anaemia	611 ( 3.4)	543 ( 4.6)
Vomiting	585 ( 3.3)	889 ( 7.5)
Vomiting	585 ( 3.3)	889 ( 7.5)
Lipase increased	568 ( 3.2)	1262 ( 10.7)
Lipase increased	568 ( 3.2)	1262 ( 10.7)
Headache	562 ( 3.2)	768 ( 6.5)
Headache	562 ( 3.2)	768 ( 6.5)
Abdominal pain	527 ( 3.0)	751 ( 6.4)
Abdominal pain	376 ( 2.1)	579 ( 4.9)
Abdominal pain upper	124 ( 0.7)	149 ( 1.3)
Abdominal discomfort	44 ( 0.2)	49 ( 0.4)
Abdominal pain lower	9 ( <0.1)	17 ( 0.1)
Abdominal tenderness	3 ( <0.1)	5 ( <0.1)
Dry mouth	509 ( 2.9)	551 ( 4.7)
Dry mouth	509 ( 2.9)	551 ( 4.7)
Cough	473 ( 2.7)	498 ( 4.2)
Cough	473 ( 2.7)	498 ( 4.2)

MedDRA Version: 26.1

Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Dry skin	470 ( 2.6)	502 ( 4.3)
Dry skin	470 ( 2.6)	502 ( 4.3)
Dyspnoea	466 ( 2.6)	489 ( 4.2)
Dyspnoea	466 ( 2.6)	489 ( 4.2)
Constipation	463 ( 2.6)	339 ( 2.9)
Constipation	463 ( 2.6)	339 ( 2.9)
Stomatitis	400 ( 2.2)	394 ( 3.3)
Stomatitis	248 ( 1.4)	238 ( 2.0)
Mucosal inflammation	141 ( 0.8)	124 ( 1.1)
Mouth ulceration	25 ( 0.1)	35 ( 0.3)
Aphthous ulcer	10 ( <0.1)	17 ( 0.1)
Mucosal ulceration	1 ( <0.1)	0
Oral mucosa erosion	1 ( <0.1)	2 ( <0.1)
Palatal ulcer	0	1 ( <0.1)
Amylase increased	397 ( 2.2)	923 ( 7.8)
Amylase increased	397 ( 2.2)	923 ( 7.8)
Neuropathy peripheral	391 ( 2.2)	414 ( 3.5)
Paraesthesia	124 ( 0.7)	148 ( 1.3)
Neuropathy peripheral	104 ( 0.6)	96 ( 0.8)
Peripheral sensory neuropathy	75 ( 0.4)	87 ( 0.7)
Hypoaesthesia	46 ( 0.3)	42 ( 0.4)
Dysaesthesia	21 ( 0.1)	12 ( 0.1)

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Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Peripheral motor neuropathy	20 ( 0.1)	18 ( 0.2)
Polyneuropathy	15 ( <0.1)	22 ( 0.2)
Burning sensation	8 ( <0.1)	8 ( <0.1)
Hyperaesthesia	3 ( <0.1)	7 ( <0.1)
Neuritis	3 ( <0.1)	2 ( <0.1)
Peripheral sensorimotor neuropathy	3 ( <0.1)	5 ( <0.1)
Autoimmune neuropathy	1 ( <0.1)	4 ( <0.1)
Axonal neuropathy	1 ( <0.1)	0
Demyelinating polyneuropathy	1 ( <0.1)	1 ( <0.1)
Skin burning sensation	1 ( <0.1)	3 ( <0.1)
Chronic inflammatory demyelinating polyradiculoneuropathy	0	1 ( <0.1)
Immune-mediated neuropathy	0	4 ( <0.1)
Multifocal motor neuropathy	0	1 ( <0.1)
Polyradiculoneuropathy	0	2 ( <0.1)
Oedema	336 ( 1.9)	299 ( 2.5)
Oedema peripheral	261 ( 1.5)	236 ( 2.0)
Peripheral swelling	33 ( 0.2)	30 ( 0.3)
Oedema	16 ( <0.1)	5 ( <0.1)
Generalised oedema	14 ( <0.1)	8 ( <0.1)
Localised oedema	13 ( <0.1)	13 ( 0.1)
Swelling	7 ( <0.1)	12 ( 0.1)
Pharyngeal swelling	2 ( <0.1)	1 ( <0.1)

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Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Skin oedema	1 ( <0.1)	0
Skin swelling	1 ( <0.1)	0
Blood creatinine increased	326 ( 1.8)	366 ( 3.1)
Blood creatinine increased	326 ( 1.8)	366 ( 3.1)
Blood alkaline phosphatase increased	316 ( 1.8)	458 ( 3.9)
Blood alkaline phosphatase increased	316 ( 1.8)	458 ( 3.9)
Vitiligo	316 ( 1.8)	325 ( 2.8)
Vitiligo	316 ( 1.8)	325 ( 2.8)
Dizziness	315 ( 1.8)	318 ( 2.7)
Dizziness	264 ( 1.5)	273 ( 2.3)
Vertigo	52 ( 0.3)	45 ( 0.4)
Dizziness postural	1 ( <0.1)	8 ( <0.1)
Vertigo positional	1 ( <0.1)	0
Dizziness exertional	0	1 ( <0.1)
Colitis	291 ( 1.6)	916 ( 7.8)
Colitis	221 ( 1.2)	701 ( 5.9)
Immune-mediated enterocolitis	35 ( 0.2)	146 ( 1.2)
Autoimmune colitis	21 ( 0.1)	69 ( 0.6)
Enterocolitis	11 ( <0.1)	34 ( 0.3)
Colitis ulcerative	6 ( <0.1)	8 ( <0.1)
Colitis microscopic	5 ( <0.1)	6 ( <0.1)
Crohn's disease	1 ( <0.1)	0

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Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Enterocolitis haemorrhagic	0	2 ( <0.1)
Chills	253 ( 1.4)	354 ( 3.0)
Chills	253 ( 1.4)	354 ( 3.0)
Blood bilirubin increased	249 ( 1.4)	273 ( 2.3)
Blood bilirubin increased	215 ( 1.2)	234 ( 2.0)
Hyperbilirubinaemia	31 ( 0.2)	36 ( 0.3)
Bilirubin conjugated increased	24 ( 0.1)	32 ( 0.3)
Blood bilirubin unconjugated increased	8 ( <0.1)	5 ( <0.1)
Hyponatremia	240 ( 1.3)	378 ( 3.2)
Hyponatraemia	232 ( 1.3)	363 ( 3.1)
Blood sodium decreased	10 ( <0.1)	18 ( 0.2)
Hyperglycaemia	212 ( 1.2)	236 ( 2.0)
Hyperglycaemia	212 ( 1.2)	236 ( 2.0)
Adrenal insufficiency	210 ( 1.2)	630 ( 5.3)
Adrenal insufficiency	164 ( 0.9)	534 ( 4.5)
Cortisol decreased	28 ( 0.2)	57 ( 0.5)
Adrenocorticotrophic hormone deficiency	11 ( <0.1)	19 ( 0.2)
Secondary adrenocortical insufficiency	5 ( <0.1)	20 ( 0.2)
Addison's disease	2 ( <0.1)	6 ( <0.1)
Adrenocortical insufficiency acute	2 ( <0.1)	12 ( 0.1)
Adrenal suppression	1 ( <0.1)	1 ( <0.1)
Immune-mediated adrenal insufficiency	1 ( <0.1)	3 ( <0.1)

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Primary adrenal insufficiency	0	3 ( <0.1)
Gamma-glutamyltransferase increased	197 ( 1.1)	186 ( 1.6)
Gamma-glutamyltransferase increased	197 ( 1.1)	186 ( 1.6)
Arthritis	192 ( 1.1)	189 ( 1.6)
Arthritis	138 ( 0.8)	142 ( 1.2)
Polyarthritis	23 ( 0.1)	18 ( 0.2)
Rheumatoid arthritis	15 ( <0.1)	11 ( <0.1)
Psoriatic arthropathy	8 ( <0.1)	0
Synovitis	6 ( <0.1)	9 ( <0.1)
Autoimmune arthritis	3 ( <0.1)	6 ( <0.1)
Immune-mediated arthritis	2 ( <0.1)	7 ( <0.1)
Periarthritis	2 ( <0.1)	3 ( <0.1)
Oligoarthritis	1 ( <0.1)	1 ( <0.1)
Seronegative arthritis	1 ( <0.1)	1 ( <0.1)
Arthritis reactive	0	1 ( <0.1)
Myositis	166 ( 0.9)	145 ( 1.2)
Blood creatine phosphokinase increased	136 ( 0.8)	98 ( 0.8)
Myositis	31 ( 0.2)	55 ( 0.5)
Dermatomyositis	2 ( <0.1)	2 ( <0.1)
Immune-mediated myositis	2 ( <0.1)	2 ( <0.1)
Orbital myositis	2 ( <0.1)	3 ( <0.1)
Polymyositis	2 ( <0.1)	2 ( <0.1)

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Autoimmune myositis	1 ( <0.1)	1 ( <0.1)
Necrotising myositis	0	1 ( <0.1)
Thrombocytopenia	161 ( 0.9)	115 ( 1.0)
Thrombocytopenia	161 ( 0.9)	115 ( 1.0)
Neutropenia	160 ( 0.9)	85 ( 0.7)
Neutropenia	160 ( 0.9)	85 ( 0.7)
Alopecia	150 ( 0.8)	119 ( 1.0)
Alopecia	150 ( 0.8)	119 ( 1.0)
Thyroiditis	138 ( 0.8)	321 ( 2.7)
Thyroiditis	97 ( 0.5)	240 ( 2.0)
Autoimmune thyroiditis	23 ( 0.1)	55 ( 0.5)
Thyroiditis subacute	6 ( <0.1)	6 ( <0.1)
Immune-mediated thyroiditis	5 ( <0.1)	6 ( <0.1)
Autoimmune thyroid disorder	4 ( <0.1)	3 ( <0.1)
Thyroiditis chronic	3 ( <0.1)	2 ( <0.1)
Thyroiditis acute	2 ( <0.1)	10 ( <0.1)
Hepatitis	134 ( 0.8)	472 ( 4.0)
Hepatitis	54 ( 0.3)	170 ( 1.4)
Autoimmune hepatitis	37 ( 0.2)	155 ( 1.3)
Immune-mediated hepatitis	22 ( 0.1)	109 ( 0.9)
Drug-induced liver injury	13 ( <0.1)	34 ( 0.3)
Hepatitis acute	7 ( <0.1)	10 ( <0.1)

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Hepatitis fulminant	1 ( <0.1)	0
Immune-mediated hepatic disorder	1 ( <0.1)	8 ( <0.1)
Suspected drug-induced liver injury	1 ( <0.1)	4 ( <0.1)
Dry eye	132 ( 0.7)	120 ( 1.0)
Dry eye	132 ( 0.7)	120 ( 1.0)
Hypophysitis	125 ( 0.7)	622 ( 5.3)
Hypophysitis	89 ( 0.5)	489 ( 4.2)
Hypopituitarism	33 ( 0.2)	120 ( 1.0)
Lymphocytic hypophysitis	4 ( <0.1)	30 ( 0.3)
Immune-mediated hypophysitis	2 ( <0.1)	13 ( 0.1)
Hypertension	119 ( 0.7)	83 ( 0.7)
Hypertension	110 ( 0.6)	82 ( 0.7)
Blood pressure increased	9 ( <0.1)	1 ( <0.1)
Influenza like illness	117 ( 0.7)	213 ( 1.8)
Influenza like illness	117 ( 0.7)	213 ( 1.8)
Renal failure	106 ( 0.6)	199 ( 1.7)
Acute kidney injury	65 ( 0.4)	134 ( 1.1)
Renal failure	29 ( 0.2)	46 ( 0.4)
Renal impairment	11 ( <0.1)	20 ( 0.2)
Renal injury	3 ( <0.1)	3 ( <0.1)
Oliguria	1 ( <0.1)	3 ( <0.1)
Prerenal failure	1 ( <0.1)	1 ( <0.1)

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Vision blurred	103 ( 0.6)	159 ( 1.3)
Vision blurred	103 ( 0.6)	159 ( 1.3)
Urticaria	100 ( 0.6)	100 ( 0.8)
Urticaria	98 ( 0.6)	100 ( 0.8)
Urticaria papular	2 ( <0.1)	0
Urticaria chronic	1 ( <0.1)	0
Insomnia	97 ( 0.5)	136 ( 1.2)
Insomnia	97 ( 0.5)	136 ( 1.2)
Hypotension	88 ( 0.5)	119 ( 1.0)
Hypotension	76 ( 0.4)	113 ( 1.0)
Orthostatic hypotension	12 ( <0.1)	8 ( <0.1)
Blood pressure decreased	0	1 ( <0.1)
Psoriasis	86 ( 0.5)	61 ( 0.5)
Psoriasis	69 ( 0.4)	46 ( 0.4)
Dermatitis psoriasiform	15 ( <0.1)	13 ( 0.1)
Erythrodermic psoriasis	1 ( <0.1)	0
Guttate psoriasis	1 ( <0.1)	1 ( <0.1)
Pustular psoriasis	1 ( <0.1)	1 ( <0.1)
Pancreatitis	85 ( 0.5)	170 ( 1.4)
Pancreatitis	70 ( 0.4)	142 ( 1.2)
Autoimmune pancreatitis	7 ( <0.1)	15 ( 0.1)
Pancreatitis acute	6 ( <0.1)	10 ( <0.1)

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Immune-mediated pancreatitis	1 ( <0.1)	5 ( <0.1)
Subacute pancreatitis	1 ( <0.1)	0
Dehydration	83 ( 0.5)	202 ( 1.7)
Dehydration	83 ( 0.5)	202 ( 1.7)
Hyperhidrosis	75 ( 0.4)	99 ( 0.8)
Hyperhidrosis	75 ( 0.4)	99 ( 0.8)
Diabetes mellitus	74 ( 0.4)	121 ( 1.0)
Diabetes mellitus	40 ( 0.2)	49 ( 0.4)
Type 1 diabetes mellitus	34 ( 0.2)	66 ( 0.6)
Fulminant type 1 diabetes mellitus	4 ( <0.1)	3 ( <0.1)
Diabetes mellitus inadequate control	0	5 ( <0.1)
Gastritis	69 ( 0.4)	87 ( 0.7)
Gastritis	61 ( 0.3)	76 ( 0.6)
Chronic gastritis	3 ( <0.1)	6 ( <0.1)
Gastritis erosive	3 ( <0.1)	2 ( <0.1)
Immune-mediated gastritis	1 ( <0.1)	4 ( <0.1)
Ulcerative gastritis	1 ( <0.1)	1 ( <0.1)
Gastritis haemorrhagic	0	2 ( <0.1)
Upper respiratory tract infection	66 ( 0.4)	26 ( 0.2)
Upper respiratory tract infection	66 ( 0.4)	26 ( 0.2)
Pemphigoid	59 ( 0.3)	40 ( 0.3)
Pemphigoid	28 ( 0.2)	18 ( 0.2)

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Blister	17 ( <0.1)	13 ( 0.1)
Dermatitis bullous	17 ( <0.1)	9 ( <0.1)
Nephritis	48 ( 0.3)	59 ( 0.5)
Tubulointerstitial nephritis	21 ( 0.1)	21 ( 0.2)
Nephritis	17 ( <0.1)	22 ( 0.2)
Autoimmune nephritis	8 ( <0.1)	11 ( <0.1)
Immune-mediated nephritis	3 ( <0.1)	4 ( <0.1)
Immune-mediated renal disorder	1 ( <0.1)	0
Nephritis allergic	0	2 ( <0.1)
Eye inflammation	46 ( 0.3)	92 ( 0.8)
Uveitis	33 ( 0.2)	70 ( 0.6)
Iridocyclitis	8 ( <0.1)	13 ( 0.1)
Iritis	4 ( <0.1)	5 ( <0.1)
Eye inflammation	3 ( <0.1)	8 ( <0.1)
Autoimmune uveitis	0	2 ( <0.1)
Tachycardia	43 ( 0.2)	101 ( 0.9)
Tachycardia	25 ( 0.1)	61 ( 0.5)
Sinus tachycardia	8 ( <0.1)	36 ( 0.3)
Heart rate increased	5 ( <0.1)	1 ( <0.1)
Supraventricular tachycardia	4 ( <0.1)	7 ( <0.1)
Ventricular tachycardia	1 ( <0.1)	0
Arrhythmia	36 ( 0.2)	47 ( 0.4)

MedDRA Version: 26.1

Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Atrial fibrillation	14 ( <0.1)	30 ( 0.3)
Arrhythmia	7 ( <0.1)	4 ( <0.1)
Ventricular extrasystoles	6 ( <0.1)	3 ( <0.1)
Supraventricular extrasystoles	4 ( <0.1)	1 ( <0.1)
Sinus bradycardia	3 ( <0.1)	6 ( <0.1)
Atrial flutter	2 ( <0.1)	2 ( <0.1)
Ventricular arrhythmia	2 ( <0.1)	3 ( <0.1)
Ventricular fibrillation	2 ( <0.1)	0
Sinus arrhythmia	1 ( <0.1)	0
Bronchitis	26 ( 0.1)	17 ( 0.1)
Bronchitis	26 ( 0.1)	17 ( 0.1)
Respiratory failure	23 ( 0.1)	17 ( 0.1)
Respiratory failure	16 ( <0.1)	11 ( <0.1)
Acute respiratory failure	7 ( <0.1)	3 ( <0.1)
Respiratory distress	0	3 ( <0.1)
Sarcoidosis	21 ( 0.1)	42 ( 0.4)
Sarcoidosis	18 ( 0.1)	38 ( 0.3)
Cutaneous sarcoidosis	2 ( <0.1)	1 ( <0.1)
Pulmonary sarcoidosis	2 ( <0.1)	5 ( <0.1)
Diabetic ketoacidosis	20 ( 0.1)	31 ( 0.3)
Diabetic ketoacidosis	19 ( 0.1)	30 ( 0.3)
Diabetic ketosis	1 ( <0.1)	1 ( <0.1)

MedDRA Version: 26.1

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Erythema multiforme	20 ( 0.1)	22 ( 0.2)
Erythema multiforme	20 ( 0.1)	22 ( 0.2)
Cranial nerve disorder	17 ( <0.1)	29 ( 0.2)
Optic neuritis	3 ( <0.1)	3 ( <0.1)
Vith nerve paralysis	3 ( <0.1)	0
Facial nerve disorder	2 ( <0.1)	4 ( <0.1)
Facial paresis	2 ( <0.1)	4 ( <0.1)
Optic nerve disorder	2 ( <0.1)	1 ( <0.1)
Facial paralysis	1 ( <0.1)	11 ( <0.1)
IIIrd nerve paralysis	1 ( <0.1)	1 ( <0.1)
IIIrd nerve paresis	1 ( <0.1)	0
Olfactory nerve disorder	1 ( <0.1)	2 ( <0.1)
Vith nerve disorder	1 ( <0.1)	2 ( <0.1)
Vestibular neuronitis	1 ( <0.1)	0
Cranial nerve disorder	0	1 ( <0.1)
Trigeminal nerve disorder	0	2 ( <0.1)
Myocarditis	14 ( <0.1)	44 ( 0.4)
Myocarditis	12 ( <0.1)	38 ( 0.3)
Autoimmune myocarditis	1 ( <0.1)	0
Immune-mediated myocarditis	1 ( <0.1)	5 ( <0.1)
Myopericarditis	0	2 ( <0.1)
Diplopia	13 ( <0.1)	22 ( 0.2)

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Diplopia	13 ( <0.1)	22 ( 0.2)
Polymyalgia rheumatica	13 ( <0.1)	17 ( 0.1)
Polymyalgia rheumatica	13 ( <0.1)	17 ( 0.1)
Encephalitis	12 ( <0.1)	49 ( 0.4)
Encephalitis	9 ( <0.1)	29 ( 0.2)
Encephalitis autoimmune	2 ( <0.1)	13 ( 0.1)
Immune-mediated encephalitis	1 ( <0.1)	7 ( <0.1)
Acute disseminated encephalomyelitis	0	1 ( <0.1)
Immune-mediated encephalopathy	0	1 ( <0.1)
Anaphylactic reaction	11 ( <0.1)	6 ( <0.1)
Anaphylactic reaction	10 ( <0.1)	5 ( <0.1)
Anaphylactic shock	1 ( <0.1)	1 ( <0.1)
Lung infiltration	10 ( <0.1)	14 ( 0.1)
Lung infiltration	10 ( <0.1)	14 ( 0.1)
Myasthenic syndrome	10 ( <0.1)	21 ( 0.2)
Myasthenia gravis	6 ( <0.1)	14 ( 0.1)
Myasthenic syndrome	3 ( <0.1)	5 ( <0.1)
Ocular myasthenia	1 ( <0.1)	2 ( <0.1)
Rosacea	10 ( <0.1)	7 ( <0.1)
Rosacea	8 ( <0.1)	7 ( <0.1)
Papulopustular rosacea	2 ( <0.1)	0
Pericarditis	7 ( <0.1)	8 ( <0.1)

MedDRA Version: 26.1

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Pericarditis	7 ( <0.1)	5 ( <0.1)
Autoimmune pericarditis	0	1 ( <0.1)
Myopericarditis	0	2 ( <0.1)
Pleuropericarditis	0	1 ( <0.1)
Rhabdomyolysis	7 ( <0.1)	12 ( 0.1)
Rhabdomyolysis	7 ( <0.1)	12 ( 0.1)
Vasculitis	7 ( <0.1)	12 ( 0.1)
Vasculitis	6 ( <0.1)	7 ( <0.1)
Pulmonary vasculitis	1 ( <0.1)	0
Cutaneous vasculitis	0	4 ( <0.1)
Ocular vasculitis	0	1 ( <0.1)
Autoimmune disorder	5 ( <0.1)	7 ( <0.1)
Autoimmune disorder	5 ( <0.1)	7 ( <0.1)
Guillain-barre syndrome	5 ( <0.1)	12 ( 0.1)
Guillain-Barre syndrome	4 ( <0.1)	10 ( <0.1)
Miller Fisher syndrome	1 ( <0.1)	2 ( <0.1)
Stevens-johnson syndrome	5 ( <0.1)	4 ( <0.1)
Stevens-Johnson syndrome	5 ( <0.1)	4 ( <0.1)
Autoimmune haemolytic anaemia	3 ( <0.1)	3 ( <0.1)
Autoimmune haemolytic anaemia	3 ( <0.1)	3 ( <0.1)
Demyelination	3 ( <0.1)	3 ( <0.1)
Demyelination	2 ( <0.1)	1 ( <0.1)

MedDRA Version: 26.1

Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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Appendix 6.2.1  
Related Adverse Event Summary by Custom Standardized MedDRA Query  
All Treated Subjects

cSMQ (%) Preferred Term (%)	Nivo N = 17791	Nivo+Ipi N = 11782
Demyelinating polyneuropathy	1 ( <0.1)	1 ( <0.1)
Chronic inflammatory demyelinating polyradiculoneuropathy	0	1 ( <0.1)
Intestinal perforation	2 ( <0.1)	12 ( 0.1)
Diverticular perforation	1 ( <0.1)	1 ( <0.1)
Gastrointestinal perforation	1 ( <0.1)	1 ( <0.1)
Duodenal perforation	0	1 ( <0.1)
Focal peritonitis	0	1 ( <0.1)
Intestinal perforation	0	4 ( <0.1)
Large intestine perforation	0	5 ( <0.1)
Small intestinal perforation	0	1 ( <0.1)
Toxic epidermal necrolysis	2 ( <0.1)	2 ( <0.1)
Toxic epidermal necrolysis	2 ( <0.1)	2 ( <0.1)
Haemophagocytic lymphohistiocytosis	1 ( <0.1)	3 ( <0.1)
Haemophagocytic lymphohistiocytosis	1 ( <0.1)	3 ( <0.1)
Histiocytic necrotising lymphadenitis	1 ( <0.1)	0
Histiocytic necrotising lymphadenitis	1 ( <0.1)	0
Meningitis	1 ( <0.1)	5 ( <0.1)
Meningitis	1 ( <0.1)	5 ( <0.1)
Diabetic coma	0	1 ( <0.1)
Diabetic coma	0	1 ( <0.1)
Vogt-koyanagi-harada disease	0	1 ( <0.1)
Vogt-Koyanagi-Harada disease	0	1 ( <0.1)

MedDRA Version: 26.1

Includes events reported between first dose date and IB cutoff date. Cutoff date is 12APR2024.

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