Official Title of Study:

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

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CLINICAL PROTOCOL 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

(**CheckMate 7C9**: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 7C9)

Short Title:

A Phase 4 Study of Combination Nivolumab and Ipilimumab in Patients with Advanced Renal Cell Carcinoma in India

Protocol Amendment Number 02

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Amendment 02	10-Nov-2023	This protocol amendment is being implemented to provide clarification of the statistical considerations and to achieve alignment of the definition of immune-mediated adverse events.
Protocol Amendment 01	10-Jan-2022	This protocol amendment is being implemented to [redacted] add guidance with regards to COVID-19. In addition, other minor editorial changes have been incorporated.
Original Protocol	06-Feb-2020	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02:

Protocol Amendment 02 includes clarifications to statistical methods and alignment of the definition of immune-mediated adverse events (IMAEs).

Additional updates have been incorporated in order to improve alignment between protocol sections.

Additional revisions, including to the sections of the Synopsis, have been made to align the protocol with respect to these changes. This protocol amendment applies to all participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Updated synopsis to align with changes to protocol	Updated to align with changes to protocol
Section 2: Schedule of Activities	Table 2-4: Updated language for Efficacy Assessment, Body Imaging	Updated to include withdrawal of consent, death, or investigator-assessed disease progression as conditions that could lead to cessation of body imaging collection
Section 2: Schedule of Activities Section 4: Objectives and Endpoints Section 9.7.3: Exploratory [redacted] Biomarkers	Changed "efficacy" to "effectiveness"	Corrected content for accuracy and consistency
Section 5.1: Overall Design	Updated language of adverse event (AE) collection	Clarified duration of AE collection

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities Section 3.1: Study Rationale Section 5.1: Overall Design Section 8.1.1: Nivolumab Treatment Beyond Disease Progression Section 9.1: Effectiveness Assessments	Updated language for tumor assessments and body imaging schedule	Updated to include initiation of subsequent systemic cancer therapy, withdrawal of consent, death, or investigator assessed disease progression as conditions that could lead to cessation of tumor assessments or body imaging collection
[redacted]		
Section 10.1: Sample Size Determination	Updated language for sample size determination and added Table 10.1-1	Clarified rationale for sample size determination
Section 10.2: Populations for Analyses	Updated language for analysis populations	Clarified the analysis population to be used for time to response (TTR) and duration of response (DOR) analyses
Section 10.3: Statistical Analyses	Updated language for subgroups in participant population output report	Removed race as a subgroup to be included in the participant population output report
Section 10.3.1: Statistical Analyses	Updated language for statistical analysis methods for effectiveness	Updated TTR analysis method, time points for analyses of DOR and overall survival (OS), [redacted] to be examined
Section 10.3.2: Safety Analyses	Updated language for statistical analysis methods for safety	Clarified that IMAEs will be summarized by category only, aligned definition of IMAEs, and removed descriptive statistics of safety

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: 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

Short Title:

A Phase 4 Study of Combination Nivolumab and Ipilimumab in Patients with Advanced Renal Cell Carcinoma in India

Study Phase: 4

Study Rationale:

In intermediate- and poor-risk participants with previously untreated advanced renal cell carcinoma (RCC) or metastatic RCC (mRCC), this study aims to determine the safety and effectiveness of nivolumab combined with ipilimumab followed by nivolumab as a single-agent maintenance therapy as measured by the primary endpoint of incidence of high-grade (Common Terminology Criteria for Adverse Events [CTCAE] v4.0 Grade 3 to 4 and Grade 5) immune-mediated adverse events (IMAEs) with the characterization of outcome of all high-grade IMAEs and overall response rate (ORR), time to response (TTR), and duration of response (DOR) as key secondary endpoints.

This first-line renal cell carcinoma (1L RCC) study is to be conducted in compliance with a condition of approval specified by the Health Authorities of India.

Study Population:

The study population includes male and female patients aged 18 or older with histologically confirmed, intermediate- or poor-risk, previously untreated, advanced (not amenable to curative surgery or radiation therapy) or mRCC.

Key Inclusion Criteria

- Histological confirmation of renal carcinoma with clear cell component including participants who may have sarcomatoid features. Advanced (not amenable to curative surgery or radiation therapy) RCC or mRCC with or without nephrectomy.
- No prior systemic therapy for renal cell carcinoma (RCC) with the following exception:
    - One prior adjuvant or neoadjuvant therapy for completely resected RCC (see Exclusion 2b). These drugs must be discontinued ≥ 6 months prior to study entry. All AEs related to prior adjuvant or neoadjuvant therapy must have returned to baseline, and eligible patients must not have experienced severe or life-threatening irAEs except those that are unlikely to reoccur with standard countermeasures (eg, hormone replacement after adrenal crisis).
- Measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria. Radiated lesions cannot be used as measurable lesions unless there is clear evidence of progression.
- Karnofsky Performance Status (KPS) of at least 70% (see Appendix 7).

- Qualifies as intermediate or poor risk by meeting least 1 of the prognostic factors as per the International Metastatic RCC Database Consortium (IMDC) criteria.
- Indian participants with Indian ethnicity living in India.
- [redacted]
- Participants must be intermediate or poor risk as per International Metastatic RCC Database Consortium (IMDC).

Key Exclusion Criteria

- Participants with active, untreated, symptomatic central nervous system (CNS) metastases.
- Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Participants with an autoimmune disease, or any other condition, requiring systemic treatment with either corticosteroids within 14 days (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Patients with serious or uncontrolled medical disorders.
- Active infection requiring systemic therapy within 14 days of first dose of study drug.
- Patients with known human immunodeficiency virus (HIV) who have had an acquired immunodeficiency syndrome (AIDS) defining opportunistic infection within the last year, or a current CD4 count < 350 cells/µL. NOTE: Testing for HIV must be performed at sites where mandated locally (see Appendix 8).
- Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study treatment.
- Radiotherapy within 4 weeks except palliative radiation to bone lesions, which requires 2 weeks of washout prior to the first dose of study treatment.
- Patients with a concurrent malignancy requiring treatment. Patient with a previously treated malignancy are eligible if treatment was completed at least 2 years before registration and the

patient has no evidence of disease. Patients who have a concurrent malignancy that is clinically stable and does not require tumor-directed treatment are also eligible.

- Presence of any toxicities attributed to prior anticancer therapy, other than alopecia, that have not resolved to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4) or baseline before administration of study treatment.
- Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study treatment administration or interfere with the interpretation of safety results (eg, a condition associated with diarrhea or acute diverticulitis).
- Women who are pregnant or breastfeeding.
- Any of the following laboratory test findings:
    - White blood cells < $2000/mm^3$
    - Neutrophils < $1500/mm^3$
    - Platelets < $100 \times 10^3/mm^3$
    - Hemoglobin < 9.0 g/dL
    - Serum creatinine > 1.5× upper limit of normal (ULN) or creatinine clearance ≥ 40 mL/min (using the Cockroft-Gault formula)

      $$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

      $$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

    - Aspartate aminotransferase/Alanine aminotransferase > 3× ULN
    - Total bilirubin (TBili) > 1.5× ULN (except participants with Gilbert syndrome, who must have TBili < 3.0× ULN)
- Serologic evidence of chronic HBV infection with an HBV viral load above the limit of quantification. Patients with chronic HBV infection must be on concurrent viral suppressive therapy.
- Serologic evidence of current HCV infection with an HCV viral load above the limit of quantification.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To assess the incidence of high-grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs in intermediate- or poor-risk participants with previously untreated, advanced RCC who are treated with combination therapy of nivolumab 3 mg/kg administered intravenously over a period of 30 minutes every 3 weeks for the first 4 doses in combination with intravenous ipilimumab 1 mg/kg over a period of 30 minutes, followed by nivolumab 3 mg/kg every 2 weeks administered intravenously over a period of 30 minutes.	• Incidence of high-grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs
Secondary	
• To characterize the outcome of all high-grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs in intermediate- or poor-risk participants with previously untreated, advanced RCC.	• Characterization of outcome of all high grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs (eg, time to onset, time to resolution, percentage of patients who received immune-modulating medication)
• To assess the effectiveness of nivolumab in combination with ipilimumab by measuring objective response rate (ORR), time to response (TTR), and duration of response (DOR), using RECIST 1.1.	• ORR, TTR, DOR
Exploratory	
• To assess the incidence of all treatment-related AEs in intermediate- or poor-risk participants with previously untreated, advanced RCC.	• Incidence of all treatment related AEs
• To assess the effectiveness of nivolumab in combination with ipilimumab by measuring progression-free survival (PFS) at time of initial progression and overall survival (OS) 1-year survival rates in intermediate- or poor-risk participants with previously untreated, advanced RCC.	• PFS, OS
• To assess the participant's cancer-related symptoms and quality of life (QoL)	• All total and subscale scores and post-baseline score changes for the FKSI-19
• To evaluate the pharmacokinetics of nivolumab and ipilimumab when administered in combination and the PK of nivolumab as a single-agent maintenance therapy. To explore exposure-response relationships between select exposure measures, and safety and effectiveness endpoints, as appropriate.	• Predose serum nivolumab and ipilimumab concentrations to be used for population pharmacokinetics (PPK) analysis to predict nivolumab pharmacokinetic parameters. Explore exposure-response relationships if data permit.
• To characterize the immunogenicity of nivolumab and ipilimumab when administered in combination and the immunogenicity of nivolumab as a single-agent maintenance therapy.	• Immunogenicity will be determined by measurement of anti-drug antibody (ADA) in serum and samples with positive ADA response may be analyzed for neutralizing ADA response to nivolumab and ipilimumab

Objective	Endpoint
[redacted]	
• To assess the impact of SARS-CoV-2 serologic status on participants receiving nivolumab in combination with ipilimumab and previously untreated, advanced RCC and to support Health Authority requests	• Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG), from serum samples collected at baseline (and additional time points, if applicable) and the potential association between these measurements and selected endpoints related to safety, effectiveness, and/or biomarkers

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; FKSI-19 = Functional Assessment of Cancer Therapy - Kidney Symptom Index; IMAE = immune-mediated adverse event; NCI = National Cancer Institute; IgG = immunoglobulin G; [redacted]; RCC = renal cell carcinoma; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Note: All AEs to be assessed using NCI CTCAE v4.

Overall Design:

This is a Phase 4, open-label, single arm, multi-center, prospective study to be conducted in India in participants with intermediate or poor risk, previously untreated, advanced renal cell carcinoma or mRCC (N = 100 treated patients). Potential participants will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Participants who meet the protocol-defined inclusion/exclusion criteria will be prospectively enrolled in a sequential manner. All enrolled participants will be treated with nivolumab 3 mg/kg administered intravenously over a period of 30 minutes plus ipilimumab 1 mg/kg administered intravenously over a period of 30 minutes, every 3 weeks for 4 doses (combination phase), followed by nivolumab 3 mg/kg administered intravenously over a period of 30 minutes every 2 weeks (single-agent maintenance phase).

Treatment will continue as long as clinical benefit is observed for a maximum of 52 weeks or until treatment is no longer tolerated by the participant or withdrawal of consent.

The treatment period for this study is 52 weeks of treatment and 2 weeks of follow-up after the final on-study dose of nivolumab. Participants who are observed to continue to receive clinical benefit at follow-up will continue nivolumab treatment via commercial supply (provided by BMS India) as long as clinical benefit is observed or until treatment is no longer tolerated by the participant or withdrawal of consent.

Any participant who discontinues treatment before 52 weeks on study treatment will be followed for safety at 30 days (Follow up Visit 1) and 100 days (Follow-up Visit 2) after discontinuation. In addition, for these patients, survival follow-up visits may be conducted in clinic or by phone 3 months (±14 Days) after follow-up Visit 2 and subsequent survival follow-up visits every 3 months (±14 days) until death, withdrawal of consent, loss to follow-up, or for a maximum of 52 weeks from the date of the first on-study dose of nivolumab.

Number of Participants:

A total of 100 treated participants with intermediate or poor-risk, previously untreated, advanced or mRCC will be enrolled.

Treatment Arms and Duration:

All participants will receive the study drug as follows:

Combination Phase

- Nivolumab 3 mg/kg administered intravenously over a period of 30 minutes plus ipilimumab 1 mg/kg administered intravenously over a period of 30 minutes, every 3 weeks for 4 doses.

Single-agent Maintenance Phase

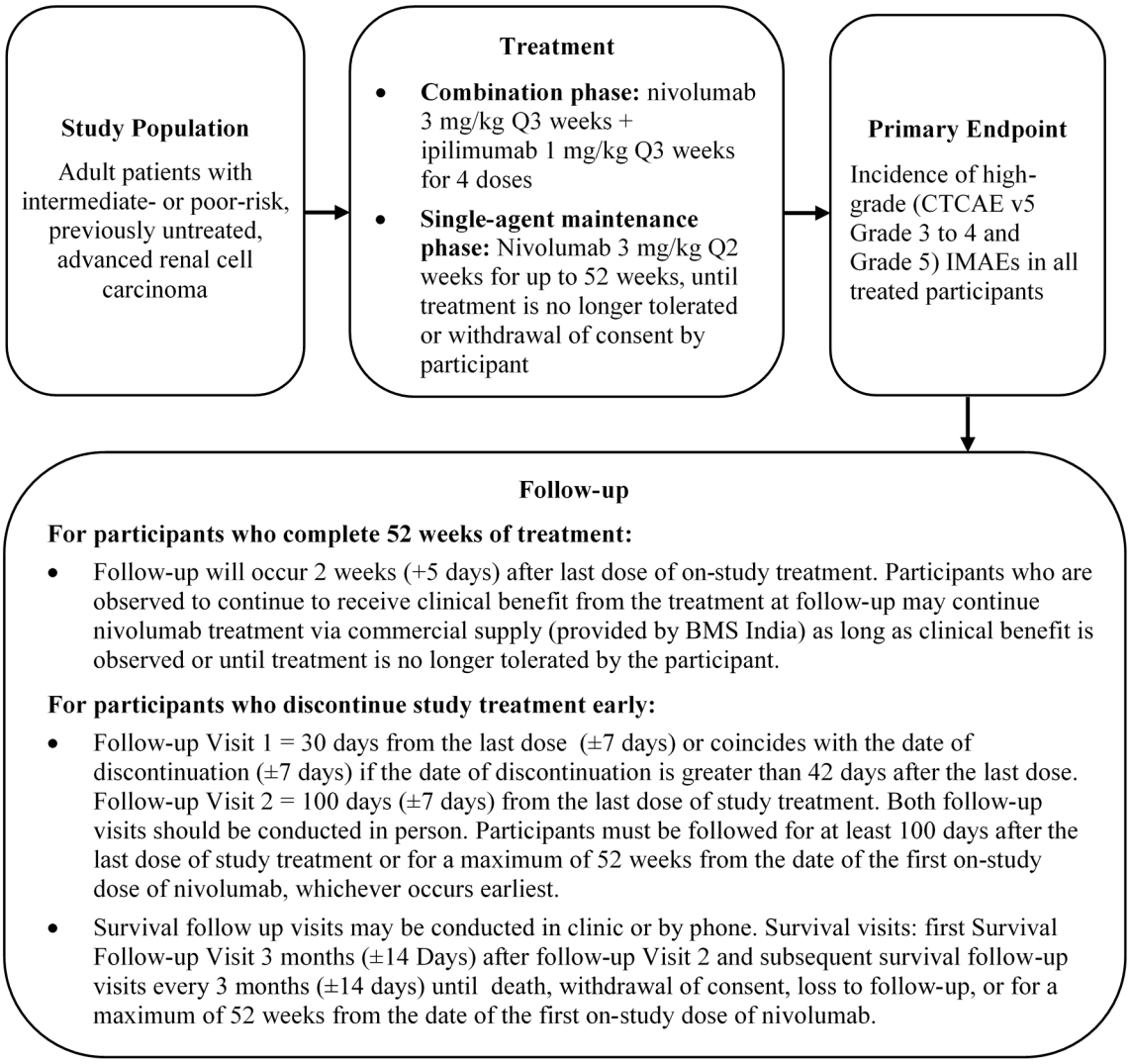
- Nivolumab 3 mg/kg administered intravenously over a period of 30 minutes every 2 weeks for up to 52 weeks.

The duration of treatment in the study for all participants is a maximum of 52 weeks. Participants who are observed to continue to receive clinical benefit from treatment at 52 weeks may continue nivolumab treatment via commercial supply (provided by BMS India) as long as clinical benefit is observed or until the participant no longer tolerates treatment.

Study Drug: Includes Investigational [Medicinal] Products (IP/IMP) as Listed:

Study Drug for CA2097C9		
Product Description / Class and Dosage Form	**Potency**	**IP/non-IMP**
Nivolumab solution for infusion	100 mg (10 mg/mL concentrate)	IP
Ipilimumab solution for infusion	50 mg (5 mg/mL)	IP

Study Design Schematic:



Data Monitoring Committee: Not applicable.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedures and Assessments (CA2097C9)

Procedure	Screening Visit[a]	Notes (Screening visit will occur within 28 days before start of combination phase)
Eligibility Assessments		
Informed Consent	X	The participant must sign the informed consent prior to any study-related assessment being performed.
Interactive Voice Response System	X	An IRT will be used to assign participant numbers.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria must be confirmed prior to treatment assignment.
Medical History	X	
IMDC Prognostic Score	X	See Appendix 6.
[redacted]		
Safety Assessments		
Full Physical Examination, Vital Signs, Performance Status	X	Height, weight, KPS (Appendix 7), BP, RR, heart rate, and temperature within 14 days of first dose, prior to study treatment initiation.
Electrocardiogram	X	Within 14 days of first dose, prior to study treatment initiation.
Assessment of Signs and Symptoms	X	Within 14 days of first dose, prior to study treatment initiation.
Concomitant Medication Use	X	Within 14 days of first dose, prior to study treatment initiation.
SAE Assessment	X	SAEs from time of consent. See Section 9.2. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent.
Laboratory Tests	X	See Section 9.4.4 for additional details on tests required. To be completed locally at each site. Must be performed within 14 days prior to first dose (unless otherwise specified) per Table 9.4.4-1.

Table 2-1: Screening Procedures and Assessments (CA2097C9)

Procedure	Screening Visit[a]	Notes (Screening visit will occur within 28 days before start of combination phase)
		•CBC with differential and chemistry panel (AST, ALT, TBili, ALP, LDH, creatinine, BUN or serum urea level, glucose, albumin, Na, K, Cl, Ca [also Ca corrected], P, Mg) • Thyroid panel (includes TSH with free T3 and free T4) • Hepatitis B/C (HBVsAg, HCV antibody, or HCV RNA) • HIV if mandated locally (see Appendix 8)
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours of first dose of study treatment.
Biomarker Samples		
SARS-CoV-2 Serology	Serum collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.7.1])	
Effectiveness Assessments		
Body Imaging	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, within 28 days prior to first dose. See Section 9.1.1 for further details.	
Brain Imaging	MRI of the brain (without and with contrast) is required for ALL participants during screening to rule out brain metastases. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1.1 for further details.	

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase, AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; eCRF = electronic case report form; [redacted]; HBVsAg = hepatitis B virus surface antigen; HCG = human chorionic gonadotrophin; HIV = human immunodeficiency virus; IMDC = International Metastatic RCC Database Consortium; IU = international unit; IRT = Interactive response technology; KPS = Karnofsky's index of performance status; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; RNA = ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; T3 = triiodothyronine, T4 = thyroxine; Tbili = total bilirubin; TSH = thyroid-stimulating hormone, WOCBP = women of childbearing potential

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Table 2-2: On-treatment Procedural Outline Cycles 1 through 4

Procedure[a]	Cycles 1 through 4 (1 cycle = 3 weeks) Dosing Q3W for 4 Doses[b]				Notes
	Day 1 Cycle 1	Day 1 Cycle 2	Day 1 Cycle 3	Day 1 Cycle 4	
Safety Assessments					
Targeted Physical Examination, Vital Signs, Performance Status	X	X	X	X	Weight, BP, RR, heart rate, temperature, and KPS (Appendix 7) to be performed within 72 hours prior to dosing.
Assessment of Signs and Symptoms	X	X	X	X	
AE and SAE Assessment	Continuously				Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. (Appendix 3). The collection of non-serious AE information, including that associated with SARS-CoV-2 infection, must begin at initiation of study treatment until the follow-up contact. All SAEs, including those associated with SARS-CoV-2 infection, that occur during the screening period, during treatment, and within 100 days of discontinuation or a maximum of 52 weeks of treatment plus 2 weeks of follow-up, whichever is earliest, must be collected. (Appendix 3).
Concomitant Medication Use	X	X	X	X	
Laboratory Tests	X	X	X	X	See Section 9.4.4 for additional details on tests required. Laboratory tests do not need to be repeated at C1D1 if performed within 14 days prior to the first dose unless repeat of tests for eligibility prior to C1D1 dosing is clinically indicated. After C1D1, within 72 hours prior to re-dosing to include: CBC with differential and chemistry panel at every cycle (includes AST, ALT, TBili, ALP, LDH, creatinine, BUN or serum urea, glucose, Na, K, Cl, Ca, P, Mg) Thyroid panel (includes TSH with reflexive fT3 and fT4 if TSH is abnormal) at every cycle
Pregnancy Test (WOCBP Only)	X	X	X	X	Within 24 hours prior to administration of study drug. Serum or urine.

Table 2-2: On-treatment Procedural Outline Cycles 1 through 4

Procedure[a]	Cycles 1 through 4 (1 cycle = 3 weeks) Dosing Q3W for 4 Doses[b]				Notes
	Day 1 Cycle 1	Day 1 Cycle 2	Day 1 Cycle 3	Day 1 Cycle 4	
Pharmacokinetic Samples					
Pharmacokinetic Samples	For details on sampling time points, see Table 9.5-1.				
Immunogenicity Blood Sample	For details on sampling time points, see Table 9.5-1.				
Exploratory Biomarker Testing - See Section 9.7.1					
[redacted]	[redacted]				
SARS-CoV-2 Serology[c]	For details on sampling time points, see Table 9.7.1-1.				
Study Treatment					
IRT	X	X	X	X	
Administer Nivolumab (3 mg/kg) and Ipilimumab (1 mg/kg)	X	X	X	X	First dose is to be administered within 28 days after signing the ICF. Subjects may be dosed up to 3 days after the scheduled date if necessary.
Outcomes Research Assessments					
FKSI-19	X	X	X	X	This assessment should be completed at the start of the clinic visit prior to dosing and/or other study assessments. See Section 9.1.2.1.
Healthcare Resource Utilization	X	X	X	X	Healthcare resource utilization data will be collected at each visit by study site staff using the CRF. See Section 9.1.2.2.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alkaline alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; CBC = complete blood count; CRF = case report form; eCRF = electronic case report form; FKSI-19 = Functional Assessment of Cancer Therapy - Kidney Symptom Index; ICF = informed consent form; IgG = immunoglobulin G; IRT = Interactive response technology; KPS = Karnofsky's index of performance status; LDH = lactate dehydrogenase; PK = pharmacokinetics; Q3W = every 3 weeks; RR = respiratory rate; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SAE = serious adverse event; T3 = triiodothyronine, T4 = thyroxine; Tbili = total bilirubin; TSH = thyroid-stimulating hormone, WOCBP = women of childbearing potential

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[b] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.

[c] Serum collected approximately every 6 months during study treatment to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection (see Section 9.7.1). If a documented or suspected SARS-CoV-2 infection occurs within 4 weeks of the 6-month sampling time point, a single serum sample will be collected to satisfy the requirements for both the every 6 month and approximately 4 weeks after infection time points.

Table 2-3: On-study Assessments Cycle 5 and Beyond

Procedure	Cycle 5 and beyond, up to 52 weeks of treatment (1 cycle = 2 weeks)[a]	Notes
	Day 1	
Safety Assessments		
Targeted Physical Examination, Vital Signs, Performance Status	X	Weight, BP, heart rate, RR, temperature, and KPS (Appendix 7). Performance Status to be performed within 72 hours prior to dosing.
Assessment of Signs and Symptoms	X	
AE and SAE Assessment	Continuously	Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. (Appendix 3). The collection of non-serious AE information, including that associated with SARS-CoV-2 infection, must begin at initiation of study treatment until the follow-up contact. All SAEs, including those associated with SARS-CoV-2 infection, that occur during the screening period, during treatment, and within 100 days of discontinuation or a maximum of 52 weeks of treatment plus 2 weeks of follow-up, whichever is earliest, must be collected. (Appendix 3).
Concomitant Medications Use	X	
Laboratory Tests	X	See Section 9.4.4 for additional details on tests required. Within 72 hours prior to dosing to include: CBC with differential and chemistry panel at every cycle (includes AST, ALT, TBili, ALP, LDH, creatinine, BUN or serum urea, glucose, Na, K, Cl, Ca, P, Mg) Thyroid panel (includes TSH with reflexive fT3 and fT4 if TSH is abnormal) at every cycle
Pregnancy Test (WOCBP Only)	X	Within 24 hours prior to administration of study drug. Serum or Urine.
Pharmacokinetic Samples		
Pharmacokinetic Samples	For details on sampling time points, see Table 9.5-1	
Immunogenicity Blood Sample	For details on sampling time points, see Table 9.5-1	

Table 2-3: On-study Assessments Cycle 5 and Beyond

Procedure	Cycle 5 and beyond, up to 52 weeks of treatment (1 cycle = 2 weeks)[a] Day 1	Notes
Biomarker Samples		
[redacted]	[redacted]	
SARS-CoV-2 Serology[b]	For details on sampling time points, see Table 9.7.1-1.	
Effectiveness Assessments		
Body Imaging	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur at Week 12 (±7 days) following the first dose, then every 8 weeks (± 7 days) until 52 weeks of treatment plus 2 weeks of follow-up or initiation of subsequent systemic cancer therapy, whichever occurs first. These time points are independent of dosing. See Section 9.1.1 for further details.	
Brain Imaging	Participants with a history of brain metastasis or symptoms should have surveillance MRIs per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.	
Clinical Drug Supplies		
IRT	X	
Administer Nivolumab (3 mg/kg)	X	Subsequent doses may be administered within 3 days after the scheduled date if necessary.
Outcomes Research Assessments		
FKSI-19	X	Starting with Cycle 5, assessments should occur every other cycle (eg, Cycles 5, 7, 9, etc). Prior to dosing and other study assessments.
Healthcare Resource Utilization	X	Starting with Cycle 5, Healthcare Resource Utilization should be collected every other cycle (eg, Cycles 5, 7, 9, etc). Healthcare resource utilization data will be collected at each visit by study site staff using the CRF. See Section 9.1.2.2.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alkaline alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CRF = care report form; CT = computed tomography; FKSI-19 = Functional Assessment of Cancer Therapy - Kidney Symptom Index; IgG = immunoglobulin G; IRT = Interactive response technology; KPS = Karnofsky's index of performance status; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PK = pharmacokinetics; RR = respiratory rate; SARS-CoV-2 = severe acute respiratory

syndrome coronavirus 2; SAE = serious adverse event; T3 = triiodothyronine, T4 = thyroxine; Tbili = total bilirubin; TSH = thyroid-stimulating hormone, WOCBP = women of childbearing potential

[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.

[b] Serum collected approximately every 6 months during study treatment to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection (see Section 9.7.1). If a documented or suspected SARS-CoV-2 infection occurs within 4 weeks of the 6-month sampling time point, a single serum sample will be collected to satisfy the requirements for both the every 6 month and approximately 4 weeks after infection time points.

Table 2-4: Follow-up Procedural Outline

Procedure	Follow-up Visit 1[a, b]	Follow-up Visit 2[b]	Survival Follow-up Visit[c]	Notes
Safety Assessments				
Targeted Physical Examination, Vital Signs, Performance Status	X	X		Weight, BP, heart rate, RR, temperature, and KPS (Appendix 7).
Assessment of Signs and Symptoms	X			
AE and SAE Assessment	X	X	X	Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible (Appendix 3). The collection of non-serious AE information must begin at initiation of study treatment until the follow-up contact. All SAEs that occur during the screening period, during treatment, and within 100 days of discontinuation or a maximum of 52 weeks of treatment plus 2 weeks of follow-up, whichever is earliest, must be collected (Appendix 3). Participants will be followed for all SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.
Laboratory Tests	X	X		See Section 9.4.4 for additional details on tests required. CBC with differential and chemistry panel (includes AST, ALT, TBili, ALP, LDH, creatinine, BUN or serum urea, glucose, Na, K, Cl, Ca, P, Mg) Thyroid panel (includes TSH with reflexive fT3 and fT4 if TSH is abnormal)
Pregnancy Test (WOCBP Only)	X	X		Within 24 hours prior to administration of study drug. Serum or urine.
Concomitant Medication Use	X	X		
Electrocardiogram	X	X		
Pharmacokinetic Samples				
Pharmacokinetic Samples	X	X		For details on sampling time points, see Table 9.5-1

Table 2-4: Follow-up Procedural Outline

Procedure	Follow-up Visit 1[a, b]	Follow-up Visit 2[b]	Survival Follow-up Visit[c]	Notes
Immunogenicity Blood Sample	X	X		For details on sampling time points, see Table 9.5-1
Exploratory Biomarker Testing				
[redacted]		[redacted]		
SARS-CoV-2 Serology[d]	For details on sampling time points, see Table 9.7.1-1.			
Effectiveness Assessments				
Body Imaging	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur beginning at Week 12 (±7 days) from the date of first dose and continuing every 8 weeks (± 7 days) until Week 52, initiation of subsequent systemic cancer therapy, withdrawal of consent, death, or investigator-assessed disease progression, whichever occurs first. These time points are independent of dosing. See Section 9.1.1 for further details.			
Brain Imaging	Participants with a history of brain metastasis or symptoms should have surveillance MRIs per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.			
Survival Status				
Participant Status	X	X	X	During safety follow-up and every 3 months (clinic visit or by telephone) during survival phase. Include documentation of subsequent lines of therapy.
Outcomes Research Assessments				
FKSI-19	X	X		Administered prior to any procedures on that day
Healthcare Resource Utilization	X	X		Healthcare resource utilization data will be collected at each visit by study site staff using the CRF. See Section 9.1.2.2.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alkaline alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CRF = case report form; CT = computed tomography; FKSI-19 = Functional Assessment of Cancer Therapy - Kidney Symptom Index; IgG = immunoglobulin G; KPS = Karnofsky's index of performance status; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PK = pharmacokinetics; RR = respiratory rate; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SAE = serious adverse event; T3 = triiodothyronine, T4 = thyroxine; Tbili = total bilirubin; TSH = thyroid-stimulating hormone, WOCBP = women of childbearing potential

[a] For patients who complete 52 weeks of treatment: Follow-up Visit 1 = 2 weeks (+5 days) after last dose of on-study treatment.

[b] For patients who discontinue early (prior to 52 weeks of treatment): Follow-up Visit 1 = 30 days from the last dose (±7 days) or coincides with the date of discontinuation (±7 days) if date of discontinuation is greater than 42 days after the last dose. Follow-up Visit 2 = 100 days (±7 days) from the last dose of study treatment. Both follow-up visits should be conducted in person. Participants must be followed for at least 100 days after the last dose of study treatment or for a maximum of 52 weeks from the date of the first on-study dose of nivolumab, whichever occurs earliest.

[c] For patients who discontinue early only (prior to 52 weeks of treatment): Survival follow-up visits may be conducted in clinic or by phone. Survival visits: first survival follow-up Visit 3 months (±14 days) after follow-up Visit 2 and subsequent survival follow-up visits every 3 months (±14 days) until death, withdrawal of consent, loss to follow-up, or for a maximum of 52 weeks from the date of the first on-study dose of nivolumab. BMS may request that survival data be collected on all treated participants outside of the 3-month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

[d] Serum collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.7.1]).

3 INTRODUCTION

In India, the incidence of RCC is 1.2/100,000 in males and 0.5/100,000 in females, annually.[1] Approximately 20% to 30% of patients present with metastatic disease at diagnosis, and about one-third of patients undergoing nephrectomy for localized disease will develop metastases.[2,3] However, there is no satisfactory treatment for advanced RCC.[4] The 5-year overall survival (OS) for patients with metastatic disease at presentation remains less than 20%.[5,6]

RCC remains a disease with significant burden and unmet medical need. New agents that have meaningful clinical efficacy in RCC are needed.[6]

The CA209214 study was a Phase 3 study of nivolumab in combination of ipilimumab compared with sunitnib in previously untreated patients with locally advanced RCC or metastatic renal cell carcinoma (mRCC). The study has demonstrated a favorable benefit/risk profile for the combination of nivolumab and ipilimumab over current standard of care sunitinib in International Metastatic RCC Database Consortium (IMDC) intermediate/poor risk patients as shown by the unprecedented OS benefit in this population. It also showed superior objective response rate (ORR), higher rate of complete response (CR) as well as a clinically meaningful increase in progression-free survival (PFS) compared to sunitinib.

The combination of nivolumab and ipilimumab is approved by the United States (US) Food and Drug Administration for the treatment of intermediate- and poor-risk, previously untreated patients with advanced RCC, and it is incorporated into the European Association of Urology guidelines.

In India, nivolumab, a programmed death 1 (PD-1) immune checkpoint inhibitor antibody, is approved for the treatment of advanced renal cell carcinoma after treatment with antiangiogenic therapy, second line renal cell carcinoma (2L RCC) treatment based on an overall survival benefit.[7]

Ipilimumab is an anti-cytotoxic T-lymphocyte-associated antigen 4 antibody. Although ipilimumab at a dose of 3 mg per kilogram of body weight was associated in 1 trial with an objective response rate of 13% among patients with metastatic renal cell carcinoma, its toxic effects precluded further development as a single-agent therapy for this disease. [7]

Clinical data from a comprehensive set of early clinical studies (CA209009, CA209010, CA209004, CA209003, and CA209016) provided early evidence of the activity of both nivolumab and ipilimumab as monotherapies in RCC and melanoma, which supported the incremental benefit of the combination and led to the study design of Study CA209214.

The combination of nivolumab and ipilimumab has not been approved in India.

3.1 Study Rationale

This is a Phase 4 study in India to establish the safety and effectiveness of the combination of nivolumab with ipilimumab followed by nivolumab as a single-agent maintenance therapy as first-line renal cell carcinoma (1L RCC) treatment in patients with intermediate- or poor-risk, previously untreated, advanced RCC, to be conducted in compliance with a condition of approval specified by the Health Authorities of India.

Approval in India has been granted for the use of nivolumab (1) as a single agent for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy; (2) as a single agent for the treatment of patients with advanced RCC after prior therapy in adults; (3) as monotherapy for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) after platinum-based therapy; (4) as a single agent for the treatment of patients with BRAF V600 wildtype unresectable or metastatic melanoma; (5) for the treatment of adult patients with classical Hodgkin lymphoma 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; (6) for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; (7) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; and (8) for the treatment of 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 fluoropyrimidine, oxaliplatin, and irinotecan.

This will be the first indication (1L RCC) for which ipilimumab in combination with nivolumab is approved in India.

As a condition of approval for the indication of 1L RCC, Bristol-Myers Squibb (BMS) is required to conduct a Phase 4 clinical trial to provide effectiveness and safety data. Adverse reactions related to treatment will be reported to the Health Authorities in India and subsequently, any regulatory action resulting from the review of reported adverse reactions should be complied with by the Sponsor. This Phase 4 clinical trial is to be conducted in addition to the Periodic Safety Update Report, which must be submitted to the health authorities in India every 6 months for the first 2 years after approval, and annually for subsequent 2 years.

Safety will be evaluated throughout the treatment period and during the follow-up of participants who discontinue treatment before 52 weeks by assessing the incidence of high-grade immune-mediated adverse events (IMAEs) in patients who are treated.

The evaluation of patient-reported outcomes (PROs) is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting.

[redacted]

Effectiveness will be evaluated throughout the treatment period by tumor assessments (computed tomography [CT]/magnetic resonance imaging (MRI) of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease) at screening, and then at Week 12 (± 7 days) following first dose; subsequent tumor assessments will occur every 8 weeks (±7 days) until 52 weeks of treatment plus 2 weeks of follow-up or initiation of subsequent systemic cancer therapy, withdrawal of consent, death, or investigator-assessed disease progression, whichever occurs first

These time points are independent of dosing. See Section 9.1.1 for further details. Endpoint analysis of PFS, ORR, time to response (TTR), and duration of response (DOR) will be done based on these assessments.

[redacted]

Collecting immunogenicity/pharmacokinetic (PK) data on the India population will allow comparison between the India population and the global population.

3.1.1 Research Hypothesis

There is an unmet medical need in India in the setting of advanced or mRCC. Combination therapy of nivolumab and ipilimumab as first-line treatment for patients with clear-cell RCC has been evaluated in the CA209214 clinical trial. The present study will aim to evaluate a combination dosing regimen of nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (Q3W) followed by a single-dose agent of nivolumab 3 mg/kg every 2 weeks (Q2W) for a maximum of 52 weeks or until treatment is no longer tolerated by the participant or withdrawal of consent.

The research hypothesis is that this dosing regimen will result in a comparable safety profile as assessed by the incidence of high-grade (Common Terminology Criteria for Adverse Events [CTCAE] v4.0 Grade 3 to 4 and Grade 5) IMAEs observed in patients with advanced or mRCC in India with clear-cell histology who are treated in the first-line setting, when compared to Study CA209214 safety data in this patient population.

3.2 Background

3.2.1 Indication Background

Renal Cell Carcinoma Background and Standard Treatments

According to the GLOBOCAN estimates, 403,262 new cases of kidney cancer were diagnosed in 2018 worldwide accounting for 2.2% of all adult cancers.[8] In India, 15,454 new cases of kidney cancer were diagnosed in 2018, with an age-standardized incidence rate of 1.3%.[9] Renal cell carcinoma (RCC) is the most common form of kidney cancer (90% of cases). It is nearly twice as common in men as in women, with a median age at diagnosis of 64 years. Clear cell tumors are the most common pathological subtype of RCC (80% of cases); some other less common subtypes include papillary, chromophobe, and collecting duct tumors. Smoking, obesity, and hypertension are well-known risk factors for RCC. It primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain.[10] Although the 5-year OS of early-stage RCC is as high as 66%, metastatic or advanced stage disease is only 8% to 10%. Moreover, local recurrence or distant metastasis develops in up to 30% to 40% of patients treated for localized stage disease. Metastatic RCC responds very poorly to conventional chemotherapy. Cytokine therapy is associated with modest response rates of 15% to 20% but at the cost of significant toxicities. [10]

Multiple scoring systems are available to characterize prognosis in treatment-naive RCC. Two of the most commonly used are the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic

scoring system and the IMDC prognostic scoring system.[11,12] Each of these systems categorizes patients as favorable, intermediate, or poor-risk based on how many adverse prognostic factors are present (0: favorable risk, 1 to 2: intermediate risk, 3 or more: poor-risk). The 6 parameters of importance for IDMC prognostic score classification are Karnofsky Performance Status (KPS), time from diagnosis to treatment, hemoglobin value, corrected calcium concentration, absolute neutrophil count, and platelet count. The 5 parameters included in the MSKCC prognostic score are KPS, nephrectomy status, hemoglobin value, lactate dehydrogenase (LDH), and corrected calcium concentration. Time from diagnosis to treatment is often used in place of nephrectomy status. With each system, total number of adverse prognostic factors present has been shown to correlate with OS.

Approximately 25% of patients are in the favorable-risk group, 50% are in the intermediate-risk group, and 25% are in the poor-risk group (median OS: ~ 9 months). In an analysis of 1,028 patients scored using the IMDC system, median OS for favorable-, intermediate-, and poor-risk patients is 43.2, 22.5, and 7.8 months, respectively.[13]

Until recently, the cytokines interleukin-2 and interferon-α were the only active treatments for advanced or metastatic RCC. However, due to each of these agent's limited clinical benefit and substantial toxicity profile, newer targeted agents have largely replaced cytokines in the treatment of advanced or mRCC.[14,15,16,17] The recognition of the importance of hypoxia inducible factor alpha (HIFα) signaling in the pathogenesis of clear-cell RCC has led to widespread study of 2 classes of targeted therapies: anti-angiogenic agents and mammalian target of rapamycin (mTOR) inhibitors.[18] Targeting of angiogenesis is rational because constitutive HIFα activation leads to the upregulation or activation of several proteins including vascular endothelial growth factor (VEGF), which can subsequently lead to tumor proliferation and neovasculature formation.

Targeting of the mTOR pathway is important because activation of the upstream PI3K/Akt/mTOR signaling pathway is one method by which constitutive HIFα activation or upregulation occurs. There are 7 agents for the treatment of RCC in the US and European Union (EU): 5 that target angiogenesis (ie, the VEGF-receptor tyrosine kinase inhibitors sorafenib, sunitinib, pazopanib, axitinib, and the VEGF-binding monoclonal antibody bevacizumab) and 2 that target the mTOR pathway (ie, everolimus and temsirolimus). Among these approved agents, none has demonstrated a statistically significant improvement in OS except for temsirolimus in poor-risk patients. According to National Comprehensive Cancer Network (NCCN) guidelines, sunitinib, temsirolimus (poor-risk only), bevacizumab plus interferon, and pazopanib are Category 1 recommendations for first-line therapy of mRCC.[19]

According to ESMO guidelines, sunitinib, bevacizumab plus interferon, and pazopanib are all standard treatment options for favorable- and intermediate-risk patients, but sunitinib is the only one also considered an alternative to temsirolimus for the treatment of poor-risk patients.[20]

3.2.2 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cluster of differentiation

(CD) 279 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.[21] Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation 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 cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab (OPDIVO™) is approved for the treatment of several types of cancer in multiple regions including the US (Dec-2014), the EU (Jun-2015), and Japan (Jul-2014).

A detailed description of the chemistry, pharmacology, effectiveness, and safety of nivolumab is provided in the India prescribing information for nivolumab (Appendix 5).

3.2.3 Ipilimumab Mechanism of Action

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal immunoglobulin G1 kappa specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4, CD152), which is expressed on a subset of activated T cells. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell (Treg) function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

A detailed description of the chemistry, pharmacology, effectiveness, and safety of ipilimumab is provided in the India prescribing information for ipilimumab (Appendix 5).

3.2.4 Nivolumab in Renal Cell Carcinoma

Nivolumab monotherapy has been studied in participants with RCC in several BMS-sponsored studies, with the largest amount of data coming from 3 studies in participants with mRCC: CA209010, CA209009, and CA209025. In Study CA209010, 168 participants who received at least 1 prior anti-angiogenic therapy were randomized to receive nivolumab 0.3 mg/kg (n = 60), 2 mg/kg (n = 54), and 10 mg/kg (n = 54).[22] Median PFS was 2.7, 4.0, and 4.2 months at 0.3, 2, and 10 mg/kg, respectively. The ORR ranged from 20% to 22% across dose levels. Median OS was 18.2 months at 0.3 mg/kg, but was not yet reached at the 2 highest dose levels. CA209009 enrolled a similar population to Study CA209010, but also included 24 participants with treatment-naive RCC. Among treatment-naive participants, all of whom received nivolumab 10 mg/kg Q3W, the ORR was 13% (3/23).

Study CA209010 includes the largest safety database for nivolumab monotherapy in mRCC. All treated participants (n = 167) were included in the safety analyses. Drug-related AEs of any grade occurred in 74.6%, 66.7%, and 77.8% of participants treated at 0.3, 2, and 10 mg/kg, respectively. The most common (≥ 10% in any group) drug-related AEs included fatigue, dry skin, rash,

pruritus, arthralgia, nausea, diarrhea, decreased appetite, dry mouth, and hypersensitivity. Grade 3 drug-related AEs occurred in 5.1%, 16.7%, and 13% of participants treated at 0.3, 2, and 10 mg/kg, respectively. Related Grade 3 events in at least 2 patients across dose levels included nausea, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) increased, and anemia. No drug-related Grade 4 or Grade 5 events occurred. No dose-toxicity relationship was identified except for hypersensitivity/infusion reaction, which occurred most frequently in the 10 mg/kg treatment group.

Based on the clinical activity of nivolumab observed in these Phase 1 and 2 studies, a large Phase 3 trial (CA209025) was conducted in 821 participants with advanced RCC previously treated with 1 or 2 anti-angiogenic therapies who were randomized to receive nivolumab 3 mg/kg Q2W or everolimus 10 mg daily. A planned interim analysis, after a minimum follow-up of 14 months, demonstrated a statistically significant and clinically meaningful improvement in OS of nivolumab monotherapy versus everolimus (median OS, 25.0 months vs 19.6 months, respectively; hazard ratio [HR] 0.73 [98.5% confidence interval (CI): 0.57 to 0.93, P = 0.002]). ORR was 25% for nivolumab versus 5% for everolimus. Among 756 participants with quantifiable PD-L1 tumor expression in pre-treatment samples, 24% had PD-L1 expression ≥ 1%. Among participants with PD-L1 expression ≥ 1%, median OS was 21.8 months in the nivolumab group and 18.8 months in the everolimus group (HR 0.79 [95% CI: 0.53 to 1.17]). Among participants with PD-L1 expression < 1%, the median OS was 27.4 months in the nivolumab group and 21.2 months in the everolimus group (HR, 0.77 [95% CI: 0.60 to 0.97]). No new safety concerns were identified, and nivolumab monotherapy showed a favorable safety profile as compared to everolimus, evidenced by the lower rates of drug-related AEs (all grades, 79% vs 88%; Grade 3 to 4, 19% vs 37%, respectively) and drug-related AEs leading to discontinuation (all grades, 8% vs 13%, respectively) in the nivolumab group. These results were the basis for regulatory approval of nivolumab monotherapy in advanced RCC.

Based on the limited data from Studies CA209009 and CA209010, when Study CA209214 was initiated in 2014, the observed preliminary anti-tumor activity was not considered to be sufficient to test against sunitinib, the standard of care in 1L RCC. As the treatment of RCC landscape continues to evolve, accumulative evidence showed a single-agent activity for anti-PD-1 or anti-PD-L1 monotherapy in the 1L treatment of advanced RCC. In a Phase 2, nonrandomized, noncomparative study (Keynote-427),[23] pembrolizumab was studied as monotherapy in 110 patients with advanced clear cell RCC who had not received prior systemic therapy, including 41 IMDC favorable-risk patients. The interim data showed single-agent activity with an overall response rate of 38.2% including a CR rate of 2.7%. Responses lasting for 6 months or more were observed in 74.8% of patients. The median PFS was 8.7 months (95% CI: 6.7 to 12.2 months) and the 6-month PFS rate was 60.2%. In an analysis based on PD-L1 status, patients whose tumors expressed PD-L1 (combined positive score [CPS] ≥ 1) (n = 46) had an ORR of 50.0% (95% CI: 34.9 to 65.1), with a CR rate of 6.5%. In patients whose tumors did not express PD-L1 (CPS < 1) (n = 53), ORR was 26.4% (95% CI: 15.3 to 40.3) (all responses were PRs).

Atezolizumab was evaluated in the IMmotion 150 study, a randomized Phase 2 study comparing the combination of atezolizumab with bevacizumab (a VEGF-targeted antibody) and atezolizumab

monotherapy versus sunitinib, as a 1L treatment for previously untreated RCC.[24] In the atezolizumab monotherapy arm (n = 103 patients), an ORR of 25%, including 11% of CR, was reported. Among 54% of PD-L1 positive patients treated with atezolizumab monotherapy, an ORR of 28%, with 15% of CR, was observed. The median PFS for atezolizumab was 5.4 months, which was not statistical significant compared with sunitinib (HR 1.03 [95% CI: 0.63 to 1.67, P = 0.917]). Taken together, agents targeting PD-1/PD-L1 pathway demonstrated initial anticancer activities. However, the role of single agents of PD-1 and PD-L1 inhibitors versus those agents in combination with other agents with different targeted pathways, such as anti-CTLA-4 or anti-VEGF agents, remains to be defined.

3.2.5 *Ipilimumab in Renal Cell Carcinoma*

Ipilimumab monotherapy for the treatment of mRCC was studied in the Phase 2 clinical trial MDX010-11.[25] Two sequential cohorts were studied, each with a loading dose of 3 mg/kg followed by 3 doses of either 1 mg/kg (group 3-1; n = 21) or 3 mg/kg (group 3-3; n = 40).

Participants with stable disease or partial response (PR) or CR were allowed additional treatment. In group 3-1 (n = 21), 1 participant (5%) had a PR.[26] In group 3-3 (n = 40), 5 participants (12.5%) had a PR. Among 14 treatment-naive participants in group 3-3, 3 participants (21%) had a PR.

In the ipilimumab monotherapy Phase 2 clinical trial MDX010-11, the major toxicities were colitis (all Grade 3/4: 14% in group 3-1, 33% in group 3-3) and hypophisitis (1 grade 3/4, 1 grade 1/2 in group 3-3; none in group 3-1). Most reported AEs were Grade 1/2 (57% in group 3-1, 35% in group 3-3) or Grade 3 (38% in group 3-1, 48 % in group 3-3).[27] Most reported AEs were Grade 1/2 (57% in group 3-1, 35% in group 3-3) or Grade 3 (38% in group 3-1, 48% in group 3-3). There were 6 participants (15%) with Grade 4 AEs in group 3-3. The most common treatment-related AEs in group 3-1 (total 81%) and group 3-3 (total 93%) were diarrhea (38% and 40%, respectively) and fatigue (33% and 38%, respectively). Most AEs were manageable with appropriate treatment, including high dose corticosteroids and hormone replacement.

3.2.6 *Nivolumab Combined with Ipilimumab Clinical Activity*

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules. The following information describes the results of initial early phase clinical studies that were the basis for the nivolumab plus ipilimumab combination regimens that have been explored in late phase clinical development.

Based on the safety data from the completed and ongoing advanced RCC studies, the safety profile of nivolumab in combination with ipilimumab, and nivolumab monotherapy using the acceptable dosing regimens, in the context of the observed clinical activity, are manageable using well-established guidelines and present a favorable benefit/risk profile in patients with advanced RCC. The indication for which there is clear benefit are as follows: Nivolumab in combination with ipilimumab in previously untreated, advanced RCC based on Study CA209214: nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg Q3W administered as an intravenous (IV) infusion for 4 doses followed by nivolumab 3 mg/kg Q2W. Treatment was to continue until disease progression or unacceptable toxicity. This is the first Phase 3 trial to demonstrate improved OS in

this population compared to the current standard of care sunitinib. The nivolumab + ipilimumab combination also demonstrated a significantly higher IRRC-assessed ORR compared to sunitinib (41.6% vs 26.5%), with objective responses that were deeper, including 9.4% of subjects achieving a CR, and more durable, with a median DOR not reached at the time of database lock. Clinically meaningful improvement in PFS was also demonstrated with the nivolumab + ipilimumab combination vs sunitinib. In Study CA209214, the overall safety profile observed in the nivolumab + ipilimumab group (using nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg) was consistent with the known and well-characterized safety profile of nivolumab monotherapy (using nivolumab 3 mg/kg) and more tolerable than the nivolumab + ipilimumab combination (using nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg) in melanoma. There were no new safety signals relative to combination therapy in melanoma (nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg) as well as nivolumab monotherapy (using nivolumab 3 mg/kg), and it was well tolerated with 23.4% of patients remaining on therapy at the time of analysis. Overall, the benefit-risk profile of nivolumab + ipilimumab is favorable relative to sunitinib. The clinically meaningful benefit, including significant improvement in OS, and acceptable safety profile in Study CA209214 provide evidence for a new standard of care for nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in treatment-naive patients with advanced RCC with an intermediate/poor-risk prognosis.

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab and ipilimumab is provided in the India prescribing information for nivolumab and ipilimumab (Appendix 5).

3.2.7 *Adverse Event Rates Associated with Nivolumab in Combination with Ipilimumab in Previously Untreated Advanced or Metastatic RCC*

In Study CA209214, the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n = 547), with a minimum follow-up of 17.5 months, the most frequent adverse reactions (≥ 10%) were fatigue (48%), rash (34%), pruritus (28%), diarrhea (27%), nausea (20%), hypothyroidism (16%), musculoskeletal pain (15%), arthralgia (14%), decreased appetite (14%), pyrexia (14%), vomiting (11%), and hyperthyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).[28]

Among the patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in Study CA209214, 169/547 (31%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 382 patients in this group who continued treatment in the single-agent phase, 144 (38%) experienced at least 1 Grade 3 or 4 adverse reaction during the single-agent phase. [28]

The treatment-related AEs and SAEs, and discontinuations due to treatment-related AEs in the Checkmate 214 study are presented in Table 3.2.7-1. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and very rare (< 1/10,000).

Table 3.2.7-1: Adverse Reactions in Patients Receiving Nivolumab Plus Ipilimumab (Checkmate-214)

	Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg in RCC[a]
Infections and infestations	
Common	pneumonia, upper respiratory tract infection
Uncommon	bronchitis, aseptic meningitis
Blood and lymphatic system disorders	
Common	NA
Uncommon	eosinophilia
Immune system disorders	
Common	infusion-related reaction, hypersensitivity
Uncommon	NA
Endocrine disorders	
Very common	hypothyroidism, hyperthyroidism
Common	adrenal insufficiency[b], hypophysitis[b], thyroiditis, diabetes mellitus[b]
Uncommon	diabetic ketoacidosis[b], hypopituitarism
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration
Uncommon	metabolic acidosis
Hepatobiliary disorders	
Common	hepatitis[b]
Nervous system disorders	
Very common	NA
Common	headache, peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis[b]
Eye disorders	
Common	blurred vision
Uncommon	uveitis
Cardiac disorders	
Common	tachycardia
Uncommon	arrhythmia (including ventricular arrhythmia), myocarditis[b]

Table 3.2.7-1: Adverse Reactions in Patients Receiving Nivolumab Plus Ipilimumab (Checkmate-214)

	Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg in RCC[a]
Vascular disorders	
Common	hypertension
Uncommon	NA
Respiratory, thoracic and mediastinal disorders	
Very common	NA
Common	pneumonitis, dyspnoea, pleural effusion, cough
Uncommon	NA
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea
Common	colitis, stomatitis, pancreatitis, abdominal pain, constipation, dry mouth
Uncommon	gastritis
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus
Common	dry skin, erythema, urticaria
Uncommon	Stevens-Johnson syndrome, vitiligo, erythema multiforme, alopecia, psoriasis
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[d], arthralgia
Common	arthritis, muscle spasms, muscular weakness
Uncommon	polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis
Common	renal failure (including acute kidney injury)[b]
Uncommon	tubulointerstitial nephritis
General disorders and administration site conditions	
Very common	fatigue, pyrexia
Common	oedema (including peripheral oedema), pain, chest pain, chills
Uncommon	NA
Investigations[b]	
Common	weight decreased

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte antigen 4; NA = not applicable; RCC = renal cell carcinoma

[a] Nivolumab in combination with ipilimumab for the first 4 doses followed by nivolumab as a single-agent maintenance therapy in RCC.

[b] Life-threatening cases have been reported in completed or ongoing clinical studies.

[c] Rash is a composite term that 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, and pemphigoid.

[d] Musculoskeletal pain is a composite term that includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

3.3 Benefit/Risk Assessment

Extensive details on the safety profile of nivolumab are available in the India prescribing information for nivolumab (Appendix 5) and will not be repeated herein.

Overall, the safety profile of nivolumab as a single-agent therapy, as well as in combination with ipilimumab, is manageable and generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related AEs has been defined; these are provided in the India prescribing information for nivolumab (Appendix 5). Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the India prescribing information for nivolumab.

Patients with mRCC have multiple treatment options available to them, but none of the available targeted agents have been able to demonstrate a significant improvement in OS when compared to each other. Median OS remains less than 4 years for treatment-naive patients with the most favorable prognosis and is substantially shorter for patients who possess adverse prognostic factors. Therefore, new therapeutic options with the potential to provide greater survival across risk groups are needed.

Nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg has demonstrated substantial clinical activity, as measured by ORR, while still exhibiting an acceptable safety profile in the Checkmate-214 study, and the magnitude of OS benefit from the combination is unprecedented in studies of mRCC for intermediate- and poor-risk participants.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of nivolumab and ipilimumab may be found in the India prescribing information for nivolumab and ipilimumab.

Non-live coronavirus disease 2019 (COVID-19) vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving investigational agents is unknown.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objective	Endpoint
Primary	
• To assess the incidence of high-grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs in intermediate- or poor-risk participants with previously untreated, advanced RCC who are treated with combination therapy of nivolumab 3 mg/kg administered intravenously over a period of 30 minutes Q3W for the first 4 doses in combination with intravenous ipilimumab 1 mg/kg over a period of 30 minutes, followed by nivolumab 3 mg/kg Q2W administered IV over a period of 30 minutes.	• Incidence of high-grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs
Secondary	
• To characterize the outcome of all high grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs in intermediate or poor risk participants with previously untreated, advanced RCC.	• Characterization of outcome of all high grade (CTCAE v4.0 Grade 3 to Grade 5) IMAEs (eg, time to onset, time to resolution, percentage of patients who received immune modulating medication)
• To assess the effectiveness of nivolumab in combination with ipilimumab by measuring ORR, TTR, and DOR, using RECIST 1.1.	• ORR, TTR, DOR
Exploratory	
• To assess the incidence of all treatment-related AEs in intermediate or poor risk participants with previously untreated, advanced RCC.	• Incidence of all treatment related AEs
• To assess the effectiveness of nivolumab in combination with ipilimumab by measuring PFS (at time of initial progression) and OS 1-year survival rates in intermediate- or poor-risk participants with previously untreated, advanced RCC.	• PFS, OS
• To assess the participant's cancer-related symptoms and QoL.	• All total and subscale scores and post-baseline score changes for the FKSI-19
• To evaluate the PK of nivolumab and ipilimumab when administered in combination and the PK of nivolumab as a single-agent maintenance therapy. To explore the exposure-response relationships between select exposure measures, and safety and effectiveness endpoints, as appropriate.	• Predose serum nivolumab and ipilimumab concentrations to be used for PPK analysis to predict nivolumab PK parameters. Explore exposure-response relationships if data permit.
• To characterize the immunogenicity of nivolumab and ipilimumab when administered in combination and the immunogenicity of nivolumab as a single-agent maintenance therapy.	• Immunogenicity will be determined by measurement of ADA in serum and samples with positive ADA response may be analyzed for neutralizing ADA response to nivolumab and ipilimumab

Table 4-1: Objectives and Endpoints

Objective	Endpoint
[redacted]	
• To assess the impact of SARS-CoV-2 serologic status on participants receiving nivolumab in combination with ipilimumab and previously untreated, advanced RCC and to support Health Authority requests	• Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG) from serum samples collected at baseline (and additional time points if applicable) and the potential association between these measurements and selected endpoints related to safety, effectiveness, and/or biomarkers

Abbreviations: ADA = antidrug antibody; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; FKSI-19 = Functional Assessment of Cancer Therapy - Kidney Symptom Index; IgG = immunoglobulin G; IMAE = immune-mediated adverse event; IV = intravenous(ly); NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; [redacted]; PFS = progression-free survival; PK = pharmacokinetics; PPK = population pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; QoL = quality of life; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TTR = time to response

Note: All AEs to be assessed using NCI CTCAE v4.0.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 4, open-label, single-arm, multi-center, prospective study of nivolumab 3 mg/kg Q2W combined with ipilimumab 1 mg/kg Q3W for 4 doses followed by nivolumab 3 mg/kg for up to 52 weeks. The study is to be conducted in India and will enroll intermediate- or poor-risk participants with previously untreated, advanced RCC or mRCC (N = 100).

Potential participants will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Participants who meet the protocol-defined inclusion/exclusion criteria will be prospectively enrolled in a sequential manner.

The study treatment will continue until participants experienced disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, unacceptable toxicity, withdrawal of consent, or a maximum 1 year of study treatment of nivolumab. There are a maximum 4 doses of ipilimumab.

Participants who are observed to continue to receive clinical benefit at follow-up will continue nivolumab treatment via commercial supply (provided by BMS India) as long as clinical benefit is observed or until treatment is no longer tolerated by the participant.

For drug-related toxicities, dosing of both drugs can be delayed and resumed after resolution per protocol-specified criteria (Section 7.4.1). No dose increases or reductions are allowed for either drug. Management of the drug-related toxicities, including the use of corticosteroids and other immunomodulating agents, is provided in the India prescribing information (Appendix 5).

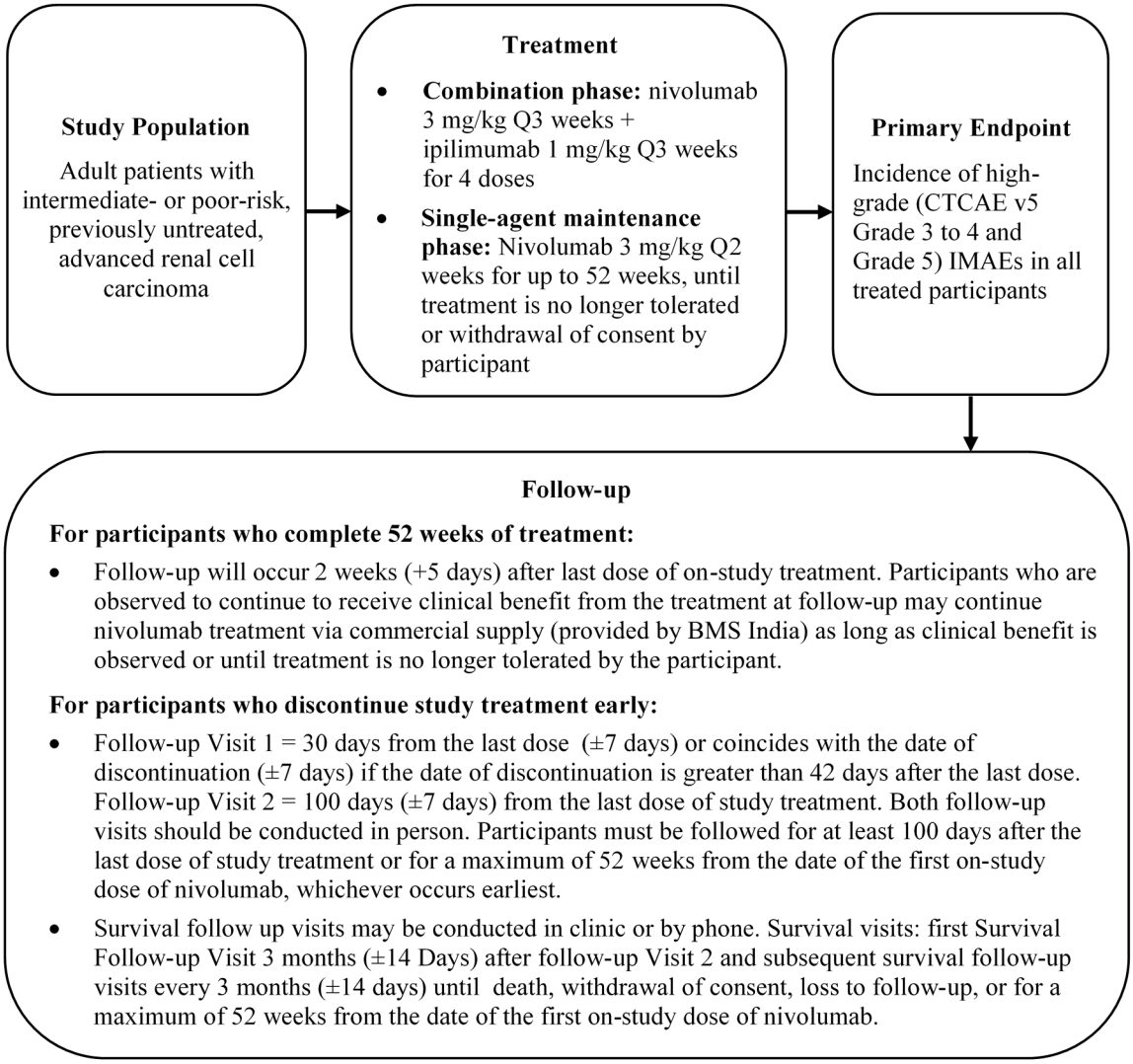
Participants should have baseline CT/MRI with measurable disease lesion(s) per RECIST 1.1 and first post-baseline tumor assessment at Week 12 followed by subsequent tumor assessments every 8 weeks in the first 52 weeks (Section 9.1.1 for more details). The tumor assessment schedule will continue until a maximum of 52 weeks of treatment plus 2 weeks of follow-up or initiation of subsequent systemic cancer therapy, withdrawal of consent, death, or investigator-assessed disease progression, whichever occurs first. These time points are independent of dosing. See Section 9.1.1 for further details. The scans will be submitted to the blinded independent central review (BICR)-designated imaging laboratory.

AE should be collected throughout the study until 100 days after the last dose or for a maximum of 52 weeks from the date of the first on-study dose of nivolumab, whichever occurs earlier. Safety laboratory including complete blood count (CBC) and chemistry will be obtained at each scheduled visit and unscheduled visit as indicated. PK and biomarker samples should be collected per protocol-specified schedule (see Table 9.5-1 and Table 9.7.1-1, respectively). PROs will be completed by the participant per the protocol-specified Schedule of Activities in Section 2.

Participants who discontinue the study treatment will be followed for safety at 30 days (Follow-up Visit 1) and 100 days (Follow-up Visit 2) of the last dose, thereafter for survival until death, withdrawal of consent, loss to follow-up, or for a maximum of 52 weeks from the date of the first on-study dose of nivolumab. Tumor assessments schedule will continue in the follow-up period per schedule until a maximum of 52 weeks of treatment plus 2 weeks of follow-up or initiation of subsequent systemic cancer therapy, withdrawal of consent, death, or investigator-assessed disease progression, whichever occurs first. These time points are independent of dosing. See Section 9.1.1 for further details.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



This study will consist of 3 phases: screening, treatment, and follow-up.

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using Interactive Response Technology (IRT).
- [redacted]

[redacted]

- Participants will be assessed for complete study eligibility prior to treatment assignment as specified in Table 2-1.
- The Screening stage ends with either confirmation of full eligibility or with the confirmation that the participant is a screen failure.
- This study permits the re-enrollment of a participant who discontinued the study as a pre-treatment failure prior to the treatment phase. If re-enrolled, the participant must be re-consented. A new participant identification number will be assigned by IRT at the time of re-enrollment.

Treatment Phase:

- Each visit begins with a call to the IRT system.
- The first dose is to be administered within 28 days of signing informed consent.
- For the first 4 cycles (cycle = 3 weeks):
  - Nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV Q3W will be administered for 4 doses (12 weeks total).
- Starting with Cycle 5 (cycle = 2 weeks):
  - Nivolumab 3 mg/kg IV will be administered Q2W.
- Nivolumab and ipilimumab to be continued until disease progression or unacceptable toxicity, with maximum nivolumab treatment of 52 weeks from the first dose in Cycle 1.
- See Table 7.1-1 for the dosing schedule and Section 5.6 for dose and timing justification. Study treatments may be delayed for toxicity (see Section 7.4.1). Treatment may be continued beyond investigator-assessed progression if the investigator confirms that the participant meets the criteria specified in Section 7.4.2.
- A negative pregnancy test must be documented within 24 hours prior to the start of investigational product.
- PRO instruments must be completed according to the Schedule of Activities in Section 2.
- Potential participants will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Participants who meet the protocol-defined inclusion/exclusion criteria will be prospectively enrolled in a sequential manner.
- On-study laboratory assessments (Cycle 2 and beyond) should be drawn within 72 hours prior to dosing.
- AE assessments should be documented at each clinic visit.

- WOCB must have a pregnancy test within 24 hours prior to administration of study drug.
- PK samples and immunogenicity samples will be collected according to the schedule in Table 9.5-1 and biomarkers according to Section 9.7.1.
- Study drug dosing may be delayed for toxicity.

For all subjects:

- Treated subjects will be evaluated for response by the investigator according to the RECIST 1.1 guidelines beginning at Week 12 (± 7days) following the first dose, then every 8 weeks (± 7 days) until Week 52, then until a maximum of 52 weeks of treatment plus 2 weeks of follow-up or initiation of subsequent systemic cancer therapy, withdrawal of consent, death, or investigator-assessed disease progression, whichever occurs first. These time points are independent of dosing. See Section 9.1.1 for further details.
- Patients treated beyond progression with nivolumab will continue to have tumor assessments beginning 12 weeks (±7 days) after the first dose and continuing every 8 weeks (±7 days) until Week 52, then until a maximum of 52 weeks of treatment plus 2 weeks of follow-up or initiation of subsequent systemic cancer therapy, withdrawal of consent, death, or investigator-assessed disease progression, whichever occurs first. These time points are independent of dosing. See Section 9.1.1 for further details.

Follow-up Phase

The follow-up stage begins when the decision to discontinue a participant from study therapy is made or the participant completes treatment (no further study treatment).

- For patients who complete 52 weeks of study treatment:
  - Follow-up Visit 1 will be conducted 2 weeks (+5 days) after the final dose of study treatment.
  - PRO instruments must be completed according to the Schedule of Activities in Section 2.
- For patients who discontinue early (prior to 52 weeks of treatment):
  - Follow-up Visit 1 = 30 days from the last dose (±7 days) or coincides with the date of discontinuation (±7 days) if date of discontinuation is greater than 42 days after the last dose.
  - Follow-up Visit 2 = 100 days (±7 days) from the last dose of study treatment.
  - Both follow-up visits should be conducted in person.
  - Participants must be followed for at least 100 days after the last dose of study treatment or for a maximum of 52 weeks from the date of the first on-study dose of nivolumab, whichever occurs earlier.
  - All AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose or for a maximum of 52 weeks from the date of the first on-study dose of nivolumab, whichever occurs earlier.

- Events with an "Outcome" of death, regardless of the type of event or relationship (ie, including study drug toxicity) are required to be also reported as Grade 5 events.
- All SAEs after 52 weeks of study duration and 2 weeks of follow-up for participants on commercial nivolumab supply will be reported to India Health Authority as part of spontaneous reporting.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible.
- The 2 follow-up visits include collection of PK/immunogenicity samples.
- After follow-up, patients who discontinue early (prior to 52 weeks of treatment) will be followed for OS status every 3 months (±14 days) after follow-up Visit 2, and subsequent survival follow-up visits every 3 months (±14 days) until death, withdrawal of consent, loss to follow-up, or for a maximum of 52 weeks from the date of the first on-study dose of nivolumab.
- If new anti-tumor therapy is initiated for either progression or a secondary malignancy at any time during this period, this and all other pertinent data obtained should be recorded on the appropriate case report form (CRF).
- PRO instruments will be completed according to the Schedule of Activities in Section 2.

The total duration of the study from enrollment to final analysis is expected to be 36 months (52 weeks of patients treatment + 24 months for patient accrual), assuming a fixed accrual rate of approximately 5 subjects per month.

Safety will be evaluated throughout treatment and during the follow-up of participants who discontinue treatment before 52 weeks by physical examinations including vital signs, AE/SAE monitoring, laboratory evaluations, and recording of concomitant medications.

Data analyses will be conducted only on the safety data collected within the maximum of the 52 weeks of treatment and 2-week follow-up study period, which will include safety collected during the follow-up of participants who discontinue treatment before 52 weeks.

All SAEs for patients who continue on commercial nivolumab supply after the 52 weeks of treatment and 2-week follow-up study duration will be reported to India Health Authority as part of spontaneous reporting.

Physical examinations, vital sign measurements, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval and during follow-up for those participants who discontinue treatment before the end of the treatment period (52 weeks). Participants will be closely monitored for AEs throughout the study.

5.2 Data Monitoring Committee and Other External Committees

Not applicable.

5.3 Number of Participants

A total of 100 treated participants with intermediate- or poor-risk, previously untreated, advanced RCC will be enrolled.

The sample size calculation is presented in Section 10.1.

5.4 End of Study Definition

The start of the trial is defined as the first visit of the first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities in Section 2 for the last participant. Study completion is defined as the final date on which data for the primary endpoint are expected to be collected, if this is not the same.

In this trial, the study will be completed on the date on which safety data (primary endpoint) are collected for the last participant on study.

5.5 Scientific Rationale for Study Design

This is a Phase 4 study in India to establish the safety and effectiveness of the combination of nivolumab with ipilimumab followed by nivolumab as a single-agent maintenance therapy in patients with intermediate- or poor-risk, previously untreated, advanced RCC.

This Phase 4 clinical trial is to be conducted in addition to the Periodic Safety Update Report, which must be submitted to the health authorities in India every 6 months for the first 2 years after approval and annually for the subsequent 2 years.

The results of this study of nivolumab in combination with ipilimumab followed by nivolumab as a single-agent maintenance therapy for the treatment of intermediate- or poor-risk, previously untreated, advanced RCC in a limited number of participants in India will be submitted in accordance with the requirements of the health authorities in India.

5.6 Duration of Treatment with Nivolumab + Ipilimumab

The study treatment will continue until participants experience disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, unacceptable toxicity, withdrawal of consent, or a maximum of 1 year of study treatment of nivolumab. There is a maximum of 4 doses of ipilimumab.

At the conclusion of the study, participants who continue to benefit clinically from nivolumab at 52 weeks will continue treatment via commercial supply (provided by BMS) as long as clinical benefit is observed or until treatment is no longer tolerated by the participant. AEs/SAEs for participants receiving commercial supply will be reported via spontaneous reporting.

5.7 Clinical Pharmacology Summary

Nivolumab PK was assessed using a population PK approach for both single-agent nivolumab and nivolumab with ipilimumab.

Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients 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 IV infusion every 2 or 3 weeks. Nivolumab clearance (CL) decreased over time, with a mean maximal reduction (percent coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss was not considered clinically relevant. Nivolumab CL does not decrease over time in patients with completely resected melanoma, as the

geometric mean population CL is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. The predicted exposure (average concentration and maximum observed concentration) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Nivolumab 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 unchanged compared to nivolumab administered alone. When nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab and ipilimumab were unchanged. When nivolumab was administered in combination with ipilimumab, the presence of anti-nivolumab antibodies increased the CL of nivolumab by 20% and the CL of ipilimumab was unchanged in presence of anti-ipilimumab antibodies.

Specific Populations: The population PK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 years to 87 years), weight (35 kg to 160 kg), gender, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the CL of nivolumab was evaluated by a population PK analysis in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. No clinically important differences in the CL of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the CL of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [TBili] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TBili greater than 1 to 1.5× ULN and any AST) and in HCC patients with moderate hepatic impairment (Tbili greater than 1.5 to 3×ULN and any AST). No clinically important differences in the CL of nivolumab were found between patients with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the India prescribing information for nivolumab and ipilimumab (Appendix 5).

Nivolumab 3 mg/kg is approved in the following indications in India:

1) As a single agent for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy
2) As a single agent for the treatment of patients with advanced RCC after prior therapy in adults
3) As monotherapy for the treatment of recurrent or metastatic SCCHN after platinum-based therapy

4) As a single agent for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma
5) For the treatment of adult patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous HSCT and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT
6) For the treatment of patients with HCC who have been previously treated with sorafenib
7) For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
8) For the treatment of adult and pediatric (12 years and older) patients with MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Nivolumab 3mg/kg will be used in this study.

Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg Q3W for 4 cycles followed by nivolumab 3 mg/kg Q2W is approved in India and will be used in this study.

5.8 Justification for Combination Nivolumab and Ipilimumab Dose

Nivolumab 3 mg/kg Q3W IV for 30 minutes will be combined with ipilimumab 1 mg/kg Q3W IV for 30 minutes for 4 cycles and then switched to nivolumab 3 mg/kg Q2W IV for 30 minutes during the maintenance phase, 3 weeks after the last combination dose.

Data in support of the nivolumab 3 mg/kg Q3W and ipilimumab 1 mg/kg Q3W regimen in RCC come from a Phase 2 clinical study (CA209016) and a Phase 3 clinical study (CA209214).

Data from Study CA209016 demonstrated a level of clinical activity, as measured by ORR, for the combination of nivolumab 3 mg/kg Q3W combined with ipilimumab 1 mg/kg Q3W for 4 cycles, followed by nivolumab 3 mg/kg Q2W that was substantially greater with an ORR (95% CI) of 40.4% (26.4 to 55.7) than that observed in a previous phase 3 clinical study (CA209-025) evaluating nivolumab 3 mg/kg Q2W with an ORR (95% CI) of 25.1% (21.0 to 29.6). The combination dosing regimen of nivolumab 3 mg/kg Q3W combined with ipilimumab 1 mg/kg Q3W for 4 cycles, followed by nivolumab monotherapy was chosen because it exhibited a similar ORR and a more favorable safety profile than that of nivolumab 1 mg/kg Q3W combined with ipilimumab 3 mg/kg Q3W for 4 cycles, followed by nivolumab monotherapy.

In the Phase 3 clinical study (CA209214), the clinical benefit of OS was demonstrated in the intermediate- or poor-risk population (HR 0.63 [99.8% CI: 0.44 to 0.89]) for the nivolumab 3 mg/kg Q3W combined with ipilimumab 1 mg/kg Q3W regimen dosed for 4 cycles followed by nivolumab 3 mg/kg Q2W maintenance compared to sunitinib in 1L RCC.

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, biomarker and PK testing, and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

a) Histological confirmation of renal cell carcinoma with clear cell component including participants who may have sarcomatoid features. Advanced (not amenable to curative surgery or radiation therapy) RCC or mRCC with or without prior nephrectomy.

b) No prior systemic therapy for RCC with the following exception:

i) One prior adjuvant or neoadjuvant therapy for completely resected RCC (see Exclusion 2b). These drugs must be discontinued ≥ 6 months prior to study entry. All AEs related to prior adjuvant or neoadjuvant therapy must have returned to baseline, and eligible patients must not have experienced severe or life-threatening immune-related AEs except those that are unlikely to reoccur with standard countermeasures (e.g., hormone replacement after adrenal crisis).

c) Measurable disease lesion by CT or MRI per RECIST 1.1 criteria. Radiated lesions cannot be used as measurable lesions unless there is clear evidence of progression.

d) KPS of at least 70% (see Appendix 7).

e) Qualifies as intermediate or poor risk by meeting least 1 of the following prognostic factors as per the IMDC criteria:

i) KPS less than 80

ii) Less than 1 year from diagnosis including original localized disease (if applicable) to study enrollment

iii) Hemoglobin less than the lower limit of normal

iv) Corrected calcium concentration greater than 10 mg/dL

v) Absolute neutrophil count greater than the ULN

vi) Platelet count greater than the ULN

3) Age and Reproductive Status

a) Male and female participants must be 18 years or older at the time of informed consent (ICF)

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study treatment.

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of study treatment plus 5 half-lives of study treatment plus 30 days (duration of ovulatory cycle) for a total of 5 months after the last dose of study treatment.

e) ***No Longer Applicable per Protocol Amendment 01:*** Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (Appendix 4) for the duration of treatment with nivolumab and ipilimumab plus 7 months after the last dose of study treatment. In addition, male participants must be willing to refrain from sperm donation during this time.

f) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

g) ***No Longer Applicable per Protocol Amendment 01:*** Azoospermic males are exempt from contraceptive requirements unless the potential exists for fetal toxicity due to study drug being present in seminal fluid, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

Investigators will counsel WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy and when applicable, the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant. Investigators will advise on the use of highly effective methods of contraception (Appendix 4) that have a failure rate of < 1% when used consistently and correctly.

4) Other Inclusion Criteria

a) Indian participants with Indian ethnicity living in India.

[redacted]

6.2 Exclusion Criteria

1) Medical History and Concurrent Diseases

a) Favorable risk as per IMDC classification defined as having none of the 6 risk factors used to evaluate IMDC risk score.

b) Untreated, symptomatic central nervous system (CNS) metastases. Patients are eligible if CNS metastases are asymptomatic and do not require immediate treatment, or have been treated and patients have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, patients must have been either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to enrollment.

c) Participants with an autoimmune disease, or any other condition, requiring systemic treatment with either corticosteroids within 14 days (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

d) Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

e) Patients with serious or uncontrolled medical disorder. Previous SARS-CoV-2 infection (either suspected or confirmed) within 4 weeks prior to screening. Additionally, in the case of prior SARS-CoV-2 infection, acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

f) Active infection requiring systemic therapy within 14 days of first dose of study drug.

g) Patients with known human immunodeficiency virus (HIV) who have had an acquired immunodeficiency syndrome (AIDS) defining opportunistic infection within the last year, or a current CD4 count < 350 cells/µL. NOTE: Testing for HIV must be performed at sites where mandated locally (see Appendix 8). Patients enrolled with known HIV need monitoring of CD4 counts and viral load during the study and ART therapy administered as clinically indicated.

h) Major surgery (e.g., nephrectomy) less than 28 days prior to the first dose of study treatment.

i) Radiotherapy within 4 weeks except palliative radiation to bone lesions which requires 2 weeks of washout prior to the first dose of study treatment.

j) Patients with a concurrent malignancy requiring treatment. Patient with a previously treated malignancy are eligible if treatment was completed at least 2 years before registration and the patient has no evidence of disease. Patients who have a concurrent malignancy that is clinically stable and does not require tumor-directed treatment are also eligible.

k) Presence of any toxicities attributed to prior anti-cancer therapy, other than alopecia, that have not resolved to Grade 1 (National Cancer Institute [NCI] CTCAE v4.0) or baseline before administration of study treatment.

l) Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study treatment administration or interfere with the interpretation of safety results (e.g., a condition associated with diarrhea or acute diverticulitis).

m) Women who are pregnant or breastfeeding.

2) Prior/Concomitant Therapy

a) Use of an investigational agent or an investigational device within 28 days before administration of first dose of study treatment

b) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

c) Prior treatment with a VEGF-targeted agent except when used as a neoadjuvant or adjuvant therapy and discontinued ≥ 6 months prior to study entry.

d) Treatment with botanical preparations (e.g., herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to treatment. Refer to Section 7.7.1 for prohibited therapies.

e) Participants who have received a live/attenuated vaccine within 30 days of first treatment.

f) The use of inactivated seasonal influenza vaccines (e.g., Fluzone®) will be permitted on study without restriction.

g) Participants currently in other interventional trials, including those for COVID-19, may not participate in BMS clinical trials until the protocol-specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the Investigator and the Medical Monitor.

3) Physical and Laboratory Test Findings

a) White blood cells < $2000/mm^3$

b) Neutrophils < $1500/mm^3$

c) Platelets < $100 \times 10^3/mm^3$

d) Hemoglobin < 9.0 g/dL

e) Serum creatinine > 1.5× ULN, unless calculated creatinine clearance (CrCl) ≥ 40 mL/min (using the Cockcroft-Gault formula):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

f) AST/ALT: > 3.0× ULN

g) Tbili > 1.5× ULN (except participants with Gilbert Syndrome who must have a Tbili level of < 3.0× ULN)

h) Serologic evidence of chronic hepatitis B virus (HBV) infection with an HBV viral load above the limit of quantification. Patients with chronic HBV infection must be on concurrent viral suppressive therapy.

i) Serologic evidence of current hepatitis C virus (HCV) infection with an HCV viral load above the limit of quantification.

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components.

b) Known history of severe hypersensitivity reaction to any monoclonal antibody.

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required).

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs.

6.4.1 Retesting During Screening or Lead-in Period

Participant Re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pre-treatment failure (ie, participant has not been enrolled / has not been treated). If re-enrolled, the participant must be re-consented and assigned a new participant number in the IRT.

Retesting of laboratory parameters and/or other assessments within any single screening or lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to enrollment is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in the Schedule of Activities in Section 2 may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Testing for asymptomatic SARS-CoV-2 infection, for example by reverse transcription polymerase chain reaction (RT-PCR) or viral antigen is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection, or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR of viral antigen test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (e.g. cough, shortness of breath) have resolved and
- In the opinion of the investigator, there are no COVID-19-related sequelae that may place the participant at a higher risk of receiving investigational treatment, and
- Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local or regional guidelines.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device intended to be administered to a study participant according to the study treatment allocation.

Study treatment includes both investigational product (IP)/investigational medicinal product (IMP) and non-IP/non-IMP and can consist of the following:

- Nivolumab concentrate for solution for infusion
- Ipilimumab concentrate for solution for infusion

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IPs.

Medications used to treat BMS-936558 (nivolumab)- and BMS-734016 (ipilimumab)-related infusion reactions are (eg, diphenhydramine, acetaminophen/paracetamol, and corticosteroids) considered non-IPs and will not be provided by the sponsor. These will be obtained by the investigational sites as marketed product, which should be stored in accordance to the package insert. For further details related to these medications and nivolumab-related infusion reactions, see Section 7.4.3.1.

Study treatments are listed in Table 7-1.

Table 7-1: Study Treatments for Study CA2097C9

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Solution for infusion[a,b]	100 mg (10 mg/mL concentrate)	IP	Open label	Vial (1 or more vials per carton)	Store at 2°C to 8°C Protect from light and freezing
Ipilimumab Solution for infusion[b]	50 mg (5 mg/mL concentrate)	IP	Open label	Vial (1 or more vials per carton)	Store at 2°C to 8°C Protect from light and freezing

Abbreviations: IP = investigational product; IMP = investigational medicinal product; SmPC = summary of product characteristics

[a] May be labeled as "BMS-936558-01" or "nivolumab."

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or SmPC.

7.1 Treatments Administered

Participants will receive a combination dosing regimen of nivolumab 3 mg/kg as a 30-minute IV infusion + ipilimumab 1 mg/kg as a 30-minute IV infusion Q3W followed by a single-dose agent of nivolumab 3 mg/kg Q2W for a maximum of 52 weeks or until treatment is no longer tolerated by the participant or withdrawal of consent. The first dose is to be administered within 28 days after signing the ICF. Subjects may be dosed up to 3 days after the scheduled date if necessary.

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

There will be no dose escalations or reductions of nivolumab allowed.

During the combination phase, participants may be dosed no less than 19 days between doses during Q3W cycles. During the single agent-maintenance phase, subjects may be dosed no less than 12 days from the previous dose during Q2W cycles.

If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab should be resumed on the same day.

Subjects may be dosed up to 3 days after the scheduled date if necessary. Subsequent dosing should be based on the actual date of administration of the previous dose of drug.

Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during study treatment administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.3.1.

Study treatments may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Please refer to the current India prescribing information (Appendix 5) for further details regarding storage, preparation, and administration of nivolumab and/or ipilimumab.

Separate infusion bags and filters should be used when administering nivolumab and ipilimumab on the same day.

Care must be taken to assure sterility of the prepared solutions, as the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

The selection and timing of dose for each participant are described in Table 7.1-1.

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
Nivolumab	3 mg/kg	Q3W (Cycles 1 to 4) Q2W (Cycle 5 onward)	IV
Ipilimumab	1 mg/kg	Q3W (Cycles 1 to 4)	IV

Abbreviations: IV = intravenous; Q2W = every 2 weeks; Q3W = every 3 weeks

7.2 Method of Treatment Assignment

An IRT will be used to assign participant numbers.

All participants will be centrally assigned to treatment using the IRT system. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities in Section 2.

Enrolled participants, including those not dosed, will be assigned sequential participant numbers [redacted]. Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dosage Modification Criteria for Nivolumab and Ipilimumab

I-O agents are associated with AEs that can differ in type, severity, and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered I-O agents in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity. The safety profile of nivolumab and in combination of ipilimumab is described in the India prescribing information for nivolumab and ipilimumab. Management of drug-related AE includes dose modification and medical interventions, and supportive care should be carefully considered. The recommended management algorithms for IMAEs are outlined in the India prescribing information (Appendix 5) in the following groups: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathy, Skin, Neurological, and Myocarditis. In general, both nivolumab and ipilimumab have similar safety profiles and overlapping IMAEs. The management algorithms and criteria for dose delay, resumption, or discontinuation should be applicable for both drugs. Both drugs should be delayed, resumed, or discontinued when the criteria are met.

Dose reductions or dose increases of nivolumab or ipilimumab are not permitted.

7.4.1 Dose Delay Criteria for Nivolumab and Ipilimumab

Nivolumab and ipilimumab administration should be delayed for the following:

- Grade 2 nonskin, drug-related AE, with the exception of fatigue

- Grade 2 drug-related creatinine, AST, ALT and/or TBili abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, and TBili will require dose discontinuation (see Section 7.4.3)
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication.
- SARS-CoV-2 infection, either confirmed or suspected

During Cycles 1 through 4, both nivolumab and ipilimumab must be delayed at the same time.

Participants who require delay of study treatment should be re-evaluated weekly or more frequently if clinically indicated and resume study treatment dosing when re-treatment criteria are met. Tumor assessments should continue as per protocol even if dosing is delayed.

The algorithms recommended for utilization in CA2097C9 are included in the India prescribing information in Appendix 5.

7.4.2 Criteria to Resume Treatment

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks for nivolumab and > 8 weeks for ipilimumab, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Delayed doses of study treatment should be administered as soon as the participant meets criteria to resume treatment. If a dose has been delayed, the participant should not wait until the next scheduled dosing date.

Participants may resume treatment with study treatment when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or Tbili abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a

steroid taper over at least 1 month may be eligible for re-treatment if discussed with and approved by the BMS Medical Monitor (or designee).

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee).

Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after **all of the following:**

- at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (e.g. RT-PCR or viral antigen),
- resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications),
- evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, **and**
- consultation by the medical monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

7.4.3 Criteria for Treatment Discontinuation

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

Please refer to Section 7.4.3.1 for discontinuation criteria for nivolumab and Section 7.4.3.1 for discontinuation criteria for ipilimumab.

7.4.3.1 Nivolumab Dose Discontinuation

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

- Any Grade 3 non-skin, drug-related AE lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement, do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT or Tbili requires discontinuation*
      - Concurrent AST or ALT > 3 x ULN and Tbili > 2 x ULN

      *In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor (or designee) must occur.
- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Tbili), except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 10 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

- Any AE, laboratory abnormality, or intercurrent illness, which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q3W during induction, Q2W during maintenance, or more frequently if clinically indicated during such dosing delays.

7.4.3.2 Ipilimumab Dose Discontinuation

Ipilimumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, or recurs, with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug related LFT abnormality that meets the following criteria requires discontinuation:
      - Grade ≥ 3 drug-related AST, ALT, or TBili requires discontinuation*
      - Concurrent AST or ALT > 3 x ULN and TBili > 2 x ULN

        *In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor (or designee) must occur.

- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, and TBili), except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as hyper- or hypothyroidism or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (eg, corticosteroids, thyroid hormones) or glucose- controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor (or designee).
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug- related reasons may be allowed if approved by the BMS Medical Monitor (or designee).
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued ipilimumab dosing.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor (or designee) must be consulted. Tumor and other assessments should continue per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q3W during induction, Q2W during maintenance, or more frequently if clinically indicated during such dosing delays.

7.4.4 Treatment of Related Infusion Reactions

Because nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension or hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Medical Monitor, or designee, and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE 4.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated).

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms (therapy or infusion interruption indicated but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab and/or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms (severe reaction, Grade 3: Prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion], recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; pressor or ventilatory support indicated).

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline, and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

7.5 Preparation/Handling/Storage/Accountability

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and BMS should be contacted immediately.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration, and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents and administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, and 0.9% sodium chloride solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the India prescribing information (Appendix 5) for nivolumab or ipilimumab for complete storage, handling, dispensing, and infusion information.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Treatment Compliance

Not applicable because treatment is injected and/or infused.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.4.3.1)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of RCC)

- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are allowed if they are used as supportive care.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella) during treatment and until 100 days after the last dose.

Antiemetic premedications should not be routinely administered prior to dosing of drugs. See Section 7.4.3.1 for premedication recommendations following a nivolumab- or ipilimumab-related infusion reaction.

7.7.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids within 14 days (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 30 days of treatment initiation are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted, if the following criteria are met:

- The subject will be considered to have progressed at the time of palliative therapy and must meet criteria to continue with treatment beyond progression (Section 8.1.1).
- The case is discussed with the BMS Medical Monitor or Study Director.

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, eGFR < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis, therefore MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image manual.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and standards set by the local ethics committee.

7.7.3 Permitted Therapy

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions or over the counter

medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

7.8 Post Study Drug Access

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study treatment at the duration specified in Section 7.1. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. In this study, participants who are observed to continue to receive clinical benefit from treatment with nivolumab at the end of 52 weeks plus 2 weeks of follow-up, may continue treatment via commercial supply, with nivolumab supplied by BMS.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of the treatment regimen is terminated for other reasons, including, but not limited to, lack of effectiveness and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

Please refer to Section 7.4.3 for discontinuation criteria for nivolumab and ipilimumab.

Participants MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant’s request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

- Any clinical AE, laboratory abnormality, or intercurrent illness, which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration or compulsory detainment for treatment of either a psychiatric or physical illness (eg, infectious disease). (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
  - Criteria listed in Section 7.4.2
- Disease progression of RCC or occurrence of a secondary malignancy that requires systemic therapy for treatment.
- Additional criteria for the discontinuation of nivolumab and ipilimumab as recommended in the India prescribing information for nivolumab and ipilimumab (Appendix 5).

Refer to the Schedule of Activities in Section 2 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy in a participant, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor (or designee) of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor (or designee) must occur. Refer to Section 9.2.5.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely through imprisonment or involuntarily incarceration or compulsory detainment for the treatment of either a psychiatric or physical illness.

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate CRF page.

8.1.1 Nivolumab Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.[29]

Participants will be permitted to continue study treatment beyond initial RECIST 1.1-defined (Appendix 9) progressive disease, assessed by the Investigator up to a maximum of 52 weeks from date of first dose in Cycle 1 as long as they meet the following criteria:

- Investigator-assessed clinical benefit.

- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to Section 2. Radiographic assessment/scan(s) should continue in accordance with the Schedule of Activities in Section 2 for the duration of the treatment beyond progression and until a maximum of 52 weeks of treatment plus 2 weeks of follow-up or initiation of subsequent systemic cancer therapy, withdrawal of consent, death, or investigator-assessed disease progression, whichever occurs first. Radiographic assessment/scan(s) should be submitted to the central imaging vendor. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

For the participants who continue nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5-mm absolute increase from time of initial progressive disease. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial progressive disease. It is recommended that study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions that become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.2 Post-study Treatment Study Follow-up

In this study, incidence of high-grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 8 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated participants outside of the protocol-defined window (see the Schedule of Activities in Section 2). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Loss to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails, as well as lack of response by participant to 1 registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local laboratories until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (hypoxia or fever) or symptoms (eg, dyspnea, cough, or fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the India prescribing information for nivolumab and ipilimumab (Appendix 5).

Some of the assessments referred to in this section may not be captured as data in the electronic case report form (eCRF). They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Effectiveness Assessments

Study evaluations will take place in accordance with the Schedule of Activities (Section 2). Baseline assessments should be performed within 28 days prior to the patient receiving the first dose, utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subjects who cannot receive IV contrast at the start of study should be imaged by MRI of abdomen/pelvis with IV contrast and CT of chest without contrast. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Patients initially imaged with CT of chest, abdomen, and pelvis with IV contrast who can no longer receive contrast can be

monitored by CT of chest, abdomen, and pelvis without IV contrast. Subjects will be evaluated for tumor response beginning 12 weeks (±7 days) from dosing and continuing every 8 weeks (±7 days) until a maximum of 52 weeks of treatment plus 2 weeks of follow-up or initiation of subsequent systemic cancer therapy, withdrawal of consent, death, or investigator-assessed disease progression, whichever occurs first. These time points are independent of dosing. Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST 1.1 criteria.

9.1.1 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor and may undergo BICR at any time during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the Imaging Manual provided by the central imaging vendor.

Screening and on-study images should be acquired as outlined in the Schedule of Activities (Section 2).

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) should be collected for tumor assessment and submitted to the BICR. Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to the central imaging vendor. X-rays and bone scans that clearly demonstrate interval progressive disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to the central imaging vendor. Otherwise, they do not need to be submitted centrally.

Consider including brain imaging at baseline if the disease under study is known for developing brain metastasis.

9.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments within 28 days prior to first dose. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment, whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the same investigator, if possible, using the RECIST 1.1 criteria.

If a participant has a contraindication for CT IV contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for both MRI and CT IV contrasts, then a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT IV contrast, then a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of the CT component of a positron-emission tomography (PET)-CT scanner: Combined modality scanning, such as with PET-CT, is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low-dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically based RECIST 1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST 1.1 measurements. Note, however, that the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

Bone scans or PET scans are not adequate for the assessment RECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole method used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Bone scans may be collected per local standards, as clinically indicated.

MRI of the brain (without and with contrast) should be acquired as outlined in the Schedule of Activities in Section 2. CT of the brain (without and with contrast) can be performed if an MRI is contraindicated.

Imaging and Clinical Assessment

Tumor assessments should continue, as described in Section 2, even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator using the RECIST 1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment using the RECIST 1.1 criteria (see Appendix 9) for specifics on RECIST 1.1 criteria to be used in this study. Assessments of PR and CR must be confirmed by CT/MRI at least 4 weeks apart after initial documentation of response. A best overall response of stable disease requires a minimum of 56 days on study from the date of the first dose to the date of the first imaging assessment.

9.1.2 Outcomes Research Assessments

9.1.2.1 Patient-reported Outcomes

The evaluation of PROs is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting.

Participants will be asked to complete the NCCN Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI-19) in the participant's preferred language when available. Participants will complete the FKSI-19 at the site during dosing visits and through the follow-up visits.

The NCCN FKSI-19 is a 19-item scale that measures tumor-specific HrQoL in participants with kidney cancer. The symptom index questionnaire includes 3 subscales: disease-related symptoms, treatment side effects (TSE), and general function and well-being (FWB). The FKSI-19 uses 5 Likert-type response categories that range from "not at all" to "very much." Participants are asked to select the response category that best characterizes their response over the last 7 days on 19 items that include symptoms such as lack of energy, fatigue, appetite, coughing, shortness of breath, pain, nausea, and ability to work.

If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with the Sponsor or the Sponsor's representative.

9.1.2.2 Healthcare Resource Utilization

Healthcare resource utilization data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

All nonserious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

Every AE must be assessed by the investigator with regard to whether it is considered immune mediated. For events that are potentially immune mediated, additional information will be collected on the participant's CRF.

Contacts for SAE reporting are specified in Appendix 3.

IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology, which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's CRF.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of AE information (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study treatment until the follow-up contact, at the time points specified in the Schedule of Activities.

The India prescribing information for nivolumab and ipilimumab (Appendix 5) includes the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection that occur during the screening period, during treatment, and within 100 days after treatment discontinuation must be collected. If applicable, SAEs that are related to any later protocol-specified procedure (eg, a follow-up skin biopsy) must be collected.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 100 days of discontinuation of dosing For participants enrolled and never treated with study drug, SAEs should be collected for 30 days from the date of enrollment.

For participants enrolled and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.
- All SAEs will be recorded and reported to sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant

has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

Every AE must be assessed by the investigator with regard to whether it is considered immune mediated. For events that are potentially immune-mediated, additional information will be collected on the participant's CRF.

Events with an "Outcome" of death, regardless of the type of event or relationship (ie, including study drug toxicity), are required to be also reported as Grade 5 events following the specifications below:

- Events with an outcome of death should be reported with the grade at presentation.
- No event that was initially reported then later known to have an outcome of death, should have the grade changed to Grade 5.
- A new entry for the same event (PT) should be added as a Grade 5 AE.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment, as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the India prescribing information and will notify the IRB/IEC, if appropriate according to local requirements.

The sponsor or designee will be reporting all SAEs to regulatory authorities and ethics committees according to local applicable laws.

All SAEs that occur during the screening period and during the treatment period and within 100 days after discontinuation of study drug or for a total of 52 weeks and 2 weeks of follow-up from first on-study treatment must be collected, as specified in the study design in Section 5.1.

For participants enrolled and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

All SAEs after 52 weeks of study duration for participants on commercial nivolumab supply will be reported to India Health Authority as part of spontaneous reporting.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor (or designee) of this event and complete and forward a Pregnancy Surveillance Form to the BMS Medical Monitor (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor (or designee) must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/sponsor/IRB/IEC, as applicable.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

In cases where a study drug can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (eg, vaginal, anal, or oral) has occurred between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for the sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or electronic SAE Report Form, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2.7 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

1) Aminotransferases (ALT or AST) elevation > 3× ULN, and
2) Tbili > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), and
3) no other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, X-ray filming, or any other potential safety assessment required or not required by the protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

For this study, an overdose is defined as any treatment administered to a subject that is greater than 125% of the protocol intended dose.

In the event of an overdose the investigator should:

1) Contact the Medical Monitor immediately.
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
3) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4 Clinical Safety

Safety will be assessed from the screening period, during the treatment phase, and, for those participants who discontinue treatment before 52 weeks, during the follow-up period. Safety assessments include physical examination, vital signs, AE/SAE assessments, recording of concomitant medications, and laboratory assessments. For WOCBP, a pregnancy test (serum or urine) is also required 24 hours prior to the first dose and at least monthly during the treatment phase of the study.

Data analyses will be conducted only on the safety data collected within the maximum of the 52-week study period and 2-week follow-up, which will include safety data collected during the follow-up of participants who discontinue treatment before 52 weeks.

All SAEs after 52 weeks of study duration for patients on commercial nivolumab supply will be reported to India Health Authority as part of spontaneous reporting.

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.4.1 Physical Examinations

Refer to the Schedule of Activities.

9.4.2 Vital Signs

Refer to the Schedule of Activities.

9.4.3 Electrocardiograms

Refer to the Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.

- The schedule of laboratory assessment to be conducted at screening, during treatment, and during follow-up for those participants who discontinue treatment before 52 weeks of treatment is presented in the Schedule of Activities. Specific laboratory assessments to be performed throughout the study are listed in Table 9.4.4-1.

Table 9.4.4-1: CA2097C9 - Laboratory Assessments

Hematology - Complete Blood Count (CBC) with Differential	
Hemoglobin Hematocrit Total leukocyte count, including differential Platelet count	
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen or serum urea Glucose	Albumin - screening only Sodium Potassium Chloride Calcium (also Ca corrected at screening) Phosphorus Magnesium TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment
Serology	
Hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) or HCV RNA (screening only) Human immunodeficiency virus (HIV) if mandated locally	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG) Follicle-stimulating hormone screening - only required to confirm menopause in women < 55years of age	

Abbreviations: HCG = human chorionic gonadotropin; IU = international unit; T3 = triiodothyronine, T4 = thyroxine; Tbili = total bilirubin; TSH = thyroid-stimulating hormone, WOCBP = women of childbearing potential

9.4.5 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the investigator as per standard medical/clinical judgment.

9.5 Pharmacokinetics

Samples for PK and immunogenicity assessment will be collected for participants at the time points indicated in Table 9.5-1. All on-treatment PK time points are intended to align with days on which study treatment is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample

is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

Serum concentration analyses for nivolumab and ipilimumab will be performed by validated bioanalytical methods. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. See Section 9.7.5 for information regarding immunogenicity information.

Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (eg, insufficient volume for complete assessment, to follow-up on suspected immunogenicity-related AE, etc).

Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including, but not limited to, analysis of drug-antidrug antibody (ADA) immune complexes, metabolite analyses, etc) and or for additional method purposes (including, but not limited to, cross-validation, ADA/PK selectivity, cut point, etc).

Table 9.5-1: Pharmacokinetic (PK) and Immunogenicity Sample Collections

Study Day of Sample Collection[a] 1 cycle = 3 weeks for first 4 cycles and 2 weeks starting at Cycle 5 Day 1	Event Relative To Nivolumab Dosing (Hour)	Time Relative To Nivolumab Dosing (Hour: Min)	Nivolumab Pharmacokinetic Serum Sample	Nivolumab Immunogenicity Serum Sample	Ipilimumab Pharmacokinetic Serum Sample	Ipilimumab Immunogenicity Serum Sample
Cycle 1 Day 1	Predose[b]	00:00	X	X	X	X
	EOI[c]	See Note (c)	X		X	
Cycle 2 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 3 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 4 Day 1	Predose[b]	00:00	X	X	X	X
	EOI[c]	See Note (c)	X		X	
Cycle 5 Day 1 (1st nivolumab Maintenance Dose)	Predose[b]	00:00	X	X	X	X
Every 8 cycles starting at Cycle 13 Day 1 up to 52 weeks	Predose[b]	00:00	X	X	-	-
Follow-up 1: approximately 30 days after last dose			X	X	X[d]	X[d]
Follow-up 2: approximately 100 days after last dose			X	X	X[d]	X[d]

[a] If a subject permanently discontinues study drug treatment during the sampling period, they will move to sampling at the follow-up visits. If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and ADA should be collected only for the next 2 time points (corresponding to nivolumab sample collection) according to the PK table.

[b] Predose: All predose samples for nivolumab and ipilimumab should be taken just before the start of nivolumab infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[c] Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK sample for both nivolumab and ipilimumab when all of the ipilimumab study drug (which is administered after nivolumab) has been infused. If the site

infuses drug without a flush, then collect the EOI-PK samples within approximately 5 minutes after end of infusion of ipilimumab. If a subsequent flush is administered to clear the IV lines of ipilimumab and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. EOI or predose samples may not be collected from the same IV access as the drug was administered

[d] Ipilimumab follow-up samples are only to be collected if a subject discontinues treatment prior to Cycle 7.

9.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7 Pharmacogenomics

Not applicable.

9.7.1 Biomarkers

Table 9.7.1-1: Biomarker Samples and Schedule of Collection

Study Day of Sample Collection 1 cycle = 3 weeks for first 4 cycles and 2 weeks starting at Cycle 5 Day 1	**SARS-CoV-2 Serology[a]**
Screening	X[b]
[redacted]	
On-Treatment Collections	
Approximately every 6 months (eg, Cycle 11 Day 1, Cycle 23 Day 1, etc.)	X
Approximately 4 weeks after confirmed or suspected SARS-CoV-2 infection	X
[redacted]	
Follow-Up Visit 1	X

Abbreviations: [redacted]; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted]

[redacted]

[b] To be collected at Screening or Predose Cycle 1 Day 1

[redacted]

[redacted]

9.7.3 Exploratory [redacted] Biomarkers

[redacted]

Serum will be collected for potential future measurements of anti-SARS-CoV-2 antibodies by serology (anti-SARS-CoV-2 total or IgG) to explore potential association with safety, effectiveness and/or immune biomarkers.

[redacted]

[redacted]

9.7.5 Immunogenicity Assessments

Blood samples for immunogenicity analysis will be collected according to the schedule given in Section 9.5. Samples collected will be evaluated for development of anti-drug antibody (ADA) by a validated electrochemiluminescent immunoassay. Samples may also be analyzed for neutralizing antibodies, and PK samples may be used for ADA analysis in the event of insufficient volume, to complete immunogenicity assessment, or to follow up on suspected immunogenicity-related AEs.

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size of the study is mainly determined by the feasibility concern. The study plans to treat 100 participants. The summary of 95% exact CIs and the corresponding half widths of the CIs by different levels of the assumed high-grade IMAEs rate (1% to 60%) is presented in Table 10.1-1. The maximum half width of the exact 2-sided 95% CI is 10.2% when the high-grade IMAEs rate is expected to be in the 1% to 60% range. The precision is deemed acceptable in evaluating the research hypotheses with respect to the study of this cohort in terms of high-grade IMAEs rates.

Study CA209214 reports that the combination treatment arm had 45.9% high-grade (CTCAE v4.0 Grades 3 to 4 and Grade 5) drug-related AEs in intermediate or poor risk subjects.

Table 10.1-1: 95% Exact CI and Half Width by Different High-grade IMAEs Rates for 100 Treated Participants

Incidence of High-grade IMAEs (%)	Sample size (n)	Lower bound of 95% CI	Upper bound of 95% CI	Half width of 95% CI
1	100	0.0	5.4	2.7
5	100	1.6	11.3	4.8
10	100	4.9	17.6	6.4
20	100	12.7	29.2	8.3
30	100	21.2	40.0	9.4
40	100	30.3	50.3	10.0
50	100	39.8	60.2	10.2
60	100	49.7	69.7	10.0

Abbreviations: CI = confidence interval; IMAE = immune-mediated adverse event

The total duration of the study from enrollment to final analysis is expected to be 36 months (52 weeks of patients treatment + 24 months for patient accrual), assuming a fixed accrual rate of approximately 5 subjects per month.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All enrolled participants	All participants who sign informed consent and were registered into the IRT.
All treated participants	All participants who received any nivolumab in combination with ipilimumab. This is the primary population for safety and effectiveness analysis, except TTR and DOR endpoints. Analyses of patient-reported outcomes will be based on this population.
All response evaluable participants	All treated participants who have measurable disease at baseline and at least one on-study assessment. TTR and DOR analyses will be based on this population.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will detail the selection of participants to be included in the analyses, and procedures to be used for analysis. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

The study is intended to provide information regarding the safety profile for participants in India and will contribute additional information to the overall safety profile of nivolumab in combination with ipilimumab. Due to the small sample size, this study should not be directly compared to the data from any other country.

Unless specified otherwise, all analyses will be tabulated.

A description of the participant population will be included in a statistical output report, including subgroups of age and gender.

10.3.1 Effectiveness Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable.
Secondary	The ORR is defined as the number of response evaluable subjects whose confirmed best objective (BOR) response is a complete response (CR) or partial response (PR) divided by the number of all response evaluable subjects. Assessments of PR and CR must be confirmed by CT/MRI at least 4 weeks apart after initial documentation of response. The BOR is defined as the best response, as determined per RECIST 1.1. For subjects without document progression or subsequent therapy, all available time point responses will contribute to the BOR determination. Subsequent therapy includes anticancer therapy, tumor directed radiotherapy, or tumor directed surgery. The BOR will be determined based on response designations up to the date of last evaluable tumor assessment prior to initiation of the subsequent therapy. The ORR will be summarized by binomial response rates and their corresponding 2-sided 95% exact CIs using the Clopper-Pearson method. This analysis will be performed for all treated participants. TTR is analyzed for all evaluable participants who achieved a confirmed PR or CR. Time to tumor response, which does not involve censoring, will be summarized using descriptive statistics. The assessed DOR will be summarized for all response-evaluable participants who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with 2-sided 95% CI using Brookmeyer and Crowley method, will also be calculated. In addition, the percentage of responders still in response at different time points (3 and 6 months and at end of study) will be presented based on the DOR KM plot.
Exploratory	PFS will be summarized by KM product-limit method for all treated participants. Median values of PFS, along with 2-sided 95% CI using Brookmeyer and Crowley method, will be calculated. OS will be summarized by KM product-limit method for all treated participants and all response-evaluable participants, respectively. Median values of OS, along with 2-sided 95% CI using Brookmeyer and Crowley method, will be calculated. Survival rates at 6 and 12 months will also be estimated using KM estimates for all treated participants. Associated 2-sided 95% CIs will be calculated using the Greenwood formula. [redacted]

10.3.2 Safety Analyses

Data analyses will be conducted only on the safety data collected within the maximum of the 52 week and 2-week follow-up study period, which will include safety collected during the follow-up of participants who discontinue treatment before 52 weeks.

Immune-mediated Adverse Events

Analyses of IMAEs will be conducted to further characterize AEs of special clinical interest. IMAEs are defined as specific events (or groups of Preferred Terms [PTs] describing specific events) that include diarrhea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, and endocrine (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus).

IMAE analyses includes events, regardless of causality, occurring throughout study and follow-up. These analyses are limited to subjects who received immune-modulating medication for treatment of the event, with the exception of endocrine events (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus), which will be included in the analysis regardless of treatment since these events are often managed without immunosuppression. Specific evaluations for autoimmune endocrinopathies are not required or collected systematically.

Therefore, specific laboratory criteria are not required to meet the case definition of endocrine IMAEs.

All SAEs after 52 weeks of study duration for participants on commercial nivolumab supply will be reported to India Health Authority as part of spontaneous reporting.

Endpoint	Statistical Analysis Methods
Primary	The incidence for high grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs will be summarized by immune-mediated category.
Secondary	Additional descriptive statistics of high grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs will include median values using the KM product-limit method with 95% CI using Brookmeyer and Crowley method of time to onset and time to resolution, and will be presented for all treated participants by immune-mediated category. Time to onset is calculated from first dosing date to the event onset date. If a participant never experienced the given AE, the participant will be censored at the last contact date. Time to resolution is calculated from the AE onset date to AE end date. If an AE is ongoing at the time of analysis, the time to resolution will be censored at the last contact date. Management of high-grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs for each immune-mediated category will be characterized by measuring the percentage of participants who received immune-modulating medication (or hormonal replacement therapy), percentage of participants who received ≥ 40 mg prednisone equivalents, and total duration of all immune-modulating medications given for the event, in all treated participants who have experienced high-grade (CTCAE v4.0 Grade 3 to 4 and Grade 5) IMAEs.
Exploratory	All safety data will be summarized and listed for all treated participants. All on-study AEs, SAEs, treatment-related AEs, and treatment-related SAEs will be summarized using worst grade per NCI CTCAE v4.0 by system organ class and preferred term. On-study laboratory abnormalities including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

10.3.3 Pharmacokinetic Analysis

The nivolumab and ipilimumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop population PK models.

These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady state peak, trough, and time-averaged concentration). Model-determined exposures may be used for exposure-response analyses of selected effectiveness and safety endpoints. If the analyses are conducted, the results of population PK and exposure response analyses will be reported separately.

10.3.4 Immunogenicity Analysis

Methodology for analysis of immunogenicity will be described in the statistical analysis plan.

10.3.5 Biomarker Analyses

[redacted]

PK and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and biomarker analyses will be presented separately from the main clinical study report.

10.3.6 Health Outcomes Assessment Analyses

PRO measures include FKSI-19. Summary statistics for PRO measures at each assessment point will be provided. The mean change from baseline will also be reported at each post-baseline assessment point as well as completion rates.

Clinically meaningful score changes (from baseline) reported in the literature are used to define improvement and deterioration. Table 10.3.6-1 provides the thresholds for clinically meaningful score changes to be used for the PRO scales in this study. For domains without clinically meaningful score changes in the literature, threshold values will be derived using the general guide for calculating thresholds for FACIT instruments provided by Yost and Eton (2005).[30]

Table 10.3.6-1: Threshold Values for Change Scores Judged to Be Important to Participants

Instruments and Domains	Thresholds Reported in the Literature
FKSI-19	
Total Score	--
Disease Related Symptoms Score	2-3[31,32]
Disease Related Symptoms Emotional Score	--
Disease Related Symptoms Physical Score	--
Functional Well Being Score	--
Treatment Side Effects Score	--

10.3.7 Interim Analyses

Not applicable.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L RCC	first-line renal cell carcinoma
2L RCC	second-line renal cell carcinoma
ADA	antidrug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CL	clearance
CrCl	creatinine clearance
CLss	steady-state clearance
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CNS	central nervous system
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen 4
CV%	percent coefficient of variation
dMMR	mismatch repair deficient
DOR	duration of response
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate

Term	Definition
EU	European Union
[redacted]	[redacted]
FKSI-19	Funtional Assesment of Cancer Therapy - Kidney Symptom Index
HBV	hepatitis B virus
HBVsAg	hepatitis B virus surface antigen
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIFα	hypoxia inducible factor alpha
HIV	human immunodeficiency virus
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
ICF	informed consent form
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IMAE	immune-mediated adverse event
IMDC	International Metastatic RCC Database Consortium
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
IRRC	Independent Radiology Review Committee
IRT	Interactive Response Technology
IU	international unit
IV	intravenous(ly)
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network

Term	Definition
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	respiratory rate
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
Tbili	total bilirubin
TSH	thyroid-stimulating hormone
TTR	time to response
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERANCE CONSIDERATIONS

The term "Participant" is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term "Subject" used in the electronic case report form (eCRF) is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council f or Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee immediately. A breach of the conditions and principles of Good Clinical Practice (GCP) (occurring in any country) in connection with that trial or the protocol related to the trial which is likely to affect to a significant degree the safety or physical or mental integrity of 1 or more subjects of the trial or the scientific value of the trial.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator's Brochure or product labeling information to be provided to subjects and any updates.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted, as soon as possible, to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered

electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records.

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments nivolumab or ipilimumab (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If...	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

CLINICAL STUDY REPORT AND PUBLICATIONS

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): **Refer to Contact Information list**

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*****

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

*** Local laws and regulations may require use of alternative and/or additional contraception methods.**

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix 3, Adverse Events and Serious Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting.

APPENDIX 5 INDIA PRESCRIBING INFORMATION FOR NIVOLUMAB AND IPILIMUMAB

APPENDIX 5-1 NIVOLUMAB INDIA PRESCRIBING INFORMATION

To be sold by retail on the prescription of a 'Registered Oncologist' only.

Bristol Myers Squibb™

Nivolumab
OPDYTA®

1 GENERIC NAME

Nivolumab 10 mg/mL concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nivolumab is a fully human anti-PD-1 monoclonal antibody (IgG4) produced in Chinese hamster ovary cells by recombinant DNA technology.

Each 1 mL of concentrate contains 10 mg of nivolumab.

For the full list of excipients, see Section 7. Description

3 DOSAGE FORM AND STRENGTH

Nivolumab is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid for intravenous infusion that may contain light (few) particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg.

Concentrate for solution for infusion

Injection: 40 mg/4 mL,100 mg/10 mL and 240 mg/24 mL solution in a single-dose vial.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

4.1.1 Non-Small Cell Lung Cancer (NSCLC)

Nivolumab as a single agent is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

Nivolumab, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by a validated test, with no EGFR or ALK genomic tumor aberrations.

Nivolumab, 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 non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

4.1.2 Renal cell carcinoma (RCC)

Nivolumab as a single agent is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) after prior therapy in adults.

Nivolumab is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab.

4.1.3 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Nivolumab as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based therapy.

4.1.4 Melanoma

Nivolumab as a single agent is indicated for the treatment of patients with BRAF V600 wildtype unresectable or metastatic melanoma.

Nivolumab as a single agent is indicated for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma.

Nivolumab is indicated for the treatment of patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant settings.

4.1.5 Classical Hodgkin Lymphoma (cHL)

Nivolumab 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

4.1.6 Urothelial Carcinoma (UC)

Nivolumab is indicated for the treatment of 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.

4.1.7 Colorectal Cancer (CRC)

Nivolumab as montherapy is indicated for the treatment 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

4.1.8 Esophageal Squamous Cell Carcinoma (ESCC)

Nivolumab is indicated for the treatment of patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

4.1.9 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma (GC, GEJC or EAC)

Nivolumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

4.1.10 Adjuvant treatment of Resected Esophageal or Gastroesophageal Junction Cancer (EC or GEJC)

Nivolumab is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy (CRT).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

4.2.1 Recommended dosage

The recommended doses of nivolumab as a single agent are presented in Table 1.

Table 1: Recommended doses for nivolumab as monotherapy (NSCLC, RCC, SCCHN, melanoma, cHL, UC, CRC, ESCC, EC and GEJC)

Indication^	Recommended Nivolumab Dosage	Duration of Therapy
Locally advanced or metastatic squamous non-small cell lung cancer	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated.
Advanced renal cell carcinoma		
Recurrent or metastatic squamous cell carcinoma of the head and neck		
Unresectable or metastatic melanoma		
Relapsed/refractory classical Hodgkin lymphoma		
Unresectable or metastatic urothelial carcinoma		
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer		
Esophageal Squamous Cell Carcinoma		
Adjuvant treatment of melanoma	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated. For adjuvant treatment, the maximum duration of nivolumab is 1 year.
Adjuvant treatment of resected esophageal or gastro- esophageal junction cancer		

^ As per monotherapy indications in Section 4.1 Therapeutic Indications.

Please see section 8.4 Storage and handling instructions regarding limitation of total infusion volume with the 240-mg or 480-mg dosage.

The recommended doses of nivolumab in combination with other therapeutic agents are presented in Table 2. Refer to the respective Product Information for each therapeutic agent administered in combination with nivolumab for the recommended dose information, as appropriate.

Table 2: Recommended Doses of Nivolumab in Combination with Other Therapeutic Agents

Indication^	Recommended Nivolumab Dosage	Duration of Therapy
Metastatic non- small cell lung cancer expressing PD-L1	3 mg/kg every 2 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion)	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 (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) and platinum chemotherapy every 3 weeks	After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab administered as an intravenous infusion every 3 weeks in combination with 1 mg/kg ipilimumab every 6 weeks until disease progression, is no longer tolerated, or up to 2 years in patients without disease progression.
Advanced renal cell carcinoma	3 mg/kg every 3 weeks (30-minute intravenous infusion) Administer nivolumab in combination with ipilimumab 1 mg/kg (30-minute intravenous infusion)	In combination with ipilimumab for 4 doses
	3 mg/kg every 2 weeks* (30-minute intravenous infusion) or 240 mg every 2 weeks* (30-minute intravenous infusion) or 480 mg every 4 weeks* (30-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.
Gastric cancer, Gastro-esophageal junction cancer, or Esophageal adenocarcinoma	360 mg every 3 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks or 240 mg every 2 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks	Treatment should be continued until disease progression, is no longer tolerated or up to 2 years in patients without disease progression.

* Following the last dose of the combination of nivolumab and ipilimumab, the first dose of nivolumab monotherapy should be administered after 3 weeks when using 3 mg/kg or 240 mg or 6 weeks when using 480 mg

^ As per combination indications in Section 4.1 Therapeutic Indications.

For all combination therapy

When administered in combination with ipilimumab, with ipilimumab and chemotherapy, or with other therapeutic agents, nivolumab should be given first followed by ipilimumab (if applicable) and then chemotherapy or other therapeutic agents on the same day (see 8.4 Storage and handling instructions).

Dose escalation or reduction is not recommended. 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 3. Detailed guidelines for the management of immune-related adverse reactions are described in 4.4.2 Product-specific warnings and precautions.

Table 3: Recommended treatment modifications for nivolumab or nivolumab in combination with ipilimumab

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 diarrhea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete.
	Grade 3 diarrhea or colitis - nivolumab monotherapy	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete.
	- nivolumab+ipilimumab	Permanently discontinue treatment.
	Grade 4 diarrhea or colitis	Permanently discontinue treatment.
Immune-related hepatitis	*Patients with normal AST/ALT/bilirubin at baseline* 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.

Table 3: Recommended treatment modifications for nivolumab or nivolumab in combination with ipilimumab

	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.
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 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.
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s)
	Grade 4 rash Confirmed SJS/TEN	Permanently discontinue treatment.
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete. Retreatment may be considered after recovery.
	Grade 3 or 4 myocarditis	Permanently discontinue treatment.
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s) until symptoms resolve or improve and management with corticosteroids is complete.

Table 3: Recommended treatment modifications for nivolumab or nivolumab in combination with ipilimumab

	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).

Nivolumab or nivolumab in combination with ipilimumab should be permanently discontinued for:

- Grade 4 or recurrent Grade 3 adverse reactions;
- Persistent Grade 2 or 3 adverse reactions despite management.

When nivolumab 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 nivolumab monotherapy could be resumed based on the evaluation of the individual patient.

Nivolumab in combination with chemotherapy

For GC, GEJC or EAC patients treated with nivolumab in combination with chemotherapy, refer to the product information for 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, or nivolumab monotherapy or chemotherapy alone, could be resumed based on the evaluation of the individual patient.

4.2.2 Renal impairment

Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see 5.3.1 Special populations).

4.2.3 Hepatic impairment

Based on the population PK results, no dose adjustment is required in patients with mild or moderate hepatic impairment (see 5.3.1 Special populations).

4.2.4 Geriatric

No dose adjustment is required for elderly patients (≥65 years) (see 4.4.6 Geriatric use and 5.3.1 Special populations).

4.3 CONTRAINDICATIONS

None.

4.4 Special WARNINGS AND PRECAUTIONS for use

When nivolumab is administered in combination with ipilimumab, refer to the product information for ipilimumab prior to initiation of treatment. Both agents are associated with immune-related adverse reactions. In clinical trials, immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications.

When an immune-related adverse reaction is suspected, alternate etiology should be ruled out and use of immunosuppressive therapy should be considered. Patients should be monitored continuously as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of nivolumab therapy. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1month 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.

4.4.1 Drug-class–specific warnings and precautions

Increased mortality in patients with multiple myeloma [not an approved indication] when a PD-1 blocking antibody 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 nivolumab, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

4.4.2 Product-specific warnings and precautions

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 4.8 Undesirable effects, 4.8.1 Clinical experience). Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (eg, focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Infectious and disease-related etiologies 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 diarrhea or colitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1 Clinical experience). Patients should be monitored for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Infectious and disease-related etiologies should be ruled out. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Stool infections work-up (including CMV, other viral etiology, culture, Clostridium difficile, ova, and parasite) should be performed upon presentation of diarrhea or colitis to exclude infectious or other alternate etiologies.

For Grade 4 diarrhea 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. Grade 3 diarrhea observed with nivolumab in combination with ipilimumab also requires permanent discontinuation of treatment and initiation of corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Nivolumab monotherapy should be withheld for Grade 3 diarrhea 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.

For Grade 2 diarrhea or colitis, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent diarrhea 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.

Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded (including CMV infection/reactivation evaluated with viral PCR on biopsy, and other viral, bacterial, and parasitic etiology).

Immune-related hepatitis

Severe hepatitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1. Clinical experience). Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related etiologies should be ruled out.

For Grade 3 or 4 transaminase or total bilirubin elevation, nivolumab monotherapy 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 monotherapy 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 monotherapy 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 monotherapy 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 nivolumab monotherapy or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1 Clinical experience). Patients should be monitored for signs and symptoms of nephritis and renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related etiologies should be ruled out.

For Grade 4 serum creatinine elevation, nivolumab monotherapy 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 monotherapy 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 monotherapy 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 monotherapy 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 4.8 Undesirable effects, 4.8.1 Clinical experience). Patients should be monitored for clinical signs and symptoms of endocrinopathies and for changes in thyroid function. 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 etiology 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 utilized. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening (Grade 4) 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 utilized.

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 utilized.

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 utilized. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening (Grade 4) diabetes.

Immune-related skin adverse reactions

Severe rash has been observed with nivolumab. The frequency of rash is higher when nivolumab is administered in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1 Clinical experience). 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 Stevens-Johnson syndrome (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 to a specialized unit for assessment and treatment. If the patient has confirmed SJS or TEN, permanent discontinuation of nivolumab or nivolumab in combination with ipilimumab is recommended.

Other immune-related adverse reactions

Other clinically significant immune-related adverse reactions have been observed. Across clinical trials of nivolumab or nivolumab in combination with ipilimumab investigating various doses and tumor types, the following immune-related adverse reactions were reported in less than 1% of patients: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenia gravis, myasthenic syndrome, aseptic meningitis, gastritis, sarcoidosis, duodenitis, encephalitis, myositis, myocarditis and rhabdomyolysis (see 4.8.1 Undesirable effects, Clinical experience). Cases of Vogt-Koyanagi-Harada syndrome have been reported during post approval use of nivolumab or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.2. Postmarketing experience).

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 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. Some cases of myocarditis can be asymptomatic, so a diagnosis of myocarditis requires a high index of suspicion. Therefore, patients with cardiac or cardio-pulmonary symptoms should undergo a prompt diagnostic workup to evaluate for myocarditis with close monitoring. Troponin is a sensitive but not diagnostic marker of 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 including electrocardiogram, troponin, and echocardiogram should be initiated. Additional testing may be warranted, as guided by the cardiologist, and may include cardiac magnetic resonance imaging. Once a diagnosis is established, nivolumab or nivolumab in combination with ipilimumab should be withheld. For grade 3 myocarditis, nivolumab or nivolumab in combination with ipilimumab therapy should be permanently discontinued (see section 4.2.1 Recommended dosage, Table 1). Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1/PD-L1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. (see 4.8 Undesirable effects, 4.8.2 Postmarketing experience).

Rapid-onset and severe graft-versus-host disease (GVHD), some with fatal outcome, has been reported in the post-marketing setting in patients who had undergone prior allogeneic stem cell transplant and subsequently received PD-1/PD-L1 inhibitors. (see 4.8 Undesirable effects, 4.8.2 Postmarketing experience).

Complications of allogeneic hematopoietic stem cell transplant (HSCT) after treatment with PD-1/PD-L1 inhibitors

PD-1/PD-L1 inhibitors including nivolumab, administered before allogeneic hematopoietic stem cell transplant (HSCT), may be associated with an increased risk of transplant-related complications, including GVHD. Fatal cases have been reported in clinical studies. Patients should be monitored closely for early evidence of transplant-related complications.

Infusion reactions

Severe infusion reactions have been reported in clinical trials of nivolumab or nivolumab in combination with ipilimumab (see 4.8 Undesirable effects, 4.8.1. Clinical experience). 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.

Special populations

In all registrational studies of nivolumab or nivolumab in combination with ipilimumab, patients with autoimmune disease, active brain metastases (or leptomeningeal metastases), Eastern Cooperative Oncology Group (ECOG) performance score >2 or Karnofsky performance score (KPS) <70%, and patients receiving systemic immunosuppressants prior to study entry were excluded. Specific populations excluded from clinical studies by tumor type are listed below (See 4.5 Drug interaction and 5.2.1 Clinical Trial Information):

NSCLC: patients with symptomatic interstitial lung disease

Previously untreated NSCLC: patients with sensitizing EGFR mutations or ALK translocations

RCC: patients with any history of or concurrent brain metastases

SCCHN: patients with carcinoma of the nasopharynx or salivary gland as the primary tumor site

Melanoma: patients with ocular/uveal melanoma

Adjuvant treatment of melanoma: 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 ≥6 months prior to randomization) and 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)

cHL: patients with symptomatic interstitial lung disease

GC or GEJC: patients with diverticulitis, or symptomatic gastrointestinal ulcerative disease or ascites requiring treatment

ESCC: patients with apparent tumor invasion on organs located adjacent to the esophageal disease (eg. the aorta or respiratory tract)

GC, GEJC, or EAC: patients with known human epidermal growth factor receptor 2 (HER2) positive cancer or untreated CNS metastases.

EC or GEJC: Patients who did not receive concurrent chemoradiotherapy (CRT) prior to surgery, without evidence of residual pathologic disease, or with stage IV resectable disease.

4.4.3 Pregnancy and lactation

Refer to section 4.6 -Use in Special Populations (Such as Pregnant Women, Lactating women.)

4.4.4 Labor and delivery

Data not available

4.4.5 Pediatric use

The safety and effectiveness of nivolumab have not been established in pediatric patients.

4.4.6 Geriatric use

No overall differences in safety or efficacy were reported between elderly (≥65 years) and younger patients (<65 years).

4.4.7 Renal impairment

The safety and efficacy of nivolumab have not been studied in patients with severe renal impairment (see 5.3.1 Special Populations, Renal impairment).

4.4.8 Hepatic impairment

The safety and efficacy of nivolumab have not been studied in patients with severe hepatic impairment. Nivolumab must be administered with caution in patients with severe (total bilirubin >3 times ULN and any AST) hepatic impairment (see 5.3.1 Special Populations, Hepatic impairment).

4.5 DRUG INTERACTIONS

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 coadministered 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 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN)

There are no data on the use of nivolumab in pregnant women. Studies in animals have shown embryofetal toxicity (see 6 Nonclinical properties). 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 fetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Women should be advised to use effective contraception for at least 5 months following the last dose of nivolumab.

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 breastfeeding or to discontinue from nivolumab therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND TO USE MACHINES

Based on its pharmacodynamic properties, nivolumab is unlikely to affect the ability to drive and use machines. Because of potential adverse reactions such as fatigue (see 4.8 Undesirable effects, 4.8.1 Clinical experience), 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

4.8.1 Clinical experience

Nivolumab or nivolumab in combination with ipilimumab is associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of nivolumab (see "Description of selected adverse reactions" below).

Nivolumab monotherapy

In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumor types (n=3691), the most frequent adverse reactions (≥10%) were fatigue (26%), rash (16%), diarrhea (13%), pruritus (12%), and nausea (10%).

Adjuvant Treatment of Melanoma

In the dataset of nivolumab 3 mg/kg as monotherapy for the adjuvant treatment of melanoma (n = 452), the most frequent adverse reactions (≥ 10%) were fatigue (46%), rash (29%), diarrhea (24%), pruritus (23%), nausea (15%), arthralgia (13%), neutropenia (12%), musculoskeletal pain

(11%), and hypothyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n=3691are presented in Table 4. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 4: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Infections and infestations	
Common	upper respiratory tract infection
Uncommon	pneumonia,[a] bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Common	neutropenia[f]
Uncommon	Eosinophilia
Immune system disorders	
Common	infusion related reaction,[b] hypersensitivity[b]
Rare	anaphylactic reaction[b]
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism
Uncommon	adrenal insufficiency, hypopituitarism, hypophysitis, diabetes mellitus, diabetic ketoacidosis, thyroiditis
Metabolism and nutrition disorders	
Common	decreased appetite
Uncommon	dehydration, metabolic acidosis
Nervous system disorders	
Common	peripheral neuropathy, headache, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,b]
Eye disorders	
Uncommon	uveitis, blurred vision, dry eye
Cardiac disorders	
Uncommon	tachycardia, atrial fibrillation
Rare	arrhythmia (including ventricular arrhythmia), myocarditis,[a,c]
Vascular disorders	
Uncommon	Hypertension
Rare	Vasculitis

Table 4: Adverse reactions with nivolumab monotherapy

Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis,[a,b] dyspnoea,[a] cough
Uncommon	pleural effusion
Rare	lung infiltration
Gastrointestinal disorders	
Very common	diarrhea, nausea
Common	colitis[a], stomatitis, vomiting, abdominal pain, constipation, dry mouth
Uncommon	pancreatitis, gastritis
Rare	duodenal ulcer
Hepatobiliary disorders	
Uncommon	hepatitis[b]
Skin and subcutaneous tissue disorders	
Very common	rash [d] pruritus
Common	vitiligo, dry skin, erythema, alopecia
Uncommon	erythema multiforme, psoriasis, urticaria
Rare	Rosacea, toxic epidermal necrolysis,[a,c] Stevens-Johnson syndrome[a,c]
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain,[e] arthralgia
Uncommon	polymyalgia rheumatica, arthritis
Rare	myopathy, myositis (including polymyositis),[a,c] rhabdomyolysis,[a,c] Sjogren's syndrome
Common	musculoskeletal pain,[e] arthralgia
Renal and urinary disorders	
Uncommon	tubulointerstitial nephritis, renal failure (including acute kidney injury)[a,b]
General disorders and administration site conditions	
Very common	Fatigue
Common	pyrexia, oedema (including peripheral oedema)
Uncommon	pain, chest pain
Investigations	
Common	weight decreased

[a] Fatal cases have been reported in completed or ongoing clinical studies.

[b] Life-threatening cases have been reported in completed or ongoing clinical studies.

[c] Including those reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

[d] 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 generalized, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption.

[e] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

[f] Frequency reflects the proportion of patients who experienced a worsening from baseline in laboratory measurements.

The overall safety profile of nivolumab 3 mg/kg for the adjuvant treatment of melanoma (n = 452) was generally consistent with that established across tumor types for nivolumab monotherapy.

The overall safety profile of nivolumab 3 mg/kg for the treatment of colorectal cancer (n=74) was generally consistent with that established across tumor types for nivolumab monotherapy.

Nivolumab in combination with ipilimumab

RCC

In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n = 547), with a minimum follow-up of 17.5 months, the most frequent adverse reactions (≥ 10%) were fatigue (48%), rash (34%), pruritus (28%), diarrhea (27%), nausea (20%), hypothyroidism (16%), musculoskeletal pain (15%), arthralgia (14%), decreased appetite (14%), pyrexia (14%), vomiting (11%), and hyperthyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Among the patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in CA209214, 169/547 (31%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 382 patients in this group who continued treatment in the single-agent phase, 144 (38%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase. With a minimum of 60 months follow-up from study CA209214 in RCC, no new safety signals were identified.

NSCLC

In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC (n=576), the most frequent adverse reactions (≥10%) were rash (28%), fatigue (24%), diarrhea (17%), pruritus (14%), decreased appetite (13%), hypothyroidism (13%), and nausea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Median duration of therapy was 4.19 months (95% CI 3.71, 5.09) for nivolumab in combination with ipilimumab and 2.63 months (95% CI 2.56, 2.79) for chemotherapy.

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with nivolumab in combination with ipilimumab (n=547 for RCC regimen and n=576 for NSCLC regimen) are presented in Table 5. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 5: Adverse reactions with nivolumab in combination with ipilimumab

	Nivolumab 3 mg/kg in combination with Ipilimumab 1 mg/kg in RCC**	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC***
Infections and infestations		
Common	pneumonia, upper respiratory tract infection	
Uncommon	bronchitis, aseptic meningitis	pneumonia, bronchitis, upper respiratory tract infection
Blood and lymphatic system disorders		
Uncommon	eosinophilia	eosinophilia
Immune system disorders		
Common	infusion-related reaction, hypersensitivity	infusion-related reaction
Uncommon		hypersensitivity
Endocrine disorders		
Very common	hypothyroidism, hyperthyroidism	hypothyroidism
Common	adrenal insufficiency[b], hypophysitis[b], thyroiditis, diabetes mellitus[b]	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, diabetes mellitus
Uncommon	diabetic ketoacidosis[b], hypopituitarism	Thyroiditis
Metabolism and nutrition disorders		
Very common	decreased appetite	decreased appetite
Common	Dehydration	Dehydration
Uncommon	metabolic acidosis	Hyperglycaemia
Hepatobiliary disorders		
Common	Hepatitis[b]	Hepatitis
Nervous system disorders		
Common	headache, peripheral neuropathy, dizziness	Headache
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis[b]	peripheral neuropathy, dizziness, encephalitis, neuropathy (including facial and abducens nerve paresis), myasthenia gravis
Eye disorders		
Common	blurred vision	
Uncommon	Uveitis	uveitis, blurred vision
Cardiac disorders		

Table 5: Adverse reactions with nivolumab in combination with ipilimumab

	Nivolumab 3 mg/kg in combination with Ipilimumab 1 mg/kg in RCC**	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC***
Common	Tachycardia	
Uncommon	arrhythmia (including ventricular arrhythmia), myocarditis[b]	atrial fibrillation, myocarditis[a,]
Vascular disorders		
Common	Hypertension	
Uncommon		Hypertension
Respiratory, thoracic and mediastinal disorders		
Common	pneumonitis, dyspnoea, pleural effusion, cough	Pneumonitis[a,] , dyspnoea, cough
Uncommon		pleural effusion
Gastrointestinal disorders		
Very common	diarrhea, vomiting, nausea	diarrhea, nausea
Common	colitis, stomatitis, pancreatitis, abdominal pain, constipation, dry mouth	colitis, vomiting, stomatitis, abdominal pain, constipation, dry mouth, pancreatitis
Uncommon	Gastritis	Gastritis
Skin and subcutaneous tissue disorder		
Very common	rash[c], pruritus	Rash[d], pruritus
Common	dry skin, erythema, urticaria	dry skin, erythema
Uncommon	Stevens-Johnson syndrome, vitiligo, erythema multiforme, alopecia, psoriasis	urticaria, erythema multiforme, vitiligo, alopecia
Musculoskeletal and connective tissue disorders		
Very common	musculoskeletal pain[e], arthralgia	
Common	arthritis, muscle spasms, muscular weakness	musculoskeletal pain[e], arthralgia, arthritis
Uncommon	polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis	Polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis
Renal and urinary disorders		
Common	renal failure (including acute kidney injury)[b]	renal failure (including acute kidney injury)
Uncommon	tubulointerstitial nephritis	tubulointerstitial nephritis
General disorders and administration site conditions		

Table 5: Adverse reactions with nivolumab in combination with ipilimumab

	Nivolumab 3 mg/kg in combination with Ipilimumab 1 mg/kg in RCC**	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC***
Very common	fatigue, pyrexia	Fatigue
Common	oedema (including peripheral oedema), pain, chest pain, chills	pyrexia, oedema (including peripheral oedema)
Uncommon		chest pain
Investigations[b]		
Common	weight decreased	weight decreased

** Nivolumab in combination with ipilimumab for the first 4 doses then followed by nivolumab monotherapy in RCC.

*** Nivolumab every 2 weeks in combination with ipilimumab every 6 weeks in NSCLC.

[a] Fatal cases have been reported in completed or ongoing clinical studies.

[b] Life-threatening cases have been reported in completed or ongoing clinical studies.

[c] 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 and pemphigoid.

[d] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

[e] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

Nivolumab in combination with ipilimumab and chemotherapy

NSCLC

In the dataset of nivolumab 360 mg in combination with ipilimumab 1 mg/kg and 2 cycles of chemotherapy in NSCLC (n = 358), the most frequent adverse reactions (≥10%) were fatigue (36%), nausea (26%), rash (25%), diarrhea (20%), pruritus (18%), decreased appetite (16%), hypothyroidism (15%), and vomiting (13%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Median duration of therapy was 6.1 months (95% CI 4.93, 7.06) for nivolumab in combination with ipilimumab and 2.4 months (95% CI 2.30, 2.83) for platinum-based chemotherapy.

Tabulated list of adverse reactions

Adverse reactions reported in the dataset for patients treated with nivolumab in combination with ipilimumab and platinum-based chemotherapy (n = 358) are presented in Table 6. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 6: Adverse reactions with nivolumab in combination with ipilimumab and chemotherapy

Infections and infestations	
Common	conjunctivitis, pneumonia, respiratory tract infection
Blood and lymphatic system disorders	
Common	febrile neutropenia
Uncommon	Eosinophilia
Immune system disorders	
Common	infusion-related reaction, hypersensitivity
Endocrine disorders	
Very common	Hypothyroidism
Common	hyperthyroidism, adrenal insufficiency, hypophysitis, thyroiditis
Uncommon	hypopituitarism, hypoparathyroidism
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration, hypoalbunaemia, hypophosphatemia
Nervous system disorders	
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis
Eye disorders	
Common	dry eye
Uncommon	blurred vision, episcleritis
Cardiac disorders	
Uncommon	tachycardia, atrial fibrillation, bradycardia
Vascular disorders	
Uncommon	Hypertension
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis, dyspnoea, cough
Uncommon	pleural effusion
Gastrointestinal disorders	
Very common	nausea, diarrhea, vomiting

Table 6: Adverse reactions with nivolumab in combination with ipilimumab and chemotherapy

Common	constipation, stomatitis, abdominal pain, colitis, dry mouth, pancreatitis
Hepatobiliary disorders	
Common	Hepatitis
Skin and subcutaneous tissue disorders	
Very common	rash[a], pruritus
Common	alopecia, dry skin, erythema, urticaria
Uncommon	psoriasis, Stevens-Johnson syndrome, vitiligo
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain[b], arthralgia, arthritis
Uncommon	muscular weakness, muscle spasms, polymyalgia rheumatica
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)
Uncommon	Nephritis
General *disorders* and administration site conditions	
Very common	Fatigue
Common	pyrexia, oedema (including peripheral oedema)
Uncommon	chills, chest pain
Investigations	
Common	increased thyroid-stimulating hormone
Uncommon	increased gamma-glutamyl transferase

* Nivolumab every 3 weeks in combination with ipilimumab every 6 weeks and platinum-based chemotherapy every 3 weeks for 2 cycles, then followed by nivolumab every 3 weeks in combination with ipilimumab every 6 weeks in NSCLC.

[a] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash, macular, rash morbilliform, rash papular, rash generalised, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, and drug eruption.

[b] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, and spinal pain

Nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy GC, GEJC, or EAC

In the dataset of nivolumab 240 mg or 360 mg in combination with fluoropyrimidine- and platinum-containing chemotherapy in GC, GEJC, or EAC (n=782), with a minimum follow-up of

12.1 months, the most frequent adverse reactions (≥10%) were peripheral neuropathy (53%), nausea (48%), fatigue (44%), diarrhea (39%), vomiting (31%), decreased appetite (29%), abdominal pain (27%), constipation (25%), musculoskeletal pain (20%), pyrexia (19%), rash (18%), stomatitis (17%), lipase increased (14%), palmar-plantar erythrodysaesthesia syndrome (13%), alkaline phosphatase increased (13%), cough (13%), edema (including peripheral edema) (12%), amylase increased (12%), headache (11%), and upper respiratory tract infection (10%). Median duration of therapy was 6.75 months (95% CI: 6.11, 7.36) for nivolumab in combination with chemotherapy and 4.86 months (95% CI: 4.47, 5.29) for chemotherapy.

Tabulated list of adverse reactions

Adverse reactions reported in the dataset for patients treated with nivolumab 240 mg or 360 mg in combination with fluoropyrimidine- and platinum-containing chemotherapy (n=782) are presented in Table 7. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7: Adverse reactions with nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy

Infections and infestations	
Very common	upper respiratory tract infection
Common	Pneumonia
Blood and lymphatic system disorders	
Common	febrile neutropenia, eosinophilia
Immune system disorders	
Common	hypersensitivity, infusion related reaction
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism
Uncommon	hypopituitarism, adrenal insufficiency, hypophysitis, diabetes mellitus
Metabolism and nutrition disorders	
Very common	decreased appetite
Nervous system disorders	
Very common	peripheral neuropathy, headache
Common	paraesthesia, dizziness
Uncommon	Guillain-Barre syndrome
Eye disorders	
Common	dry eye, blurred vision
Uncommon	Uveitis
Cardiac disorders	
Common	Tachycardia
Uncommon	Myocarditis
Vascular disorders	
Common	thrombosis, hypertension
Respiratory, thoracic and mediastinal disorders	
Very common	cough
Common	pneumonitis, dyspnoea
Gastrointestinal disorders	
Very common	diarrhea, stomatitis, vomiting, nausea, abdominal pain, constipation
Common	colitis, dry mouth
Uncommon	Pancreatitis

Table 7: Adverse reactions with nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy

Hepatobiliary disorders	
Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthesia syndrome, rash[a]
Common	pruritus, skin hyperpigmentation, alopecia, dry skin, erythema
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[b]
Common	arthralgia, muscular weakness
Renal and urinary disorders	
Common	renal failure
Uncommon	Nephritis
General disorders and administration site conditions	
Very common	Fatigue, pyrexia, edema (including peripheral edema)
Investigations	
Very common	increased lipase, increased alkaline phosphatase, increased amylase

[a] Rash is a composite term that includes maculopapular rash, rash erythematous, rash pruritic, rash macular, rash morbilliform, rash papular, rash generalised, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, drug eruption, and exfoliative rash, nodular rash, rash vesicular.

[b] Musculoskeletal pain is a composite term that includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, spinal pain, and musculoskeletal discomfort.

Description of selected adverse reactions - nivolumab monotherapy

Management guidelines for the following immune-related adverse reactions are described in Section (4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Immune-related pneumonitis

In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.5% (131/3691). The majority of cases were Grade 1 or 2 in severity reported in 1.0% (36/3691) and 1.7% (63/3691) of patients, respectively. Grade 3 and 4 cases were reported in 0.8% (29/3691) and <0.1% (1/2950) of patients, respectively. Grade 5 cases were reported in <0.1% (2/ 3691) of patients in these studies.

Median time to onset was 3.3 months (range: 0.2-19.6). Fifty-six patients (1.5%) required permanent discontinuation of nivolumab. Eighty-four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.0 mg/kg (range: 0.5- 25.3) for

a median duration of 3.4 weeks (range: 0.1-13.1). Resolution occurred in 87 patients (66.4%) with a median time to resolution of 6.6 weeks (range: 0.1^{+}-96.7^{+}); ($^{+}$ denotes a censored observation).

Immune-related colitis

In patients treated with nivolumab monotherapy, the incidence of diarrhea, colitis or frequent bowel movements was 12.5% (369/2950). The majority of cases were Grade 1 or 2 in severity reported in 8.0% (236/2950) and 3.0% (88/2950) of patients, respectively. Grade 3 cases were reported in 1.5% (45/2950) of patients. No Grade 4 or 5 cases were reported.

Median time to onset was 1.6 months (range: 1 day-26.6 months). Twenty-six patients (0.7%) required permanent discontinuation of nivolumab. Sixty-two patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.0 mg/kg (range: 0.4-4.7) for a median duration of 2.4 weeks (range: 0.1-30.7). Resolution occurred in 417 patients (87.6 %) with a median time to resolution of 2.7 weeks (range: 0.1-124.4^{+}).

Immune-related hepatitis

In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 6.9% (256/3691). The majority of cases were Grade 1 or 2 in severity reported in 3.8% (139/3691) and 1.4% (53/3691) of patients, respectively. Grade 3 and Grade 4 cases were reported in 1.5% (55/3691) and 0.2% (9/ 3691) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 1.9 months (range: 1 day - 27.6 months). Thirty-one patients (0.8%) required permanent discontinuation of nivolumab. Forty-five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.2 mg/kg (range: 0.4-4.7) for a median duration of 2.8 weeks (range: 0.1-22.1). Resolution occurred in 193 patients (76.6%) with a median time to resolution of 16.1 weeks (range: 0.1- 126.4^{+}).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab monotherapy, the incidence of nephritis and renal dysfunction was 2.2% (82/3691). The majority of cases were Grade 1 or 2 in severity reported in 1.2% (45/3691) and 0.6% (23/3691) of patients, respectively. Grade 3 and 4 cases were reported in 0.4% (13/3691) and <0.1% (1/3691) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported.

Median time to onset was 2.3 months (range: 1 day - 18.2 months). Seven patients (0.3%) required permanent discontinuation of nivolumab. Twenty-one patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.9 mg/kg (range: 0.5-3.6) for a median duration of 2.9 weeks (range: 0.1-67.0). Resolution occurred in 51 patients (65.4%) with a median time to resolution of 9.6 weeks (range: 0.3+-79.1+).

Immune-related endocrinopathies

In patients treated with nivolumab monotherapy, the incidence of thyroid disorders including hypothyroidism or hyperthyroidism was 10.2% (376/3691). The majority of cases were Grade 1 or 2 in severity reported in 4.9% (180/3691) and 5.2% (191/3691) of patients, respectively. Grade 3 thyroid disorders were reported in 0.1% (5/3691) of patients. Hypophysitis (1 Grade 1, 2 Grade

2, 5 Grade 3 and 1 Grade 4), hypopituitarism (5 Grade 2 and 1 Grade 3), adrenal insufficiency including secondary adrenocortical insufficiency (1 Grade 1, 11 Grade 2, and 6 Grade 3), diabetes mellitus (10 cases, including Type 1 diabetes mellitus), and diabetic ketoacidosis (3 Grade 3 and 1 Grade 4) were also reported. Twelve patients experienced a shift from baseline to Grade 3 or 4 hyperglycemia. No Grade 5 endocrinopathies were reported.

Median time to onset of these endocrinopathies was 2.7 months (range: 0.3-29.1). Three patients (0.3%) required permanent discontinuation of nivolumab. Twenty-five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.9 mg/kg (range: 0.4-2.2) for a median duration of 2.0 weeks (range: 0.1-51.1). Resolution occurred in191 patients (46.7%). Time to resolution ranged from 0.4 to 150.0^{+} weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab monotherapy, the incidence of rash was 25.2% (931/3691). The majority of cases were Grade 1 in severity reported in 18.9% (696/3691) of patients. Grade 2 and Grade 3 cases were reported in 5.1% (189/3691) and 1.2% (46/3691) of patients, respectively. No Grade 4 or 5 cases were reported.

Median time to onset was 1.3 months (range: 1 day-27.9 months). Nineteen patients (0.5%) required permanent discontinuation of nivolumab. Thirty-six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.9 mg/kg (range: 0.4-363.6) for a median duration of 1.9 weeks (range: 0.1- 11.9). Resolution occurred in 581 patients (63.1%) with a median time to resolution of 17.7 weeks (range: 0.1- 163.1+).

Infusion reactions

In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions, including anaphylactic reaction, was 3.7% (136/3691), including 6 Grade 3 (0.2%) and 3 Grade 4 (<0.1%) cases. No Grade 5 cases were reported.

Description of selected adverse reactions - nivolumab in combination with ipilimumab

The management guidelines for these adverse reactions are described in section (4.4.2 PRODUCT-SPECIFIC WARNINGS AND PRECAUTIONS).

Immune-related pneumonitis

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of pneumonitis including interstitial lung disease was 6.2% (34/547). Grade 2 and Grade 3 cases were reported in 3.1% (17/547) and 1.1% (6/547) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 2.6 months (range: 0.25-20.6). Resolution occurred in 31 patients (91.2%) with a median time to resolution of 6.1 weeks (range: 0.7-85.9+).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of pneumonitis including interstitial lung disease was 8.0% (48/576). Grade 2, Grade 3, and Grade 4 cases were reported in 4.0% (23/576), 3% (17/576), and 0.3% (2/576) of patients, respectively. Four patients died due to pneumonitis. Median time to onset was 3.6 months (range:

0.9-23.7). Resolution occurred in 41 patients (85.4%) with a median time to resolution of 6.0 weeks (range: 0.7-109.4+).

Immune-related colitis

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of diarrhea or colitis was 28.2% (154/547). Grade 2 and Grade 3 cases were reported in 10.4% (57/547) and 4.9% (27/547) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 1.2 months (range: 0.0-24.7). Resolution occurred in 140 patients (91.5%) with a median time to resolution of 2.4 weeks (range: 0.1-103.1+).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of diarrhea or colitis was 18.2% (105/576). Grade 2, Grade 3 and Grade 4 cases were reported in 7.5% (43/576), 2.1% (12/576) and 0.3% (2/576) of patients, respectively. Median time to onset was 2 months (range: 0.0-22.5). Resolution occurred in 98 patients (94.2%) with a median time to resolution of 2.1 weeks (range: 0.1-149.3+).

Immune-related hepatitis

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of liver function test abnormalities was 18.5% (101/547). Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (26/547), 6.6% (36/547), and 1.6% (9/547) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.0 months (range: 0.4-26.8). Resolution occurred in 86 patients (85.1%) with a median time to resolution of 6.1 weeks (range: 0.1+-82.9+).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of liver function test abnormalities was 15.8% (91/576). Grade 2, Grade 3, and Grade 4 cases were reported in 2.8% (16/576), 7.5% (43/576), and 0.7% (4/576) of patients, respectively. Median time to onset was 2.4 months (range: 0.2-20.3). Resolution occurred in 82 patients (90.1%) with a median time to resolution of 5.3 weeks (range: 0.4-155.1+).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of nephritis or renal dysfunction was 8.8% (48/547). Grade 2, Grade 3, and Grade 4 cases were reported in 4.4% (24/547), 0.7% (4/547), and 0.5% (3/547) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.1 months (range: 0.0-16.1). Resolution occurred in 37 patients (77.1%) with a median time to resolution of 13.2 weeks (range: 0.1+-106.0+).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of nephritis or renal dysfunction was 4.3% (25/576). Grade 2, Grade 3, and Grade 4 cases were reported in 1.4% (8/576), 0.5% (3/576), and 0.2% (1/576) of patients, respectively. Median time to onset was 4.9 months (range: 0.5-21.2). Resolution occurred in 23 patients (92.0%) with a median time to resolution of 2.4 weeks (range: 0.3-152.4+).

Immune-related endocrinopathies

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of thyroid disorders was 27.2% (149/547). Grade 2 and Grade 3 thyroid disorders were reported in 15.7% (86/547) and 1.3% (7/547) of patients, respectively. Hypophysitis occurred in 4.0% (22/547) of patients. Grade 2, Grade 3, and Grade 4 cases were reported in 0.5% (3/547), 2.4% (13/547), and 0.4% (2/547) of patients, respectively. Grade 2 hypopituitarism occurred in 0.4% (2/547) of patients. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 2.9% (16/547), 2.2% (12/547) and 0.4% (2/547) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus (3 Grade 2, 2 Grade 3, and 3 Grade 4), and diabetic ketoacidosis (1 Grade 4) were reported. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 1.9 months (range: 0.0-22.3). Resolution occurred in 76 patients (42.7%). Time to resolution ranged from 0.4 to 130.3+ weeks.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of thyroid disorders was 20.0% (115/576). Grade 2, Grade 3 and Grade 4 thyroid disorders were reported in 10.6% (61/576), 0.3% (2/576) and 0.2% (1/576) of patients, respectively. Hypophysitis occurred in 2.1% (12/576) of patients. Grade 2, Grade 3, and Grade 4 cases were reported in 0.7% (4/576), 0.9% (5/576), and 0.2% (1/576) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (1/576) and 0.5% (3/576) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 1% (6/576) and 1.7% (10/576) of patients, respectively. Diabetes mellitus including, Type 1 diabetes mellitus, occurred in 0.9% (5/576) of patients (1 Grade 2, 3 Grade 3, and 1 Grade 4). Median time to onset of these endocrinopathies was 2.3 months (range: 0.5-16.1). Resolution occurred in 57 patients (41.9%). Time to resolution ranged from 0.7 to 176.6+ weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of rash was 48.8% (267/547). Grade 2 and Grade 3 cases were reported in 13.7% (75/547) and 3.7% (20/547) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 0.9 months (range: 0.0-17.9). Resolution occurred in 192 patients (72.2%) with a median time to resolution of 11.6 weeks (range: 0.1-126.7+).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of rash was 34.0% (196/576). Grade 2 and Grade 3 cases were reported in 10.6% (61/576) and 4.2% (24/576) of patients, respectively. Median time to onset was 1.0 month (range: 0.0-18). Resolution occurred in 148 patients (75.5%) with a median time to resolution of 9.9 weeks (range: 0.1-165.0+).

Infusion reactions

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg//kg in RCC, the incidence of hypersensitivity/infusion reactions was 4.0% (22/547); all were Grade 1 or 2 in

severity. Grade 2 cases were reported in 2.4% (13/547) of patients. No Grade 3-5 cases were reported.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of hypersensitivity/infusion reactions was 4.0% (23/576); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.4% (14/576) of patients.

Description of selected adverse reactions - nivolumab in combination with ipilimumab and chemotherapy

The management guidelines for these adverse reactions are described in section 4.4.2.

Immune-related pneumonitis

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of pneumonitis including interstitial lung disease was 5.3% (19/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.1% (4/358), and 0.6% (2/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 18.1 weeks (range: 0.6-52.4). Resolution occurred in 14 patients (74%) with a median time to resolution of 4.3 weeks (range: 0.7-27.9+).

Immune-related colitis

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of diarrhea or colitis was 22.3% (80/358). Grade 2, Grade 3, Grade 4, and Grade 5 cases were reported in 7% (25/358), 5% (18/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively. Median time to onset was 5.1 weeks (range: 0.1- 53.6). Resolution occurred in 70 patients (87.5%) with a median time to resolution of 1.4 weeks (range: 0.1-76.9+).

Immune-related hepatitis

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of liver function test abnormalities was 13.4% (48/358). Grade 2, Grade 3, and Grade 4 cases were reported in 3.1% (11/358), 3.4% (12/358), and 1.1% (4/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 10.6 weeks (range: 1.1-68.3). Resolution occurred in 37 patients (80.4%) with a median time to resolution of 5 weeks (range: 0.3+-45.0+).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of nephritis or renal dysfunction was 7% (25/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.7% (6/358), and 0.6% (2/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 10.6 weeks (range: 0.1-51.3). Resolution occurred in 14 patients (56%) with a median time to resolution of 6.3 weeks (range: 0.1+-82.9+).

Immune-related endocrinopathies

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of thyroid disorders was 24% (86/358). Grade 2 and Grade 3 thyroid disorders were reported in 12.3% (44/358) and 0.3% (1/358) of patients, respectively. Hypophysitis occurred in 1.4% (5/358) of patients. Grade 2 and Grade 3 cases were reported in 0.6% (2/358) and 0.8% (3/358) of patients, respectively. Grade 2 hypopituitarism occurred in 0.3% (1/358) of patients. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (6/358) and 1.4% (5/358) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus was not reported. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 12.1 weeks (range: 1.9-58.3). Resolution occurred in 30 patients (35.3%). Time to resolution ranged from 1.4 to 72.4+ weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of rash was 37.7% (135/358). Grade 2, Grade 3, and Grade 4 cases were reported in 11.5% (41/358), 4.2% (14/358), and 0.3% (1/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 3.3 weeks (range: 0.1-83.1). Resolution occurred in 96 patients (71.6%) with a median time to resolution of 9.4 weeks (range: 0.1+-84.1+).

Infusion reactions

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of hypersensitivity/infusion reactions was 4.7% (17/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively. No Grade 5 cases were reported.

Description of selected adverse reactions - nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy

Immune-related pneumonitis

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC, or EAC, the incidence of pneumonitis including interstitial lung disease was 5.1% (40/782). Grade 2, Grade 3, and Grade 4 cases were reported in 2.3% (18/782), 1.4% (11/782), and 0.4% (3/782) of patients, respectively. No Grade 5 cases were reported in this study. Median time to onset was 23.9 weeks (range: 1.6-96.9). Resolution occurred in 28 patients (70%) with a median time to resolution of 10.1 weeks (range: 0.3+-121.3+).

Immune-related colitis

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC or EAC, the incidence of diarrhea or colitis was 33.5% (262/782). Grade 2, Grade 3, and Grade 4 cases were reported in 10.2% (80/782), 4.9% (38/782), and 0.6% (5/782) of patients, respectively. No Grade 5 cases were reported in this study. Median time to onset was 4.3 weeks

(range: 0.1-93.6). Resolution occurred in 228 patients (87.4%) with a median time to resolution of 1.6 weeks (range: 0.1-117.6+).

Immune-related hepatitis

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC or EAC, the incidence of liver function test abnormalities was 26% (203/782). Grade 2 and Grade 3 cases were reported in 9.0% (70/782) and 3.7% (29/782) of patients, respectively. No Grade 4 or Grade 5 cases were reported in this study. Median time to onset was 7.9 weeks (range: 0.1-61.3). Resolution occurred in 156 patients (78%) with a median time to resolution of 10.1 weeks (range: 0.4-150.6+).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC or EAC, the incidence of nephritis or renal dysfunction was 3.3% (26/782). Grade 2, Grade 3, and Grade 4 cases were reported in 1% (8/782), 0.6% (5/782), and 0.1% (1/782) of patients, respectively. No Grade 5 cases were reported in this study. Median time to onset was 12.4 weeks (range: 1.7-59.4). Resolution occurred in 19 patients (73.1%) with a median time to resolution of 3.1 weeks (range: 0.1-42.4+).

Immune-related endocrinopathies

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC or EAC, the incidence of thyroid disorders was 12.3% (96/782). Grade 2 thyroid disorder was reported in 6% (47/782) of patients. There were no cases of Grade 3 thyroid disorder. Grade 3 hypophysitis occurred in 0.1% (1/782) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.3% (2/782) and 0.3% (2/782) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 0.4% (3/782) and 0.1% (1/782) of patients, respectively. Grade 2 and Grade 3 Diabetes mellitus including Type 1 diabetes mellitus were reported in 0.3% (2/782) of patients. Median time to onset of these endocrinopathies was 15.0 weeks (range: 2.0-124.3). Resolution occurred in 46 patients (43%). Time to resolution ranged from 0.4 to 139.1+ weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC, or EAC, the incidence of rash was 27.4% (214/782). Grade 2 and Grade 3 cases were reported in 7% (55/782) and 3.3% (26/782) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 9.6 weeks (range: 0.1-97.4). Resolution occurred in 124 patients (57.9%) with a median time to resolution of 23.4 weeks (range: 0.1-153.6+).

Infusion reactions

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, the incidence of hypersensitivity/infusion reactions was 14.2% (111/782). Grade 2, Grade 3 and Grade 4 cases were reported in 8.8% (69/782), 1.9% (15/782) and 0.3% (2/782) of patients, respectively.

4.8.2 Postmarketing experience

The following event has 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.

Eye disorders: Vogt-Koyanagi-Harada syndrome

Immune system disorders: solid organ transplant rejection, graft-versus-host-disease

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH) autoimmune hemolytic anemia

Cardiac disorder: pericarditis

4.8.3 Laboratory findings

A summary of laboratory abnormalities that worsened from baseline is presented in Table 8 and 9, 10 11 and 12.

Table 8: Laboratory abnormalities: nivolumab monotherapy

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
	Nivolumab monotherapy		
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**
Anemia[b]	3614	1320 (36.5)	207 (5.7)
Thrombocytopenia	3611	493 (13.7)	33 (0.9)
Leukopenia	3620	581 (16.0)	31 (0.9)
Lymphopenia	3600	1507 (41.9)	407 (11.3)
Neutropenia	3602	469 (13.0)	37 (1.0)
Increased alkaline phosphatase	3584	1004 (28.0)	109 (3.0)
Increased AST	3593	1075 (29.9)	130 (3.6)
Increased ALT	3600	818 (22.7)	96 (2.7)
Increased total bilirubin	3598	359 (10.0)	65 (1.8)
Increased creatinine	3608	1059 (29.4)	29 (0.8)
Increased total amylase	1560	270 (17.3)	56 (3.6)
Increased total lipase	1722	334 (19.4)	113 (6.6)
Hypercalcemia	2990	326 (10.9)	41 (1.4)
Hypocalcemia	2990	536 (17.9)	19 (0.6)

Table 8: Laboratory abnormalities: nivolumab monotherapy

Hyperkalemia	3551	696 (19.6)	58 (1.6)
Hypokalemia	3551	404 (11.4)	59 (1.7)
Hypermagnesemia[d]	2256	111 (4.9)	15 (0.7)
Hypomagnesemia[d]	2256	365 (16.2)	10 (0.4)
Hypernatremia	3555	185 (5.2)	4 (0.1)
Hyponatremia	3555	1059 (29.8)	225 (6.3)
Hyperglycemia[c,d]	485	195(40.2)	13(2.7)
Hypoglycemia[e]	1016	118(11.6)	13 (1.3)

Toxicity scale: CTC Version 4.0.

Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy, except for ONO-4538-12. For ONO-4538-12 includes events reported between the first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period. The frequencies are regardless of causality.

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

[b] Per anemia criteria in CTC version 4.0, there is no Grade 4 for hemoglobin.

[c] Life-threatening hyperglycemia has been reported in completed or ongoing clinical studies.

[d] Does not include ONO-4538-12.

[e] Does not include CA209066, CA209037, CA209017, CA209057, CA209025, and CA209039

Table 9: Laboratory abnormalities: nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg (RCC)

Number (%) of Patients with Worsening Laboratory Test from Baseline			
	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC		
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**
Anemia[b]	541	231 (42.7)	18 (3.3)
Thrombocytopenia	541	96 (17.7)	7 (1.3)
Leukopenia	541	85 (15.7)	8 (1.5)
Lymphopenia	540	204 (37.8)	36 (6.7)
Neutropenia	540	76 (14.1)	11 (2)
Increased alkaline phosphatase	542	167 (30.8)	14 (2.6)
Increased AST	541	225 (41.6)	33 (6.1)
Increased ALT	542	235 (43.4)	44 (8.1)
Increased total bilirubin	541	74 (13.7)	8 (1.5)

Table 9: Laboratory abnormalities: nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg (RCC)

Number (%) of Patients with Worsening Laboratory Test from Baseline			
	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC		
Test	N[a]	Grades 1-4	Grades 3-4
Increased creatinine	541	215 (39.7)	14 (2.6)
Increased total amylase	491	188 (38.3)	61 (12.4)
Increased total lipase	518	236 (45.6)	97 (18.7)
Hypercalcemia	529	71 (13.4)	9 (1.7)
Hypocalcemia	529	115 (21.7)	6 (1.1)
Hyperkalemia	534	147 (27.5)	15 (2.8)
Hypokalemia	534	61 (11.4)	13 (2.4)
Hypermagnesemia	528	34 (6.4)	6 (1.1)
Hypomagnesemia	528	86 (16.3)	2 (0.4)
Hypernatremia	534	40 (7.5)	0
Hyponatremia	534	206 (38.6)	56 (10.5)

Toxicity scale: CTC Version 4.0.

Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

[b] Per anemia criteria in CTC version 4.0, there is no Grade 4 for hemoglobin.

Table 10: Laboratory abnormalities: nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg (NSCLC)

Number (%) of Patients with Worsening Laboratory Test from Baseline			
	Nivolumab 3mg/kg in combination with ipilimumab 1 mg/kg in NSCLC		
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**
Anemia	556	255 (45.9)	20 (3.6)
Thrombocytopenia	555	58 (10.5)	5 (0.9)
Leukopenia	559	35 (6.3)	3 (0.5)
Lymphopenia	553	254 (45.9)	29 (5.2)
Neutropenia	555	53 (9.5)	5 (0.9)
Increased alkaline phosphatase	552	185 (33.5)	21 (3.8)
Increased AST	551	217 (39.4)	30 (5.4)
Increased ALT	555	202 (36.4)	39 (7.0)
Increased total Bilirubin	554	63 (11.4)	6 (1.1)
Increased Creatinine	554	119 (21.5)	5 (0.9)
Increased total amylase	494	139 (28.1)	46 (9.3)
Increased total lipase	524	181 (34.5)	73 (13.9)
Hypernatremia	552	42 (7.6)	2 (0.4)
Hyponatremia	552	227 (41.1)	64 (11.6)
Hyperkalemia	551	151 (27.4)	19 (3.4)
Hypokalemia	551	83 (15.1)	22 (4.0)
Hypercalcemia	545	75 (13.8)	10 (1.8)
Hypocalcemia	545	155 (28.4)	9 (1.7)
Hypermagnesemia	542	62 (11.4)	19 (3.5)
Hypomagnesemia	542	115 (21.2)	3 (0.6)

Toxicity scale: CTC Version 4.0.

Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

Table 11: Laboratory abnormalities: nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy (NSCLC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
	Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC		
Test	N[a]	Grades 1-	Grades 3-4
Anemia[b]	347	243 (70.0)	32 (9.2)
Thrombocytopenia	347	80 (23.1)	15 (4.3)
Leukopenia	347	126 (36.3)	34 (9.8)
Lymphopenia	257	105 (40.9)	15 (5.8)
Neutropenia	346	140 (40.5)	51 (14.7)
Increased alkaline phosphatase	342	106 (31.0)	4 (1.2)
Increased AST	345	102 (29.6)	12 (3.5)
Increased ALT	345	118 (34.2)	15 (4.3)
Increased total bilirubin	344	26 (7.6)	0
Increased creatinine	346	91 (26.3)	4 (1.2)
Increased total amylase	312	95 (30.4)	21 (6.7)
Increased total lipase	337	105 (31.2)	40 (11.9)
Hypercalcemia	345	39 (11.3)	4 (1.2)
Hypocalcemia	345	95 (27.5)	5 (1.4)
Hyperkalemia	345	77 (22.3)	6 (1.7)
Hypokalemia	345	53 (15.4)	12 (3.5)
Hypermagnesemia	334	35 (10.5)	1 (0.3)
Hypomagnesemia	334	107 (32.0)	4 (1.2)
Hypernatremia	345	15 (4.3)	0
Hyponatremia	345	128 (37.1)	37 (10.7)
Hyperglycemia	197	89 (45.2)	14 (7.1)
Hypoglycemia	273	35 (12.8)	0

Toxicity scale: CTC Version 4.0.

Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

[b] Per anemia criteria in CTC version 4.0, there is no Grade 4 for hemoglobin.

Table 12: Laboratory abnormalities: nivolumab 240 mg or 360 mg in combination with fluoropyrimidine- and platinum-containing chemotherapy (GC, GEJC or EAC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
	Nivolumab 240 mg or 360 mg in combination with chemotherapy in GC, GEJC or EAC		
Test	N[a]	Grades 1-4	Grades 3-4
Hemoglobin	765	450 (58.8)	106 (13.9)
Platelet count	762	515 (67.6)	52 (6.8)
Leukocytes	764	524 (68.6)	90 (11.8)
Lymphocytes (absolute)	763	446 (58.5)	93 (12.2)
Absolute neutrophil count	764	556 (72.8)	224 (29.3)
Aspartate aminotransferase	764	395 (51.7)	35 (4.6)
Alanine aminotransferase	764	283 (37.0)	26 (3.4)
Bilirubin, total	761	182 (23.9)	23 (3.0)
Creatinine	765	115 (15.0)	8 (1.0)
Hypernatremia	767	84 (11.0)	4 (0.5)
Hyponatremia	767	258 (33.6)	48 (6.3)
Hyperkalemia	766	110 (14.4)	11 (1.4)
Hypokalemia	766	203 (26.5)	50 (6.5)
Hypercalcemia	748	46 (6.1)	2 (0.3)
Hypocalcemia	748	326 (43.6)	12 (1.6)
Hyperglycemia	408	166 (40.7)	17 (4.2)
Hypoglycemia	407	48 (11.8)	3 (0.7)

Toxicity scale: CTC Version 4.0.

Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

4.8.4 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response to nivolumab. Of 2232 patients who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks and evaluable for the presence of anti-product-antibodies, 287 patients (12.9%) tested positive for treatment-emergent anti-product-antibodies by an electrochemiluminescent (ECL) assay. Sixteen patients (0.7%) had neutralizing 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% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks 36.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks. The incidence of neutralizing antibodies against nivolumab was 0.5% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks 1.4% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 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 neutralizing antibodies against ipilimumab ranged from 0 to 0.4%.

Of the patients who were treated with nivolumab in combination with ipilimumab 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 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 neutralizing antibodies against ipilimumab, the incidence of anti-ipilimumab antibodies was 7.5%, and neutralizing antibodies was 1.6%.

Although the clearance of nivolumab was increased by approximately 20% when anti-nivolumab antibodies were present, there was no evidence of loss of efficacy or altered toxicity profile in presence of nivolumab antibodies.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Nivolumab is a fully human 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 tumors or other cells in the tumor microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumor 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 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. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumor activity.

5.2 Pharmacodynamics

5.2.1 Clinical Trial Information

Non-small cell lung cancer (NSCLC)

Randomized phase 3 study vs. docetaxel (CA209017)

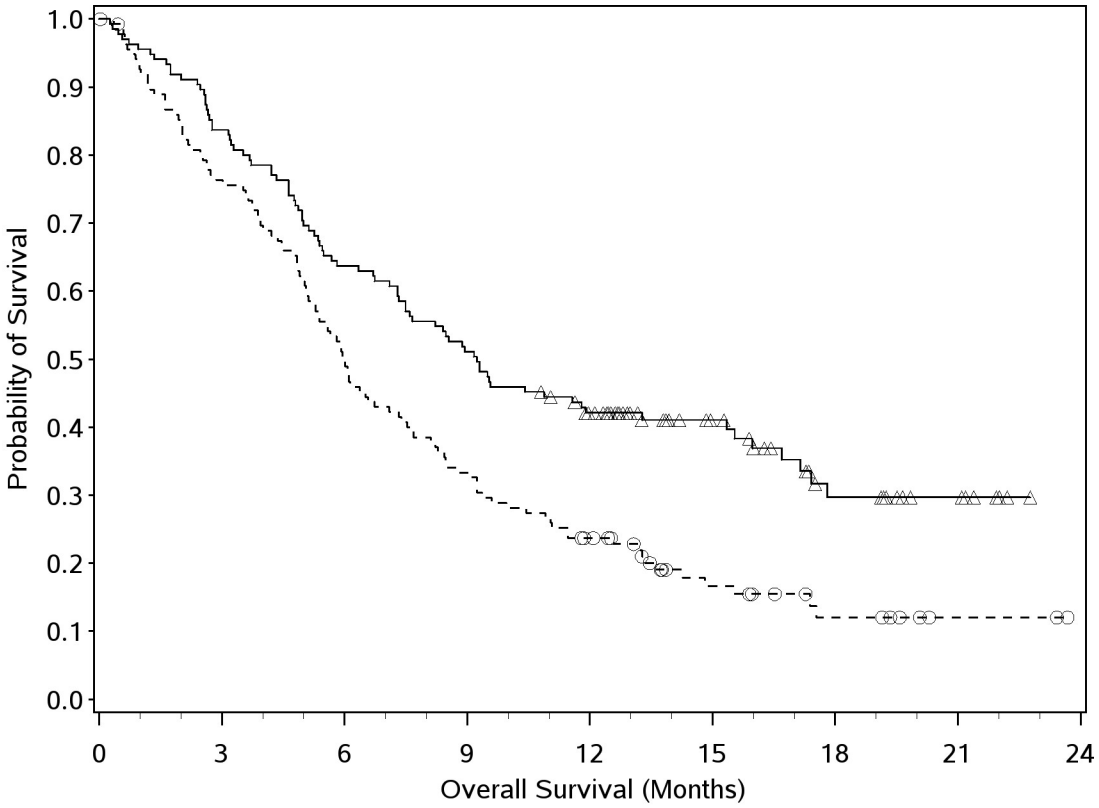
The safety and efficacy of nivolumab 3 mg/kg or the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomized, open-label study (CA209017). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an ECOG performance status score of 0 or 1. Patients were enrolled regardless of their PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis 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.

Patients were randomized on a 1:1 basis to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks or docetaxel 75 mg/m2 every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments, according to RECIST, version 1.1, were conducted 9 weeks after randomization 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.

A total of 272 patients were randomized to either nivolumab (n=135) or docetaxel (n=137). Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 39-85) with 44% ≥65 years of age and 11% ≥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 was 0 (24%) or 1 (76%).

Nivolumab demonstrated a statistically significant improvement in OS compared with docetaxel. At the pre-defined PD-L1 tumor membrane expression cut-off levels of 1%, 5%, and 10%, similar survival was observed regardless of PD-L1 expression status. OS results are shown in Figure 1. The observed OS benefit was consistently demonstrated across subgroups of patients.

Figure 1: Kaplan-Meier curves of OS (CA209017)



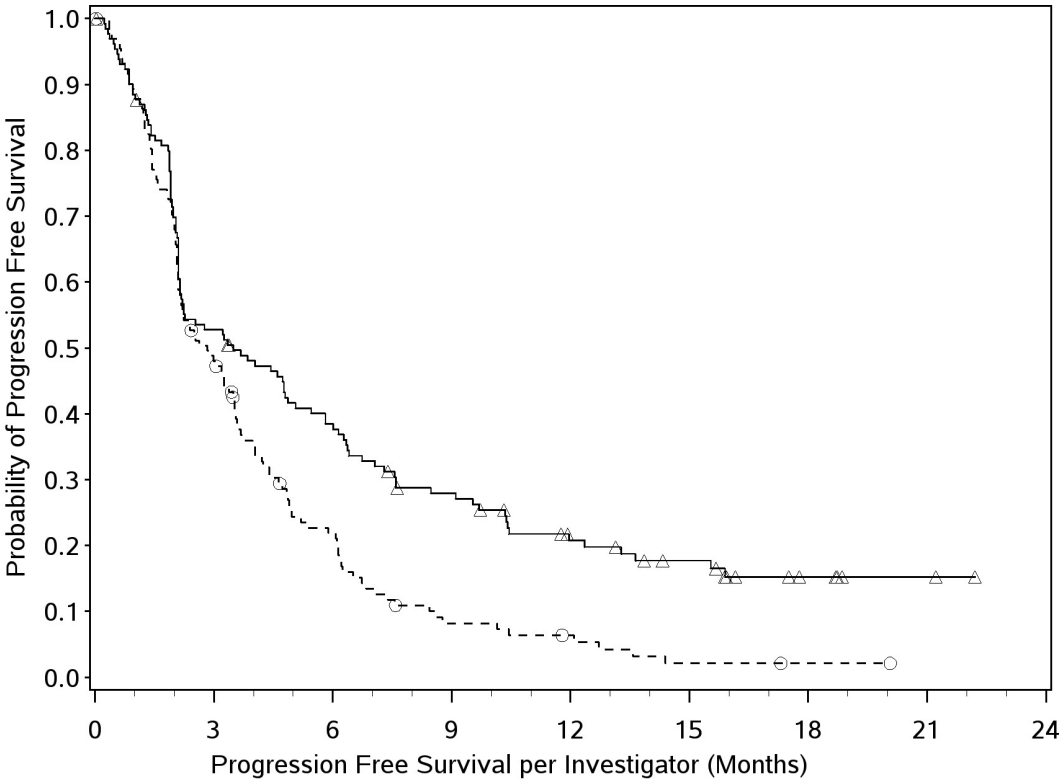
Number of Subjects at Risk

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)
Hazard Ratio (Nivolumab 3 mg/kg over Docetaxel) and 96.85% CI: 0.59 (0.43, 0.81)
Stratified log-rank p-value: 0.0002

The investigator-assessed ORR using RECIST version 1.1 criteria was significantly higher in the nivolumab group than in the docetaxel group. Nivolumab treatment also demonstrated statistically significant improvement in PFS compared with docetaxel (Figure 2). Efficacy results based on the primary and updated analyses are shown in Table 13.

Figure 2: Kaplan-Meier curves of PFS (CA209017)



Number of Subjects at Risk

Nivolumab 3 mg/kg	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

Nivolumab 3 mg/kg (events : 105/135), median and 95% CI : 3.48 (2.14, 4.86)
Docetaxel (events : 122/137), median and 95% CI : 2.83 (2.10, 3.52)
Hazard Ratio (Nivolumab 3 mg/kg over Docetaxel) and 95% CI: 0.62 (0.47, 0.81)
Stratified log-rank p-value: 0.0004

Table 13: Efficacy results (CA209017)

	nivolumab (n = 135)		docetaxel (n = 137)	
Primary analysis Minimum follow-up: 10.6 months				
Overall survival				
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)	9.2 months (7.3, 13.3)		6.0 months (5.1, 7.3)	
Rate (95% CI) at 12 months	42.1% (33.7, 50.3)		23.7% (16.9, 31.1)	
Confirmed objective response n (%)	27	(20.0%)	12	(8.8%)
(95% CI)	(13.6, 27.7)		(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%)
Median duration of response				
(range)	Not reached	(2.9-20.5+)	8.4 months	(1.4+-15.2+)
Median time to response				
(range)	2.2 months	(1.6-11.8)	2.1 months	(1.8-9.5)
Progression-free survival				
Events	105 (77.8%)		122 (89.1%)	
Hazard ratio	0.62			
95% CI	(0.47, 0.81)			
p-value	< 0.0004			
Median (95% CI)	3.5 months (2.1, 4.9)		2.8 months (2.1, 3.5)	
Rate (95% CI) at 12 months	20.8% (14.0, 28.4)		6.4% (2.9, 11.8)	
Updated analysis Minimum follow-up: 24.2 months				
Overall survival[a]				
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)		8.0% (4.3, 13.3)	
Confirmed objective response	20.0%		8.8%	
(95% CI)	(13.6, 27.7)		(4.6, 14.8)	
Median duration of response				
(range)	25.2 months (2.9-30.4)		8.4 months (1.4+-18.0+)	

Table 13: Efficacy results (CA209017)

	nivolumab (n = 135)	docetaxel (n = 137)
Progression-free survival		
Rate (95% CI) at 24 months	15.6% (9.7, 22.7)	All patients had either progressed, were censored, or lost to follow-up

[a] Six patients (4%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
"+" 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 LCSS symptom score in the nivolumab group generally decreased (improved) over time and the change from baseline exceeded the clinically meaningful threshold at about 10 months; in the docetaxel group, the average symptom index was stable over the period for which there were enough patients to interpret the data (about 6 months). 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)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of squamous NSCLC were evaluated in a phase 2, single-arm, multinational, multicenter study (CA209063). All patients had progressed after receiving a platinum doublet-based therapy and at least one additional systemic treatment regimen. Patients were enrolled regardless of their PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis 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.

Patients received 3 mg/kg of nivolumab administered intravenously over 60 minutes every 2 weeks as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments took place at week 8 and every 6 weeks thereafter. The primary efficacy outcome measure was confirmed ORR as assessed by an independent review committee (IRC) according to RECIST version 1.1. Duration and timing of responses were also assessed. Additional outcome measures included IRC-assessed PFS and OS, as exploratory endpoints.

A total of 117 patients received treatment with nivolumab. The median age of patients was 65 years (range: 37-87) with 50% ≥65 years of age and 14% ≥75 years of age. The majority of patients were male (73%) and white (85%). All patients received two or more prior systemic treatments: 35% received two, 44% received three, and 21% received four or more. Sixty-one percent had progressive disease reported as the best response to their most recent prior regimen. The majority of patients (76%) received nivolumab within 3 months of completing their most recent prior regimen.

The most common tumor sites at baseline were lung (86%), lymph node (46%), liver (25%), mediastinum (20%), bone (18%), and kidney (10%). Fifty percent of patients had 3 or more baseline disease sites. Baseline ECOG performance status was 0 (22%) or 1 (78%).

Efficacy results based on a minimum follow up of approximately 11 months are shown in Table 14 and Figure 3.

Table 14: Efficacy Results (CA209063)

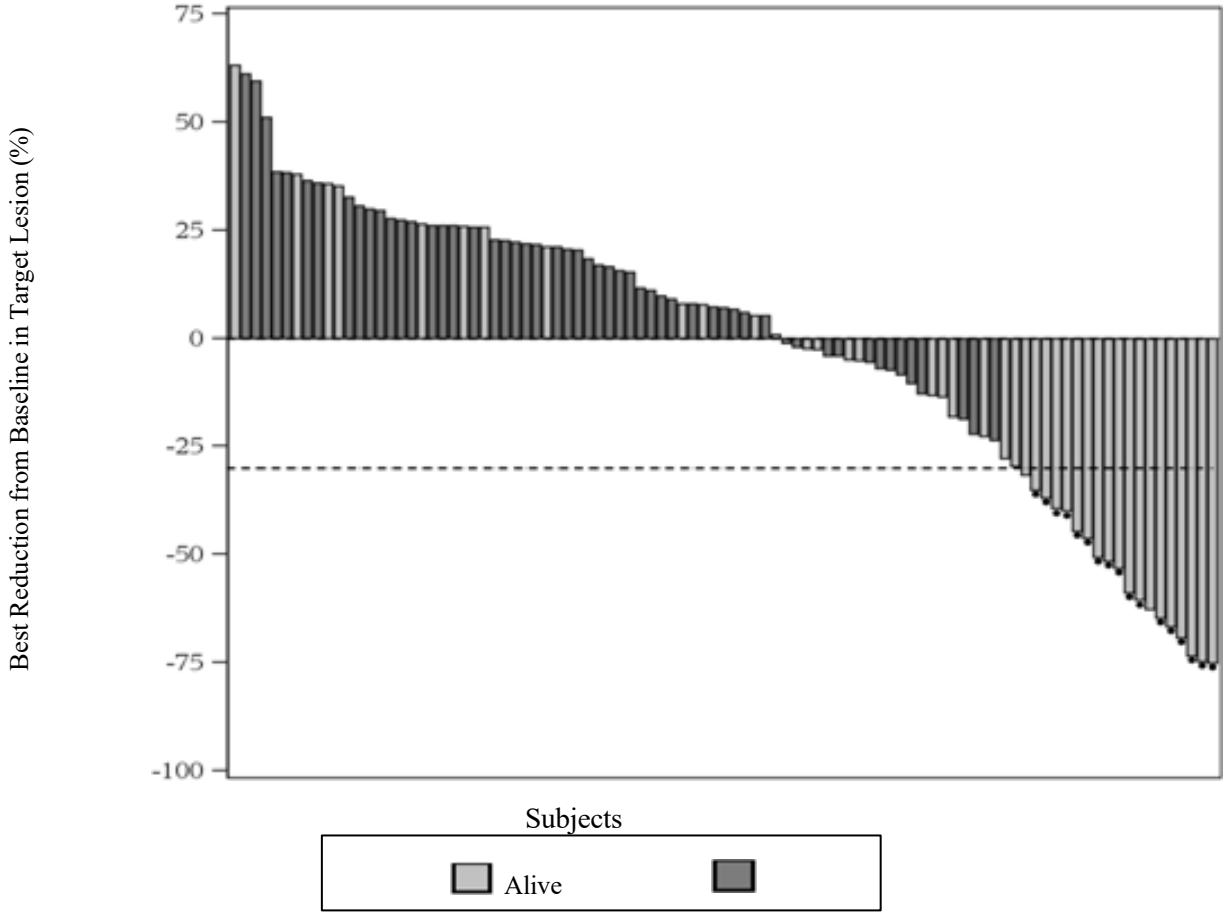
	nivolumab (n = 117)
Confirmed objective response n (%)	17 (14.5%)
(95% CI)	(8.7, 22.2)
Complete response (CR)	0
Partial response (PR)	17 (14.5%)
Stable disease (SD) [a]	30 (25.6%)
Median duration of response	
Months (range)	Not reached (1.9^{+}- 11.5^{+})
Median time to response	
(range)	3.25 months (1.7 - 8.8)
Median PFS (95% CI)	1.87 months (1.77, 3.15)
PFS rate at 12 months (95% CI)	20 % (12.7, 28.5)
Median OS 95% CI)	8.21 months (6.05, 10.91)
OS rate at 12 months (95% CI)	40.8% (31.6, 49.7)

[a] Median duration of SD was 6 months (95% CI: 4.7, 10.9).

"+" denotes a censored observation

At the pre-defined PD-L1 tumor membrane expression cut-off levels of 1%, 5%, and 10%, similar response rates were observed regardless of PD-L1 expression status.

Figure 3: Waterfall plot of best reduction in target lesion, per IRC according to survival status



Note: Symbol ("●") represents confirmed responders.

Randomized phase 3 study vs. docetaxel (CA209057)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced or metastatic non-squamous NSCLC were evaluated in a phase 3, randomized, 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 PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis 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.

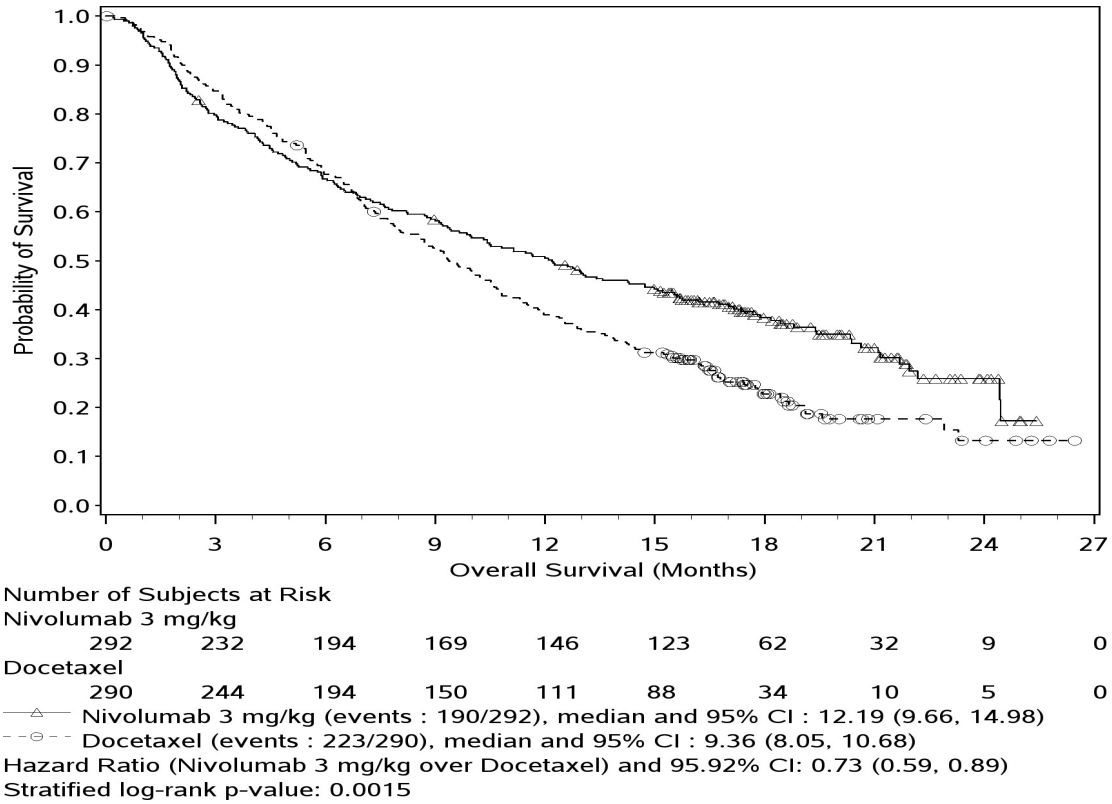
Patients were randomized to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks or docetaxel 75 mg/m2 every 3 weeks . Treatment was continued

as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments, according to RECIST, version 1.1, were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. The study evaluated whether PD-L1 expression was a predictive biomarker for efficacy. In addition, symptom improvement and overall health status were assessed using the LCSS average symptom burden index and the EQ-5D VAS, respectively.

A total of 582 patients were randomized to receive nivolumab (n = 292) or docetaxel (n = 290). Baseline characteristics were generally balanced between the two groups. 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%). Thirty-nine percent had progressive disease reported as the best response to their most recent prior regimen and 62.5% received nivolumab within 3 months of completing their most recent prior regimen. 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 4.

Figure 4: Kaplan-Meier curves of OS (CA209057)



The trial demonstrated a statistically significant improvement in OS for patients randomized 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 15.

Table 15: Efficacy Results (CA209057)

	nivolumab (n = 292)	docetaxel (n = 290)
Primary analysis Minimum follow-up: 13.2 months		
Overall survival n (%)		
Events	190 (65.1%)	223 (76.9%)
Hazard ratio[a]	0.73	
(95.92% CI)	(0.59, 0.89)	
p-value[b]	0.0015	
Median (95% CI)	12.2 months (9.7, 15.0)	9.4 months (8.1, 10.7)
Rate (95% CI) at 12 months	50.5% (44.6, 56.1)	39.0% (33.3, 44.6)
Confirmed objective response n (%)	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%)
Median duration of response (range)	17.15 months (1.8-22.6$^+$)	5.55 months (1.2$^+$-15.2$^+$)
Median time to response (range)	2.1 months (1.2-8.6)	2.6 months (1.4-6.3)
Progression-free survival		
Events n (%)	234 (80.1%)	245 (84.5%)
Hazard ratio	0.92	
95% CI	(0.77, 1.11)	
p-value	0.3932	
Median (95% CI)	2.33 months (2.17, 3.32)	4.21 months (3.45, 4.86)
Rate (95% CI) at 12 months	18.5% (14.1, 23.4)	8.1% (5.1, 12.0)
Updated analysis Minimum follow-up: 24.2 months		
Overall survival[c]		
Events n (%)	228 (78.1%)	247 (85.2%)
Hazard ratio[a]	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)
Confirmed objective response	19.2%	12.4%
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Median duration of response (range)	17.2 months (1.8-33.7$^+$)	5.6 months (1.2$^+$-16.8)
Progression-free survival		
Rate (95% CI) at 24 months	11.9% (8.3, 16.2)	1.0% (0.2, 3.3)

[a] Derived from a stratified proportional hazards model.

[b] 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.

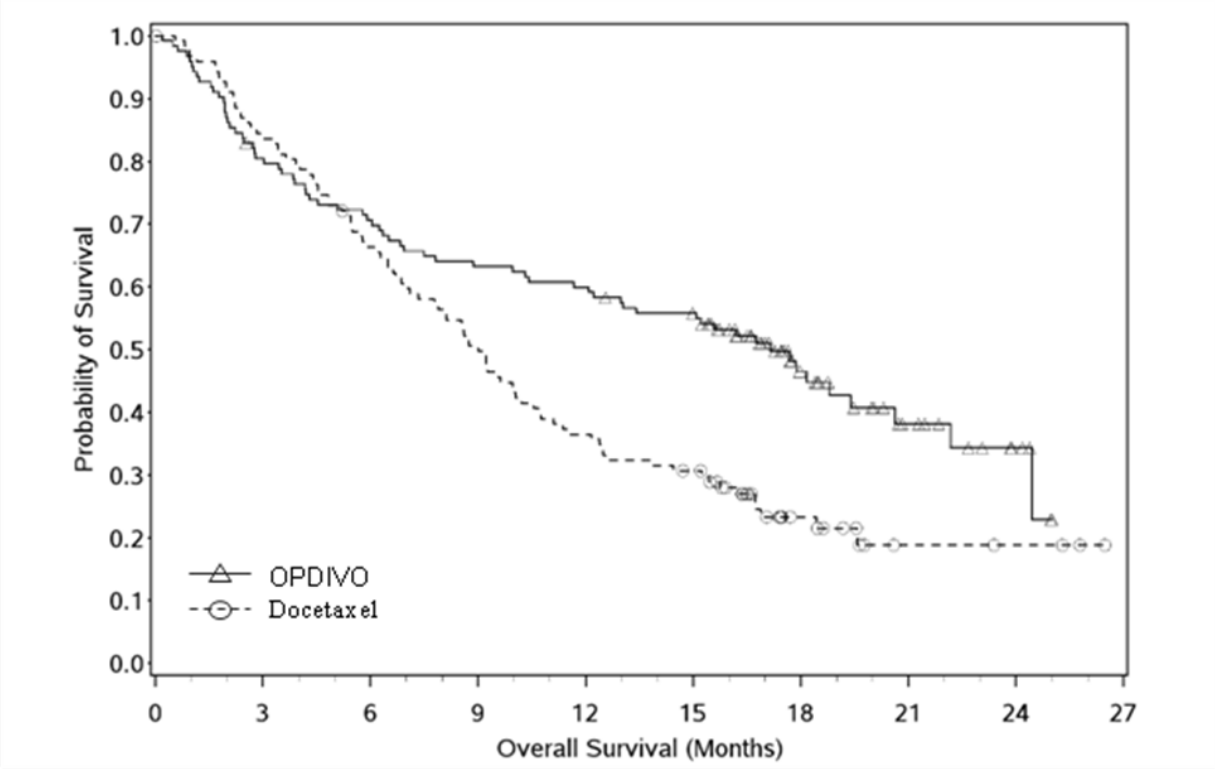
[c] Sixteen patients (6%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.

"+" denotes a censored observation.

Pre-study tumor tissue specimens were systematically collected prior to randomization in order to conduct pre-planned analyses of efficacy according to tumor PD-L1 expression. Quantifiable PD-L1 expression was measured in 79% of patients in the nivolumab group and 77% of patients in the docetaxel group. Tumor PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs docetaxel) at each of the predefined PD-L1 expression levels of ≥1% (53% vs 55%), ≥5% (41% vs 38%), or ≥10% (37% vs 35%). Tumor PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Patients with tumor PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of enhanced survival compared to docetaxel, whereas survival was similar to docetaxel in patients with low or no tumor PD-L1 expression. Results are shown below in Figures 5, 6, and 7.

Figure 5: Overall Survival: Patients with ≥1% PD-L1 Expression (CA209057)



Number at Risk									
OPDIVO									
123	98	86	77	73	65	27	13	5	0
Docetaxel									
123	102	80	61	44	36	13	4	3	0

Figure 6: Overall Survival: Patients with <1% PD-L1 Expression (CA209057)

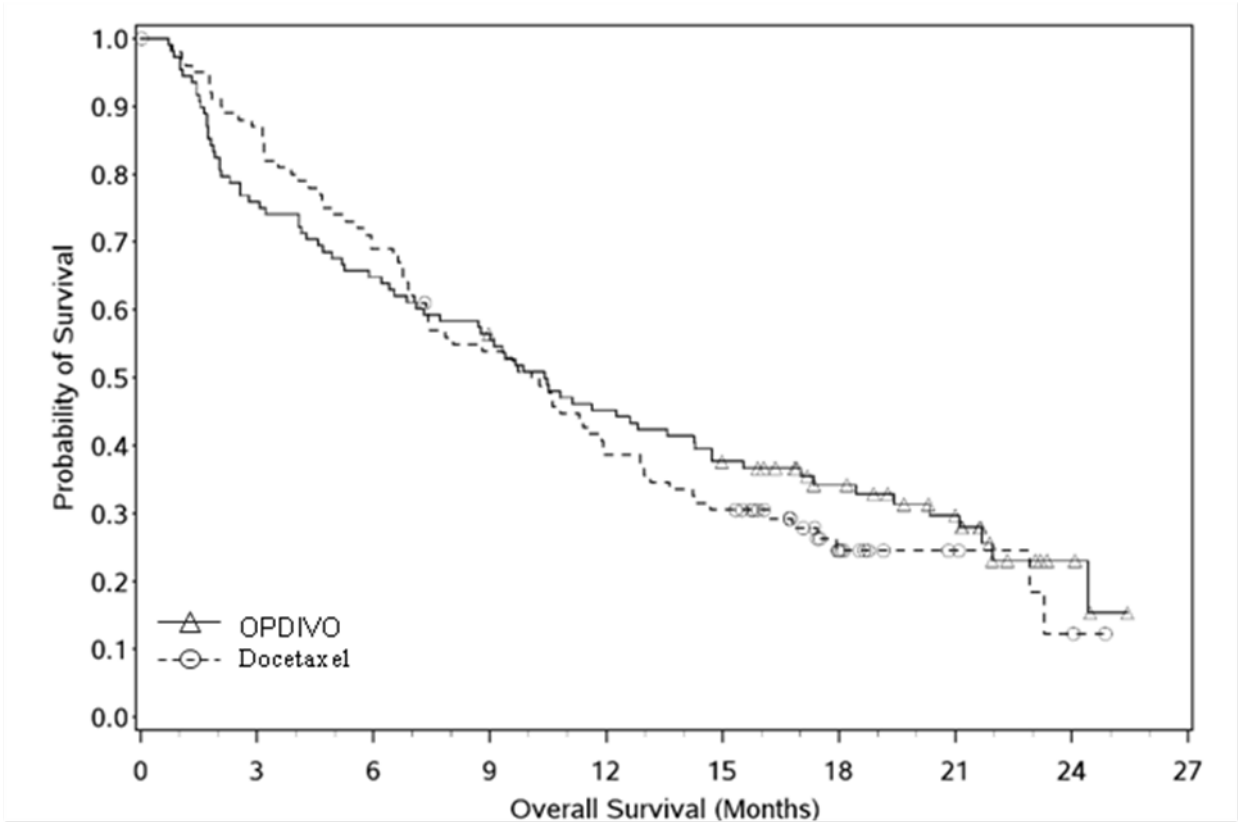
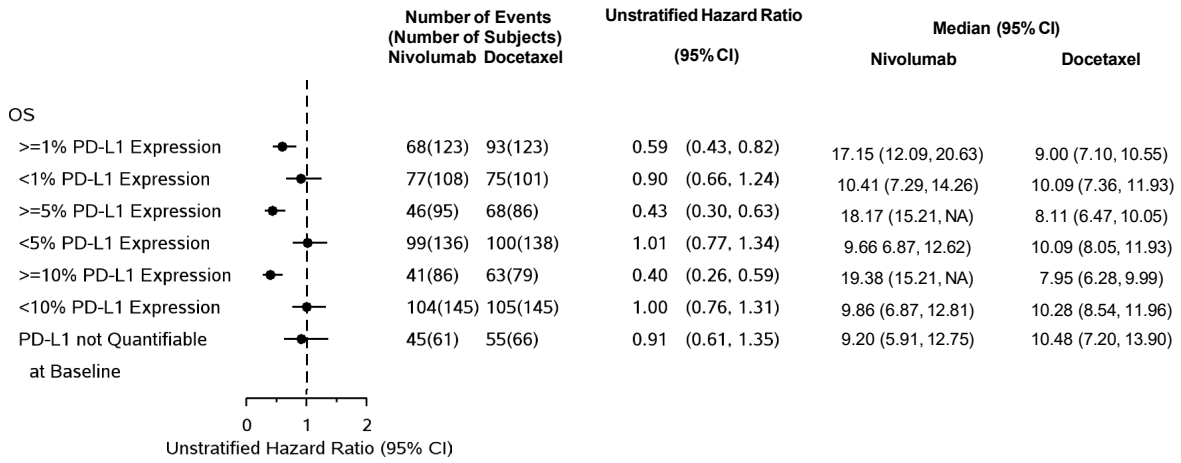


Figure 7: Forest Plot for OS based on PD-L1 Expression (CA209057)



The rate of disease-related symptom improvement, as measured by LCSS, was similar between the nivolumab group (17.8%) and the docetaxel group (19.7%). The average EQ-VAS increased over time for both treatment groups, indicating better overall health status for patients remaining on treatment.

As compared to the overall study population, no meaningful differences in safety were observed based on PD-L1 expression levels of 1% or 5%.

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 NSCLC. Of the 306 patients enrolled in the study, 129 had NSCLC and received nivolumab at a dose of 1 mg/kg (n=33), 3 mg/kg (n=37), or 10 mg/kg (n=59) every 2 weeks for a maximum of 2 years. Objective response was reported in 22/129 patients (17% [95% CI: 11.0, 24.7]) in the entire NSCLC cohort (across histologies and dose levels) and 4/18 patients (22% [95% CI: 6.4, 47.6]) with squamous NSCLC treated at the 3 mg/kg dose level.

In the entire NSCLC cohort, the median duration of response was 17 months. The median PFS was 2.3 months (95% CI: 1.8, 3.7). The estimated milestone PFS rates were 22% (95% CI: 15, 30) at 1 year and 9% (95% CI: 4, 15) at 2 years. The median OS was 9.9 months (95% CI: 7.8, 12.4), and the estimated milestone OS rates were 42% (95% CI: 34, 51) at 1 year and 24% (95% CI: 16, 32) at 2 years.

Randomized, open-label, Phase 3 study of nivolumab alone or in combination with ipilimumab or platinum-doublet chemotherapy vs platinum-doublet chemotherapy (CA209227, Part 1)

The safety and efficacy of nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks for the treatment of NSCLC were evaluated in a Phase 3, randomized, open-label study (CA209227, Part 1). 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 classification ((ASLC)), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors). 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.

Patients were enrolled into Part 1a or Part 1b according to PD-L1 status. In Part 1a, patients with PD-L1 tumor expression ≥1% were randomized 1:1:1 to either nivolumab 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; platinum-doublet chemotherapy administered every 3 weeks for up to 4 cycles; or nivolumab 240 mg administered intravenously over 30 minutes every 2 weeks. In Part 1b, patients with PD-L1 tumor expression <1% were

randomized 1:1:1 to either nivolumab 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; platinum-doublet chemotherapy administered every 3 weeks for up to 4 cycles; or nivolumab 360 mg administered intravenously over 30 minutes in combination with platinum-doublet chemotherapy every 3 weeks for 4 cycles, followed by nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks. Stratification factors were identical between Part 1a and Part 1b (tumor histology [non-squamous versus squamous]). Platinum-doublet chemotherapy consisted of:

- pemetrexed (500 mg/m2) and cisplatin (75 mg/m2), or pemetrexed (500 mg/m2) and carboplatin (AUC 5 or 6) for non-squamous NSCLC;
- or gemcitabine (1000 or 1250 mg/m2) and cisplatin (75 mg/m2), or gemcitabine (1000 mg/m2) 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 nivolumab monotherapy. 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 nivolumab 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, 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 benefit in OS, and a clinically meaningful benefit in PFS, ORR, and duration of response for patients randomized to nivolumab in combination with ipilimumab compared to platinum-doublet chemotherapy alone. Efficacy results for patients whose tumors expressed PD-L1 ≥1% are presented in Table 16 and Figure 8 below.

Table 16: Efficacy results (PD-L1 ≥1%) - CA209227 Part 1a

	nivolumab + ipilimumab (n=396)	**Chemotherapy (n=397)**
Overall Survival		
Events (%)	258 (65.2)	298 (75.1)
Median (months)	17.1	14.9
(95% CI)	(15, 20.1)	(12.7, 16.7)
Hazard ratio (97.72% CI)[a]	0.79 (0.65, 0.96)	
Stratified log-rank p-value	0.0066	
Rate (95% CI) at 12 months	62.6 (57.7, 67.2)	56.2 (51.1, 61.0)
Rate (95% CI) at 24 months	40.0 (35.1, 44.9)	32.8 (28.2, 37.5)
Progression-Free Survival		
Events (%)	288 (72.7)	286 (72.0)
Hazard ratio (95% CI)[a]	0.82 (0.69, 0.97)	
Median (months)[b]	5.1	5.6
(95% CI)	(4.07, 6.31)	(4.63, 5.82)
Objective Response Rate (%)[c]	142 (35.9)	119 (30.0)
(95% CI)	(31.1, 40.8)	(25.5, 34.7)
Complete response (%)	23 (5.8)	7 (1.8)
Partial response (%)	119 (30.1)	112 (28.2)
Duration of Response		
Median (months) (95% CI)[b]	23.2 (15.2, 32.2)	6.2 (5.6, 7.4)
% with duration ≥12 months[d]	64	28
% with duration ≥24 months[d]	49	11

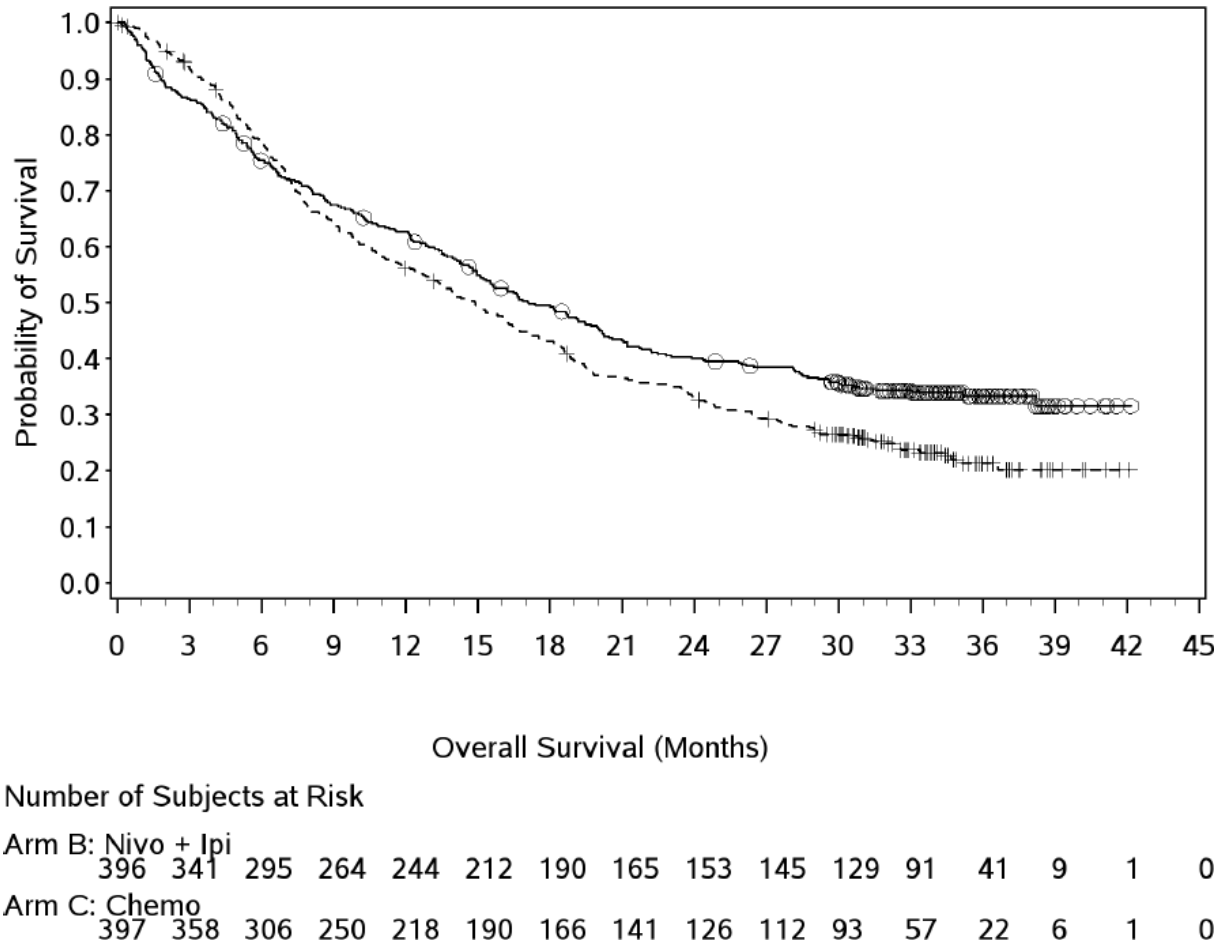
[a] Based on a stratified Cox proportional hazard model.

[b] Kaplan-Meier estimate.

[c] Proportion with complete or partial response; confidence interval based on the Clopper and Pearson Method.

[d] Based on Kaplan-Meier estimates of duration of response.

Figure 8: Kaplan-Meier plot of OS (PD-L1 ≥1%) - CA209227 Part 1a



Randomized, open-label, Phase 3 study of nivolumab in combination with ipilimumab and platinum-based chemotherapy vs platinum-based chemotherapy (CA2099LA)

The safety and efficacy of nivolumab 360 mg every 3 weeks in combination with ipilimumab 1mg/kg every 6 weeks and 2 cycles of platinum-based chemotherapy were evaluated for the treatment of NSCLC in a Phase 3, randomized, open-label study (CA2099LA). 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 classification ((IASLC)), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors). 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.

Patients were randomized 1:1 to receive either 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; or platinum-based chemotherapy administered every 3 weeks for 4 cycles; patients with non-squamous NSCLC could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1%), histology (squamous versus non-squamous), and gender (male versus female). Platinum-based chemotherapy consisted of:

- carboplatin (AUC 5 or 6) and pemetrexed 500 mg/mg2; or cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 for non-squamous NSCLC;
- or carboplatin (AUC 6) and paclitaxel 200 mg/m2 for squamous NSCLC.

Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months in patients without disease progression. 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 nivolumab monotherapy. 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 nivolumab in combination with ipilimumab and platinum-based chemotherapy (n=361) or platinum-based 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, 89% White, 70% male. Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% with PD-L1 ≥1% and 37% with PD-L1 <1%, 31% with squamous and 69% with non-squamous histology, 17% had brain metastases, and 86% were former/current smokers.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR, and a clinically meaningful benefit in duration of response for patients randomized to nivolumab in combination with ipilimumab and platinum-based chemotherapy compared to platinum-based chemotherapy alone. Minimum follow-up for OS was 8.1 months. Efficacy results are presented in Table 17and Figure 9.

Table 17: Efficacy results - CA2099LA

	Nivolumab + ipilimumab + chemotherapy (n=361)	Chemotherapy (n=358)
OS		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.24, 16.16)	10.7 (9.46, 12.45)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Rate (95% CI) at 6 months	80.9 (76.4, 84.6)	72.3 (67.4, 76.7)
PFS		
Events (%)	232 (64.3)	249 (69.6)
Hazard ratio (97.48% CI)[a]	0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]	0.0001	
Median (months)[d] (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)
ORR (%)[e]	136 (37.7)	90 (25.1)
(95% CI)	(32.7, 42.9)	(20.7, 30.0)
Stratified CMH test p-value[f]	0.0003	
Complete response (%)	7 (1.9)	3 (0.8)
Partial response (%)	129 (35.7)	87 (24.3)
Duration of Response		
Median (months) (95% CI)[d]	10.02 (8.21, 13.01)	5.09 (4.34, 7.00)
% with duration ≥6 months[g]	74	41

[a] Based on a stratified Cox proportional hazard model.

[b] p-value is compared with the allocated alpha of 0.0329 for this interim analysis.

[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.

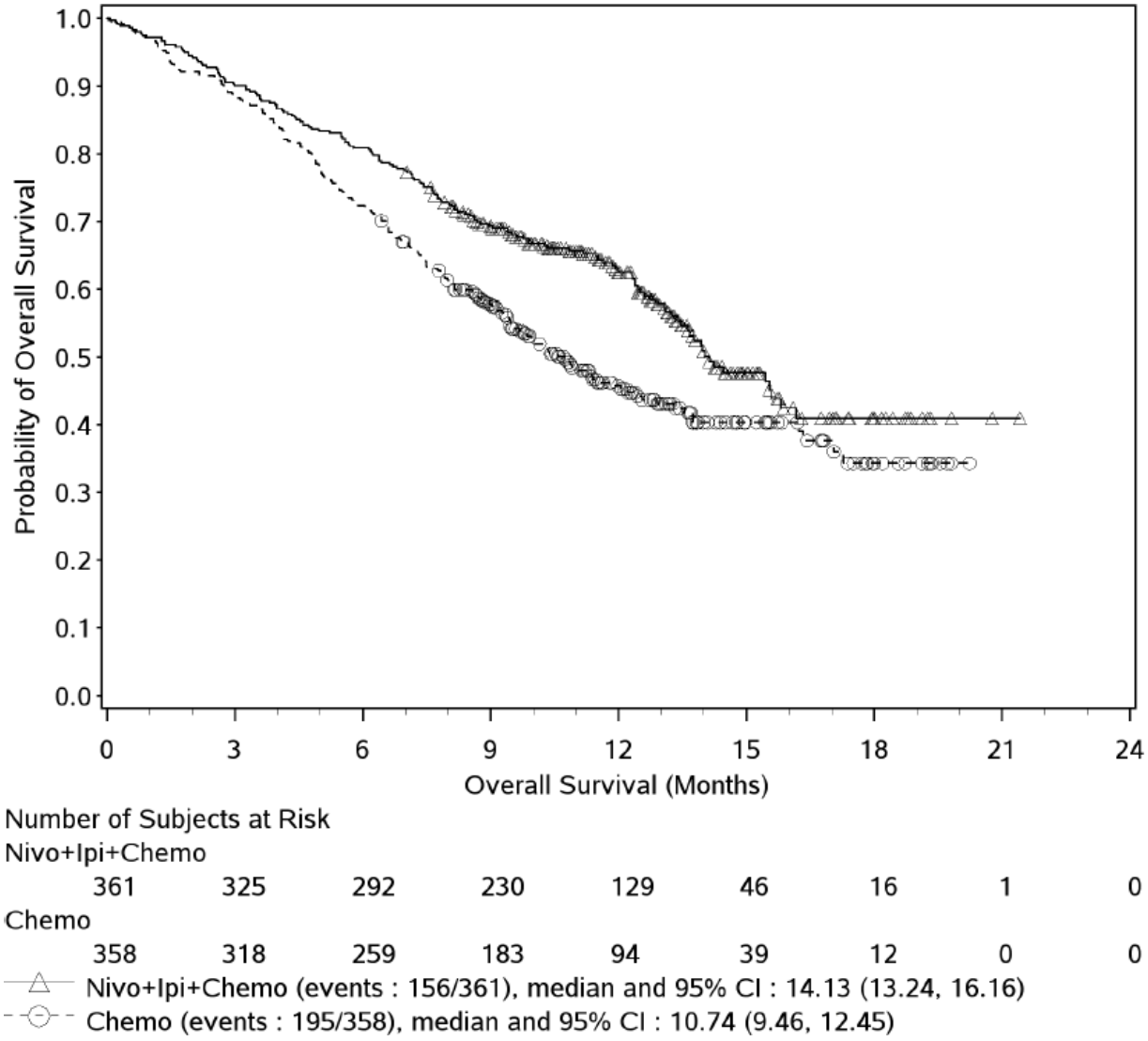
[d] Kaplan-Meier estimate.

[e] Proportion with complete or partial response; confidence interval based on the Clopper and Pearson Method.

[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.

[g] Based on Kaplan-Meier estimates of duration of response.

Figure 9: Kaplan-Meier plot of OS - CA2099LA



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 18 summarizes efficacy results of OS by tumour PD-L1 expression in pre-specified subgroup analyses.

Table 18: Efficacy results by tumor PD-L1 expression (CA2099LA)

	PD-L1 <1% (n=264)	PD-L1 ≥1% (n=406)	PD-L1 ≥1% to 49% (n=233)	PD-L1 ≥50% (n=173)
OS hazard ratio (95% CI)[a]	0.65 (0.46, 0.92)	0.67 (0.51, 0.89)	0.69 (0.48, 0.98)	0.64 (0.41, 1.02)

[a] Hazard ratio based on unstratified Cox proportional hazards model.

Renal cell carcinoma (RCC)

Randomized, open-label, phase 3 study vs. everolimus (CA209025)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced RCC was evaluated in a Phase 3, randomized, 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 PD-L1 status. Patients with any history of or concurrent brain metastases, prior treatment with a mammalian target of rapamycin (mTOR) inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

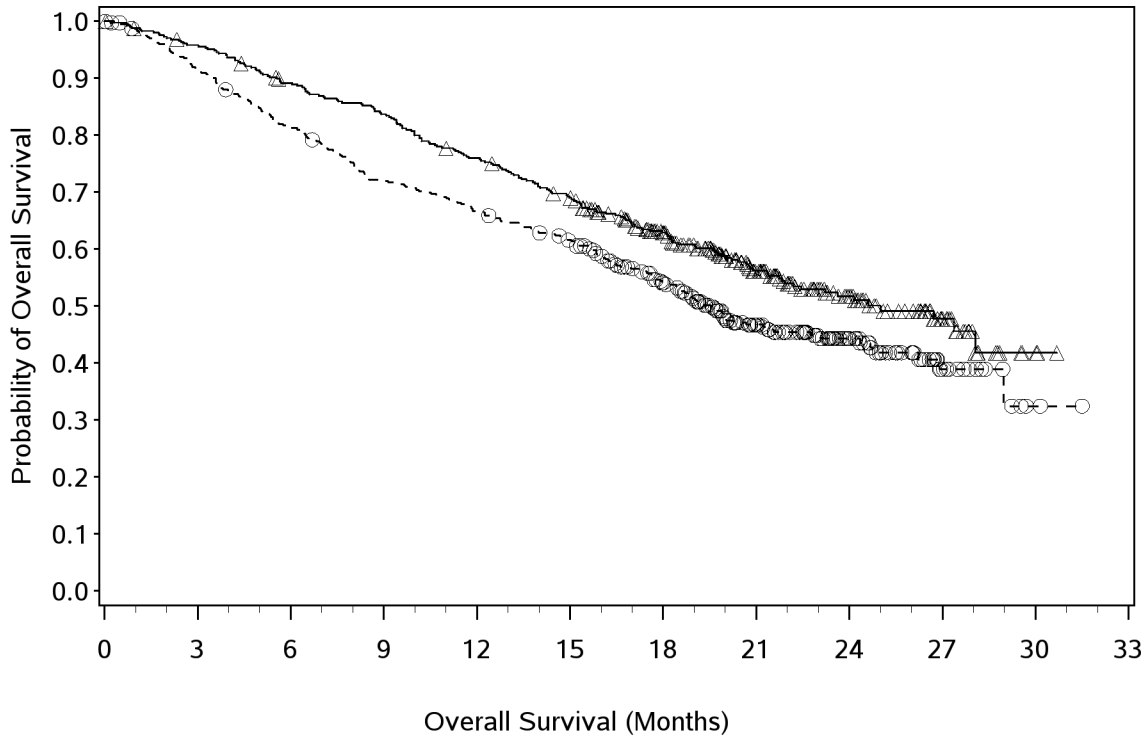
Patients were randomized to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks or everolimus 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumor assessments 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. Tumor assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST 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.

A total of 821 patients were randomized to receive either nivolumab (n=410) or everolimus (n=411). Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40% ≥65 years of age and 9% ≥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 randomization 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) for nivolumab and 3.7 months (range: 6 days-25.7^{+} months) for everolimus.

Nivolumab was continued beyond progression in 44% of patients.

The Kaplan-Meier curves for OS are shown in Figure 10.

Figure 10: 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 (events: 183/410), median and 95% CI: 25.00 (21.75, N.A.)
Everolimus (events: 215/411), median and 95% CI: 19.55 (17.64, 23.06)
Nivolumab vs Everolimus - hazard ratio and 98.52% CI: 0.73 (0.57, 0.93); p-value: 0.0018

The trial demonstrated a statistically significant improvement in OS for patients randomized 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 19 and Figure 12). OS benefit was observed regardless of PD-L1 expression level.

Table 19: Efficacy results (CA209025)

	nivolumab (n = 410)	everolimus (n = 411)
Overall survival		
Events n (%)	183 (45%)	215 (52%)
Hazard ratio	0.73	
98.52% CI	(0.57, 0.93)	
p-value	0.0018	
Median (95% CI)	25.0 months (21.7, NE)	19.6 months (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)
Objective response n (%)	103 (25.1%)	22 (5.4%)
(95% CI)	(21.0, 29.6)	(.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%)
Median duration of response		
(range)	12.0 months (0.0-27.6^{+})	12.0 months (0.0^{+}-22.2^{+})
Median time to response		
(range)	3.5 months (1.4-24.8)	3.7 months (1.5-11.2)
Progression-free survival		
Events n (%)	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 months (3.7, 5.4)	4.4 months (3.7, 5.5)

NE=not estimable

"+" denotes a censored observation.

The Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) subscale of the FKSI-15 was used to assess disease-related symptom progression rate in each treatment arm. With a completion rate of 80% in the first year, nivolumab demonstrated a favourable impact on disease-related symptom progression rate. The scores for the nivolumab group increased over time and differed significantly from median changes in the everolimus group at each assessment point through week 104.

Randomized 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, randomized, open-label study

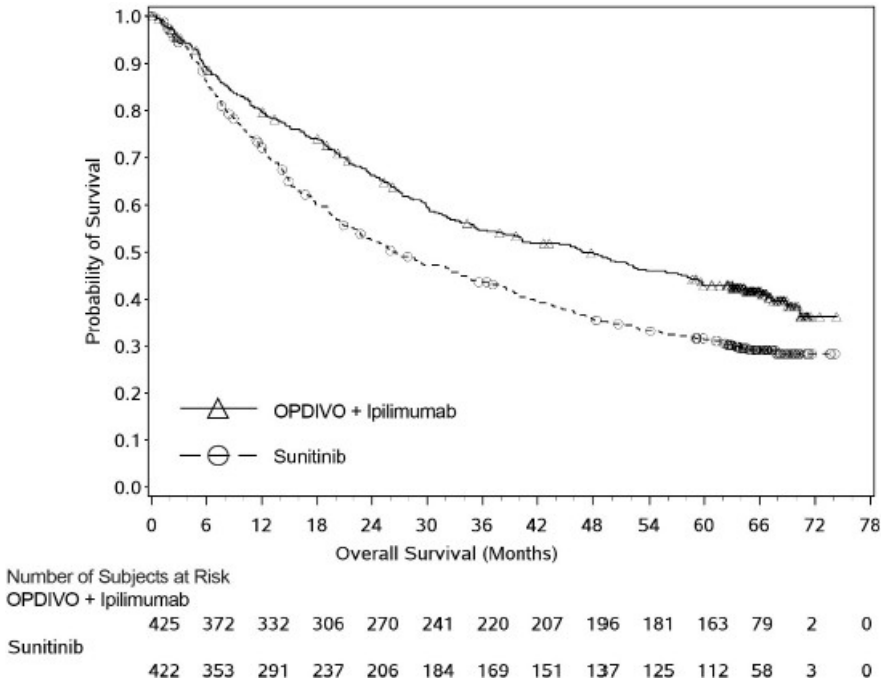
(CA209214). The study included patients (18 years or older) with previously untreated, advanced or metastatic renal cell carcinoma with a clear-cell component. The primary efficacy population included those intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the International Metastatic RCC Database Consortium (IMDC) criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, 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 tumor 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 randomized 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 tumor assessments were conducted 12 weeks after randomization 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 Blinded Independent Central Review (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 randomization 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.

The Kaplan-Meier curves for OS (with a minimum follow-up of 60 months) in intermediate/poor-risk patients are shown in Figure 11.

Figure 11: Kaplan-Meier curves of OS in intermediate/poor-risk patients (CA209214)



The trial demonstrated statistically significant improvement in OS, clinically relevant improvement in ORR, and a numerical improvement (not statistically significant) in PFS for intermediate/poor-risk patients randomized to nivolumab in combination with ipilimumab as compared with sunitinib (Table 10). With a longer follow-up (a minimum follow-up of 60 months), as shown in Figure 11, the trial continued to demonstrate significant improvement in OS for patients randomized to nivolumab and ipilimumab as compared with sunitinib.

In intermediate/poor-risk patients, OS benefit was observed in the nivolumab in combination with ipilimumab arm vs. sunitinib regardless of tumor PD-L1 expression. Median OS for tumor PD-L1 expression ≥1% was not reached for nivolumab in combination with ipilimumab, and was 19.61 months in the sunitinib arm (HR=0.45; 95% CI: 0.29, 0.71). For tumor PD-L1 expression <1%, the median OS was not reached for the nivolumab in combination with ipilimumab and the sunitinib arms (HR=0.73; 95% CI: 0.56, 0.96).

CA209214 also randomized 249 favorable-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. With 60 month minimum follow-ups. OS in favorable-risk patients receiving nivolumab plus ipilimumab compared to sunitinib had a hazard ratio of 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.

Efficacy results for the intermediate/poor risk patients are shown in Table 20.

Table 20: Efficacy results in intermediate/poor-risk patients (CA209214)

	nivolumab + ipilimumab (n = 425)		sunitinib (n = 422)	
Overall survival[a]				
Events	140 (33%)		188 (45%)	
Hazard ratio[b]	0.63			
99.8% CI	(0.44, 0.89)			
p-value[c,d]	<0.0001			
Median (95% CI)	NE (32.5, NE)		27.0 (22.1, 34.8)	
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)	
Progression-free survival				
Events	228 (53.6%)		228 (54.0%)	
Hazard ratio[b]	0.82			
99.1% CI	(0.64, 1.05)			
p-value[c,i]	0.0331			
Median (95% CI)	11.6 (8.71, 15.51)		8.4 (7.03, 10.81)	
Confirmed objective response (BICR)	177	(41.6%)	112	(26.5%)
(95% CI)	(36.9, 46.5)		(22.4, 31.0)	
Difference in ORR (95% CI)[e]	16.0 (9.8, 22.2)			
p-value[f,g]	<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%)
Median duration of response[h]				
Months (range)	NE	(1.4+, 25.5+)	18.2	(1.3+, 23.6+)
Median time to response				
Months (range)	2.8	(0.9-11.3)	3.0	(0.6-15.0)

[a] Results are based on the final analysis with 24 months of minimum follow-up.

[b] Based on a stratified proportional hazards model.

[c] Based on a stratified log-rank test.

[d] p-value is compared to alpha 0.002 in order to achieve statistical significance.

[e] Strata adjusted difference.

[f] Based on the stratified DerSimonian-Laird text.

[g] p-value is compared to alpha 0.001 in order to achieve statistical significance.

[h] Computed using Kaplan-Meier method.

[i] p-value is compared to alpha 0.009 in order to achieve statistical significance.

"+" denotes a censored observation.

NE = non-estimable.

An updated 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. At 18 months, the OS rate was 74.3% (95% CI: 69.8-78.2) for nivolumab in combination with ipilimumab and 59.9 (95% CI: 54.9-64.5) for sunitinib. At 24 months, the OS rate was 66.5% (95% CI: 61.8-70.9) for nivolumab in combination with ipilimumab and 52.9 (95% CI: 47.9- 57.7) for sunitinib. An updated OS analysis was performed when all patients had a minimum follow-up of 60 months. At the time of analysis the median OS was 47.0 months in the nivolumab and ipilimumab arm and 26.6 months in the sunitinib arm (HR: 0.68; 95% CI: 0.58, 0.81).

The median time to onset of objective response was 2.8 months (range: 0.9-11.3 months) after the start of nivolumab with ipilimumab treatment. Among the 177 responders, 128 (72.3%) had an ongoing response with a duration ranging from 1.4+-25.5+ months.

Patients ≥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. Because of the small size of this subgroup, no definitive conclusions can be drawn from these data.

Overall survival was accompanied by fewer patients experiencing patient-reported deterioration on disease-related symptoms, cancer symptoms and non-disease specific Quality of Life (QoL) as assessed using valid and reliable scales in the FKSI-19, FACT-G, and EQ-5D. In those patients who deteriorated, the time to deterioration was significantly longer for all three scales for those in the nivolumab in combination with ipilimumab arm relative to those in the sunitinib arm ($p<0.0001$). 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.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of metastatic or recurrent SCCHN were evaluated in a Phase 3, randomized, open-label study (CA209141). The study included patients (18 years or older) who had disease progression during or after a prior 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 tumor 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 untreated brain metastasis 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.

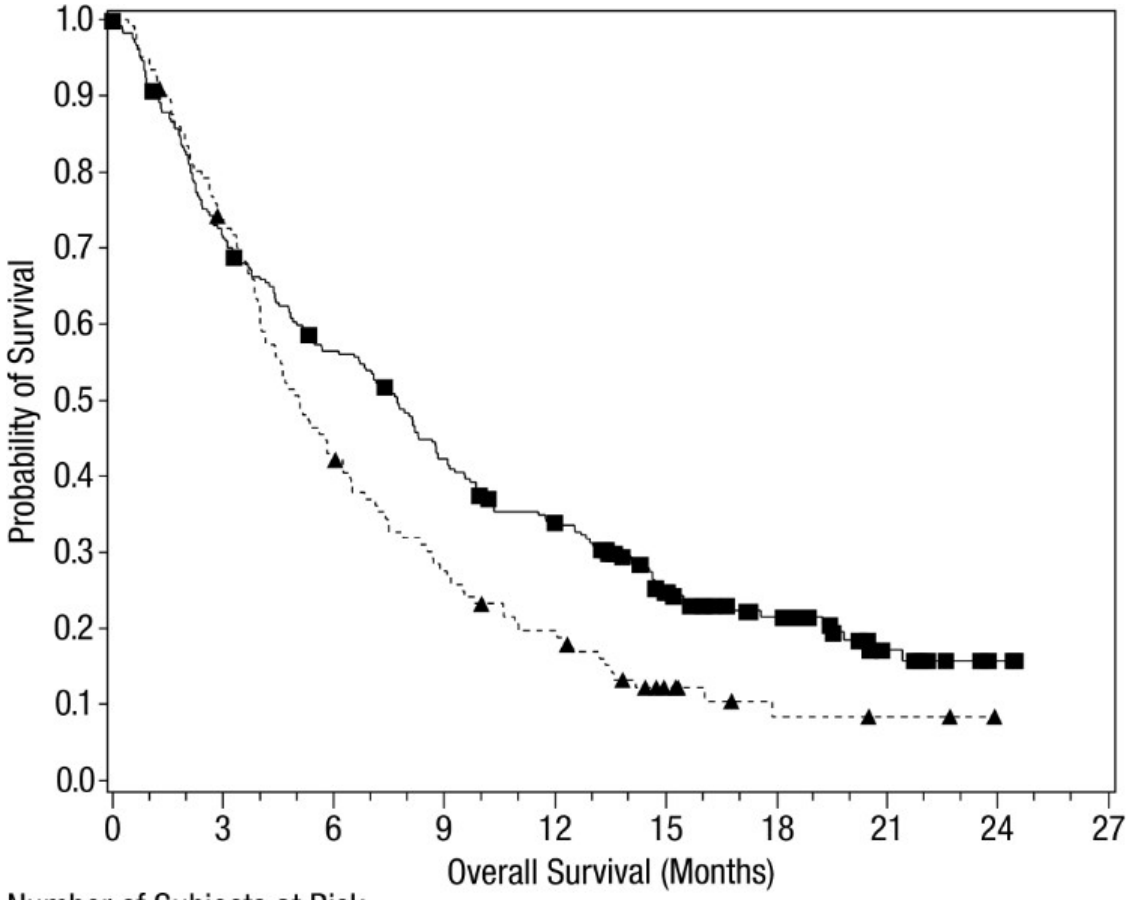
A total of 361 patients were randomized to receive either nivolumab 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n = 15), 400 mg/m2 loading dose followed by 250 mg/m2 weekly or methotrexate

(n = 52) 40 to 60 mg/m2 weekly, or docetaxel (n = 54) 30 to 40 mg/m2 weekly. Randomization was stratified by prior cetuximab treatment. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments, according to RECIST version 1.1, were conducted 9 weeks after randomization 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 tumor PD-L1 expression at predefined levels of 1%, 5%, and 10%.

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 men, 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 randomized to nivolumab compared with investigator's choice. The Kaplan-Meier curves for OS are shown in Figure 12. Efficacy results are shown in Table 21.

Figure 12: Kaplan-Meier curves of OS (CA209141)



Number of Subjects at Risk

NIVO	240	169	132	98	76	45	27	12	3
INV 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)

NIVO vs. INV Choice - hazard ratio 95%: 0.71 (0.55, 0.90), pvalue:0.0048

Symbols represent censored observations

Table 21: Efficacy results (CA209141)

	nivolumab (n = 240)	investigator's choice (n = 121)
Overall survival		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio[a]	0.71	
(95% CI)	(0.55, 0.90)	
p-value[b]	0.0048	
Median (95% CI)	7.7 months (5.7, 8.8)	5.1 months (4.0, 6.2)
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)
Progression-free survival		
Events	204 (85%)	104 (86%)
Hazard ratio	0.87	
95% CI	(0.69, 1.11)	
p-value	0.2597	
Median (95% CI)	2.0 months (1.9, 2.1)	2.3 months (2.0, 3.1)
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)
Confirmed objective response[c] n (%)	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%)
Median time to response (range)	2.1 months (1.8- 7.4)	2.0 months (1.9 - 4.6)
Median duration of response (range)	9.7 months (2.8- 20.3^{+})	4.0 months (1.5^{+}- 8.5^{+})

[a] Derived from a stratified proportional hazards model.

[b] 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.

[c] In the nivolumab group there were two patients with CRs and seven patients with PRs who had tumor PD-L1 expression < 1%.

"+" denotes a censored observation.

Pre-study tumor tissue specimens were systematically collected prior to randomisation in order to conduct pre-planned analyses of efficacy according to tumor PD-L1 expression. Tumor PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. Quantifiable tumor PD-L1

expression was measured in 67% of patients in the nivolumab group and 82% of patients in the investigator's choice group. Tumor PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. investigator's choice) at each of the predefined tumor PD-L1 expression levels of ≥ 1% (55% vs. 62%), ≥ 5% (34% vs. 43%), or ≥ 10% (27% vs. 34%).

Patients with tumor PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared with those in the investigator's choice group. The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumor PD-L1 expression levels (Table 22).

Table 22: OS by tumor PD-L1 expression (CA209141)

PD-L1 Expression	nivolumab	investigator's choice	
	OS by tumor 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)
≥ 1%	66 (88)	55 (61)	0.53 (0.37, 0.77)
≥ 5%	39 (54)	40 (43)	0.51 (0.32, 0.80)
≥ 10%	30 (43)	31 (34)	0.57 (0.34, 0.95)

Patients with investigator-assessed primary site of oropharyngeal cancer were tested for HPV. OS benefit was observed regardless of HPV status (HPV-positive oropharyngeal: HR = 0.63; 95% CI: 0.38, 1.04 and HPV-negative oropharyngeal and non-oropharyngeal SCCHN: HR = 0.74; 95% CI: 0.56, 0.98).

Patient-reported outcomes (PROs) were assessed using three measures: the EORTC QLQ-C30, EORTC QLQ-H&N35, and 3-level version of the EQ-5D. Over 15 weeks of follow-up, patients treated with nivolumab exhibited generally stable PROs, while those assigned to investigator's choice therapy exhibited statistically significant and clinically meaningful declines in functioning (e.g., physical, role, social) and health status as well as increases in symptomatology (e.g., fatigue, dyspnea, appetite loss, pain, sensory problems, social contact problems).

Unresectable or metastatic melanoma

Randomized phase 3 study vs. dacarbazine (CA209066)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomized, double-blind study (CA209066). The study included patients (18 years or older) with confirmed, treatment-naive, Stage III or IV BRAF wild-type melanoma and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients who had received previous adjuvant therapy were not excluded. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

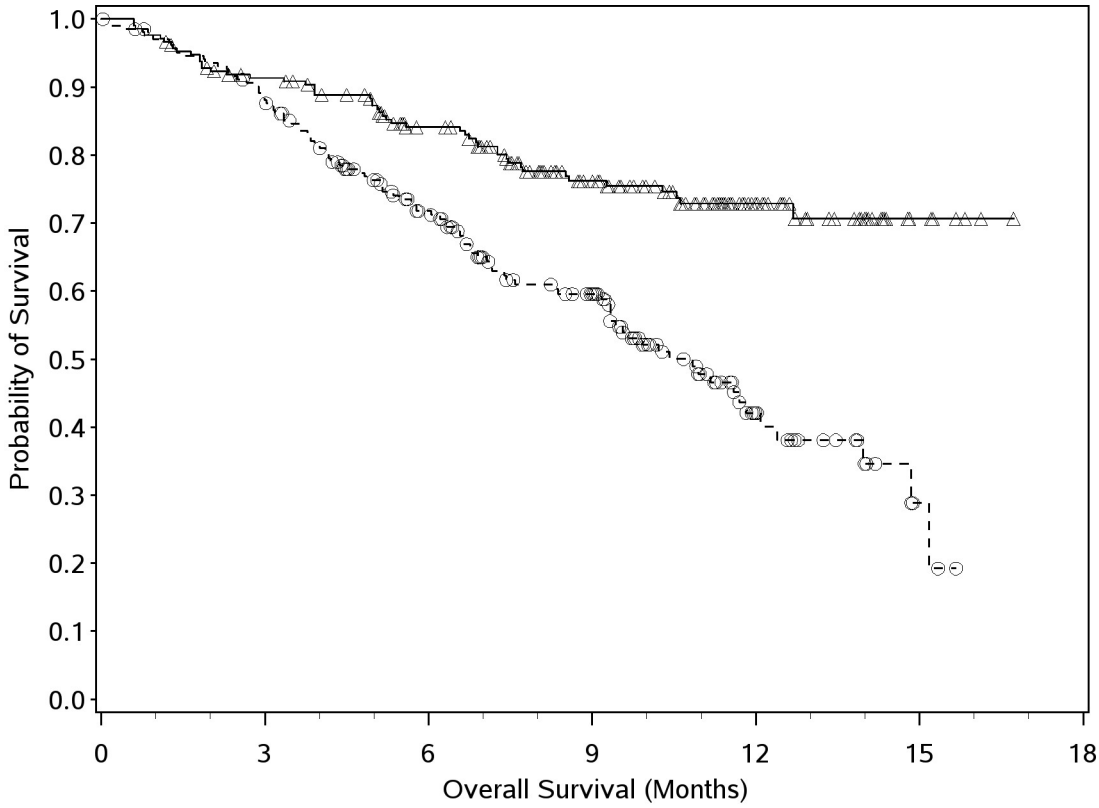
Patients were randomized on a 1:1 basis to receive either nivolumab administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine at 1000 mg/m2 every 3 weeks. Randomization was stratified by PD-L1 status and M stage (M0/M1a/M1b versus M1c). Treatment was continued as long as clinical 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 effects with the study drug, as determined by the investigator. Tumor assessments, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, were conducted 9 weeks after randomization and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed progression-free survival (PFS) and objective response rate (ORR).

A total of 418 patients were randomized to either nivolumab (n=210) or dacarbazine (n=208). Baseline characteristics were balanced between the two groups. The median age was 65 years (range: 18-87), 59% were men, and 99% 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 (>5% tumor cell membrane expression). 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.

Nivolumab demonstrated a statistically significant improvement in OS over dacarbazine in treatment-naive patients with BRAF wild-type advanced (unresectable or metastatic) melanoma (HR = 0.42; 99.79% CI: 0.25, 0.73; p-value <0.0001). Median OS was not reached for nivolumab and was 10.8 months (95% CI: 9.33, 12.09) for dacarbazine. The estimated OS rates at 12 months were 73% (95% CI: 65.5, 78.9) and 42% (95% CI: 33.0, 50.9), respectively.

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 PD-L1 expression was above or below a PD-L1 tumor membrane expression cut-off of 5% or 10%. The Kaplan-Meier curves for OS are shown in Figure 13.

Figure 13: Kaplan-Meier curves of OS (CA209066)



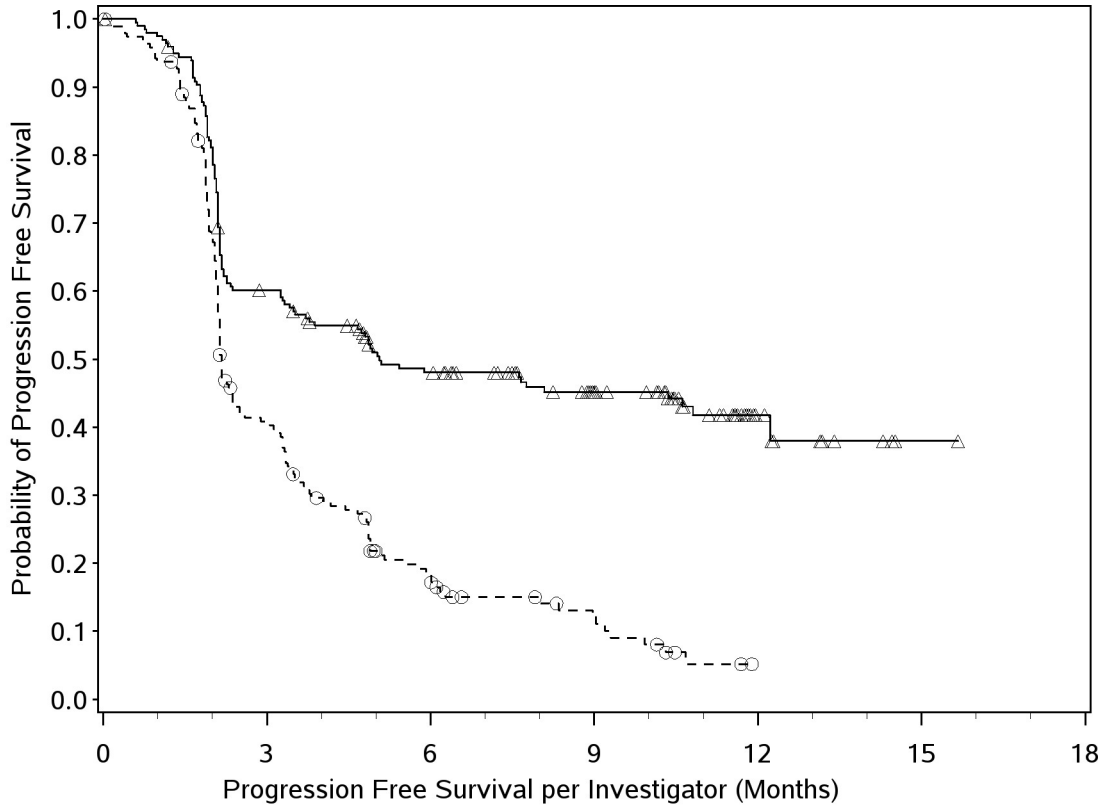
Number of Subjects at Risk

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)
Hazard Ratio (Nivolumab over Dacarbazine) and 95% CI (1): 0.42 (0.30, 0.60)
Hazard Ratio (Nivolumab over Dacarbazine) and 99.79% CI (1): 0.42 (0.25, 0.73)
Stratified log-rank p-value: <0.0001

Nivolumab also demonstrated statistically significant improvement in PFS compared with dacarbazine (HR = 0.43 [95% CI: 0.34, 0.56]; p <0.0001). The median PFS was 5.1 months (95% CI: 3.48, 10.81) for nivolumab and 2.2 months (95% CI: 2.10, 2.40) for dacarbazine. The estimated PFS rates at 6 months were 48% (95% CI: 40.8, 54.9) and 18% (95% CI: 13.1, 24.6), respectively. The estimated PFS rate at 12 months was 42% (95% CI: 34.0, 49.3) for nivolumab. The Kaplan-Meier curves for PFS are shown in Figure 14.

Figure 14: Kaplan-Meier curves of progression-free survival (CA209066)



Number of Subjects at Risk

Nivolumab						
210	116	82	57	12	1	0
Dacarbazine						
208	74	28	12	0	0	0

Nivolumab (events : 108/210), median and 95% CI : 5.06 (3.48, 10.81)
Dacarbazine (events : 163/208), median and 95% CI : 2.17 (2.10, 2.40)
Hazard Ratio (Nivolumab over Dacarbazine) and 95% CI (1): 0.43 (0.34, 0.56)
Stratified log-rank p-value: <0.0001

The investigator-assessed ORR using RECIST v1.1 criteria was significantly higher in the nivolumab group than in the dacarbazine group (Odds Ratio: 4.06 [95% CI: 2.52, 6.54], p <0.0001). Response rates, time to response, and duration of response are shown in Table 23.

Table 23: Best overall response, time, and duration of response (CA209066)

	nivolumab (n=210)	dacarbazine (n=208)
Objective response n (%)	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%)
Median duration of response		
(range)	Not reached (0^+ - 12.5^+)	6.0 months (1.1 - 10.0^+)
Median time to response		
(range)	2.1 months (1.2 - 7.6)	2.1 months (1.8 - 3.6)

"+" denotes a censored observation.

At the time of analysis, 82% (69/84) of nivolumab-treated patients and 31% (9/29) of dacarbazine-treated patients had ongoing responses, which included 46 and 4 patients, respectively, with ongoing response of 6 months or longer.

In 54 nivolumab-treated patients, treatment was continued beyond an initial investigator assessment of RECIST disease progression if the investigator determined the patient had sufficient ongoing clinical benefit and was tolerating therapy. Of these patients, 12 (22.2%) had target lesion reductions (>30% compared to baseline).

Randomized phase 3 study vs. chemotherapy (CA209037)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomized, 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 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.

Patients were randomized on a 2:1 basis to receive either nivolumab administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or chemotherapy. Chemotherapy consisted of the investigator's choice of either dacarbazine (1000 mg/m^2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks). Randomization was stratified by BRAF and PD-L1 status and best response to prior ipilimumab. Tumor assessments were

conducted 9 weeks after randomization and continued every 6 weeks for the first year and then every 12 weeks thereafter.

The co-primary efficacy outcome measures were confirmed ORR, as measured by independent radiology review committee (IRRC) using RECIST 1.1, and comparison of OS of nivolumab to chemotherapy. Additional outcome measures included duration and timing of response.

A total of 405 patients were randomized to receive either nivolumab (n=272) or chemotherapy (n = 133). 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 were BRAF mutation positive and 50% of patients were 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 analyzed. Efficacy results are presented in Table 24 and Figure 15.

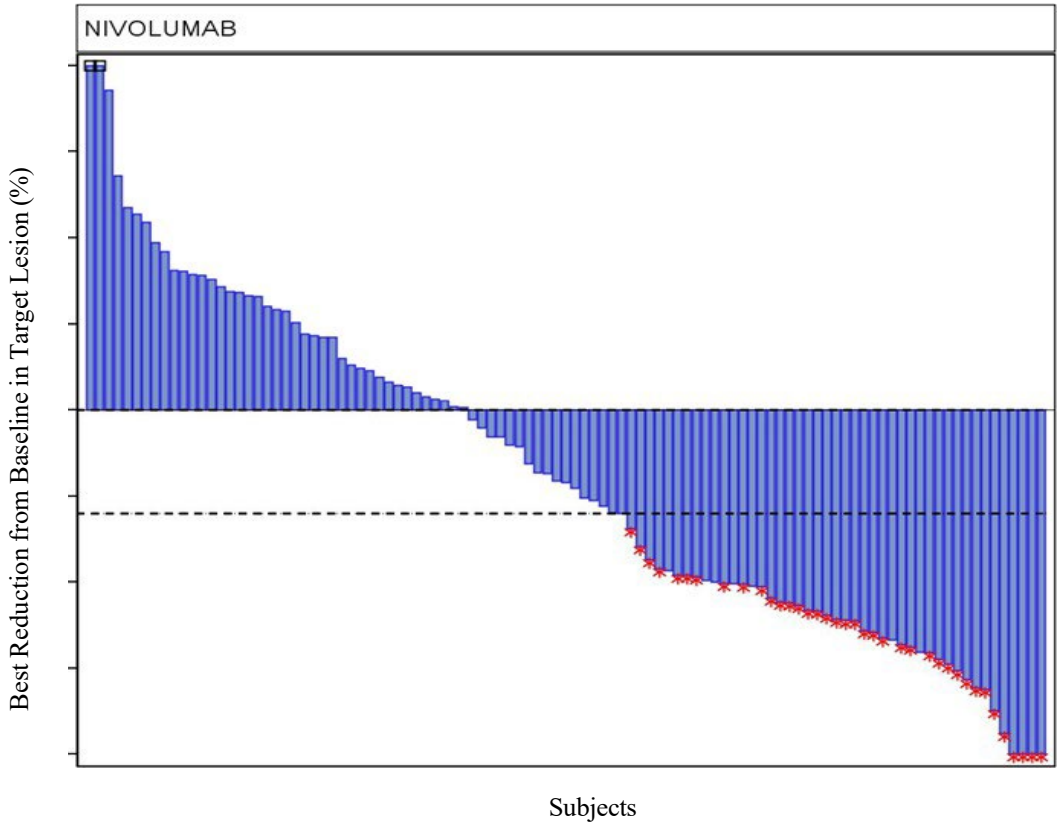
Table 24: Best overall response, time, and duration of response (CA209037)

	nivolumab (n=120)	**chemotherapy (n=47)**
Confirmed Objective Response (IRRC) n (%)	38 (31.7%)	5 (10.6%)
(95% CI)	(23.5, 40.8)	(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%)
Median Duration of Response		
(range)	Not Reached	3.6 months (Not available)
Median Time to Response		
(range)	2.1 months (1.6-7.4)	3.5 months (2.1-6.1)

Of the 38 nivolumab-treated patients with a confirmed response, 33 were still in response at the time of analysis.

Objective responses to nivolumab were observed in patients with or without BRAF mutation-positive melanoma. Of the patients who received nivolumab, the ORR in the BRAF mutation-positive subgroup was 23% (95% CI: 9.0, 43.6), and 34% (95% CI: 24.6, 44.5) in patients whose tumors were BRAF wild-type. Objective responses to nivolumab were observed regardless of whether PD-L1 expression was above or below a PD-L1 tumor membrane expression cut-off of 5% or 10%.

Figure 15: Waterfall plot of best reduction in target lesion, per IRRC (CA209037)



Note: Symbol ("*") represents confirmed responders.

In 37 (31%) nivolumab-treated patients, treatment was continued beyond an initial investigator assessment of RECIST disease progression if the investigator determined that the patient had sufficient ongoing clinical benefit and was tolerating therapy. Of these patients, 10 (27%) had target lesion reductions (>30% compared to baseline).

Updated analysis (24-month follow-up)

Among all randomized 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 duration of response was 31.9 months (range: 1.4+-31.9) and 12.8 months (range: 1.3+-13.6+), respectively.

There was no statistically significant difference between nivolumab and chemotherapy in the primary OS analysis. The OS analysis was not adjusted to account for subsequent therapies, with 54 (41%) 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.

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 tumor 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, 36.7), and the estimated OS rates were 63% (95% CI: 53, 71) at 1 year, 48% (95% CI: 38, 57) at 2 years, and 41% (95% CI: 31, 51) at 3 years.

Randomized phase 3 study of nivolumab in combination with ipilimumab or nivolumab as monotherapy vs ipilimumab (CA209067)

The safety and efficacy of nivolumab in combination with ipilimumab and nivolumab monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomized, double-blind study (CA209067). The study included adult patients (18 years or older) with confirmed unresectable Stage III or Stage IV melanoma, regardless of PD-L1 expression. 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 randomization. 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 randomized to receive nivolumab in combination with ipilimumab (n = 314), nivolumab as monotherapy (n = 316), or ipilimumab as monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg 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. Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor 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. Tumor assessments were conducted 12 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter. The co-primary outcome measures were progression-free survival and OS. ORR and the duration of response were also assessed. This

study evaluated whether PD-L1 expression was a predictive biomarker for the co-primary endpoints. The efficacy of nivolumab in combination with ipilimumab and nivolumab monotherapy was each compared with that of ipilimumab. In addition, the differences between the two nivolumab-containing groups were evaluated descriptively, but not included in formal hypothesis testing. Health Related Quality of Life (HRQoL) was assessed by the European Organization for Research and Treatment of Care (EORTC) QLQ-C30.

Baseline characteristics were balanced across the three treatment groups. The median age was 61 years (range: 18-90 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 ≥5% tumor 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.

Note: *The results for nivolumab monotherapy compared with ipilimumab monotherapy are included here.*

Nivolumab arm demonstrated a significant PFS and OS benefit and greater ORR compared with ipilimumab monotherapy. Efficacy results for the randomized patients are shown in Table 25, Figure 16, and Figure 17.

The observed PFS, OS, and ORR results for nivolumab monotherapy 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.

Table 25: Efficacy results (CA209067)

	nivolumab (n=316)	ipilimumab (n=315)
Progression-free survival[a]		
Events n (%)	174 (55%)	234 (74%)
Hazard ratio (vs. ipilimumab) (99.5% CI)	0.57 (0.43, 0.76)	
p-value	p<0.0001	
Median (95% CI)	6.9 months (4.3, 9.5)	2.9 months (2.8, 3.4)
Rate (95% CI)		
At 6 months	52% (46, 57)	29% (24, 34)
At 9 months	45% (40, 51)	21% (17, 26)
Overall survival[b]		
Events n (%)	142 (45%)	197 (63%)
Hazard ratio (vs. ipilimumab) (98% CI)	0.63 (0.48, 0.81)	
p-value	p<0.0001	
Median (95% CI)	Not reached (29.1, NE)	20.0 months (17.1, 24.6)
Rate (95% CI)		
At 12 months	74% (69, 79)	67% (61, 72)
At 24 months	59% (53, 64)	45% (39, 50)
Objective response[b] n (%)	141 (45%)	60 (19%)
(95% CI)	(39.1, 50.3)	(14.9, 23.8)
Odds ratio (vs ipilimumab)	3.54	
(95% CI)	(2.10, 5.95)	
Complete response (CR)	47 (15%)	14 (4%)
Partial response (PR)	94 (30%)	46 (15%)
Stable disease (SD)	31 (10%)	67 (21%)
Duration of response		
Median (range)	31.1 months (0^+ - 32.3^+)	18.2 months (0^+ - 31.5^+)
Proportion >12 months in duration	70%	53%
Proportion >24 months in duration	49%	32%

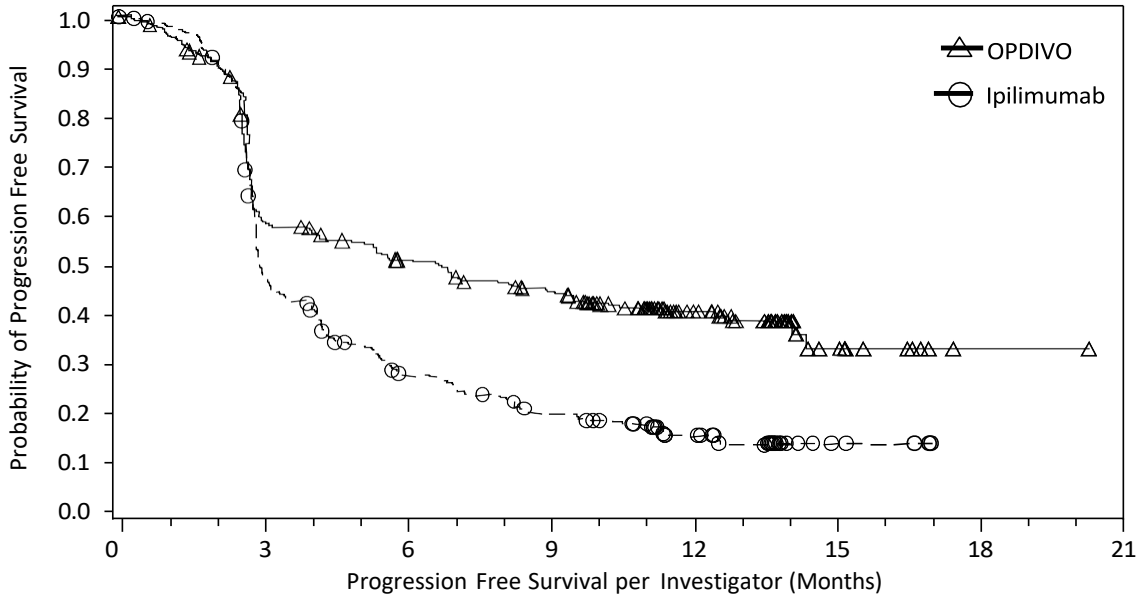
[a] Minimum follow up of 9 months.

[b] Minimum follow up of 28 months.

NE=not estimable.

"+" denotes a censored observation.

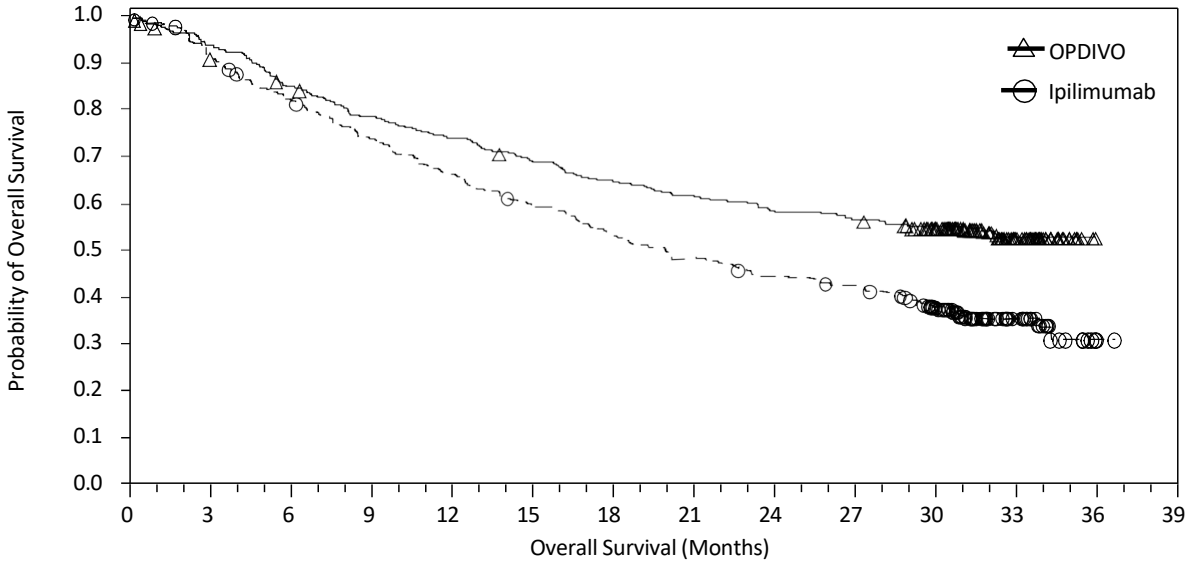
Figure 16: Progression-free survival (CA209067)



Number of Subjects at Risk

OPDIVO	316	177	147	124	50	9	1	0
Ipilimumab	315	137	77	54	24	4	0	0

Figure 17: Overall survival (CA209067)



Number of Subjects at Risk

OPDIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
Ipilimumab	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Quality of life measured by the EORTC QLQ-C30 Global Health Status remained stable in both treatment groups, with no mean change in score from baseline reaching the minimal important difference for the patient (i.e., mean change ≥10 points) at any time point for any of the three treatment arms.

Efficacy by BRAF status: Efficacy results by BRAF status are shown in Table 26 for PFS, Table 27 for OS, and Table 28 for ORR.

Table 26: PFS by BRAF [V600]-mutation status (CA209067)

	BRAF [V600] mutation-positive		BRAF wild-type	
Treatment	**Median PFS (95% CI)**	**HR vs ipilimumab (95% CI)**	**Median PFS (95% CI)**	**HR vs ipilimumab (95% CI)**
nivolumab	5.6 months (2.8, 9.5)	0.77 (0.54, 1.09)	7.9 months (4.9, 12.7)	0.50 (0.39, 0.63)
ipilimumab	4.0 months (2.8, 5.5)	--	2.8 months (2.8, 3.1)	--

Minimum follow up of 9 months.
NE=not estimable.

Table 27: OS by BRAF[V600]-mutation status (CA209067)

	BRAF [V600] mutation-positive		BRAF wild-type	
Treatment	**Median OS (95% CI)**	**HR vs ipilimumab (95% CI)**	**Median OS (95% CI)**	**HR vs ipilimumab (95% CI)**
Nivolumab	Not reached (26.4, NE)	0.60 (0.40, 0.89)	Not reached (25.8, NE)	0.64 (0.49, 0.83)
Ipilimumab	24.6 months (17.9, 31.0)	--	18.5 months (14.8, 23.0)	--

Minimum follow up of 28 months.
NE=not estimable.

Table 28: Objective response by BRAF[V600]-mutation status[a] (CA209067)

	BRAF [V600] mutation-positive		BRAF wild-type	
Treatment	**Number of responses/patients**	**ORR (95% CI)**	**Number of responses/patients**	**ORR (95% CI)**
Nivolumab	36/98	37% (27, 47)	105/218	48% (41, 55)
Ipilimumab	23/100	23% (15, 33)	37/215	17% (12, 23)

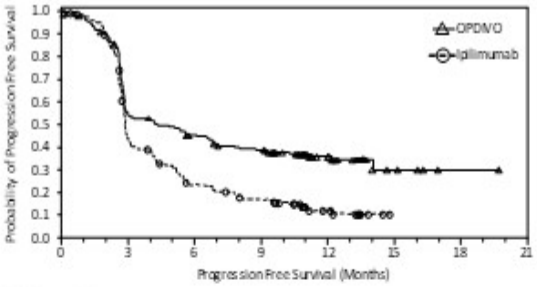
Minimum follow up of 28 months.

Efficacy by PD-L1 tumor Expression: Baseline tumor tissue specimens were systematically collected prior to randomization in order to conduct planned analyses of efficacy according to PD-L1 expression. Quantifiable tumor PD-L1 expression was measured in 91% (288/316) of patients randomized to nivolumab monotherapy, and 88% (277/315) of patients randomized to ipilimumab monotherapy. Among patients with quantifiable tumor PD-L1 expression, the distribution of patients was balanced across the three treatment groups at each of the predefined tumor PD-L1 expression levels of ≥1% (59% in the nivolumab monotherapy arm, and 59% in the ipilimumab arm) and ≥5% (24%, 28%, and 27%, respectively). Tumor PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

In patients with low or no tumor PD-L1 expression (based on the predefined expression level of <5% and <1%), nivolumab monotherapy demonstrated significant improvements in PFS and OS compared with ipilimumab monotherapy. In patients with ≥5% and ≥1% tumor PD-L1 expression, a significant improvement in PFS and OS relative to ipilimumab was also observed for nivolumab arm. Results by PD-L1 expression level are shown in Figure 18 for PFS and in Figure 19 for OS.

Figure 18: Progression-free survival by tumor PD-L1 expression level (CA209067)

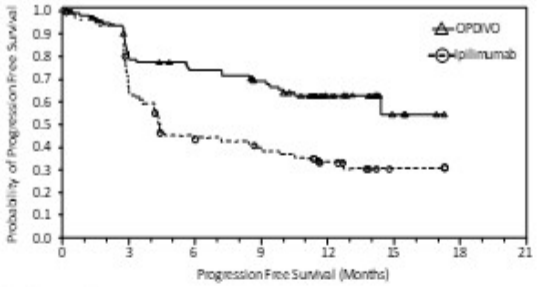
≥ 5%



Number of Subjects at Risk								
OPDIVO	208	108	88	74	31	5	1	0
Ipilimumab	202	82	44	31	12	1	0	0

OPDIVO (events : 122/208), median and 95% CI : 5.32 (2.83, 7.06)
Ipilimumab (events : 154/202), median and 95% CI : 2.83 (2.76, 3.09)
OPDIVO vs Ipilimumab – hazard ratio and 95% CI: 0.59 (0.47, 0.75)

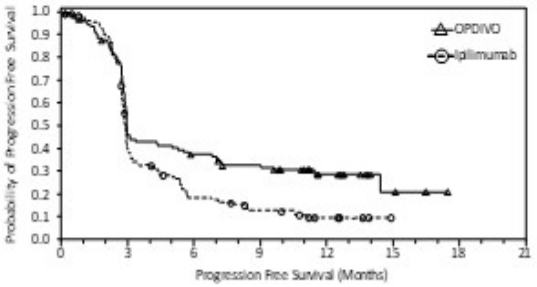
< 5%



Number of Subjects at Risk								
OPDIVO	80	57	51	43	16	4	0	0
Ipilimumab	75	40	22	17	9	2	0	0

OPDIVO (events : 33/80), median and 95% CI : 14.00 (9.07, N.A)
Ipilimumab (events : 53/75), median and 95% CI : 3.94 (2.79, 4.21)
OPDIVO vs Ipilimumab – hazard ratio and 95% CI: 0.41 (0.26, 0.63)

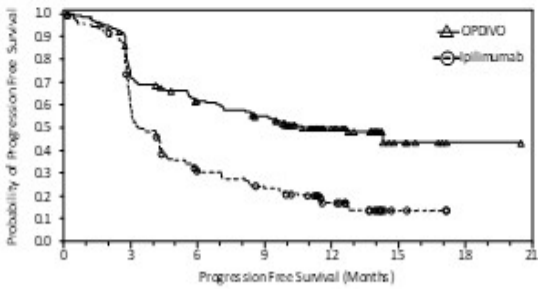
< 1%



Number of Subjects at Risk								
OPDIVO	117	50	42	34	13	2	0	0
Ipilimumab	113	39	19	12	5	0	0	0

OPDIVO (events : 76/117), median and 95% CI : 2.83 (2.76, 5.13)
Ipilimumab (events : 85/113), median and 95% CI : 2.79 (2.66, 2.96)
OPDIVO vs Ipilimumab – hazard ratio and 95% CI: 0.67 (0.49, 0.92)

≥ 1%



Number of Subjects at Risk								
OPDIVO	171	115	97	83	34	7	1	0
Ipilimumab	164	83	47	36	16	3	0	0

OPDIVO (events : 79/171), median and 95% CI : 12.39 (8.11, N.A.)
Ipilimumab (events : 122/164), median and 95% CI : 3.91 (2.83, 4.17)
OPDIVO vs Ipilimumab – hazard ratio and 95% CI: 0.46 (0.34, 0.61)

Figure 19: Overall survival by tumor PD-L1 expression level (CA209067)

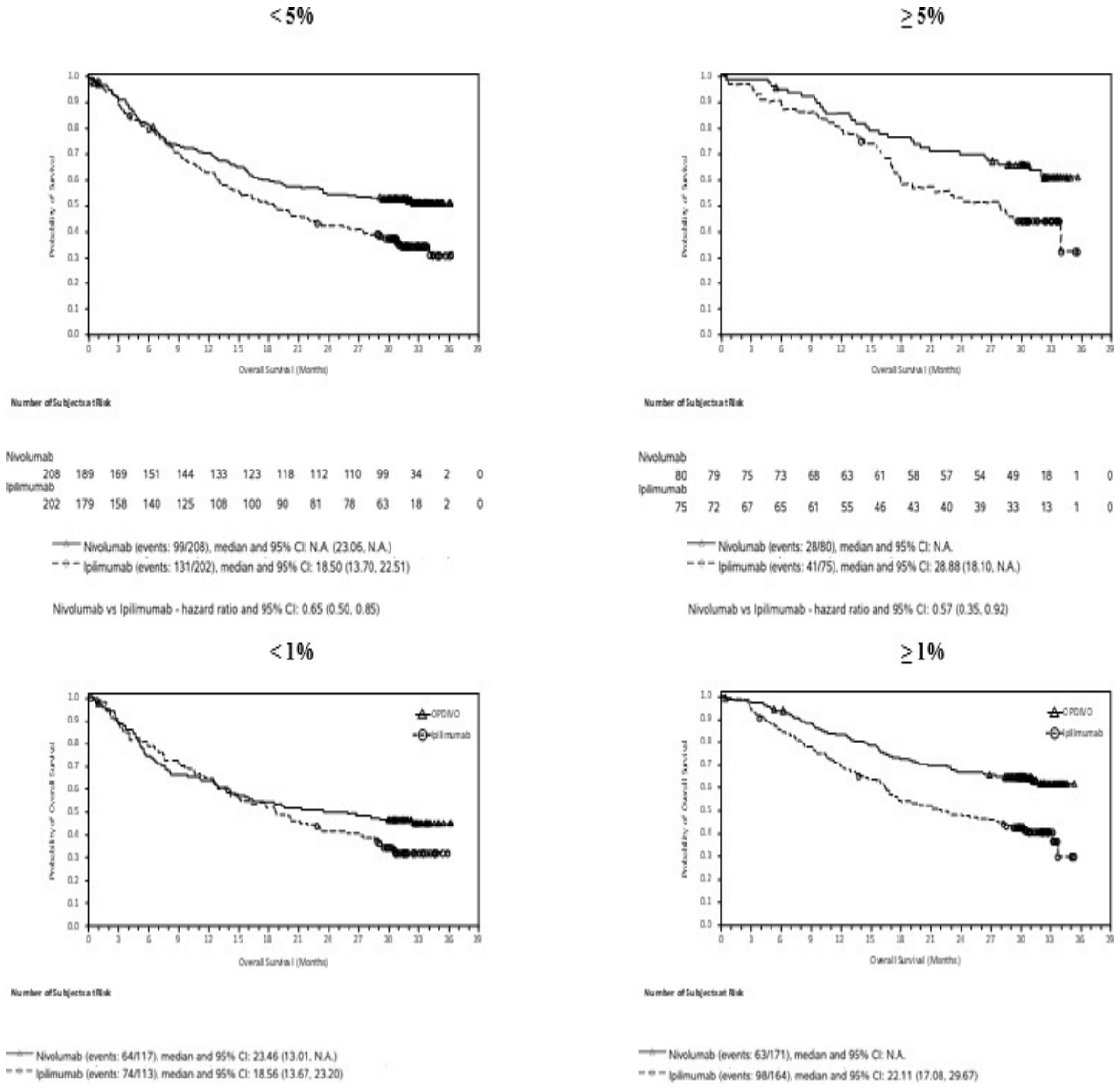


Table 29 shows the objective response rates in CA209067 based on PD-L1 expression level. Nivolumab arm demonstrated greater objective response rates than ipilimumab regardless of tumor PD-L1 expression levels.

Table 29: Objective response by PD-L1 Expression Level (CA209067)

	ORR % (95% CI)	
	nivolumab (n=316)	**ipilimumab (n=315)**
<5%	42% (35.5, 49.3) n=208	18% (12.8, 23.8) n=202
≥5%	59% (47.2, 69.6) n=80	21% (12.7, 32.3) n=75
<1%	35% (26.5, 44.4) n=117	19% (11.9, 27.0) n=113
≥1%	55% (47.2, 62.6) n=171	19% (13.2, 25.7) n=164

No clear cutoff for PD-L1 expression can reliably be established when considering the relevant endpoints of tumor response, PFS, and OS.

As compared to the overall study population, no meaningful differences in safety were observed based on BRAF status or tumor PD-L1 expression levels of 1% or 5%.

Randomized 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, randomized, 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), 7th edition, histologically confirmed melanoma that was completely surgically resected. Per the AJCC 8th edition, this corresponds to patients with lymph node involvement or metastases. Patients were enrolled regardless of their tumor PD-L1 status. Patients with prior autoimmune disease, and 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 patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomization) 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 randomized 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. Randomization was stratified by tumor PD-L1 expression (≥5% vs. < 5%/indeterminate), and stage of disease per the AJCC staging system. Tumor 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 randomization 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 tumor ulceration. Forty-two percent of patients were BRAF V600 mutation positive while 45% were BRAF wild type and 13% BRAF status was unknown. For tumor PD-L1 expression, 34% of patients had PD-L1 expression ≥ 5% and 62% had < 5% as determined by clinical trial assay. Among patients with quantifiable tumor PD-L1 expression, the distribution of patients was balanced across the treatment groups. Tumor PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Minimum follow-up was approximately 24 months. OS was not mature at the time of this analysis. RFS results are shown in Table 30 and Figure 20 (all randomized population).

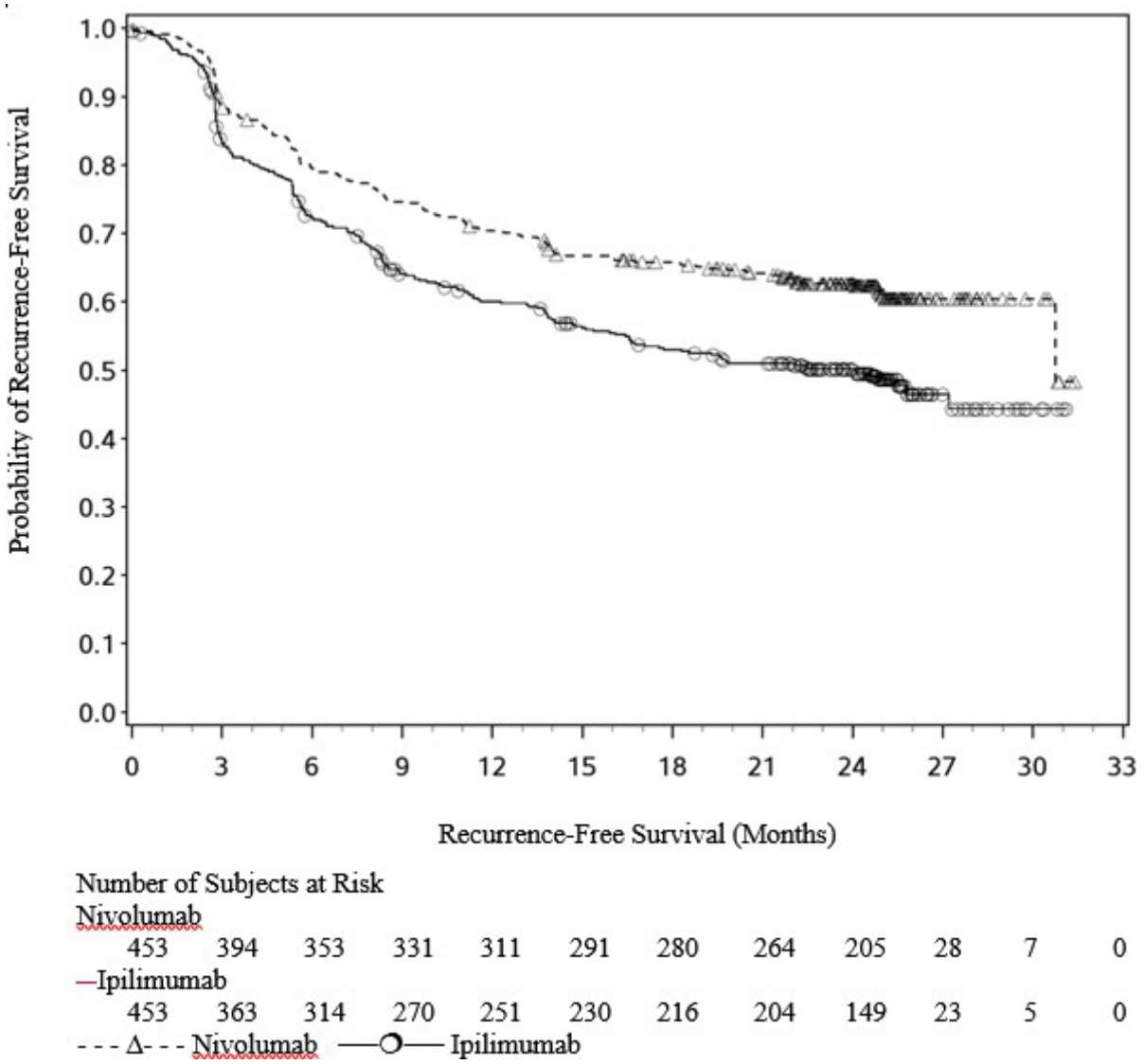
Table 30: Efficacy results (CA209238)

	nivolumab (n = 453)		**ipilimumab 10 mg/kg (n = 453)**
Recurrence-free Survival			
Events	171 (37.7%)		221 (48.8%)
Hazard ratio[a]		0.66	
95% CI		(0.54, 0.81)	
p-value		p<0.0001	
Median (95% CI) months	30.75 (30.75, NR)[b]		24.08 (16.56, NR)[b]
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)

[a] Derived from a stratified Cox proportional hazards model.

[b] Based on Kaplan-Meier estimates.

Figure 20: Recurrence-free Survival (CA209238)



The trial demonstrated a statistically significant improvement in RFS for patients randomized to the nivolumab arm compared with the ipilimumab 10 mg/kg arm. RFS benefit was consistently demonstrated across subgroups, including tumor PD-L1 expression, BRAF status, and stage of disease.

Quality of life (QoL) with nivolumab remained stable and close to baseline values during treatment, as assessed by valid and reliable scales like the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EQ-5D utility index and visual analog scale (VAS).

Classical Hodgkin lymphoma (cHL)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of relapsed or refractory cHL following ASCT and treatment with brentuximab vedotin were evaluated in two global, multicenter, open-label, single-arm studies (CA209205 and CA209039).

CA209205 is an ongoing Phase 2, open-label, multi-cohort, single-arm study of nivolumab in cHL. Cohort A included 63 patients who had received ASCT and were brentuximab vedotin naïve; Cohort B included 80 patients who had received brentuximab vedotin after ASCT failure; Cohort C included 100 patients who had received brentuximab vedotin before and/or after ASCT out of which 33 patients received brentuximab vedotin only prior to ASCT. The first tumor 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 IRRC. Additional efficacy measures included duration of response and PFS.

CA209039 was a Phase 1b open-label, multicenter, dose-escalation, and multidose study of nivolumab in relapsed or refractory hematologic malignancies, including 23 patients with cHL; amongst which, 15 patients received prior brentuximab vedotin treatment as a salvage therapy following ASCT, similar to Cohort B of study CA209205. The first tumor 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.

Both studies included patients regardless of their PD-L1 status, and excluded patients with autoimmune disease, symptomatic interstitial lung disease, known central nervous system (CNS) lymphoma or patients with nodular lymphocyte-predominant HL. Patients received 3 mg/kg of nivolumab administered intravenously over 60 minutes every 2 weeks.

Data from the 80 patients from CA209205 Cohort B and the 15 patients from CA209039 who received prior brentuximab vedotin treatment following ASCT were integrated. Baseline characteristics were similar across the two studies (Table 31). Efficacy from both studies was evaluated by the same IRRC. Results are shown in Table 32.

Table 31: Baseline patient characteristics (CA209205 Cohort B and CA209039)

	CA209205 Cohort B and CA209039 (n = 95)	CA209205 Cohort B a (n = 80)	CA209039 (n = 15)
Median age (range)	37.0 years (18–72)	37.0 years (18–72)	40.0 years (24–54)
Gender	61 (64%)M / 34 (36%)F	51 (64%)M / 29 (36%)F	10 (67%)M / 5 (33%)F
ECOG status			
0	49 (52%)	42 (52.5%)	7 (47%)
1	46 (48%)	38 (47.5%)	8 (53%)
≥5 prior lines of systemic therapy	49 (52%)	39 (49%)	10 (67%)
Prior ASCT			
1	87 (92%)	74 (92.5%)	13 (87%)
≥2	8 (8%)	6 (7.5%)	2 (13%)
Years from most recent transplant to first dose of study therapy, median (range)	3.5 years (0.2-19.0)	3.4 years (0.2-19.0)	5.6 years (0.5-15.0)

[a] 18/80 (22.5%) of the patients in CA209205 Cohort B presented B-Symptoms at baseline.

Table 32: Efficacy results (CA209205 Cohort B and CA209039)

	CA209205 Cohort B[a] and CA209039 (n = 95)	CA209205 Cohort B[a] (n = 80)	CA209039 (n = 15)
Objective Response Rate; (95% CI)	63 (66%); (56, 76)	54 (68%); (56, 78)	9 (60%); (32, 84)
Complete Remission Rate; (95% CI)	6 (6%); (2, 13)	6 (8%); (3, 16)	0 (0%); (0, 22)
Partial Remission Rate; (95% CI)	57 (60%); (49, 70)	48 (60%); (48, 71)	9 (60%); (32, 84)
Stable disease, n (%)	22 (23%)	17 (21%)	5 (33%)
Median Duration of Response[b]	13.1 months	13.1 months	12.0 months
(95% CI)	(9.5, NE)	(8.7, NE)	(1.8, NE)
Range	0.0^{+} - 23.1^{+}	0.0^{+} - 14.2^{+}	1.8 - 23.1^{+}
Median Time to Response	2.0 months	2.1 months	0.8 months
Range	0.7 - 11.1	1.6 - 11.1	0.7 - 4.1
Median Duration of Follow-up	15.8 months	15.4 months	21.9 months
Range	1.9 - 27.6	1.9 - 18.5	11.2 - 27.6
PFS rate at 12 months	57%	55%	69%
(95% CI)	(45, 68)	(41, 66)	(37, 88)

[a] Follow-up was ongoing at the time of data submission

[b] Data unstable due to the limited duration of response for Cohort B resulting from censoring.

NE=not estimable.
"+" denotes a censored observation.

Nine patients received allogeneic stem cell transplant (5 in CA209205 and 4 in CA209039) as subsequent therapy.

Objective response per IRRC with nivolumab was observed regardless of baseline tumor PD-L1 expression status.

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 59.5% (22/37). The median duration of response is 13.1 months (13.1, NE) for the 22 responders to nivolumab who had failed to achieve response with prior brentuximab vedotin treatment.

B-symptoms were present in 22.5% (18/80) of the patients in CA209205 Cohort B at baseline. Nivolumab treatment resulted in rapid resolution of B-symptoms in 88.9% (16/18) of the patients, with a median time to resolution of 1.9 months.

Efficacy was also evaluated in 258 patients who had relapsed or progressive cHL after autologous HSCT (243 patients in Cohorts A+B+C from CA209205 and 15 patients from CA209039). The median age was 34 years (range: 18-72). The majority were male (59%) and white (86%). Patients had a median of 4 prior systemic regimens (range: 2-15), 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. Efficacy results for this population are shown in Table 33.

Table 33: Efficacy in cHL after autologous HSCT (CA209205 Cohort A+B+C and CA209039)

	Nivolumab (n=258)
Objective Response Rate, n (%)	179 (69%)
(95% CI)	(63, 75)
Complete Remission Rate	37 (14%)
(95% CI)	(10, 19)
Partial Remission Rate	142 (55%)
(95% CI)	(49, 61)
Duration of Response (months)	
Median[a,b]	Not reached
(95% CI)	(12.0, NE)
Range	0^{+} - 23.1^{+}
Time to Response	
Median	2.0 months
Range	0.7 - 11.1

[a] Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 6.7 months.

[b] The estimated median duration of PR was 13.1 months (95% CI, 9.5, NE). The median duration of CR was not reached.

NE=not estimable.

"+" denotes a censored observation.

Health related Quality of Life (QoL) was assessed among overall patients (Cohort A+B+C) in CA209205 using the patient reported EQ 5D VAS and EORTC-QLQ-C30 (global health status). Over 81 weeks of follow up, mean EQ-5D VAS scores increased over time, indicating superior overall health status for patients remaining on treatment with clinically relevant improvements. EORTC QLQ-C30 scores remained generally stable over time with mean changes from baseline trending toward an improvement on treatment in global health status.

Urothelial Carcinoma (UC)

Open-label Phase 2 study (CA209275)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of locally advanced or metastatic UC were evaluated in a Phase 2, multicenter, open-label, single-arm study (CA209275).

The study included patients (18 years or older) who had disease progression during or after 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 tumor 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 received nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. 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. The first tumor assessments were conducted 8 weeks after the start of treatment and continued every 8 weeks up to 48 weeks, then every 12 weeks thereafter until disease progression or treatment discontinuation, whichever occurred later. Tumor assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. The primary efficacy outcome measure was ORR as determined by IRRC. Additional efficacy measures included duration of response, PFS, and OS.

A total of 270 patients with a minimum follow-up of 8.3 months were evaluable for efficacy. The median age was 66 years (range: 38-90) with 55% ≥65 years of age and 14% ≥75 years of age. The majority of patients were white (86%) and male (78%). Baseline ECOG performance status was 0 (54%) or 1 (46%).

Efficacy results are shown in Table 34.

Table 34: Efficacy results (CA209275)[a]

	nivolumab (n = 270)
Confirmed objective response n (%)	54 (20.0%)
(95% CI)	(15.4, 25.3)
Complete response (CR)	8 (3.0%)
Partial response (PR)	46 (17.0%)
Stable disease (SD)	60 (22.2%)
Median duration of response[b] (range)	10.4 months (1.9^{+}-12.0^{+})
Median time to response (range)	1.9 months (1.6-7.2)
Progression-Free Survival	
Events (%)	216 (80%)
Median (95% CI)	2.0 months (1.9, 2.6)
Rate (95% CI) at 6 months	26.1% (20.9, 31.5)
Overall survival	
Events n (%)	154 (57%)
Median (95% CI)	8.6 months (6.1, 11.3)
Rate (95% CI) at 12 months	41.0% (34.8, 47.1)

	Tumor PD-L1 expression level	
	< 1%	**≥ 1%**
Confirmed objective response (95% CI)	16% (10.3, 22.7) n=146	25% (17.7, 33.6) n=124
Median duration of response (range)	10.4 months (3.7-12.0^{+})	Not Reached (1.9^{+}-12.0^{+})
Progression-free survival		
Median (95% CI)	1.9 months (1.8, 2.0)	3.6 months (1.9, 3.7)
Rate (95% CI) at 6 months	22.0% (15.6, 29.2)	30.8% (22.7, 39.3)
Overall survival		
Median (95% CI)	5.9 months (4.4, 8.1)	11.6 months (9.1, NE)
Rate (95% CI) at 12 months	34.0% (26.1, 42.1)	49.2% (39.6, 58.1)

[a] Median follow-up 11.5 months.

[b] Data unstable due to the limited duration of response.

NE=not estimable.

"+" denotes a censored observation.

Objective response per IRRC with nivolumab was observed regardless of baseline tumor PD-L1 expression status.

Disease related and non-disease specific quality of life (QoL) was assessed using the validated European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and the

EuroQoL EQ-5D. Overall QoL scores remained stable while Global Health Status (GHS) based on the EORTC-QLQ-C30, continued to improve through Week 49. EQ-5D VAS scores showed clinically relevant improvement in QoL by Week 9, with continued improvement through Week 49. Both scales showed no detriment.

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 with UC. Inclusion criteria were similar to those in study CA209275. Patients were treated with nivolumab 3 mg/kg as monotherapy. 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+ months). The median OS was 9.7 months (95% CI: 7.3, 16.2) 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.

Colorectal Cancer (CRC)

The safety and efficacy of nivolumab as a single agent or in combination with ipilimumab were evaluated for the treatment of dMMR or MSI-H metastatic CRC in a Phase 2, multicenter, 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, and had an ECOG performance status score of 0 or 1. This study included patients regardless of their tumor PD-L1 status. Patients with active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

Nivolumab monotherapy

A total of 74 patients received treatment with nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumor assessments according to RECIST version 1.1 were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The primary and secondary outcome measures were investigator-assessed ORR and blinded independent central review (BICR) ORR, respectively. Exploratory outcome measures included duration of and time to response, PFS, OS, and QoL.

The median age was 53 years [redacted] 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%) or 1 (55%), 16% of patients were BRAF mutation positive, 35% were KRAS mutation positive, and 11% were unknown. 15%, 30%, 30%, and 24% received 1, 2, 3, or 4 or more prior lines of therapy, respectively, and 42% of patients had received EGFR inhibitor therapy.

Efficacy results based on a minimum follow-up of approximately 15.7 months for all 74 patients and a subgroup of 53 patients who had prior fluoropyrimidine, oxaliplatin and irinotecan therapy are shown in Table 35.

Table 35: Nivolumab monotherapy efficacy results (CA209142)

	nivolumab All patients (n = 74)	nivolumab Prior treatment with fluoropyrimidine, oxaliplatin and irinotecan (n = 53)
Confirmed objective response[a], n (%)	24 (32.4)	15 (28.3)
(95% CI)	(22.0, 44.3)	(16.8, 42.3)
Complete response (CR), n (%)	2 (2.7)	1 (1.9)
Partial response (PR), n (%)	22 (29.7)	14 (26.4)
Stable disease (SD), n (%)	25 (33.8)	16 (30.2)
Median duration of response[a]		
Months (range)	NE (1.4+, 26.5+)	NE (2.8+, 22.1+)
Median time to response[a]		
Months (range)	2.79 (1.2, 22.6)	2.89 (1.2, 22.6)
Disease control rate[a,b], n (%)	47 (63.5)	30 (56.6)
(95% CI)	(51.5, 74.4)	(42.3, 70.2)
Progression-free survival[a]		
Events	40	30
Median (months) (95% CI)	6.6 (3.0, NE)	4.2 (1.4, NE)
Overall survival		
Events	25	19
Median (months) (95% CI)	Not reached (19.6, NE)	Not reached (18.0, NE)
6-month rate (%) (95% CI)	83.3 (72.4, 90.1)	80.3 (66.5, 88.9)
12-month rate (%) (95% CI)	72.0 (60.0, 80.9)	68.3 (53.5, 79.2)

"+" denotes a censored observation.

[a] BICR assessment.

[b] CR + PR + SD (for at least 12 weeks).

NE = non-estimable.

Confirmed responses were observed regardless of BRAF and KRAS mutation status, and tumor PD-L1 expression levels.

Esophageal Squamous Cell Carcinoma (ESCC)

Randomized, open-label, multicenter Phase 3 study (CA209473/ONO-24/ ATTRACTION-3)

The safety and efficacy of nivolumab monotherapy for the treatment of ESCC were evaluated in a Phase 3, multicenter, randomized (1:1), active-controlled, open-label study in patients with unresectable advanced, recurrent, or metastatic ESCC, refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen (CA209473/ONO-24). The study included patients regardless of PD-L1 status. The study excluded patients with a baseline performance score ≥ 2,

brain metastases that were symptomatic or required treatment, apparent tumor invasion on organs located adjacent to the esophagus (e.g., the aorta or respiratory tract), active autoimmune disease, or use of systemic corticosteroids or immunosuppressants. Patients received nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=210) or investigator's choice taxane chemotherapy of either:

- docetaxel (n=65) 75 mg/m2 intravenously every 3 weeks, or
- paclitaxel (n=144) 100 mg/m2 intravenously once a week for 6 weeks followed by 1 week off.

Patients were treated until disease progression, assessed by the investigator per RECIST v1.1, or unacceptable toxicity. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab or chemotherapy if there was no worsening of symptoms due to progression, treatment could be safely administered and there was an expectation continued treatment would lead to clinical benefit, as determined by the investigator.

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 included ORR and PFS, as assessed by the investigator using RECIST v1.1, and DOR. 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. Baseline ECOG performance status was 0 (50%) or 1 (50%).

The study demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with investigator's choice 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 36 and Figure 21.

Table 36: Efficacy Results - CA209473/ONO-24/ ATTRACTION-3

	Nivolumab (n=210)	**Chemotherapy (n=209)**
Overall Survival[a]		
Deaths (%)	160 (76%)	173 (83%)
Median (months) (95% CI)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)
Hazard ratio (95% CI)[b]	0.77 (0.62, 0.96)	
p-value[c]	0.0189	
Progression-free Survival[a]		
Disease progression or death (%)	187 (89)	176 (84)
Median (months) (95% CI)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
Hazard ratio (95% CI)b	1.1 (0.9, 1.3)	
Objective Response Rated, [e]	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)
Median duration of response (months) **(95% CI)**	6.9 (5.4, 11.1)	3.9 (2.8, 4.2)

[a] Based on ITT analysis.

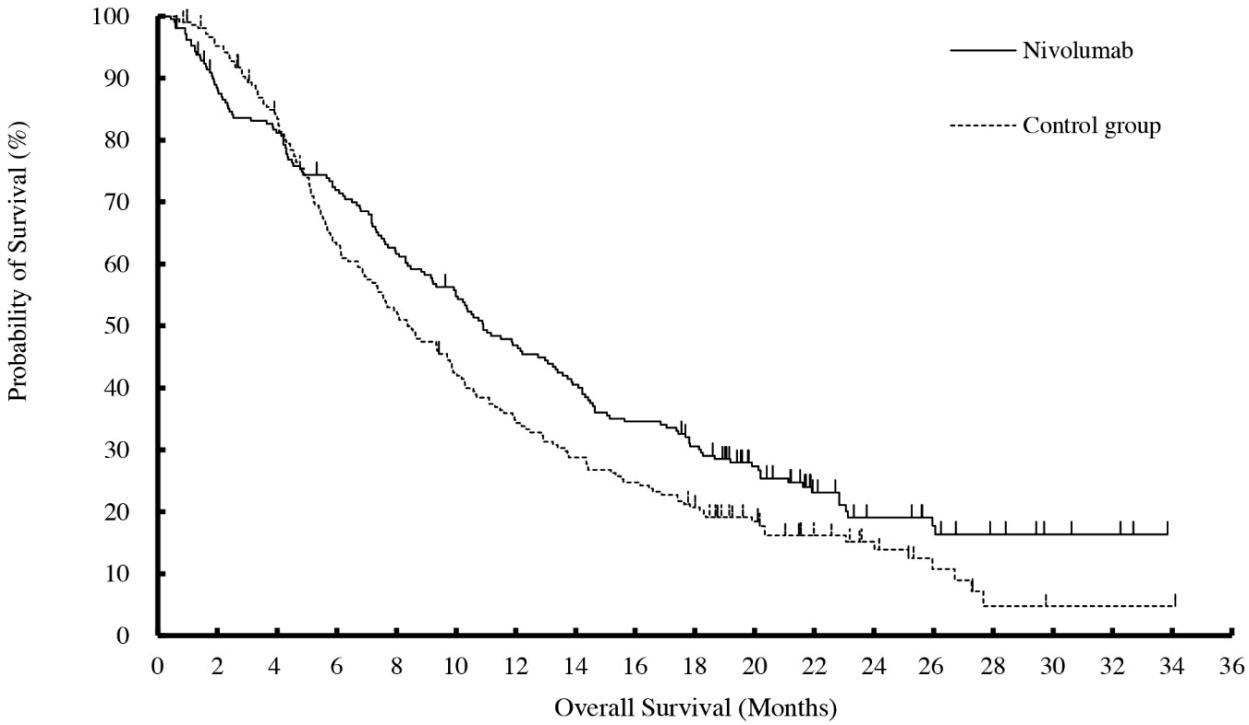
[b] Based on a stratified proportional hazards model.

[c] Based on a stratified log-rank test.

[d] Based on Response Evaluable Set (RES) analysis, n=171 in nivolumab group and n=158 in investigator's choice group.

[e] Not significant, p-value 0.6323.

Figure 21: Overall Survival - CA209473/ONO-24/ ATTRACTION-3



Number at Risk

Nivolumab	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
Control group	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0

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 prespecified analyses. Of the 419 patients, 48% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 52% of patients were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1).

The hazard ratio (HR) for survival was 0.69 (95% CI: 0.51, 0.94) with median survivals of 10.9 and 8.1 months for the nivolumab and chemotherapy arms, respectively, in the tumor PD-L1 ≥1% subgroup. The HR for survival 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, in the tumor PD-L1 <1% subgroup.

Gastric, Gastroesophageal Junction or Esophageal Adenocarcinoma (GC, GEJC or EAC)

The safety and efficacy of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy 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-esophageal junction (GEJ) or esophageal adenocarcinoma, no prior systemic treatment (including HER2 inhibitors), and ECOG performance status score 0

or 1. Patients were enrolled regardless of their tumour PD-L1 status, and tumour PD-L1 expression was determinated using the PD-L1 IHC 28-8 pharmDx assay. Patients with known HER2-positive tumours, baseline performance score ≥2 or who had untreated central nervous system metastases were excluded from the study. Randomization was stratified by tumor 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. 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 (n=789) or chemotherapy (n=792). 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/m2, leucovorin 400 mg/m2, and fluorouracil 400 mg/m2 intravenously on Day 1 and fluorouracil 1200 mg/m2 intravenously daily 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/m2 intravenously on Day 1 and capecitabine 1000 mg/m2 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. Tumor 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. The median age was 61 years (range: 18 to 90), 39% were ≥65 years of age, 70% were male, 24% were Asian and 69% were white. Baseline ECOG performance status was 0 (42%) or 1 (58%). Tumor locations were distributed as gastric (70%), gastro-esophageal junction (16%), and esophagus (13%).

Primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with PD-L1 combined positive score (CPS) ≥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 ≥1 and in all randomized patients; further endpoints included ORR (BICR) in PD-L1 CPS ≥5 and all randomized patients.

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 ≥5. Statistically significant improvement in OS was also demonstrated for all randomized patients. Efficacy results are shown in Figures 22, 23, and 24 and Table 37

Figure 22: Kaplan-Meier curves of OS in patients with PD-L1 CPS ≥5 (CA209649)

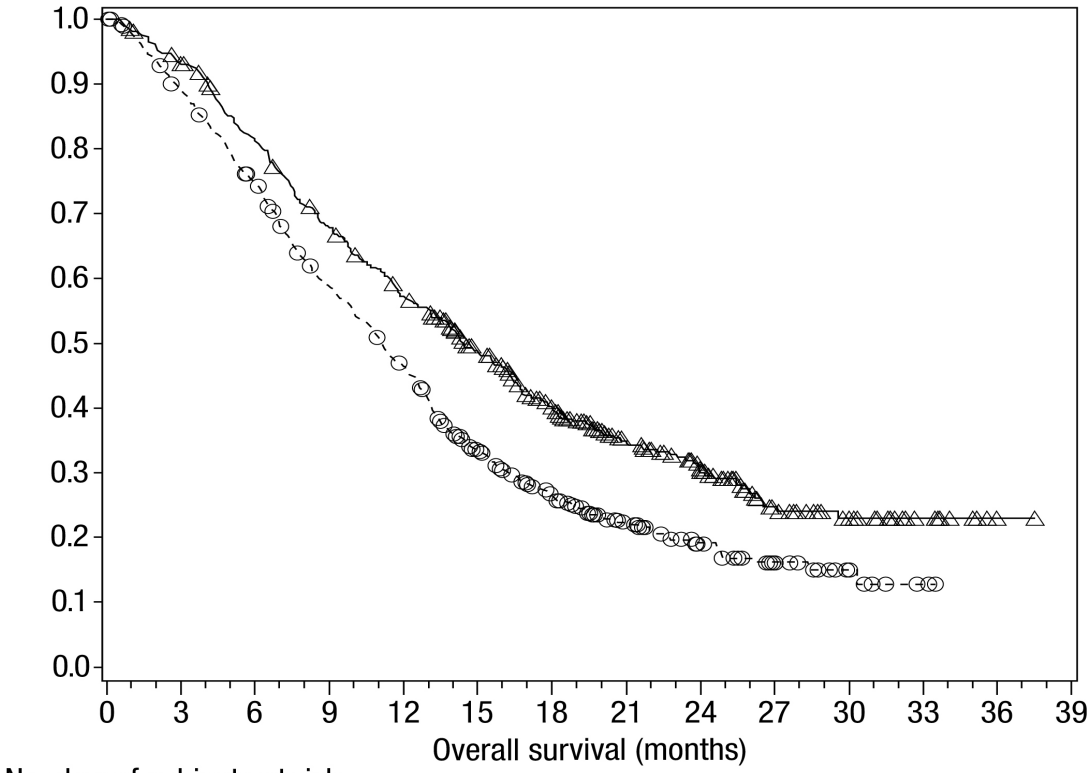


Figure 23: Kaplan-Meier curves of PFS in patients with PD-L1 CPS ≥5 (CA209649)

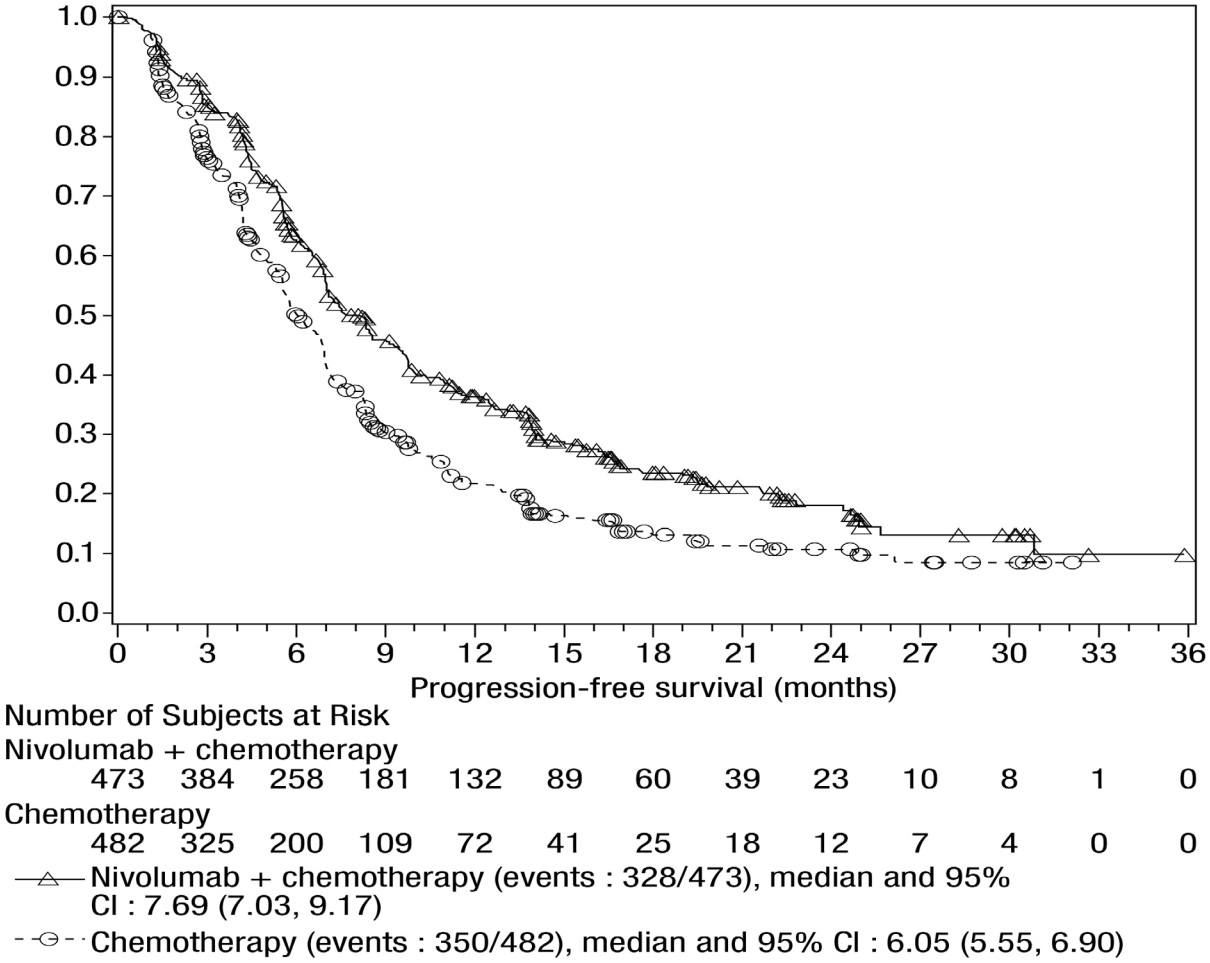
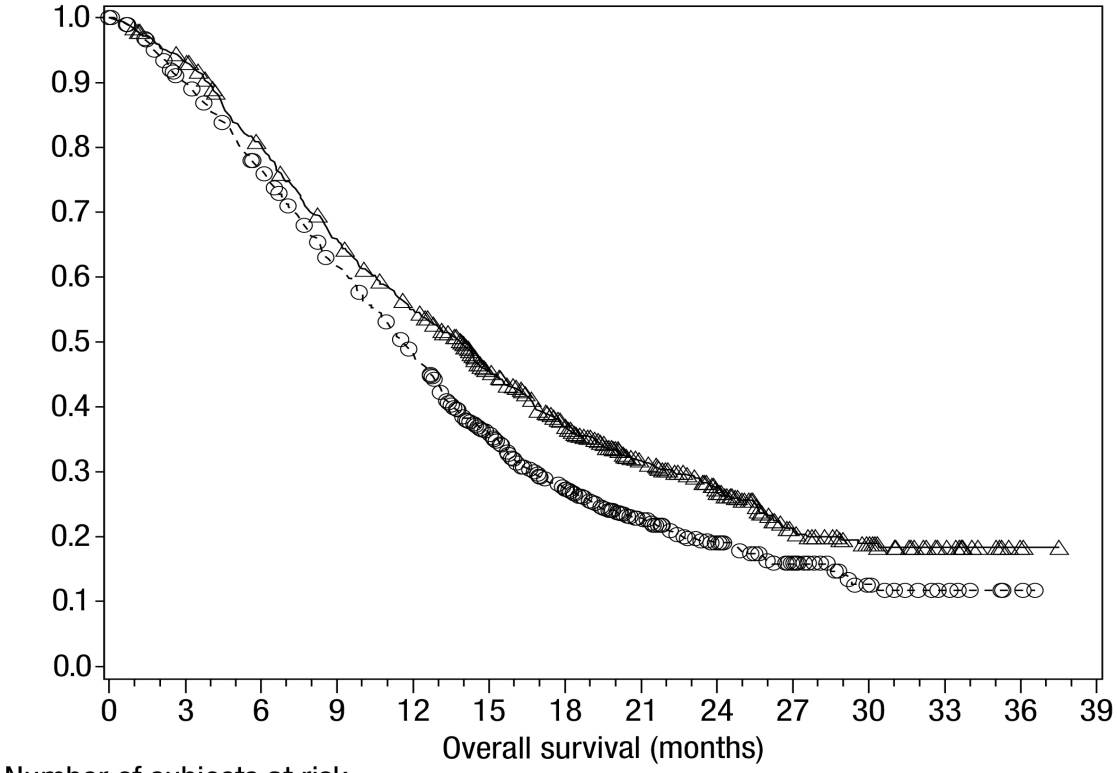


Figure 24: Kaplan-Meier curves of OS in all randomized patients (CA209649)



Number of subjects at risk

Nivolumab + chemotherapy

789 731 621 506 420 308 226 147 100 49 34 14 2 0

Chemotherapy

792 697 586 469 359 239 160 94 59 35 15 7 2 0

Nivolumab + chemotherapy (events : 544/789), median and 95% CI : 13.83 (12.55, 14.55)

Chemotherapy (events: 591/792), median and 95% CI : 11.56 (10.87, 12.48)

Table 37: Efficacy results (CA209649)

	nivolumab + chemotherapy (n=473)	chemotherapy (n=482)	nivolumab + chemotherapy (n=789)	chemotherapy (n=792)
	PD-L1 CPS ≥5		All patients	
Overall survival				
Events (%)	309 (65)	362 (75)	544 (69)	591 (75)
Hazard ratio (CI)[a]	0.71 (98.4% CI: 0.59, 0.86)		0.80 (99.3% CI: 0.68, 0.94)	
p-value[b]	<0.0001		0.0002	
Median (95% CI) (months)[c]	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)
Rate (95% CI) at 12 months	57.3 (52.6, 61.6)	46.4 (41.8, 50.8)	55.0 (51.4, 58.4)	47.9 (44.4, 51.4)
Progression-free survival[d]				
Events(%)	328 (69.3)	350 (72.6)	559 (70.8)	557 (70.3)
Hazard ratio (CI)[a]	0.68 (98% CI: 0.56, 0.81)		0.77 (95% CI: 0.68, 0.87)	
p-value[b]	<0.0001		-[e]	
Median (95% CI) (months)[c]	7.69 (7.03, 9.17)	6.05 (5.55, 6.90)	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)
Rate (95% CI) at 12 months	36.3 (31.7, 41.0)	21.9 (17.8, 26.1)	33.4 (29.9, 37.0)	23.2 (19.9, 26.7)
Overall response rate, n (%)[d,f]	226/378 (60)	177/391 (45)	350/603 (58)	280/608 (46)
(95% CI)	(55, 65)	(40, 50)	(54, 62)	(42, 50)
Complete response	44 (12)	27 (7)	59 (10)	39 (6)
Partial response	182 (48)	150 (38)	291 (48)	241 (40)
Duration of response[d,f]				
Median (95% CI) (months)[c]	9.49 (7.98, 11.37)	6.97 (5.65, 7.85)	8.51 (7.23, 9.92)	6.93 (5.82, 7.16)
Range	1.1+, 29.6+	1.2+, 30.8+	1.0+, 29.6+	1.2+, 30.8+

[a] Based on stratified log Cox proportional hazard model.

[b] Based on stratified log-rank test.

[c] Kaplan-Meier estimate.

[d] Confirmed by BICR.

[e] Not evaluated for statistical significance.

[f] Based on patients with measurable disease at baseline.

Statistically significant improvement in OS was also demonstrated for patients with PD-L1 CPS ≥1 (HR = 0.77; 99.3% CI: 0.64, 0.92; p-value <0.0001). The median OS was 13.96 months (95% CI: 12.55, 14.98) for nivolumab plus chemotherapy and 11.33 months (95% CI: 10.64, 12.25) for chemotherapy.

Further exploratory analyses were performed in patients who had PD-L1 CPS <1 [nivolumab plus chemotherapy n=140 (17.9%) vs. chemotherapy n=125 (16.0%)] and PD-L1 CPS <5 [nivolumab plus chemotherapy n=308 (39.4%) vs. chemotherapy n=298 (38.2%)] (see Table 38).

Table 38: OS by PD-L1 CPS <1 and <5 (CA209649)

PD-L1 Expression	nivolumab +chemotherapy	chemotherapy	
	OS by PD-L1 CPS expression Number (%) of patients with event		Unstratified hazard ratio (95% CI)
CPS <1	103 (74%)	91 (73%)	0.92 (0.70, 1.23)
CPS <5	228 (74%)	221 (74%)	0.94 (0.78, 1.13)

Microsatellite instability (MSI) status was also assessed in CA209649 and determined retrospectively on pre-treatment tissues using the Idylla™ MSI Test. Of the 1581 randomised patients, 44 (2.8%) patients were MSI-high (MSI-H), and 1377 (87.1%) patients were microsatellite stable (MSS). The HR of OS in MSI-H was 0.37 (95% CI: 0.16, 0.87) and in MSS was 0.80 (95% CI: 0.71, 0.91).

Adjuvant treatment of Resected Esophageal or Gastroesophageal Junction Cancer (EC or GEJC)

The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of esophageal or gastro-esophageal junction cancer was evaluated in a phase 3 multicentre, randomized, placebocontrolled, double-blinded study (CA209577). The study included adult patients who had received CRT, followed by complete resection of carcinoma prior to randomisation, and who had residual pathologic disease, with at least ypN1 or ypT1. Patients who did not receive concurrent CRT prior to surgery or had stage IV resectable disease, autoimmune disease, any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications were excluded from the study. Patients were enrolled regardless of tumor PD-L1 expression level.

A total of 794 patients were randomized 2:1 to receive either nivolumab (n=532) or placebo (n=262). Patients were administered nivolumab 240 mg intravenously over 30 minutes every 2 weeks for 16 weeks followed respectively 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. Randomization was stratified by tumour 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). 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 randomization 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 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% ≥65 years of age and 5% ≥75 years of years. The majority of patients were white (82%) and male (85%). Baseline ECOG performance status was 0 (58%) or 1 (42%).

With a minimum of 6.2 months and a median of 24.4 months follow-up (range 6.2 to 44.9 months), the study demonstrated a statistically significant improvement for patients randomised to nivolumab compared with placebo, with DFS observed in 241 (45%) patients and a hazard ratio of 0.69 (95% CI: 0.56, 0.86). Efficacy results are shown in Table 39 and Figure 25.

Table 39: Efficacy results (CA209577)

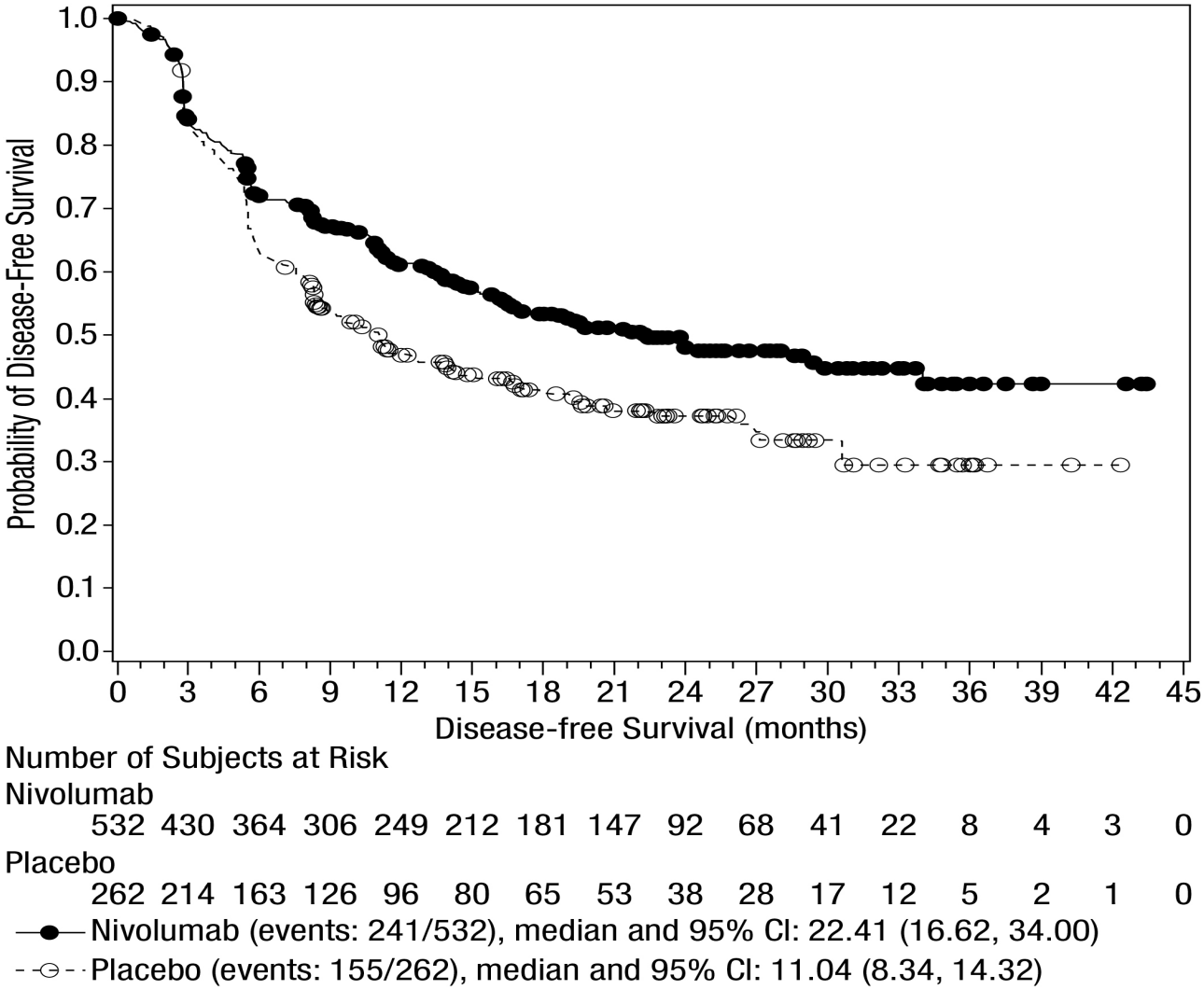
	nivolumab (n=532)	**placebo (n=262)**
Disease-free Survival[a]		
Events (%)	241 (45%)	155 (59%)
Hazard ratio (96.4% CI)[b]	0.69 (0.56, 0.86)	
p-value[c]	0.0003	
Median (95% CI) (months)	22.4 (16.6, 34.0)	11.0 (8.3, 14.3)

[a] Based on all randomized patients

[b] Based on a stratified cox proportional hazards model.

[c] Based on a stratified log-rank test.

Figure 25: Kaplan-Meier curves of DFS (CA 209577)



DFS benefit was observed regardless of histology and tumor cell PD-L1 expression.

In the adenocarcinoma subgroup (n=376), the hazard ratio (HR) for DFS was 0.75 (95% CI: 0.59, 0.96) with median DFS of 19.35 and 11.10 months for the nivolumab and placebo arms, respectively. In the squamous cell carcinoma subgroup (n=155), the HR for DFS was 0.61 (95 CI: 0.42, 0.88) with median DFS of 29.73 and 11.04 months for the nivolumab and placebo arms, respectively.

Of the 794 patients, 16.2% had tumor cell PD-L1 expression ≥1%, 71.8% had tumor cell PD-L1 expression <1%, and 12.0% had tumor cell PD-L1 expression indeterminate or non-evaluable. In the tumor cell PD-L1 ≥1% subgroup, the HR for DFS was 0.75 (95% CI: 0.45, 1.24) with median DFS of 19.65 and 14.13 months for the nivolumab and placebo arms, respectively. In the tumor cell PD-L1 <1% subgroup, the HR for DFS was 0.73 (95 % CI: 0.57, 0.92) with median DFS of 21.26 and 11.10 months for the nivolumab and placebo arms, respectively. In the tumor cell PD-

L1 indeterminate or non-evaluable subgroup, the HR for DFS was 0.54 (95% CI: 0.27, 1.05) with median DFS not reached and of 9.49 months for the nivolumab and placebo arms, respectively.

Patient-reported outcomes were assessed using the EQ-5D-3L and FACT-E. At baseline, mean FACT-E or mean FACT-E total scores in all randomized subjects were similar between treatment arms. From baseline through week 53 of follow-up, patients in both treatment arms had improvements in mean change from baseline score in both measures.

5.3 Pharmacokinetics

The PK of nivolumab is linear in the dose range of 0.1 to 10 mg/kg. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 26 (32.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 7.91 mL/h (46%) in patients with metastatic tumors; the decrease in CLss 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 volume of distribution at steady state (Vss) (CV%) is 6.6 L (24.4%) and geometric mean elimination half-life (t1/2) is 25 days (55.4%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks and systemic accumulation was approximately 4-fold.

The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Nivolumab CL increased with increasing body weight. Body weight normalized dosing produced approximately uniform steady-state trough concentration over a wide range of body weights (34-162 kg).

The metabolic pathway of nivolumab has not been characterized. As a fully human IgG4 monoclonal antibody, 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 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 2-cycles of chemotherapy: When nivolumab 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy, the CL of nivolumab decreased approximately 10% and the CL of ipilimumab increased approximately 22%, which were not considered clinically relevant.

When administered in combination with ipilimumab and chemotherapy, the CL of nivolumab increased by approximately 29% in the presence of anti-nivolumab antibodies. There was no apparent impact on efficacy or safety with nivolumab ADA-positive subjects.

5.3.1 Special populations

A population PK analysis suggested no difference in CL of nivolumab based on age, gender, race, solid tumor type, tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin and body weight had an effect on nivolumab CL, the effect was not clinically meaningful.

Renal impairment

The effect of renal impairment on the CL of nivolumab was evaluated in patients with mild* (n=1399), moderate* (n=651), or severe* (n=6) renal impairment compared to patients with normal* renal function (n=1354) in the population PK analysis. 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 4.2 Posology and method of administration, renal impairment).

** Definitions*

- *Normal: GFR ≥90 mL/min/1.73 m^2*
- *Mild: GFR <90 and ≥60 mL/min/1.73 m^2*
- *Moderate: GFR <60 and ≥30 mL/min/1.73 m^2*
- *Severe: GFR <30 and ≥15 mL/min/1.73 m^2*

Hepatic impairment

The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with different tumor types (NSCLC, SCLC, melanoma, RCC, SCCHN, UC, gastric cancer, and cHL) with mild* hepatic impairment (n=351) and in patients with moderate* hepatic impairment (n=10) compared to patients with normal* hepatic function (n=3096) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate hepatic impairment and normal hepatic function. Nivolumab has not been studied in patients with severe* hepatic impairment (see 4.2 Posology and method of administration, Hepatic impairment).

**Per National Cancer Institute criteria of hepatic dysfunction:*

- *Normal: total bilirubin and AST ≤ ULN*
- *Mild: total bilirubin >1.0 to 1.5 times ULN or AST > ULN*
- *Moderate: total bilirubin >1.5 to 3 times ULN and any AST*
- *Severe: total bilirubin >3 times ULN and any AST*

6 NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Nivolumab was well tolerated by cynomolgus monkeys when administered intravenously, twice weekly, up to three months and at doses up to approximately 35 times the human exposure at the clinical dose of 3 mg/kg based on AUC.

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 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). No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, dose-dependent increases in fetal losses and increased neonatal mortality was observed.

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, fetal 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.

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.

7 DESCRIPTION

Nivolumab is a fully human anti-PD-1 monoclonal antibody (IgG4) produced in Chinese hamster ovary cells by recombinant DNA technology.

Nivolumab is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid for intravenous infusion that may contain light (few) particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg.

List of excipients: Sodium citrate dihydrate, Sodium chloride, Mannitol , Pentetic acid (diethylenetriaminepentaacetic acid), Polysorbate 80, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment), Water for injections.

8 PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Nivolumab should not be infused concomitantly in the same intravenous line with other medicinal products.

8.2 Shelf life

Unopened vial

Refer to the outer carton, for the expiry date.

The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

After opening

- From a microbiological point of view, once opened, the medicinal product should be prepared for infusion immediately.

After preparation of infusion

- The prepared infusion solution may be stored under refrigeration conditions: 2°C to 8°C and protected from light for up to 7 days (a maximum of 8 hours of the total 7 days can be at room temperature 20°C to 25°C and room light – the maximum 8-hour period under room temperature and room light conditions should be inclusive of the product administration period). The administration of the nivolumab infusion must be completed within 7 days of preparation.

8.3 Packaging information

Each 10 mL vial contains 40 mg of nivolumab in 4 mL.

Each 10 mL vial contains 100 mg of nivolumab in 10 mL.

Each 25 mL vial contains 240 mg of nivolumab in 24 mL.

Pack of 1 Vial.

8.4 Storage and handling instructions

Store in a refrigerator (2°C-8°C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after preparation of the infusion, see 8.2 Shelf life.

Preparation and administration

Calculating the dose

More than one vial of nivolumab concentrate may be needed to give the total dose for the patient.

Flat dose (240 mg, 360 mg or 480 mg)	Weight-based dose
• The prescribed dose for the patient is 240 mg,360 mg or 480 mg given regardless of body weight.	The prescribed dose for the patient 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 nivolumab concentrate to prepare the dose (mL) = the total dose in mg, divided by 10 (the nivolumab concentrate strength is 10 mg/mL).

Preparing the infusion

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Nivolumab can be used for intravenous administration either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting,

Flat dose (240 mg, 360 mg or 480 mg)*	Weight-based dose
The concentrate may be diluted so as not to exceed a total infusion volume of 160 mL.	The final infusion concentration should range between 1 and 10 mg/mL.

* *For adult and pediatric patients with body weight less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of body weight*

- Nivolumab 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 nivolumab concentrate for particulate matter or discoloration. Do not shake the vial. Nivolumab concentrate is a clear to opalescent, colorless to pale-yellow liquid. Discard the vial if the solution is cloudy, is discolored, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of nivolumab 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

Nivolumab infusion must not be administered as an intravenous push or bolus injection.

Administer the nivolumab infusion intravenously over a period of 30 minutes.

Nivolumab 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).

Nivolumab 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.

When administered in combination with ipilimumab, or other therapeutic agents, nivolumab should be given first followed by ipilimumab and/or other therapeutic agents (if applicable) on the same day. Use separate infusion bags and filters for each infusion.

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.

9 PATIENT COUNSELLING INFORMATION

Please refer to section: SPECIAL WARNINGS AND PRECAUTIONS FOR USE (4.4) and 4.6 - Use in Special Populations (Such as Pregnant Women, Lactating Women) and see Use in Specific Populations (5.3.1) for Patient Counselling Information.

10 DETAILS OF MANUFACTURER

Bristol-Myers Squibb Holdings Pharma, Ltd. Liability Company, Road 686 Km 2.3, Bo. Tierras Nuevas, Manatí, Puerto Rico 00674, USA

And

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11 DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Form 45 Permission No.IMP-88/2016 dated 09-June 2016

12 DATE OF REVISION

Date of Revision – 02 May 2023

Document Version Number – 14.2

Source – Nivolumab CCDS dated –16 Nov 2021

Opdyta® is a registered trademark of Bristol-Myers Squibb.

APPENDIX 5-2 IPILIMUMAB INDIA PRESCRIBING INFORMATION

To be sold by retail on the prescription of a Registered Oncologist only

Bristol Myers Squibb™

Ipilimumab
YERVOI®

1 GENERIC NAME

Ipilimumab 5 mg/mL concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

YERVOI® (Ipilimumab) is a recombinant, fully human monoclonal antibody that binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture by recombinant DNA technology.

Each ml of concentrate contains 5 mg Ipilimumab.

Each 10 ml vial contains 50 mg of Ipilimumab.

For the full list of excipients, see section 7 Description.

3 DOSAGE FORM AND STRENGTH

Injection: 50 mg/10 mL (5 mg/mL) as a clear to slightly opalescent, colorless to pale-yellow solution in a single-dose vial.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Renal Cell Carcinoma (RCC)

Ipilimumab is indicated for treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab.

Non-Small Cell Lung Cancer (NSCLC)

Ipilimumab, in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by a validated test, with no EGFR or ALK genomic tumor aberrations.

Ipilimumab, in combination with nivolumab 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.

4.2 Posology and method of administration

Ipilimumab should be administered under the supervision of physicians experienced in the treatment of cancer.

4.2.1 Recommended dosage

RCC

Combination phase: The recommended dose during the combination phase is Ipilimumab 1 mg/kg administered intravenously over a period of 30 minutes every 3 weeks for the first 4 doses in combination with Nivolumab 3 mg/kg administered intravenously over a period of 30 minutes, followed by the single-agent phase.

Single-agent phase: The recommended dose of Nivolumab during the single-agent phase is 3 mg/kg every 2 weeks or 240 mg every 2 weeks or 480 mg every 4 weeks administered intravenously over a period of 30 minutes.

The first dose of nivolumab monotherapy should be administered 3 weeks following the last dose of the combination of ipilimumab and nivolumab.

When administered in combination with nivolumab, nivolumab should be given first followed by ipilimumab on the same day.

Review the Prescribing Information for nivolumab for dosage information.

NSCLC

The recommended dose of ipilimumab in combination with nivolumab is nivolumab 3 mg/kg administered as an intravenous infusion over 30 minutes every 2 weeks and ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes every 6 weeks until disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression.

The recommended dose of ipilimumab in combination with nivolumab and platinum-doublet chemotherapy is nivolumab 360 mg administered as an intravenous infusion over 30 minutes every 3 weeks and ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes every

6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progressio*n.*

Review the Prescribing Information for nivolumab and platinum-based chemotherapy for recommended dosing information.

Recommended Dosage Modifications for Adverse Reactions

No dose reduction for ipilimumab is recommended. In general, withhold ipilimumab for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue ipilimumab for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, persistent moderate (Grade 2) or severe (Grade 3) reactions lasting 12 weeks or longer after last ipilimumab dose (excluding endocrinopathy), 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 ipilimumab or ipilimumab in combination with nivolumab for adverse reactions that require management different from these general guidelines are summarized in Table 1.

When ipilimumab is administered in combination with nivolumab, withhold or permanently discontinue both ipilimumab and nivolumab for toxicity.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity***	**Dosage Modifications**
Immune-Mediated Adverse Reactions *[See Warnings and Precautions (5.1)]*		
Colitis/diarrhea	Grade 2	Withhold[a]
	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 or ALT increases to more than 3 times and up to 5 times the ULN or Total bilirubin increases to more than 1.5 times and up to 3 times the ULN	Withhold[a]
	AST or ALT more than 5 times the ULN or Total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[b]	Baseline AST/ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST/ALT is more than 3 and up to 5 times ULN and	Withhold[a]

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modifications
	increases to more than 8 and up to 10 times ULN.	
	AST/ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN.	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Endocrinopathies[c]	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Pneumonitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Ophthalmologic	Grade 2, 3, or 4 that does not improve to Grade 1 within 2 weeks while receiving topical therapy or that requires systemic treatment	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[see 4.4 Special warnings and precautions for use]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

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 of normal

* Based on Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03

[a] Resume in patients with complete or partial resolution (Grade 0 or 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.

[b] If AST/ALT are less than or equal to ULN at baseline, withhold or permanently discontinue ipilimumab based on recommendations for hepatitis with no liver involvement.

[c] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

4.3 Contraindications

None.

4.4 Special warnings and precautions for use

Severe and Fatal Immune-Mediated Adverse Reactions

Ipilimumab is a fully human monoclonal antibody that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, thereby removing inhibition of the immune response with the potential for induction of immune-mediated adverse reactions. Immune-mediated adverse reactions listed herein may not be inclusive of 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 ipilimumab. While immune-mediated adverse reactions usually manifest during treatment, immune-mediated adverse reactions can also manifest after discontinuation of ipilimumab.

Early identification and management are essential to ensure safe use of ipilimumab. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue ipilimumab depending on severity [see4.2 Posology and method of administration]. In general, if ipilimumab 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 reaction is not controlled with corticosteroid therapy.

<u>Immune-Mediated Colitis</u>

Ipilimumab can cause immune-mediated colitis, which may be fatal. 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.

Immune-mediated colitis occurred in 10% (52/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 1.7 months (range: 2 days to 19.2 months). Immune-mediated colitis led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 3.5% and 4.2% of patients, respectively. Approximately 83% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 21 days (range: 1 day to 27 months). Approximately 23% of patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 89% of patients. Two patients had recurrence of colitis after re-initiation of nivolumab with Ipilimumab.

Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in 7% (38/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 2 months (range: 14 days to 26.8 months). Immune-mediated hepatitis led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 3.7% and 3.1% of patients, respectively. Approximately 92% of patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.0 month (range: 1 day to 4.0 months). Complete resolution occurred in 87% of patients without recurrence of hepatitis after re-initiation of nivolumab with Ipilimumab.

Immune-Mediated Dermatologic Adverse Reactions

Ipilimumab can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens Johnson Syndrome, toxic epidermal necrolysis (TEN) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue ipilimumab depending on severity *[see 4.2 Posology and method of administration].*

Immune-mediated rash occurred in 16.6% (91/547) of patients. Median time to onset was 1.5 months (range: 1 day to 20.9 months). Immune-mediated rash led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 0.5% and 2.9% of patients, respectively. Approximately 19% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 25 days (range: 1 day to 23.1 months). Complete resolution occurred in 64% of patients. Approximately 3.6% of patients who resumed nivolumab and Ipilimumab after resolution had recurrence of rash.

Immune-Mediated Endocrinopathies

Hypophysitis:

Ipilimumab can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue ipilimumab depending on severity *[see 4.2 Posology and method of administration].*

Hypophysitis occurred in 4.6% (25/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 2.8 months (range: 1.3 months to 7.3 months). Hypophysitis led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 1.3% and 2.6% of patients, respectively. Approximately 72% of patients with hypophysitis received hormone replacement therapy and 60% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 10 days (range: 1 day to 1.6 months).

Adrenal Insufficiency:

Adrenal insufficiency occurred in 7% (41/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 3.4 months (range: 2.0 months to 22.3 months). Adrenal insufficiency led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 1.3% and 2.0% of patients, respectively. Approximately 93% of patients with adrenal insufficiency received hormone replacement therapy and 18% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 1 day to 5.6 months).

Hypothyroidism and Hyperthyroidism:

Hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 2.2 months (range: 1 day to 21.4 months). Approximately 76% of patients with hypothyroidism or thyroiditis received levothyroxine. Resolution occurred in 31% of patients.

Hyperthyroidism occurred in 12% (66/547) of patients with RCC. Median time to onset was 1.4 months (range: 6 days to 14.2 months) in RCC. Approximately 14% of patients with hyperthyroidism received methimazole and 3% received carbimazole. Resolution occurred in 85% of patients.

Type 1 Diabetes Mellitus:

Diabetes occurred in 2.7% (15/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 3.2 months (range: 19 days to 16.8 months). Nivolumab with Ipilimumab was withheld in 33% of patients and permanently discontinued in 20% of patients who developed diabetes.

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis occurred in 4.4% (24/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 2.6 months (range: 8 days to 9.2 months). Immune-mediated pneumonitis led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 2.0% and 1.6% of patients, respectively. Approximately 92% of patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 19 days (range: 4 days to 3.2 months). Approximately 8% of patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 79% of patients without recurrence of pneumonitis after re-initiation of nivolumab with Ipilimumab.

In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving Ipilimumab 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 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. The median duration was 1.5 months (range: 5 days to 25^{+} months). Immune-mediated pneumonitis led to permanent discontinuation of Ipilimumab with nivolumab in 5% of patients and withholding of Ipilimumab with nivolumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis followed by a corticosteroid taper. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after re-initiation of Ipilimumab with nivolumab.

Immune-Mediated Nephritis with Renal Dysfunction

Immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients who received Ipilimumab 1 mg/kg with nivolumab for the treatment of RCC. Median time to onset was 2.5 months (range: 1 day to 13.2 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation or withholding of nivolumab with Ipilimumab in 1.1% and 2.7% of patients, respectively. Approximately 76% of patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 15 days (range: 1 day to 5.9 months). Complete resolution occurred in 64% of patients. One patient had recurrence of nephritis or renal dysfunction after re-initiation of nivolumab with Ipilimumab.

Other Immune-Mediated Adverse Reactions

Across clinical trials of ipilimumab administered as a single agent or in combination with nivolumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified, as shown below:

Nervous System: Autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, motor dysfunction

Cardiovascular: Angiopathy, myocarditis, pericarditis, temporal arteritis, vasculitis

Ocular: Blepharitis, episcleritis, iritis, orbital myositis, scleritis, uveitis. Some cases can be associated with retinal detachment. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving ipilimumab and may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Gastrointestinal: Duodenitis, gastritis, pancreatitis (1.3%)

Musculoskeletal and Connective Tissue: Arthritis, myositis, polymyalgia rheumatica, polymyositis, rhabdomyolysis

Other (hematologic/immune): Aplastic anemia, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), hypersensitivity vasculitis, meningitis, neurosensory hypoacusis, psoriasis, sarcoidosis, systemic inflammatory response syndrome and solid organ transplant rejection.

Infusion-Related Reactions

Severe infusion-related reactions can occur with ipilimumab. Discontinue ipilimumab in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions *[see 4.2 Posology and method of administration]*.

Infusion-related reactions occurred in 5.1% (28/547) of patients.

Complications of Allogeneic Hematopoietic Stem Cell Transplant after Ipilimumab

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive ipilimumab either before or after allogeneic hematopoietic stem cell transplantation (HSCT). These complications may occur despite intervening therapy between CTLA-4 receptor blocking antibody and allogeneic HSCT.

Follow patients closely for evidence of GVHD and intervene promptly [see 4.8 Undesirable effects]. Consider the benefit versus risks of treatment with ipilimumab after allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, ipilimumab can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight) and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ipilimumab and for 3 months after the last dose *[see 4.6 Use in Specific Populations (such as pregnant women, lactating women, pediatric patients, geriatric patients, etc.)]*.

Risks Associated When Administered in Combination with Nivolumab

Ipilimumab is indicated for use in combination with nivolumab for patients with advanced RCC and NSCLC. Refer to the nivolumab Full Prescribing Information for additional risk information that applies to the combination use treatment.

4.5 DRUG INTERACTIONS

Ipilimumab is a human monoclonal antibody that is not metabolized by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes. In a drug-interaction study, ipilimumab did not have a significant effect on the pharmacokinetics of substrates of CYP1A2, CYP2E1, CYP2C8, and CYP3A4 when coadministered with substrates of these CYP isozymes (dacarbazine or paclitaxel/carboplatin).

Other forms of interaction

Corticosteroids

The use of systemic corticosteroids at baseline, before starting ipilimumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of ipilimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting ipilimumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting ipilimumab treatment does not appear to impair the efficacy of ipilimumab.

Anticoagulants

The use of anticoagulants is known to increase the risk of gastrointestinal hemorrhage. Since gastrointestinal hemorrhage is an adverse reaction with ipilimumab *(see 4.8 Undesirable effects)*, patients who require concomitant anticoagulant therapy should be monitored closely.

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, ipilimumab can cause fetal harm when administered to a pregnant woman. There is insufficient human data for ipilimumab exposure in pregnant women. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner *(see Data)*. The effects of Ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

In a combined study of embryo-fetal and peri-postnatal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, administration of ipilimumab at doses resulting in exposures approximately 2.6 to 7.2 times the human exposure at a dose of 3 mg/kg resulted in dose-related increases in abortion, stillbirth, premature delivery (with corresponding lower birth weight), and an increased incidence of infant mortality. In addition, developmental abnormalities were identified in the urogenital system of 2 infant monkeys exposed in utero to 30 mg/kg of ipilimumab (7.2 times the humans exposure based on area under the curve at a dose of 3 mg/kg). One female infant monkey had unilateral renal agenesis of the left kidney

and ureter, and 1 male infant monkey had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/−), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/− heterozygous offspring. Mated CTLA-4+/− heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4−/−). The CTLA-4−/− homozygous negative offspring appeared healthy at birth, exhibited signs of multiorgan lymphoproliferative disease by 2 weeks of age, and all died by 3 to 4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

Lactation

Risk Summary

There are no data on the presence of ipilimumab in human milk or its effects on the breastfed child or milk production. In monkeys, ipilimumab was present in milk *(see Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with ipilimumab and for 3 months following the last dose.

Data

In monkeys treated at dose levels resulting in exposures 2.6 and 7.2 times higher than those in humans at a 3 mg/kg dose, ipilimumab was present in milk at concentrations of 0.1 mcg/mL and 0.4 mcg/mL, representing a ratio of up to 0.3% of the steady-state serum concentration of the drug.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating Ipilimumab *[see 4.6 Use in Special Populations-Pregnancy]*.

Contraception

Ipilimumab can cause fetal harm when administered to a pregnant woman [see 4.6 Use in Special Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with Ipilimumab and for 3 months following the last dose.

Pediatric use

The safety and effectiveness for pediatric patients 12 years and older have not been established or for the treatment of renal cell carcinoma. In addition, the safety and effectiveness have not been established with ipilimumab for any indication in pediatric patients less than 12 years of age.

Ipilimumab was evaluated in a total of 45 pediatric patients across two clinical trials. In a dose finding trial (NCT01445379), 33 pediatric patients with relapsed or refractory solid tumors were evaluated. The median age was 13 years (range 2 to 21 years) and 20 patients were ≥12 years old.

Geriatric use

Of the 550 patients randomized to ipilimumab 1 mg/kg with nivolumab in CA209227, Part 1 [CHECKMATE-214] (renal cell carcinoma), 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was observed between these patients and younger patients. In geriatric patients with intermediate or poor risk, no overall difference in effectiveness was observed.

Of the 576 patients randomized to Ipilimumab 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227 (NSCLC), 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 Ipilimumab with nivolumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to Ipilimumab 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks with in CHECKMATE-227, 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 5.2.1 Clinical Trials]*.

Of the 361 patients randomized to Ipilimumab 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CA2099LA [CHECKMATE-9LA] (NSCLC), 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 Ipilimumab with nivolumab 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 Ipilimumab in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, 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.

4.7 Effects on ability to drive and to use machines

Because of potential adverse reactions such as fatigue *(see 4.8 Undesirable effects)*, patients should be advised to use caution when driving or operating machinery until they are certain that ipilimumab does not adversely affect them.

4.8 Undesirable effects

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and fatal immune-mediated adverse reactions [see 4.4 Special warnings and precautions for use].

- Infusion-related reactions [see 4.4 Special warnings and precautions for use].

4.8.1 Clinical 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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

RCC

The safety of ipilimumab in combination with nivolumab was evaluated in 1082 patients with previously untreated advanced RCC in CHECKMATE-214 *[see 5.2.1 Clinical Trial Studies]*. Patients received ipilimumab 1 mg/kg with nivolumab 3 mg/kg intravenously every 3 weeks for 4 doses followed by nivolumab as a single agent at a dose of 3 mg/kg every 2 weeks (n=547) or sunitinib 50 mg orally daily for first 4 weeks of each 6-week cycle (n=535). The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in ipilimumab and nivolumab arm. In this trial, 57% of patients in the ipilimumab and nivolumab arm were exposed to treatment for greater than 6 months and 38% of patients were exposed to treatment for greater than 1 year.

Serious adverse reactions occurred in 59% of patients receiving ipilimumab with nivolumab. The most frequent serious adverse reactions reported in >2% of patients treated with Ipilimumab and nivolumab were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

In patients who received ipilimumab with nivolumab, study therapy was discontinued for adverse reactions in 31% and delayed for adverse reactions in 54%.

The most common adverse reactions (>20%) in the ipilimumab and nivolumab arm were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, vomiting, dyspnea, and decreased appetite. Table 2 summarizes adverse reactions in CHECKMATE-214.

Table 2: Adverse Reactions (>15%) in Patients Receiving Ipilimumab with Nivolumab in CHECKMATE-214

Adverse Reaction	Ipilimumab 1 mg/kg with Nivolumab n=547		Sunitinib n=535	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
General and Administration Site Conditions				
Fatigue[a]	58	8	69	13
Pyrexia	25	0.7	17	0.6
Edema[b]	16	0.5	17	0.6
Skin and Subcutaneous Tissue				
Rash[c]	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
Gastrointestinal				
Diarrhea	38	4.6	58	6
Nausea	30	2.0	43	1.5
Vomiting	20	0.9	28	2.1
Abdominal pain	19	1.6	24	1.9
Constipation	17	0.4	18	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	37	4.0	40	2.6
Arthralgia	23	1.3	16	0
Respiratory, Thoracic, and Mediastinal				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
Metabolism and Nutrition				
Decreased appetite	21	1.8	29	0.9
Nervous System				
Headache	19	0.9	23	0.9
Endocrine				
Hypothyroidism	18	0.4	27	0.2

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema, peripheral swelling.

[c] 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.

[d] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

Table 3 summarizes the laboratory abnormalities in CHECKMATE-214.

Table 3: Laboratory Abnormalities (>15%) Worsening from Baseline in Patients Receiving Ipilimumab with Nivolumab in CHECKMATE-214

Laboratory Abnormality	Ipilimumab 1 mg/kg with Nivolumab[a]		Sunitinib[a]	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
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	2.0	32	1.0
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	21	0.4	35	0.6
Hypomagnesemia	16	0.4	26	1.6
Hematology				
Anemia	43	3.0	64	9
Lymphopenia	36	5	63	14

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: nivolumab 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 > ULN in the ipilimumab with nivolumab group compared to the sunitinib group (31% and 61%, respectively).

First-line Treatment of Metastatic NSCLC: In Combination with Nivolumab

The safety of Ipilimumab in combination with nivolumab 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 5.2.1 Clinical Trials]*. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received Ipilimumab 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks and nivolumab 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in Ipilimumab and nivolumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received Ipilimumab and nivolumab for >6 months and 23% of patients received Ipilimumab and nivolumab 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. Ipilimumab and nivolumab 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 4 and 5 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 4: Adverse Reactions in ≥10% of Patients Receiving Ipilimumab and Nivolumab - CHECKMATE-227

	Ipilimumab and Nivolumab (n=576)		Platinum-doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema[b]	14	0.2	12	0.5
Skin and Subcutaneous Tissue				
Rash[c]	34	4.7	10	0.4
Pruritus[d]	21	0.5	3.3	0
Metabolism and Nutrition				
Decreased appetite	31	2.3	26	1.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[e]	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
Gastrointestinal				
Diarrhea/colitis[f]	26	3.6	16	0.9
Nausea	21	1.0	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1.0	18	2.3
Abdominal pain[g]	10	0.2	9	0.7

Table 4: Adverse Reactions in ≥10% of Patients Receiving Ipilimumab and Nivolumab - CHECKMATE-227

	Ipilimumab and Nivolumab (n=576)		Platinum-doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Respiratory, Thoracic, and Mediastinal				
Dyspnea[h]	26	4.3	16	2.1
Cough[i]	23	0.2	13	0
Hepatobiliary				
Hepatitis[j]	21	9	10	1.2
Endocrine				
Hypothyroidism[k]	16	0.5	1.2	0
Hyperthyroidism[l]	10	0	0.5	0
Infections and Infestations				
Pneumonia[m]	13	7	8	4.0
Nervous System				
Headache	11	0.5	6	0

[a] Includes fatigue and asthenia.

[b] Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.

[c] 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 generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.

[d] Includes pruritus and pruritus generalized.

[e] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.

[f] Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.

[g] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.

[h] Includes dyspnea and dyspnea exertional.

[i] Includes cough and productive cough.

[j] 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.

[k] Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.

[l] Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.

[m] 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 5: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on Ipilimumab and Nivolumab - CHECKMATE-227

Laboratory Abnormality	Ipilimumab and Nivolumab		Platinum-doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	46	3.6	78	14
Lymphopenia	46	5	60	15
Chemistry				
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

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Ipilimumab and nivolumab 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 Nivolumab and Platinum-Doublet Chemotherapy

The safety of Ipilimumab in combination with nivolumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see 5.2.1 Clinical Trials]*. Patients received either Ipilimumab 1 mg/kg administered every 6 weeks in combination with nivolumab 360 mg administered every 3 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 Ipilimumab in combination with nivolumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received Ipilimumab and nivolumab for >6 months and 13% of patients received Ipilimumab and nivolumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with Ipilimumab in combination with nivolumab 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 Ipilimumab in combination with nivolumab 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 6 and 7 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 6: Adverse Reactions in >10% of Patients Receiving Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9

Table 6: Adverse Reactions in >10% of Patients Receiving Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia

[b] 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

[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis

[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain

[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blenorrhagica, palmar-plantar erythrodysaesthesia 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

[f] Includes pruritus and generalized pruritus

[g] Includes cough, productive cough, and upper-airway cough syndrome

[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea

[i] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine

[j] Includes dizziness, vertigo and positional vertigo

Table 7: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	Ipilimumab and Nivolumab and Platinum-Doublet		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
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
Chemistry				
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

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Ipilimumab and nivolumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

4.8.2 Post-marketing experience

The following adverse reactions have been identified during post approval use of ipilimumab. 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.

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH)

Immune System: graft-versus-host disease, solid organ transplant rejection

Skin and Subcutaneous Tissue: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

4.8.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidences of antibodies to other studies or to other products may be misleading.

Of 483 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-227 Part 1, 8.5% were positive for treatment-emergent anti-ipilimumab antibodies. No patients had neutralizing antibodies against ipilimumab. In Part 1 of the same study, of 491 patients evaluable for anti-nivolumab antibodies, 36.7% were positive for anti-nivolumab antibodies and 1.4% had neutralizing antibodies against nivolumab.

Of 305 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-9LA, 8% were positive for anti-ipilimumab antibodies and 1.6% were positive for anti-ipilimumab neutralizing antibodies. There was no evidence of increased incidence of infusion reactions to Ipilimumab in patients with anti-ipilimumab antibodies. Of 308 patients evaluable for anti-nivolumab antibodies in CHECKMATE-9LA, 34% were positive for anti-nivolumab antibodies and 2.6% had neutralizing antibodies against nivolumab.

4.9 Overdose

The maximum tolerated dose of ipilimumab has not been determined. In clinical trials, patients received up to 20 mg/kg without apparent toxic effects.

In case of overdosage, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

5.2 Pharmacodynamics Properties

5.2.1 Clinical Trials

Renal cell carcinoma (RCC)

The efficacy of ipilimumab with nivolumab was evaluated in CHECKMATE-214 (NCT02231749), a randomized (1:1), open-label study 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 randomized to nivolumab 3 mg/kg and ipilimumab 1 mg/kg administered intravenously every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every two weeks or to sunitinib administered orally 50 mg daily for the first 4 weeks of each 6-week cycle. Treatment continued until disease progression or unacceptable toxicity. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. The major efficacy outcome measures were OS, PFS (IRRC-assessed), and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. Intermediate/poor risk patients had at least 1 or more of 6 prognostic risk factors as per the IMDC criteria: less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status (KPS) <80%, hemoglobin less than the lower limit of normal, corrected calcium >10 mg/dL, platelet count > ULN, and absolute neutrophil count > ULN.

A total of 847 patients were randomized, 425 to ipilimumab with nivolumab and 422 to sunitinib. The 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.

Efficacy results from CHECKMATE-214 are presented in Table 8 and Figure 1. In intermediate/poor risk patients, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to ipilimumab and nivolumab arm as compared with sunitinib arm. OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS.

Table 8: Efficacy Results for CHECKMATE-214

Efficacy Parameter	Intermediate/Poor-Risk	
	Ipilimumab 1 mg/kg with Nivolumab n=425	**Sunitinib n=422**
Overall Survival		
Number of deaths	140 (32.9%)	188 (44.5%)
Median in months	NE	25.9
Hazard ratio (99.8% CI)[a]	0.63 (0.44, 0.89)	
p-value[b,c]	<0.0001	
Confirmed Objective Response Rate (95% CI)	41.6% (36.9%, 46.5%)	26.5% (22.4%, 31.0%)
Complete Response	40 (9.4%)	5 (1.2%)
Partial Response	137 (32.2%)	107 (25.4%)
Median duration of response in months (95% CI)	NE (21.8, NE)	18.2 (14.8, NE)
p-value[d,e]	<0.0001	
Progression-free Survival		
Number of events (progression or death)	228 (53.6%)	228 (54.0%)
Median in months	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	
p-value[b]	NS[f]	

[a] Based on a stratified proportional hazards model.

[b] Based on a stratified log-rank test.

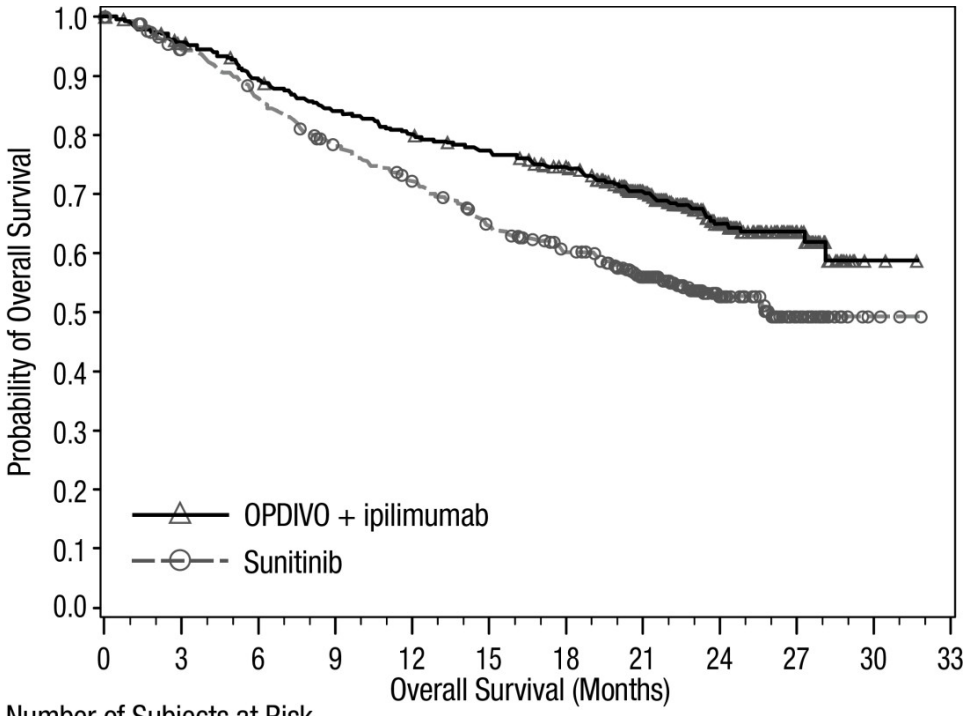
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.

[d] Based on the stratified DerSimonian-Laird test.

[e] p-value is compared to alpha 0.001 in order to achieve statistical significance.

[f] Not Significant at alpha level of 0.009

Figure 1: Kaplan-Meier Curves for Overall Survival (Intermediate/Poor Risk Population) in CHECKMATE-214



CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to nivolumab 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 nivolumab and ipilimumab compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of nivolumab and ipilimumab in previously untreated renal cell carcinoma with favorable risk disease has not been established.

Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Nivolumab

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 [ASLC] 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 enrolment, 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:

- Ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks in combination with nivolumab 3 mg/kg administered intravenously over 30 minutes every 2 weeks; or
- Platinum-doublet chemotherapy

Chemotherapy regimens consisted of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) or pemetrexed (500 mg/m^2) and carboplatin (AUC 5 or 6) for non-squamous NSCLC or gemcitabine (1000 or 1250 mg/m^2) and cisplatin (75 mg/m^2) or gemcitabine (1000 mg/m^2) 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 nivolumab 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 Ipilimumab in combination with nivolumab (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 Ipilimumab and nivolumab arm compared to platinum-doublet chemotherapy arm. The OS results are presented in Table 9 and Figure 2.

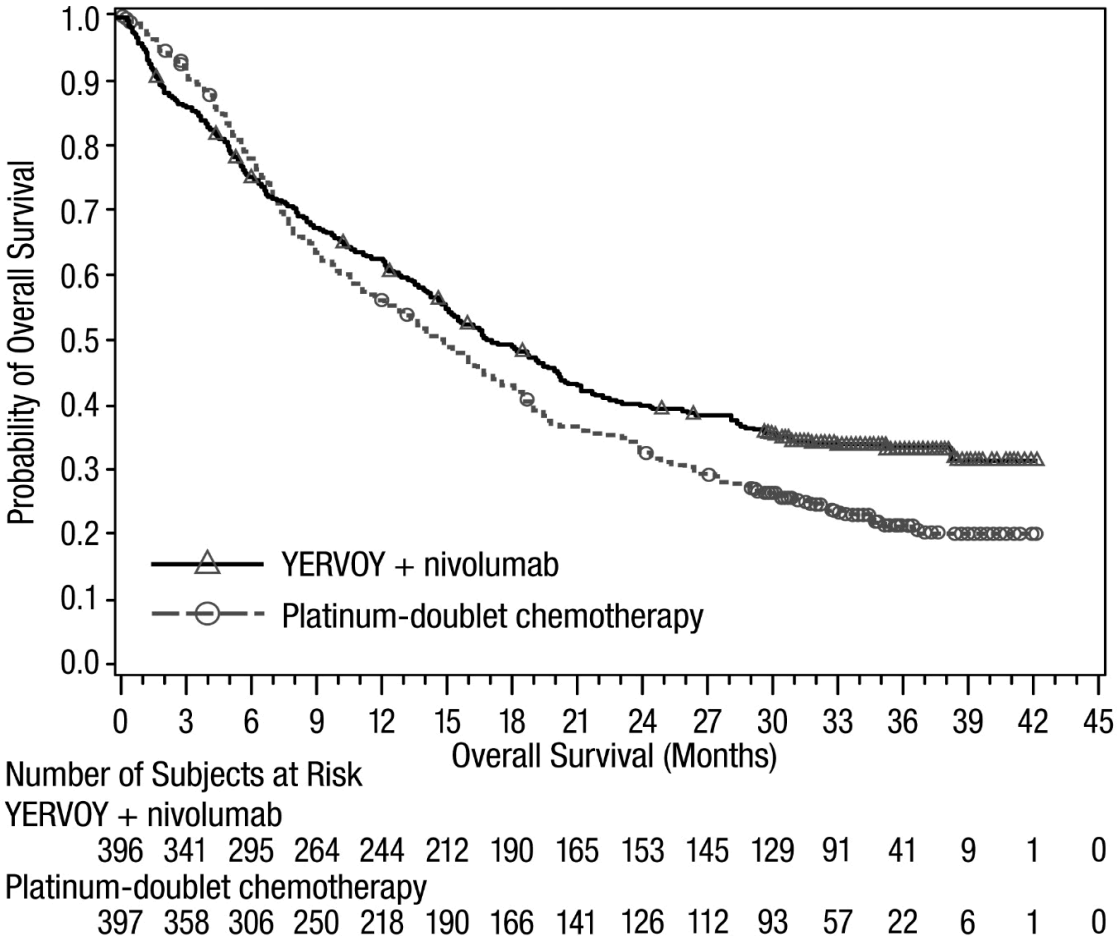
Table 9: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

	Ipilimumab and Nivolumab (n=396)	Platinum-Doublet Chemotherapy (n=397)
Overall Survival		
Events (%)	258 (65%)	298 (75%)
Median (months)[a] (95% CI)	17.1 (15, 20.1)	14.9 (12.7, 16.7)
Hazard ratio (95% CI)[b]	0.79 (0.67, 0.94)	
Stratified log-rank p-value	0.0066	

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

Figure 2: 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 Ipilimumab and nivolumab 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 Ipilimumab and nivolumab arm and 30% (95% CI: 26, 35) in the platinum-doublet chemotherapy arm. Median duration of response observed in the Ipilimumab and nivolumab 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 Nivolumab 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:

- Ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks, nivolumab 360 mg administered intravenously over 30 minutes every 3 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/mg^2, or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 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 nivolumab 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 Ipilimumab in combination with nivolumab 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 10.

Table 10: Efficacy Results - CHECKMATE-9LA

	Ipilimumab and Nivolumab and Platinum-Doublet Chemotherapy (n=361)	**Platinum-Doublet Chemotherapy (n=358)**
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Progression-free Survival per BICR		
Events (%)	232 (64.3)	249 (69.6)
Hazard ratio (97.48% CI)[a]	0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]	0.0001	
Median (months)[d] (95% CI)	6.8 (5.6, 7.7)	5.0 (4.3, 5.6)
Overall Response Rate per BICR (%)	38	25
(95% CI)[e]	(33, 43)	(21, 30)
Stratified CMH test p-value[f]	0.0003	
Duration of Response per BICR		
Median (months) (95% CI)[d]	10.0 (8.2, 13.0)	5.1 (4.3, 7.0)

[a] Based on a stratified Cox proportional hazard model.

[b] p-value is compared with the allocated alpha of 0.033 for this interim analysis.

[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.

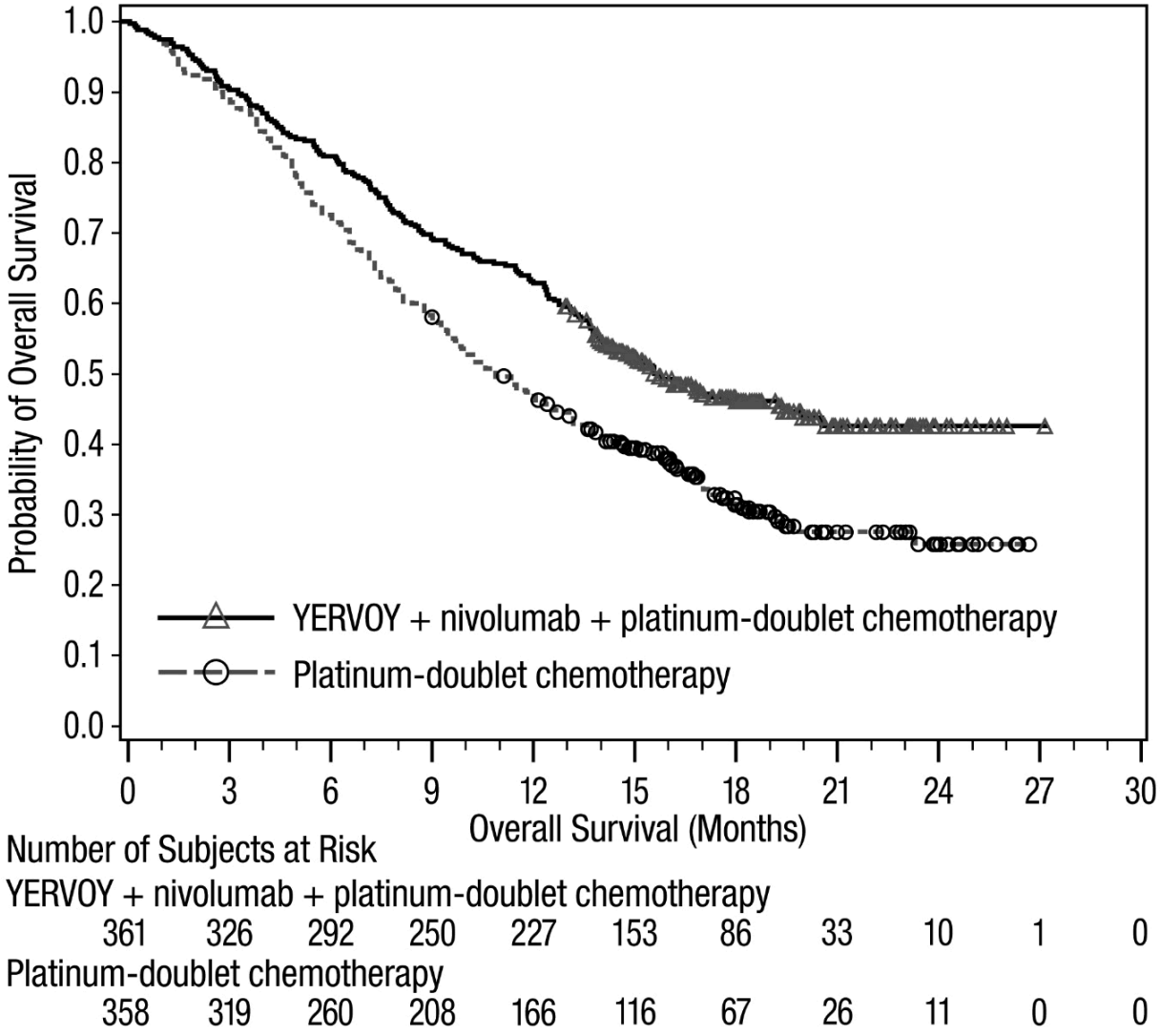
[d] Kaplan-Meier estimate.

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

[f] 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 ipilimumab and nivolumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 3).

Figure 3: Overall Survival - CHECKMATE-9LA



5.3 Pharmacokinetic Properties

The pharmacokinetics (PK) of ipilimumab was studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every 3 weeks for 4 doses. The PK of ipilimumab is linear in the dose range of 0.3 mg/kg to 10 mg/kg. Following administration of Ipilimumab every 3 weeks, the systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean minimum

concentration (Cmin) at steady state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks.

Elimination

The mean (percent coefficient of variation) terminal half-life (t1/2) was 15.4 days (34%) and then mean (percent coefficient of variation) clearance (CL) was 16.8 mL/h (38%).

The CL of ipilimumab was unchanged in presence of anti-ipilimumab antibodies.

Specific Populations

The CL of ipilimumab increased with increasing body weight supporting the recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23 to 88 years), sex, performance status, renal impairment (glomerular filtration rate ≥15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin [TB] >1 to 1.5 times the upper limit of normal [ULN] or AST > ULN), previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-White racial groups. ipilimumab has not been studied in patients with moderate (TB > 1.5 to 3 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment.

Pediatric Patients: Based on a population PK analysis using available pooled data from 565 patients from four adult studies (n=521) and two pediatric studies (n=44), body weight normalized clearance of ipilimumab is comparable between adult and pediatric patients. In pediatric patients with a dosing regimen of 3 mg/kg every 3 weeks, the model simulated geometric mean (CV%) steady-state serum peak and trough concentrations of ipilimumab were 65.8 (17.6%) and 20.7 (33.1%) mcg/mL (for 2 to 6 years old), 70.1 (19.6%) and 19.6 (42.9%) mcg/mL (for 6 to <12 years old), and 73.3 (20.6%) and 17.8 (50.8%) mcg/mL (for 12 years and older), which are comparable to those in adult patients.

Drug Interaction Studies

Ipilimumab with Nivolumab

When ipilimumab 1 mg/kg was administered with nivolumab 3 mg/kg every 3 weeks, the CL of ipilimumab was unchanged compared to when ipilimumab was administered alone.

When Ipilimumab 1 mg/kg every 6 weeks was administered in combination with nivolumab 3 mg/kg every 2 weeks, the CL of ipilimumab increased by 30% compared to Ipilimumab administered alone and the CL of nivolumab was unchanged compared to nivolumab administered alone.

When Ipilimumab 1 mg/kg every 6 weeks was administered in combination with nivolumab 360 mg every 3 weeks and chemotherapy, the CL of ipilimumab increased by 22% compared to Ipilimumab administered alone and the CL of nivolumab was unchanged compared to nivolumab administered alone.

6 NON CLINICALPROPERTIES

6.1 Animal Toxicology

Please refer section 4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.), sub-section Animal data.

Carcinogenesis, mutagenesis, impairment of fertility

The carcinogenic potential of ipilimumab has not been evaluated in long-term animal studies, and the genotoxic potential of ipilimumab has not been evaluated.

Fertility studies have not been performed with ipilimumab.

7 DESCRIPTION

Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. Ipilimumab is a recombinant IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

- Ipilimumab injection, for intravenous use is a sterile, preservative-free, clear to slightly opalescent,
  colorless to pale-yellow solution, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-dose vials of 50 mg/10 mL. Each milliliter contains 5 mg of ipilimumab and the following excipients: Tris hydrochloride (2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride), Sodium chloride, Mannitol, Pentetic acid (diethylenetriaminepentaacetic acid), Polysorbate 80, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment) and Water for injection.

8 PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

8.2 Shelf life

Unopened vial: Refer to the outer carton, for the expiry date.

Solution for infusion: Once opened, the product should be infused or diluted and infused immediately. The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 mg/mL and 4 mg/mL) has been demonstrated for 24 hours at 25°C (77°F) and 2°C to 8°C (36°F to 46°F). If not used immediately, the infusion solution (undiluted or diluted) may be stored for up to 24 hours either under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).

Ipilimumab must be stored in a refrigerator (2°C - 8°C). Do not freeze.Store in the original package in order to protect from light.

8.3 Packaging Information

Each 10 ml vial contains 50 mg of ipilimumab.

Pack of 1 Vial.

8.4 Storage and handling instructions

Preparation for administration

- Do not shake product.
- Visually inspect for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

Preparation of Solution

- Allow the vial(s) to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of ipilimumab and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- After preparation, store the diluted solution either refrigerated at 2°C to 8°C (36°F to 46°F) or at room temperature of 20°C to 25°C (68°F to 77°F) for no more than 24 hours from the time of preparation to the time of infusion.
- Discard partially used or empty vials of ipilimumab.

Administration

- Do not co-administer other drugs through the same intravenous line.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose
- Injection, USP after each dose.
- Administer diluted solution through an intravenous line containing a sterile, non-pyrogenic,
- low-protein-binding in-line filter.
- When administered in combination with nivolumab, infuse nivolumab first followed by ipilimumab on the same day. When administered with nivolumab and platinum-doublet chemotherapy, infuse nivolumab first followed by ipilimumab and then platinum-doublet chemotherapy on the same day. Use separate infusion bags and filters for each infusion.

9 PATIENT COUSELLING INFORMATION

Immune-Mediated Adverse Reactions

Advise patients that ipilimumab can cause immune-mediated adverse reactions including the following *[see 4.4 Special warnings and precautions for use]*:

- Immune-Mediated Diarrhea or Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of diarrhea or colitis.
- Immune-Mediated Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Immune-Mediated Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.
- Immune-Mediated Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus
- Immune-Mediated Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening symptoms of pneumonitis.
- Immune-Mediated Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.

Infusion-Related Reactions

- Advise patients who are receiving ipilimumab of the potential risk of an infusion-related reaction *[see 4.4 Special warnings and precautions for use]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see 4.4 Special warnings and precautions for use and 4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.)]*.
- Advise females of reproductive potential to use effective contraception during treatment with ipilimumab and for 3 months after the last dose *[see 4.4 Special warnings and precautions for use]*.

Lactation

- Advise women not to breastfeed during treatment with Ipilimumab and for 3 months after the last dose *[see 4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.)]*.

10 DETAILS OF MANUFACTURER

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And

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11 DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

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APPENDIX 6 INTERNATIONAL METASTATIC RCC DATABASE CONSORTIUM (IMDC) PROGNOSTIC CRITERIA

Adverse Prognostic Factors
Clinical
KPS < 80% Time from initial diagnosis (including original localized disease if applicable) to treatment < 1 year
Laboratory
Hemoglobin < LLN Corrected calcium > 10 mg/dL Absolute neutrophil count > ULN Platelet count > ULN

Abbreviations: KPS = Karnofsky Performance Status; LLN = lower limit of normal; ULN = upper limit of normal

Note: The corrected calcium criterion was adapted from to Heng et al, 2009 to account for local laboratories that may not provide an ULN for corrected calcium.

Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL.

Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 (40 - serum albumin [g/L]), where 40 represents the average albumin level in g/L

Risk Group Based on Number of Adverse Prognostic Factors	
Number of Adverse Prognostic Factors Present	**Risk Group**
0	Favorable
1-2	Intermediate
3-6	Poor

Reference: Heng D, Xie W, Regan M, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009; 27(34):5794-5799.

APPENDIX 7 PERFORMANCE STATUS SCALES

STATUS	SCALES		STATUS
	KARNOFSKY	ZUBROD-ECOG-WHO	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	0	Symptoms, but fully ambulatory
Normal activity with effort	80	1	
Cares for self. Unable to carry on normal activity or to do active work	70	1	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60	2	
Requires considerable assistance and frequent medical care	50	2	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40	3	
Severely disabled. Hospitalization indicated though death non imminent	30	3	Unable to get out of bed
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	
Moribund	10	4	
Dead	0	5	Dead

APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS

Any Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

	Country-specific language
Section 2 Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments- Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion 1.a	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".

APPENDIX 9 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline with BMS modifications.[1]

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥2x slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan and plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition:

if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up

CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCES

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.