Bristol Myers Squibb

OPDIVO® (Nivolumab)
Concentrate For Solution For Infusion 10mg/mL

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 10 mg of nivolumab.
One vial of 4 mL contains 40 mg of nivolumab.
One vial of 10 mL contains 100 mg of nivolumab.
One vial of 12 mL contains 120 mg of nivolumab.
One vial of 24 mL contains 240 mg of nivolumab.

Nivolumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipient with known effect
Each mL of concentrate contains 0.1 mmol (or 2.5 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colorless to pale yellow liquid that may contain few light particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (see sections 4.4 and 5.1).

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Non-Small Cell Lung Cancer (NSCLC)

OPDIVO, in combination with ipilimumab and 2 cycles of platinum-based chemotherapy, is indicated for the first-line treatment of metastatic or recurrent NSCLC in adult patients with no EGFR or ALK genomic tumor mutations.

OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

Neoadjuvant treatment of NSCLC

OPDIVO, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of adult patients with resectable (tumours ≥4 cm or node positive) NSCLC.

Malignant pleural mesothelioma (MPM)

OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Renal Cell Carcinoma (RCC)

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

OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (see section 5.1).

Classical Hodgkin Lymphoma (cHL)

OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin (see section 5.1).

Squamous Cell Cancer of the Head and Neck (SCCHN)

OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy in adults (see section 5.1).

Gastric/ Gastroesophageal Junction (GEJ) Cancer

OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable locally advanced or recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma after two or more prior systemic therapies.

Oesophageal Squamous Cell Carcinoma (OSCC)

OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Gastric Cancer, Gastroesophageal Junction (GEJ) Cancer or Oesophageal Adenocarcinoma

OPDIVO, in combination with fluoropyrimidine- and platinum-based chemotherapy, is indicated for the treatment of patients with unresectable HER2 negative advanced or metastatic gastric cancer, gastroesophageal junction cancer, or oesophageal adenocarcinoma (see section 5.1).

Adjuvant treatment of oesophageal or gastroesophageal junction cancer (OC or GEJC)

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

Urothelial carcinoma
OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumor cell PD-L1 expression ≥1% who are at high risk of recurrence after undergoing radical resection of MIUC.

4.2 Posology and method of administration

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

Posology

OPDIVO as monotherapy
The recommended dose of OPDIVO is 3 mg/kg administered intravenously over 30-60 minutes every 2 weeks.

Oesophageal Squamous Cell Carcinoma (OSCC)

The recommended dose of OPDIVO is 240 mg administered intravenously over 30-60 minutes every 2 weeks.

Adjuvant treatment of oesophageal or gastroesophageal junction cancer (OC or GEJC)

The recommended dose of OPDIVO is 240 mg administered intravenously over 30-60 minutes every 2 weeks, or 480 mg administered intravenously over 30-60 minutes every 4 weeks.

Muscle invasive urothelial carcinoma (MIUC) adjuvant treatment
The recommended dose of OPDIVO is 240 mg administered intravenously over 30-60 minutes every 2 weeks, or 480 mg administered intravenously over 30-60 minutes every 4 weeks.

OPDIVO in combination with ipilimumab

Melanoma
The recommended dose is 1 mg/kg nivolumab administered as an intravenous infusion over 30-60 minutes every 3 weeks for the first 4 doses in combination with 3 mg/kg ipilimumab administered intravenously over 30-90 minutes.

This is then followed by a second phase in which 3 mg/kg nivolumab is administered as an intravenous infusion over 30-60 minutes every 2 weeks.

Non-Small Cell Lung Cancer (NSCLC)
The recommended dose is 360 mg nivolumab administered as an intravenous infusion every 3 weeks in combination wth 1 mg/kg ipilimumab administered as an intravenous infusion every 6 weeks, and platinum chemotherapy administered 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. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Malignant pleural mesothelioma (MPM)
The recommended dose of nivolumab is either 3 mg/kg every 2 weeks or 360 mg every 3 weeks administered as an intravenous infusion over 30-60 minutes in combination with 1 mg/kg ipilimumab administered as an intravenous infusion over 30 minutes every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Renal Cell Carcinoma (RCC)
The recommended dose is 3 mg/kg nivolumab administered as an intravenous infusion over 30-60 minutes every 3 weeks for the first 4 doses in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes.

This is then followed by a second phase in which 3 mg/kg nivolumab is administered as an intravenous infusion over 30-60 minutes every 2 weeks. The first dose of nivolumab monotherapy should be administered 3 weeks following the last dose of the combination of nivolumab and ipilimumab.

OPDIVO in combination with cabozantinib

Renal Cell Carcinoma (RCC)
The recommended dose is nivolumab administered intravenously at either 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes in combination with 40 mg cabozantinib administered orally every day.

OPDIVO in combination with chemotherapy

Neoadjuvant treatment of non-small cell lung cancer
The recommended dose is 360 mg nivolumab administered intravenously over 30-60 minutes in combination with platinum-based chemotherapy every 3 weeks for 3 cycles (see section 5.1).

Gastric cancer, gastroesophageal junction cancer and oesophageal adenocarcinoma
The recommended dose is 360 mg nivolumab administered intravenously over 30-60 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy every 3 weeks **or** 240 mg nivolumab administered intravenously over 30-60 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy every 2 weeks (see section 5.1). Treatment is recommended until disease progression or unacceptable toxicity. The maximum treatment duration for OPDIVO is 24 months.

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

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

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

For OPDIVO in combination with cabozantinib, nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Cabozantinib should be continued until disease progression or unacceptable toxicity. Refer to the product insert for cabozantinib.

Dose escalation or reduction is not recommended for OPDIVO as monotherapy or in combination with other therapeutic agents. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 1. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4. When nivolumab is administered in combination with other therapeutic agents, refer to the product insert of these other combination therapeutic agents regarding dosing.

Table 1: Recommended treatment modifications for OPDIVO or OPDIVO in combination with other therapeutic agents

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis - OPDIVO monotherapy	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	- OPDIVO + ipilimumab[a]	Permanently discontinue treatment
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis **NOTE**: for RCC patients treated with **OPDIVO in combination with cabozantinib** with liver enzyme elevations, see dosing guidelines following this table.	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
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[b] as long as no symptoms are present
	Grade 4 hypothyroidism, hyperthyroidism, hypophysitis and diabetes Grade 3 or 4 adrenal insufficiency	Permanently discontinue treatment
Immune-related encephalitis	New onset moderate or severe neurologic signs or symptoms	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Immune-related encephalitis	Permanently discontinue treatment

Table 1:	**Recommended treatment modifications for OPDIVO or OPDIVO in combination with other therapeutic agents**	
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Suspected SJS/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[c].
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3 ; persistent Grade 2 or 3 despite treatment modification ; inability to reduce corticosteroids dose to 10mg 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).

[a] During the administraton of the second phase of treatment (nivolumab monotherapy) following combination treatment, permanently discontinue treatment if Grade 3 diarrhoea or colitis occurs.

[b] Recommendation for the use of hormone replacement therapy is provided in section 4.4.

[c] The safety of re-initiating nivolumab or nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known.

OPDIVO as monotherapy or in combination with other therapeutic agents should be permanently discontinued for:

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

When OPDIVO is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or OPDIVO monotherapy could be resumed based on the evaluation of the individual patient.

OPDIVO in combination with cabozantinib in RCC

When nivolumab is used in combination with cabozantinib, the above treatment modifications in Table 1 also apply to the nivolumab component. In addition, for liver enzyme elevations, in patients with RCC being treated with nivolumab in combination with cabozantinib:

- If ALT or AST > 3 times ULN but ≤ 10 times ULN without concurrent total bilirubin ≥ 2 times ULN, both nivolumab and cabozantinib should be withheld until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or rechallenge with both medicines after recovery may be considered. If rechallenging with cabozantinib, refer to cabozantinib product insert.
- If ALT or AST > 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both nivolumab and cabozantinib should be permanently discontinued and corticosteroid therapy may be considered.

For RCC patients treated with nivolumab in combination with cabozantinib, refer to the product insert regarding treatment modifications of cabozantinib.

OPDIVO in combination with chemotherapy
When OPDIVO is administered in combination with chemotherapy, refer to the product information of the other combination therapy agents regarding dosing. Dose escalation or reduction is not recommended for OPDIVO. If any agents are withheld, the other agents may be continued. If dosing is resumed after a delay, either the combination treatment, OPDIVO monotherapy or chemotherapy alone could be resumed based on the evaluation of the individual patient.

Special populations

Paediatric population
The safety and efficacy of OPDIVO in children below 18 years of age have not been established. No data are available.

Elderly
No dose adjustment is required for elderly patients (≥ 65 years) (see sections 5.1 and 5.2).

Renal impairment
Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Hepatic impairment
Based on the population PK results, no dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Data from patients with moderate (total bilirubin > 1.5 x to 3 x the upper limits of normal [ULN] and any AST) or severe (total bilirubin >3 x ULN and any AST) hepatic impairment are too limited to draw conclusions on these populations.

Method of administration

OPDIVO is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30-60 minutes. The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 μm. Do not coadminister other drugs through the same intravenous line.

OPDIVO must not be administered as an intravenous push or bolus injection.

The total dose of OPDIVO required can be infused directly as a 10 mg/mL solution or can be diluted to as low as 1 mg/mL with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection.

When administered in combination with ipilimumab and/or chemotherapy, OPDIVO should be given first followed by ipilimumab (if applicable) and then chemotherapy on the same day. Use separate infusion bags and filters for each infusion.

For instructions on the handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When nivolumab is administered in combination with other therapeutic agents, refer to the product insert of the other combination therapy agents prior to initiation of treatment. Both agents are associated with immune-related adverse reactions. Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Immune-related adverse reactions have occurred at similar frequencies when nivolumab was administered in combination with cabozantinib relative to nivolumab monotherapy. Therefore, the guidance below for immune-related adverse reactions applies to the nivolumab component of the combination, except where specifically noted. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see section 4.2).

Cardiac and pulmonary adverse events including pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions.

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.

For suspected immune related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

Nivolumab or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune related adverse reaction that recurs and for any life threatening immune related adverse reaction.

Use of nivolumab in melanoma patients with rapidly progressing disease
Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with rapidly progressing disease (see section 5.1).

Immune-related pneumonitis
Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 pneumonitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

For Grade 2 (symptomatic) pneumonitis, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune related colitis
Severe diarrhoea or colitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Infectious and disease-related aetiologies 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 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 3 diarrhoea or colitis, nivolumab monotherapy should be withheld and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab monotherapy may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab monotherapy must be permanently discontinued. Grade 3 diarrhoea or colitis observed with

nivolumab in combination with ipilimumab requires permanent discontinuation of treatment and initiation of corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent diarrhoea or colitis should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

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 section 4.8). Patients should be monitored periodically for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 transaminase or total bilirubin elevation, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 transaminase or total bilirubin elevation, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related nephritis and renal dysfunction

Severe nephritis and renal dysfunction have been observed with nivolumab monotherapy treatment or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of nephritis or renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.

For Grade 4 serum creatinine elevation, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 or 3 serum creatinine elevation, nivolumab or nivolumab in combination with ipilimumab should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related endocrinopathies

Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), diabetes mellitus, and diabetic ketoacidosis have been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8).

Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycaemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate 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 anti-thyroid medication should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening hyperthyroidism or hypothyroidism.

For symptomatic Grade 2 adrenal insufficiency, nivolumab or nivolumab in combination with ipilimumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Monitoring of adrenal function and hormone levels should be continue to ensure appropriate corticosteroid replacement is utilised.

For symptomatic Grade 2 or 3 hypophysitis, nivolumab or nivolumab in combination with ipilimumab should be withheld, and hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the pituitary gland is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening (Grade 4) hypophysitis. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.

For symptomatic diabetes, nivolumab or nivolumab in combination with ipilimumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening diabetes.

Immune-related skin adverse reactions

Severe rash has been observed with nivolumab. The frequency of rash is higher when nivolumab is administered in combination with ipilimumab. (see section 4.8). Nivolumab or nivolumab in combination with ipilimumab should be withheld for Grade 3 rash and discontinued for Grade 4 rash. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Rare cases of Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some of them 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 specialised 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 (see section 4.2).

Caution should be used when considering the use of nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Immune-related encephalitis

Immune-related encephalitis can occur with nivolumab or nivolumab in combination with ipilimumab treatment. Withhold nivolumab or nivolumab in combination with ipilimumab in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infections or other causes of moderate to severe neurologic deterioration. Evaluation may include, but not limited to, consultation with a neurologist, brain MRI and lumbar puncture.

If other aetiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents for patients with immune-related encephalitis, followed by corticosteroid taper. Permanently discontinue nivolumab or nivolumab in combination with ipilimumab for immune-related encephalitis.

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 tumour 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, encephalitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis and rhabdomyolysis.

Cases of Vogt-Koyanagi-Harada syndrome have been reported during post approval use of nivolumab or nivolumab in combination with ipilimumab.

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs, immune-related adverse reaction that is persistent despite treatment modification 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).

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. The benefit of treatment with nivolumab versus the possible risk should be considered in these patients.

In patients treated with nivolumab post allogenic hematopoietic stem cell transplant (HSCT), rapid- onset and severe graft-versus-host disease (GVHD), some with fatal outcome, has been reported in the post-marketing setting. Treatment with nivolumab may increase the risk of severe GVHD and death in patients who had prior allogeneic HSCT. The benefit of treatment with nivolumab versus the possible risk should be considered in these patients.

Infusion reactions

Severe infusion reactions have been reported in clinical trials of nivolumab or nivolumab in combination with ipilimumab (see section 4.8). In case of a severe or life-threatening infusion reaction, the nivolumab or nivolumab in combination with ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab or nivolumab in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Disease-specific precautions

Melanoma

Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the clinical trials of nivolumab or nivolumab in combination with ipilimumab. Patients with ocular/uveal melanoma were excluded from clinical trials of melanoma. In addition, CA209037 excluded patients who have had a Grade 4 adverse reaction that was related to anti-CTLA-4 therapy (see section 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential risk-benefit on an individual basis.

Relative to nivolumab monotherapy, an increase in PFS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy (see sections 4.8 and 5.1).

Adjuvant treatment of melanoma

There are no data on adjuvant treatment in patients with melanoma with the following risk factors (see sections 4.5 and 5.1)

- patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications,
- patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥ 6 months prior to randomisation),
- patients treated with prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways),
- subjects under the age of 18 years.

In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Non-Small Cell Lung Cancer
Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry and patients with sensitizing EGFR mutations or ALK translocations were excluded from the clinical trials of NSCLC (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential risk-benefit on an individual basis.

Neoadjuvant treatment of NSCLC
Patients with a baseline performance score ≥ 2, active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, unresectable or metastatic disease, who received prior anti-cancer treatment for resectable disease, or who had known EGFR mutations or ALK translocations were excluded from the pivotal trial in neoadjuvant treatment of resectable NSCLC (see sections 5.1). In the absence of data, nivolumab in combination platinum-based chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Malignant pleural mesothelioma
Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the pivotal trial in first-line treatment of MPM (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Renal Cell Carcinoma
OPDIVO or OPDIVO in combination with ipilimumab
Patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of nivolumab or nivolumab with ipilimumab (see sections 4.5 and 5.1). In the absence of data, nivolumab or nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential risk-benefit on an individual basis.

OPDIVO in combination with cabozantinib
Patients with any active brain metastases, autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of nivolumab in combination with cabozantinib (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with cabozantinib should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

When nivolumab is given with cabozantinib, higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported relative to nivolumab monotherapy in patients with advanced RCC (see section 4.8). Liver enzymes should be monitored before initiation of and periodically throughout treatment. Medical management guidelines for both medicines should be followed (see section 4.2 and refer to the product insert for cabozantinib).

Classical Hodgkin Lymphoma (cHL)
Patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL. In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT) in classical Hodgkin Lymphoma

Preliminary results from the follow up of patients undergoing allogeneic HSCT after previous exposure to nivolumab showed a higher than expected number of cases of acute graft-versus-host-disease (aGVHD) and transplant related mortality (TRM). Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications should be made case by case (see section 4.8).

Head and Neck Cancer
Patients with a baseline performance score ≥ 2, untreated brain metastasis or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or carcinoma of the nasopharynx or salivary gland as the primary tumour sites were excluded from the SCCHN clinical trial (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Gastric Cancer
Patients with history of chronic or recurrent autoimmune disease, interstitial lung disease or pulmonary fibrosis, symptomatic brain metastases, diverticulitis, or symptomatic gastrointestinal ulcerative disease were excluded from the pivotal trial in gastric cancer (see section 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Oesophageal Squamous Cell Carcinoma (OSCC)
The majority of clinical data available in oesophageal squamous cell carcinoma are in patients of Asian origin (see section 5.1).
Patients with a baseline performance score ≥ 2, brain metastases that were symptomatic or required treatment, apparent tumour invasion on organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in OSCC (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.
Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with OSCC. A higher number of deaths within 2.5 months after randomisation was observed with nivolumab compared to chemotherapy. No specific factor(s) associated with early deaths could be identified (see section 5.1).

Gastric cancer, gastroesophageal junction cancer or oesophageal adenocarcinoma
Patients who had known human epidermal growth factor receptor (HER2) positive cancer, baseline performance score ≥ 2, or had untreated central nervous system metastases were excluded from the clinical study in gastric cancer, GEJ cancer or oesophageal adenocarcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Adjuvant treatment of oesophageal or gastroesophageal junction cancer
Patients with a baseline performance score ≥ 2, who did not receive concurrent chemoradiotherapy (CRT) prior to surgery, with stage IV resectable disease, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in oesophageal and gastro-oesophageal junction cancer (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Adjuvant treatment of urothelial carcinoma
Patients with a baseline performance score of ≥2 (except patients with a baseline performance score of 2 who have not received cisplatin based neoadjuvant chemotherapy and are considered ineligible for cisplatin adjuvant chemotherapy), evidence of disease after surgery, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trial of adjuvant treatment of urothelial carcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

<u>Increased mortality in patients with multiple myeloma when a PD-1 blocking antibody is added to a thalidomide analogue and dexamethasone</u>

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.

Patients on controlled sodium diet
Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Nivolumab is a human monoclonal antibody, as such pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab.

Other forms of interaction

Systemic immunosuppression
The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions. The preliminary results show that systemic immunosuppression after starting nivolumab treatment does not appear to preclude the response on nivolumab.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the use of nivolumab in pregnant women. Studies in animals have shown embryofetal toxicity (see section 5.3). Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore nivolumab has the potential to be transmitted from the mother to the developing foetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of OPDIVO.

Breast-feeding
It is unknown whether nivolumab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from nivolumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Studies to evaluate the effect of nivolumab on fertility have not been performed. Thus, the effect of nivolumab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

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 section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that nivolumab does not adversely affect them.

4.8 Undesirable effects

Summary of the safety profile
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 as monotherapy across tumour types (n=4494), the most frequent adverse reactions (≥ 10%) were fatigue (43%), musculoskeletal pain (30%), diarrhoea (25%), nausea (23%), rash (23%), cough (22%), pruritus (19%), decreased appetite (18%), constipation (17%), abdominal pain (17%), dyspnoea (17%), upper respiratory tract infection (15%), vomiting (14%), pyrexia (14%), arthralgia (13%), headache (12%), oedema (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Adverse reaction frequencies in the paragraph above and in Table 2 below are based on all-causality adverse event incidence rates.

Tabulated summary of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n=4494) are presented in Table 2. 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Infections and infestations	
Very common	upper respiratory tract infection
Common	pneumonia[a], bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Uncommon	eosinophilia
Immune system disorders	
Common	infusion related reaction[b], hypersensitivity (including anaphylactic reaction)[b]
Uncommon	sarcoidosis
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism
Uncommon	adrenal insufficiency[h], hypopituitarism, hypophysitis, diabetes mellitus, diabetic ketoacidosis, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration
Uncommon	metabolic acidosis
Nervous system disorders	
Very common	headache
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,b,i]
Eye disorders	
Common	blurred vision, dry eye
Uncommon	uveitis
Cardiac disorders	
Common	tachycardia, atrial fibrillation
Uncommon	arrhythmia (including ventricular arrhythmia), pericardial disorders[g], myocarditis,[a,c]
Vascular disorders	
Common	hypertension
Uncommon	vasculitis
Respiratory, thoracic and mediastinal disorders	
Very common	cough, dyspnoea[a]
Common	pneumonitis[a,b], pleural effusion
Uncommon	lung infiltration
Gastrointestinal disorders	

Very common	diarrhoea, nausea, constipation, abdominal pain, vomiting
Common	colitis[a], stomatitis, dry mouth, gastritis
Uncommon	pancreatitis
Rare	duodenal ulcer
Hepatobiliary disorders	
Uncommon	hepatitis[b], cholestasis
Skin and subcutaneous tissue disorders	
Very common	rash[d], pruritus
Common	vitiligo, dry skin, erythema, alopecia, urticaria
Uncommon	erythema multiforme, psoriasis, rosacea
Rare	toxic epidermal necrolysis[a,c], Stevens-Johnson syndrome[a]
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[e], arthralgia
Common	arthritis
Uncommon	polymyalgia rheumatica
Rare	myopathy, myositis (including polymyositis)[a,c], rhabdomyolysis[a,c], Sjogren's syndrome
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)[a,b]
Rare	tubulointerstitial nephritis
General disorders and administration site conditions	
Very common	fatigue, pyrexia, oedema (including peripheral oedema)
Common	chest pain, pain
Investigations[f]	
Very common	lymphopenia, hyperglycaemia[b], anaemia[j], increased AST, hyponatraemia, hypoalbuminemia, increased alkaline phosphatase, increased creatinine, increased ALT, increased lipase, hyperkalaemia, increased amylase, hypocalcaemia, leucopoenia, hypomagnesaemia, neutropaenia[a,f], thrombocytopenia, hypokalaemia, hypoglycaemia, hypercalcaemia
Common	increased total bilirubin, hypernatraemia, hypermagnesaemia, weight decreased

Adverse reaction frequencies may not be fully attributable to nivolumab alone but may contain contributions from the underlying disease.

[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 generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, and 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, and spinal pain.

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

[g] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.

[h] Includes adrenal insufficiency, adrenocortical insufficiency acute, and secondary adrenocortical insufficiency.

[i] Includes encephalitis and limbic encephalitis

[j] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia.

Nivolumab in combination with ipilimumab

Summary of the safety profile
When nivolumab is administered in combination with ipilimumab, refer to the product insert for ipilimumab prior to initiation of treatment. For additional information on the safety profile of ipilimumab monotherapy, please refer to the ipilimumab product insert.

Melanoma
In the pooled dataset of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n=448), the most frequent adverse reactions (≥ 10%) were rash (52%), fatigue (46%), diarrhoea (43%), pruritus (36%), nausea (26%), pyrexia (19%), decreased appetite (16%), hypothyroidism (16%), colitis (15%), vomiting (14%), arthralgia (13%), abdominal pain (13%), headache (11%) and dyspnoea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Among the patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in CA209067, 154/313 (49%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 147 patients in this group who continued treatment in the single-agent phase, 47 (32%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase.

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%), diarrhoea (27%), nausea (20%), hypothyroidism (16%), musculoskeletal pain (15%), arthralgia (14%), decreased appetite (14%), pyrexia (14%), vomiting (11%), 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.

MPM
In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM (n = 300), with a minimum follow-up of 17.4 months, the most frequent adverse reactions (≥ 10%) were rash (25%), fatigue (22%), diarrhoea (21%), pruritus (16%), hypothyroidism (11%), and nausea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Tabulated summary of adverse reactions
Adverse reactions reported in the pooled dataset for patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n = 448) and for patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n = 547), and for patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1mg/kg in MPM (n=300) are presented in Table 3. 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions with nivolumab in combination with ipilimumab

	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma *	**Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC ****	**Nivolumab 3 mg/kg in combination with ipilimumab 1mg/kg in MPM*****
Infections and infestations			
Common	pneumonia, upper respiratory tract infection	pneumonia, upper respiratory tract infection, conjunctivitis	
Uncommon	bronchitis	bronchitis, aseptic meningitis	
Blood and lymphatic system disorders			
Common	eosinophilia		

Uncommon		eosinophilia	
Immune system disorders			
Common	infusion related reaction, hypersensitivity	infusion-related reaction, hypersensitivity	Infusion-related reaction, hypersensitvitiy
Uncommon	sarcoidosis		
Endocrine disorders			
Very common	hypothyroidism	hypothyroidism, hyperthyroidism	hypothyroidism
Common	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis	adrenal insufficiency[c], hypophysitis[c], thyroiditis, diabetes mellitus[c]	hyperthyroidism, adrenal insufficiency, hypophysitis, hypopituitarism
Uncommon	diabetic ketoacidosis[c], diabetes mellitus[c]	diabetic ketoacidosis[c], hypopituitarism	thyroiditis
Metabolism and nutrition disorders			
Very common	decreased appetite	decreased appetite	
Common	dehydration	dehydration	decreased appetite
Uncommon		metabolic acidosis	
Hepatobiliary disorders			
Common	hepatitis[c]	hepatitis[c]	hepatitis
Nervous system disorders			
Very common	headache		
Common	peripheral neuropathy, dizziness	headache, peripheral neuropathy, dizziness	
Uncommon	Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis[c]	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis[c]	encephalitis
Eye disorders			
Common	uveitis, blurred vision	blurred vision	
Uncommon		uveitis	
Cardiac disorders			
Common	tachycardia	tachycardia	
Uncommon	arrhythmia (including ventricular arrhythmia)[a], atrial fibrillation, myocarditis[a,c]	arrhythmia (including ventricular arrhythmia), myocarditis[c]	myocarditis
Not known	pericardial disorders[g]		
Vascular disorders			
Common	hypertension	hypertension	
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea		
Common	pneumonitis[a,c], pulmonary embolism[a], cough	pneumonitis, dyspnoea, pleural effusion, cough	pneumonitis
Uncommon	pleural effusion		
Gastrointestinal disorders			
Very common	colitis[a], diarrhoea, vomiting, nausea, abdominal pain	diarrhoea, vomiting, nausea	diarrhoea, nausea
Common	stomatitis, pancreatitis, constipation, dry mouth	colitis, stomatitis, pancreatitis, abdominal pain, constipation, dry mouth	constipation, colitis, pancreatitis

Uncommon	intestinal perforation[a], gastritis, duodenitis	gastritis	
Skin and subcutaneous tissue disorders			
Very common	Rash[d], pruritus	Rash[d], pruritus	Rash[d], pruritus
Common	vitiligo, dry skin, erythema, alopecia, urticaria	dry skin, erythema, urticaria	
Uncommon	psoriasis	Stevens-Johnson syndrome, vitiligo, erythema multiforme, alopecia, psoriasis	
Rare	Stevens-Johnson syndrome[e], toxic epidermal necrolysis[a,e]		
Musculoskeletal and connective tissue disorders			
Very common	arthralgia	musculoskeletal pain[f], arthralgia	
Common	musculoskeletal pain[f]	arthritis, muscle spasms, muscular weakness	musculoskeletal pain[f], arthritis
Uncommon	spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis)[a,e], rhabdomyolysis[a,c]	polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis	myositis
Renal and urinary disorders			
Common	renal failure (including acute kidney injury)[a,c]	renal failure (including acute kidney injury)[c]	acute kidney injury
Uncommon	tubulointerstitial nephritis	tubulointerstitial nephritis	renal failure
General disorders and administration site conditions			
Very common	fatigue, pyrexia	fatigue, pyrexia	fatigue
Common	oedema (including peripheral oedema), pain	oedema (including peripheral oedema), pain, chest pain, chills	
Uncommon	chest pain		
Investigations[b]			
Very common	increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia[c], hypoglycaemia, lymphopaenia, leucopoenia, neutropaenia, thrombocytopaenia, anaemia[h], hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia	increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia[c], hypoglycaemia, lymphopaenia, leucopoenia, neutropaenia[c], thrombocytopaenia, anaemia[h], hypercalcaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia	increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia[c], lymphopaenia, anaemia[h], hypercalcaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypomagnesaemia
Common	hypercalcaemia, hypermagnesaemia, hypernatraemia, weight decreased	hypermagnesaemia, hypernatraemia, weight decreased	increased total bilirubin, hypoglycaemia, leucopoenia, neutropaenia[c], thrombocytopaenia, hypernatraemia, hypermagnesaemia

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

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

*** nivolumab in combination with ipilimumab in MPM

[a] Fatal cases have been reported in completed or ongoing clinical studies
[b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.
[c] Life-threatening cases have been reported in completed or ongoing clinical studies.
[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 generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.
[e] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.
[f] 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.
[g] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.
[h] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia.

Nivolumab in combination with other therapeutic agents

Summary of the safety profile

When nivolumab is administered in combination, refer to the product insert for the respective combination therapy components prior to initiation of treatment.

In the pooled dataset of nivolumab 240 mg or 360 mg in combination with chemotherapy across tumour types (n=958), with a minimum follow-up of 12.1 months for gastric, GEJ or oesophageal adenocarcinoma or following 3 cycles of treatment for resectable NSCLC, the most frequent adverse reactions (≥10%) were nausea (46%), peripheral neuropathy (45%), fatigue (41%), diarrhea (34%), vomiting (28%), decreased appetite (27%), constipation (26%), abdominal pain (23%), rash (18%), musculoskeletal pain (17%), pyrexia (17%), stomatitis (15%), hypoalbuminaemia (13%), cough (12%), palmar-plantar erythrodysaesthesia syndrome (11%), and edema (including peripheral edema) (11%). 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 for gastric, GEJ or oesophageal adenocarcinoma. Ninety-three percent (93%) of patients received 3 cycles of nivolumab for resectable NSCLC.
Four fatal cases of pneumonitis were reported in patients treated with nivolumab in combination with chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma.

In the dataset of nivolumab 360 mg in combination with ipilimumab 1 mg/kg and 2 cycles of chemotherapy in NSCLC (n = 358), with a minimum follow-up of 6.5 months, the most frequent adverse reactions (>10%) were fatigue (36%), nausea (26%), rash (25%), diarrhoea (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 chemotherapy 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 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma or resectable NSCLC (n =958) and for patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC (n = 358) are 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4: Adverse reactions with nivolumab in combination with other therapeutic agents

	Nivolumab in combination with chemotherapy	Nivolumab in combination with ipilimumab and chemotherapy
Infections and infestations		
Common	upper respiratory tract infection, pneumonia	Conjunctivitis, pneumonia, respiratory tract infection
Blood and lymphatic system disorders		
Common	febrile neutropaenia	Febrile neutropenia
Uncommon	eosinophilia	Eosinophilia
Immune system disorders		
Common	hypersensitivity, infusion related reaction	Infusion-related reaction, hypersensitivity
Endocrine disorders		
Very common		Hypothyroidism
Common	hypothyroidism, hyperthyroidism	Hyperthyroidism, adrenal insufficiency, hypophysitis, thyroiditis
Uncommon	hypopituitarism, adrenal insufficiency, thyroiditis, hypophysitis, diabetes mellitus	Hypopituitarism, hypoparathyroidism
Metabolism and nutrition disorders		
Very common	decreased appetite	Decreased appetite
Common		Dehydration, hypoalbuminemia, hypophosphatemia
Nervous system disorders		
Very common	peripheral neuropathy	
Common	headache, paraesthesia, dizziness	Peripheral neuropathy, dizziness
Uncommon	Guillain-Barré syndrome	Polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis
Eye disorders		
Common	dry eye, blurred vision	Dry eye
Uncommon	uveitis	Blurred vision, episcleritis
Cardiac disorders		
Common	tachycardia	
Uncommon	atrial fibrillation, myocarditis	Tachycardia, atrial fibrillation, bradycardia
Vascular disorders		
Common	thrombosis, hypertension	
Uncommon	vasculitis	Hypertension
Respiratory, thoracic and mediastinal disorders		
Very common	cough	
Common	pneumonitis[e], dyspnoea	Pneumonitis, dyspnoea, cough
Uncommon		Pleural effusion
Gastrointestinal disorders		
Very common	diarrhoea, stomatitis, vomiting, nausea, abdominal pain, constipation	Nausea, diarrhoea, vomiting
Common	colitis, dry mouth	Constipation, stomatitis, abdominal pain, colitis, dry mouth, pancreatitis
Uncommon	pancreatitis	
Hepatobiliary disorders		
Common		Hepatitis
Uncommon	hepatitis	
Skin and subcutaneous tissue disorders		

Very common	palmar-plantar erythrodysaesthaesia syndrome, rash[a]	Rash[a], pruritus
Common	pruritus, skin hyperpigmentation, alopecia, dry skin, erythema	Alopecia, dry skin, erythema, urticaria
Uncommon		Psoriasis, Stevens-Johnson syndrome, vitiligo
Musculoskeletal and connective tissue disorders		
Very common	musculoskeletal pain[b]	
Common	arthralgia, muscular weakness	Musculoskeletal pain[b], arthralgia, arthritis
Uncommon		Muscular weakness, muscle spasms, polymyalgia rheumatica
Renal and urinary disorders		
Common	renal failure	Renal failure (including acute kidney injury)
Uncommon	nephritis	Nephritis
General disorders and administration site conditions		
Very common	fatigue, pyrexia, oedema (including peripheral oedema)	Fatigue
Common	malaise	Pyrexia, oedema (including peripheral oedema)
Uncommon		Chills, chest pain
Investigations[a]		
Very common	anaemia[c,d], thrombocytopaenia[c], leucopoenia[c], lymphopaenia[c], neutropaenia[c], increased transaminases[c], increased total bilirubin[c], increased creatinine[c], hyponatraemia[c], hyperkalaemia[c], hypokalaemia[c], hypocalcaemia[c], hypoglycaemia[c], hyperglycaemia[c], increased lipase, increased alkaline phosphatase, increased amylase	Anaemia[c,d], thrombocytopenia[c], leucopenia[c], lymphopenia[c], neutropenia[c], increased alkaline phosphatase[c], increased transaminases[c], increased creatinine[c], increased amylase[c], increased lipase[c], hypokalemia[c], hypomagnesaemia[c], hyponatraemia[c]
Common	hypernatraemia[c], hypercalcaemia[c]	Increased total bilirubin[c], increased thyroid stimulating hormone
Uncommon		Increased gamma-glutamyltransferase

[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, drug eruption, exfoliative rash, nodular rash, and rash vesicular.

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

[c] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements.

[d] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia.

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

Nivolumab in combination with cabozantinib (see section 4.2)

Summary of the safety profile

When nivolumab is administered in combination with cabozantinib, refer to the product insert for cabozantinib prior to initiation of treatment. For additional information on the safety profile of cabozantinib monotherapy, please refer to the cabozantinib product insert.

RCC

In the dataset of nivolumab 240 mg every 2 weeks in combination with cabozantinib 40 mg once daily in RCC (n =320), with a minimum follow-up of 16.0 months, the most frequent adverse reactions (≥ 10%) were diarrhoea (64.7%), fatigue (51.3%), palmar-plantar erythrodysaesthesia syndrome (40.0%), stomatitis (38.8%), musculoskeletal pain (37.5%), hypertension (37.2%), rash (36.3%), hypothyroidism (35.6%), decreased appetite (30.3%), nausea (28.8%), abdominal pain (25.0%), dysguesia (23.8%), upper respiratory tract infection (20.6%), cough (20.6%), pruritus (20.6%), arthralgia (19.4%), vomiting (18.4%), dysphonia (17.8%), headache (16.3%), dyspepsia (15.9%), dizziness (14.1%), constipation (14.1%), pyrexia (14.1%), oedema (13.4%), muscle spasm

(12.2%), dyspnoea (11.6%), proteinuria (10.9%) and hyperthyroidism (10.0%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Adverse reaction frequencies in the paragraph above and in Table 5 below are based on all-causality adverse event incidence rates.

Tabulated summary of adverse reactions
Adverse reactions reported in the dataset for patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg (n = 320) 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 5: Adverse reactions with nivolumab in combination with cabozantinib

Infections and infestations	
Very Common	upper respiratory tract infection
Common	pneumonia
Blood and lymphatic system disorders	
Common	eosinophilia
Immune system disorders	
Common	hypersensitivity (including anaphylactic reaction)
Uncommon	infusion related hypersensitivity reaction
Endocrine disorders	
Very common	hypothyroidism, hyperthyroidism
Common	adrenal insufficiency
Uncommon	hypophysitis, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration
Nervous system disorders	
Very common	dysgeusia, dizziness, headache
Common	peripheral neuropathy
Uncommon	encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Ear and labyrinth disorders	
Common	tinnitus
Eye disorders	
Common	dry eye, blurred vision
Uncommon	uveitis
Cardiac disorders	
Common	atrial fibrillation, tachycardia
Uncommon	myocarditis
Vascular disorders	
Very common	hypertension
Common	thrombosis[a]
Respiratory, thoracic and mediastinal disorders	
Very common	dysphonia, dyspnoea, cough
Common	pneumonitis, pulmonary embolism, pleural effusion, epistaxis
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia
Common	colitis, gastritis, oral pain, dry mouth, haemorrhoids
Uncommon	pancreatitis, small intestine perforation[b], glossodynia
Hepatobiliary disorders	
Common	hepatitis

Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus
Common	alopecia, dry skin, erythema, hair colour change
Uncommon	psoriasis, urticaria
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[d], arthralgia, muscle spasm
Common	arthritis
Uncommon	myopathy, osteonecrosis of the jaw, fistula
Renal and urinary disorders	
Very common	proteinuria
Common	renal failure, acute kidney injury
Uncommon	nephritis
General disorders and administration site conditions	
Very common	fatigue, pyrexia, oedema
Common	pain, chest pain
Investigations[e]	
Very common	anaemia, thrombocytopaenia, leucopoenia, lymphopaenia, neutropaenia, increased alkaline phosphatase, increased ALT, increased AST, increased total bilirubin, increased creatinine, increased amylase, increased lipase, hypokalaemia, hypomagnesaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hypoglycaemia, hypophosphataemia, hyperglycaemia, hyperkalaemia, hypermagnesaemia, hypernatraemia, weight decreased
Common	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 5 may not be fully attributable to nivolumab alone but may contain contributions from the underlying disease or from medicinal product used in combination.

[a] Thrombosis is a composite term which includes portal vein thrombosis, pulmonary vein thrombosis, pulmonary thrombosis, aortic thrombosis, arterial thrombosis, deep vein thrombosis, pelvic vein thrombosis, vena cava thrombosis, venous thrombosis, limb venous thrombosis

[b] Fatal cases have been reported

[c] Rash is a composite term which includes dermatitis, dermatitis anceiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash morbilliform, rash pruritic, and drug eruption

[d] 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

[e] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements (with the exception of weight decreased, blood cholesterol increased, and hypertriglyceridaemia). See "Description of selected adverse reactions; laboratory abnormalities" below

Description of selected adverse reactions

Nivolumab or nivolumab in combination with other therapeutic agents is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment was required in a greater proportion of patients receiving nivolumab in combination with ipilimumab or cabozantinib than in those receiving nivolumab monotherapy. Tables 6 and 7 present the percentage of patients who for immune-related adverse reactions were discontinued from treatment by dosing regimen or patients who experienced an event and required high-dose corticosteroids (at least 40 mg daily prednisone equivalents) by dosing regimen. Additionally, for patients who experienced an event, Tables 6 and 7 present the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents) by dosing regimen. The management guidelines for these adverse reactions are described in section 4.4.

Table 6: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab monotherapy or nivolumab in combination with ipilimumab)

	Nivolumab 3 mg/kg or 240mg monotherapy %	Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg %	Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg %	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM %

Immune-related adverse reaction leading to permanent discontinuation				
Pneumonitis	1.5	2.0	2.2	2.3
Colitis	1.0	16	4.0	5.0
Hepatitis	0.9	9	4.4	3.7
Nephritis and Renal Dysfunction	0.2	1.1	1.3	1.3
Endocrinopathies	0.3	2.7	2.9	0.3
Skin	0.6	0.9	1.5	0.7
Hypersensitivity/Infusion Reaction	0.1	0	0	1.7
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]				
Pneumonitis	100	63	59	70
Colitis	90	46	26	33
Hepatitis	63	46	35	42
Nephritis and Renal Dysfunction	25	17	27	40
Endocrinopathies	34	27	25	10
Skin	43	7	7	8
Hypersensitivity/Infusion Reaction	28	6	9	17

[a] at least 40 mg daily prednisone equivalents
[b] frequency is based on the number of patients who experienced the immune-related adverse reaction

Table 7: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab in combination with other therapeutic agents)

	Nivolumab 240 mg or 360 mg in combination with chemotherapy %	Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %	Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %
Immune-related adverse reaction leading to permanent discontinuation			
Pneumonitis	1.6	2.2	2.5
Colitis	2.3	4.2	2.5
Hepatitis	0.9	3.4	4.1
Nephritis and renal dysfunction	1.1	1.4	0.6
Endocrinopathies	0.3	2.0	1.3
Skin	1.4	1.1	2.2
Hypersensitivity/Infusion reaction	3.0	0.6	0
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]			
Pneumonitis	64	68	56
Colitis	7.7	20	8

Hepatitis	8.3	29	23
Nephritis and renal dysfunction	10	24	9
Endocrinopathies	5.1	8	4.2
Skin	6.7	10	8
Hypersensitivity/Infusion reaction	22	29	0

[a] at least 40 mg daily prednisone equivalents

[b] frequency is based on the number of patients who experienced the immune-related adverse reaction

Immune-related pneumonitis

In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.5% (156/4494). The majority of cases were Grade 1 or 2 in severity reported in 1.0% (43/4494) and 1.7% (76/4494) of patients, respectively. Grade 3 and 4 cases were reported in 0.8% (34/4494) and <0.1% (1/4494) of patients respectively. Grade 5 cases were reported in <0.1% (2/4494) of patients. Median time to onset was 3.3 months (range: 0.2-19.6). Resolution occurred in 104 patients (66.7%) with a median time to resolution of 6.7 weeks (range: 0.1^{+}-109.1^{+}); $^{+}$ denotes a censored observation.

In patients treated with nivolumab 1mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of pneumonitis including interstitial lung disease was 7.8% (35/448). Grade 2, Grade 3, and Grade 4 cases were reported in 4.7% (21/448), 1.1% (5/448), and 0.2% (1/448) of patients, respectively. One of the Grade 3 pneumonitis worsened over 11 days with a fatal outcome. Median time to onset was 2.6 months (range: 0.7-12.6). Resolution occurred in 33 patients (94.3%) with a median time to resolution of 6.1 weeks (range: 0.3-35.1).

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, 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 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^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of pneumonitis including interstitial lung disease was 6.7% (20/300). Grade 2 and Grade 3 cases were reported in 5.3% (16/300) and 0.7% (2/300) of patients, respectively. Median time to onset was 1.8 months (range: 0.3-20.8). Resolution occurred in 16 patients (80%) with a median time to resolution of 6.1 weeks (range: 1.1-113.1^{+}).

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC the incidence of pneumonitis including interstitial lung disease was 5.6% (18/320). Grade 2 and Grade 3 cases were reported in 1.9% (6/320) and 1.6% (5/320), of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 26.9 weeks (range: 12.3-74.3 weeks). Resolution occurred in 14 patients (77.8%) with a median time to resolution of 7.5 weeks (range: 2.1-60.7+ weeks).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of pneumonitis including interstitial lung disease was 4.4% (42/958). Grade 2, Grade 3, and Grade 4 cases were reported in 2.1% (20/958), 1.1% (11/958), and 0.3% (3/958), of patients, respectively. Median time to onset was 23.7 weeks (range: 1.6-96.9). Resolution occurred in 30 patients (71%) with a median time to resolution of 10.1 weeks (range: 0.3^{+}-121.3^{+}).

Immune-related colitis

In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, and frequent bowel movements was 14.7% (661/4494). The majority of cases were Grade 1 or 2 in severity reported in 9.5% (425/4494) and 3.8% (170/4494) of patients respectively. Grade 3 and 4 cases were reported in 1.4% (65/4494) and <0.1% (1/4494) of patients. No Grade 5 cases were reported. Median time to onset was 1.7 months (range: 0.0-26.6). Resolution occurred in 588 patients (89.9%) with a median time to resolution of 2.7 weeks (range: 0.1-124.4^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of diarrhoea or colitis was 46.7% (209/448). Grade 2, Grade 3, and Grade 4 cases were reported in 13.6% (61/448), 15.8% (71/448), and 0.4% (2/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.2 months (range: 0.0-22.6). Resolution occurred in 186 patients (89.4%) with a median time to resolution of 3.0 weeks (range: 0.1-159.4^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of diarrhoea 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 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of diarrhoea 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^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of diarrhoea or colitis was 22.0% (66/300). Grade 2 and Grade 3 cases were reported in 7.3% (22/300) and 5.3% (16/300) of patients, respectively. Median time to onset was 3.9 months (range: 0.0-21.7). Resolution occurred in 62 patients (93.9%) with a median time to resolution of 3.1 weeks (range: 0.1-100.0^{+}).

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of diarrhoea, colitis, frequent bowel movements or enteritis was 59.1% (189/320). Grade 2 and Grade 3 cases were reported in 25.6% (82/320) and 6.3% (20/320) of patients, respectively. Grade 4 were reported in 0.6% (2/320). No Grade 5 cases were reported. Median time to onset was 12.9 weeks (range: 0.3-110.9-weeks). Resolution occurred in 143 patients (76.1%) with a median time to resolution of 12.9 weeks (range: 0.1-139.7^{+} weeks).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of diarrhoea or colitis was 28.4% (272/958). Grade 2, Grade 3, and Grade 4 cases were reported in 8.5% (81/958), 4.1% (39/958), and 0.5% (5/958) of patients, respectively. No Grade 5 cases were reported in this study. Median time to onset was 4.1 weeks (range: 0.1-93.6). Resolution occurred in 237 patients (87.8%) with a median time to resolution of 1.4 weeks (range: 0.1-117.6^{+}).

Immune-related hepatitis

In patients treated with nivolumab monotherapy, the incidence of hepatic adverse reactions was 7.3% (326/4494). The majority of cases were Grade 1 or 2 in severity reported in 3.9% (175/4494) and 1.6% (73/4494) of patients, respectively. Grade 3 and Grade 4 cases were reported in 1.5% (66/4494) and 0.3% (12/4494) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.0 months (range: 0.0-27.6). Resolution occurred in 254 patients (78.9%) with a median time to resolution of 6.3 weeks (range: 0.1-126.4^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of liver function test abnormalities was 29.5% (132/448). Grade 2, Grade 3, and Grade 4 cases were reported in 6.7% (30/448), 15.4% (69/448), and 1.8% (8/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.5 months (range: 0.0-30.1). Resolution occurred in 124 patients (94%) with a median time to resolution of 5.1 weeks (range: 0.1-106.9).

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 6.1weeks (range: 0.1^{+}-82.9^{+}).

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^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of liver function test abnormalities was 12.0% (36/300). Grade 2, Grade 3, and Grade 4 cases were reported in 1.7% (5/300), 4.3% (13/300), and 1.0% (3/300) of patients, respectively. Median time to onset was 1.8 months (range: 0.5-20.3). Resolution occurred in 31 patients (86.1%) with a median time to resolution of 4.1 weeks (range: 1.0-78.3^{+}).

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of liver function test abnormalities was 41.6% (133/320). Grade 2, Grade 3, and Grade 4 cases were reported in 14.7% (47/320), 10.3% (33/320), and 0.6% (2/320) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 8.3 weeks (range: 0.1-107.9 weeks). Resolution occurred in 101 patients (75.9%) with a median time to resolution of 9.6 weeks (range: 0.1-89.3+ weeks).

In patients treated with nivolumab 240 mg or 360 mg in combination chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of liver function test abnormalities was 23% (217/958). Grade 2 and Grade 3 cases were reported in 7.4% (71/958) and 3.0% (29/782) of patients, respectively. No Grade 4 or Grade 5 cases were reported in this study. Median time to onset was 7.7 weeks (range: 0.1-61.3). Resolution occurred in 170 patients (79.4%) with a median time to resolution of 9.4 weeks (range: 0.4-150.6^{+}).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab monotherapy, the incidence of nephritis and renal dysfunction was 2.5% (113/4494). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (66/4494) and 0.6% (29/4494) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (17/4494) and <0.1% (1/4494) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported in these studies. Median time to onset was 2.6 months (range: 0.0-18.2). Resolution occurred in 74 patients (68.5%) with a median time to resolution of 8.1 weeks (range: 0.3^{+}-79.1^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of nephritis or renal dysfunction was 5.1% (23/448). Grade 2, Grade 3, and Grade 4 cases were reported in 1.6% (7/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.6 months (range: 0.5-21.8). Resolution occurred in 21 patients (91%) with a median time to resolution of 2.1 weeks (range: 0.1-125.1^{+}).

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 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^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of renal dysfunction was 5.0% (15/300). Grade 2 and Grade 3 cases were reported in 2.0% (6/300) and 1.3% (4/300) of patients, respectively. Median time to onset was 3.6 months (range: 0.5-14.4). Resolution occurred in 12 patients (80.0%) with a median time to resolution of 6.1 weeks (range: 0.9-126.4^{+}).

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of nephritis, immune mediated nephritis, renal failure, acute kidney injury, blood creatinine increased or blood urea increased was 10.0% (32/320). Grade 2 and Grade 3 cases were reported in 3.4% (11/320), and 1.3% (4/320) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 14.2 weeks (range: 2.1-87.1 weeks). Resolution occurred in 18 patients (58.1%) with a median time to resolution of 10.1 weeks (range: 0.6-90.9+ weeks).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of nephritis or renal dysfunction was 4.1% (39/958). Grade 2, Grade 3, and Grade 4 cases were reported in 1% (10/958), 0.6% (6/958), and 0.1% (1/958) of patients, respectively. No Grade 5 cases were reported in this study. Median time to onset was 9 weeks (range: 0.9-59.4). Resolution occurred in 29 patients (74.4%) with a median time to resolution of 2.9 weeks (range: 0.1-140.7^{+}).

Immune-related endocrinopathies
In patients treated with nivolumab monotherapy, the incidence of thyroid disorders including hypothyroidism and hyperthyroidism was 11.9% (533/4494). The majority of cases were Grade 1 or 2 in severity reported in 5.9% (263/4494) and 5.8% (262/4494) of patients, respectively. Grade 3 thyroid disorders were reported in 0.2% (8/4494) of patients.

The incidence of pituitary disorders, including hypophysitis and hypopituitarism was 0.6% (25/4494) (0.1% Grade 1, 0.2% Grade 2, 0.2% Grade 3, and <0.1% Grade 4).

The incidence of adrenal disorders, including adrenal insufficiency, secondary adrenocortical insufficiency, and acute adrenocorticol insufficiency, was 0.6% (26/4494) (<0.1% Grade 1, 0.4% Grade 2, and 0.2% Grade 3).

The incidence of diabetes mellitus, including Type I diabetes mellitus and diabetic ketoacidosis was 0.3% (15/4494) (<0.1% Grade 1, <0.1% Grade 2, 0.2% Grade 3, and <0.1% Grade 4). Thirteen 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 2.5 months (range: 0.0-29.1). Resolution occurred in 284 patients (49.1%) with a median time to resolution of 44.1 weeks (range: 0.4 to 204.4^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of thyroid disorders was 25.2% (113/448). Grade 2 and Grade 3 thyroid disorders were reported in 14.5% (65/448) and 1.3% (6/448) of patients, respectively. Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 5.8% (26/448) and 2.0% (9/448) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.4% (2/448) and 0.7% (3/448) of patients, respectively. Grade 2, Grade 3 and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 1.6% (7/448), 1.3% (6/448) and 0.2% (1/448) of patients, respectively. Grade 1, Grade 2, Grade 3 and Grade 4 diabetes mellitus and Grade 4 diabetic ketoacidosis were each reported in 0.2% (1/448) of patients. No Grade 5 endocrinopathies were reported. Median time to onset of these endocrinopathies was 1.9 months (range: 0.0-28.1). Resolution occurred in 64 patients (45.4%). Time to resolution ranged from 0.4 to 155.4^{+} weeks.

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 endocrinopathies were 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 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 endocrinopathies were 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.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of thyroid disorders was 14% (43/300). Grade 2 and Grade 3 thyroid disorders were reported in 9.3% (28/300) and 1.3% (4/300) of patients, respectively. Hypophysitis occurred in 2% (6/300) of patients. Grade 2 cases were reported in 1.3% (4/300) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 1.0% (3/300) and 1.0% (3/300) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (5/300) and 0.3% (1/300) of patients, respectively. No cases of immune-related diabetes mellitus were reported. Median time to onset of these endocrinopathies was 2.8 months (range: 0.5-20.8). Resolution occurred in 17 patients (32.7%). Time to resolution ranged from 0.3 to 144.1^{+} weeks.

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of thyroid disorders was 43.1% (138/320). Grade 2 and Grade 3 thyroid disorders were reported in 23.1% (74/320) and 0.9% (3/320) of patients, respectively. Hypophysitis occurred in 0.6% (2/320) of patients, all Grade 2. Adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 4.7% (15/320) of patients. Grade 2 and Grade 3 adrenal insufficiency cases were reported in 2.2% (7/320) and 1.9% (6/320) of patients, respectively. No Grade 4 or 5 endocrinopathies were reported. Median time to onset of these endocrinopathies was 12.3 weeks (range: 2.0-89.7 weeks). Resolution occurred in 50 patients (35.2%). Time to resolution ranged from 0.9 to 132.0+ weeks.

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of thyroid disorders was 11% (105/958). Grade 2 thyroid disorder was reported in 5% (48/958) patients. There were no cases of Grade 3 thyroid disorder. Grade 3 hypophysitis occurred in 0.1% (1/958) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (2/958) and 0.2% (2/958) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 0.3% (3/958) and 0.1% (1/958) of patients, respectively. Grade 2 and Grade 3 diabetes mellitus including Type 1 diabetes mellitus were reported in 0.3% (3/958) of patients. Median time to onset of these endocrinopathies was 13 weeks (range: 2.0-124.3). Resolution occurred in 53 patients (45.3%). Time to resolution ranged from 0.4 to 169.1^{+} weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab monotherapy, the incidence of rash and pruritis was 28.4% (1278/4494). The majority of cases were Grade 1 in severity reported in 21.7% (975/4494) of patients. Grade 2 and Grade 3 cases were reported in 5.5% (246/4494) and 1.3% (57/4494) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 1.4 months (range: 0.0-27.9). Resolution occurred in 817 patients (64.4%) with a median time to resolution of 18.0 weeks (range: 0.1-192.7^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of rash was 65.0% (291/448). Grade 2 and Grade 3 cases were reported in 20.3% (91/448) and 7.6% (34/448) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 0.5 months (range: 0.0-19.4). Resolution occurred in 191 patients (65.9%) with a median time to resolution of 11.4 weeks (range: 0.1-150.1^{+}).

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 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^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of rash was 36.0% (108/300). Grade 2 and Grade 3 cases were reported in 10.3% (31/300) and 3.0% (9/300) of patients, respectively. Median time to onset was 1.6 months (range: 0.0-22.3). Resolution occurred in 71 patients (66.4%) with a median time to resolution of 12.1 weeks (range: 0.4-146.4^{+}).

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of rash was 62.8% (201/320). Grade 2 and Grade 3 cases were reported in 23.1% (74/320) and 10.6% (34/320) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 6.14 weeks (range: 0.1-104.4 weeks). Resolution occurred in 137 patients (68.2%) with a median time to resolution of 18.1 weeks (range: 0.1-130.6+ weeks).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of rash was 26.4% (253/958). Grade 2 and Grade 3 cases were reported in 6.8% (65/958), and 3.1% (30/958) of patients, respectively. Median time to onset was 7 weeks (range: 0.1-97.4). Resolution occurred in 161 patients (63.6%) with a median time to resolution of 15.7 weeks (range: 0.1-153.6^{+}).

Rare cases of SJS and TEN, some of them with fatal outcome, have been observed (see sections 4.2 and 4.4).

Infusion reactions
In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions, including anaphylactic reaction, anaphylactic shock, and brochospasm, was 3.6% (163/4494), including 9 Grade 3 (0.2%) and 3 Grade 4 (<0.1%) cases. No Grade 5 cases were reported.

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of hypersensitivity/infusion reactions was 3.8% (17/448); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.2% (10/448) 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 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 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.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of hypersensitivity/infusion reactions was 12% (36/300); Grade 2 and Grade 3 cases were reported in 5.0% (15/300) and 1.3% (4/300) of patients, respectively.

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of hypersensitivity/infusion reactions was 2.5% (8/320). All 8 patients were Grade 1 or 2 in severity. Grade 2 cases were reported in 0.3% (1/320) of patients. No Grade 3-5 cases were reported.

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of hypersensitivity/infusion reactions was 12.6% (121/958). Grade 2, Grade 3, and Grade 4 cases were reported in 7.3% (70/958), 1.9% (18/958) and 0.3% (3/958) of patients, respectively.

Complication of allogeneic HSCT in classical Hodgkin Lymphoma
In 40 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 7/40 patients (17.5%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in two patients (5%). A steroid requiring febrile syndrome, without an identified infectious cause, was reported in six patients (15%) within the first 6 weeks post-transplantation, with five patients responding to steroids. Hepatic veno-occlusive disease occurred in one patient, who died of GVHD and multi-organ failure. Six of 40 patients (15%) died from complications of allogeneic HSCT after nivolumab. The 40 patients had a median follow-up from subsequent allogeneic HSCT of 2.9 months (range: 0-22 months).

Elevated liver enzymes when OPDIVO is combined with cabozantinib in RCC
In a clinical study of previously untreated patients with RCC receiving nivolumab in combination with cabozantinib, a higher incidence of Grades 3 and 4 ALT increased (10.1%) and AST increased (8.2%) were observed relative to nivolumab monotherapy in patients with advanced RCC. In patients with Grade ≥2 increased ALT or AST (n=85): median time to onset was 10.1 weeks (range: 2.0 to 106.6 weeks), 26% received corticosteroids for median duration of 1.4 weeks (range: 0.9 to 75.3 weeks), and resolution to Grades 0-1 occurred in 91% with median time to resolution of 2.3 weeks (range: 0.4 to 108.1+ weeks). Among the 45 patients with Grade ≥2 increased ALT or AST who were rechallenged with either nivolumab (n=10) or cabozantinib (n=10) administered as a single agent or with both (n=25), recurrence of Grade ≥2 increased ALT or AST was observed in 3 patients receiving nivolumab, 4 patients receiving cabozantinib, and 8 patients receiving both nivolumab and cabozantinib.

Postmarketing experience
The following events have been identified during post approval use of nivolumab or nivolumab in combination with ipilimumab. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Eye disorders: Vogt-Koyanagi-Harada syndrome

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

Blood and lymphatic system disorders: haemophagocytic lymphohistiocytosis (HLH), autoimmune haemolytic anaemia, aplastic anaemia

Cardiac disorders: pericarditis

Metabolism and nutrition disorders: tumour lysis syndrome

Laboratory abnormalities
In patients treated with nivolumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.8% for anaemia (all Grade 3), 0.8% for thrombocytopenia, 0.7% for leucopoenia, 9.5% for lymphopenia, 0.9% for neutropenia, 2.7% for increased alkaline phosphatase, 3.4% for increased AST, 2.6% for increased ALT, 1.5% for increased total bilirubin, 0.8% for increased creatinine, 2.7% for hyperglycaemia, 1.3% for hypoglycaemia, 4.2% for increased amylase, 7.4% for increased lipase, 5.6% for hyponatraemia, 1.8% for hyperkalaemia, 1.5% for hypokalaemia, 1.1% for hypercalcaemia, 0.7% for hypermagnesaemia, 0.4% for hypomagnesaemia, 0.7% for hypocalcaemia, <0.1% for hypernatraemia, and 0.9% for hypoalbuminaemia.

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.8% for anaemia (all Grade 3), 1.2% for thrombocytopenia, 0.5% for leucopoenia, 6.7% for lymphopenia, 0.7% for neutropenia, 4.3% for increased alkaline phosphatase, 12.4% for increased AST, 15.3% for increased ALT, 1.2% for increased total bilirubin, 2.4% for increased creatinine, 5.3% for hyperglycaemia, 8.7% for increased amylase, 19.5% for increased lipase, 1.2% for hypocalcaemia, 0.2% each for hypernatraemia and hypercalcaemia, 0.5% for hyperkalaemia, 0.3% for hypermagnesaemia, 4.8% for hypokalaemia, and 9.5% for hyponatraemia.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.0% for anaemia (all Grade 3), 0.7% for thrombocytopenia, 0.6% for leucopoenia, 5.1% for lymphopenia, 1.1% for neutropenia, 2.0% for increased alkaline phosphatase, 4.8% for increased AST, 6.5% for increased ALT, 1.1% for increased total bilirubin, 2.1% for increased creatinine, 7.2% for hyperglycaemia, 1.8% hypoglycaemia, 12.2% for increased amylase, 20.1% for increased lipase, 0.4% for hypocalcaemia, 1.3% for hypercalcaemia, 2.4% for hyperkalaemia, 1.1% for hypermagnesaemia 0.4% for hypomagnesaemia, 1.9% for hypokalaemia, and 9.9% for hyponatraemia.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.4% for anaemia, 1.0% each for thrombocytopaenia and leucopoenia, 8.4% for lymphopaenia, 1.3% for neutropaenia, 3.1% for increased alkaline phosphatase, 7.1% each for increased AST and increased ALT, 1.7% for increased total bilirubin, 0.3% for increased creatinine, 2.8% for hyperglycaemia, 5.4% for increased amylase, 12.8% for increased lipase, 0.7% for hypernatraemia, 8.1% for hyponatraemia, 4.1% for hyperkalaemia, 2.0% for hypokalaemia, and 0.3% for hypocalcaemia.

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.5% for anaemia (all Grade 3), 0.3% for thrombocytopaenia, 0.3% for leucopoenia, 7.5% for lymphopaenia, 3.5% for neutropaenia, 3.2% for increased alkaline phosphatase, 8.2% for increased AST, 10.1% for increased ALT, 1.3% for increased total bilirubin, 1.3% for increased creatinine, 11.9% for increased amylase, 15.6% for increased lipase, 3.5% for hyperglycaemia, 0.8% for hypoglycaemia, 2.2% for hypocalcaemia, 0.3% for hypercalcaemia, 5.4% for hyperkalaemia, 4.2% for hypermagnesaemia, 1.9% for hypomagnesaemia 3.2% for hypokalaemia, 12.3% for hyponatraemia, and 21.2% for hypophosphataemia.

In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 9.2% for anaemia, 4.3% for thrombocytopaenia, 9.8% for leucopoenia, 5.8% for lymphopaenia, 14.7% for neutropaenia, 1.2% for increased alkaline phosphatase, 3.5% for increased AST, 4.3% for increased ALT, 0% for increased total bilirubin, 1.2% for increased creatinine, 7.1% for hyperglycaemia, 0% for hypoglycaemia, 6.7% for increased amylase, 11.9% for increased lipase, 1.4% for hypocalcaemia, 1.2% for hypercalcaemia, 1.7% for hyperkalaemia, 0.3% for hypermagnesaemia, 1.2% for hypomagnesaemia 3.5% for hypokalaemia, and 10.7% for hyponatraemia.

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma, or resectable NSCLC, the proportion of patients who experienced a

worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 12% for anaemia, 6.1% for thrombocytopaenia, 10.6% leukopaenia, 10.8% for lymphopaenia, 27.9% neutropaenia, 3.7% for increased AST, 2.8% for increased ALT, 2.5% for increased bilirubin, 0.9% for increased creatinine, 0.4% for hypernatraemia, 5.5% for hyponatraemia, 1.4% for hyperkalaemia, 5.4% for hypokalaemia, 0.2% for hypercalcaemia, 1.4% for hypocalcaemia, 1.7% for hypomagnesaemia, 4.4% for hyperglycaemia, and 0.6% for hypoglycaemia.

Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response to nivolumab. Of the 3874 patients who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks and evaluable for the presence of anti-product-antibodies, 373 patients (9.6%) tested positive for treatment-emergent anti-product-antibodies with 21 patients (0.5%) testing positive for neutralising antibodies. Co-administration with chemotherapy did not affect nivolumab immunogenicity. Of the patients who were treated with nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of anti-product-antibodies, 8.8% tested positive for treatment emergent anti-product-antibodies with 0.3% tested positive for neutralising antibodies.

Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 25.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. 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%. The incidence of neutralising antibodies against nivolumab was 0.5% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 0.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks, and 2.6% with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-based chemotherapy. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged for 6.3 to 13.7% and neutralising antibodies against ipilimumab ranged from 0 to 0.4%.

Although the clearance of nivolumab was increased by 20% when anti-nivolumab-antibodies were present, there was no evidence of loss of efficacy or altered toxicity profile in the presence of nivolumab antibodies based on the pharmacokinetic and exposure-response analyses for both monotherapy and combination.

4.9 Overdose

No cases of overdose have been reported in clinical trials. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01FF01.

Mechanism of action
Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.

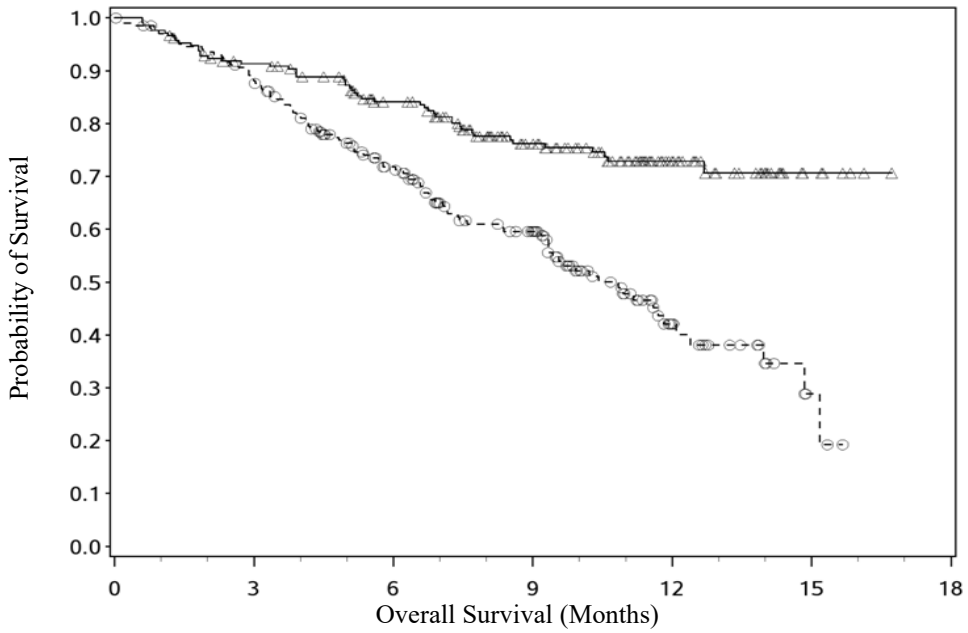
Clinical efficacy and safety

Unresectable or Metastatic Melanoma

Randomised phase 3 study vs. dacarbazine (CA209066)
The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209066). The study included adult patients (18 years or older) with confirmed, treatment-naive, Stage III or IV BRAF wild-type melanoma and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

A total of 418 patients were randomised to receive either nivolumab (n = 210) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine (n = 208) at 1000 mg/m^2 every 3 weeks. Randomisation 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. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed progression-free survival (PFS) and objective response rate (ORR).
Baseline characteristics were balanced between the two groups. The median age was 65 years (range: 18-87), 59% were men, and 99.5% were white. Most patients had ECOG performance score of 0 (64%) or 1 (34%). Sixty-one percent of patients had M1c stage disease at study entry. Seventy-four percent of patients had cutaneous melanoma, and 11% had mucosal melanoma; 35% of patients had PD-L1 positive melanoma (≥5% tumour cell membrane expression). Sixteen percent of patients had received prior adjuvant therapy; the most common adjuvant treatment was interferon (9%). Four percent of patients had a history of brain metastasis, and 37% of patients had a baseline LDH level greater than ULN at study entry. The Kaplan-Meier curves for OS are shown in Figure 1.

Figure 1: **Kaplan-Meier curves of OS (CA209066)**



Number of Subjects at Risk

Nivolumab						
210	185	150	105	45	8	0
Dacarbazine						
208	177	123	82	22	3	0

—Δ— Nivolumab (events: 50/210), median and 95% CI: N.A.
- - -O- - - Dacarbazine (events: 96/208), median and 95% CI: 10.84 (9.33, 12.09)

The observed OS benefit was consistently demonstrated across subgroups of patients including baseline ECOG performance status, M stage, history of brain metastases, and baseline LDH level. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 5% or 10%).
Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Response rates, time to response, and duration of response are shown in Table 8.

Table 8: **Efficacy Results (CA209066)**

	nivolumab (n = 210)		**dacarbazine (n = 208)**
Overall survival			
Events	50 (23.8%)		96 (46.2%)
Hazard ratio		0.42	
99.79% CI		(0.25, 0.73)	
95% CI		(0.30, 0.60)	
p-value		< 0.0001	
Median (95% CI)	Not reached		10.8 (9.33, 12.09)
Rate (95% CI)			
At 6 months	84.1 (78.3, 88.5)		71.8 (64.9, 77.6)
At 12 months	72.9 (65.5, 78.9)		42.1 (33.0, 50.9)
Progression-free survival			
Events	108 (51.4%)		163 (78.4%)
Hazard ratio		0.43	
95% CI		(0.34, 0.56)	
p-value		< 0.0001	
Median (95% CI)	5.1 (3.48, 10.81)		2.2 (2.10, 2.40)
Rate (95% CI)			
At 6 months	48.0% (40.8, 54.9)		18.5% (13.1, 24.6)
At 12 months	41.8% (34.0, 49.3)		N.A.
Objective response	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			
Months (range)	Not reached (0^+ - 12.5^+)		6.0 (1.1 - 10.0^+)
Median time to response			
Months (range)	2.1 (1.2 - 7.6)		2.1 (1.8 - 3.6)

"$^+$" denotes a censored observation.

Randomised phase 3 study vs. chemotherapy (CA209037)

The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, open-label study (CA209037). The study included adult patients who had progressed on or after ipilimumab and if BRAF V600 mutation positive had also progressed on or after BRAF kinase inhibitor therapy. Patients with active autoimmune disease, ocular melanoma or a known history of prior ipilimumab-related high-grade (Grade 4 per CTCAE v4.0) adverse reactions, except for resolved nausea, fatigue, infusion reactions, or endocrinopathies, were excluded from the study.

A total of 405 patients were randomised to receive either nivolumab (n = 272) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or chemotherapy (n = 133) which consisted of the investigator's choice of either dacarbazine (1000 mg/m^2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks). Randomisation was stratified by BRAF and PD-L1 status and best response to prior ipilimumab.

The co-primary efficacy outcome measures were confirmed ORR in the first 120 subjects treated with nivolumab, as measured by independent radiology review committee (IRRC) using RECIST version 1.1, and comparison of OS of nivolumab to chemotherapy. Additional outcome measures included duration and timing of response.

The median age was 60 years (range: 23-88). Sixty-four percent of patients were men and 98% were white. ECOG performance scores were 0 for 61% of patients and 1 for 39% of patients. The majority (75%) of patients

had M1c stage disease at study entry. Seventy-three percent of patients had cutaneous melanoma and 10% had mucosal melanoma. The number of prior systemic regimen received was 1 for 27% of patients, 2 for 51% of patients, and > 2 for 21% of patients. Twenty-two percent of patients had tumours that tested BRAF mutation positive and 50% of patients had tumours that were considered PD-L1 positive. Sixty-four percent of patients had no prior clinical benefit (CR/PR or SD) on ipilimumab. Baseline characteristics were balanced between groups except for the proportions of patients who had a history of brain metastasis (19% and 13% in the nivolumab group and chemotherapy group, respectively) and patients with LDH greater than ULN at baseline (51% and 35%, respectively).

At the time of this final ORR analysis, results from 120 nivolumab-treated patients and 47 chemotherapy-treated patients who had a minimum of 6 months of follow-up were analyzed. Efficacy results are presented in Table 9.

Table 9: **Best overall response, time and duration of response (CA209037)**

	nivolumab (n = 120)	**chemotherapy (n = 47)**
Confirmed Objective Response (IRRC)	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		
Months (range)	Not Reached	3.6 (Not available)
Median Time to Response		
Months (range)	2.1 (1.6-7.4)	3.5 (2.1-6.1)

Objective responses to nivolumab (according to the definition of the co-primary endpoint) 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 (n=26) was 23% (95% CI: 9.0, 43.6), and 34% (95% CI: 24.6, 44.5) in patients whose tumours were BRAF wild-type (n=94). Objective responses to nivolumab were observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 5% or 10%). However the role of this biomarker (PD-L1 expression) has not been fully elucidated.

The OS data were not mature at the time of the PFS analysis. There was no statistically significant difference between nivolumab and chemotherapy in the preliminary OS analysis that was not adjusted for the potentially confounding effects of subsequent therapy. It is of note that 42 (31.6%) patients in the chemotherapy arm subsequently received an anti-PD1 treatment.
Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Investigator assessed, confirmed ORRs in all treated patients were 25.7% [95% CI: 20.6, 31.4] in the nivolumab group (n=268) vs. 10.8% [95% CI: 5.5, 18.5]) in the chemotherapy group, (n=102), with an ORR difference of 15.0% (95% CI: 6.0, 22.2). Investigator assessed, confirmed ORRs in BRAF mutation-positive patients (n=79) were 19.3% [95% CI: 10.0, 31.9] vs. 13.6% [95% CI: 2.9, 34.9]), respectively, and in BRAF wild-type patients (n=291) were 27.5% [95% CI: 21.6, 34.0] vs. 10.0% [95% CI: 4.4, 18.8]), respectively.

PFS numerically favoured the nivolumab group vs the chemotherapy group in all randomised patients, BRAF mutation positive patients, and BRAF wild-type patients (HRs 0.74 [95% CI: 0.57, 0.97], 0.98 [95% CI: 0.56, 1.70], and 0.63 [95% CI: 0.47, 0.85], respectively).

Open-label phase 1 dose-escalation study (MDX1106-03)
The safety and tolerability of nivolumab were investigated in a phase 1, open-label dose-escalation study in various tumour types, including malignant melanoma and NSCLC.

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.

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.

Randomised phase 3 study of nivolumab in combination with ipilimumab or nivolumab as monotherapy vs. ipilimumab as monotherapy (CA209067)

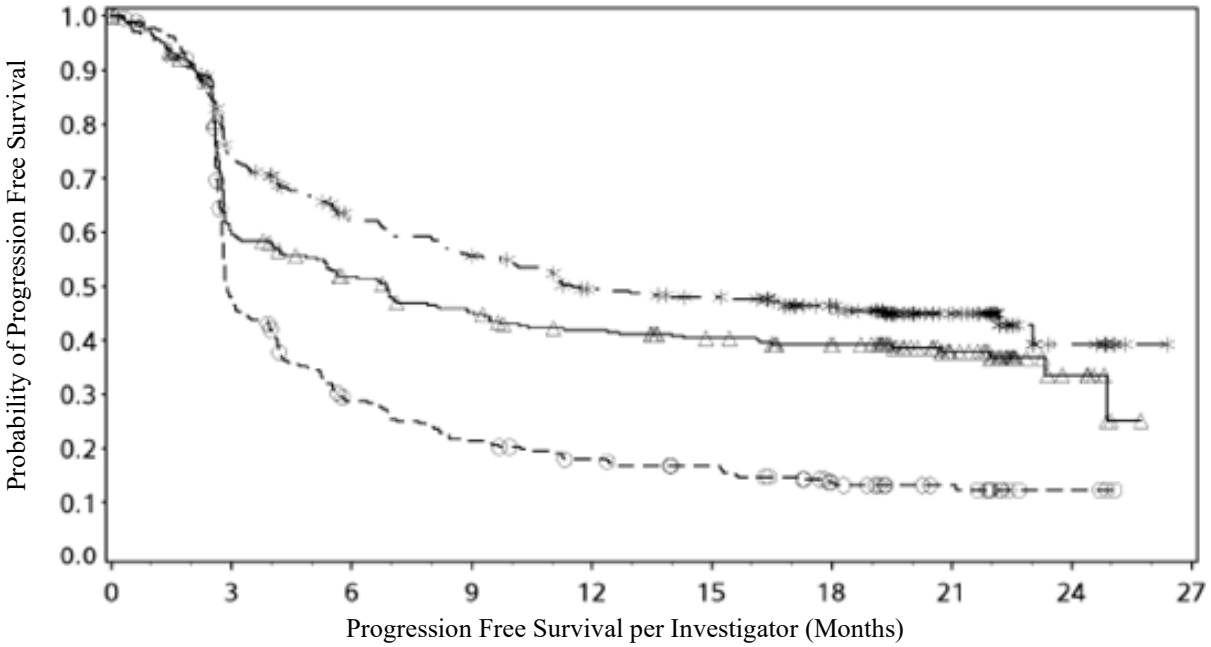
The safety and efficacy of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg or nivolumab 3 mg/kg vs. ipilimumab 3 mg/kg monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209067). The differences between the two nivolumab-containing groups were evaluated descriptively. The study included adult patients with confirmed unresectable Stage III or Stage IV melanoma. Patients were to have ECOG performance status score of 0 or 1. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled. Prior adjuvant or neoadjuvant therapy was allowed if it was completed at least 6 weeks prior to randomisation. Patients with active autoimmune disease, ocular/uveal melanoma, or active brain or leptomeningeal metastases were excluded from the study.

A total of 945 patients were randomised to receive nivolumab in combination with ipilimumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks. Patients in the nivolumab monotherapy arm received nivolumab 3 mg/kg every 2 weeks. Patients in the comparator arm received ipilimumab 3 mg/kg and nivolumab-matched placebo intravenously every 3 weeks for 4 doses followed by placebo every 2 weeks. Randomisation was stratified by PD-L1 expression (≥5% vs. <5% tumour cell membrane expression), BRAF status, and M stage per the American Joint Committee on Cancer (AJCC) staging system. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments were conducted 12 weeks after randomisation then every 6 weeks for the first year, and every 12 weeks thereafter. The co-primary outcome measures were progression-free survival and OS. ORR and the duration of response were also assessed.

Baseline characteristics were balanced across the three treatment groups. The median age was 61 years (range: 18 to 90 years), 65% of patients were men, and 97% were white. ECOG performance status score was 0 (73%) or 1 (27%). The majority of the patients had AJCC Stage IV disease (93%); 58% had M1c disease at study entry. Twenty-two percent of patients had received prior adjuvant therapy. Thirty-two percent of patients had BRAF mutation-positive melanoma; 26.5% of patients had PD-L1 ≥5% tumour cell membrane expression. Four percent of patients had a history of brain metastasis, and 36% of patients had a baseline LDH level greater than ULN at study entry. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the three treatment groups Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Minimum follow up was 18 months. Overall survival was not mature at time of this analysis. PFS results are shown in Figure 2 (all randomised population), Figure 3 (at the tumour PD-L1 5% cut-off), and Figure 4 (at the tumour PD-L1 1% cut-off). Responses are summarised in Table 10.

Figure 2: Progression-free survival (CA209067)



Number of Subjects at Risk

Nivolumab + Ipilimumab									
314	219	174	156	133	126	103	48	8	0
Nivolumab									
316	177	148	127	114	104	94	46	8	0
Ipilimumab									
315	137	78	58	46	40	25	15	3	0

- - -*- - - Nivolumab+ipilimumab (events: 161/314), median and 95% CI: 11.50 (8.90, 22.18).
PFS rate at 12 months and 95% CI: 49% (44, 55)

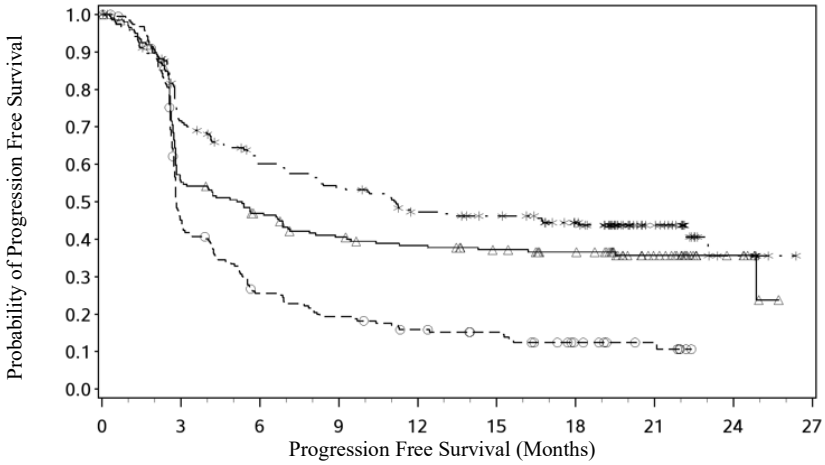
——Δ—— Nivolumab (events: 183/316), median and 95% CI: 6.87 (4.34, 9.46).
PFS rate at 12 months and 95% CI: 42% (36, 47)

- - -O- - - Ipilimumab (events: 245/315), median and 95% CI: 2.89 (2.79, 3.42).
PFS rate at 12 months and 95% CI: 18% (14, 23)

Nivolumab+ipilimumab vs ipilimumab (primary analysis) - HR (99.5% CI): 0.42 (0.32, 0.56); p-value: <0.0001
Nivolumab vs ipilimumab (primary analysis) - HR (99.5% CI): 0.55 (0.42, 0.73); p-value: <0.0001
Nivolumab+ipilimumab vs nivolumab (descriptive analysis) - HR (95% CI): 0.76 (0.62, 0.95)

Figure 3: Progression-free survival by PD-L1 expression: 5% cut-off (CA209067)

PD-L1 expression < 5%



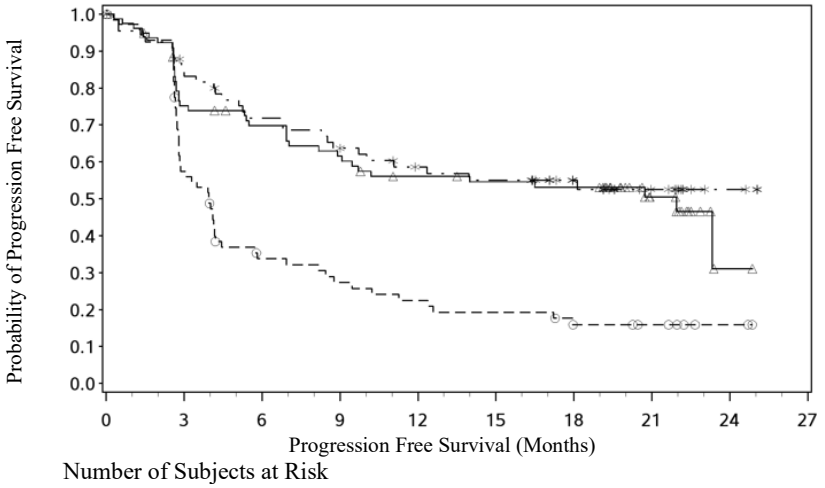
Number of Subjects at Risk

Nivolumab + Ipilimumab									
210	142	113	101	86	81	69	31	5	0
Nivolumab									
208	108	89	75	69	62	55	29	7	0
Ipilimumab									
202	82	45	34	26	22	12	7	0	0

- - -*- - - Nivolumab+Ipilimumab (events: 111/210), median and 95% CI: 11.10 (7.98, 22.18)
——Δ—— Nivolumab (events: 125/208), median and 95% CI: 5.32 (2.83, 7.06)
- - -❍- - - Ipilimumab (events: 159/202), median and 95% CI: 2.83 (2.76, 3.09)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.42 (0.33, 0.54)
Nivolumab vs. Ipilimumab - hazard ratio: 0.57 (0.45, 0.72)
Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.74 (0.58, 0.96)

PD-L1 expression ≥ 5%



Number of Subjects at Risk

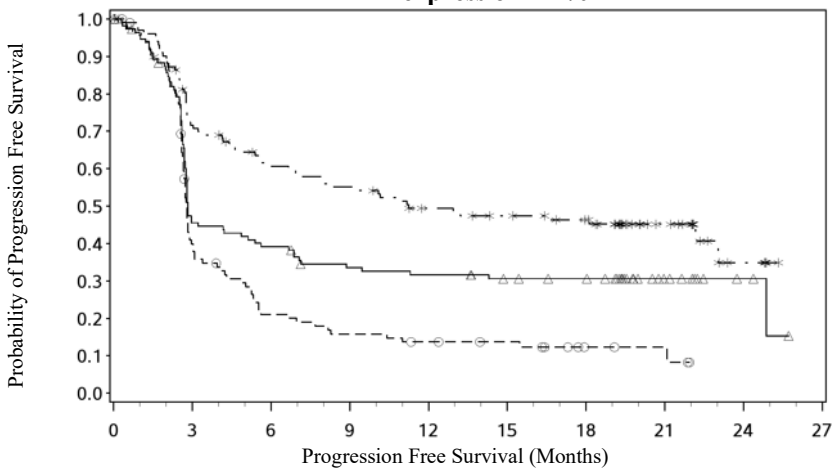
Nivolumab + Ipilimumab									
68	53	44	39	33	31	22	13	3	0
Nivolumab									
80	57	51	45	39	37	36	16	1	0
Ipilimumab									
75	40	21	17	14	12	8	6	2	0

- - -*- - - Nivolumab+Ipilimumab (events: 29/68), median and 95% CI: N.A. (9.72, N.A.)
——Δ—— Nivolumab (events: 38/80), median and 95% CI: 21.95 (8.90, N.A.)
- - -❍- - - Ipilimumab (events: 57/75), median and 95% CI: 3.94 (2.79, 4.21)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.35 (0.22, 0.55)
Nivolumab vs. Ipilimumab - hazard ratio: 0.41 (0.27, 0.62)
Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.87 (0.54, 1.41)

Figure 4: Progression-free survival by PD-L1 expression: 1% cut-off (CA209067)

PD-L1 expression < 1%



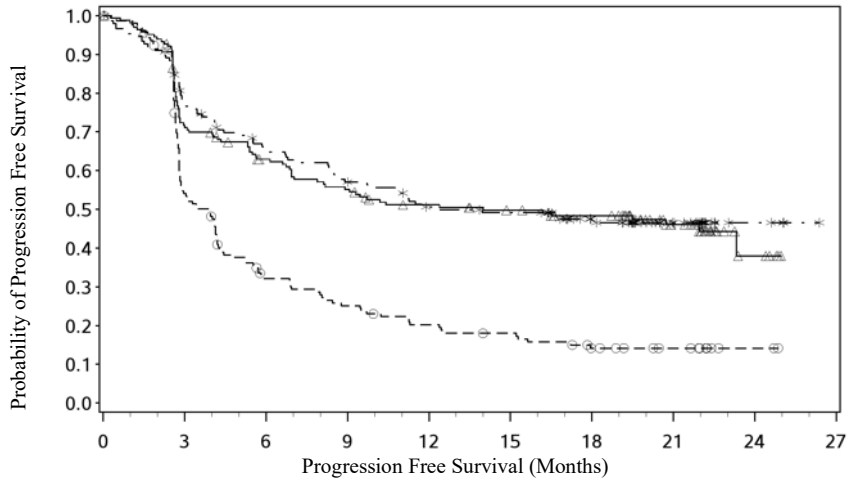
Number of Subjects at Risk

Nivolumab + Ipilimumab									
123	82	65	59	50	46	41	18	4	0
Nivolumab									
117	50	43	35	33	29	27	11	3	0
Ipilimumab									
113	39	20	15	12	10	4	3	0	0

- - -*- - - Nivolumab+Ipilimumab (events: 63/123), median and 95% CI: 11.24 (6.93, 23.03)
——Δ—— Nivolumab (events: 77/117), median and 95% CI: 2.83 (2.76, 5.13)
- - -❍- - - Ipilimumab (events: 87/113), median and 95% CI: 2.79 (2.66, 2.96)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.39 (0.28, 0.54)
Nivolumab vs. Ipilimumab - hazard ratio: 0.65 (0.48, 0.88)
Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.60 (0.43, 0.84)

PD-L1 expression ≥ 1%



Number of Subjects at Risk

Nivolumab + Ipilimumab									
155	113	92	81	69	66	50	26	4	0
Nivolumab									
171	115	97	85	75	70	64	34	5	0
Ipilimumab									
164	83	46	36	28	24	16	10	2	0

- - -*- - - Nivolumab+Ipilimumab (events: 77/155), median and 95% CI: 12.35 (8.74, N.A.)
——Δ—— Nivolumab (events: 86/171), median and 95% CI: 14.00 (7.03, N.A.)
- - -❍- - - Ipilimumab (events: 129/164), median and 95% CI: 3.91 (2.83, 4.17)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.42 (0.31, 0.55)
Nivolumab vs. Ipilimumab - hazard ratio: 0.44 (0.34, 0.58)
Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.94 (0.69, 1.28)

Table 10: Objective response (CA209067)

	nivolumab + ipilimumab (n=314)	nivolumab (n=316)	ipilimumab (n=315)
Objective response	181 (58%)	138 (44%)	60 (19%)
(95% CI)	(52.0, 63.2)	(38.1, 49.3)	(14.9, 23.8)
Odds ratio (vs. ipilimumab)	6.09	3.40	
(99.5% CI)	(3.59, 10.33)	(2.02, 5.72)	
p-value	p<0.0001	p<0.0001	
Complete response (CR)	38 (12%)	31 (10%)	7 (2%)
Partial response (PR)	143 (46%)	107 (34%)	53 (17%)
Stable disease (SD)	41 (13%)	33 (10%)	69 (22%)
Median duration of response			
Months (range)	Not reached (0^+ - 24^+)	22.3 (0^+ - 23^+)	14.4 (1.4 - 22.3^+)
ORR (95% CI) by tumour PD-L1 expression level			
<5%	55% (47.8, 61.6) n=210	41% (34.6, 48.4) n=208	18% (12.8, 23.8) n=202
≥5%	72% (59.9, 82.3) n=68	58% (45.9, 68.5) n=80	21% (12.7, 32.3) n=75
<1%	52% (42.8, 61.1) n=123	33% (24.9, 42.6) n=117	19% (11.9, 27.0) n=113
≥1%	65% (56.4, 72.0) n=155	54% (46.6, 62.0) n=171	19% (13.2, 25.7) n=164

Both nivolumab-containing arms demonstrated a significant PFS benefit and greater ORR compared with ipilimumab alone, and the observed PFS and ORR results at 12 months of follow-up were consistently demonstrated across subgroups of patients including baseline ECOG performance status, BRAF status, M stage, age, history of brain metastases, and baseline LDH level.

Among 128 patients who discontinued nivolumab in combination with ipilimumab due to adverse reaction, median PFS was 16.7 months (95% CI: 10.2, NA), and the ORR was 69% (88/128) with 15% (19/128) achieving a complete response.

Both nivolumab-containing arms demonstrated greater objective response rates than ipilimumab regardless of PD-L1 expression levels. ORRs were higher for the combination of nivolumab and ipilimumab relative to nivolumab monotherapy across tumour PD-L1 expression levels (Table 10). Median durations of response for patients with tumour PD-L1 expression level ≥5% were not reached (range: 0^+-22.3^+) in the combination arm, 20.8 months (range: 2.8-20.8) in the nivolumab monotherapy arm and not reached (range: 1.4-19.9^+) in the ipilimumab arm. At tumour PD-L1 expression <5%, median durations of response were not reached (range: 0^+-24^+) in the combination arm, 22.3 months (range: 0^+-23^+) in the nivolumab monotherapy arm and 18.2 months (range: 1.4-19.8^+) in the ipilimumab monotherapy arm.

No clear cut-off for PD-L1 expression can reliably be established when considering the relevant endpoints of tumour response and PFS. Results from post-hoc, exploratory multivariate analyses indicate that other patient and tumour characteristics (e.g. ECOG performance status, M stage, AJCC stage, gender, region and baseline LDH) might contribute to the clinical outcome.

Efficacy by BRAF status: BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had a median PFS of 15.5 months (95% CI: 8.0, NA) and 11.3 months (95% CI: 8.3, 22.2), and ORR of 66.7% (95% CI: 56.6, 75.7; n=102) and 53.3% (95% CI: 46.3, 60.2; n=212), respectively while those randomised to nivolumab monotherapy had a median PFS of 5.6 months (95% CI: 2.8, 9.3) and 7.1 months (95% CI: 4.9, 14.3) and ORR of 36.7% (95% CI: 27.2, 47.1; n=98) and 46.8% (95% CI: 40.0, 53.6; n=218), respectively.

Randomised phase 2 study of nivolumab in combination with ipilimumab and ipilimumab (CA209069)
Study CA209069 was a randomised, Phase 2, double-blind study comparing the combination of nivolumab and ipilimumab with ipilimumab alone in 142 patients with advanced (unresectable or metastatic) melanoma with similar inclusion criteria to study CA209067 and the primary analysis in patients with BRAF wild-type melanoma (77% of patients). Investigator assessed ORR was 61% (95% CI: 48.9, 72.4) in the combination arm (n=72) versus 11% (95% CI: 3.0, 25.4) for the ipilimumab arm (n=37). The estimated 12 and 18 month OS rates were 79% (95% CI: 67, 87) and 73% (95% CI: 61, 82) respectively for the combination and 62% (95% CI: 44, 75) and 56% (95% CI: 39, 70) respectively for ipilimumab.

Adjuvant treatment of melanoma

Randomised phase 3 study of nivolumab vs ipilimumab 10 mg/kg (CA209238)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with completely resected melanoma were evaluated in a Phase 3, 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.

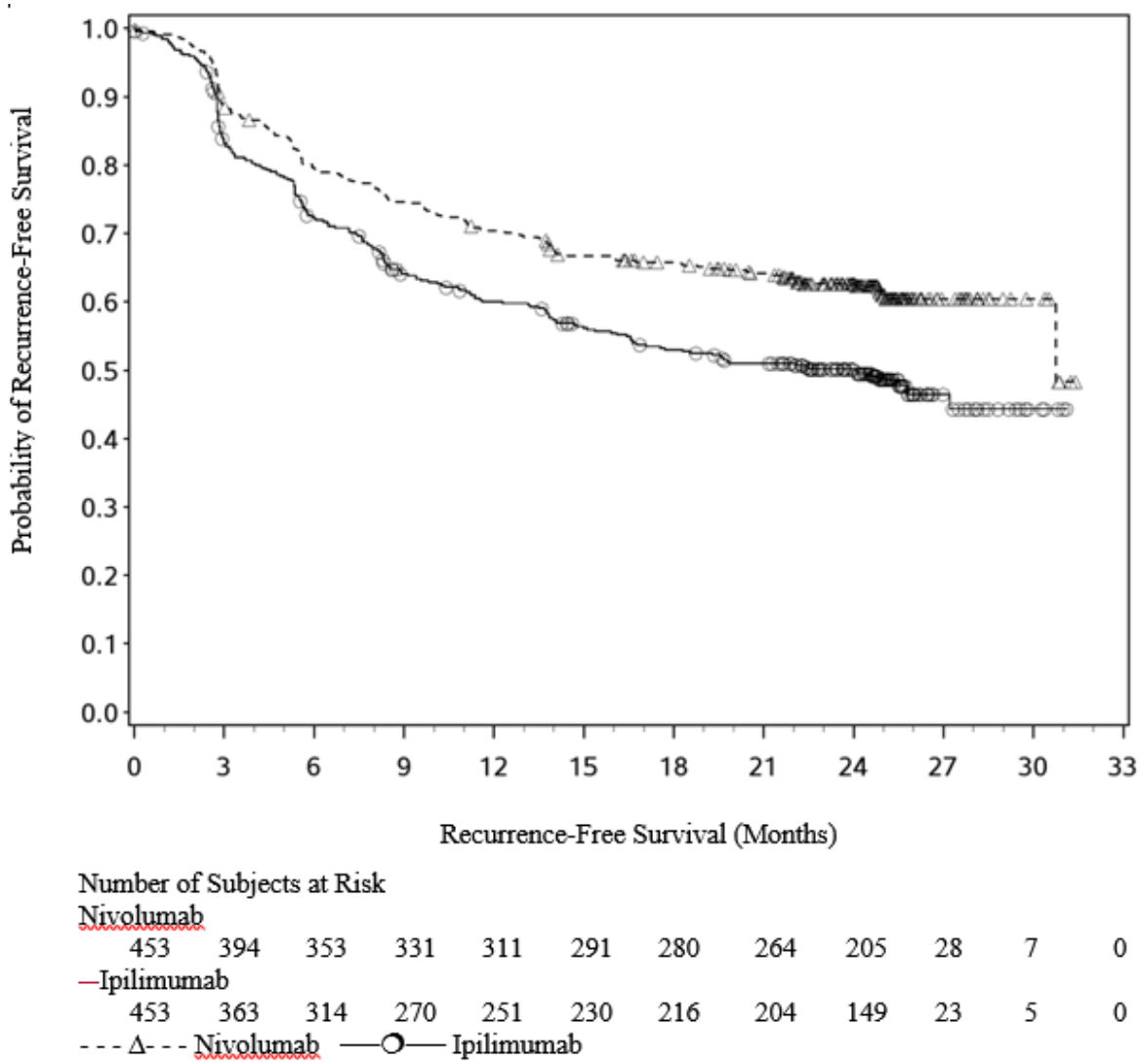
Minimum follow-up was approximately 24 months. OS was not mature at the time of this analysis. RFS results are shown in Table 11 and Figure 5 (all randomized population).

Table 11: 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 5: 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).

Non-small Cell Lung Cancer (NSCLC*)*

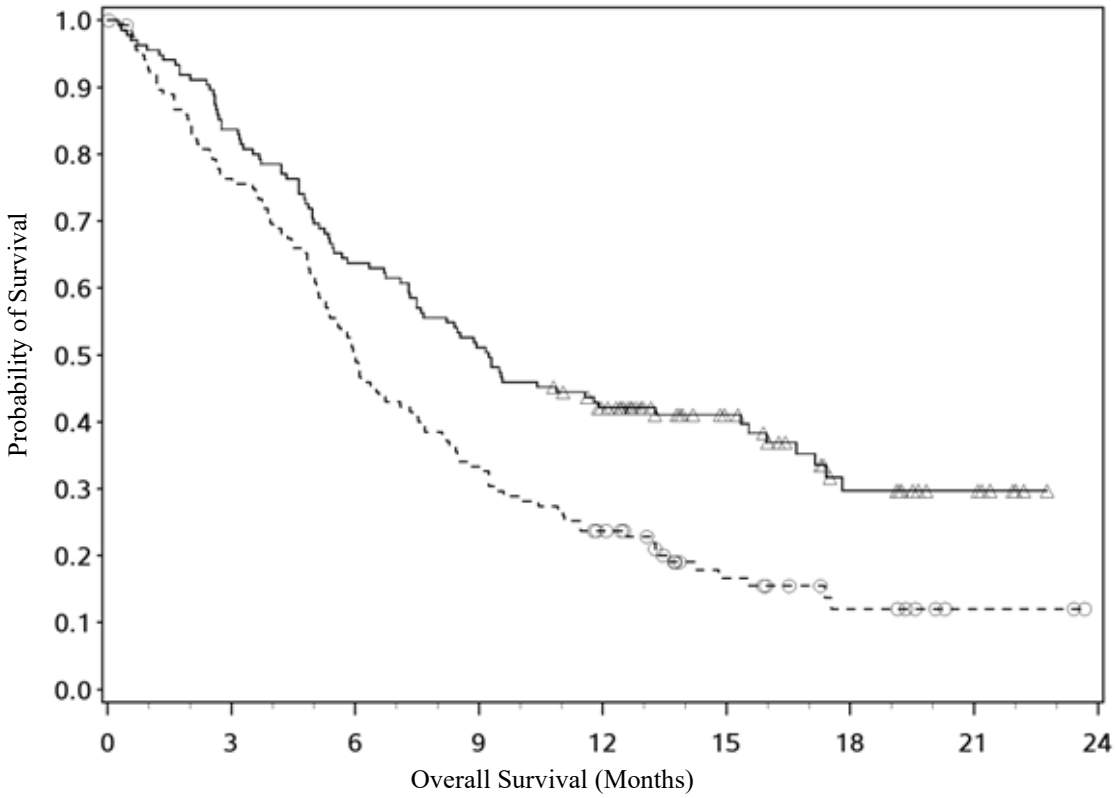
Randomised phase 3 study vs. docetaxel (CA209017)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209017). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an Eastern Cooperative Oncology Group (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 enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (N = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m^2 every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed objective response rate (ORR) and progression-free survival (PFS). In addition, symptom improvement and overall health status were assessed using the Lung Cancer Symptom Score (LCSS) average symptom burden index and the EQ-5D Visual Analogue Scale (EQ-VAS), respectively.

Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 39-85) with 44% ≥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 score was 0 (24%) or 1 (76%).

The Kaplan-Meier curves for OS are shown in Figure 6.

Figure 6: Kaplan-Meier curves of OS (CA209017)



Nivolumab 3 mg/kg

135	113	86	69	52	31	15	7	0

Docetaxel

137	103	68	45	30	14	7	2	0

Number at Risk

Nivolumab 3 mg/kg (events: 86/135), median and 95% CI: 9.23 (7.33, 13.27)

Docetaxel (events: 113/137), median and 95% CI: 6.01 (5.13, 7.33)

The observed OS benefit was consistently demonstrated across subgroups of patients. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 1%, 5% or 10%). However, the role of this biomarker (PD-L1 expression) has not been fully elucidated.

Study CA209017 included a limited number of patients ≥ 75 years (11 in the nivolumab group and 18 in the docetaxel group). Nivolumab showed numerically less effect on OS (HR 1.85; 95% CI: 0.76, 4.51), PFS (HR=1.76; 95%-CI: 0.77, 4.05) and ORR (9.1% vs 16.7%). Because of the small sample size, no definitive conclusions can be drawn from these data.

Efficacy results are shown in Table 12.

Table 12: **Efficacy results (CA209017)**

	nivolumab (n = 135)		**docetaxel (n = 137)**
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) (months)	9.23 (7.33, 13.27)		6.01 (5.13, 7.33)
Rate (95% CI) at 12 months	42.1% (33.7, 50.3)		23.7% (16.9, 31.1)
Confirmed objective response	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			
Months (range)	Not reached (2.9 - 20.5^{+})		8.4 (1.4^{+} - 15.2^{+})
Median time to response			
Months (range)	2.2 (1.6 - 11.8)		2.1 (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) (months)	3.48 (2.14, 4.86)		2.83 (2.10, 3.52)
Rate (95% CI) at 12 months	20.8% (14.0, 28.4)		6.4% (2.9, 11.8)

The rate of disease-related symptom improvement, as measured by LCSS, was similar between the nivolumab group (18.5%) and the docetaxel group (21.2%). The average EQ-VAS increased over time for both treatment groups, indicating better overall health status for patients remaining on treatment.

Single-arm phase 2 study (CA209063)

Study CA209063 was a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous-NSCLC after two or more lines of therapy; otherwise similar inclusion criteria as study CA209017 were applied. Nivolumab 3 mg/kg showed an overall response rate of 14.5% (95% CI: 8.7-22.2%), a median OS of 8.21 months (95% CI: 6.05-10.9 months), and a median PFS of 1.87 months (95% CI 1.77-3.15 months. The PFS was measured by RECIST version 1.1. The estimated 1-year survival rate was 41%.

Randomised phase 3 study vs. Docetaxel (CA209057)

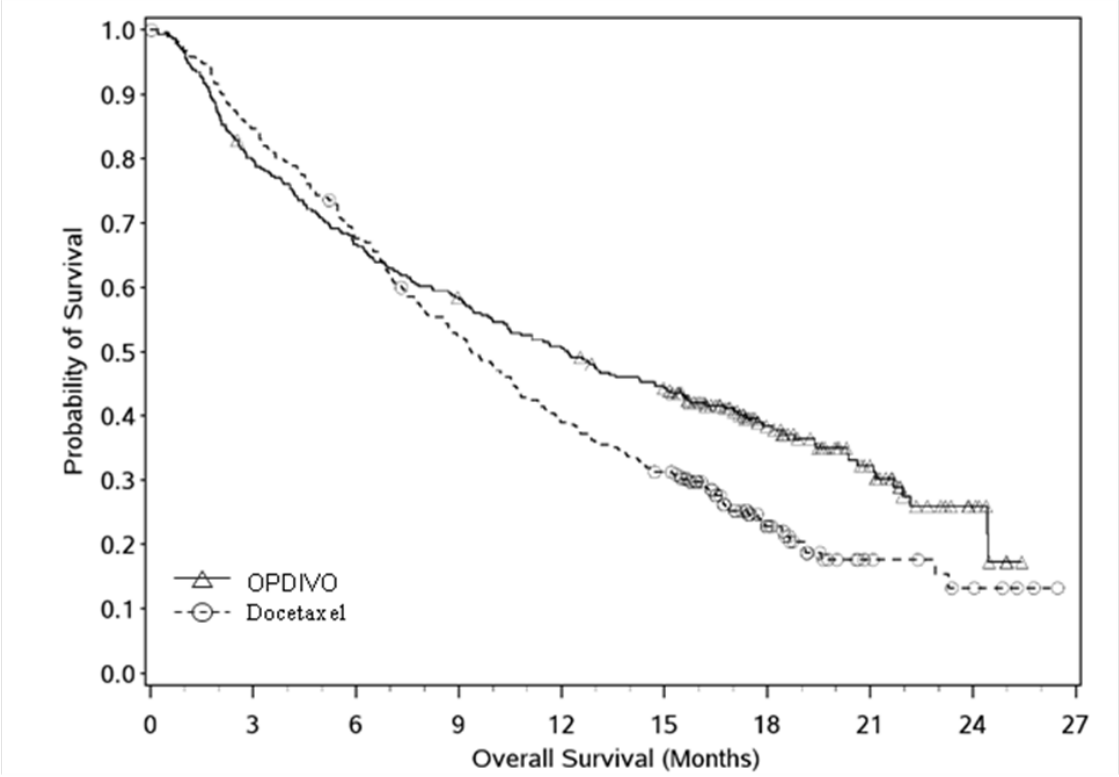
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic non-squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209057). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen which may have included maintenance therapy and who had an Eastern Cooperative Oncology Group (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 enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

A total of 582 patients were randomised to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks (n = 292) or docetaxel 75 mg/m^2 every 3 weeks (n = 290). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were

conducted 9 weeks after randomisation and continued every 6 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed objective response rate (ORR) and progression-free survival (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 Lung Cancer Symptom Scale (LCSS) average symptom burden index and the EQ-5D Visual Analogue Scale (EQ-VAS), respectively.

Baseline characteristics were generally balanced between the two groups. The median age was 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 7.

Figure 7: 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 13.

Table 13: **Efficacy Results (CA209057)**

	nivolumab (n = 292)	docetaxel (n = 290)
Prespecified interim analysis		
Overall survival		
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)	12.19 months (9.66, 14.98)	9.36 months (8.05, 10.68)
Rate (95% CI) at 12 months	50.5% (44.6, 56.1)	39.0% (33.3, 44.6)
Confirmed objective response	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		
Months (range)	17.15 (1.8, 22.6^{+})	5.55 (1.2^{+}, 15.2^{+})
Median time to response		
Months (range)	2.10 (1.2, 8.6)	2.61 (1.4, 6.3)
Progression-free survival		
Events	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)

"$^{+}$" Denotes a censored observation.

[a] Derived from a stratified proportional hazards model.

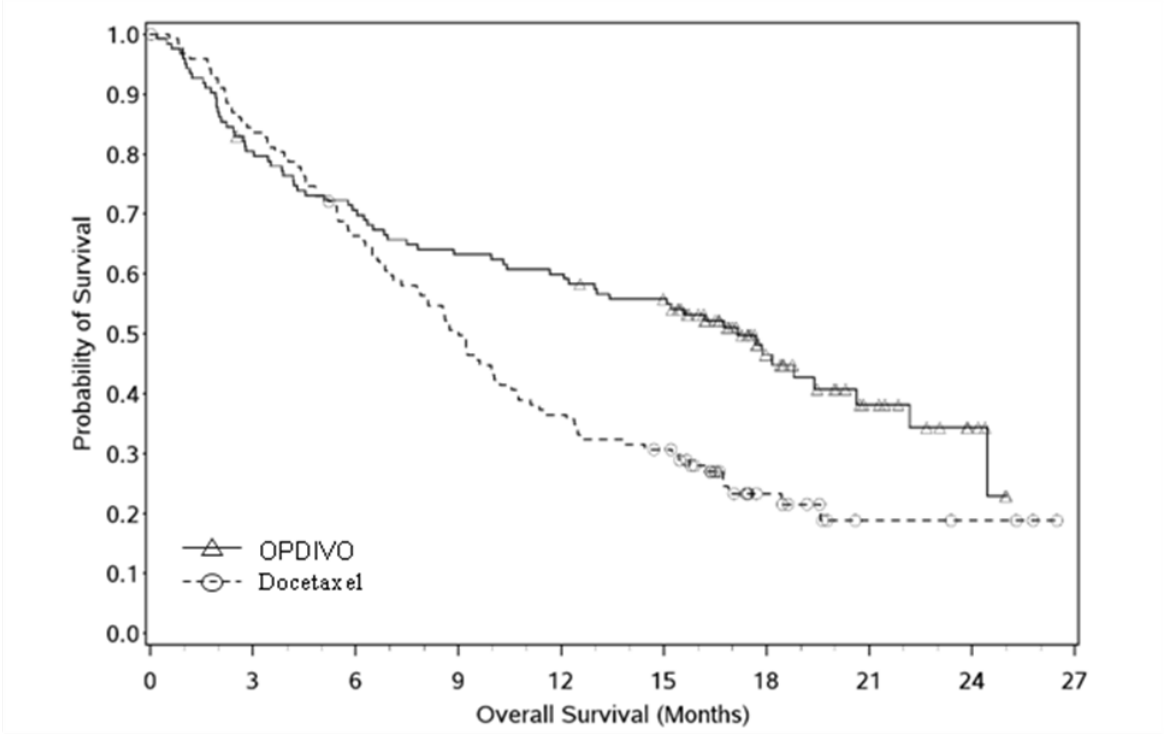
[b] P-value is derived from a log-rank test stratified by prior maintenance therapy and line of therapy; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0408.

At the time of this analysis, 29/56 (52%) of nivolumab patients and 5/36 (14%) of docetaxel patients with a confirmed response had ongoing responses (as of the last tumour assessment before censoring) with durations ranging from 1.8^{+} to 22.6^{+} months for nivolumab patients and 1.2^{+} to 15.2^{+} months for docetaxel patients.

Pre-study tumour tissue specimens were systematically collected prior to randomization in order to conduct pre-planned analyses of efficacy according to PD-L1 expression status. Quantifiable PD-L1 expression was measured in 79% of patients in the OPDIVO group and 77% of patients in the docetaxel group. 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%). PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

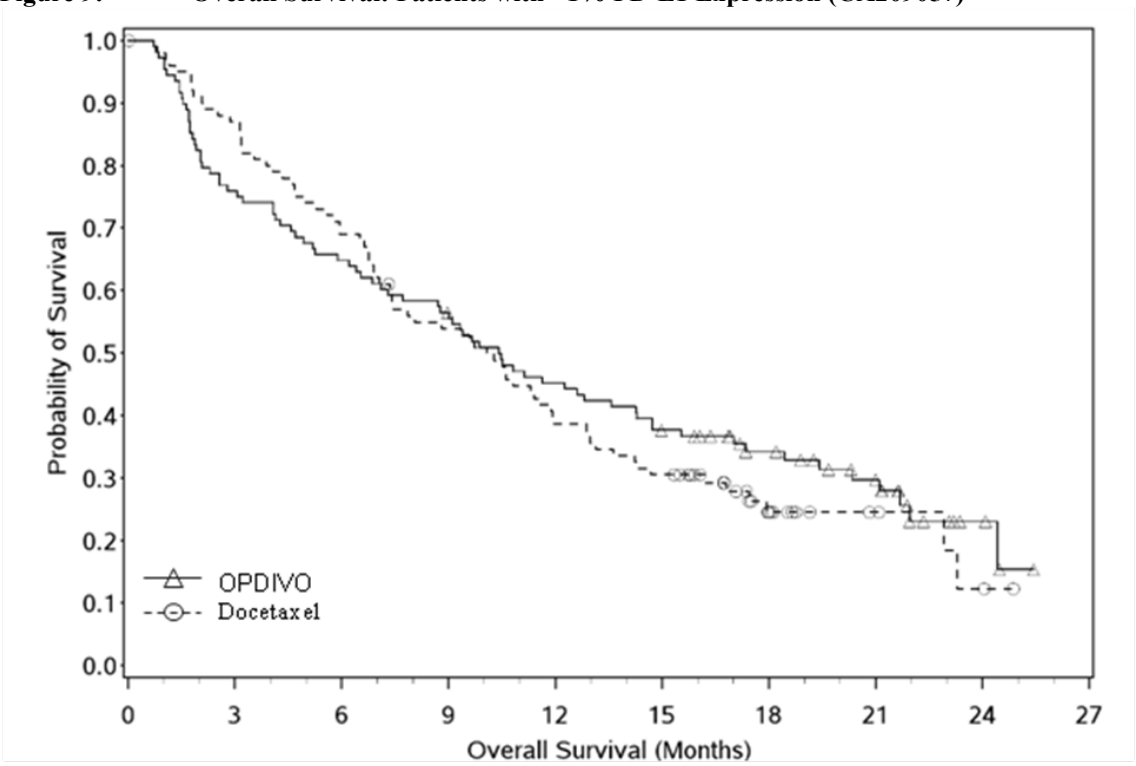
Patients with PD-L1 expression by all predefined expression levels in the OPDIVO group demonstrated greater likelihood of enhanced survival compared to docetaxel, whereas survival was similar to docetaxel in patients with no PD-L1 expression. Results are shown below in Figures 8, 9 and 10.

Figure 8: Overall Survival: Patients with ≥1% PD-L1 Expression (CA209057)



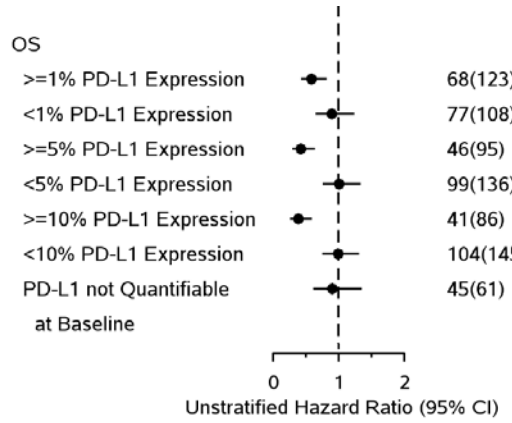
Number at Risk									
OPDIVO									
123	98	86	77	73	65	27	13	5	0
Docetaxel									
123	102	80	61	44	36	13	4	3	0

Figure 9: Overall Survival: Patients with <1% PD-L1 Expression (CA209057)



Number at Risk									
OPDIVO									
108	82	70	60	48	39	26	17	4	0
Docetaxel									
101	87	69	53	38	30	13	5	2	0

Figure 10: Forest Plot for OS based on PD-L1 Expression (CA209057)



	Number of Events (Number of Subjects) Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)	Median (95% CI) Nivolumab	Docetaxel
OS					
>=1% PD-L1 Expression	68(123)	93(123)	0.59 (0.43, 0.82)	17.15 (12.09, 20.63)	9.00 (7.10, 10.55)
<1% PD-L1 Expression	77(108)	75(101)	0.90 (0.66, 1.24)	10.41 (7.29, 14.26)	10.09 (7.36, 11.93)
>=5% PD-L1 Expression	46(95)	68(86)	0.43 (0.30, 0.63)	18.17 (15.21, NA)	8.11 (6.47, 10.05)
<5% PD-L1 Expression	99(136)	100(138)	1.01 (0.77, 1.34)	9.66 (6.87, 12.62)	10.09 (8.05, 11.93)
>=10% PD-L1 Expression	41(86)	63(79)	0.40 (0.26, 0.59)	19.38 (15.21, NA)	7.95 (6.28, 9.99)
<10% PD-L1 Expression	104(145)	105(145)	1.00 (0.76, 1.31)	9.86 (6.87, 12.81)	10.28 (8.54, 11.96)
PD-L1 not Quantifiable at Baseline	45(61)	55(66)	0.91 (0.61, 1.35)	9.20 (5.91, 12.75)	10.48 (7.20, 13.90)

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 level.

Randomised, open-labeled, phased 3 of nivolumab in combination with ipilimumab and chemotherapy vs. chemotherapy (CA2099LA)

The safety and efficacy of nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for treatment of metastatic or recurrent NSCLC were evaluated 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 enrolment, 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 OPDIVO 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 in the control arm 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/mg^2 ; or cisplatin 75 mg/mg^2 and pemetrexed 500 mg/mg^2 for non-squamous NSCLC;
- or carboplatin (AUC 6) and paclitaxel 500 mg/m^2 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 OPDIVO as a single

agent. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued.
The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

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, and a clinically meaningful benefit in PFS, ORR, and duration of response for patients randomised 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 14 and Figure 11.

Table 14: Efficacy Results - CA2099LA

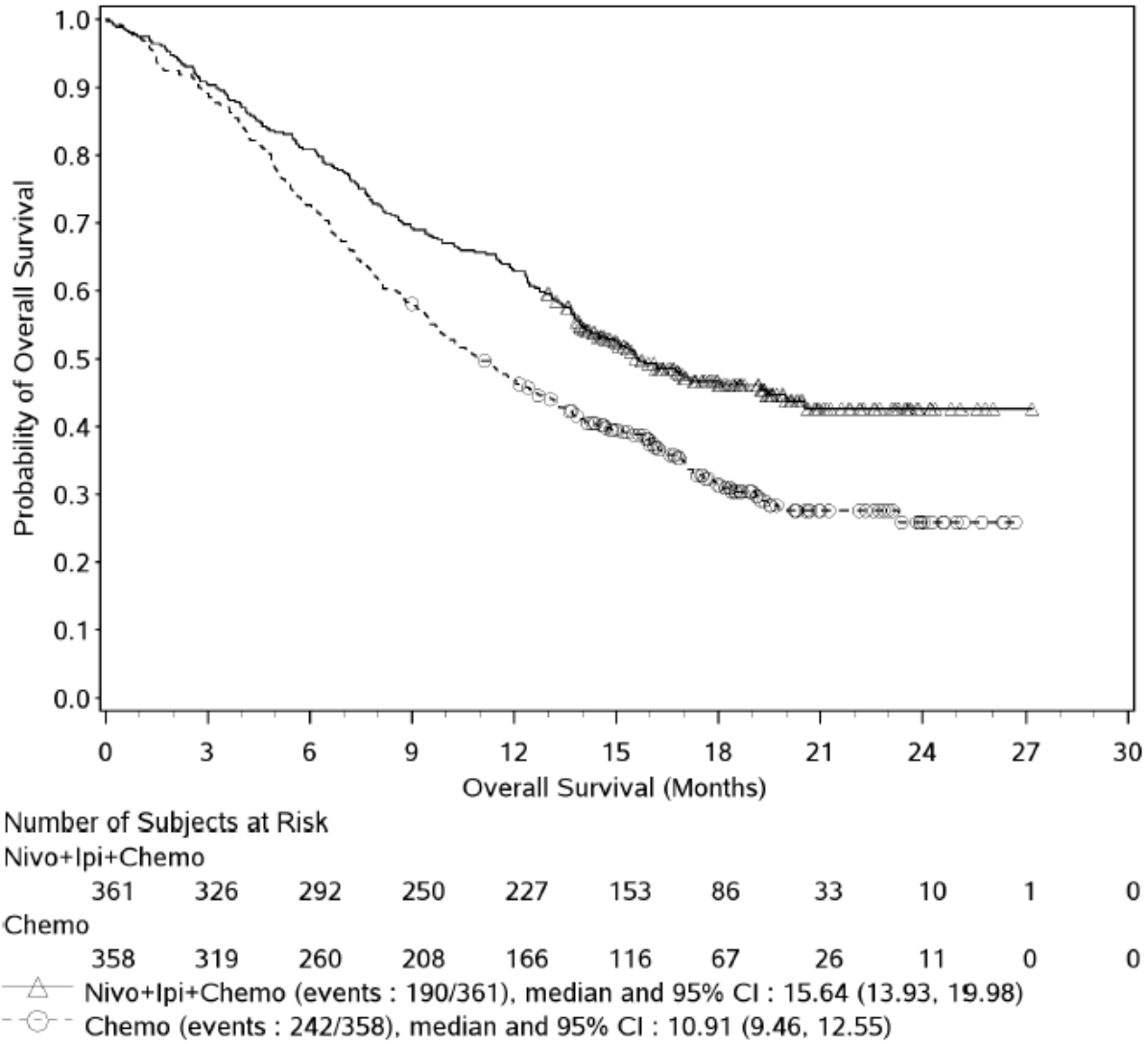
	OPDIVO and Ipilimumab and Chemotherapy (n=361)	**Chemotherapy (n=358)**
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.24, 16.16)	10.7 (9.46, 12.45)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Rate (95% CI) at 6 months	80.9 (76.4,84.6)	72.3 (67.4,76.7)
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)	6.83 (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)
Overall Response Rate per BICR (%)[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 per BICR		
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.

With an additional 4.6 months of follow-up, the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving OPDIVO and ipilimumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 11). The 12-month survival rate was 63% (95% CI: 57.7, 67.6) for patients receiving

OPDIVO and ipilimumab and platinum-doublet chemotherapy and 47% (95% CI: 41.6, 51.9) for patients receiving platinum-doublet chemotherapy.

Figure 11: Kaplan-Meier plot of OS - CA2099LA



Neoadjuvant treatment of NSCLC

Randomised, open-label, phase 3 study of nivolumab in combination with platinum-based chemotherapy vs platinum-based chemotherapy (CA209816)

The safety and efficacy of nivolumab 360 mg every 3 weeks in combination with platinum-based chemotherapy for 3 cycles were evaluated in a phase 3, randomised, open-label study (CA209816). The study included patients with ECOG performance status 0 or 1, measurable disease (per RECIST version 1.1), and whose tumours were resectable, histologically confirmed Stage IB (≥ 4 cm), II, or IIIA NSCLC (per the 7th edition AJCC/Union for International Cancer Control (UICC) staging criteria). Patients were enrolled regardless of their tumour PD-L1 status. Patients with unresectable or metastatic NSCLC, known EGFR mutations or ALK translocations, Grade 2 or greater peripheral neuropathy, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Randomisation was stratified by tumour PD-L1 expression level (≥ 1% vs < 1% or non-quantifiable), disease stage (IB/II vs IIIA), and gender (male vs female).

A total of 358 patients were randomised to receive either nivolumab in combination with platinum-based chemotherapy (n = 179) or platinum-based chemotherapy (n = 179). Patients in the nivolumab in combination with platinum-based chemotherapy arm received nivolumab 360 mg administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for up to 3 cycles. Patients in the chemotherapy arm received platinum-based chemotherapy administered every 3 weeks for up to 3 cycles.

Platinum-based chemotherapy consisted of investigator's choice of:

- paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology);

- pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (non-squamous histology); or
- gemcitabine 1000 mg/m^2 or 1250 mg/m^2 and cisplatin 75 mg/m^2 (squamous histology).

In the chemotherapy arm, two additional treatment regimen options included vinorelbine 25 mg/m^2 or 30 mg/m^2 and cisplatin 75 mg/m^2; or docetaxel 60 mg/m^2 or 75 mg/m^2 and cisplatin 75 mg/m^2 (any histology).

Tumour assessments were performed at baseline, within 14 days of surgery, every 12 weeks after surgery for 2 years, then every 6 months for 3 years, and every year for 5 years until disease recurrence or progression. The primary efficacy outcome measures were event free survival (EFS) based on BICR assessment and pathological complete response rate (pCR) by blinded-independent pathology review (BIPR). OS was a key secondary efficacy outcome measure and exploratory endpoints included feasibility of surgery. Baseline characteristics were generally balanced across treatment groups. The median age was 65 years (range: 34-84) with 51% of patients ≥ 65 years and 7% of patients ≥ 75 year. 50% of patients were Asian, 47% were white and 71 % were male. Baseline ECOG performance status was 0 (67%) or 1 (33%); 50% of patients with PD-L1 ≥ 1% and 43% with PD-L1 < 1%, 5% had Stage IB, 17% had Stage IIA, 13% had Stage IIB, and 64% had Stage IIIA disease; 51% had squamous and had 49% non-squamous histology; and 89% were former/current smokers. Numerically more patients in the nivolumab in combination with chemotherapy arm (83%) had definitive surgery compared to patients in the chemotherapy arm (75%).

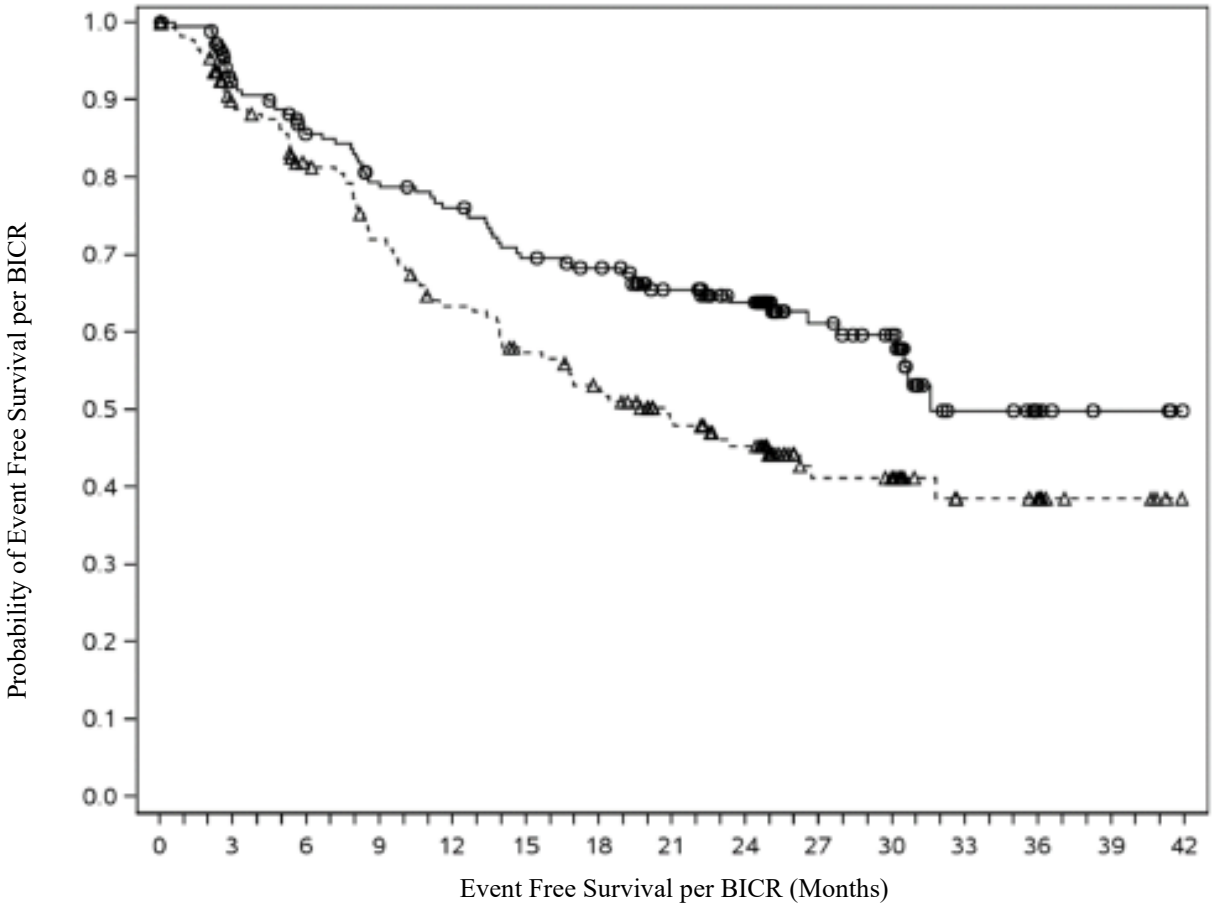
At the final pCR analysis and pre-specified interim EFS analysis (minimum follow-up 21 months), statistically significant improvement was demonstrated in pCR and EFS for patients randomised to nivolumab in combination with chemotherapy as compared to chemotherapy alone. Efficacy results are presented in Table 15 and Figure 12.

Table 15: Efficacy results - CA209816 (global population)

	nivolumab + chemotherapy (n = 179)		**chemotherapy (n = 179)**
Event-free Survival (EFS) per BICR			
Events	64 (35.8)		87 (48.6)
Hazard ratio[a] (97.38% CI)		0.63 (0.43, 0.91)	
Stratified log-rank p-value[b]		0.0052	
Median (months)[c] (95% CI)	31.6 (30.2, NR)		20.8 (14.0, 26.7)
Rate (95% CI) at 12 months	76.1 (68.8, 81.9)		63.4 (55.3, 70.4)
Rate (95% CI) at 24 months	63.8 (55.7, 70.9)		45.3 (37.0, 53.2)
Pathologic Complete Response (pCR) per BIPR			
Responses (%)	43 (24.0)		4 (2.2)
95% CI[d]	18.0, 31.0		0.6, 5.6
Difference of pCR (99% CI)[e]		21.6 (13.0, 30.3)	
Odds ratio of pCR (99% CI)[f]		13.9 (3.49, 55.75)	
Stratified p-value[g]		<0.0001	

[a] Based on a stratified Cox proportional hazard model.
[b] Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0262.
[c] Kaplan-Meier estimate.
[d] Based on Clopper and Pearson method.
[e] Strata-adjusted difference based on Cochran-Mantel-Haenszel method of weighting.
[f] Strata-adjusted using Mantel-Haenszel method.
[g] From stratified CMH test.
Minimum follow-up for EFS was 21 months, data cut-off 08 Sept 2021
pCR data cut-off: 28-Jul-2020

Figure 12: Kaplan-Meier curves of EFS (CA209816)



Number of Subjects at Risk

Nivolumab + chemotherapy														
179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy														
179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

Nivolumab + chemotherapy (events: 64/179), median and 95% CI:31.6 (30.2, NR)

Chemotherapy (events: 87/179), median and 95% CI: 20.8 (14.0, 26.7)

Based on data cut-off: 8-Sept-2021, minimum follow-up of 21 months

In a descriptive, exploratory subgroup analysis relative to chemotherapy, EFS benefit was shown in patients treated with nivolumab in combination with chemotherapy with PD-L1 <1% (HR [95% CI] 0.85 [0.54, 1.32], n = 155) and PD-L1 ≥1% (HR [95% CI] 0.41 [0.24, 0.70], n = 178), in patients with Stage IB/II disease (HR [95% CI] 0.87 [0.48, 1.56], n = 127) and Stage IIIA disease (HR [95% CI] 0.54 [0.37, 0.80], n = 228), and in patients with squamous histology (HR [95% CI] 0.77 [0.49, 1.22], n = 182) and non-squamous histology (HR [95% CI] 0.50 [0.32, 0.79], n = 176).

At the time of the EFS analysis, a prespecified, interim analysis for OS was performed. The HR for OS was 0.57 (99.67% CI: 0.30, 1.07) for nivolumab in combination with chemotherapy vs. chemotherapy.

Within the CA209816 study, 27% (97/358) of the primary analysis population for efficacy were Chinese by race and enrolled from mainland China, Hong Kong or Taiwan sites. Consistent with observations in the global population, neoadjuvant treatment with nivolumab in combination with chemotherapy demonstrated a clinically meaningful benefit in EFS and pCR compared with chemotherapy.

Table 16: Efficacy Results - CA209816 study subpopulation consisting of subjects who were Chinese by race and enrolled from mainland China, Hong Kong or Taiwan Sites[a]

	Nivo+chemo (Arm C) N = 44	Chemo (Arm B) N = 53
EFS per BICR (1°Definition; Primary Endpoint)		
Events, n (%)	13 (29.5)	31 (58.5)
Median EFS (95% CI), mo[b]	Not reached (30.16, NA)	13.86 (8.34, 20.80)
HR[c] (95% CI)	0.37 (0.19, 0.72)	
EFS Rates (95% CI), %[b]		
At 12 months	76.9 (60.2, 87.3)	51.0 (35.8, 64.2)
At 24 months	68.7 (51.4, 80.9)	33.2 (20.2, 46.9)
pCR[d,e] per BIPR (Primary Endpoint)		
N responders (%)	11 (25.0)	1 (1.9)
95% CI[f]	(13.2, 40.3)	(0.0, 10.1)
Difference, %[g,h], (95% CI)	20.9 (7.7, 34.1)	
Estimate of odds ratio[h,i], (95% CI)	11.05 (1.41, 86.49)	

[a] The endpoint analyses for this subpopulation are descriptive with no statistical power.
[b] Based on Kaplan-Meier Estimates
[c] Hazard ratio of Arm C to concurrent Arm B from a Cox Model unstratified
[d] Subjects without samples for evaluation count as non-responders.
[e] Based on database lock date of 16-Sep-2020.
[f] Confidence interval based on the Clopper and Pearson method.
[g] Strata adjusted difference (Arm C - Concurrent Arm B) based on Cochran-Mantel-Haenszel (CMH) method of weighting.
[h] Stratified by PD-L1 (≥ 1% vs < 1%/unevaluable/indeterminate), disease stage (IB/II vs IIIA), sex (male vs female) as entered into the IRT.
[i] Strata adjusted odds ratio (Arm C over Concurrent Arm B) using CMH method

Malignant pleural mesothelioma

Randomised phase 3 study of nivolumab in combination with ipilimumab vs. chemotherapy (CA209743)
The safety and efficacy of nivolumab 3 mg/mg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks were evaluated in a phase 3, randomised, open-label study (CA209743). The study included patients (18 years or older) with histologically confirmed and previously untreated malignant pleural mesothelioma of epithelioid or non-epithelioid histology, ECOG performance status 0 or 1, and no palliative radiotherapy within 14 days of first study therapy. Patients were enrolled regardless of their tumour PD-L1 status.

Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the trial. Randomisation was stratified by histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and gender (male vs. female).

A total of 605 patients were randomised to receive either nivolumab in combination with ipilimumab (n = 303) or chemotherapy (n = 302). Patients in the nivolumab in combination with ipilimumab arm received nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks in combination with ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years. Patients in the chemotherapy arm received chemotherapy for up to 6 cycles (each cycle was 21 days). Chemotherapy consisted of cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 or carboplatin 5 AUC and pemetrexed 500 mg/m^2.

Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab monotherapy. Tumour assessments were performed every 6 weeks after first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued.

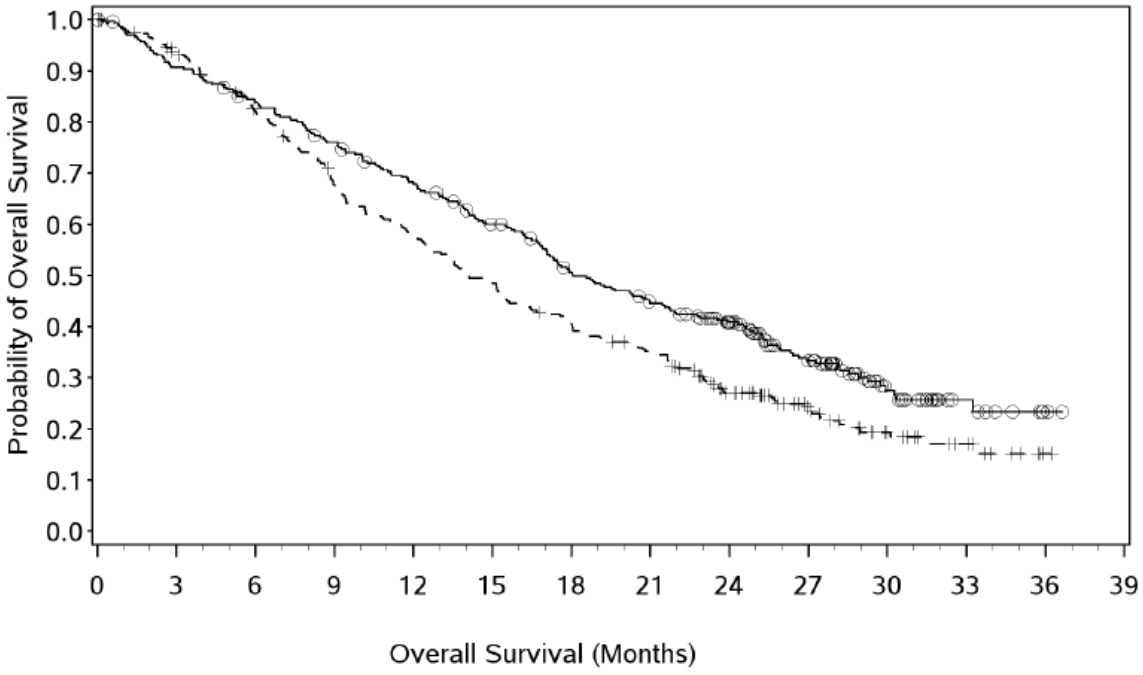
CA209743 baseline characteristics were generally balanced across all treatment groups. The median age was 69 years (range: 25-89) with 72% ≥ 65 years of age and 26% ≥ 75 years of years. The majority of patients were white (85%) and male (77%). Baseline ECOG performance status was 0 (40%) or 1 (60%), 80% of patients with PD-L1 ≥ 1% and 20% with PD-L1 < 1%, 75% had epithelioid and 25% had non-epithelioid histology.

CA209743 primary efficacy outcome measure was OS. Additional efficacy endpoints were PFS, ORR, duration of response, and disease control rate (DCR) as assessed by Blinded Independent Central Review (BICR) utilising modified RECIST criteria.

The study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab in combination with ipilimumab as compared to chemotherapy at the prespecified interim analysis when at least 403 events were observed (85% of the planned number of events for final analysis). Minimum follow-up for OS was 22 months.

Efficacy results are shown in Figure 13 and Table 17.

Figure 13: Kaplan-Meier Plot of OS - CA209743



Number of Subjects at Risk

Nivo + Ipi	303	273	251	226	200	173	143	124	101	65	30	11	2	0
Chemo	302	268	233	190	162	136	113	95	62	38	20	11	1	0

--○-- Nivolumab + ipilimumab (events: 200/303), median and 95% CI: 18.07 (16.82, 21.45)
--+-- Chemotherapy (events: 219/302), median and 95% CI: 14.09 (12.45, 16.23)

Table 17: Efficacy results - CA209743

	Nivolumab and Ipilimumab (n=303)	**Chemotherapy (n=302)**
Overall Survival		
Events (%)	200 (66%)	219 (73%)
Median (months) [a] (95% CI)	18.1 (16.8, 21.5)	14.1 12.5, 16.2)
Hazard ratio (96.6% CI) [b]	0.74 (0.60, 0.91)	
Stratified log-rank p-value [c]	0.002	
Rate (95% CI) at 24 months [a]	41% (35.1, 46.5)	27% (21.9, 32.4)

	Nivolumab and Ipilimumab (n=303)	Chemotherapy (n=302)
Progression-free Survival		
Events (%)	218 (72%)	209 (69%)
Hazard ratio (95% CI) [b]	1.0 (0.82, 1.21)	
Median (months) [a] (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)
Overall Response Rate (%)	40%	43%
(95% CI)	(34.1, 45.4)	(37.1, 48.5)
Complete response (%)	1.7%	0
Partial response (%)	38%	43%
Duration of Response		
Median (months) [a] (95% CI)	11.0 (8.1, 16.5)	6.7 (5.3, 7.1)
% with duration ≥6 months	69%	53%
% with duration >24 months	32%	8%
Disease Control Rate (95% CI)	77% (71.4, 81.2)	85% (80.6, 88.9)

[a] Kaplan-Meier estimate.
[b] Stratified Cox proportional hazard model.
[c] p-value is compared with the allocated alpha of 0.0345 for this interim analysis.

Subsequent systemic therapy was received by 44.2% and 40.7% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA4) was received by 3.3% and 20.2% of patients in the combination and chemotherapy arms, respectively.

In study CA209743, prespecified subgroup analyses relative to chemotherapy, OS benefit was shown in patients treated with nivolumab in combination with ipilimumab with epithelioid histology (HR (95% CI) 0.85 (0.68, 1.06), n = 236) and in patients with non-epithelioid histology (HR (95% CI) 0.46 (0.31, 0.70), n = 67). OS benefit was also shown in patients with tumour PD-L1 expression < 1% (HR (95% CI) 0.94 (0.62, 1.40), n = 57) and tumour PD-L1 expression ≥ 1% (HR (95% CI) 0.69 (0.55, 0.87), n = 232).

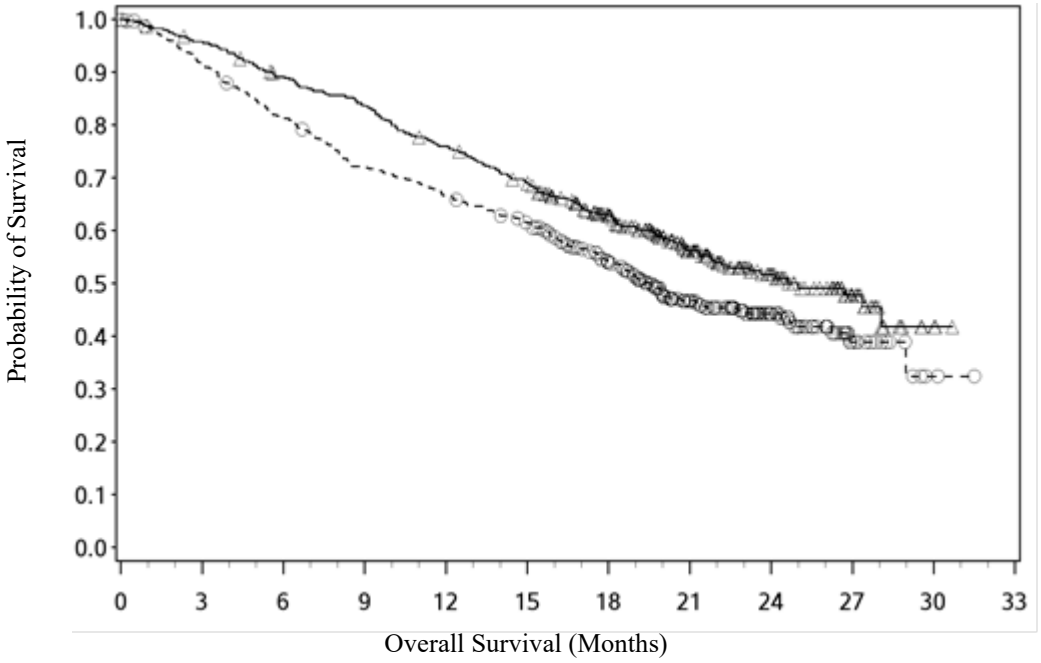
Renal Cell Carcinoma (RCC)

Randomised, open-labeled, phased 3 study of nivolumab as monotherapy vs. everolimus (CA209025)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced RCC was evaluated in a Phase 3, randomized, opened-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.
A total of 821 patients were randomized to receive either nivolumab 3 mg/kg (n=410) administered intravenously over 60 minutes every 2 weeks or everolimus (n=411) 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was OS. Secondary efficacy assessments included investigator-assessed ORR and PFS.

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40% ≥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) in nivolumab-treated patients and was 3.7 months (range: 6 days-25.7+ months) in everolimus-treated patients.
Nivolumab was continued beyond progression in 44% of patients.

The Kaplan-Meier curves for OS are shown in Figure 14.

Figure 14: Kaplan-Meier curves of OS (CA209025)



Number of Subjects at Risk

Nivolumab											
410	389	359	337	305	275	213	139	73	29	3	0
Everolimus											
411	366	324	287	265	241	187	115	61	20	2	0

Nivolumab 3 mg/kg (events: 183/410), median and 95% CI: 25.00 (21.75, N.A.)

Everolimus 10 mg (events: 215/411), median and 95% CI: 19.55 (17.64, 23.06)

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 18 and Figure 14). OS benefit was observed regardless of tumour PD-L1 expression level.

Efficacy results are shown in Table 18.

Table 18: Efficacy results (CA209025)

	nivolumab (n = 410)		everolimus (n = 411)
Overall survival			
Events	183 (45%)		215 (52%)
Hazard ratio		0.73	
98.52% CI		(0.57, 0.93)	
p-value		0.0018	
Median (95% CI)	25.0 (21.7, NE)		19.6 (17.6, 23.1)
Rate (95% CI)			
At 6 months	89.2 (85.7, 91.8)		81.2 (77.0, 84.7)
At 12 months	76.0 (71.5, 79.9)		66.7 (61.8, 71.0))
Objective response	103 (25.1%)		22 (5.4%)
(95% CI)	(21.0, 29.6)		(3.4, 8.0)
Odds ratio (95% CI)		5.98 (3.68, 9.72)	
p-value		< 0.0001	
Complete response (CR)	4 (1.0%)		2 (0.5%)
Partial response (PR)	99 (24.1%)		20 (4.9%)
Stable disease (SD)	141 (34.4%)		227 (55.2%)
Median duration of response			
Months (range)	11.99 (0.0-27.6^{+})		11.99 (0.0^{+}-22.2^{+})
Median time to response			
Months (range)	3.5 (1.4-24.8)		3.7 (1,5-11,2)
Progression-free survival			
Events	318 (77.6%)		322 (78.3%)
Hazard ratio		0.88	
95% CI		(0.75, 1.03)	
p-value		0.1135	
Median (95% CI)	4.6 (3.71, 5.39)		4.4 (3.71, 5.52)

"$^{+}$" denotes a censored observation.

The median time to onset of objective response was 3.5 months (range: 1.4-24.8 months) after the start of nivolumab treatment. Fourty-nine (47.6%) responders had ongoing responses with a duration ranging from 0.0-27.6^{+} months.

Overall survival could be accompanied by an improvement over time in disease related symptoms and non-disease specific quality of life (QoL) as assessed using valid and reliable scales in the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) and the EuroQoL EQ-5D. Apparently meaningful symptom improvement (MID=2 point change in FKSI-DRS score; $p < 0.001$) and time to improvement (HR= 1.66 (1.33,2.08), $p < 0.001$) were significantly better for patients on the nivolumab arm. While both arms of the study received active therapy, the QoL data should be interpreted in the context of the open-label study design and therefore cautiously taken.

Randomised, open-labeled, phased 3 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 RCC was evaluated in a Phase 3, randomised, open-label study (CA209214). The study included patients (18 years or older) with previously untreated, advanced (not amenable to curative surgery or radiation) or metastatic renal cell carcinoma with a clear-cell component. The primary efficacy population includes 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 tumour PD-L1 status. Patients with Karnofsky performance status <70% and patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic

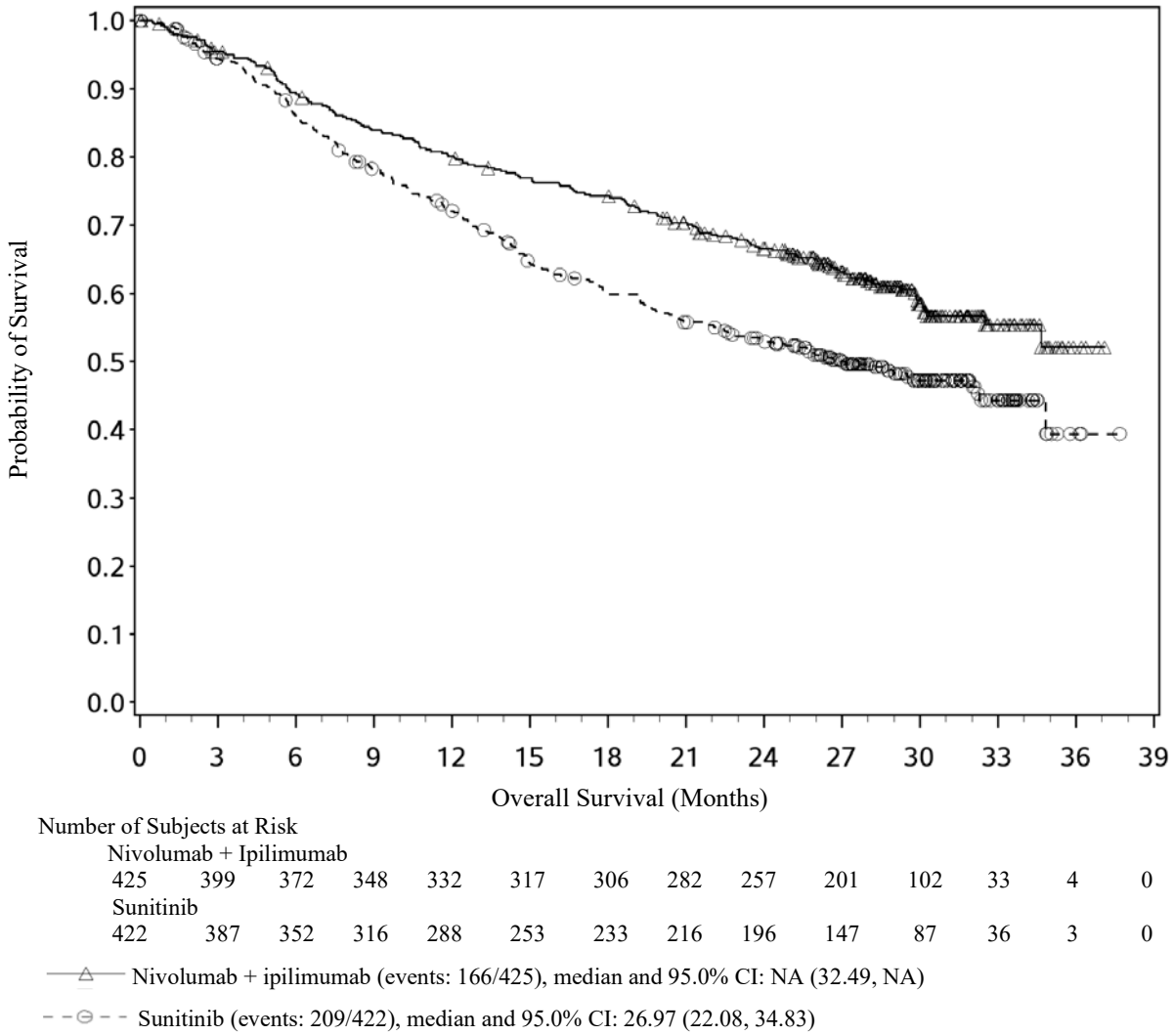
immunosuppression were excluded from the study. Patients were stratified by (IMDC) prognostic score and region.

A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either nivolumab 3 mg/kg (n = 425) administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes (with ipilimumab given at least 30 minutes after completion of nivolumab) every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks or sunitinib (n = 422) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off, every cycle. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 12 weeks after randomisation and continued every 6 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measures were OS, ORR and PFS as determined by a 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 randomisation was 0.4 years in both the nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg and sunitinib groups. The median duration of treatment was 7.9 months (range: 1 day- 21.4^{+} months) in nivolumab with ipilimumab- treated patients and was 7.8 months (range: 1 days- 20.2^{+} months) in sunitinib-treated patients. Nivolumab with ipilimumab was continued beyond progression in 29% of patients

The Kaplan-Meier curves for OS (with a minimum follow-up of 24 months) in intermediate/poor risk patients is shown in Figure 15.

Figure 15: Kaplan-Meier curves of OS in intermediate/poor risk (CA209214)



The trial demonstrated superior OS and ORR and an improvement in PFS for patients randomised to nivolumab plus ipilimumab as compared with sunitinib. (Table 19 and Figure 15).

In intermediate/poor-risk patients, OS benefit was observed in the nivolumab in combination with ipilimumab arm vs. sunitinib regardless of tumour PD-L1 expression. Median OS for tumour PD-L1 expression ≥ 1% was not reached for nivolumab in combination with ipilimumab, and was 19.61 months in the sunitinib arm (HR = 0.52; 95% CI: 0.34, 0.78). For tumour PD-L1 expression < 1%, the median OS was 34.7 months for the nivolumab in combination with ipilimumab, and was 32.2 months in the sunitinib arm (HR = 0.70; 95% CI: 0.54, 0.92).

Median OS for all randomized intermediate-risk subjects in both the nivolumab in combination with ipilimumab arm and the sunitinib arm were not reached (HR = 0.678; 95% CI: 0.518, 0.886). Median OS for all randomized poor-risk subjects was 21.45 months in the nivolumab in combination with ipilimumab arm, and was 9.72 months in the sunitinib arm (HR = 0.531; 95% CI: 0.361, 0.782).

There are no data on the use of nivolumab in combination with ipilimumab in patients with only a non clear-cell histology in first line RCC.

Patients ≥ 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. Efficacy results are shown in Table 19.

Table 19: **Efficacy results in intermediate/poor risk patients (CA209214)**

	nivolumab + ipilimumab (n = 425)		**sunitinib (n = 422)**
Overall survival			
Events	140 (33%)		188 (45%)
Hazard ratio[a]		0.63	
99.8% CI		(0.44, 0.89)	
p-value[b, c]		< 0.0001	
Median (95% CI)	NE (28.2, NE)		25.9 (22.1, NE)
Rate (95% CI)			
At 6 months	89.5 (86.1, 92.1)		86.2 (82.4, 89.1)
At 12 months	80.1 (75.9, 83.6)		72.1 (67.4, 76.2)
Progression-free survival			
Events	228 (53.6%)		228 (54.0%)
Hazard ratio[a]		0.82	
99.1% CI		(0.64, 1.05)	
p-value[b,h]		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)[d]		16.0 (9.8, 22.2)	
p-value[e,f]		< 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[g]			
Months (range)	NE (1.4^{+}-25.5^{+})		18.17 (1.3^{+}-23.6^{+})
Median time to response			
Months (range)	2.8 (0.9-11.3)		3.0 (0.6-15.0)

[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] Strata adjusted difference.
[e] Based on the stratified DerSimonian-Laird test.
[f] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[g] Computed using Kaplan-Meier method.
[h] p-value is compared to alpha 0.009 in order to achieve statistical significance.
"+" denotes a censored observation.
NE = non-estimable

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.

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.

Randomised phase 3 study of nivolumab in combination with cabozantinib vs. sunitinib (CA2099ER)

The safety and efficacy of nivolumab 240 mg in combination with cabozantinib 40 mg for the first-line treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA2099ER). The study included patients (18 years or older) with advanced or metastatic RCC with a clear cell component, Karnofsky Performance Status (KPS) ≥ 70%, and measurable disease as per RECIST v1.1 regardless of their PD-L1 status

or IMDC risk group. The study excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression, patients who had prior treatment with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, poorly controlled hypertension despite antihypertensive therapy, active brain metastases and uncontrolled adrenal insufficiency. Patients were stratified by IMDC prognostic score, PD-L1 tumour expression, and region.

A total of 651 patients were randomised to receive either nivolumab 240 mg (n = 323) administered intravenously every 2 weeks in combination with cabozantinib 40 mg once daily orally or sunitinib (n = 328) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off. Treatment continued until disease progression or unacceptable toxicity with nivolumab administration for up to 24 months. Treatment beyond initial investigator-assessed RECIST version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. First tumour assessment post-baseline was performed at 12 weeks (± 7 days) following randomisation. Subsequent tumour assessments occurred at every 6 weeks (± 7 days) until Week 60, then every 12 weeks (± 14 days) until radiographic progression, confirmed by the BICR. The primary efficacy outcome measure was PFS as determined by a BICR. Additional efficacy measures included OS and ORR as key secondary endpoints.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 28-90) with 38.4% ≥ 65 years of age and 9.5% ≥ 75 years of age. The majority of patients were male (73.9%) and white (81.9%). Eight percent of patients were Asian, 23.2% and 76.5% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. Patient distribution by IMDC risk categories was 22.6% favourable, 57.6% intermediate, and 19.7% poor. For tumour PD-L1 expression, 72.5% of patients had PD-L1 expression < 1% or indeterminate and 24.9% of patients had PD-L1 expression ≥ 1%. 11.5% of patients had tumours with sarcomatoid features. The median duration of treatment was 14.26 months (range: 0.2-27.3 months) in nivolumab with cabozantinib-treated patients and was 9.23 months (range: 0.8-27.6 months) in sunitinib-treated patients.

The study demonstrated a statistically significant benefit in PFS, OS, and ORR for patients randomised to nivolumab in combination with cabozantinib as compared to sunitinib. Efficacy results from the primary analysis (minimum follow-up 10.6 months; median follow-up 18.1 months) are shown in Table 20.

Table 20: **Efficacy results (CA2099ER)**

	nivolumab + cabozantinib (n = 323)		**sunitinib (n = 328)**
Progression-free survival			
Events	144 (44.6%)		191 (58.2%)
Hazard ratio[a]		0.51	
95% CI		(0.41, 0.64)	
p-value[b, c]		< 0.0001	
Median (95% CI)[d]	16.59 (12.45, 24.94)		8.31 (6.97, 9.69)
Overall survival			
Events	67 (20.7%)		99 (30.2%)
Hazard ratio[a]		0.60	
98.89% CI		(0.40, 0.89)	
p-value[b,c,e]		0.0010	
Median (95% CI)	N.E.		N.E. (22.6, N.E.)
Rate (95% CI)			
At 6 months	93.1 (89.7, 95.4)		86.2 (81.9, 89.5)
Confirmed objective response (BICR)	180 (55.7%)		89 (27.1%)
(95% CI)[f]	(50.1, 61.2)		(22.4, 32.3)
Difference in ORR (95% CI) [g]		28.6 (21.7, 35.6)	
p-value[h]		< 0.0001	
Complete response (CR)	26 (8.0%)		15 (4.6%)
Partial response (PR)	154 (47.7%)		74 (22.6%)
Stable disease (SD)	104 (32.2%)		138 (42.1%)
Median duration of response[d]			
Months (range)	20.17 (17.31, N.E.)		11.47 (8.31, 18.43)
Median time to response			
Months (range)	2.83 (1.0-19.4)		4.17 (1.7-12.3)

[a] Stratified Cox proportional hazards model. Hazard ratio is nivolumab and cabozantinib over sunitinib.

[b] Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥1% versus <1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.

[c] 2-sided p-values from stratified regular log-rank test.

[d] Based on Kaplan-Meier estimates.

[e] Boundary for statistical significance p-value <0.0111.

[f] CI based on the Clopper and Pearson method.

[g] Strata adjusted difference in objective response rate (nivolumab + cabozantinib - sunitinib) based on DerSimonian and Laird.

[h] 2-sided p-value from CMH test.

NE = non-estimable

The primary analysis of PFS included censoring for new anti-cancer treatment (Table 20). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

PFS benefit was observed in the nivolumab in combination with cabozantinib arm vs. suntinib regardless of the IMDC risk category. Median PFS for the favourable risk group was not reached for nivolumab in combination with cabozantinib, and was 12.81 months in the sunitinib arm (HR = 0.60; 95% CI: 0.37, 0.98). Median PFS for the intermediate risk group was 17.71 months for nivolumab in combination with cabozantinib and was 8.38 months in the sunitinib arm (HR = 0.54; 95% CI: 0.41, 0.73). Median PFS for the poor risk group was 12.29 months for nivolumab in combination with cabozantinib and was 4.21 months in the sunitinib arm (HR = 0.36; 95% CI: 0.23, 0.58).

PFS benefit was observed in the nivolumab in combination with cabozantinib arm vs. sunitinib regardless of tumour PD-L1 expression. Median PFS for tumour PD-L1 expression ≥ 1% was 13.08 months for nivolumab in combination with cabozantinib, and was 4.67 months in the sunitinib arm (HR = 0.45; 95% CI: 0.29, 0.68). For

tumour PD-L1 expression < 1%, the median PFS was 19.84 months for nivolumab in combination with cabozantinib, and 9.26 months in the sunitinib arm (HR = 0.50; 95% CI: 0.38, 0.65).

An updated PFS and OS analysis were performed when all patients had a minimum follow-up of 16.0 months and a median follow-up of 23.5 months (see Figures 16 and 17). The PFS hazard ratio was 0.52 (95% CI: 0.43, 0.64). The OS hazard ratio was 0.66 (95% CI: 0.50, 0.87). Updated efficacy data (PFS and OS) in subgroups for the IMDC risk categories and PD-L1 expression levels confirmed the original results. With the updated analysis, median PFS is reached for the favourable risk group.

Figure 16: Kaplan-Meier curves of PFS (CA2099ER)

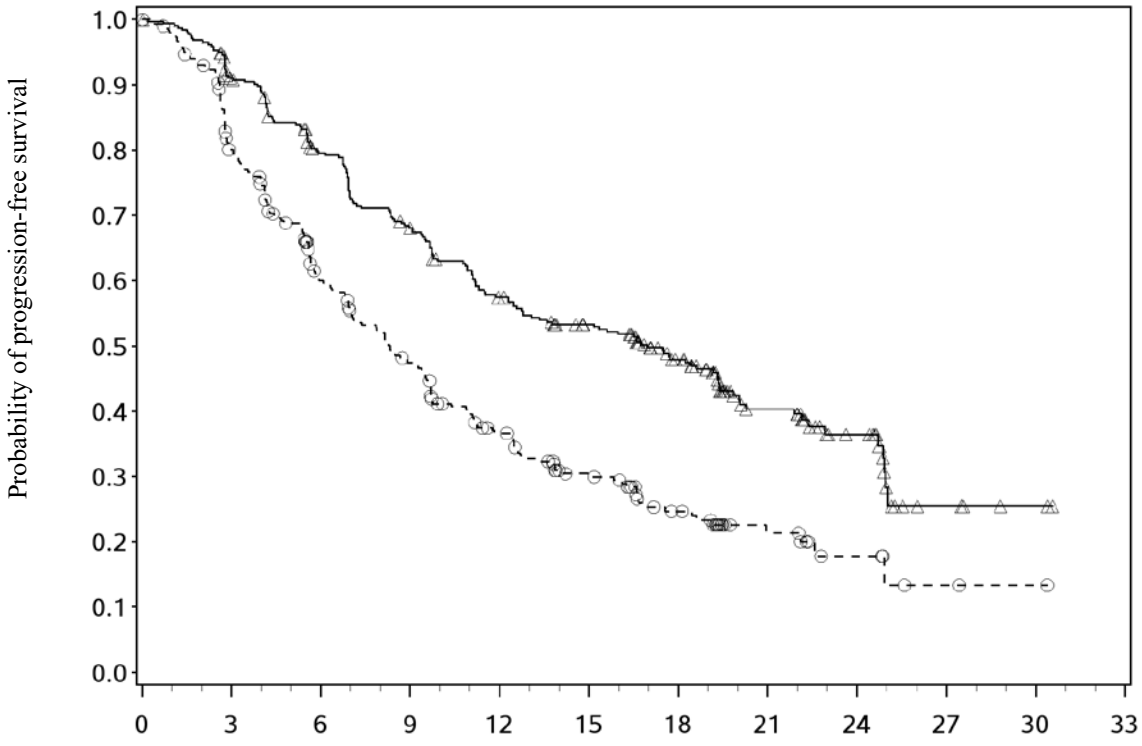
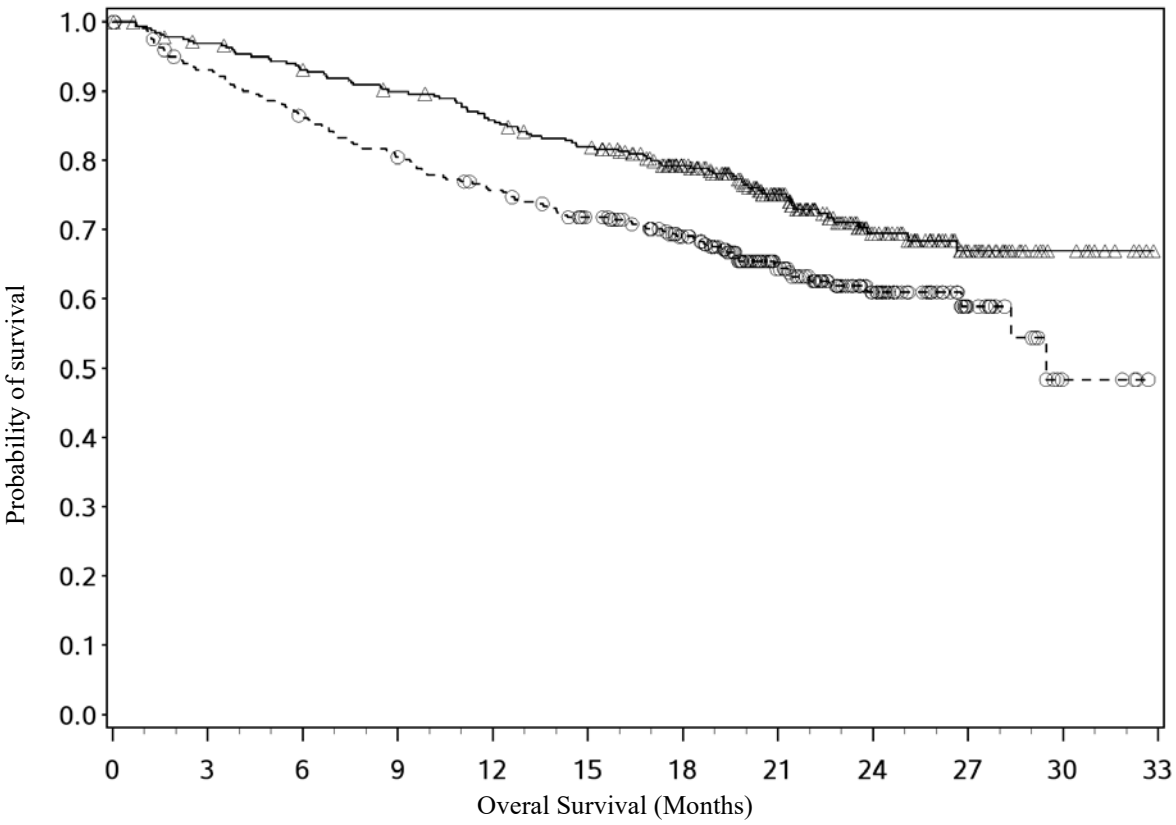


Figure 17: Kaplan-Meier curves of OS (CA2099ER)



Number of subjects at risk

Nivolumab + cabozantinib											
323	308	295	283	269	255	220	147	84	40	10	0
Sunitinib											
328	295	272	254	236	217	189	118	62	22	4	0

Nivolumab + cabozantinib (events: 86/323), median and 95% CI: NE

Sunitinib (events: 116/328), median and 95% CI: 29.47 (28.35, NE)

The Asian subjects included in the study represented a relatively small number of subjects and small number of events. A total of 51 Asian patients were randomized, 26 in the cabozantinib in combination with nivolumab arm and 25 in the sunitinib arm. As these patients were randomized late in the study, the number of events (progression or death) was small: 11 in the cabozantinib in combination with nivolumab arm and 6 in the sunitinib arm. The median PFS was 12.45 months (6.97, N.A.) in the cabozantinib in combination with nivolumab arm and N.A. (6.93, N.A.) in the sunitinib arm (HR 1.29; 95% CI 0.47; 3.54). The median OS was N.A. in both arms. The ORR was greater in the cabozantinib in combination with nivolumab arm 42.3% versus 28% in the sunitinib arm.

Classical Hodgkin lymphoma (cHL)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of relapsed or refractory cHL following ASCT and treatment with brentuximab vedotin was evaluated in two 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 B included 80 patients that received nivolumab 3 mg/kg monotherapy administered intravenously over 60 minutes every 2 weeks, following ASCT and brentuximab vedotin treatment. The first tumour assessments were conducted 9 weeks after the start of treatment and continued thereafter until disease progression or treatment discontinuation. The primary efficacy outcome measure was ORR as determined by IRRC. Additional efficacy measures included duration of response.

CA209039 was a Phase 1b open-label, multicenter, dose-escalation, and multidose study of nivolumab in relapsed/refractory hematologic malignancies, including 23 patients with cHL treated with nivolumab 3 mg/kg monotherapy; amongst which, 15 patients received prior brentuximab vedotin treatment as a salvage therapy following ASCT, similar to Cohort B of study CA209205. The first tumour assessments were conducted 4 weeks after the start of treatment and continued thereafter until disease progression or treatment discontinuation. Efficacy assessments included investigator-assessed ORR, retrospectively evaluated by an IRRC, and duration of response.

Data from the 80 patients from CA209205 Cohort B and from the 15 patients from CA209039 who received prior brentuximab vedotin treatment following ASCT were integrated. Baseline characteristics were similar across the two studies (see Table 21 below).

Table 21: **Baseline patient characteristics in CA209205 and CA209039**

	CA209205 Cohort B and CA209039 (n = 95)	**CA209205 Cohort B [a] (n = 80)**	**CA209039 (n = 15)**
Median age, years (range)	37.0 (18–72)	37.0 (18–72)	40.0 (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 (min-max)	3.5 (0.2–19.0)	3.4 (0.2–19.0)	5.6 (0.5–15.0)

[a] 18/80 (25%) of the patients in CA209205 Cohort B presented B-Symptoms at baseline.

Efficacy from both studies was evaluated by the same IRRC. Results are shown in Table 22.

Table 22: Efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma

Number (n)/ minimum follow-up (months)	**CA209205 Cohort B[a] and CA209039 (n = 95/12.0)**	**CA209205 Cohort B[a] (n = 80/12.0)**	**CA209039 (n = 15/12.0)**
Objective response, n (%); (95% CI)	63 (66%); (56, 76)	54 (68%); (56, 78)	9 (60%); (32, 84)
Complete remission (CR), n (%); (95% CI)	6 (6%); (2, 13)	6 (8%); (3, 16)	0 (0%); (0, 22)
Partial remission (PR), n (%); (95% CI)	57 (60%); (49, 70)	48 (60%); (48, 71)	9 (60%); (32, 84)
Stable disease, n (%)	22 (23)	17 (21)	5 (33)
Duration of response (months)[b]			
Median (95% CI)	13.1 (9.5, NE)	13.1 (8.7, NE)	12.0 (1.8, NE)
Range	0.0^{+}-23.1^{+}	0.0^{+}-14.2^{+}	1.8-23.1^{+}
Median time to response			
Months (range)	2.0 (0.7-11.1)	2.1 (1.6-11.1)	0.8 (0.7-4.1)
Median duration of follow-up			
Months (range)	15.8 (1.9-27.6)	15.4 (1.9-18.5)	21.9 (11.2-27.6)
Progression-free survival			
Rate (95% CI) at 12 months	57 (45, 68)	55 (41, 66)	69 (37, 88)

"+" denotes a censored observation.

[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 = non-estimable

Nine patients received transplant (6 in CA209205 and 3 in CA209039) as subsequent therapy.

In a post-hoc analysis of the 80 patients in CA209205 Cohort B, it was found that 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 13.14 months (13.14, N.A.) for the 22 responders to nivolumab who had failed to achieve response with prior brentuximab vedotin treatment.

B-symptoms were present in 25% (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.

Squamous Cell Cancer of the Head and Neck (SCCHN)

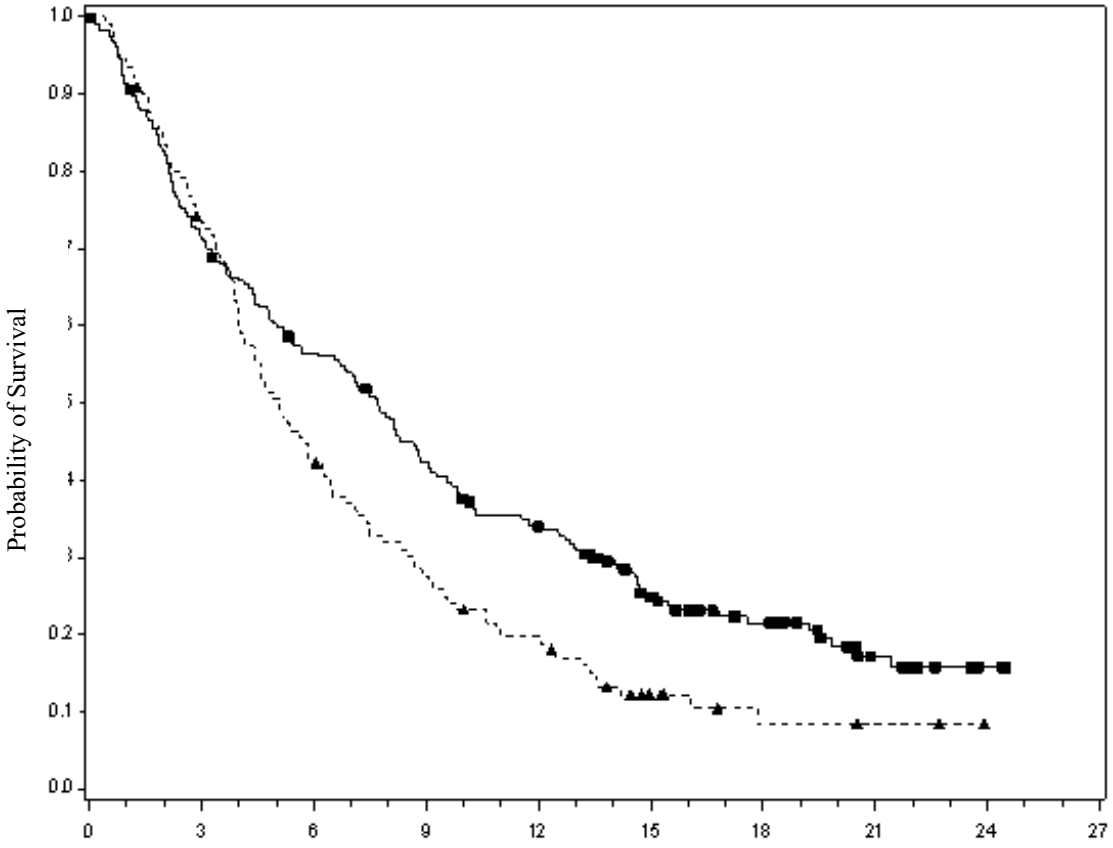
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of metastatic or recurrent SCCHN were evaluated in a phase 3, randomised, open-label study (CA209141). The study included patients (18 years or older) who have experienced disease progression during or within 6 months of receiving platinum-based therapy regimen and had an ECOG performance status score of 0 or 1. Prior platinum-based therapy was administered in either the adjuvant, neo-adjuvant, primary, recurrent, or metastatic setting. Patients were enrolled regardless of their tumour PD-L1 or human papilloma virus (HPV) status. Patients with active autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary salivary gland or non-squamous histologies (e.g., mucosal melanoma), or 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 enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

A total of 361 patients were randomised to receive either nivolumab 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n = 15), 400 mg/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. Randomisation was stratified by prior cetuximab treatment. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to RECIST version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. Treatment beyond initial investigator-assessed RECIST version 1.1-defined progression was permitted in patients receiving nivolumab, if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and ORR. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at predefined levels of 1%, 5%, and 10%.

Baseline characteristics were generally balanced between the two groups. The median age was 60 years (range: 28- 83) with 31% ≥ 65 years of age and 5% ≥ 75 years of age, 83% were male, and 83% were white. Baseline ECOG performance status score was 0 (20%) or 1 (78%), 77% were former/current smokers, 90% had Stage IV disease, 66% had two or more lesions, 45%, 34% and 20% received 1, 2, or 3 or more prior lines of systemic therapy, respectively, and 25% were HPV-16 status positive.

With a minimum follow-up of 11.4 months, the trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice. The Kaplan-Meier curves for OS are shown in Figure 18. Efficacy results are shown in Table 23.

Figure 18: Kaplan-Meier curves of OS (CA209141)



Number of Subjects at Risk

Nivolumab								
240	169	132	98	76	45	27	12	3
Investigator's choice								
121	88	51	32	22	9	4	3	0

Nivolumab 3 mg/kg (events: 184/240), median and 95% CI: 7.72 (5.68, 8.77)
Investigator's choice (events: 105/121), median and 95% CI: 5.06 (4.04, 6.24)
Nivo vs Investigator's choice - hazard ratio 95%: 0.71 (0.55, 0.90), p value: 0.0048
Symbols represent censored observations

Table 23: 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 tumour PD-L1 expression < 1%.

"+" Denotes a censored observation

Quantifiable tumour PD-L1 expression was measured in 67% of patients in the nivolumab group and 82% of patients in the investigator's choice group. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. investigator's choice) at each of the predefined tumour PD-L1 expression levels of ≥ 1% (55% vs. 62%), ≥ 5% (34% vs. 43%), or ≥ 10% (27% vs. 34%).

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to investigator's choice. The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumour PD-L1 expression levels (see Table 24).

Table 24: OS by tumour 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: HR = 0.64; 95% CI: 0.40, 1.03, and HPV -unknown: HR=0.78; CI: 0.55, 1.10).

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).

Gastric/Gastroesophageal Junction (GEJ) Cancer

Randomised double-blinded Phase 3 study (ONO-4538-12/CA209316)
The safety and efficacy of nivolumab monotherapy for the treatment of advanced or recurrent gastric cancer (including GEJ cancer) were evaluated in a phase 3, randomised, double-blind study (ONO-4538-12/CA209316). The study included adult patients previously treated with two or more regimens and whose disease was refractory to or who were intolerant of standard therapy. Patients had ECOG performance status of 0 or 1 and were enrolled regardless of PD-L1 expression level. Patients with history of chronic or recurrent autoimmune disease, interstitial lung disease or pulmonary fibrosis, symptomatic brain or meningeal metastases, diverticulitis, or symptomatic gastrointestinal ulcerative disease or ascites requiring treatment were excluded from the study.

A total of 493 patients were randomised to receive nivolumab monotherapy (n=330) or placebo (163 patients were randomised; of these, 161 patients received at least one dose) administered over 60 minutes every 2 weeks. Randomisation was stratified by location (Japan vs. Korea vs. Taiwan), ECOG performance status (0 vs. 1), and the number of organs with metastases (≤1 vs. ≥2). Nivolumab-treated patients with disease progression per RECIST version 1.1 were allowed to continue treatment until a second RECIST assessment of progressive disease provided that they were receiving a clinical benefit, tolerating nivolumab, and maintaining a stable ECOG performance status score. Tumour assessments were conducted every 6 weeks for the first year and then every 12 weeks thereafter. The primary outcome measure was OS. Additional outcome measures included investigator-assessed PFS and ORR.

Baseline characteristics were balanced between treatment groups. The median age was 62 years (range: 20 to 83 years) in the nivolumab group, with 141/330 (42.7%) ≥65 years of age and 30/330 (9.1%) ≥75 years of age. The majority of patients were male and 99.7% were Asian. Disease characteristics were balanced between treatment groups. In the nivolumab group, 41% of patients had recurrent disease, 82.4% of patients had gastric and 9.1% had GEJ cancer as the primary site of disease, and 71% had an ECOG score of 1. All patients had received at least 2 prior treatment regimens and most nivolumab-treated patients had received prior fluoropyrimidine (99.7%), platinum (94.2%), or taxane (86.1%), or irinotecan (74.8%) therapy.

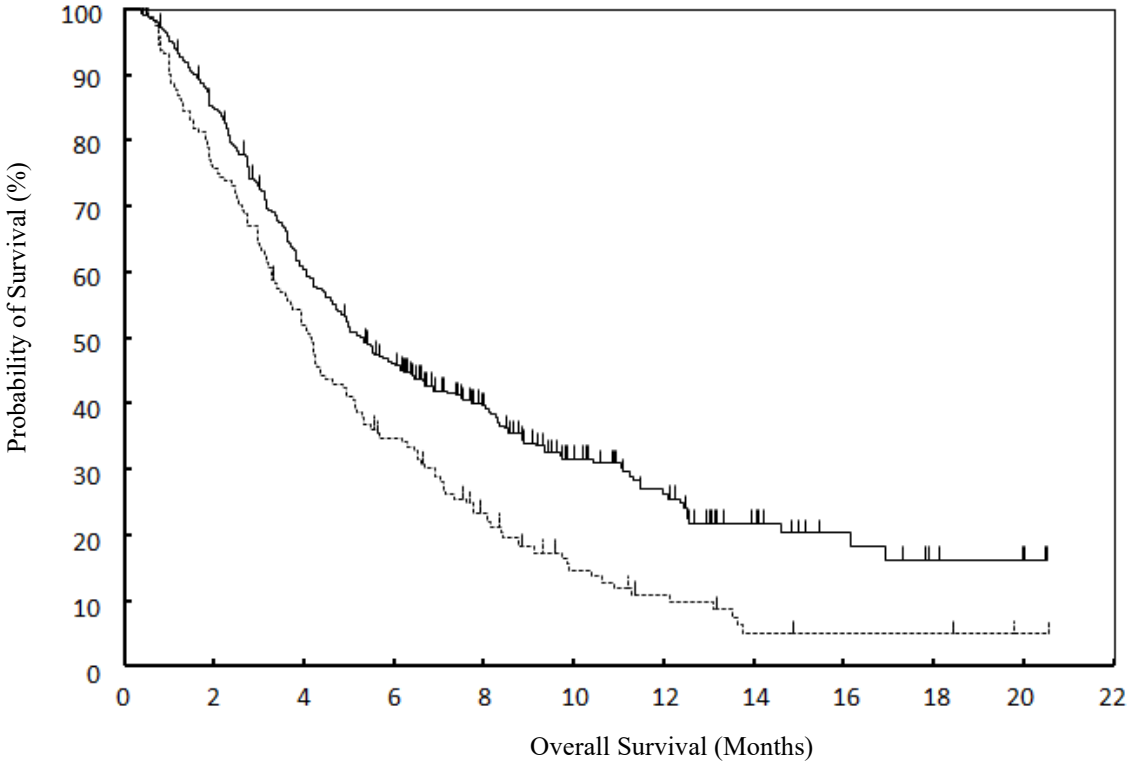
With a minimum duration of follow-up of approximately 6 months, nivolumab demonstrated a statistically significant improvement in OS compared with placebo. Improved OS was also demonstrated at 12 months and 18 months. Efficacy results are shown in Table 25, Figure 19 and Figure 20.

Table 25: Efficacy results (ONO-4538-12/CA209316)

	Nivolumab (n=330)	Placebo (n=163)
Overall Survival		
Events (%)	226 (68.5%)	141 (86.5%)
Hazard ratio[a] (95% CI)	0.63 (0.51, 0.78)	
p-value[b]	<0.0001[c]	
Median (95% CI)	5.26 (4.60, 6.37)	4.14 (3.42, 4.86)
Rate (95% CI) at 6 months	46.1 (40.5, 51.4)	34.7 (27.4, 42.1)
Rate (95% CI) at 12 months	26.2 (20.7, 32.0)	10.9 (6.2, 17.0)
Rate (95% CI) at 18 months	16.2 (10.0, 23.7)	5.0 (1.8, 10.6)
Progression-free Survival		
Events (%)	253 (76.7%)	145 (89.0%)
Hazard ratio[a] (95% CI)	0.60 (0.49, 0.75)	
p-value[b]	<0.0001	
Median (95% CI)	1.61 (1.54, 2.30)	1.45 (1.45, 1.54)
Rate (95% CI) at 6 months	20.2 (15.7, 25.1)	6.8 (3.3, 11.8)
Objective Response Rate[d]	30 (11.2%)	0
(95% CI)	(7.7, 15.6)	(0.0, 2.8)
p-value[e]	<0.0001	
Complete response (CR)	0	0
Partial response (PR)	30 (11.2%)	0
Stable disease (SD)	78 (29.1%)	33 (25.2%)
Disease control rate[f]	108 (40.3%)	33 (25.2%)
Median time to response		
Months (range)	1.61 (1.4 to 7.0)	N.A.
Median duration of response[g]		
Months (95% CI)	9.53 (6.14, 9.82)	N.A.
% with duration ≥6 months (95% CI)[g]	75.0 (52.2, 88.0)	N.A.

[a] Based on a stratified proportional hazards model.
[b] Based on a one-sided stratified log-rank test.
[c] Boundary significance level is 0.025.
[d] ORR (CR + PR) in patients with measurable target lesions at baseline (nivolumab: n=268; placebo: n=131).
[e] Based on the stratified Cochran-Mantel-Haenszel test.
[f] Disease control rate (DCR) consists of CR+PR+SD.
[g] Based on Kaplan-Meier estimation

Figure 19: Kaplan-Meier curves of OS (ONO-4538-12/CA209316)

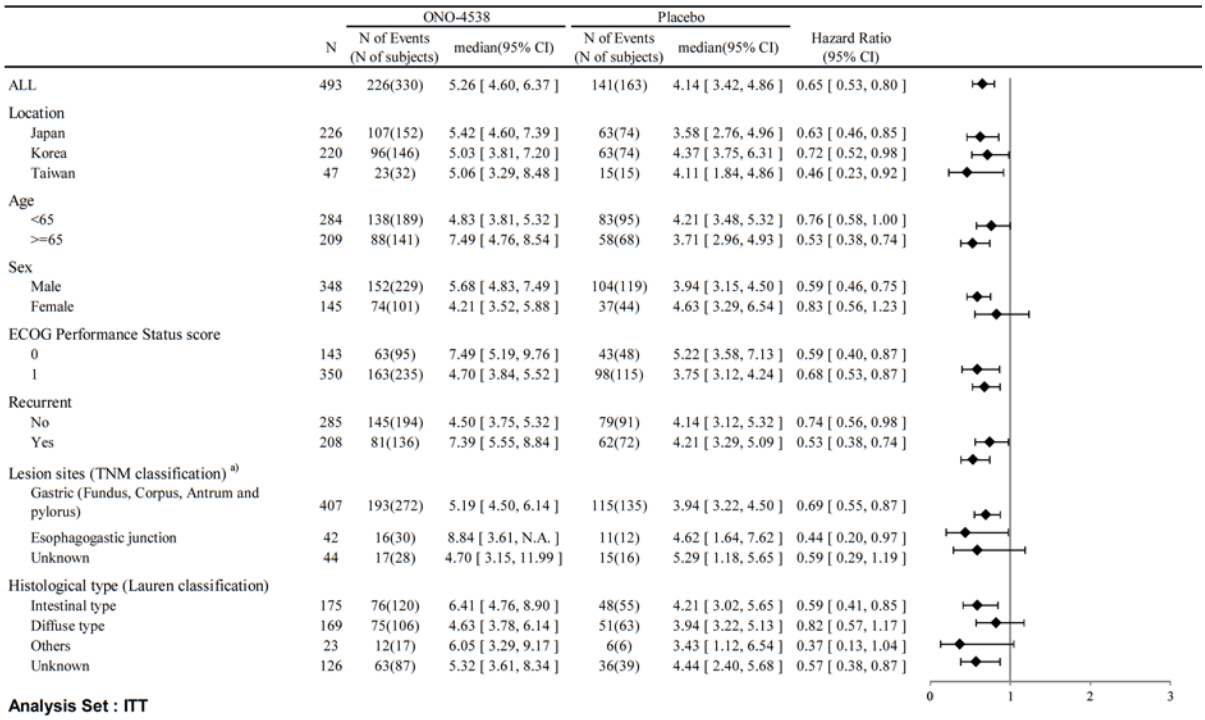


Number of Subjects at Risk

Nivolumab											
330	275	192	141	94	56	38	19	10	5	3	0
Placebo											
163	121	82	53	32	16	10	4	3	3	1	0

——— Nivolumab 3 mg/kg (events: 226/330), median and 95% CI: 5.26 (4.60, 6.37)
- - - - - Placebo (events: 141/163), median and 95% CI: 4.14 (3.42, 4.86)

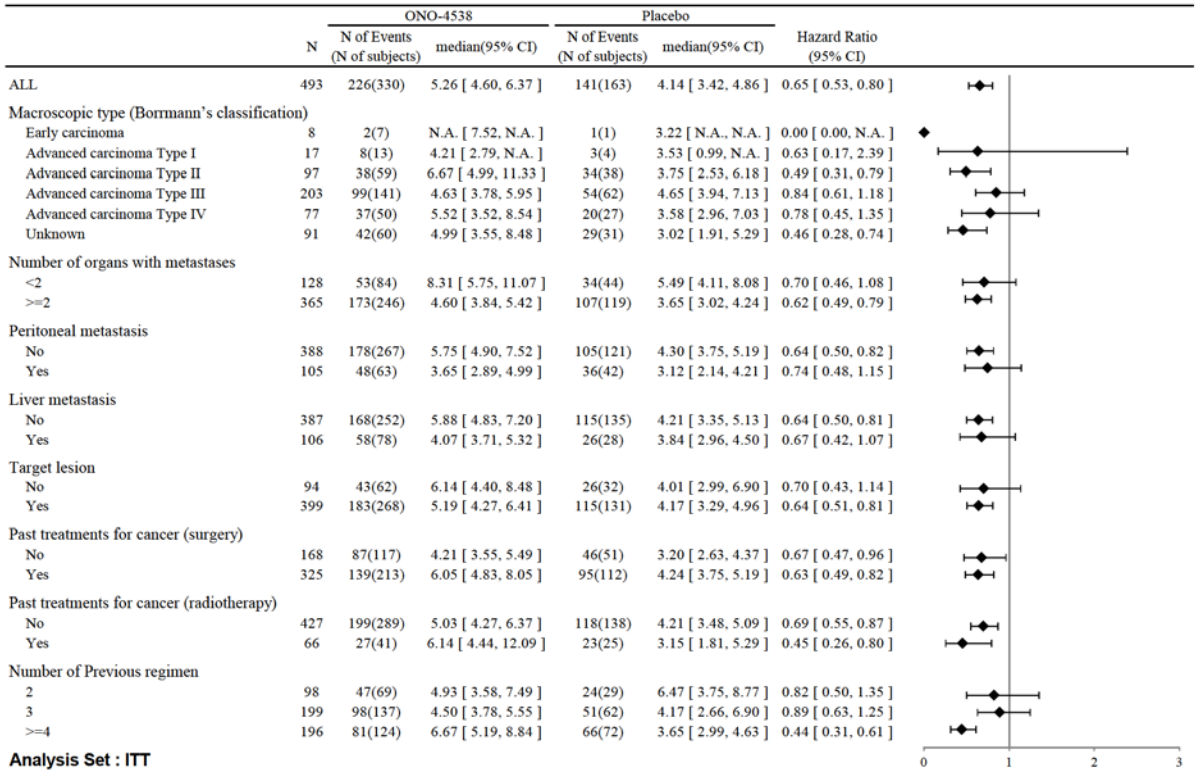
Figure 20: Forest Plot of Subgroup Analyses for Overall Survival (ONO-4538-12/CA209316)



	N	ONO-4538 N of Events (N of subjects)	ONO-4538 median(95% CI)	Placebo N of Events (N of subjects)	Placebo median(95% CI)	Hazard Ratio (95% CI)
ALL	493	226(330)	5.26 [4.60, 6.37]	141(163)	4.14 [3.42, 4.86]	0.65 [0.53, 0.80]
Location						
Japan	226	107(152)	5.42 [4.60, 7.39]	63(74)	3.58 [2.76, 4.96]	0.63 [0.46, 0.85]
Korea	220	96(146)	5.03 [3.81, 7.20]	63(74)	4.37 [3.75, 6.31]	0.72 [0.52, 0.98]
Taiwan	47	23(32)	5.06 [3.29, 8.48]	15(15)	4.11 [1.84, 4.86]	0.46 [0.23, 0.92]
Age						
<65	284	138(189)	4.83 [3.81, 5.32]	83(95)	4.21 [3.48, 5.32]	0.76 [0.58, 1.00]
>=65	209	88(141)	7.49 [4.76, 8.54]	58(68)	3.71 [2.96, 4.93]	0.53 [0.38, 0.74]
Sex						
Male	348	152(229)	5.68 [4.83, 7.49]	104(119)	3.94 [3.15, 4.50]	0.59 [0.46, 0.75]
Female	145	74(101)	4.21 [3.52, 5.88]	37(44)	4.63 [3.29, 6.54]	0.83 [0.56, 1.23]
ECOG Performance Status score						
0	143	63(95)	7.49 [5.19, 9.76]	43(48)	5.22 [3.58, 7.13]	0.59 [0.40, 0.87]
1	350	163(235)	4.70 [3.84, 5.52]	98(115)	3.75 [3.12, 4.24]	0.68 [0.53, 0.87]
Recurrent						
No	285	145(194)	4.50 [3.75, 5.32]	79(91)	4.14 [3.12, 5.32]	0.74 [0.56, 0.98]
Yes	208	81(136)	7.39 [5.55, 8.84]	62(72)	4.21 [3.29, 5.09]	0.53 [0.38, 0.74]
Lesion sites (TNM classification) [a)]						
Gastric (Fundus, Corpus, Antrum and pylorus)	407	193(272)	5.19 [4.50, 6.14]	115(135)	3.94 [3.22, 4.50]	0.69 [0.55, 0.87]
Esophagogastric junction	42	16(30)	8.84 [3.61, N.A.]	11(12)	4.62 [1.64, 7.62]	0.44 [0.20, 0.97]
Unknown	44	17(28)	4.70 [3.15, 11.99]	15(16)	5.29 [1.18, 5.65]	0.59 [0.29, 1.19]
Histological type (Lauren classification)						
Intestinal type	175	76(120)	6.41 [4.76, 8.90]	48(55)	4.21 [3.02, 5.65]	0.59 [0.41, 0.85]
Diffuse type	169	75(106)	4.63 [3.78, 6.14]	51(63)	3.94 [3.22, 5.13]	0.82 [0.57, 1.17]
Others	23	12(17)	6.05 [3.29, 9.17]	6(6)	3.43 [1.12, 6.54]	0.37 [0.13, 1.04]
Unknown	126	63(87)	5.32 [3.61, 8.34]	36(39)	4.44 [2.40, 5.68]	0.57 [0.38, 0.87]

Analysis Set : ITT

a) Subjects with lesion sites in both gastric and esophagogastric junction included gastric category.



	N	ONO-4538 N of Events (N of subjects)	ONO-4538 median(95% CI)	Placebo N of Events (N of subjects)	Placebo median(95% CI)	Hazard Ratio (95% CI)
ALL	493	226(330)	5.26 [4.60, 6.37]	141(163)	4.14 [3.42, 4.86]	0.65 [0.53, 0.80]
Macroscopic type (Borrmann's classification)						
Early carcinoma	8	2(7)	N.A. [7.52, N.A.]	1(1)	3.22 [N.A., N.A.]	0.00 [0.00, N.A.]
Advanced carcinoma Type I	17	8(13)	4.21 [2.79, N.A.]	3(4)	3.53 [0.99, N.A.]	0.63 [0.17, 2.39]
Advanced carcinoma Type II	97	38(59)	6.67 [4.99, 11.33]	34(38)	3.75 [2.53, 6.18]	0.49 [0.31, 0.79]
Advanced carcinoma Type III	203	99(141)	4.63 [3.78, 5.95]	54(62)	4.65 [3.94, 7.13]	0.84 [0.61, 1.18]
Advanced carcinoma Type IV	77	37(50)	5.52 [3.52, 8.54]	20(27)	3.58 [2.96, 7.03]	0.78 [0.45, 1.35]
Unknown	91	42(60)	4.99 [3.55, 8.48]	29(31)	3.02 [1.91, 5.29]	0.46 [0.28, 0.74]
Number of organs with metastases						
<2	128	53(84)	8.31 [5.75, 11.07]	34(44)	5.49 [4.11, 8.08]	0.70 [0.46, 1.08]
>=2	365	173(246)	4.60 [3.84, 5.42]	107(119)	3.65 [3.02, 4.24]	0.62 [0.49, 0.79]
Peritoneal metastasis						
No	388	178(267)	5.75 [4.90, 7.52]	105(121)	4.30 [3.75, 5.19]	0.64 [0.50, 0.82]
Yes	105	48(63)	3.65 [2.89, 4.99]	36(42)	3.12 [2.14, 4.21]	0.74 [0.48, 1.15]
Liver metastasis						
No	387	168(252)	5.88 [4.83, 7.20]	115(135)	4.21 [3.35, 5.13]	0.64 [0.50, 0.81]
Yes	106	58(78)	4.07 [3.71, 5.32]	26(28)	3.84 [2.96, 4.50]	0.67 [0.42, 1.07]
Target lesion						
No	94	43(62)	6.14 [4.40, 8.48]	26(32)	4.01 [2.99, 6.90]	0.70 [0.43, 1.14]
Yes	399	183(268)	5.19 [4.27, 6.41]	115(131)	4.17 [3.29, 4.96]	0.64 [0.51, 0.81]
Past treatments for cancer (surgery)						
No	168	87(117)	4.21 [3.55, 5.49]	46(51)	3.20 [2.63, 4.37]	0.67 [0.47, 0.96]
Yes	325	139(213)	6.05 [4.83, 8.05]	95(112)	4.24 [3.75, 5.19]	0.63 [0.49, 0.82]
Past treatments for cancer (radiotherapy)						
No	427	199(289)	5.03 [4.27, 6.37]	118(138)	4.21 [3.48, 5.09]	0.69 [0.55, 0.87]
Yes	66	27(41)	6.14 [4.44, 12.09]	23(25)	3.15 [1.81, 5.29]	0.45 [0.26, 0.80]
Number of Previous regimen						
2	98	47(69)	4.93 [3.58, 7.49]	24(29)	6.47 [3.75, 8.77]	0.82 [0.50, 1.35]
3	199	98(137)	4.50 [3.78, 5.55]	51(62)	4.17 [2.66, 6.90]	0.89 [0.63, 1.25]
>=4	196	81(124)	6.67 [5.19, 8.84]	66(72)	3.65 [2.99, 4.63]	0.44 [0.31, 0.61]

Analysis Set : ITT

Open-label phase 1/2 study (CA209032)

Efficacy was also evaluated in a separate phase 1/2 study conducted in Europe and the United States, which included a cohort of 42 patients treated with OPDIVO monotherapy 3 mg/kg for gastric cancer (16/42; 38%) or GEJ cancer (26/42; 62%) who had received at least 2 prior regimens.

At a minimum follow-up of 8 months, the median OS was 8.97 months (95% CI: 3.35, 14.88), with an OS rate at 6 months of 57.4% (95% CI: 40.5, 71.1) for this cohort. Investigator-assessed confirmed ORR was 16.7% (95% CI: 7.0, 31.4).

The safety profile of the gastric/GEJ cancer cohort of CA209032 was comparable to that observed in ONO-4538-12/CA209316.

Oesophageal Squamous Cell Carcinoma (OSCC)

Randomised, open-label, multicenter Phase 3 study CA209473/ONO-24

The safety and efficacy of nivolumab 240mg monotherapy for the treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) was evaluated in a phase 3, multicenter, randomised active-controlled, open-label study (CA209473/ ONO-4538-24).

The study included adult patients who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen, and patients were enrolled regardless of tumour PD-L1 expression level.
Patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had active autoimmune disease, medical conditions requiring systemic immunosuppression, and patients with apparent tumour invasion on organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), were excluded from the study.

A total of 419 patients were randomised 1:1 to receive either nivolumab 240 mg administered intravenously over 30 minutes every 2 weeks (n=210) or investigator's choice of taxane chemotherapy: either docetaxel (n=65) 75 mg/m^2 intravenously every 3 weeks, or paclitaxel (n=144) 100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off.

Randomisation was stratified by location (Japan vs. rest of world), number of organs with metastases (≤1 vs. ≥2) and tumour PD-L1 expression (≥1% vs. <1% or indeterminate). Treatment continued until disease progression, assessed by the investigator per RECIST version 1.1, or unacceptable toxicity.

Tumour assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab with no rapid progression, investigator assessed benefit, tolerance to treatment, stable performance status, and for whom treatment beyond progression would not delay an imminent intervention to prevent serious complications associated with disease progression (e.g. brain metastasis). The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were ORR and PFS as assessed by the investigator using RECIST v1.1 and DOR. Additional pre-specified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at a predefined level of 1%. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Baseline characteristics were generally balanced between the two groups. The median age was 65 years (range: 33 to 87 years), 53% were ≥65 years of age, 10% were aged ≥75 years; 87% were male, 96% were Asian and 4% were white. Baseline ECOG performance status was 0 (50%) or 1 (50%).

With a minimum follow-up of 17.6 months, the study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice taxane chemotherapy. OS benefit was observed regardless of PD-L1 expression level. Efficacy results are shown in Table 26 and Figure 21.

A higher proportion of patients experienced death within the first 2.5 months in the nivolumab arm (32/210, 15.2%) as compared to the chemotherapy arm (15/209, 7.2%). No specific factor(s) associated with early deaths could be identified.

Table 26: Efficacy results (CA209473/ ONO-4538-24)

	Nivolumab (n=210)	Investigator's choice (n=209)
Overall Survival[a]		
Events (%)	160 (76%)	173 (83%)
Hazard ratio (95% CI)[b]	0.77 (0.62, 0.96)	
p-value[c]	0.0189	
Median (months) (95% CI)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)
Progression-free Survival[a]		
Events (%)	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 Rate[d,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.

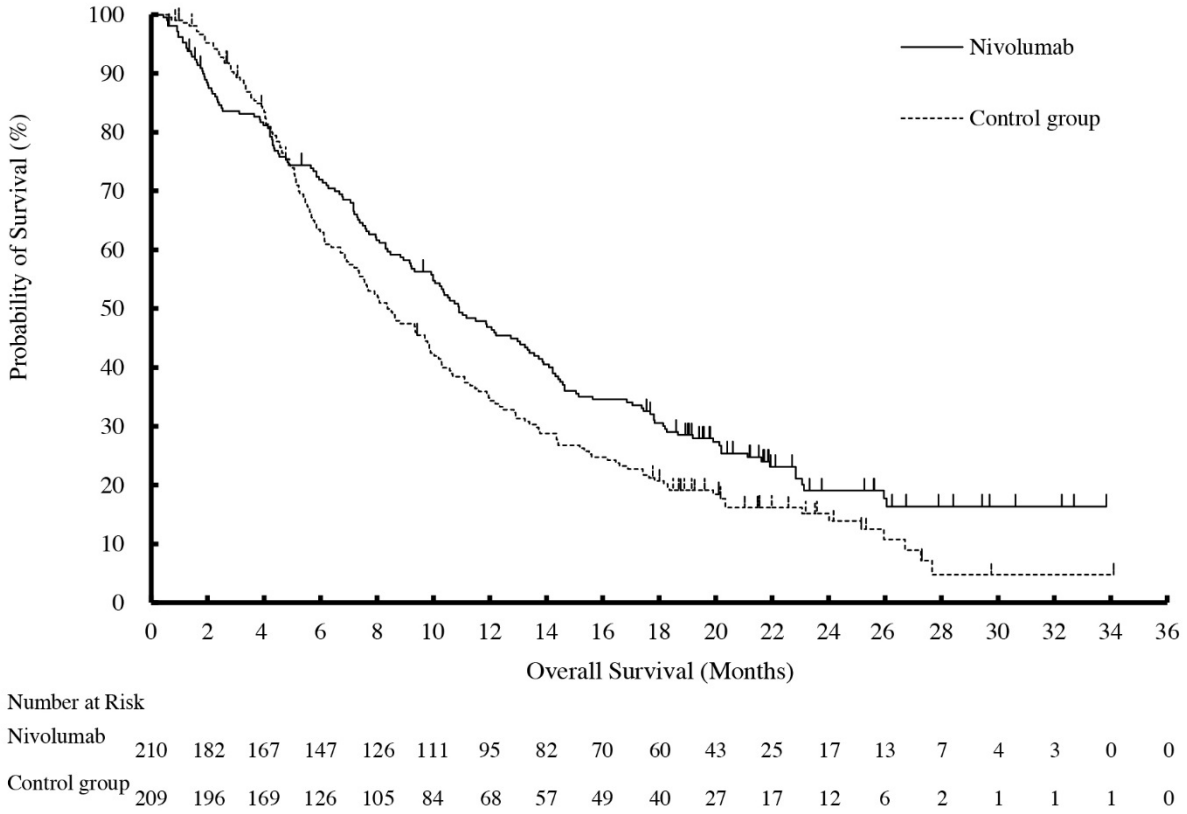
[b] Based on a stratified proportional hazards model.

[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: Kaplan-Meier curves of OS (CA209473/ ONO-4538-24)



Of the 419 patients, 48% had tumour PD-L1 expression of ≥1% of tumour cells expressing PD-L1. The remaining 52% of patients had tumour PD-L1 expression of <1% (defined as <1% of tumour cells expressing PD-L1).
The hazard ratio (HR) for OS was 0.69 (95% CI: 0.51, 0.94) with median survivals of 10.9 and 8.1 months for the nivolumab and investigator's choice taxane chemotherapy arms, respectively, in the tumour PD-L1 positive subgroup. In the tumour PD-L1 negative OSCC subgroup, the HR for OS was 0.84 (95% CI: 0.62, 1.14) with median survivals of 10.9 and 9.3 months for the nivolumab and chemotherapy arms, respectively.

Gastric cancer, gastro-oesophageal junction cancer or oesophageal adenocarcinoma

CA209-649 was a randomized, multicenter, open-label trial in patients (n=1581) with previously untreated advanced or metastatic gastric cancer, gastro-oesophageal junction cancer, and oesophageal adenocarcinoma. The trial enrolled patients regardless of PD-L1 status, and tumour specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were known human epidermal growth factor (HER2) positive, or had untreated central nervous system metastases. Patients were randomized to receive OPDIVO in combination with chemotherapy (n=789) or chemotherapy (n=792). Patients received one of the following treatments:

- OPDIVO 240 mg in combination with mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or mFOLFOX6 every 2 weeks.
- OPDIVO 360 mg in combination with CapeOX (capecitabine and oxaliplatin) every 3 weeks or CapeOX every 3 weeks.

Patients were treated until disease progression, unacceptable toxicity, or up to 2 years. In patients who received OPDIVO in combination with chemotherapy and in whom chemotherapy was discontinued, OPDIVO monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks up to 2 years after treatment initiation.

Randomization was stratified by tumor cell PD-L1 status (≥1% vs. <1% or indeterminate), region (Asia vs. US vs. Rest of World), ECOG performance status (0 vs. 1), and chemotherapy regimen (mFOLFOX6 vs. CapeOX). The major efficacy outcome measures, assessed in patients with PD-L1 CPS ≥5, were PFS assessed by BICR and OS. Additional efficacy outcome measures included OS and PFS in patients with PD-L1 CPS ≥1 and in all randomized patients, and ORR and DOR as assessed by BICR in patients with PD-L1 CPS ≥1 and ≥5, and in all randomized patients. Tumor assessments were conducted per RECIST v1.1 every 6 weeks up to and including week 48, then every 12 weeks thereafter.

The trial population characteristics were: median age 61 years (range: 18 to 90), 39% were ≥65 years of age, 70% were male, 24% were Asian, 69% were white, and 1% were black. Baseline ECOG performance status was 0 (42%) or 1 (58%). Seventy percent of patients had adenocarcinoma tumors in the stomach, 16% in the gastroesophageal junction, and 13% in the esophagus.

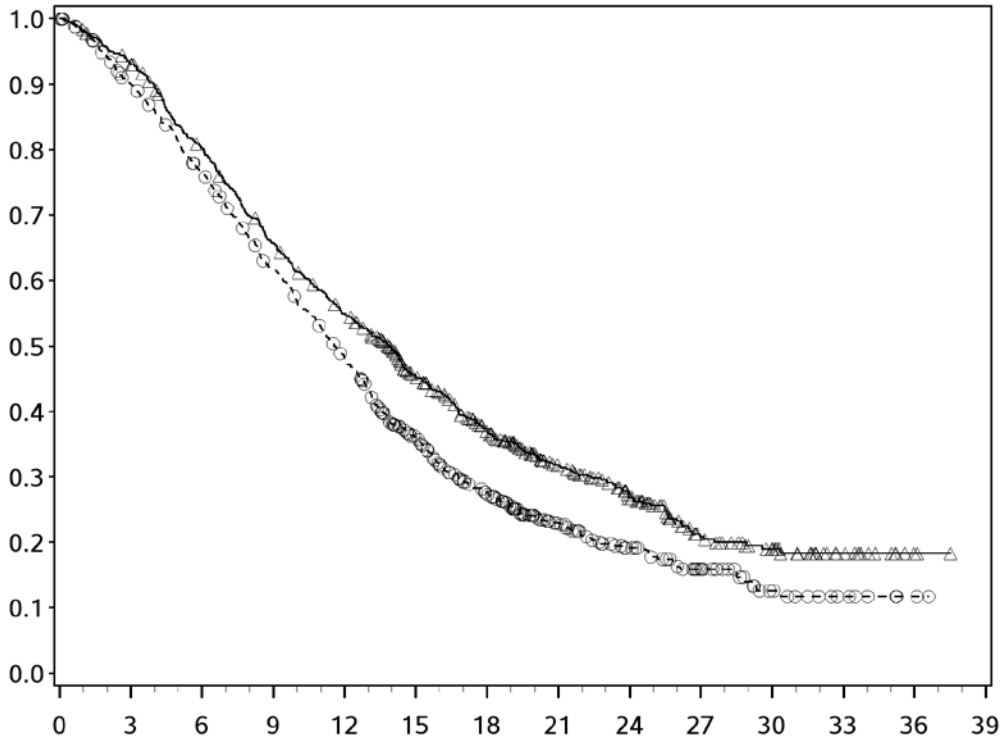
CA209-649 demonstrated a statistically significant improvement in OS and PFS for patients with PD-L1 CPS ≥5. Statistically significant improvement in OS was also demonstrated for all randomized patients. The minimum follow-up was 12.1 months. Efficacy results are shown in Table 27, and Figures 22 and 23.

Table 27: Efficacy results (CA209649)

	nivolumab + chemotherapy (n=789)	chemotherapy (n=792)	nivolumab + chemotherapy (n=641)	chemotherapy (n=655)	nivolumab + chemotherapy (n=473)	chemotherapy (n=482)
	All patients		**PD-L1 CPS≥1**		**PD-L1 CPS≥5**	
Overall survival						
Events(%)	544 (68.9)	591 (74.6)	434 (67.7)	492 (75.1)	309 (65.3)	362 (75.1)
Hazard ratio (CI)[a]	0.80 (99.3% CI: 0.68, 0.94)		0.77 (99.3% CI: 0.64, 0.92)		0.71 (98.4% CI: 0.59. 0.86)	
p-value[b]	0.0002		<0.0001		<0.0001	
Median (95% CI) (months)[c]	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)	14.0 (12.6, 15.0)	11.3 (10.6, 12.3)	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)
Rate (95% CI) at 12 months	55.0 (51.4, 58.4)	47.9 (44.4, 51.4)	55.5 (51.5, 59.3)	47.0 (43.1, 50.9)	57.3 (52.6, 61.6)	46.4 (41.8, 50.8)
Progression-free survival[d]						
Events(%)	559 (70.8)	557 (70.3)	454 (70.8)	472 (72.1)	328 (69.3)	350 (72.6)
Hazard ratio (CI)[a]	0.77 (95% CI: 0.68, 0.87)		0.74 (95% CI: 0.65, 0.85)		0.68 (98% CI: 0.56, 0.81)	
p-value[b]	-[e]		-[e]		<0.0001	
Median (95% CI) (months)[c]	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)	7.49 (7.03, 8.41)	6.90 (6.08, 7.03)	7.69 (7.03, 9.17)	6.05 (5.55, 6.90)
Rate (95% CI) at 12 months	33.4 (29.9, 37.0)	23.2 (19.9, 26.7)	34.2 (30.3, 38.2)	22.4 (18.8, 26.1)	36.3 (31.7, 41.0)	21.9 (17.8, 26.1)
Overall response rate, n (%)[d,f]	350/603 (58.0)	280/608 (46.1)	300/504 (59.5)	239/515 (46.4)	226/378 (59.8)	177/391 (45.3)
(95% CI)	(54.0, 62.0)	(42.0, 50.1)	(55.1, 63.8)	(42.0, 50.8)	(54.7, 64.8)	(40.3, 50.4)
Complete response	59 (9.8)	39 (6.4)	51 (10.1)	32 (6.2)	44 (11.6)	27 (6.9)
Partial response	291 (48.3)	241 (39.6)	249 (49.4)	207 (40.2)	182 (48.1)	150 (38.4)
Duration of response[d,f]						
Median (95% CI) (months)[c] Range	8.51 (7.23, 9.92) 1.0+, 29.6+	6.93 (5.82, 7.16) 1.2+, 30.8+	8.54 (7.69, 10.22) 1.1+, 29.6+	6.93 (5.78, 7.56) 1.2+, 30.8+	9.49 (7.98, 11.37) 1.1+, 29.6+	6.97 (5.65, 7.85) 1.2+, 30.8+

[a] Based on stratified long 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.

Figure 22. Kaplan-Meier curves of OS in all randomised patients (CA209649)



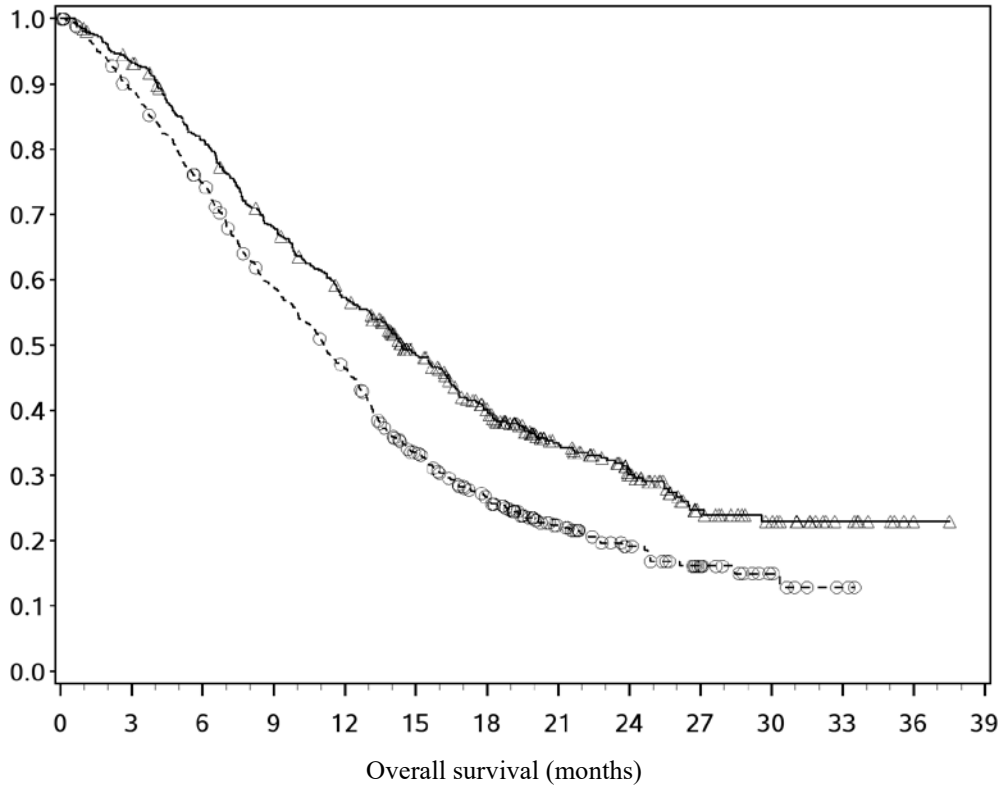
Number of subjects at risk

Nivolumab + chemotherapy	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemotherapy	792	697	586	496	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)

Figure 23. Kaplan-Meier curves of OS in patients with PD-L1 CPS ≥5 (CA209649)



Number of subjects at risk

Nivolumab + chemotherapy													
473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemotherapy													
482	421	350	271	211	138	98	56	34	19	8	2	0	0

Nivolumab + chemotherapy (events: 309/473), median and 95% CI: 14.39 (13.11, 16.23)

Chemotherapy (events: 362/482), median and 95% CI: 11.10 (10.02, 12.09)

In an exploratory analysis in patients with PD-L1 CPS <1 (n=265), the median OS was 13.1 months (95% CI: 9.8, 16.7) for the OPDIVO and chemotherapy arm and 12.5 months (95% CI: 10.1, 13.8) for the chemotherapy arm, with a stratified HR of 0.85 (95% CI: 0.63, 1.15). In an exploratory analysis in patients with PD-L1 CPS <5 (n=606), the median OS was 12.4 months (95% CI: 10.6, 14.3) for the OPDIVO and chemotherapy arm and 12.3 months (95% CI: 11.0, 13.2) for the chemotherapy arm, with a stratified HR of 0.94 (95% CI: 0.78, 1.14).

Adjuvant treatment of oesophageal or gastroesophageal junction cancer

CA209577 was a randomized, multicenter, double-blind trial in 794 patients with completely resected (negative margins) oesophageal or gastroesophageal junction cancer who had residual pathologic disease following concurrent chemoradiotherapy (CRT). Patients were randomized (2:1) to receive either nivolumab 240 mg or placebo by intravenous infusion over 30 minutes every 2 weeks for 16 weeks followed by 480 mg or placebo by intravenous infusion over 30 minutes every 4 weeks beginning at week 17. Treatment was until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. Enrollment required complete resection within 4 to 16 weeks prior to randomization. The trial excluded patients who did not receive CRT prior to surgery, had stage IV resectable disease, autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications. Randomization was stratified by tumor PD-L1 status (≥1% vs. <1% or indeterminate or non-evaluable), pathologic lymph node status (positive ≥ypN1 vs. negative ypN0), and histology (squamous vs. adenocarcinoma). The major efficacy outcome measure was disease-free survival (DFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant from the primary resected site) or death, from any cause, whichever occurred first as assessed by the investigator prior to

subsequent anti-cancer therapy. Patients on treatment underwent imaging for tumor recurrence every 12 weeks for 2 years, and a minimum of one scan every 6 to 12 months for years 3 to 5.

The trial population characteristics were: median age 62 years (range: 26 to 86), 36% were ≥65 years of age, 85% were male, 15% were Asian, 82% were White, and 1.1% were Black. Disease characteristics were AJCC Stage II (35%) or Stage III (65%) at initial diagnosis carcinoma, EC (60%) or GEJC (40%) at initial diagnosis, with pathologic positive lymph node status (58%) at study entry and histological confirmation of predominant adenocarcinoma (71%) or squamous cell carcinoma (29%). The baseline Tumor PD-L1 status ≥1% was positive for 16% of patients and negative for 72% of patients. Baseline ECOG performance status was 0 (58%) or 1 (42%).

With a minimum of 6.2 months and a median of 24.4 months follow-up, CA209577 demonstrated a statistically significant improvement in DFS for patients randomized to the nivolumab arm as compared with the placebo arm. DFS benefit was observed regardless of tumor PD-L1 expression and histology.

Efficacy results are shown in Table 28 and Figure 24.

Table 28: Efficacy results (CA209577)

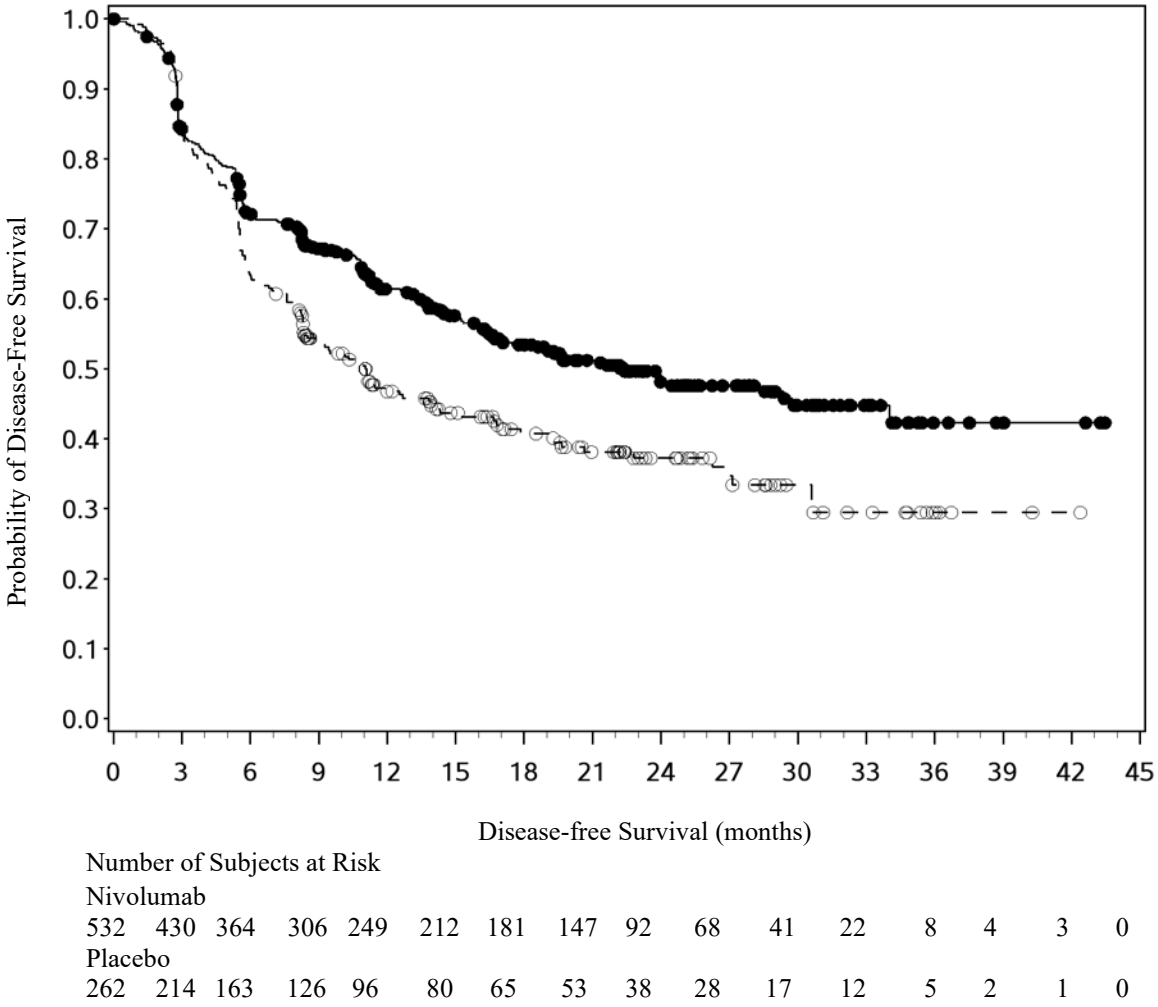
	nivolumab (n=532)	**placebo (n=262)**
Disease-free Survival[a]		
Events (%)	241 (45%)	155 (59%)
Hazard ratio (96.4% CI)[b]	0.69 (0.56, 0.86)	
p-value[c]	0.0003	
Median (95% CI) (months)	22.4 (16.6, 34.0)	11.0 (8.3, 14.3)

[a] Based on all randomized patients

[b] Based on a stratified cox proportional hazards model.

[c] Based on a stratified log-rank test.

Figure 24: Kaplan-Meier curves of DFS (CA209577)



Adjuvant Treatment of Urothelial Carcinoma

Randomised phase 3 study of adjuvant nivolumab vs. placebo (CA209274)

The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of urothelial carcinoma was evaluated in a phase 3 multicentre, randomised, placebo-controlled, double-blinded study (CA209274). The study included patients (18 years or older) who have undergone radical resection of muscle invasive urothelial carcinoma (MIUC) originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence. The MIUC pathologic staging criteria that defines high risk patients was ypT2-ypT4a or ypN^+ for adult patients who received neo-adjuvant cisplatin chemotherapy, and pT3-pT4a or pN^+ for adult patients who did not receive neo-adjuvant cisplatin chemotherapy and were not eligible or refused adjuvant cisplatin chemotherapy. The study included patients regardless of their PD-L1 status, who had an ECOG performance status score of 0 or 1 (an ECOG PS of 2 was allowed for patients ineligible for neo-adjuvant cisplatin chemotherapy). The study excluded patients with active, known or suspected autoimmune disease, patients who had treatment with any chemotherapy, radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment.

A total of 709 patients were randomised to receive either nivolumab 240 mg (n = 353) every 2 weeks or placebo (n = 356) every 2 weeks until recurrence or unacceptable toxicity for a maximum treatment duration of 1 year. Randomisation was stratified by pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), tumour PD-L1 expression (≥ 1% vs. < 1%/indeterminate), and use of cisplatin neo-adjuvant chemotherapy. Tumour imaging assessments were to be performed every 12 weeks from the date of first dose to week 96, then every 16 weeks from week 96 to week 160, then every 24 weeks until non-urothelial tract

recurrence or treatment was discontinued (whichever occurred later) for a maximum of 5 years. The primary efficacy outcome measures were disease-free survival (DFS) in all randomised patients and DFS in randomised patients with tumours expressing PD-L1 ≥ 1%. DFS was defined as the time between the date of randomisation and the date of the first documented recurrence assessed by investigator (local urothelial tract, local non-urothelial tract or distant), or death (from any cause), whichever occurred first. Secondary efficacy outcome measures included overall survival (OS) and non-urothelial tract recurrence free survival (NUTRFS).

Baseline characteristics were generally balanced between the two groups. The median age was 67 years (range: 30 to 92), 76% were male and 76% were white. Twenty one percent had upper tract urothelial carcinoma, 43% of patients received prior cisplatin in the neo-adjuvant setting, 47% of patients were N+ at radical resection, patients had ECOG performance status of 0 (63%), 1 (35%), or 2 (2%), and 7% of patients had a haemoglobin < 10 g/dL.

Of the 709 patients, 40% had tumour cell PD-L1 expression of ≥ 1%, 59% had tumour cell PD-L1 expression of < 1%, and 1% had tumour cell PD-L1 expression indeterminate, not evaluable or not reported. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

In all randomised patients and all randomised patients with tumor cell PD-L1 expression ≥ 1%, the median follow-up was 20.9 and 22.1 months for the nivolumab arm, respectively. With a minimum follow-up of 5.9 months in the all randomised patients and a minimum follow-up of 6.3 months in randomised patients with tumours expressing PD-L1 ≥ 1%, the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab as compared to placebo, as shown in Table 29 and Figure 25.

Table 29: Efficacy Results CA209274

	All randomized nivolumab N=353	**All randomized placebo N=356**	**PD-L1 ≥ 1% nivolumab N=140**	**PD-L1 ≥ 1% placebo N=142**
Disease-Free Survival, n (%)	170 (48.2)	204 (57.3)	55 (39.3)	81 (57.0)
Median DFS	20.76	10.84	N.R	8.41
(95% CI) months[a]	(16.49, 27.63)	(8.25, 13.86)	(21.19, N.E.)	(5.59, 21.19)
HR[b]	0.70		0.55	
(alpha adjusted[c] % CI)	(0.55, 0.90)		(0.35, 0.85)	
p-value	0.0008[d]		0.0005[e]	
Rate (95%) at 6 months	74.9	60.3	74.5	55.7
	(69.9, 79.2)	(54.9, 65.3)	(66.2, 81.1)	(46.8, 63.6)

N.R. Not reached, N.E. Not estimable

[a] Based on Kaplan-Meier estimates

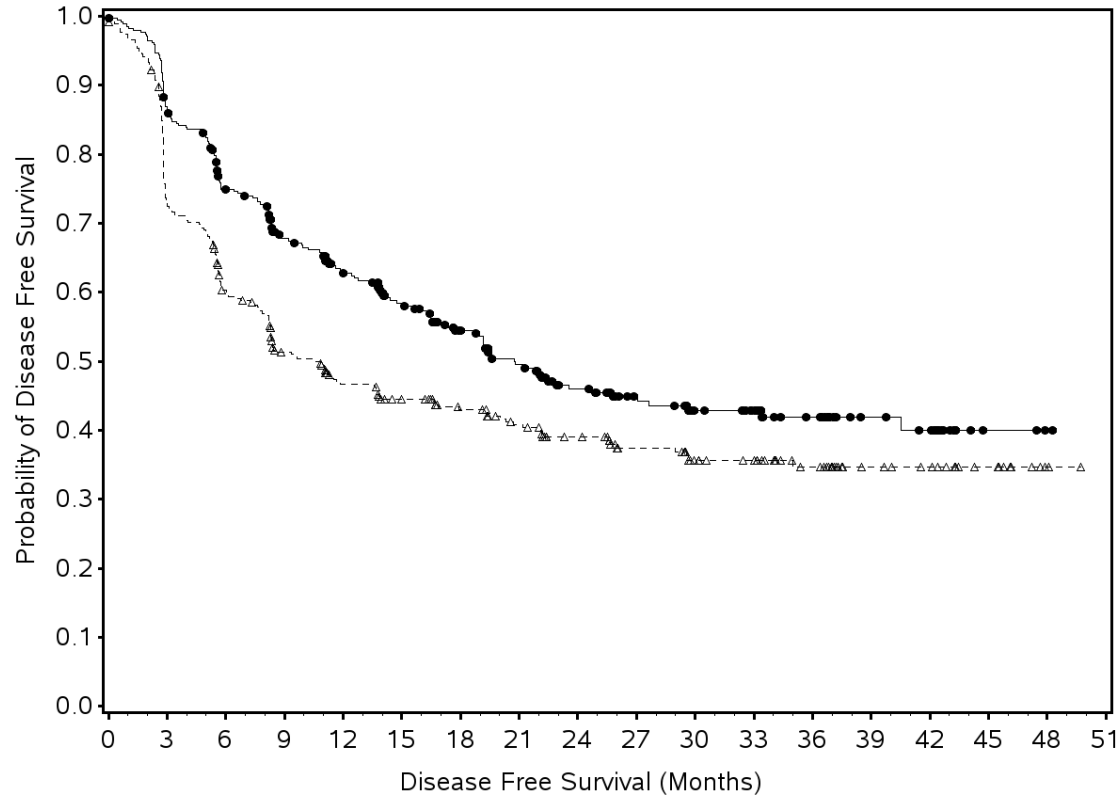
[b] Stratified Cox proportional hazard model. Hazard Ratio is nivolumab over placebo.

[c] alpha adjusted CI is 98.22% for all randomized patients and 98.72% for all randomized patients with PD-L1≥1%.

[d] Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, PD-L1 status (≥ 1% vs < 1%/indeterminate) as entered in the IRT. Boundary for statistical significance in all randomized patients: p-value < 0.01784.

[e] Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status as entered in the IRT. Boundary for statistical significance in all randomized patients with PD-L1 ≥ 1%: p-value < 0.01282.

Figure 25: Disease-Free Survival - All Randomized Patients CA209274



Number of Subjects at Risk

Placebo

356 248 198 157 134 121 105 94 80 65 54 50 37 22 19 10 2 0

Nivolumab

353 296 244 212 178 154 126 106 85 68 57 51 36 23 20 3 1 0

Placebo (events : 204/356), median and 95% CI : 10.84 (8.25, 13.86)

Nivolumab (events : 170/353), median and 95% CI : 20.76 (16.49, 27.63)

Nivolumab vs Placebo - hazard ratio (98.22% CI) : 0.70 (0.55, 0.90), p-value : 0.0008

Additional secondary outcome included non-urothelial tract recurrence free survival (NUTRFS) analysis. Treatment with nivolumab resulted in NUTRFS improvement with HR of 0.72 (95% CI:0.59, 0.89) in all randomised patients and HR of 0.55 (95% CI:0.39, 0.79) in patients with tumours expressing PD-L1 ≥ 1%.

In the subgroup of patients in all randomised with tumour cell PD-L1 <1% (n=419), the exploratory HR for DFS was 0.82 (95% CI: 0.63, 1.06) with median DFS of 16.49 and 11.07 months for the nivolumab and placebo arms, respectively.

Single-arm Phase 2 study (CA209040- second-line expansion cohort)

CA209040 is a phase 2, open-label, multi-cohort trial using nivolumab as a single agent for treatment of advanced hepatocellular carcinoma in patients previously treated with sorafenib (patients had either progressed on or were intolerant to sorafenib).

The single-arm second-line expansion cohort of this study included patients with histologic confirmation of HCC and Child-Pugh Class A at screening. Patients were enrolled regardless of PD-L1 status or aetiological subtypes; i.e., uninfected, HCV-infected, or HBV-infected. Patients with a baseline ECOG performance score > 1, active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites on physical exam, infection with HIV, or active coinfection with HBV/HCV or HBV/HDV 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. Tumour assessments were conducted every 6 weeks for 48 weeks and every 12 weeks thereafter. The primary efficacy outcome measure was confirmed ORR, as determined by blinded independent central review (BICR) using

RECIST version 1.1 and duration of action. Additional efficacy measures included ORR by BICR using modified RECIST (mRECIST) for HCC and OS.

A total of 145 patients in the single-arm expansion cohort received treatment with nivolumab. The median age was 63 years (range: 19 to 81) with 44% (64/145) ≥ 65 years of age and 11% (16/145) ≥ 75 years of age; 77% were men, and 46% were white. 50% were uninfected, 21% were infected with HCV, and 30% were infected with HBV. Baseline ECOG performance status was 0 (64%) or 1 (36%). Child-Pugh class/score was A5 for 67%, A6 for 32% and B7 for 1.4% of patients. Seventy one percent (71%) of patients had extrahepatic spread, 28% macrovascular invasion and 38% alfa-fetoprotein (AFP) levels ≥ 400 µg/L. Prior treatment history included surgical resection (66%), radiotherapy (25%), or locoregional treatment (59%). All patients had prior sorafenib with 19% of patients receiving 2 or more prior therapies. Among those patients, 23% were unable to tolerate sorafenib.

As study CA209040 was a single-arm, non-comparative study, there were limitations in the study design which did not allow firm conclusion on the benefit-risk of OPDIVO in the treatment of patients with hepatocellular carcinoma post sorafenib therapy. The efficacy results of the study, in terms of objective response rates, after a minimum follow-up of 15 months are summarized in Table 30. An improvement in survival or disease-related symptoms has not been established.

Table 30: Efficacy Results as determined by BICR- Study CA209040

	Second-line expansion cohort (n = 145)
Confirmed objective response rate, RECIST v1.1 n (%)	21 (14.5%)
(95% CI)	(9.2, 21.3)
Complete response (CR)	2 (1.4%)
Partial response (PR)	19 (13.1%)
Stable disease (SD)	60 (41.4%)
Median duration of response (range), RECIST v1.1	16.6 months (3.2, 16.8^{+})
Median time to response (range), RECIST v1.1	2.8 months (1.2, 7.0)
Confirmed objective response rate, mRECIST v1.1 n (%)	27 (18.6%)
(95% CI)	(12.6, 25.9)
Complete response (CR)	4 (2.8%)
Partial response (PR)	23 (15.9%)
Stable disease (SD)	53 (36.6%)

"$^{+}$"denotes a censored observation

The safety profile of nivolumab in CA209040 was generally similar to that observed in other tumour types, with the exception of a higher frequency of pruritus (18.6%), abdominal pain (6.2%), and hepatic and pancreatic laboratory abnormalities, including increased AST (59.2%), increased ALT (47.9%), increased total bilirubin (36.4%), increased lipase (37.1%), and increased amylase (32.1%).

Colorectal Cancer (CRC)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of dMMR or MSI-H metastatic CRC was evaluated in a Phase 2, multi-centre, open-label, single-arm study (CA209142).

The study included patients (18 years or older) with locally determined dMMR or MSI-H status, who had disease progression during, after, or were intolerant to, prior therapy with fluoropyrimidine and oxaliplatin or irinotecan. This study included patients regardless of their tumour PD-L1 status. Patients with active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 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. Tumour assessments according to RECIST version 1.1 were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures included confirmed ORR as determined by an IRRC, duration and timing of responses, PFS, and OS.

The median age was 53 years (range: 26 to 79) with 23% ≥ 65 years of age and 5% ≥ 75 years of age, 59% were male and 88% were white. Baseline ECOG performance status was 0 (43%), 1 (55%), or 3 (1.4%) and 36% were reported to have Lynch Syndrome. Across the 74 patients, 72% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 15%, 30%, 30%, and 24% received 1, 2, 3, or ≥ 4 prior lines of therapy, respectively, and 42% of patients had received an anti-EGFR antibody.

Efficacy results based on a minimum follow-up of approximately 6 months are shown in Table 31.

Table 31: Efficacy results (CA209142)

	All patients (n = 74)	**Prior treatment with Fluoropyrimidine, Oxaliplatin, and Irinotecan (n=53)**
Confirmed objective response, n (%)	20 (27.0)	12 (22.6)
(95% CI)	(17.4, 38.6)	(12.3, 36.2)
Complete response (CR), n (%)	2 (2.7)	1 (1.9)
Partial response (PR), n (%)	18 (24.3)	11 (20.8)
Stable disease (SD), n (%)	28 (37.8)	19 (35.8)
Median duration of response		
Months (range)	Not reached (1.8^+, 22.0^+)	Not reached (1.8^+, 16.6^+)
Median time to response		
Months (range)	2.71 (1.2, 17.7)	2.79 (1.2, 17.7)
Disease control rate[a], n (%)	46 (62.2)	30 (56.6)
(95% CI)	(50.1, 73.2)	(42.3, 70.2)
Progression-free survival		
Events	35	27
Median (months) (95% CI)	7.6 (3.0, NA)	4.9 (1.5, NA)
Overall survival		
Events	19	15
Median (months) (95% CI)	NA (17.1, NA)	NA (16.3, NA)
6-month rate (%) (95% CI)	83.4 (72.5, 90.2)	80.5 (66.7, 89.0)
12-month rate (%) (95% CI)	73.8 (59.8, 83.5)	69.8 (52.4, 81.9)

"+" denotes a censored observation.

[a] CR + PR + SD (for at least 12 weeks).

Confirmed responses were observed regardless of tumour PD-L1 expression levels.

Patient-reported outcomes (PROs) were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire and 3-level EQ-5D. The majority of patients did not experience any meaningful deterioration in functioning, symptoms, or overall health status during follow-up. As early as 13 weeks after initiating treatment, subjects exhibited meaningful improvements (ie. mean change ≥ 10 points) in emotional, role, and social functioning, with improvements remaining fairly consistent over time. Meaningful improvements in symptoms of fatigue, pain, insomnia, appetite loss, constipation, and diarrhea, as well as financial difficulties, were also observed. Patients who continued treatment for 19 weeks achieved a level of health as indicated by the EQ-5D visual analogue scale that would be regarded as equal to or exceeding the general health of many populations. These PRO data should be interpreted cautiously in the context of the open-label study design.

The overall safety profile of nivolumab 3mg/kg in dMMR or MSI-H metastatic colorectal cancer patients was consistent with that established across tumour types for nivolumab monotherapy.

Safety and efficacy in elderly patients

No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from NSCLC and SCCHN, and adjuvant melanoma patients 75 years of age or older are too limited to draw conclusions on this population. Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population. Data from MPM patients showed a higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older (68% and 35%, respectively) relative to all patients who received nivolumab in combination with ipilimumab (54% and 28%, respectively).

For patients treated with nivolumab in combination with cabozantinib, data from RCC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of nivolumab is linear in the dose range of 0.1 to 10 mg/kg. The geometric mean clearance (CL), terminal half-life, and average exposure at steady state at 3 mg/kg every 2 weeks of nivolumab were 9.5 mL/h, 26.7 days, and 75.3 μg/mL, respectively, based on a population PK analysis.

Nivolumab CL increased with increasing body weight. Body weight normalised 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 characterised. Nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

OPDIVO in combination with ipilimumab: The geometric mean CL, Vss, and terminal half-life of nivolumab were 9.83 mL/h, 7.62 L, and 24.1 days, respectively. When administered in combination, the CL of nivolumab was increased by 35%, whereas there was no effect on the CL of ipilimumab.

When administered in combination, the CL of nivolumab increased by 25% in the presence of anti-nivolumab antibodies. There was no effect of anti-ipilimumab antibodies on the CL of ipilimumab.

Special populations

A population PK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumour type, tumour size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful.

Renal impairment
The effect of renal impairment on the CL of nivolumab was evaluated in patients with mild (GFR < 90 and ≥ 60 mL/min/1.73 m^2; n = 379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 m^2; n = 179), or severe (GFR < 30 and ≥ 15 mL/min/1.73 m^2; n = 2) renal impairment compared to patients with normal renal function (GFR ≥ 90 mL/min/1.73 m^2; n = 342) in population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 4.2).

Hepatic impairment
The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 92) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 804) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in patients with moderate (total bilirubin > 1.5 × to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST) (see section 4.2).

5.3 Preclinical safety data

Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to increase foetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels either 8 or 35 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). There was a dose-dependent increase in foetal losses and increased neonatal mortality beginning in the third trimester.

The remaining offspring of nivolumab-treated females survived to scheduled termination, with no treatment-related clinical signs, alterations to normal development, organ-weight effects, or gross and microscopic pathology changes. Results for growth indices, as well as teratogenic, neurobehavioral, immunological, and clinical pathology parameters throughout the 6-month postnatal period were comparable to the control group. However, based on its mechanism of action, foetal exposure to nivolumab may increase the risk of developing immune-related disorders or altering the normal immune response and immune-related disorders have been reported in PD-1 knockout mice.

Fertility studies have not been performed with nivolumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
Sodium chloride
Mannitol (E421)
Pentetic acid (diethylenetriaminepentaacetic acid)
Polysorbate 80
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. OPDIVO should not be infused concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

Unopened vial
3 years.

After opening
From a microbiological point of view, once opened, the medicinal product should be prepared for infusion immediately.

After preparation of infusion
From a microbiological point of view, the product should be used immediately.
If not used immediately, chemical and physical in-use stability of OPDIVO has been demonstrated for 7 days at 2ºC to 8ºC protected from light and a maximum of 8 hours at 20°C-25°C and room light (this 8-hour period of the total 7 days should be inclusive of the product administration period).

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after preparation of the infusion, see section 6.3.

6.5 Nature and contents of container

4 mL of concentrate in a 10 mL vial (Type I glass) with a stopper (coated butyl rubber) and a dark blue flip-off seal (aluminium). Pack size of 1 vial.
10 mL of concentrate in a 10 mL vial (Type I glass) with a stopper (coated butyl rubber) and a grey flip-off seal (aluminium). Pack size of 1 vial.
12 mL of concentrate in a 25 mL vial (Type I glass) with a stopper (coated butyl rubber) and a blue flip-off seal (aluminium). Pack size of 1 vial.
24 mL of concentrate in a 25R vial (Type I glass) with a stopper (coated butyl rubber) and a red matte flip-off seal (aluminium). Pack size of 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Preparation and administration

Calculating the dose
More than one vial of OPDIVO concentrate may be needed to give the total dose for the patient.

When the prescribed dose for the patient is 3 mg/kg or 1 mg/kg, calculate the total dose to be given.
- The total nivolumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The volume of OPDIVO concentrate to prepare the dose (mL) = the total dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

When the prescribed dose for the patient is 240 mg, 360 mg or 480 mg, it is given regardless of body weight.

Preparing the infusion
Take care to ensure aseptic handling when you prepare the infusion. The infusion should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents.

OPDIVO can be used for intravenous administration either:
- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting with either sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection, according to the following instructions:
  - the final infusion concentration should range between 1 to 10 mg/mL
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kilogram of patient weight

STEP 1
- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake the vial.
  OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid. Discard the vial if the solution is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of OPDIVO concentrate using an appropriate sterile syringe.

STEP 2
- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Gently mix the infusion by manual rotation. Do not shake.

Administration
OPDIVO infusion must not be administered as an intravenous push or bolus injection.
Administer the OPDIVO infusion intravenously over a period of 30-60 minutes.

OPDIVO infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm).

OPDIVO infusion is compatible with:
- PVC containers
- Polyolefin containers
- Glass bottles
- PVC infusion sets
- In-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

After administration of the nivolumab dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

Disposal
Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb (S) Pte Ltd
80 Marine Parade Road,
#20-01/09 Parkway Parade,
Singapore 449269

8. DATE OF REVISION OF THE TEXT

February 2023