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 and adolescents 12 years of age and older.

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).

Adjuvant treatment of melanoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see section 5.1).

Non-Small Cell Lung Cancer (NSCLC)

OPDIVO, in combination with ipilimumab and 2 cycles of platinum-based chemotherapy, is indicated for the first-line treatment of metastatic 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.

Neoadjuvant and adjuvant treatment of NSCLC

OPDIVO, in combination with platinum-doublet chemotherapy as neoadjuvant treatment, followed by monotherapy as adjuvant treatment, is indicated in adult patients with resectable (tumors ≥4 cm or node positive) NSCLC and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements.

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 in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥1%.

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥1%.

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

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).

Hepatocellular carcinoma (HCC)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma.

Urothelial carcinoma

OPDIVO, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

OPDIVO as monotherapy is indicated for the 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.

Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable or metastatic colorectal cancer.

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.

Melanoma (advanced or adjuvant treatment)

Indication	**Recommended dose and infusion time**
• Treatment of advanced melanoma • Adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection	3 mg/kg every 2 weeks over 30-60 minutes
• Adjuvant treatment of Stage IIB or IIC melanoma who have undergone complete resection	Adults and adolescents (12 years of age and older and weighing at least 50 kg): 240 mg every 2 weeks over 30-60 minutes or 480 mg every 4 weeks over 30-60 minutes
	Adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30-60 minutes or 6mg/kg every 4 weeks over 60 minutes

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.

dMMR or MSI H colorectal cancer
The recommended dose for first-line treatment of dMMR or MSI H CRC is 240 mg of nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks over 30 minutes for a maximum of 4 doses, followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks over 30 minutes or at 480 mg every 4 weeks over 30 minutes. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Oesophageal squamous cell carcinoma
The recommended dose is either 3 mg/kg nivolumab every 2 weeks or 360 mg nivolumab every 3 weeks administered intravenously over 30-60 minutes in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Hepatocellular carcinoma
The recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for up to 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks (see

sections 5.1 and 5.2), as presented in Table 1. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months. For the monotherapy phase, the first dose of nivolumab should be administered:

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

Table 1: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for HCC

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

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).

Neoadjuvant and adjuvant treatment of non-small cell lung cancer
The recommended dose in the neoadjuvant phase is 360 mg nivolumab administered intravenously over 30 minutes in combination with platinum-doublet chemotherapy every 3 weeks for up to 4 cycles or until disease progression or unacceptable toxicity. This is then followed after surgery by nivolumab 480 mg administered intravenously over 30 minutes every 4 weeks as monotherapy in the adjuvant phase for up to 13 cycles or until disease recurrence or unacceptable toxicity.

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.

Oesophageal squamous cell carcinoma
The recommended dose of nivolumab is 240 mg every 2 weeks or 480 mg every 4 weeks administered intravenously over 30-60 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

First-line treatment of unresectable or metastatic urothelial carcinoma
The recommended dose of nivolumab is 360 mg administered intravenously over 30-60 minutes in combination with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks over 30-60 minutes **or** at 480 mg every 4 weeks over 30-60 minutes. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months from first dose, whichever comes first.

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

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

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 2. 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 2: 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 without HCC **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 hepatitis with HCC	If AST/ALT is within normal limits at baseline and increases to > 3 and ≤ 10 times ULN or Baseline AST/ALT is > 1 and ≤ 3 times ULN and increases to > 5 and ≤ 10 times ULN or Baseline AST/ALT is > 3 and ≤ 5 times ULN and increases to > 8 and ≤ 10 times ULN	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	AST/ALT increases to > 10 times ULN or Total bilirubin increases to > 3 times ULN	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

Table 2:	**Recommended treatment modifications for OPDIVO or OPDIVO in combination with other therapeutic agents**	
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis	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 2 adrenal insufficiency Grade 3 diabetes	
	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
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.

When OPDIVO is administered in combination with chemotherapy, refer to the product information of the other combination therapy agents regarding dosing. If any agents are withheld, the other agents may be continued. If dosing is resumed after a delay, either the combination treatment, OPDIVO monotherapy or chemotherapy alone could be resumed based on the evaluation of the individual patient.

OPDIVO in combination with cabozantinib in RCC
When nivolumab is used in combination with cabozantinib, the above treatment modifications in Table 2 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.

Special populations

Paediatric population
The safety and efficacy of OPDIVO in children below 18 years of age have not been established, except in adolescents 12 years of age and older with melanoma.

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 or moderate hepatic impairment (see section 5.2). Data from patients with severe hepatic impairment are too limited to draw conclusions on this population. OPDIVO must be administered with caution in patients with severe (total bilirubin >3 x ULN and any AST) hepatic impairment.

Method of administration

OPDIVO is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30-60 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. 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.

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, Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome, 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.

Cases of Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome (presenting as an overlap of either two or all three conditions), some with fatal outcome, have been reported with nivolumab and nivolumab in combination with other therapeutic agents. Early recognition and aggressive management are essential to address associated morbidity and risk of mortality.

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).

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

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

- patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 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.

Neoadjuvant and adjuvant treatment of non-small cell lung cancer
Patients with a baseline performance score ≥ 2, Grade 2 or greater peripheral neuropathy, 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, who had EGFR mutations or known ALK translocations, or who had brain metastasis, were excluded from the pivotal trial in neoadjuvant and adjuvant treatment of NSCLC (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.

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 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)

First-line treatment of OSCC
Patients with a baseline performance score ≥ 2, any history of concurrent brain metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the clinical trial in OSCC (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with ipilimumab or chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

In the first-line OSCC trial, a higher number of deaths within 4 months was observed with nivolumab in combination with ipilimumab compared to chemotherapy. Physicians should consider the delayed onset of effect

of nivolumab in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease such as presenting liver metastases. Additionally, other potential prognostic factors that were associated with early death included baseline neutrophil/lymphocyte ratio ≥ 4, high tumor burden and ECOG performance score 1.

Treatment of OSCC after prior first-line chemotherapy
The majority of clinical data available in oesophageal squamous cell carcinoma are in patients of Asian origin (see section 5.1).
Patients with a baseline performance score ≥ 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.

Hepatocellular carcinoma
Patients who had baseline ECOG performance score ≥ 2, prior liver transplant, Child-Pugh C liver disease, a history of concurrent brain metastases, a history of hepatic encephalopathy (within 12 months of randomisation), clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in HCC (see sections 4.5 and 5.1). Limited data are available in HCC patients with Child-Pugh B. In the absence of data, nivolumab in combination with ipilimumab followed by nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

In HCC, a higher number of deaths within 6 months was observed with nivolumab in combination with ipilimumab compared to lenvatinib or sorafenib. A higher risk of death may be associated with poor prognostic features. Physicians should consider this risk before initiating treatment with nivolumab in combination with ipilimumab in patients with poor prognostic features.

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.

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

In randomized clinical trials in patients with multiple myeloma, the addition of a PD-1 blocking antibody, including nivolumab, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

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=4646) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (44%), musculoskeletal pain (28%), diarrhoea (26%), rash (24%), cough (22%), nausea (22%), pruritus (19%), decreased appetite (17%), arthralgia (17%), constipation (16%), dyspnoea (16%), abdominal pain (15%), upper respiratory tract infection (15%), pyrexia (13%), headache (13%),anaemia (13%) and vomiting (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). The incidence of Grade 3-5 adverse reactions was 44%, with 0.3% fatal adverse reactions attributed to study drug. With a minimum of 63 months follow-up in NSCLC, no new safety signals were identified.

Adverse reaction frequencies in the paragraph above and in Table 3 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=4646) 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 monotherapy

	Nivolumab monotherapy
Infections and infestations	
Very common	upper respiratory tract infection
Common	pneumonia[a], bronchitis
Rare	aseptic meningitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Very common	lymphopenia[b], anaemia[b,g], leucopoenia[b], neutropaenia[a,b] , thrombocytopenia[b]
Uncommon	eosinophilia
Immune system disorders	
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity (including anaphylactic reaction)
Uncommon	sarcoidosis
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism, thyroiditis
Uncommon	adrenal insufficiency[h], hypopituitarism, hypophysitis, diabetes mellitus
Rare	diabetic ketoacidosis, hypoparathyroidism
Metabolism and nutrition disorders	
Very common	decreased appetite, hyperglycaemia[b]
Common	dehydration, weight decreased, hypoglycaemia[b]
Uncommon	metabolic acidosis
Nervous system disorders	
Very common	headache
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome[m]
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,i]
Eye disorders	
Common	blurred vision, dry eye
Uncommon	uveitis
Cardiac disorders	
Common	tachycardia, atrial fibrillation
Uncommon	myocarditis[a] , pericardial disorders[f], arrhythmia (including ventricular arrhythmia),
Vascular disorders	
Common	hypertension
Rare	vasculitis
Respiratory, thoracic and mediastinal disorders	
Very common	dyspnoea[a], cough

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

Adverse reaction frequencies presented in Table 3 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] 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] Rash is a composite term which includes rash maculopapular, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular,rash vesicular, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.

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

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

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

[g] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia, haemoglobin decreased, iron deficiency anaemia and red blood cell count decreased.

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

[i] Includes encephalitis and limbic encephalitis

[j] Oedema is a composite term which includes generalised oedema, oedema peripheral, peripheral swelling and swelling.

[m] Cases of Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome (presenting as an overlap of either two or all three conditions), some with fatal outcome, have been reported with nivolumab and nivolumab in combination with other therapeutic agents (see section 4.4).

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.

Nivolumab in combination with ipilimumab (with or without chemotherapy)

In the pooled dataset of nivolumab administered in combination with ipilimumab (with or without chemotherapy) across tumour types (n = 2626) with minimum follow-up ranging from 6 to 47 months, the most frequent adverse reactions (≥ 10%) were fatigue (47%), rash (37%), diarrhoea (35%), nausea (27%), pruritus (29%), musculoskeletal pain (26%), pyrexia (23%), decreased appetite (22%), cough (21%), abdominal pain (18%), vomiting (18%), constipation (18%), arthralgia (18%), dyspnoea (17%), hypothyroidism (16%), headache (15%), upper respiratory tract infection (13%), oedema (13%), and dizziness (10%). The incidence of Grade 3-5 adverse reactions was 66% for nivolumab in combination with ipilimumab (with or without chemotherapy), with 1.0% fatal adverse reactions attributed to study drug. Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, fatigue (62%), rash (57%), diarrhoea (52%), nausea (42%), pruritus (40%), pyrexia (36%), and headache (26%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate. Among patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy for NSCLC, anaemia (32%) and neutropaenia (15%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate.

Nivolumab in combination with chemotherapy

In the pooled dataset of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy across tumour types (n=1800), with a minimum follow-up ranging from 7.4 to 23.6 months, or following 3 cycles of treatment for resectable NSCLC, the most frequent adverse reactions (≥10%) were nausea (48%), fatigue (40%), peripheral neuropathy (33%), decreased appetite (31%), constipation (31%), diarrhoea (28%), vomiting (24%), rash (19%), abdominal pain (18%), stomatitis (18%), musculoskeletal pain (18%), pyrexia (16%), cough (13%), edema (including peripheral edema) (12%),and pruritus (11%). Incidences of Grade 3-5 adverse reactions were 69% for nivolumab in combination with chemotherapy, with 1.2% fatal adverse reactions attributed to nivolumab in combination with chemotherapy. Median duration of therapy was 6.14 months (95% CI: 5.78, 6.60) for nivolumab in combination with chemotherapy. For resectable NSCLC, ninety-three percent (93%) of patients received 3 cycles of nivolumab in combination with chemotherapy. Four fatal cases of pneumonitis were reported in patients treated with nivolumab in combination with chemotherapy in gastric cancer, GEJ cancer or oesophageal adenocarcinoma.

Nivolumab in combination with cabozantinib (see section 4.2)

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%), dysgeusia (23.8%), upper respiratory tract infection (20.6%), cough (20.6%), pruritus (20.6%), arthralgia (19.4%), vomiting (18.4%), dysphonia (17.8%), headache (16.3%), dyspepsia (15.9%), dizziness (14.1%), constipation (14.1%), pyrexia (14.1%), oedema (13.4%), muscle spasm (12.2%), dyspnoea (11.6%), proteinuria (10.9%) and hyperthyroidism (10.0%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). The incidence of Grade 3-5 adverse reactions was 78%, with 0.3% fatal adverse reactions attributed to study drug.

Tabulated summary of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy) (n = 2626), nivolumab in combination with chemotherapy (n =1800), and nivolumab in combination with cabozantinib (n = 320) 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

	Combination with ipilimumab (with or without chemotherapy)	**Combination with chemotherapy**	**Combination with cabozantinib**
Infections and infestations			
Very common	upper respiratory tract infection		upper respiratory tract infection
Common	pneumonia, bronchitis, conjunctivitis	upper respiratory tract infection, pneumonia[a]	pneumonia
Rare	aseptic meningitis		
Blood and lymphatic system disorders			
Very common	anaemia[b,i], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]	neutropaenia[b], anaemia[b,i], leucopoenia[b], lymphopaenia[b], thrombocytopaenia[b]	anaemia[b], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]
Common	eosinophilia	febrile neutropaenia[a]	eosinophilia
Uncommon	febrile neutropenia	eosinophilia	
Immune system disorders			
Common	infusion-related reaction (including cytokine release syndrome), hypersensitivity	hypersensitivity, infusion related reaction (including cytokine release syndrome)	hypersensitivity (including anaphylactic reaction)
Uncommon			infusion related hypersensitivity reaction
Rare	sarcoidosis		
Endocrine disorders			
Very common	hypothyroidism		hypothyroidism, hyperthyroidism
Common	hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, hypopituitarism, diabetes mellitus	hypothyroidism, hyperthyroidism, diabetes mellitus	adrenal insufficiency
Uncommon	diabetic ketoacidosis	adrenal insufficiency, thyroiditis, hypopituitarism, hypophysitis	hypophysitis, thyroiditis
Rare	hypoparathyroidism		
Metabolism and nutrition disorders			
Very common	decreased appetite, hyperglycaemia[b], hypoglycaemia[b]	decreased appetite, , hyperglycaemia[b], hypoglycaemia[b]	decreased appetite, hypoglycaemia[b], hyperglycaemia[b], weight decreased
Common	dehydration, hypoalbuminemia, hypophosphatemia, weight decreased	hypoalbuminaemia, hypophosphataemia	dehydration
Uncommon	metabolic acidosis		
Rare		tumour lysis syndrome	
Nervous system disorders			
Very common	headache	peripheral neuropathy	dysgeusia, dizziness, headache
Common	dizziness, peripheral neuropathy	paraesthesia, dizziness, headache	peripheral neuropathy

Uncommon	polyneuropathy, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis, myasthenia gravis, Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome[k]	Guillain-Barré syndrome,	encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Rare	Guillain-Barré syndrome, neuritis, myelitis (including transverse myelitis)	encephalitis, Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome[k]	
Ear and labyrinth disorders			
Common			tinnitus
Eye disorders			
Common	blurred vision,dry eye	dry eye, blurred vision	dry eye, blurred vision
Uncommon	uveitis, episcleritis	uveitis	uveitis
Rare	Vogt-Koyanagi-Harada syndrome		
Cardiac disorders			
Common	tachycardia, atrial fibrillation	tachycardia, atrial fibrillation	atrial fibrillation, tachycardia
Uncommon	myocarditis[a], arrhythmia (including ventricular arrhythmia)[a], bradycardia	myocarditis	myocarditis
Vascular disorders			
Very Common			hypertension
Common	hypertension	thrombosis[a,j], hypertension, vasculitis	thrombosis[j]
Respiratory, thoracic and mediastinal disorders			
Very common	cough, dyspnoea	cough	dysphonia, dyspnoea, cough
Common	pneumonitis[a], pulmonary embolism[a], pleural effusion	pneumonitis[a], dyspnoea	pneumonitis, pulmonary embolism, pleural effusion, epistaxis
Gastrointestinal disorders			
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation	diarrhoea[a], stomatitis, vomiting, nausea, abdominal pain, constipation	diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia
Common	colitis[a], pancreatitis, stomatitis, gastritis, dry mouth	colitis, dry mouth	colitis, gastritis, oral pain, dry mouth, haemorrhoids
Uncommon	duodenitis	pancreatitis	pancreatitis, small intestine perforation[a], glossodynia
Rare	intestinal perforation[a], pancreatic exocrine insufficiency, coeliac disease		
Hepatobiliary disorders			
Common	hepatitis		hepatitis
Uncommon		hepatitis	
Skin and subcutaneous tissue disorders			

Very common	rash[c], pruritus	rash[c], pruritus	palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus
Common	alopecia, vitiligo, urticaria, dry skin, erythema	palmar-plantar erythrodysaesthaesia syndrome, skin hyperpigmentation, alopecia, dry skin, erythema	alopecia, dry skin, erythema, hair colour change
Uncommon	Stevens-Johnson syndrome, erythema multiforme, psoriasis, other lichen disorders[d]		psoriasis, urticaria
Rare	toxic epidermal necrolysis[a,c], lichen sclerosus		
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[f], arthralgia	musculoskeletal pain[f]	musculoskeletal pain[f], arthralgia, muscle spasm
Common	muscle spasms, muscular weakness, arthritis	arthralgia, muscular weakness	arthritis
Uncommon	polymyalgia rheumatica, myopathy, myositis (including polymyositis)[a]		myopathy, osteonecrosis of the jaw, fistula
Rare	spondyloarthropathy, Sjogren's syndrome, rhabdomyolysis[a]		
Renal and urinary disorders			
Very common			proteinuria
Common	renal failure (including acute kidney injury)[a]	renal failure[a]	renal failure, acute kidney injury
Uncommon	tubulointerstitial nephritis, nephritis	cystitis noninfective, nephritis	nephritis
Rare	cystitis noninfective		cystitis noninfective[h]
General disorders and administration site conditions			
Very common	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema
Common	chest pain, pain, chills	malaise	pain, chest pain
Investigations			
Very common	increased alkaline phosphatase[b], increased AST[b], increased ALT[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hyponatraemia[b], hyperkalaemia[b] hypokalemia[b], hypercalcaemia[b], hypocalcaemia[b]	hypocalcaemia[b], increased AST[b], increased ALT[b], hyponatraemia[b], increased amylase[b], hypomagnesaemia[b], increased alkaline phosphatase[b], hypokalaemia[b], increased creatinine[b], increased lipase[b], hyperkalaemia[b], increased total bilirubin[b]	increased alkaline phosphatase[b], increased ALT[b], increased AST[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hypokalaemia[b], hypomagnesaemia[b], hyponatraemia[b], hypocalcaemia[b], hypercalcaemia[b], hypophosphataemia[b], hyperkalaemia[b], hypermagnesaemia[b], hypernatraemia[b]

Common	hypernatraemia[b], hypermagnesaemia[b], increased thyroid stimulating hormone, increased gamma-glutamyltransferase	hypernatraemia[b], hypercalcaemia[b], hypermagnesaemia[b]	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 4 may not be fully attributable to nivolumab alone or in combination with other therapeutic agents, but may contain contributions from the underlying disease or from medicinal product used in combination.

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

[d] Lichen disorders is a composite term which includes lichen keratosis and lichen planus.

[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, myalgia intercostal, neck pain, pain in extremity, and spinal pain.

[g] Reported in clinical studies and in the post-marketing setting.

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

[i] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia, haemoglobin decreased, iron deficiency anaemia and red blood cell decreased.

[j] 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.

[k] Cases of Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome (presenting as an overlap of either two or all three conditions), some with fatal outcome, have been reported with nivolumab and nivolumab in combination with other therapeutic agents (see section 4.4).

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. Table 5 presents the percentage of patients who for immune-related adverse reactions were discontinued from treatment by dosing regimen. Additionally, for patients who experienced an event, Table 5 presents the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents) by dosing regimen. The management guidelines for these adverse reactions are described in section 4.4.

Table 5: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab monotherapy or nivolumab in combination with other therapeutic agents)

	Nivolumab monotherapy %	Nivolumab in combination with ipilimumab (with or without chemotherapy) %	Nivolumab in combination with chemotherapy %	Nivolumab in combination with cabozantinib %
Immune-related adverse reaction leading to permanent discontinuation				
Pneumonitis	1.4	2.1	2.0	2.5
Colitis	1.2	6	1.8	2.5
Hepatitis	1.1	5	0.7	4.1
Nephritis and renal dysfunction	0.3	1.1	3.1	0.6
Endocrinopathies	0.5	2.2	0.6	1.3
Skin	0.8	1.0	0.9	2.2
Hypersensitivity/Infusion reaction	0.1	0.3	1.7	0
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]				

Pneumonitis	65	59	59	56
Colitis	14	32	9	8
Hepatitis	21	39	7	23
Nephritis and renal dysfunction	22	27	9	9
Endocrinopathies	5	18	4.3	4.2
Skin	3.3	8	6	8
Hypersensitivity/Infusion reaction	18	18	22	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 3.3% (155/4646). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (42/4646) and 1.7% (77/4646) of patients, respectively. Grade 3 and 4 cases were reported in 0.7% (33/4646) and <0.1% (1/4646) of patients respectively. No Grade 5 cases were reported. Six patients (0.1%) had a fatal outcome. Median time to onset was 15.1 weeks (range: 0.7-85.1). Resolution occurred in 107 patients (69.0%) with a median time to resolution of 6.7 weeks (range: 0.1^{+}-109.1^{+}); $^{+}$ denotes a censored observation.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of pneumonitis including interstitial lung disease was 6.0% (157/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 3.0% (78/2626), 1.0% (27/2626), and 0.3% (8/2626) of patients, respectively. Four patients (0.2%) had a fatal outcome. Median time to onset was 2.7 months (range: 0.1-56.8). Resolution occurred in 129 patients (82.2%) with a median time to resolution of 6.1 weeks (range: 0.1^{+}-149.3^{+}).

In patients treated with nivolumab in combination with chemotherapy, the incidence of pneumonitis including interstitial lung disease was 4.4% (80/1800). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (40/1800), 0.9% (17/1800), and 0.2% (3/1800), of patients, respectively. Three patients (0.2%) had a fatal outcome. Median time to onset was 24.6 weeks (range: 0.6-96.9). Resolution occurred in 58 patients (72.5%) with a median time to resolution of 10.4 weeks (range: 0.3^{+}-171.4^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of pneumonitis including interstitial lung disease was 5.6% (18/320). Grade 2 and Grade 3 cases were reported in 1.9% (6/320) and 1.6% (5/320), of patients, respectively. 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).

Immune-related colitis

In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, and frequent bowel movements was 15.4% (716/4646). The majority of cases were Grade 1 or 2 in severity reported in 9.9% (462/4646) and 4.0% (186/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.4% (67/4646) and <0.1% (1/4646) of patients. No Grade 5 cases were reported. Median time to onset was 8.3 weeks (range: 0.1-115.6). Resolution occurred in 639 patients (90.3%) with a median time to resolution of 2.9 weeks (range: 0.1-124.4^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of diarrhoea or colitis was 26.0% (682/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 8.1% (212/2626), 6.4% (167/2626), and 0.2% (4/2626), of patients, respectively. Two patients (<0.1%) had a fatal outcome. Median time to onset was 1.4 months (range: 0.0-48.9). Resolution occurred in 618 patients (91%) with a median time to resolution of 2.9 weeks (range: 0.1-170.0^{+}). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, the incidence of diarrhoea or colitis was 46.7%, including Grade 2 (13.6%), Grade 3 (15.8%), and Grade 4 (0.4%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of diarrhoea or colitis was 22.5% (405/1800). Grade 2, Grade 3, and Grade 4 cases were reported in 7.2% (130/1800), 3.1% (56/1800), and 0.3% (6/1800) of patients, respectively. One patient (< 0.1%) had a fatal outcome. Median time to onset was 4.4 weeks (range: 0.1-93.6). Resolution occurred in 357 patients (88.6%) with a median time to resolution of 1.6 weeks (range: 0.1-212.3^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of diarrhoea, colitis, frequent bowel movements or enteritis was 59.1% (189/320). Grade 2 and Grade 3 cases were reported in 25.6% (82/320)

and 6.3% (20/320) of patients, respectively. Grade 4 were reported in 0.6% (2/320). Median time to onset was 12.9 weeks (range: 0.3-110.9 weeks). Resolution occurred in 143 patients (76.1%) with a median time to resolution of 12.9 weeks (range: 0.1-139.7^{+} weeks).

Immune-related hepatitis
In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 8.0% (371/4646). The majority of cases were Grade 1 or 2 in severity reported in 4.3% (200/4646) and 1.8% (82/4646) of patients, respectively. Grade 3 and Grade 4 cases were reported in 1.6% (74/4646) and 0.3% (15/4646) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 10.6 weeks (range: 0.1-132.0). Resolution occurred in 298 patients (81.4%) with a median time to resolution of 6.1 weeks (range: 0.1-126.4^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of liver function test abnormalities was 21.2% (556/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 5.0% (132/2626), 8.3% (218/2626), and 1.3% (34/2626) of patients, respectively. Seven patients (0.3%) had a fatal outcome. Median time to onset was 1.5 months (range: 0.0-36.6). Resolution occurred in 482 patients (87.0%) with a median time to resolution of 5.9 weeks (range: 0.1-175.9^{+}). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, the incidence of liver function test abnormalities was 30.1% including Grade 2 (6.9%), Grade 3 (15.8%), and Grade 4 (1.8%). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for HCC, the incidence of liver function test abnormalities was 34.3% including Grade 2 (8.4%), Grade 3 (14.2%), and Grade 4 (2.7%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of liver function test abnormalities was 18% (322/1800). Grade 2, Grade 3 and Grade 4 cases were reported in 5.1% (92/1800), 2.6% (47/1800) and < 0.1% (1/1800) of patients, respectively. Median time to onset was 7.0 weeks (range: 0.1-99.0). Resolution occurred in 258 patients (81.1%) with a median time to resolution of 7.4 weeks (range: 0.4-240.0^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of liver function test abnormalities was 41.6% (133/320). Grade 2, Grade 3, and Grade 4 cases were reported in 14.7% (47/320), 10.3% (33/320), and 0.6% (2/320) of patients, respectively. Median time to onset was 8.3 weeks (range: 0.1-107.9 weeks). Resolution occurred in 101 patients (75.9%) with a median time to resolution of 9.6 weeks (range: 0.1-89.3^{+} weeks).

Immune-related nephritis and renal dysfunction
In patients treated with nivolumab monotherapy, the incidence of nephritis and renal dysfunction was 2.6% (121/4646). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (69/4646) and 0.7% (32/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (18/4646) and <0.1% (2/4646) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported in these studies. Median time to onset was 12.1 weeks (range: 0.1-79.1). Resolution occurred in 80 patients (69.0%) with a median time to resolution of 8.0 weeks (range: 0.3^{+}-79.1^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of nephritis or renal dysfunction was 5.4% (141/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 2.0% (52/2626), 0.8% (21/2626), and 0.4% (11/2626) of patients, respectively. Two patients (< 0.1%) had a fatal outcome. Median time to onset was 2.6 months (range: 0.0-34.8). Resolution occurred in 110 patients (78.0%) with a median time to resolution of 5.9 weeks (range: 0.1-172.1^{+}).

In patients treated with nivolumab in combination with chemotherapy, the incidence of nephritis or renal dysfunction was 10.9% (196/1800). Grade 2, Grade 3, and Grade 4 cases were reported in 3.7% (66/1800), 1.4% (25/1800), and 0.2% (3/1800) of patients, respectively. Two patients (0.1%) had a fatal outcome. Median time to onset was 6.7 weeks (range: 0.1-60.7). Resolution occurred in 133 patients (67.9%) with a median time to resolution of 9.1 weeks (range: 0.1-226.0^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of nephritis, immune mediated nephritis, renal failure, acute kidney injury, blood creatinine increased or blood urea increased was 10.0% (32/320). Grade 2 and Grade 3 cases were reported in 3.4% (11/320), and 1.3% (4/320) of patients, respectively. Median time to onset was 14.2 weeks (range: 2.1-87.1 weeks). Resolution occurred in 18 patients (58.1%) with a median time to resolution of 10.1 weeks (range: 0.6-90.9^{+} weeks).

Immune-related endocrinopathies
In patients treated with nivolumab monotherapy, the incidence of thyroid disorders including hypothyroidism and hyperthyroidism was 13.0% (603/4646). The majority of cases were Grade 1 or 2 in severity reported in 6.6% (305/4646) and 6.2% (290/4646) of patients, respectively. Grade 3 thyroid disorders were reported in 0.2% (8/4646) of patients. Hypophysitis (3 Grade 1, 7 Grade 2, 9 Grade 3, and 1 Grade 4), hypopituitarism (6 Grade 2

and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute and blood corticotrophin decreased) (2 Grade 1, 23 Grade 2, and 11 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) (1 Grade 1, 3 Grade 2 and 8 Grade 3 and 2 Grade 4), were reported. Median time to onset of these endocrinopathies was 11.1 weeks (range: 0.1-126.7). Resolution occurred in 323 patients (48.7%). Median time to resolution was 48.6 weeks (range: 0.4-204.4^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of thyroid disorders was 23.2% (608/2626). Grade 2 and Grade 3 thyroid disorders were reported in 12.7% (333/2626) and 1.0% (27/2626) of patients, respectively. Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 1.9% (49/2626) and 1.5% (40/2626) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.6% (16/2626) and 0.5% (13/2626) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 2.7% (72/2626), 1.6% (43/2626) and 0.2% (4/2626) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) occurred in < 0.1% (1/2626), 0.3% (8/2626), 0.3% (7/2626), and 0.2 (6/2626) of patients, respectively. Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-28.1). Resolution occurred in 297 patients (40.0%). Time to resolution ranged from 0.3 to 257.1^{+} weeks.

In patients treated with nivolumab in combination with chemotherapy, the incidence of thyroid disorders was 12.8% (230/1800). Grade 2 and Grade 3 thyroid disorders were reported in 6.3% (114/1800) and 0.1% (2/1800) of patients, respectively. Grade 3 hypophysitis occurred in 0.1% (2/1800) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (4/1800) and 0.2% (4/1800) of patients, respectively. Grade 2, Grade 3 and Grade 4 adrenal insufficiency occurred in 0.6% (11/1800), 0.2% (3/1800) and <0.1% (1/1800) of patients, respectively. One patient (<0.1%) had a fatal outcome due to adrenal insufficiency. Diabetes mellitus including Type 1 diabetes mellitus, fulminant Type 1 diabetes mellitus (4 Grade 2, 2 Grade 3, and 1 Grade 4), and diabetic ketoacidosis (1 Grade 2 and 1 Grade 4) were reported. Median time to onset of these endocrinopathies was 15.3 weeks (range: 1.1-124.3). Resolution occurred in 101 patients (40.1%). Time to resolution ranged from 0.3^{+} to 233.6^{+} weeks.

In patients treated with nivolumab in combination with cabozantinib, the incidence of thyroid disorders was 43.1% (138/320). Grade 2 and Grade 3 thyroid disorders were reported in 23.1% (74/320) and 0.9% (3/320) of patients, respectively. Hypophysitis occurred in 0.6% (2/320) of patients, all Grade 2. Adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 4.7% (15/320) of patients. Grade 2 and Grade 3 adrenal insufficiency cases were reported in 2.2% (7/320) and 1.9% (6/320) of patients, respectively. Median time to onset of these endocrinopathies was 12.3 weeks (range: 2.0-89.7 weeks). Resolution occurred in 50 patients (35.2%). Time to resolution ranged from 0.9 to 132.0^{+} weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab monotherapy, the incidence of rash and pruritis was 30.0% (1396/4646). The majority of cases were Grade 1 in severity reported in 22.8% (1060/4646) of patients. Grade 2 and Grade 3 cases were reported in 5.9% (274/4646) and 1.3% (62/4646) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 6.7 weeks (range: 0.1-121.1). Resolution occurred in 896 patients (64.6%) with a median time to resolution of 20.1 weeks (range: 0.1-192.7^{+}).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of rash was 46.1% (1210/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 14.3% (375/2626), 4.6% (120/2626), and 0.1% (3/2626) of patients, respectively. Median time to onset was 0.7 months (range: 0.0-33.8). Resolution occurred in 843 patients (70%) with a median time to resolution of 12.1 weeks (range: 0.1-268.7^{+}). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, the incidence of rash was 65.2%, including Grade 2 (20.3%) and Grade 3 (7.8%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of rash was 25.4% (457/1800). Grade 2 and Grade 3 cases were reported in 6.2% (111/1800), and 2.3% (42/1800) of patients, respectively. Median time to onset was 6.4 weeks (range: 0.1-97.4). Resolution occurred in 320 patients (70.2%) with a median time to resolution of 12.1 weeks (range: 0.1-258.7^{+}).

In patients treated with nivolumab in combination with cabozantinib, the incidence of rash was 62.8% (201/320). Grade 2 and Grade 3 cases were reported in 23.1% (74/320) and 10.6% (34/320) of patients, respectively. Median time to onset was 6.14 weeks (range: 0.1-104.4 weeks). Resolution occurred in 137 patients (68.2%) with a median time to resolution of 18.1 weeks (range: 0.1-130.6^{+} weeks).

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

Infusion reactions
In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions, including anaphylactic reaction, anaphylactic shock, and brochospasm, was 4.0% (188/4646), including 9 Grade 3 (0.2%) and 3 Grade 4 (<0.1%) cases. No Grade 5 cases were reported.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of hypersensitivity/infusion reactions was 4.5% (118/2626). Grade 1, Grade 2, Grade 3, and Grade 4 cases were reported in 1.9% (49/2626), 2.4% (62/2626), 0.2% (6/2626), and < 0.1% (1/2626) of patients, respectively. Among patients with MPM treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg, the incidence of hypersensitivity/infusion reactions was 12%.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of hypersensitivity/infusion reactions was 4.9% (103/2094). Grade 1, Grade 2, Grade 3, and Grade 4 cases were reported in 2.1% (44/2094), 2.5% (53/2094), 0.2% (5/2094), and < 0.1% (1/2094) of patients, respectively. Among patients with MPM treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg, the incidence of hypersensitivity/infusion reactions was 12%.

In patients treated with nivolumab in combination with chemotherapy, the incidence of hypersensitivity/infusion reactions was 8.2% (148/1800). Grade 2, Grade 3, and Grade 4 cases were reported in 4.6% (83/1800), 1.1% (20/1800) and 0.2% (3/1800) of patients, respectively.

In patients treated with nivolumab in combination with cabozantinib, the incidence of hypersensitivity/infusion reactions was 2.5% (8/320). All 8 patients were Grade 1 or 2 in severity. Grade 2 cases were reported in 0.3% (1/320) of patients.

Complication of allogeneic HSCT in classical Hodgkin Lymphoma
Rapid onset of GVHD has been reported with nivolumab use before and after allogeneic HSCT (see section 4.4). In 62 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 17/62 patients (27.4%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in four patients (6%). A steroid requiring febrile syndrome, without an identified infectious cause, was reported in six patients (12%) within the first 6 weeks post-transplantation. Steroids were used in four patients and three patients responded to steroids. Hepatic veno-occlusive disease occurred in two patients, one of whom died of GVHD and multi-organ failure. Nineteen of 62 patients (30.6%) died from complications of allogeneic HSCT after nivolumab. The 62 patients had a median follow-up from subsequent allogeneic HSCT of 38.5 months (range: 0-68 months).

Elevated liver enzymes when 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 or other therapeutic agents. 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

Nervous system disorders: myelitis (including transverse myelitis), Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome

Gastrointestinal disorders: pancreatic exocrine insufficiency

Laboratory abnormalities
In patients treated with nivolumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.4% for anaemia (all Grade 3), 0.7% for thrombocytopenia, 0.7% for leucopoenia, 8.7% for lymphopenia, 0.9% for neutropenia, 1.7% for increased alkaline phosphatase, 2.6% for increased AST, 2.4% for increased ALT, 0.8% for increased total bilirubin, 0.7% for increased creatinine, 2.0% for hyperglycaemia, 0.7% for hypoglycaemia, 3.8% for increased amylase, 6.9% for increased lipase, 4.7% for hyponatraemia, 1.6% for hyperkalaemia, 1.3% for hypokalaemia, 1.1% for hypercalcaemia, 0.6% for hypermagnesaemia, 0.4% for hypomagnesaemia, 0.6% for hypocalcaemia, 0.6% for hypoalbuminaemia and <0.1% for hypernatraemia.

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.8% for anaemia, 1.8% for thrombocytopaenia, 2.2% for leucopoenia, 6.9% for lymphopaenia, 3.3% for neutropaenia, 2.7% for increased alkaline phosphatase, 9.8% for increased AST, 9.3% for increased ALT, 2.3% for increased total bilirubin, 1.8% for increased creatinine, 1.4% for hypoalbuminaemia, 7.1% for hyperglycaemia, 0.7% for hypoglycaemia, 7.8% for increased amylase, 16.3% for increased lipase, 0.8% for hypocalcaemia, 0.2% for hypernatraemia, 0.8% for hypercalcaemia, 2.0% for hyperkalaemia, 0.8% for hypermagnesaemia, 0.4% for hypomagnesaemia, 3.0% for hypokalaemia, and 8.7% for hyponatraemia.

Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, a higher proportion of patients experienced a worsening from baseline to Grade 3 or 4 increased ALT (15.3%).

In patients treated with nivolumab in combination with chemotherapy, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 14.7% for anaemia, 6.2% for thrombocytopaenia, 11.7% leukopaenia, 13.6% for lymphopaenia, 26.3% neutropaenia, 2.0% for increased alkaline phosphatase, 3.3% for increased AST, 2.6% for increased ALT, 1.9% for increased bilirubin, 1.3% for increased creatinine, 4.5% for increased amylase, 5.2% for increased lipase, 0.4% for hypernatraemia, 8.1% for hyponatraemia, 1.8% for hyperkalaemia, 5.1% for hypokalaemia, 0.7% for hypercalcaemia, 1.8% for hypocalcaemia, 1.5% for hypermagnesaemia, 2.9% for hypomagnesaemia, 3.7% for hyperglycaemia, and 0.6% for hypoglycaemia.

In patients treated with nivolumab in combination with cabozantinib, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.5% for anaemia (all Grade 3), 0.3% for 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.

Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response to nivolumab. Of the 3529 patients who were treated with nivolumab monotherapy 3 mg/kg or 240 mg every 2 weeks and evaluable for the presence of anti-product-antibodies, 328 patients (9.3%) tested positive for treatment-emergent anti-product-antibodies with 21 patients (0.6%) testing positive for neutralising antibodies. Co-administration with chemotherapy did not affect nivolumab immunogenicity. Of the patients who were treated with nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of anti-product-antibodies, 7.5% tested positive for treatment emergent anti-product-antibodies with 0.5% tested positive for neutralising antibodies.

Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 24.9% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. 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 0.8% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3

weeks, 1.5% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged for 6.3 to 13.7% and neutralising antibodies against ipilimumab ranged from 0 to 0.4%.

Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-nivolumab antibodies or neutralising antibodies against nivolumab, the incidence of anti-nivolumab antibodies was 33.8% and the incidence of neutralising antibodies was 2.6%. Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-ipilimumab antibodies or neutralising antibodies against ipilimumab, the incidence of anti-ipilimumab antibodies was 7.5%, and the neutralising antibodies was 1.6%.

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

Paediatric population
The safety of nivolumab as monotherapy (3 mg/kg every 2 weeks) and in combination with ipilimumab (nivolumab 1 mg/kg or 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks) was evaluated in 97 paediatric patients aged ≥ 1 year to < 18 years (including 53 patients 12 to < 18 years) with recurrent or refractory solid or haematological tumours, including advanced melanoma, in clinical study CA209070. The safety profile in paediatric patients was generally similar to that seen in adults treated with nivolumab as monotherapy or in combination with ipilimumab. No new safety signals were observed. Long-term safety data is unavailable on the use of nivolumab in adolescents 12 years of age and older.

The most common adverse reactions (reported in at least 20% of paediatric patients) treated with nivolumab monotherapy were fatigue (35.9%) and decreased appetite (21.9%). The majority of adverse reactions reported for nivolumab monotherapy were Grade 1 or 2 in severity. Twenty-one patients (33%) had one or more Grades 3 to 4 adverse reactions.
The most common adverse reactions (reported in at least 20% of paediatric patients) treated with nivolumab in combination with ipilimumab were fatigue (33.3%) and rash maculo-papular (21.2%). The majority of adverse reactions reported for nivolumab in combination with ipilimumab were Grade 1 or 2 in severity. Ten patients (30%) had one or more Grades 3 to 4 adverse reactions.

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

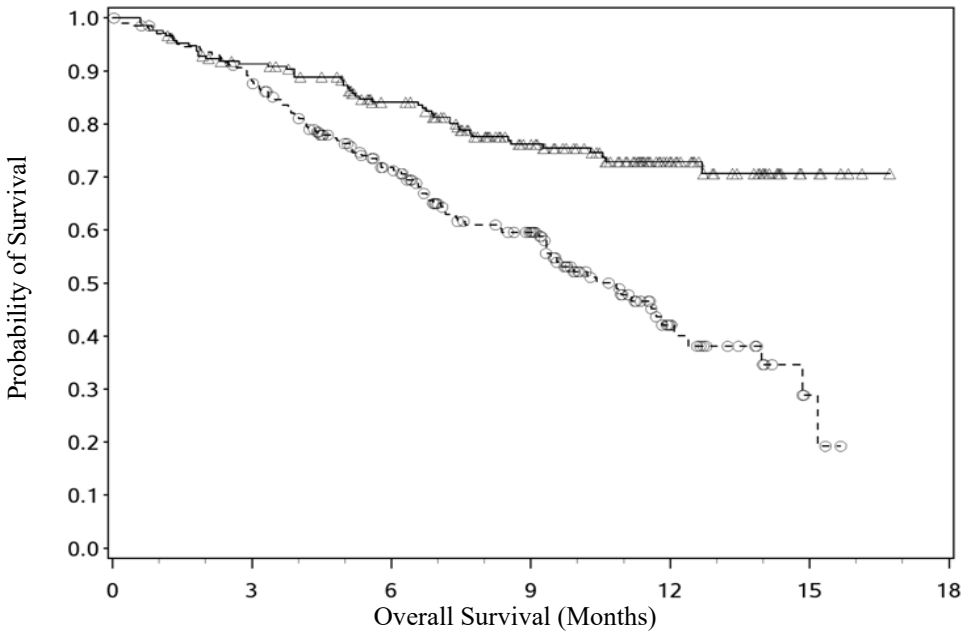
Unresectable or Metastatic Melanoma

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.
- - -❍- - - Dacarbazine (events: 96/208), median and 95% CI: 10.84 (9.33, 12.09)

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

Efficacy results are shown in Table 6.

Table 6: **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 7.

Table 7: **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)

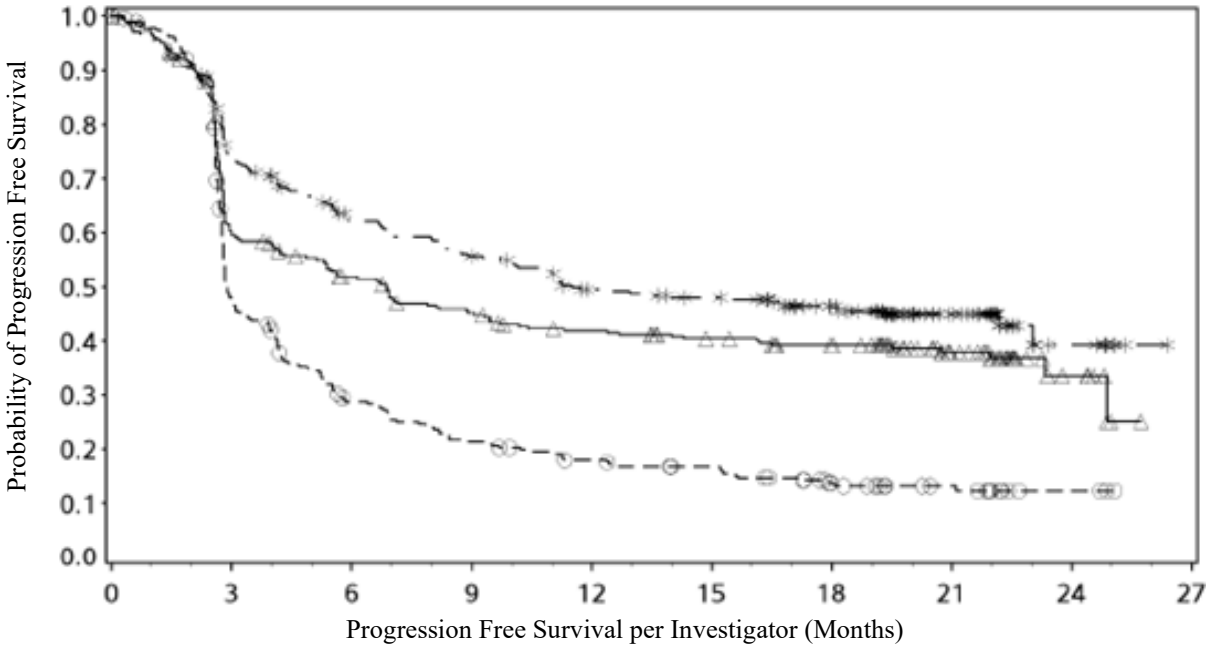
The safety and efficacy of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg or nivolumab 3 mg/kg vs. ipilimumab 3 mg/kg monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209067). The differences between 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 8.

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)

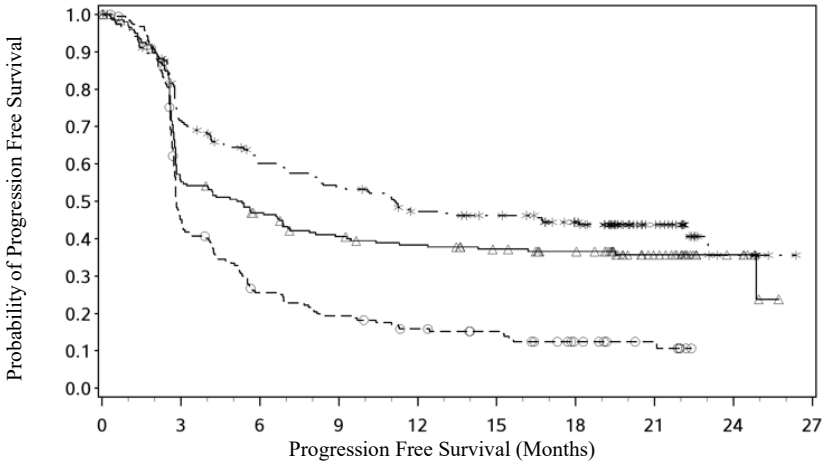
——Δ—— Nivolumab (events: 183/316), median and 95% CI: 6.87 (4.34, 9.46).
PFS rate at 12 months and 95% CI: 42% (36, 47)

- - -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%



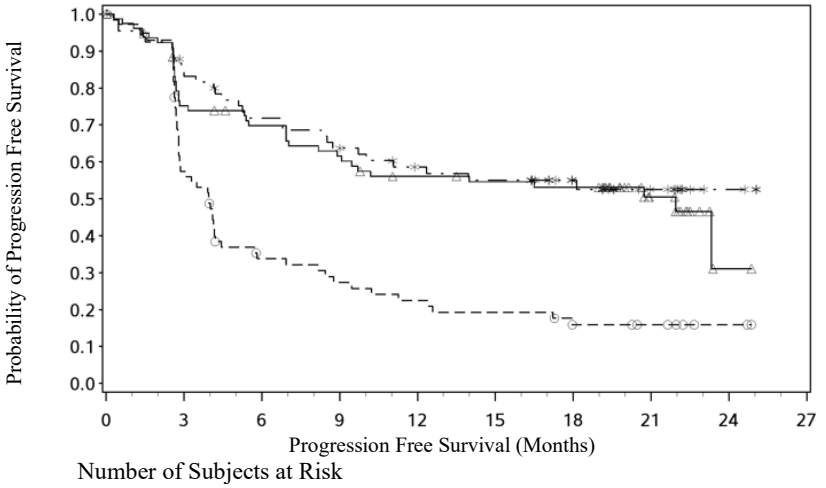
Number of Subjects at Risk

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

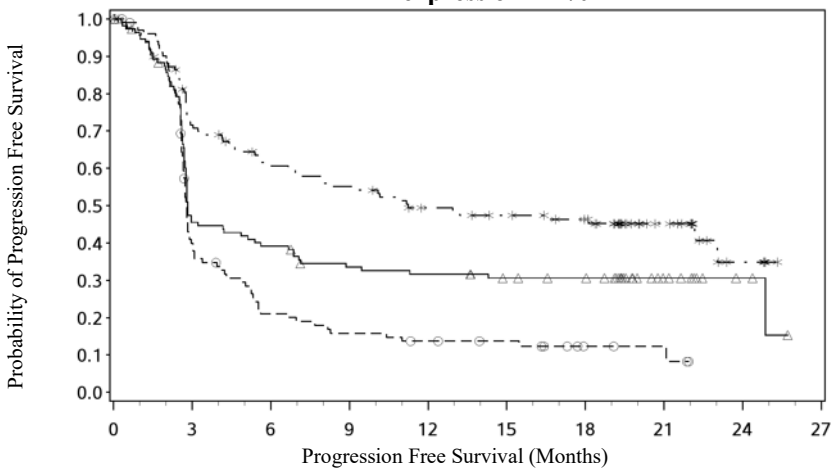
Nivolumab + Ipilimumab									
68	53	44	39	33	31	22	13	3	0
Nivolumab									
80	57	51	45	39	37	36	16	1	0
Ipilimumab									
75	40	21	17	14	12	8	6	2	0

- - -*- - - 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%



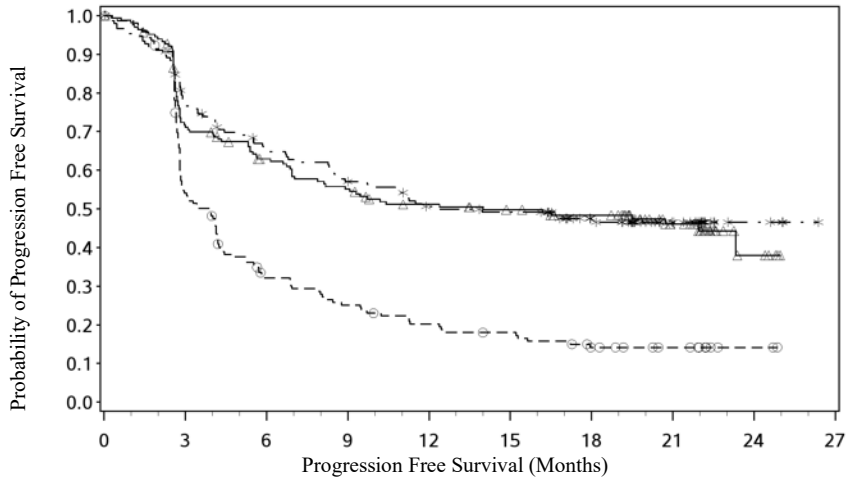
Number of Subjects at Risk

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%



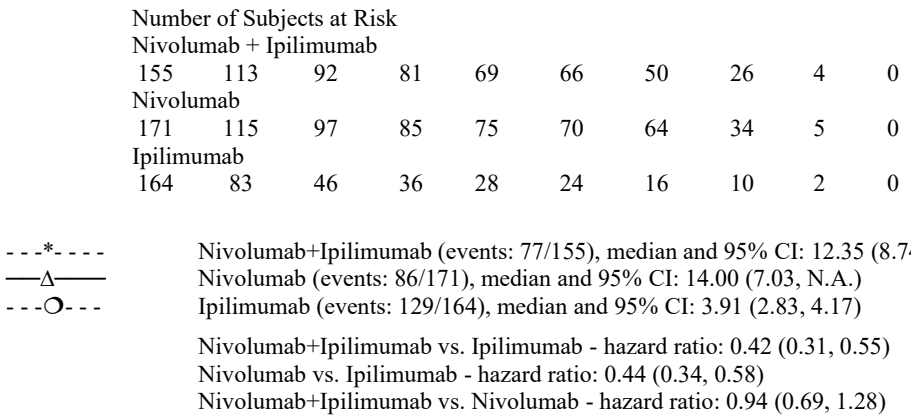

Number of Subjects at Risk
Nivolumab + Ipilimumab
155 113 92 81 69 66 50 26 4 0
Nivolumab
171 115 97 85 75 70 64 34 5 0
Ipilimumab
164 83 46 36 28 24 16 10 2 0
Nivolumab+Ipilimumab (events: 77/155), median and 95% CI: 12.35 (8.74, N.A.)
Nivolumab (events: 86/171), median and 95% CI: 14.00 (7.03, N.A.)
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 8: 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 8). 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. placebo (CA20976K)

The safety and efficacy of nivolumab 480 mg monotherapy for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study (CA20976K). The study included patients with an ECOG performance status score of 0 or 1 who had Stage IIB or IIC American Joint Committee on Cancer (AJCC), 8th edition, histologically confirmed melanoma that had been completely surgically resected. Enrolment required complete resection of the primary melanoma with negative margins and a negative sentinel lymph node biopsy within 12 weeks prior to randomisation. Patients were enrolled regardless of their tumour PD-L1 status. The study excluded patients with ocular/uveal or mucosal melanoma, active autoimmune disease, any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery.

A total of 790 patients were randomised (2:1) to receive either nivolumab (n = 526) administered intravenously over 30 minutes at 480 mg every 4 weeks or placebo (n = 264) for up to 1 year or until disease recurrence or unacceptable toxicity. Randomisation was stratified by AJCC 8th edition T-category (T3b vs. T4a vs. T4b). Tumour assessments were conducted every 26 weeks during years 1-3 and every 52 weeks from 3 years to 5 years. The primary efficacy outcome measure was recurrence-free survival (RFS). RFS, assessed by the investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first. The secondary outcome measures included OS and distant metastasis-free survival (DMFS).

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 19-92), 61% were men, and 98% were white. Baseline ECOG performance status score was 0 (94%) or 1 (6%). Sixty percent had stage IIB and 40% had stage IIC.

At a primary pre-specified interim analysis (minimum follow-up 7.8 months) a statistically significant improvement in RFS was demonstrated with nivolumab compared to placebo with a HR of 0.42 (95% CI: 0.30, 0.59; $p < 0.0001$). At an updated descriptive RFS analysis (minimum follow-up of 15.6 months), nivolumab continued to demonstrate an RFS improvement with a HR of 0.53 (95% CI: 0.40, 0.71). OS was not mature. Results reported from the analyses with minimum follow-up of 15.6 months are summarised in Table 9 and Figure 5.

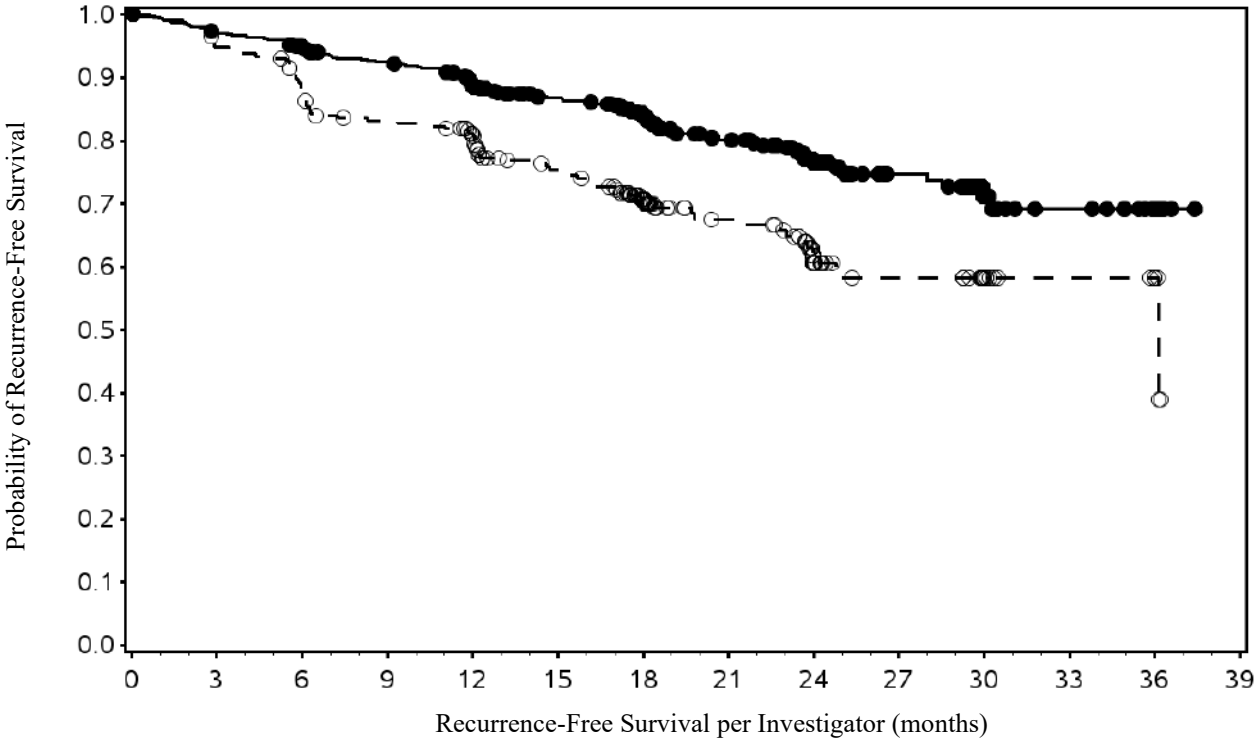
Table 9: Efficacy results (CA20976K)

	nivolumab (n = 526)	**placebo (n = 264)**
Recurrence-free survival with minimum follow-up 15.6 months		
Recurrence-free survival		
Events	102 (19.4%)	84 (31.8%)
Hazard ratio[a]	0.53	
95% CI	(0.40, 0.71)	
Median (95% CI) months	NR	36.14 (24.77, NR)
Rate (95% CI) at 12 months[b]	88.8 (85.6, 91.2)	81.1 (75.7, 85.4)
Rate (95% CI) at 18 months[b]	83.9 (80.3, 86.9)	70.7 (64.5, 76.1)

[a] Based on stratified Cox proportional hazard model.
[b] Based on Kaplan-Meier estimates.

RFS benefit was consistent across key subgroups, including disease stage, T-category, and age.

Figure 5: Recurrence-free survival (CA20976K)



Number of subjects at risk

Nivolumab													
526	492	474	456	422	386	291	210	122	74	40	22	13	0
Placebo													
264	244	224	208	193	165	120	77	44	25	12	7	4	0

—●—— Nivolumab (events 102/526), median and 95% CI: NR
- - -○- - - Placebo (events: 84/264), median and 95% CI: 36.14 (24.77, NR)
Nivolumab vs. Placebo – HR (95% CI): 0.53 (0.40, 0.71)

Based on data cut-off: 21-February-2023, minimum follow-up of 15.6 months

Tumour PD-L1 expression data were available for 302/790 (38.2%) randomised patients (36.3% and 42.0% in the nivolumab and placebo arms, respectively), as PD-L1 expression was not a stratification factor for randomisation. The exploratory RFS analyses by PD-L1 expression showed a HR for nivolumab vs placebo of 0.43 (95% CI: 0.22, 0.84) in patients (N=167) with PD- L1 expression ≥ 1%, 0.82 (95% CI: 0.44, 1.54) in patients (N=135) with PD-L1 expression < 1%, and 0.50 (95% CI: 0.34, 0.73) in patients (N=488) with indeterminate/not reported/not evaluable PD-L1 expression.

Randomised phase 3 study of nivolumab vs ipilimumab 10 mg/kg (CA209238)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with completely resected melanoma were evaluated in a Phase 3, 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.

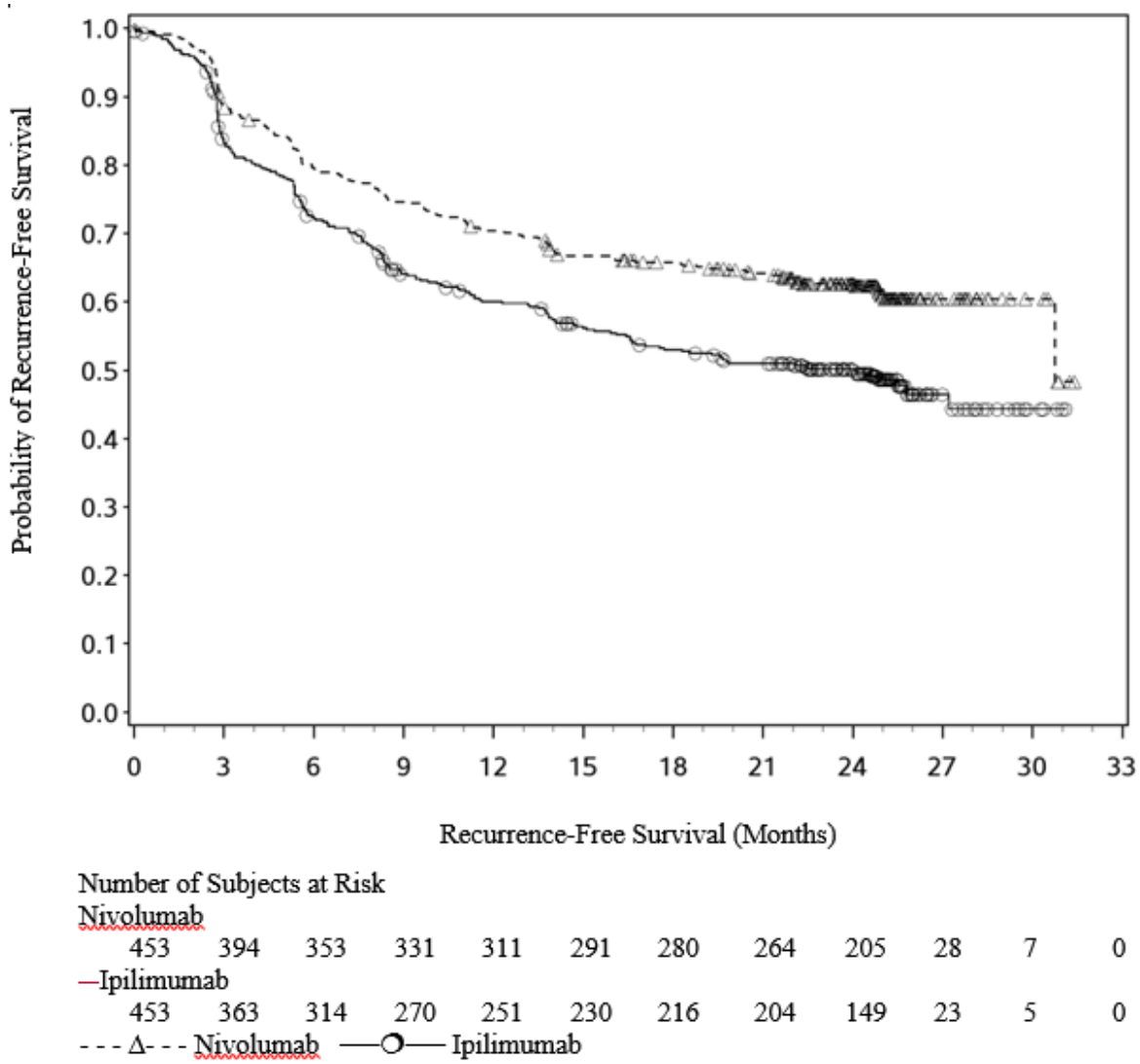
Minimum follow-up was approximately 24 months. OS was not mature at the time of this analysis. RFS results are shown in Table 10 and Figure 6 (all randomized population).

Table 10: 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 6: 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.

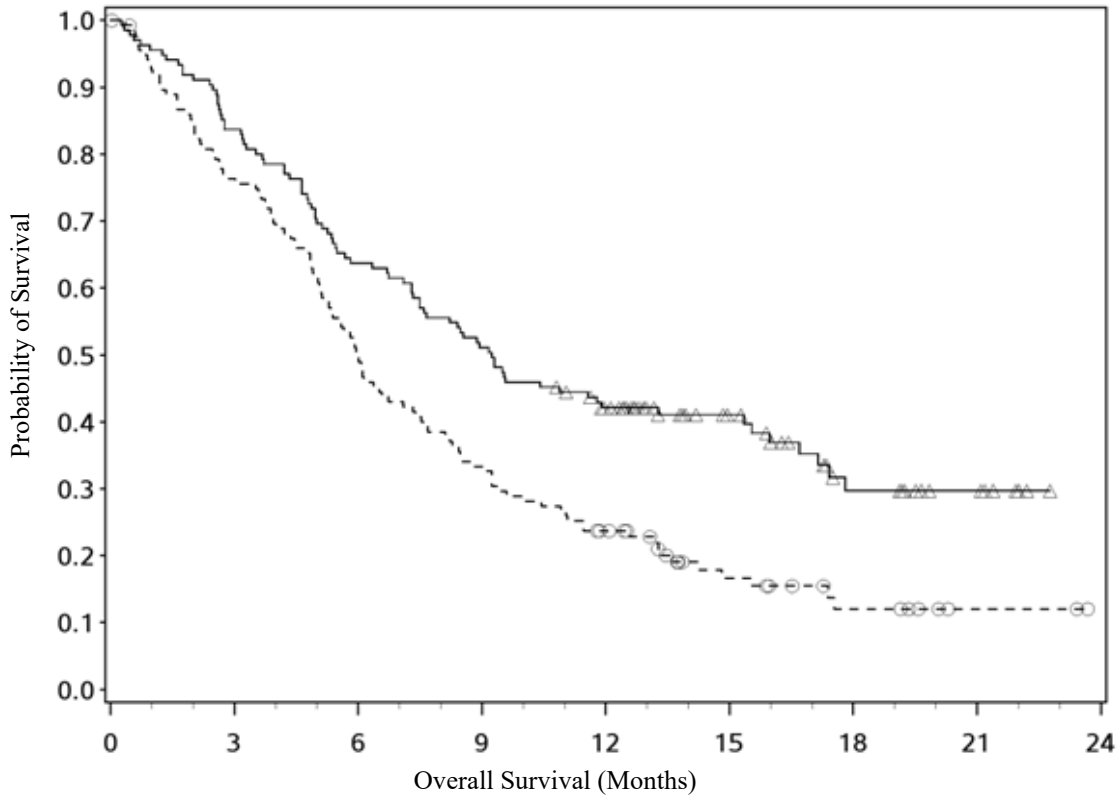
A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (N = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m^2 every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour 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 7.

Figure 7: 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 11.

Table 11: **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

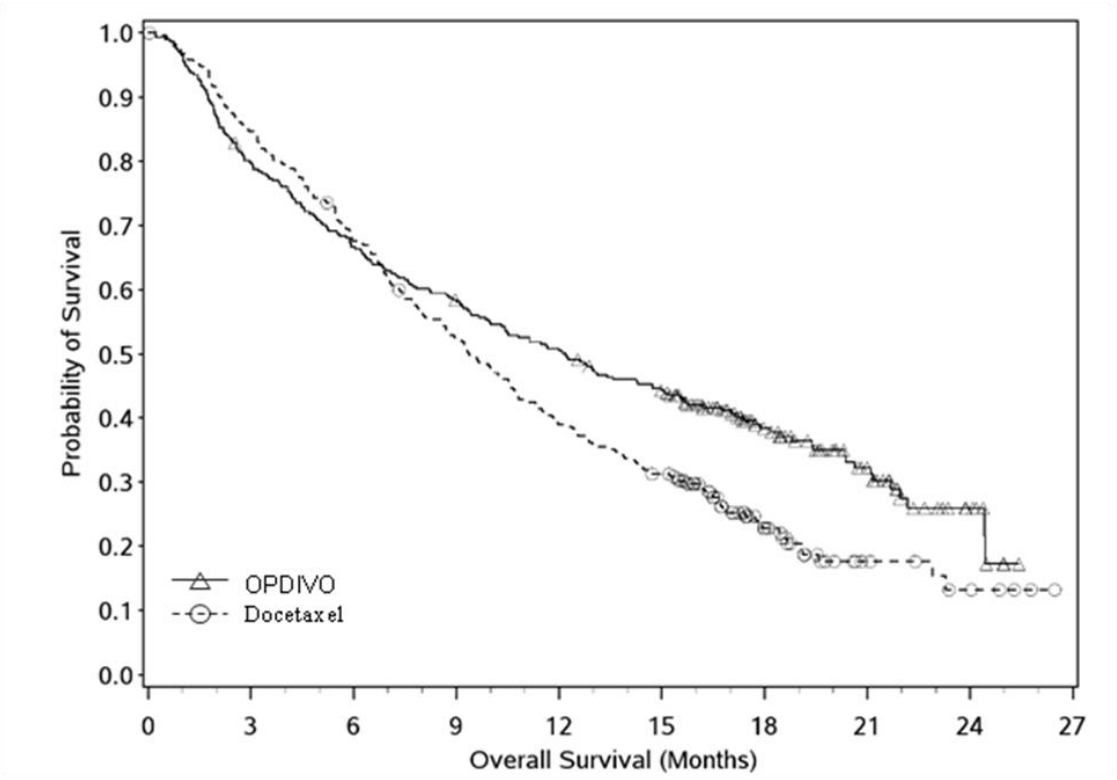
applied. Nivolumab 3 mg/kg showed an overall response rate of 14.5% (95% CI: 8.7-22.2%), a median OS of 8.21 months (95% CI: 6.05-10.9 months), and a median PFS of 1.87 months (95% CI 1.77-3.15 months. The PFS was measured by RECIST version 1.1. The estimated 1-year survival rate was 41%.

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 8.

Figure 8: Kaplan-Meier curves of OS (CA209057)



Number at Risk										
OPDIVO	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

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 12.

Table 12: **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 9, 10 and 11.

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

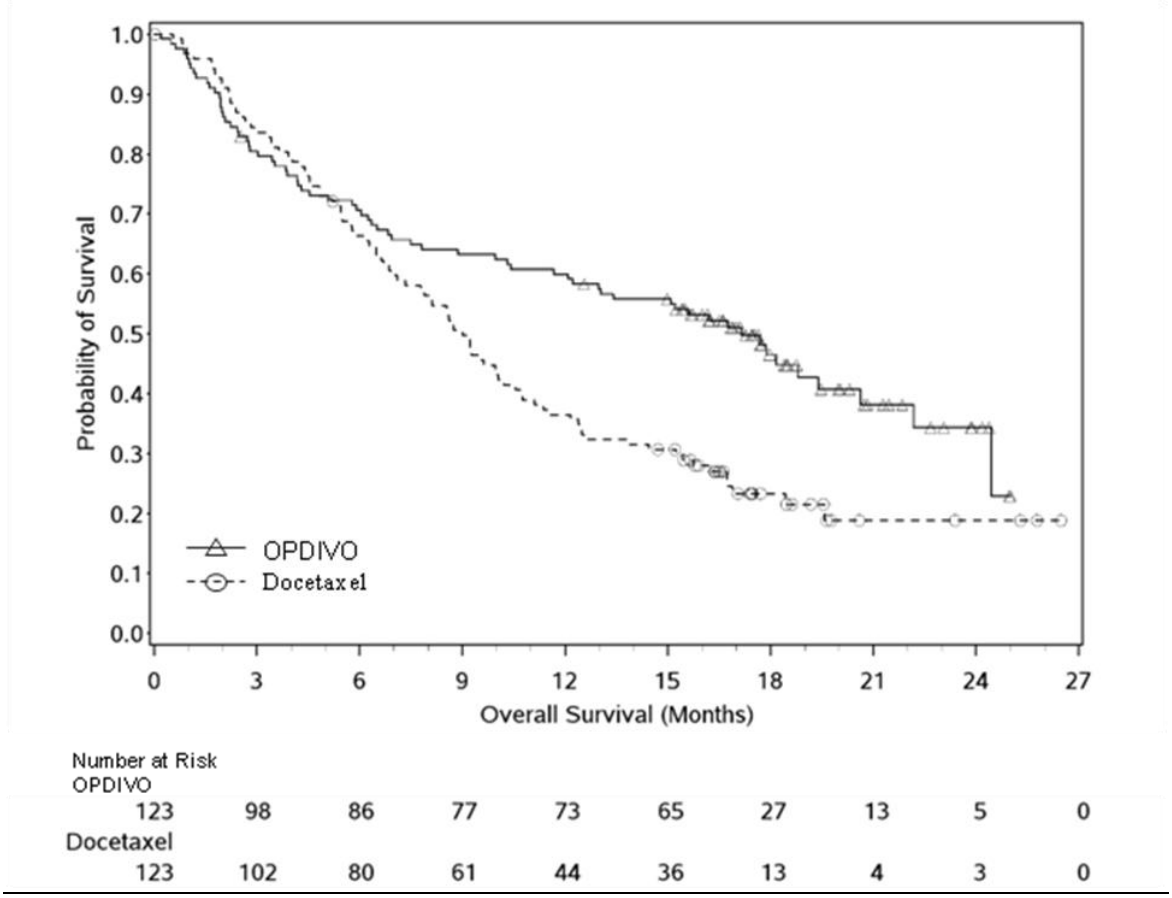


Figure 10: Overall Survival: Patients with <1% PD-L1 Expression (CA209057)

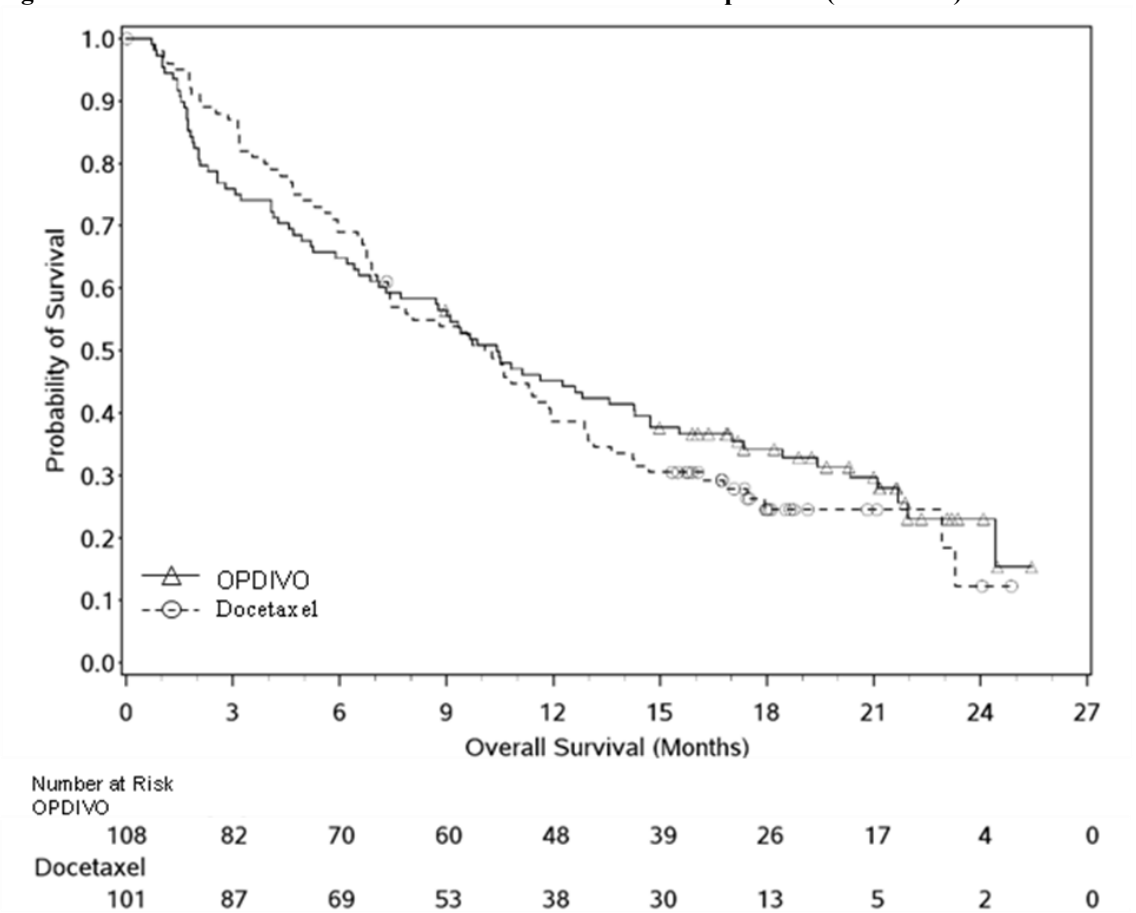
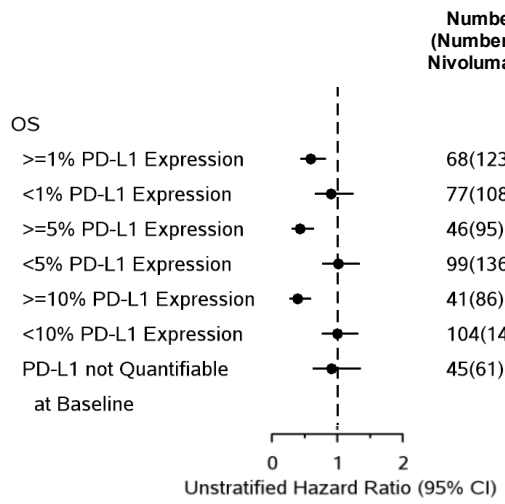


Figure 11: Forest Plot for OS based on PD-L1 Expression (CA209057)



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

As compared to the overall study population, no meaningful differences in safety were observed based on PD-L1 expression 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 13 and Figure 12.

Table 13: Efficacy Results - CA2099LA

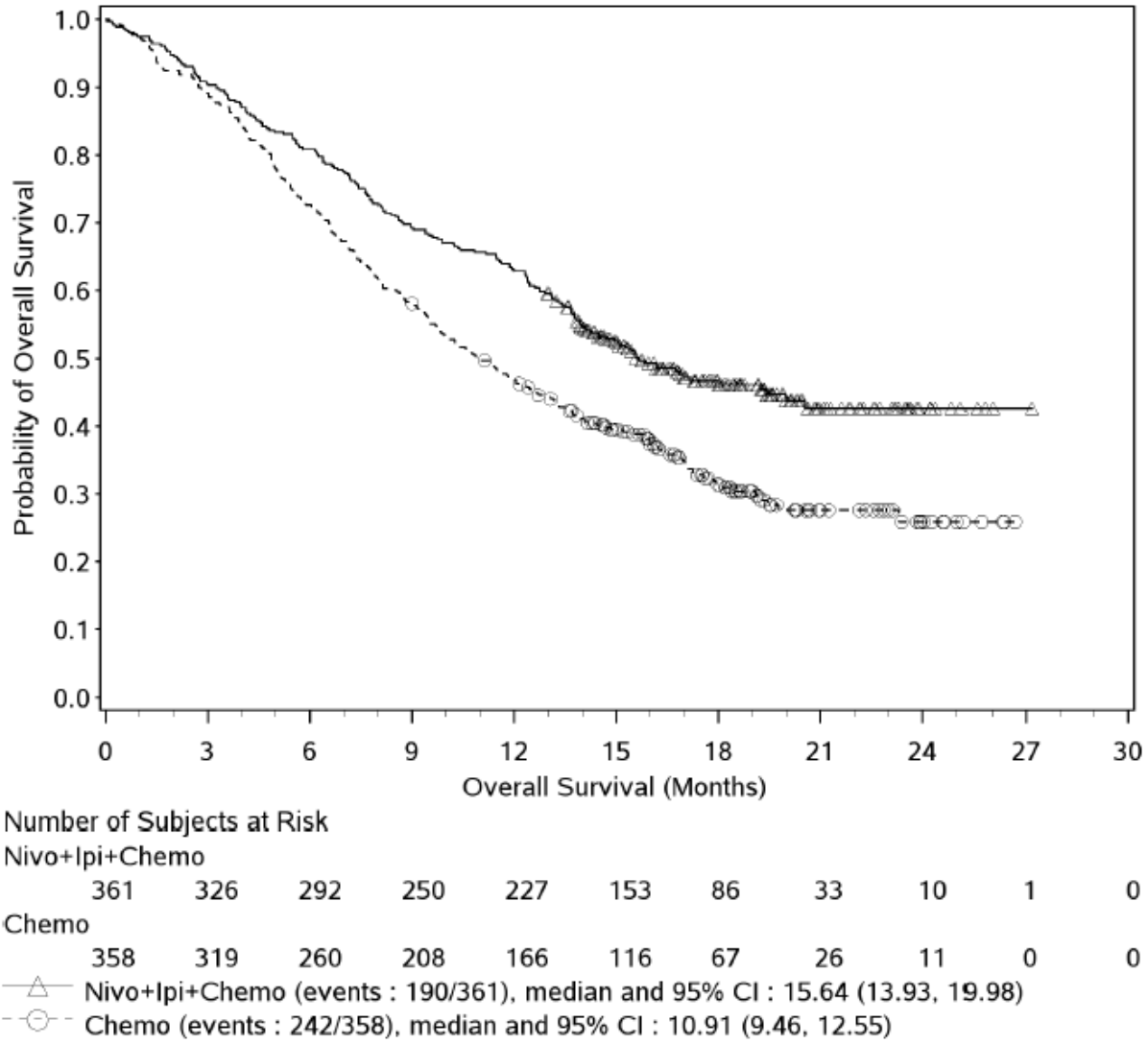
	OPDIVO and Ipilimumab and Chemotherapy (n=361)	**Chemotherapy (n=358)**
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.24, 16.16)	10.7 (9.46, 12.45)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Rate (95% CI) at 6 months	80.9 (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 12). 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 12: 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%).

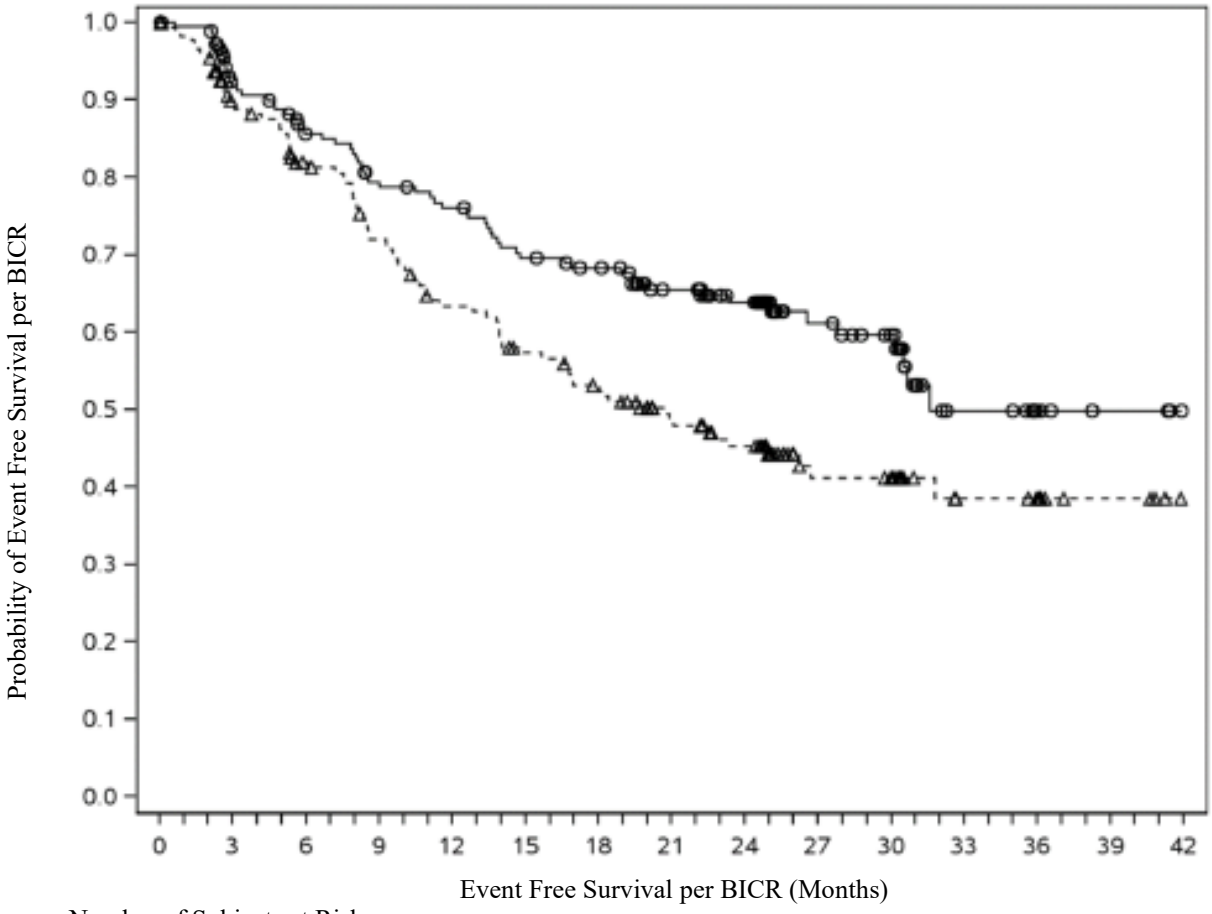
At the final pCR analysis and pre-specified interim EFS analysis (minimum follow-up 21 months), statistically significant improvement was demonstrated in pCR and EFS for patients randomised to nivolumab in combination with chemotherapy as compared to chemotherapy alone. Efficacy results are presented in Table 14 and Figure 13.

Table 14: 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 13: 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 15: 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

Neoadjuvant and adjuvant treatment of NSCLC

The efficacy of OPDIVO, in combination with platinum-doublet chemotherapy, followed by surgery, and continued adjuvant treatment with OPDIVO as a single agent, was investigated in CA20977T, a randomized, double-blind trial in 461 patients with resectable NSCLC. The trial included patients with resectable, suspected or histologically confirmed Stage IIA (>4 cm) to IIIB (T3-T4 N2) NSCLC (per the 8th edition American Joint Committee on Cancer (AJCC) Staging Manual), and ECOG performance status 0 or 1. Patients with unresectable or metastatic NSCLC, EGFR mutations or known ALK translocations, brain metastasis, Grade 2 or greater peripheral neuropathy, interstitial lung disease or active, non-infectious pneumonitis (symptomatic and/or requiring treatment), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Randomization was stratified by tumor PD-L1 expression level (≥1% versus <1% versus indeterminate/not evaluable), disease stage (Stage II versus Stage III), and tumor histology (squamous versus nonsquamous).

Patients were randomized (1:1) to receive either:

- Neoadjuvant OPDIVO 360 mg administered intravenously over 30 minutes in combination with one of the following platinum-doublet chemotherapy regimens every 3 weeks for four cycles:
  - 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 or carboplatin AUC 5 or AUC 6 (nonsquamous histology)
  - Cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 (squamous histology).

  Within 90 days after the surgery, OPDIVO 480 mg was administered intravenously over 30 minutes every 4 weeks.

or

- Neoadjuvant placebo administered intravenously over 30 minutes in combination with platinum-doublet chemotherapy *(see above)* every 3 weeks for four cycles. Within 90 days after the surgery, placebo was administered intravenously over 30 minutes every 4 weeks.

All study medications were administered via intravenous infusion. Treatment continued until disease progression, recurrence, or unacceptable toxicity for up to 13 cycles (1 year). Tumor assessments were performed every 12 weeks for 2 years, then every 24 weeks for up to 5 years or until disease recurrence or progression was confirmed by BICR.

The trial was not designed to isolate the effect of OPDIVO in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measure was event-free survival (EFS) based on BICR assessment. Additional efficacy outcome measures included overall survival (OS), pathologic complete response (pCR), and major pathologic response (MPR).

The median age was 66 years (range: 35 to 86); 71% were male; 72% were White, 25% were Asian, 1.7% were Black, and 1.5% were mixed race/ race unknown/ not reported; and 6% were Hispanic or Latino. Baseline ECOG performance status was 0 (62%) or 1 (38%); 56% had tumors with PD-L1 expression ³1% and 40% had tumors with PD-L1 expression <1%; 35% had stage II and 64% had stage III disease; 23% had N1 disease and 39% had N2 disease; 51% had tumors with squamous histology and 49% had tumors with nonsquamous histology; and 90% were former/current smokers.

Seventy-eight percent of patients in the neoadjuvant OPDIVO in combination with platinum-doublet chemotherapy followed by adjuvant OPDIVO arm had definitive surgery compared to 77% of patients in the neoadjuvant placebo and platinum-doublet chemotherapy followed by placebo arm.

The study demonstrated a statistically significant improvement in EFS for patients treated with neoadjuvant OPDIVO in combination with platinum-doublet chemotherapy followed by single agent OPDIVO compared with patients randomized to placebo in combination with platinum-doublet chemotherapy followed by placebo. Efficacy results are presented in Table 16 and Figure 14.

Table 16: Efficacy Results - CHECKMATE-77T

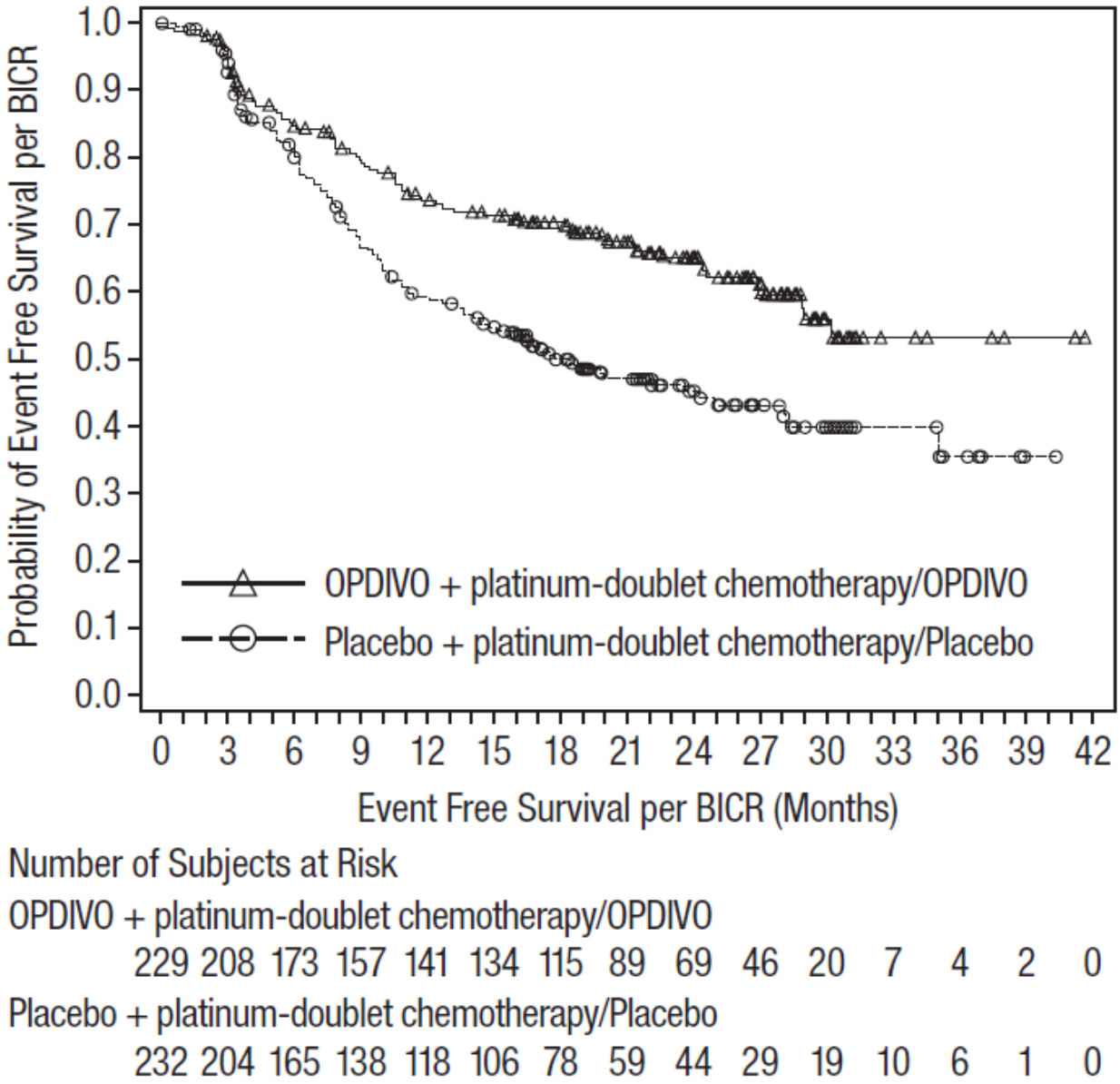
	Neoadjuvant OPDIVO and Platinum-Doublet Chemotherapy/Adjuvant OPDIVO (n=229)	**Neoadjuvant Placebo and Platinum-Doublet Chemotherapy/Adjuvant Placebo (n=232)**
Event-free Survival (EFS) per BICR		
Events (%)	76 (33%)	113 (49%)
Median (months)[a] (95% CI)	NR (28.9, NR)	18.4 (13.6, 28.1)
Hazard Ratio[b] (95% CI)	0.58 (0.43, 0.78)	
Stratified log-rank p-value[c]	0.00025	

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

[c] Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0264.

Figure 14: **Event-Free Survival - CHECKMATE-77T**



In a pre-specified descriptive analysis, the pCR rate was 25% (95% CI: 20, 31) in the OPDIVO arm and 4.7% (95% CI: 2.4, 8) in the placebo arm.

At the time of the EFS analysis, OS data were immature.

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.

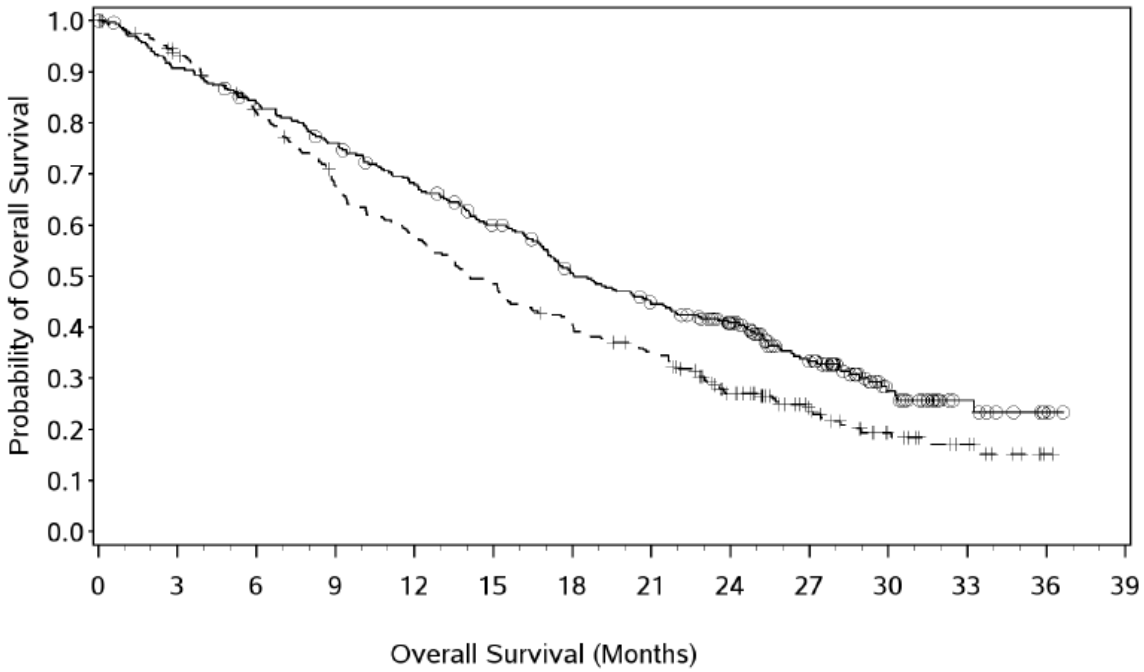
CA209743 baseline characteristics were generally balanced across all treatment groups. The median age was 69 years (range: 25-89) with 72% ≥ 65 years of age and 26% ≥ 75 years of years. The majority of patients were white (85%) and male (77%). Baseline ECOG performance status was 0 (40%) or 1 (60%), 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 15 and Table 17.

Figure 15: Kaplan-Meier Plot of OS - CA209743



--○-- 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)
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).

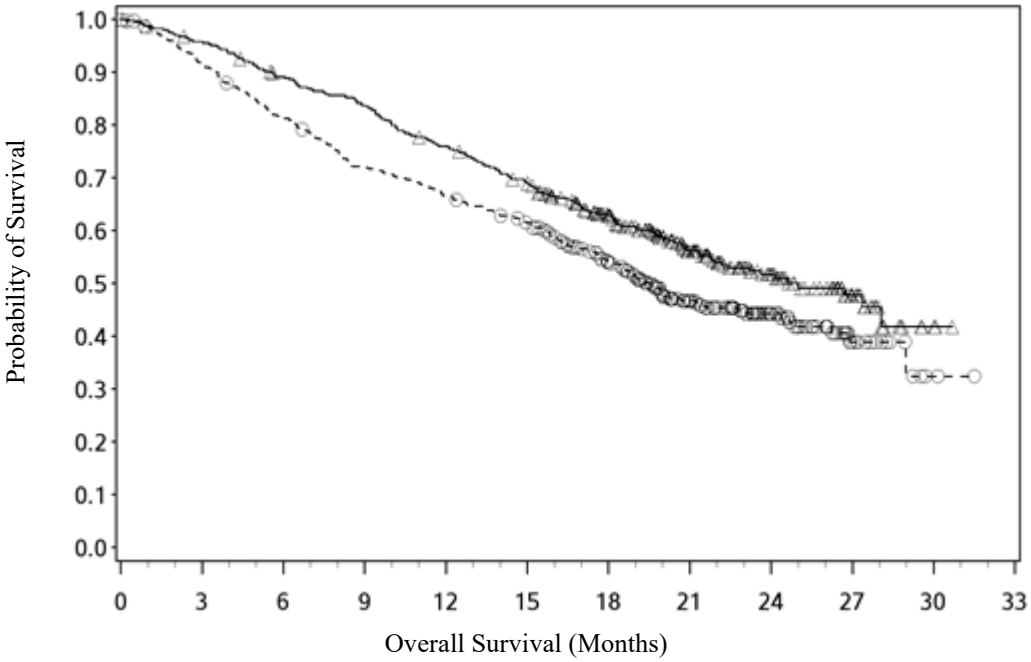
Renal Cell Carcinoma (RCC)

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 16.

Figure 16: 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 16). 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.

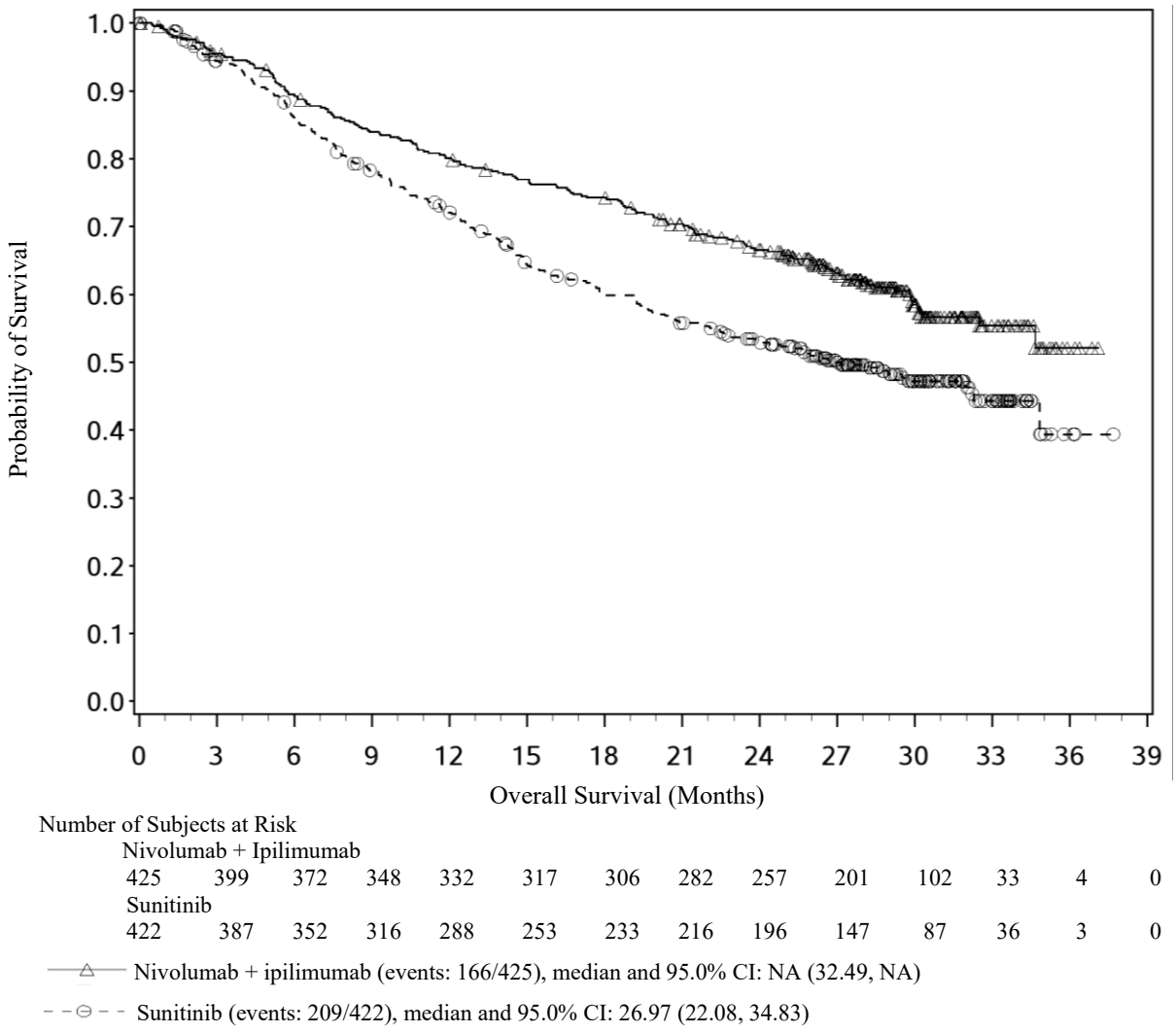
Patients with Karnofsky performance status <70% and patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were stratified by (IMDC) prognostic score and region.

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 17.

Figure 17: 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 18).

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

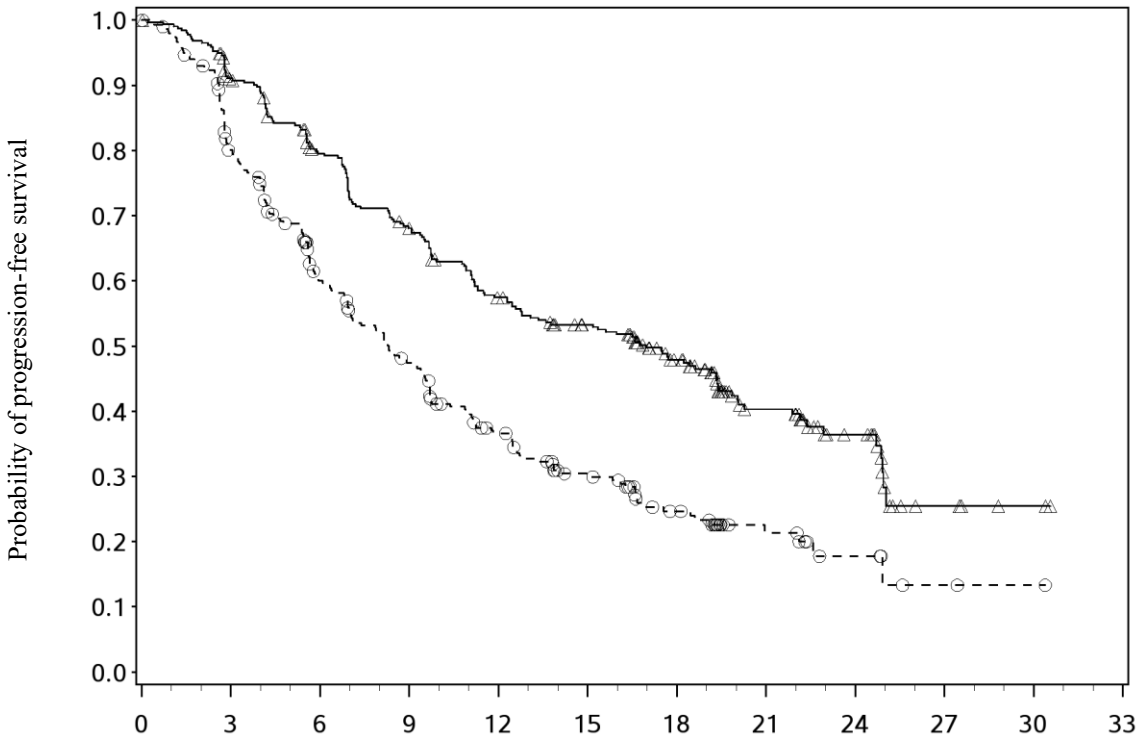
The primary analysis of PFS included censoring for new anti-cancer treatment (Table 20). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

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 17 and 18). 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 18: Kaplan-Meier curves of PFS (CA2099ER)



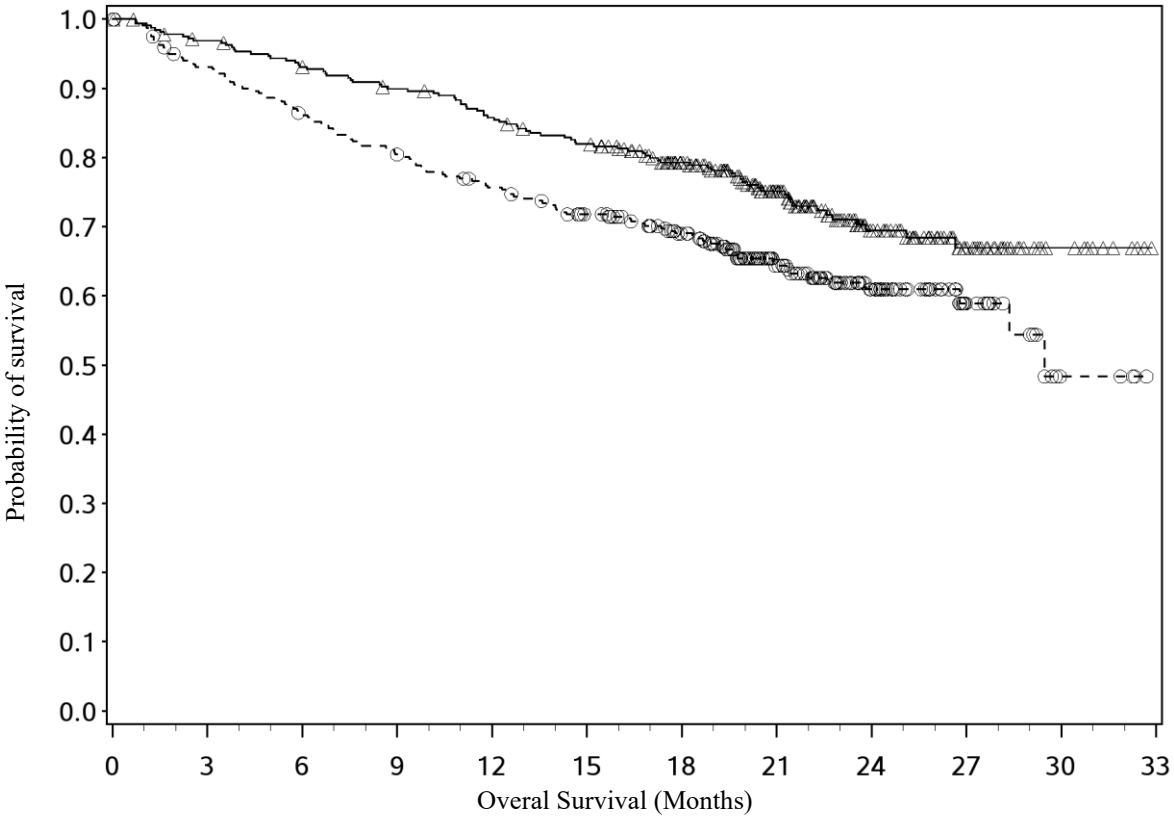
Number of subjects at risk

Nivolumab + cabozantinib											
323	280	236	201	166	145	102	56	26	5	2	0
Suntinib											
328	230	160	122	87	61	37	17	7	2	1	0

Nivolumab + cabozantinib (events: 175/323), median and 95.0% CI: 16.95 (12.58, 19.38)

Sunitinib (events: 206/328), median and 95.0% CI:8.31 (6.93, 9.69)

Figure 19: 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)

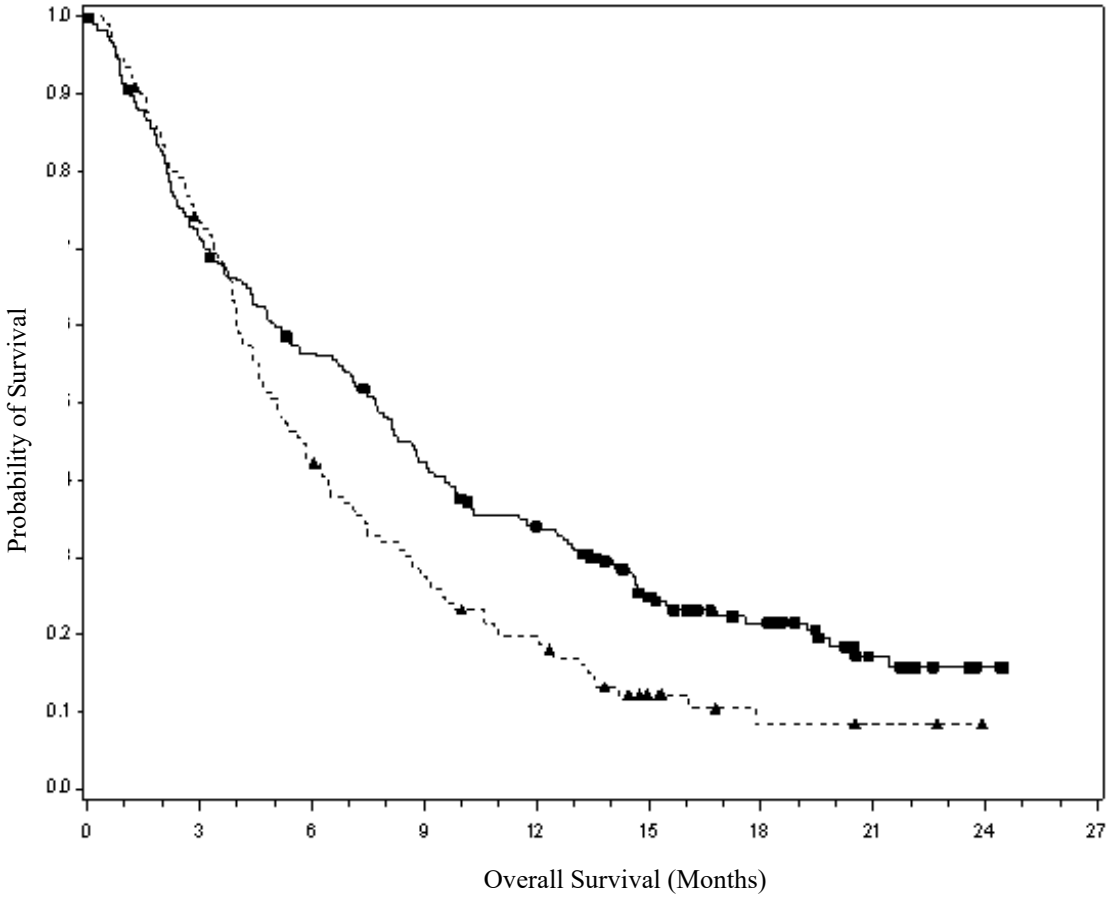
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of metastatic or recurrent SCCHN were evaluated in a phase 3, randomised, open-label study (CA209141). The study included patients (18 years or older) who have experienced disease progression during or within 6 months of 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 20. Efficacy results are shown in Table 23.

Figure 20: 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.

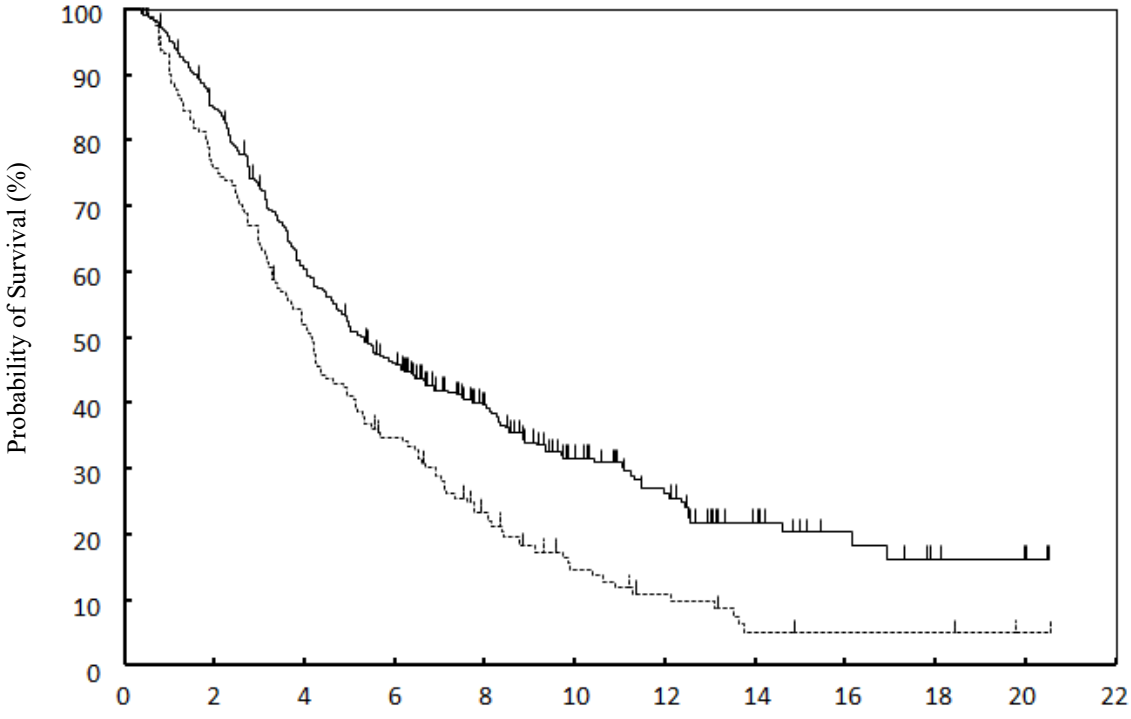
With a minimum duration of follow-up of approximately 6 months, nivolumab demonstrated a statistically significant improvement in OS compared with placebo. Improved OS was also demonstrated at 12 months and 18 months. Efficacy results are shown in Table 25, Figure 21 and Figure 22.

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

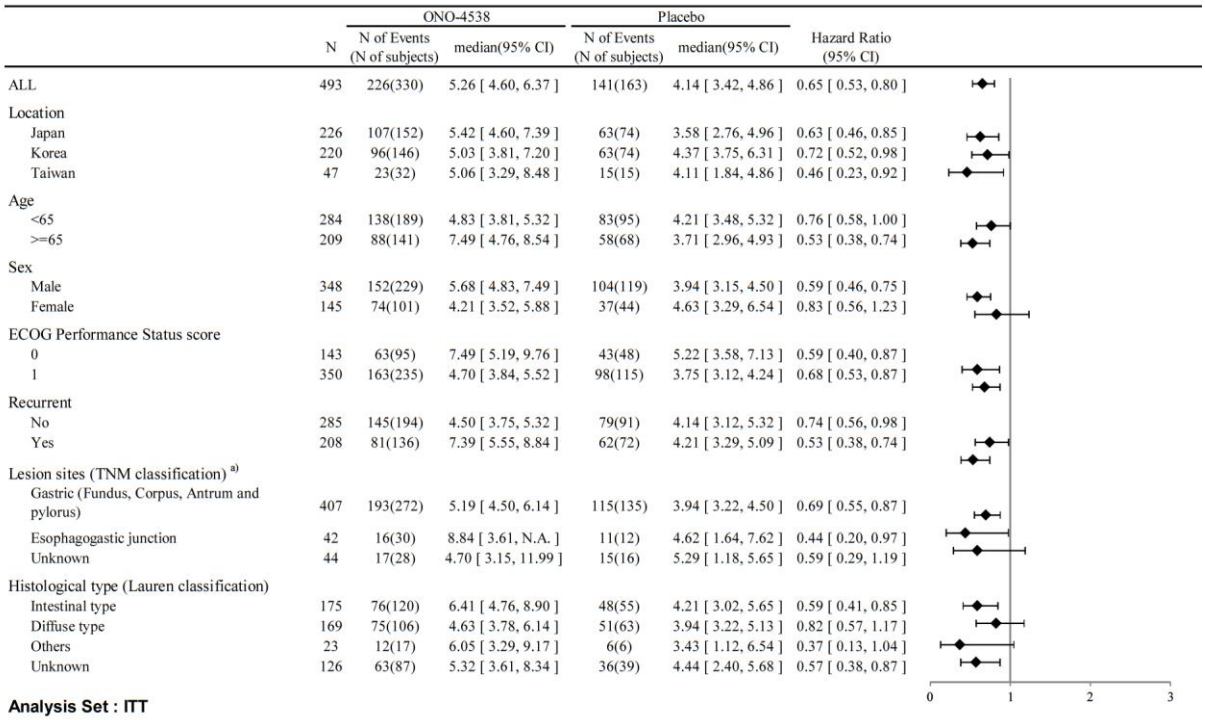


Number of Subjects at Risk

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

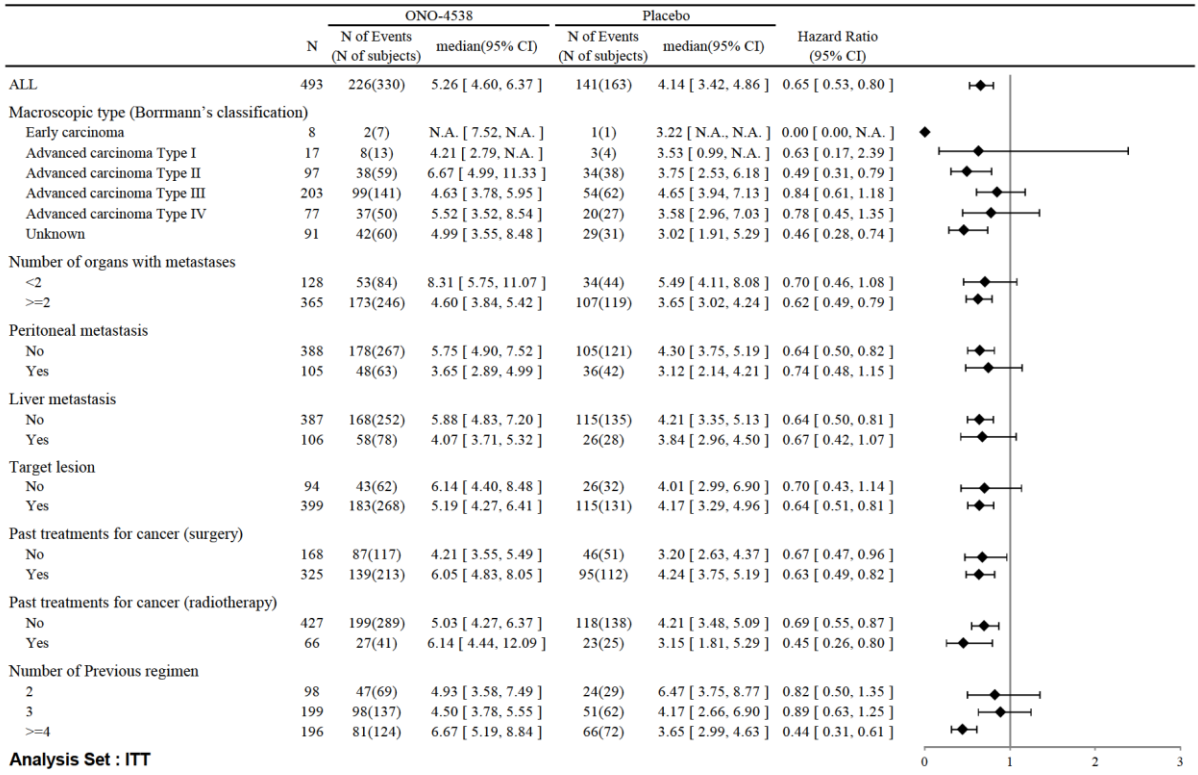


	N	ONO-4538 N of Events (N of subjects)	ONO-4538 median(95% CI)	Placebo N of Events (N of subjects)	Placebo median(95% CI)	Hazard Ratio (95% CI)
ALL	493	226(330)	5.26 [4.60, 6.37]	141(163)	4.14 [3.42, 4.86]	0.65 [0.53, 0.80]
Location						
Japan	226	107(152)	5.42 [4.60, 7.39]	63(74)	3.58 [2.76, 4.96]	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]

0 1 2 3

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]

0 1 2 3

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 23.

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.

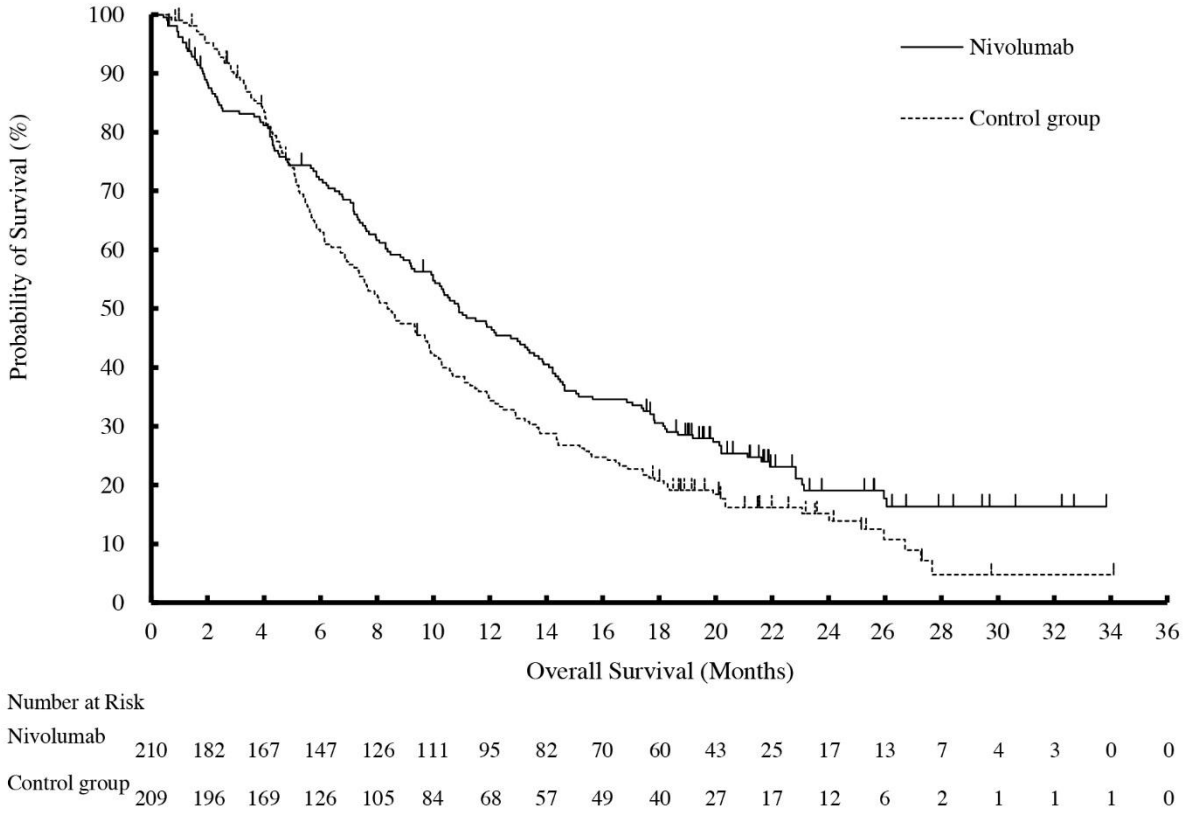
[b] Based on a stratified proportional hazards model.

[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 23: 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.

Randomised phase 3 study of nivolumab in combination with ipilimumab vs. chemotherapy and nivolumab in combination with chemotherapy vs. chemotherapy as first-line treatment (CA209648)
CA209648 was a randomised, active-controlled, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic OSCC (squamous or adenosquamous histology). The trial enrolled patients whose tumour was evaluable for tumour cell (TC) PD-L1 expression [also called PD-L1 tumour proportion score (TPS)], which was evaluated using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Patients were not amenable to chemoradiation or surgery with curative intent. Prior treatment with curative intent was allowed if completed more than six months prior to trial enrollment. The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumor to organs adjacent to the oesophageal tumour. Patients were randomised to receive one of the following treatments:

- OPDIVO 240 mg on days 1 and 15, fluorouracil 800 mg/m2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m2 intravenously on day 1 (of a 4-week cycle).
- OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks.
- Fluorouracil 800 mg/m2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m2 intravenously on day 1 (of a 4-week cycle).

Patients received OPDIVO until disease progression, unacceptable toxicity, or up to 2 years. In patients who received OPDIVO in combination with chemotherapy and in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent.

Randomisation was stratified by TC PD-L1 expression (≥1% vs. <1% or indeterminate), region (East Asia vs. Rest of Asia vs. Rest of World), ECOG performance status (0 vs. 1), and number of organs with metastases (≤1 vs. ≥ 2). The major efficacy outcome measures were OS and BICR-assessed PFS in patients with TC PD-L1 expression ≥ 1%. Additional efficacy measures included OS in all randomised patients, BICR-assessed PFS in all randomised patients, and ORR assessed by BICR in TC PD-L1 expression ≥ 1% and in all randomised patients. The tumour assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

A total of 970 patients were randomised to receive either nivolumab in combination with ipilimumab, (n = 325), nivolumab in combination with chemotherapy (n = 321), or chemotherapy (n = 324). Of these, 473 patients had tumour cell PD-L1 expression ≥ 1%,158 in the nivolumab plus ipilimumab arm, 158 in the nivolumab plus chemotherapy arm, and 157 in the chemotherapy arm. Baseline characteristics were generally balanced across treatment groups. In patients with tumour cell PD-L1 expression ≥ 1%, the median age was 63 years (range: 26-85), 8.2% were ≥ 75 years of age, 81.8% were male, 73.1% were Asian, and 23.3% were white. Patients had histological confirmation of squamous cell carcinoma (98.9%) or adenosquamous cell carcinoma (1.1%) in the oesophagus. Baseline ECOG performance status was 0 (45.2%) or 1 (54.8%).

Efficacy results are shown in Table 27 and Figures 24 to 27.

Table 27: Efficacy Results in patients with tumour cell PD-L1 ≥ 1% (CA209648)

	OPDIVO with Cisplatin and Fluorouracil (n=158)	OPDIVO and Ipilimumab (n=158)	Cisplatin and Fluorouracil (n=157)
Overall Survival			
Deaths (%)	98 (62)	106 (67)	121 (77)
Median (months) (95% CI)	15.4 (11.9, 19.5)	13.7 (11.2, 17.0)	9.1 (7.7, 10)
Hazard ratio (95% CI)[b]	0.54 (0.41, 0.71)	0.64 (0.49, 0.84)	-
p-value[c]	< 0.0001[S1]	0.0010[S2]	-
Progression-free Survival[a]			
Disease progression or death (%)	117 (74)	123 (78)	100 (64)
Median (months) (95% CI)	6.9 (5.7, 8.3)	4.0 (2.4, 4.9)	4.4 (2.9, 5.8)
Hazard ratio (95% CI)[b]	0.65 (0.49, 0.86)	1.02 (0.78, 1.34)	-
p-value[c]	0.0023[S3]	NS	-
Overall Response Rate, n (%)[a, NT]	84 (53.2)	56 (35.4)	31 (19.7)
(95% CI)	(45.1, 61.1)	(28.0, 43.4)	(13.8, 26.8)
Complete response (%)	26 (16.5)	28 (17.7)	8 (5.1)
Partial response (%)	58 (36.7)	28 (17.7)	23 (14.6)
Duration of Response (months)[a]			
Median (95% CI)	8.4 (6.9, 12.4)	11.8 (7.1, 27.4)	5.7 (4.4, 8.7)
Range	1.4+, 34.6	1.4+, 34.5+	1.4+, 31.8+

[a] Assessed by BICR.

[b] Based on stratified Cox proportional hazard model. Hazard ratios are reported for each OPDIVO containing arm compared to chemotherapy within each analysis population.

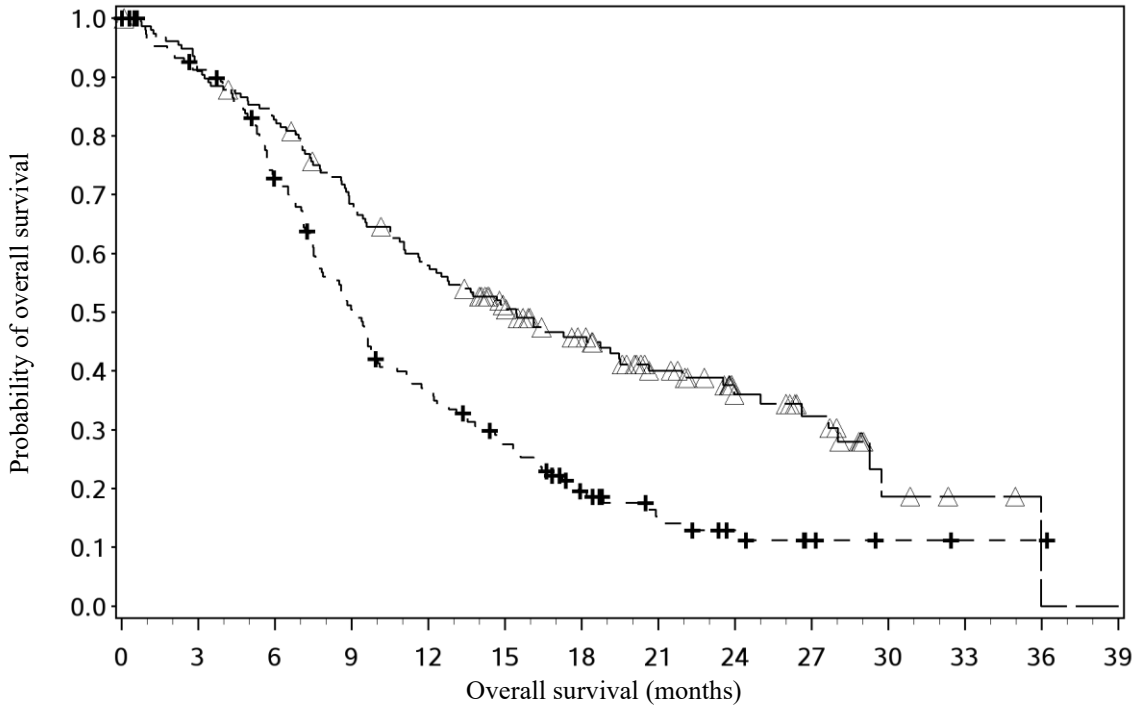
[c] Based on a stratified 2-sided log-rank test.

[S1, S2, S3] Significant p-value compared to stopping boundary of 0.005, 0.014, and 0.015 respectively.

NS: Not Statistically significant, NT: Not evaluated for statistical significance as per pre-specified hierarchical testing procedure

Symbol + indicates a censored value

Figure 24: Kaplan-Meier curves of OS in patients with tumor PD-L1 ≥1% (CA209648) - nivolumab + chemotherapy vs chemotherapy

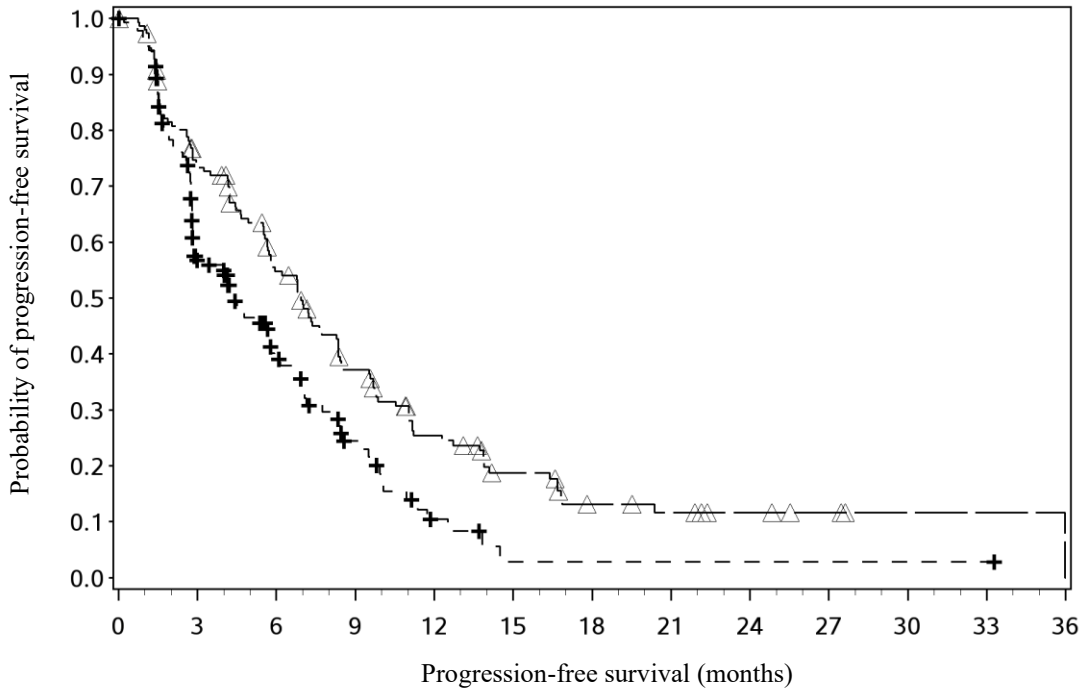


Number of subjects at risk

Nivolumab + chemotherapy													
158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemotherapy													
157	135	105	72	52	36	21	12	8	4	2	1	1	0

—Δ— Nivolumab + chemotherapy (events: 98/158), median and 95% CI: 15.44 (11.93, 19.52)
–+– Chemotherapy (events: 121/157), median and 95% CI: 9.07 (7.69, 9.95)

Figure 25: Kaplan-Meier curves of PFS in patients with tumor PD-L1 ≥1% (CA209648) - nivolumab + chemotherapy vs chemotherapy



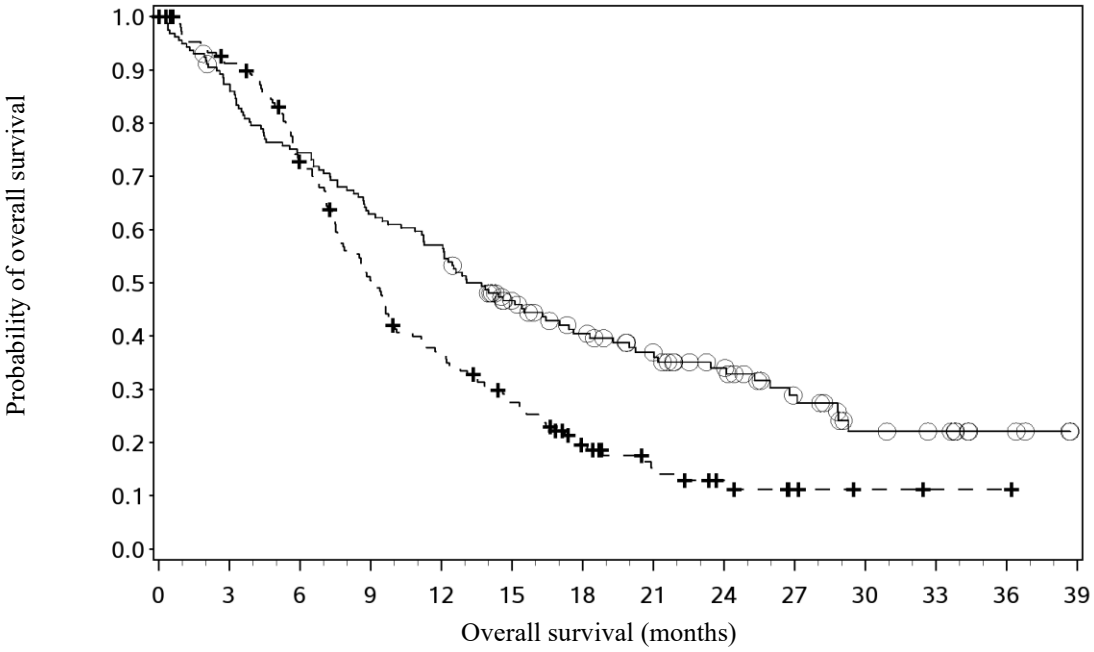
Number of subjects at risk

Nivolumab + chemotherapy	158	107	75	47	29	18	10	8	5	3	1	1	0
Chemotherapy	157	67	35	17	5	1	1	1	1	1	1	1	0

—Δ— Nivolumab + chemotherapy (events: 117/158), median and 95% CI: 6.93 (5.68, 8.34)

– – + – – Chemotherapy (events: 100/157), median and 95% CI: 4.44 (2.89, 5.82)

Figure 26: Kaplan-Meier curves of OS in patients with tumour PD-L1 ≥1% (CA209648) nivolumab + ipilimumab vs chemotherapy

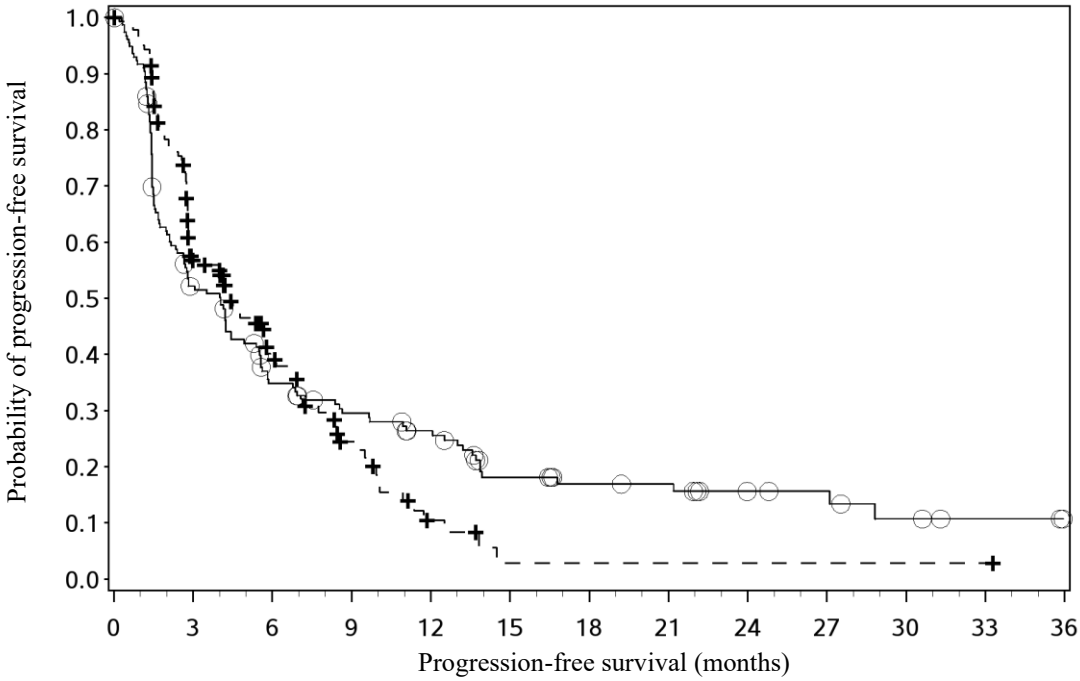


Number of subjects at risk

Nivolumab + ipilimumab													
158	136	116	98	89	63	50	40	31	20	11	9	4	0
Chemotherapy													
157	135	105	72	52	36	21	12	8	4	2	1	1	0

—○— Nivolumab + ipilimumab (events: 106/158), median and 95% CI: 13.70 (11.24, 17.02)
––+–– Chemotherapy (events: 121/157), median and 95% CI: 9.07 (7.69, 9.95)

Figure 27: Kaplan-Meier curves of PFS in patients with tumour PD-L1 ≥1% (CA209648) nivolumab + ipilimumab vs chemotherapy



Number of subjects at risk

Nivolumab + ipilimumab	158	78	48	38	31	18	14	13	8	7	4	2	0
Chemotherapy	157	67	35	17	5	1	1	1	1	1	1	1	0

—○— Nivolumab + ipilimumab (events: 123/158), median and 95% CI: 4.04 (2.40, 4.93)

– – + – – Chemotherapy (events: 100/157), median and 95% CI: 4.44 (2.89, 5.82)

In the post-hoc, exploratory early death analyses performed in all randomized subjects in the nivolumab plus ipilimumab vs chemotherapy arms from CA209648, liver metastases was identified as a predictive risk factor for early death in the nivolumab plus ipilimumab arm vs the chemotherapy arm. Additionally, other potential prognostic factors that were associated with early death included baseline neutrophil/lymphocyte ratio ≥ 4, high tumor burden and ECOG performance score 1.

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.

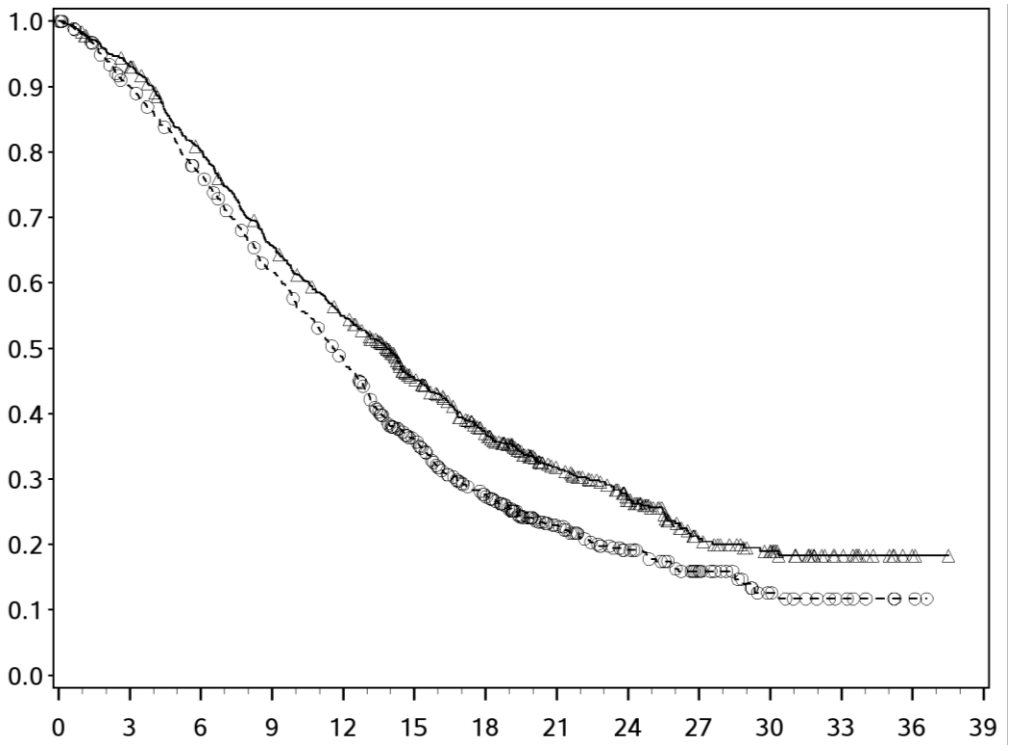
CA209-649 demonstrated a statistically significant improvement in OS and PFS for patients with PD-L1 CPS ≥5. Statistically significant improvement in OS was also demonstrated for all randomized patients. The minimum follow-up was 12.1 months. Efficacy results are shown in Table 28, and Figures 28 and 29.

Table 28: 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 28. Kaplan-Meier curves of OS in all randomised patients (CA209649)



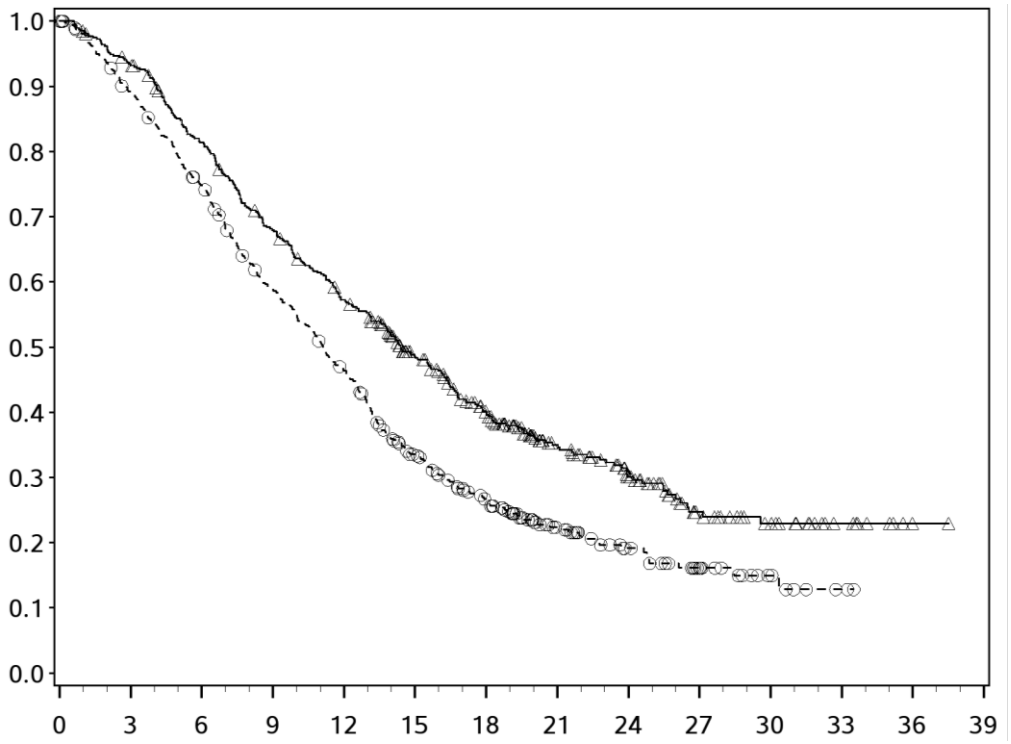
Number of subjects at risk

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 29. 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).

Hepatocellular carcinoma

The safety and efficacy of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks in the first-line treatment of unresectable or advanced hepatocellular carcinoma (HCC) were evaluated in a phase 3, randomised, active-controlled, open-label study (CA2099DW). The study included adult patients (18 years or older) with histologically confirmed HCC, Child Pugh Class A, ECOG performance status 0 or 1, and no prior systemic therapy for advanced disease. Esophagogastroduodenoscopy was not mandated prior to enrolment. The study enrolled adults whose disease was not amenable to or progressed after surgical and/or locoregional therapies. Prior neo-adjuvant or adjuvant systemic therapy was permitted. Patients with active autoimmune disease, brain or leptomeningeal metastases, prior liver transplant, a history of hepatic encephalopathy (within 12 months of randomisation), clinically significant ascites, medical conditions requiring systemic immunosuppression, infection with HIV, or active co infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV) were excluded from the study. Randomisation was stratified by aetiology (HBV vs. HCV vs. non-viral), macrovascular invasion and/or extrahepatic spread (present or absent), and alpha-fetoprotein levels (≥ 400 or < 400 ng/mL).

A total of 668 patients were randomised to receive nivolumab in combination with ipilimumab (n=335) or investigator's choice (n=333) of lenvatinib or sorafenib. In the investigator's choice arm, 85% and 15% of treated patients received lenvatinib or sorafenib, respectively. Patients in the nivolumab plus ipilimumab arm received nivolumab 1 mg/kg every 3 weeks in combination with ipilimumab 3 mg/kg every 3 weeks, for up to a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks. Patients in the investigators' choice arm received either lenvatinib 8 mg orally daily (if body weight < 60 kg) or 12 mg orally daily (if body weight ≥ 60 kg), or sorafenib 400 mg orally twice daily. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Tumour assessments were conducted at baseline, after randomisation at week 9 and week 16, then every 8 weeks up to 48 weeks, and then every 12 weeks thereafter until disease progression, treatment discontinuation, or initiation of subsequent therapy.

Baseline characteristics were generally balanced across treatment groups. The median age was 66 years (range: 20 to 89), with 53% ≥ 65 years and 16% ≥ 75 years, 53% were White, 44% were Asian, 2.2% were Black, and 82% were male. Baseline ECOG performance status was 0 (71%) or 1 (29%). Thirty-four percent (34%) of patients had HBV infection, 28% had HCV infection, and 36% had no evidence of HBV or HCV infection. Nineteen percent (19%) of patients had alcoholic liver disease and 11% had non-alcoholic fatty liver disease. The majority of patients had BCLC stage C (73%) disease at baseline, 19% had stage B, and 6% had stage A. Patients with Child-Pugh scores of 5, 6, and ≥ 7 were 77%, 20%, and 3%, respectively. A total of 54% of patients had extrahepatic spread; 25% had macrovascular invasion; and 33% had AFP levels ≥ 400 µg/L.

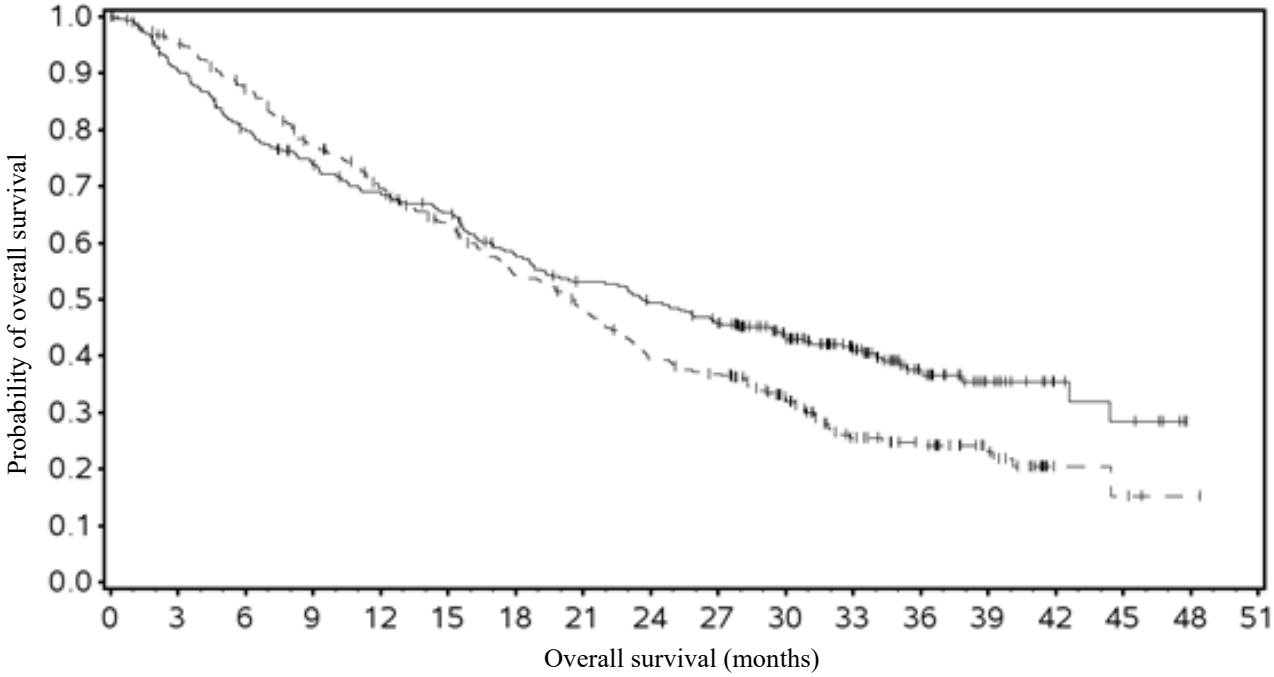
The study demonstrated a statistically significant benefit in OS and ORR for patients randomised to nivolumab in combination with ipilimumab compared to investigator's choice of lenvatinib or sorafenib. Efficacy results are presented in Table 29 and Figure 30.

Table 29: Efficacy results in first-line HCC (CA2099DW)[a]

	nivolumab + ipilimumab (n = 335)	**lenvatinib or sorafenib (n = 333)**
Overall survival		
Events	194 (58%)	228 (68%)
Median (months) (95% CI_)	23.7 (18.8, 29.4)	20.6 (17.5, 22.5)
Hazard ratio (95% CI) [b]	0.79 (0.65, 0.96)	
p-value [c]	0.0180	
Overall Response Rate, n (%)[d]	121 (36.1)	44 (13.2)
(95% CI)	(31.0, 41.5)	(9.8, 17.3)
p-value[e]	< 0.0001	
Complete response (%)	23 (6.9)	6 (1.8)
Partial response (%)	98 (29.3)	38 (11.4)
Duration of Response (months)[d]		
Median (95% CI)	30.4 (21.2, N.A.)	12.9 (10.2, 31.2)

[a] Minimum follow-up of 26.8 months. Median follow up of 35.2 months.
[b] Based on stratified Cox proportional hazard model.
[c] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value ≤0.0257.
[d] Assessed by BICR using RECIST 1.1.
[e] Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: p-value ≤0.025.

Figure 30: Kaplan-Meier curve of OS in first-line patients with HCC (CA2099DW)



Number of subjects at risk

Nivolumab + ipilimumab																	
335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
Investigator's choice																	
333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

—+— Nivolumab + ipilimumab (events: 194/335), median and 95% CI: 23.66 (18.33, 29.44)

– – + – – Lenvatinib or sorafenib (events: 228/333), median and 95% CI: 20.63 (17.48, 22.54)

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 30 and Figure 31.

Table 30: Efficacy results (CA209577)

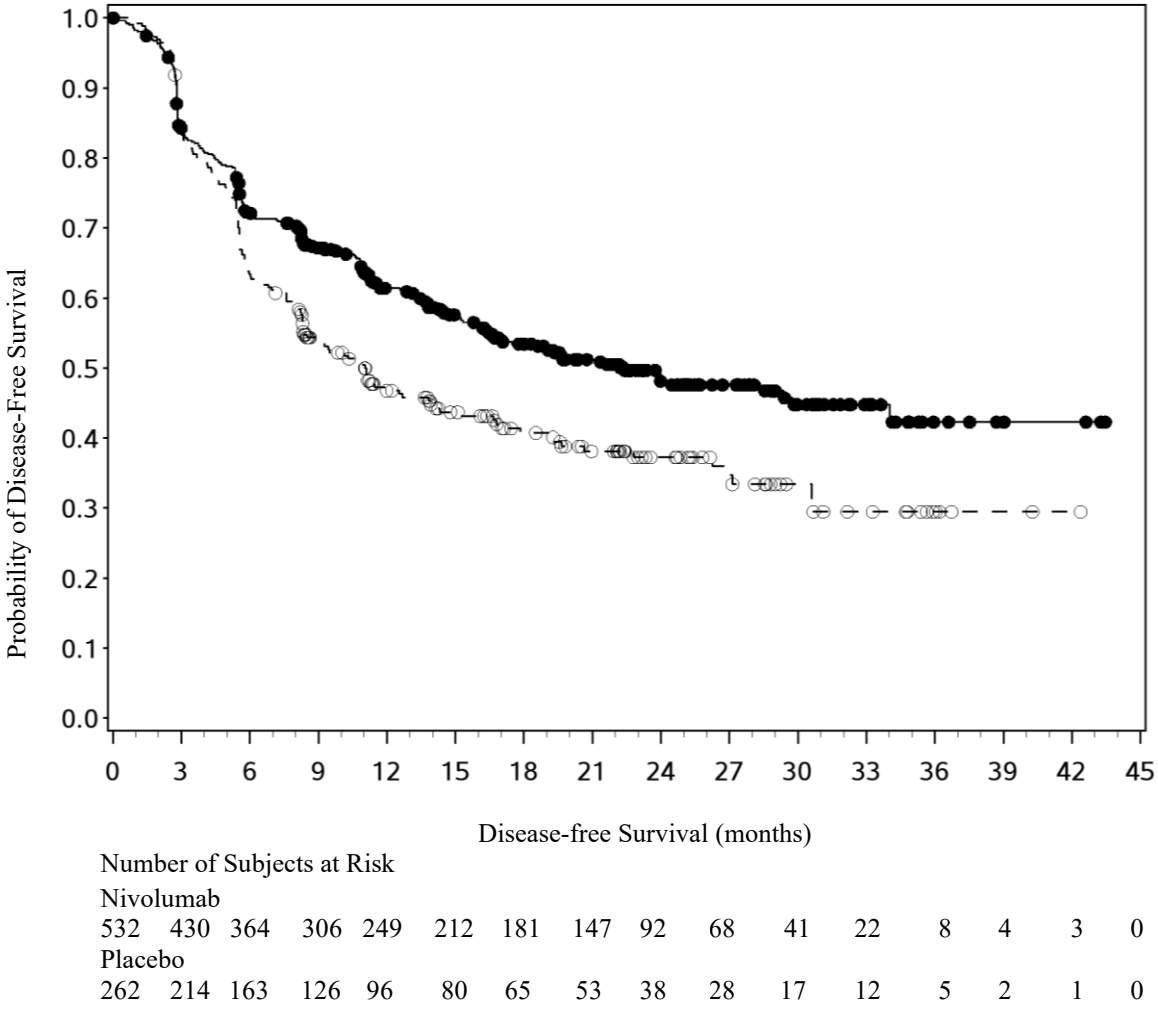
	nivolumab (n=532)	**placebo (n=262)**
Disease-free Survival[a]		
Events (%)	241 (45%)	155 (59%)
Hazard ratio (96.4% CI)[b]	0.69 (0.56, 0.86)	
p-value[c]	0.0003	
Median (95% CI) (months)	22.4 (16.6, 34.0)	11.0 (8.3, 14.3)

[a] Based on all randomized patients

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

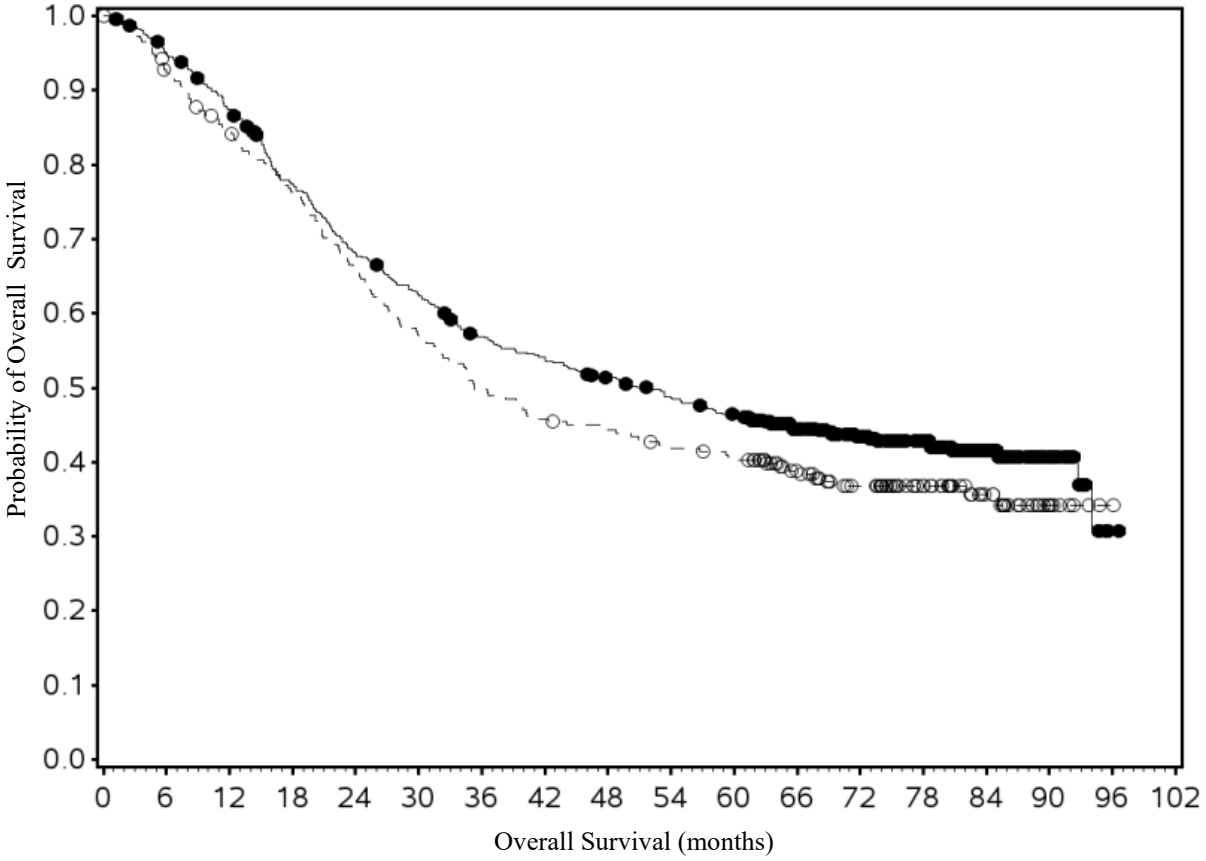
[c] Based on a stratified log-rank test.

Figure 31: Kaplan-Meier curves of DFS (CA209577)



At the final OS analysis with a minimum follow up of 60 months, the HR for OS was 0.85 (95.87% CI: 0.70, 1.04), p-value = 0.1064. Median OS was 51.71 (95% CI: 41.03, 61.63) months in the nivolumab arm compared with 35.25 (95% CI: 30.72, 48.76) months in the placebo arm. The Kaplan-Meier curves for OS with a minimum follow-up of 60 months are shown in Figure 32.

Figure 32: Kaplan-Meier curves of OS (CA209577)

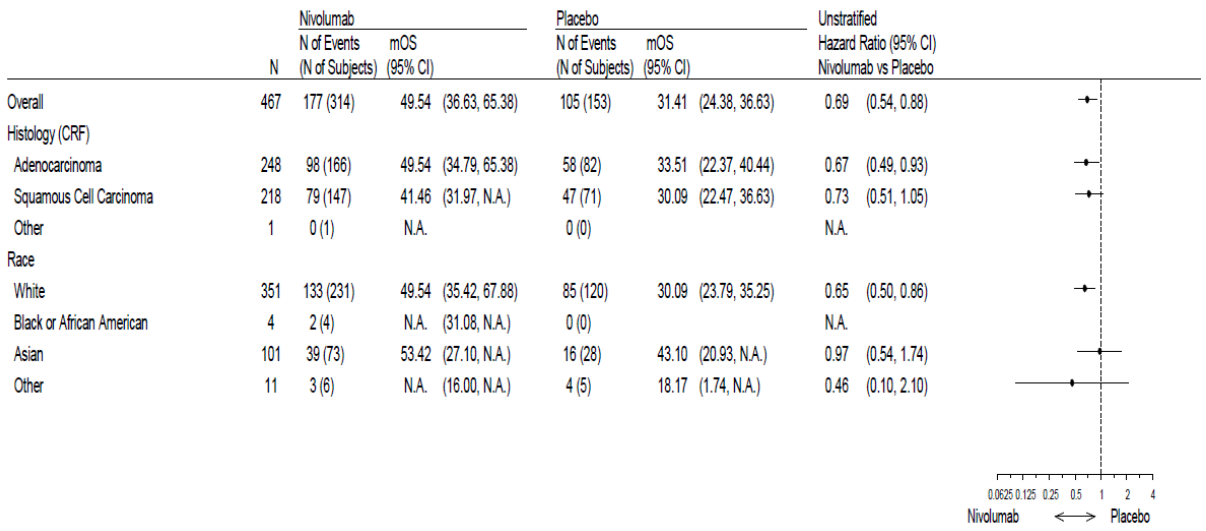


Nivolumab
532 501 460 402 354 325 292 278 261 244 230 185 150 111 59 22 1 0
Placebo
262 239 217 195 168 146 127 117 112 105 101 80 64 46 26 8 1 0

—●—— Nivolumab (events: 299/532), median and 95% CI: 51.71 (41.03, 61.63)
- - -○- - - Placebo (events: 162/262), median and 95% CI: 35.25 (30.72, 48.76)
Based on data cut-off: 17-Dec-2024, minimum follow-up of 60 months

In subgroup analysis, forest plots of OS by histology and race based on disease type (EC/GEJC) are shown below in Figures 33 and 34. Results in Figure 33 and 34 should be interpreted with caution, given the small sample sizes within EC or GEJC subgroups categorised by histology (adenocarcinoma/squamous cell carcinoma) and race (Asian/White). OS subgroup analyses may be confounded by crossover and imbalances in subsequent therapy use between treatment arms.

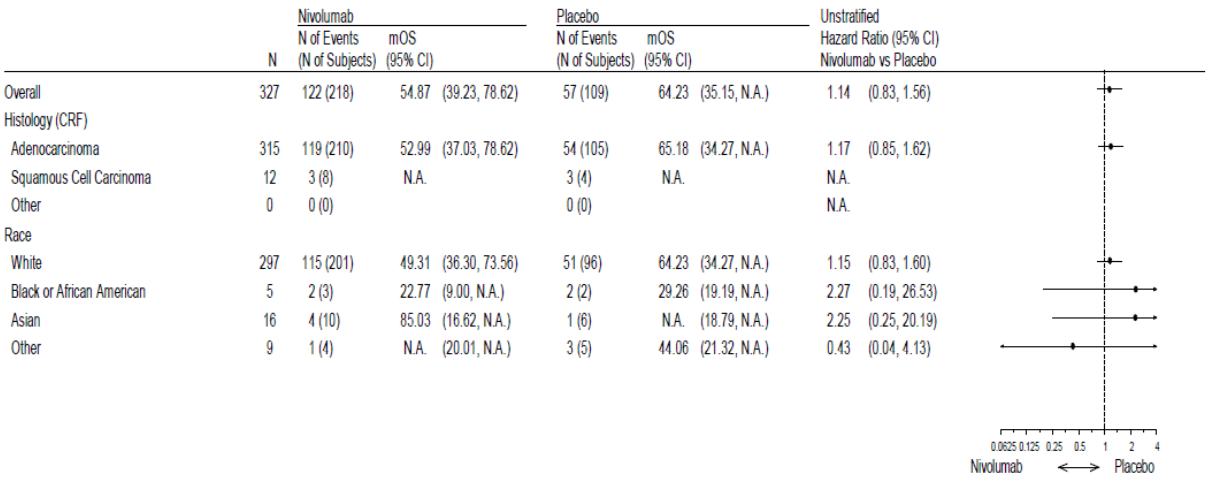
Figure 33: Forest Plot of Treatment Effect on Overall Survival in Pre-Defined Subsets - By Disease Type (EC/GEJC) - All Randomized Subjects (Esophageal Cancer)



DBL: 17-Dec-2024

HR and median estimate are not computed for subset (except age, race, region, and sex) category with less than 10 events per treatment group.

Figure 34: Forest Plot of Treatment Effect on Overall Survival in Pre-Defined Subsets - By Disease Type (EC/GEJC) - All Randomized Subjects (Gastroesophageal Junction Cancer)



DBL: 17-Dec-2024

HR and median estimate are not computed for subset (except age, race, region, and sex) category with less than 10 events per treatment group.

The HRs for DFS and DMFS consistently favored nivolumab over placebo in race (Asian/White), disease type (EC/GEJC) and histology (adenocarcinoma/squamous cell carcinoma) subgroups, as shown in the forest plots in Figure 35 and 36.

Figure 35: Forest Plot of Treatment Effect on Disease-Free Survival per Investigator in Pre-Defined Subsets - All Randomized Subjects (Final analysis based on 17-Dec-2024 DBL)

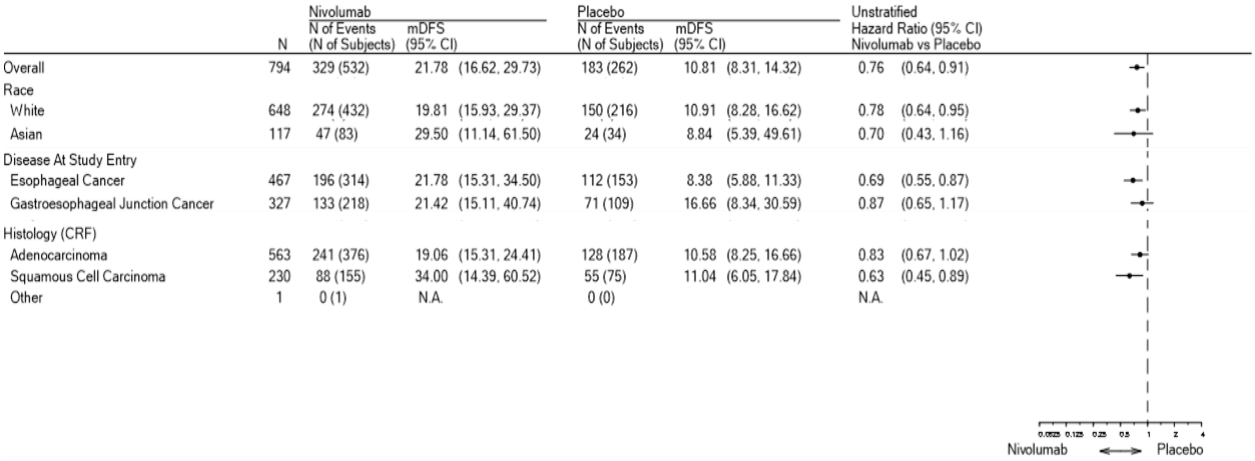
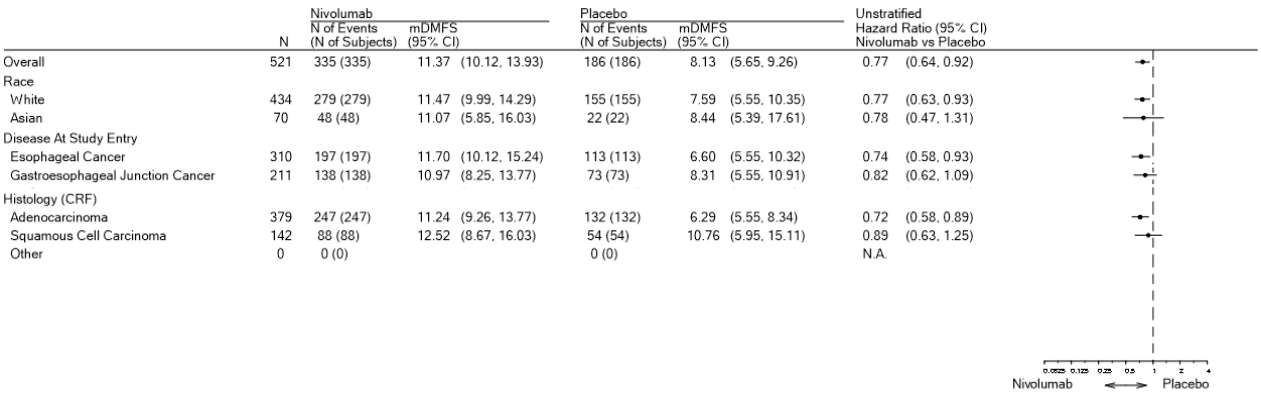


Figure 36: Forest Plot of Treatment Effect on DMFS per Investigator in Pre-Defined Subsets - All Randomized Subjects (Final analysis based on 17-Dec-2024 DBL)



Advanced Urothelial Carcinoma

Randomised open-label phase 3 study of nivolumab in combination with chemotherapy vs. chemotherapy (CA209901)

The safety and efficacy of nivolumab in combination with cisplatin and gemcitabine followed by nivolumab monotherapy were evaluated in a randomised open-label study CA209901 in cisplatin-eligible patients with unresectable or metastatic urothelial carcinoma. The study included subjects (18 years or older) with histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra, who were eligible for cisplatin and gemcitabine. Minor histologic variants (< 50% overall) were acceptable (TCC must have been the dominant histology). All subjects were required to have measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria. No prior systemic anti-cancer therapy for metastatic or surgically unresectable urothelial carcinoma was permitted. Prior neoadjuvant chemotherapy or prior adjuvant platinum-based chemotherapy following radical cystectomy were permitted as long as the disease recurrence took place ≥12 months from completion of therapy. Prior intravesical therapy was permitted if completed at least 4 weeks prior to initiation of study treatment. Radiation therapy (with or without chemotherapy) with curative intent was permitted if treatment was completed ≥12 months before enrolment. Palliative radiotherapy was permitted as long as it was completed at least 2 weeks prior to therapy.

A total of 608 patients were randomised to receive either nivolumab in combination with cisplatin and gemcitabine (n=304) or cisplatin and gemcitabine (n=304). Randomisation was stratified by tumour PD-L1 status (≥1% vs. < 1% or indeterminate) and liver metastasis (yes vs. no). The median age was 65 years of age (range: 32 to 86) with 51% of patients ≥ 65 years of age and 12% of patients ≥ 75 years of age, 23% were Asian, 72% were White, 0.3% were Black; 77% were male, 23% were female. Baseline ECOG performance status was 0 (53%) or 1 (46%). Patients in the nivolumab in combination with cisplatin and gemcitabine arm were treated with nivolumab 360 mg every three weeks, in combination with cisplatin and gemcitabine for up to 6 cycles, after which patients received nivolumab monotherapy 480 mg every 4 weeks for a total of up to 24 months. Patients received gemcitabine dosed

at 1000 mg/m2 IV over 30-minutes on Days 1 and 8 of the 3 week treatment cycle and cisplatin dosed at 70 mg/m2 IV over 30 to 120-minutes on Day 1 of the 3 week treatment cycle. A total of 92 patients (49 in the nivolumab in combination with cisplatin and gemcitabine arm and 43 in the cisplatin and gemcitabine arm) switched from cisplatin to carboplatin after at least one cycle of cisplatin.

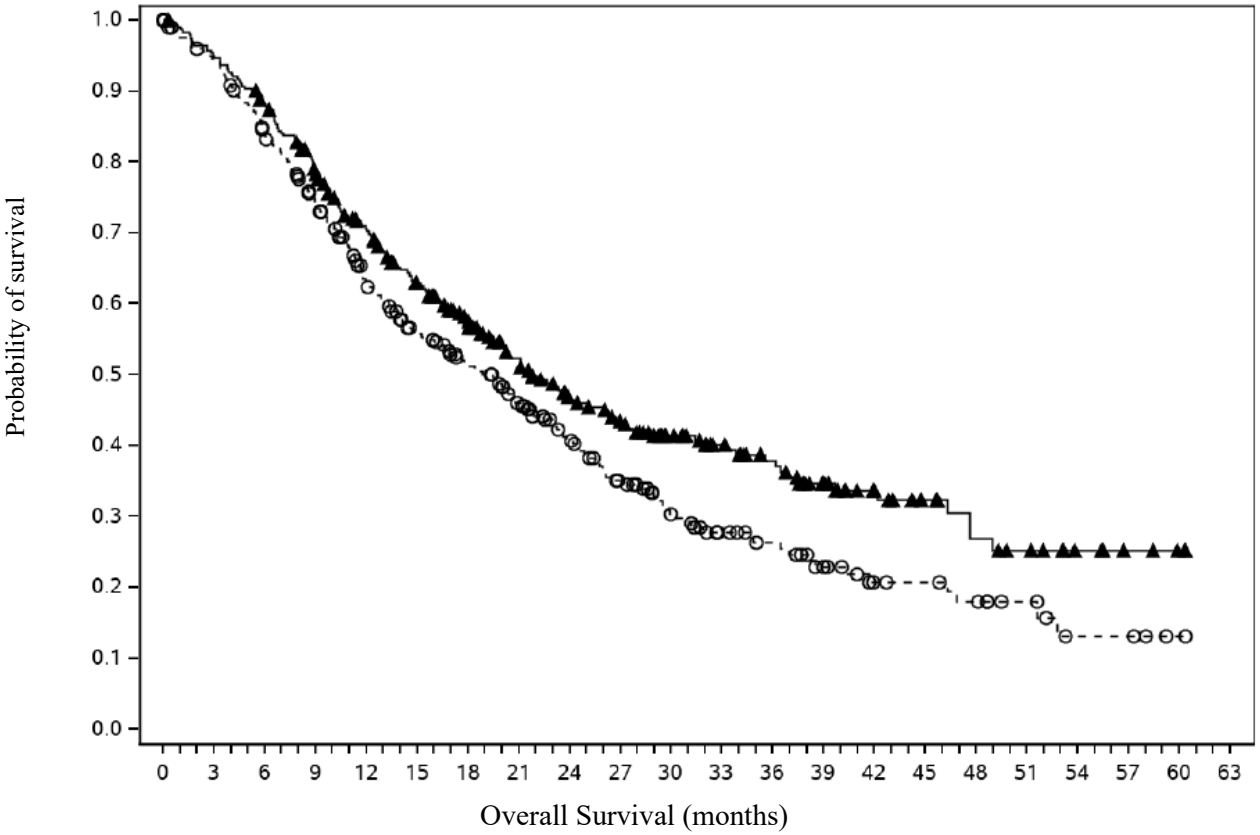
The study demonstrated a statistically significant benefit in OS and PFS for patients randomised to nivolumab in combination with cisplatin and gemcitabine compared to cisplatin and gemcitabine alone. Efficacy results are presented in Table 31 and Figures 37 and 38.

Table 31: Efficacy Results (CA209901)

	nivolumab and cisplatin-gemcitabine chemotherapy (n=304)	**cisplatin- gemcitabine chemotherapy (n=304)**
Overall Survival[a]		
Events	172 (56.6)	193 (63.5)
Median (months) (95% CI)	21.7 (18.6, 26.4)	18.9 (14.7, 22.4)
Hazard ratio (95% CI)[b]	0.78 (0.63, 0.96)	
p-value[c]	0.0171	
Progression-free Survival[a]		
Events	211 (69.4)	191 (62.8)
Median (months) (95% CI)	7.92 (7.62, 9.49)	7.56 (6.05, 7.75)
Hazard ratio (95% CI)[b]	0.72 (0.59, 0.88)	
p-value[c]	0.0012	
Objective Response Rate		
Responders	175 (57.6)	131 (43.1)
(95% CI)	(51.8, 63.2)	(37.5, 48.9)

[a] Based on Kaplan-Meier Estimates
[b] Stratified Cox proportional hazard model.
[c] 2 sided p-value from stratified log-rank test.

Figure 37: Kaplan Meier curves of OS (CA209901)



Number of subjects at risk

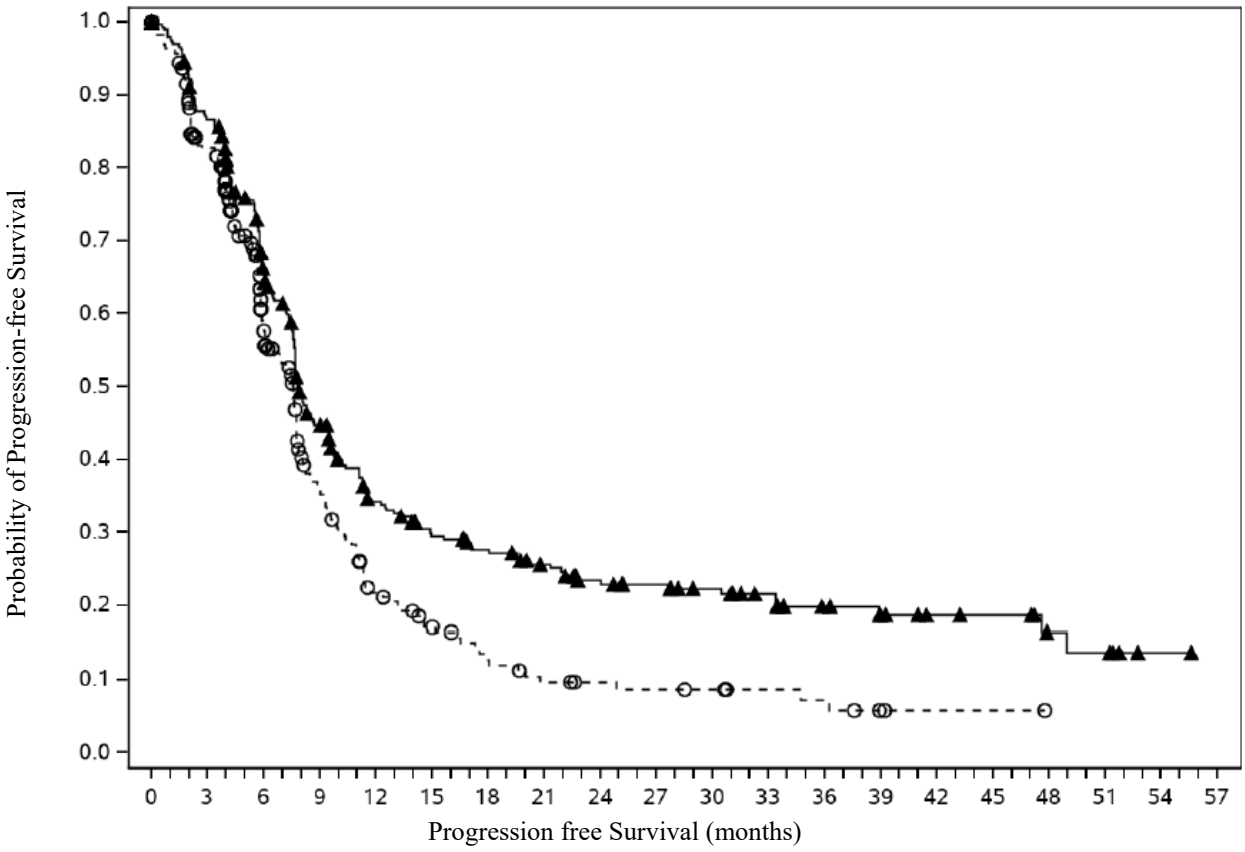
Nivolumab + gemcitabine-cisplatin chemotherapy																				
304	286	264	228	196	167	142	119	97	84	69	58	48	36	25	20	15	12	7	4	2	0
Gemcitabine-cisplatin chemotherapy																				
304	277	242	208	166	140	122	102	82	65	49	39	33	24	17	16	13	9	4	4	1	0

- - -▲- - - Nivolumab + gemcitabine-cisplatin chemotherapy (events: 172/304), median and 95% CI: 21.72 (18,63, 26.38)

- - -❍- - - Gemcitabine-cisplatin chemotherapy (events: 193/304), median and 95% CI: 18.85 (14.72, 22.44)

Based on clinical data cut-off: 09-May-2023, minimum follow-up of 7.4 months

Figure 38: Kaplan Meier curves of PFS (CA209901)



Number of subjects at risk

Nivolumab + gemcitabine-cisplatin chemotherapy																				
304	253	179	116	82	65	57	49	41	36	31	26	19	14	11	10	10	6	5	1	0
Gemcitabine-cisplatin chemotherapy																				
304	223	119	63	35	25	17	12	12	10	9	8	6	5	2	1	1	0	0	0	0

- - -▲- - - Nivolumab + gemcitabine-cisplatin chemotherapy (events: 211/304), median and 95% CI: 7.92 (7.62, 9.49)

- - -❍- - - Gemcitabine-cisplatin chemotherapy (events: 191/304), median and 95% CI: 7.56 (6.05, 7.75)

Based on clinical data cut-off: 09-May-2023, minimum follow-up of 7.4 months

The primary analysis of PFS included censoring for new anti-cancer treatment before disease progression (Table 31). Results for PFS with and without censoring for new anti-cancer treatment before disease progression were consistent.

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 32 and Figure 39.

Table 32: 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 (%) Median DFS (95% CI) months[a]	170 (48.2) 20.76 (16.49, 27.63)	204 (57.3) 10.84 (8.25, 13.86)	55 (39.3) N.R (21.19, N.E.)	81 (57.0) 8.41 (5.59, 21.19)
HR[b] (alpha adjusted[c] % CI)	0.70 (0.55, 0.90)		0.55 (0.35, 0.85)	
p-value	0.0008[d]		0.0005[e]	
Rate (95%) at 6 months	74.9 (69.9, 79.2)	60.3 (54.9, 65.3)	74.5 (66.2, 81.1)	55.7 (46.8, 63.6)

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

[a] Based on Kaplan-Meier estimates

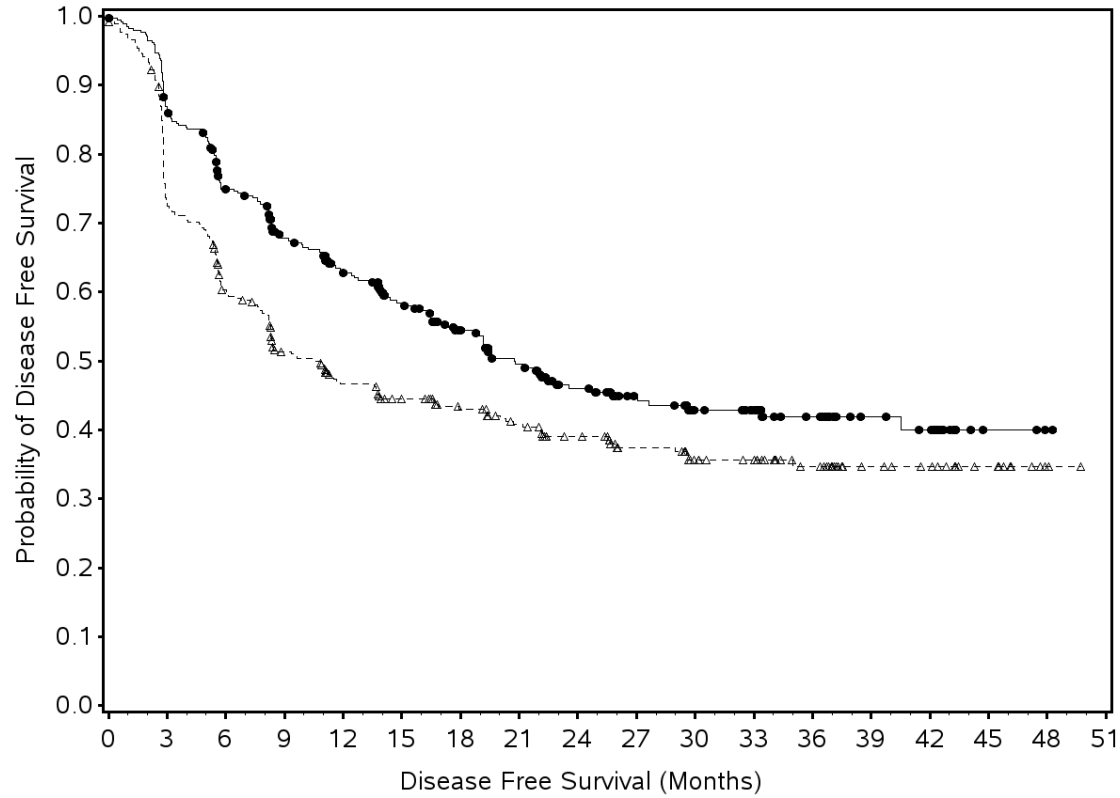
[b] Stratified Cox proportional hazard model. Hazard Ratio is nivolumab over placebo.

[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 39: 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 33. An improvement in survival or disease-related symptoms has not been established.

Table 33: 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%).

dMMR or MSI-H Colorectal Cancer (CRC)

Open-label study of nivolumab in combination with ipilimumab versus chemotherapy in dMMR or MSI H CRC patients naive to treatment in the metastatic setting (CA2098HW)

The safety and efficacy of nivolumab 240 mg in combination with ipilimumab 1 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks in the first line treatment of unresectable or metastatic CRC with known tumour MSI H or dMMR status were evaluated in a randomized, multi-arm, phase 3, open-label study (CA2098HW). Study treatment arms included nivolumab monotherapy, nivolumab in combination with ipilimumab, or investigator's choice of chemotherapy. MSI H or dMMR tumour status was determined in accordance with local standard of practice using PCR, NGS or IHC, assays. Central assessment of MSI H status using PCR (Idylla MSI) test and dMMR status using IHC (Omnis MMR) test was conducted retrospectively on patient tumour specimens used for local MSI H/dMMR status determination. Patients with confirmed MSI H/dMMR status by either central test comprised the primary efficacy population. Patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors were excluded from the study. Randomization

was stratified by tumour location (right vs left). Patients randomized to the chemotherapy arm could receive nivolumab plus ipilimumab combination upon progression assessed by BICR.

A total of 303 previously untreated patients, in the metastatic setting, were randomised to study, including 202 patients to nivolumab in combination with ipilimumab and 101 patients to chemotherapy. Among them 255 had centrally confirmed MSI H/dMMR status, 171 in the nivolumab in combination with ipilimumab arm and 84 in the chemotherapy arm. Patients in the nivolumab plus ipilimumab arm received nivolumab 240 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks. Patients in the chemotherapy arm received: mFOLFOX6 (oxaliplatin, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m2, leucovorin 400 mg/m2, and fluorouracil 400 mg/m2 bolus followed by fluorouracil 2400 mg/m2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m2 administered prior to mFOLFOX6 every 2 weeks; or FOLFIRI (irinotecan, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m2, leucovorin 400 mg/m2, and fluorouracil 400 mg/m2 bolus and fluorouracil 2400 mg/m2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m2 administered prior to FOLFIRI every 2 weeks. Treatment continued until disease progression, unacceptable toxicity, or for nivolumab in combination with ipilimumab up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Tumour assessments per RECIST v1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter until week 96, then every 16 weeks thereafter until week 146, and then every 24 weeks.

The baseline characteristics of all randomised previously untreated for metastatic disease patients were: the median age was 63 years (range: 21 to 87), with 46% ≥ 65 years of age and 18% ≥ 75 years of age; 46% were male and 86% were White. Baseline ECOG performance status was 0 (54%) and ≥ 1 (46%); tumour location was right-sided or left-sided for 68% and 32% of patients, respectively; and 39 patients had confirmed Lynch syndrome among the 223 patients with a known status. The baseline characteristics of previously untreated for metastatic disease patients with centrally confirmed MSI-H/dMMR were consistent with all randomised previously untreated patients. Among the 101 patients randomised to receive chemotherapy, 88 received chemotherapy per protocol, including oxaliplatin-containing regimens (58%) and irinotecan-containing regimens (42%). Additionally, 66 patients received a targeted agent, either bevacizumab (64%) or cetuximab (11%).

A primary efficacy outcome measure of the study was BICR-assessed PFS per RECIST 1.1. Additional efficacy measures included ORR assessed by BICR, OS, and duration of response.

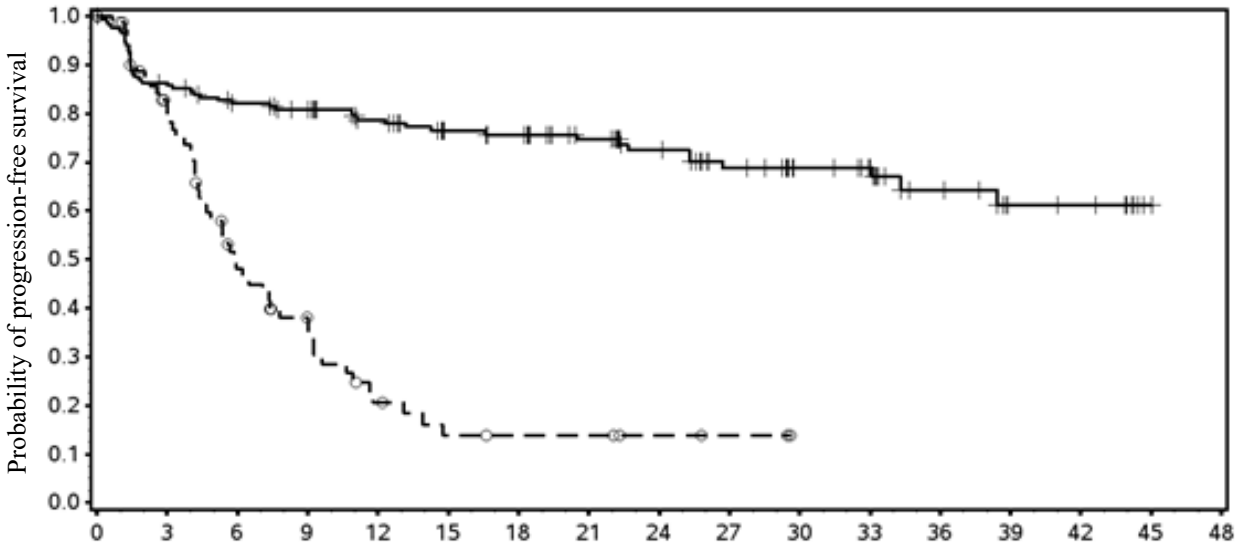
The study met the primary endpoint, at the planned interim analysis, demonstrating a statistically significant improvement in BICR assessed-PFS for patients with centrally confirmed MSI H/dMMR in the nivolumab in combination with ipilimumab arm compared with the chemotherapy arm. The BICR-assessed PFS results are presented in Table 34 and Figure 40. At the time of this interim analysis, the other endpoints, including the data from nivolumab monotherapy arm, were not tested, due to testing hierarchy.

Table 34: Efficacy results in first-line MSI-H/dMMR centrally confirmed CRC (CA2098HW)[a]

	nivolumab + ipilimumab (n = 171)	**chemotherapy (n = 84)**
Progression-free survival		
Events	48 (28%)	52 (62%)
Hazard ratio	0.21	
95% CI	(0.14, 0.32)	
p-value[b]	< 0.0001	
Median (95% CI) (months)	NR (38.4, NR)	5.9 (4.4, 7.8)

a Median follow-up of 31.5 months (range: 6.1 to 48.4 months).
b Based on stratified 2-sided log-rank test

Figure 40: Kaplan-Meier curve of PFS in first-line patients with MSI-H/dMMR centrally confirmed CRC (CA2098HW)



Number of subjects at risk

Nivolumab + ipilimumab																
171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemotherapy																
84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

—+—— Nivolumab + ipilimumab (events: 48/171), median and 95% CI: N.A. (38.44, N.A.)
- - - ❍ - - - Chemotherapy (events: 52/84), median and 95% CI: 5.85 (4.37, 7.79)

Open-label study of nivolumab in combination with ipilimumab in dMMR or MSI-H CRC in patients who received prior fluoropyrimidine based combination chemotherapy

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 35.

Table 35: 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.

Paediatric population

Open label phase 1/2 study (CA209070)

Study CA209070 was an open-label, single-arm, dose-confirmation and dose-expansion, phase 1/2 study of nivolumab as a single agent and in combination with ipilimumab in paediatric and young adult patients with recurrent or refractory solid or haematological tumours, including neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, advanced melanoma, cHL and non-Hodgkin lymphoma (NHL). Among the 126 treated patients, 97 were paediatric patients from 12 months to < 18 years of age. Of the 97 paediatric patients, 64 were treated with nivolumab monotherapy (3 mg/kg administered intravenously over 60 minutes every 2 weeks) and 33 were treated with nivolumab in combination with ipilimumab (nivolumab 1 mg/kg or 3 mg/kg administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 90 minutes every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks). Patients received either nivolumab as monotherapy for a median of 2 doses (range: 1, 89) or nivolumab in combination with ipilimumab for a median of 2 doses (range: 1, 24). The main primary outcome measures were safety, tolerability and antitumour activity as evaluated by descriptive ORR and OS.

Among the 64 paediatric patients treated with nivolumab monotherapy, 60 were response-evaluable patients (melanoma n = 1, solid tumours n = 47 and haematological tumours n = 12). In the 48 response-evaluable paediatric patients with melanoma or solid tumours, no objective responses were observed. In the 12 response-evaluable paediatric patients with haematological tumours, ORR was 25.0% (95% CI: 5.5, 57.2), including 1 complete response in cHL and 2 partial responses, one in cHL and another one in NHL. In the descriptive analyses for the 64 paediatric patients treated with nivolumab monotherapy, the median OS was

6.67 months (95% CI: 5.98, NA); 6.14 months (95% CI: 5.39, 24.67) for patients with melanoma or solid tumours, and not reached for patients with haematological tumours.

Among the 30 response-evaluable paediatric patients treated with nivolumab in combination with ipilimumab (solid tumours other than melanoma only), no objective responses were observed. For the 33 paediatric patients treated with nivolumab in combination with ipilimumab, the median OS was 8.25 months (95% CI: 5.45, 16.95) in a descriptive analysis.

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). In HCC patients, there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (67% and 35%, respectively) relative to all patients who received nivolumab with ipilimumab (53% and 27%, 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 different tumour types (NSCLC, SCLC, melanoma, RCC, SCCHN, UC, GC, and cHL) 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 = 351) and in patients with moderate hepatic impairment (total bilirubin > 1.5 × to 3 × ULN and any AST; n = 10) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 3096) in a population PK analysis. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate hepatic impairment and normal hepatic function. Similar results were observed in patients with HCC (mild hepatic impairment: n = 152; moderate hepatic impairment: n = 13). Nivolumab has not been studied in patients with severe hepatic impairment (total bilirubin > 3 × ULN and any AST) (see section 4.2).

Paediatric population
For nivolumab monotherapy, the exposures of nivolumab in adolescents 12 years of age and older who weigh at least 50 kg are expected to be comparable to those in adult patients at the recommended dose. Body weight-based dosing is recommended for adolescents 12 years of age and older who weigh less than 50 kg.

For nivolumab in combination with ipilimumab, the exposures of nivolumab and ipilimumab in adolescents 12 years of age and older are expected to be comparable to those in adult patients at the recommended dose.

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

January 2026