OPDIVO™ (Nivolumab)
Injection Concentrate 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

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 is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Adjuvant treatment of melanoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see section 5.1).

Non-Small Cell Lung Cancer (NSCLC)

OPDIVO is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving OPDIVO

Neoadjuvant treatment of NSCLC

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OPDIVO, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥ 4cm or node positive) non-small cell lung cancer (NSCLC).

Renal Cell Carcinoma (RCC)

OPDIVO as monotherapy, is indicated for the treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

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

Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

4.2 Posology and method of administration

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

PD-L1 testing
If specified in the indication, patient selection for treatment with OPDIVO based on the tumour expression of PD-L1 should be confirmed by a validated test (see sections 4.1, 4.4, and 5.1).

Posology

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

OPDIVO in combination with cabozantinib (tablets)

Renal cell carcinoma
The recommended dose is nivolumab administered intravenously at either 240 mg every 2 weeks **or** 480 mg every 4 weeks in combination with 40 mg cabozantinib (tablets) administered orally every day.

Table 1: Recommended doses and infusion times for intravenous administration of nivolumab in combination with oral administration of cabozantinib (tablets) for RCC

	Combination phase
Nivolumab	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes
Cabozantinib (tablets)	40 mg once daily

OPDIVO in combination with Chemotherapy

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 3 weeks or 240 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 2 weeks (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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

Duration of treatment

Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

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

For OPDIVO in combination with cabozantinib, OPDIVO should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Cabozantinib should be continued until disease progression or unacceptable toxicity. Refer to the package 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 package insert of these other combination therapeutic agents regarding dosing.

Table 2: Recommended treatment modifications for OPDIVO or OPDIVO in combination

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune- related colitis	Grade 2 or 3 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis **NOTE:** for RCC patients treated with **OPDIVO in combination with cabozantinib** with liver enzyme elevations, see dosing guidelines following this table.	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[a] as long as no symptoms are present
	Grade 4 hypothyroidism, hyperthyroidism, hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[b]
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)

Table 2: Recommended treatment modifications for OPDIVO or OPDIVO in combination

	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

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

[b] The safety of re-initiating nivolumab 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 chemotherapy, refer to the package insert of the other combination therapy agents regarding dosing. If any agents are withheld, the other agents may be continued. If dosing is resumed after a delay, either the combination treatment, OPDIVO monotherapy or chemotherapy alone could be resumed based on the evaluation of the individual patient.

OPDIVO in combination with cabozantinib in RCC

When OPDIVO is used in combination with cabozantinib, the above treatment modifications in Table 2 also apply to the OPDIVO component. In addition, for liver enzyme elevations, in patients with RCC being treated with OPDIVO in combination with cabozantinib:

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

Special populations

Paediatric population

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

Elderly

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

Renal impairment

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

Hepatic impairment

Based on the population PK results, no dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. OPDIVO must be administered with caution in

patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment.

Method of administration

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

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 chemotherapy, OPDIVO should be given first followed by chemotherapy on the same day. Use separate infusion bags and filters for each infusion.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Assessment of PD-L1 status
When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is used.

Immune-related adverse reactions.

When nivolumab is administered in combination, refer to the package insert of the other combination therapy agents prior to initiation of treatment. Immune-related adverse reactions have occurred at similar frequencies when OPDIVO was administered in combination with cabozantinib relative to nivolumab monotherapy. Therefore, the guidance below for immune-related adverse reactions applies to the OPDIVO component of the combination, except where specifically noted. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see section 4.2).
Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Cardiac and pulmonary adverse reactions including pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment.

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab may occur at any time during or after discontinuation of nivolumab 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 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 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 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 treatment (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 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 should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab 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 must be permanently discontinued.

Immune-related colitis
Severe diarrhoea or colitis has been observed with nivolumab treatment (see section 4.8). Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Infectious and other aetiologies of diarrhoea should be ruled out, therefore appropriate laboratory tests and additional examinations must be performed. If diagnosis of corticosteroid-refractory immune-related colitis is confirmed addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered.

For Grade 4 diarrhoea or colitis, nivolumab 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 should be withheld and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab must be permanently discontinued.

For Grade 2 diarrhoea or colitis, nivolumab 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 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 must be permanently discontinued.

Immune-related hepatitis
Severe hepatitis has been observed with nivolumab treatment (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 transaminase or total bilirubin elevation, nivolumab 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 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 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 must be permanently discontinued.

Immune-related nephritis or renal dysfunction
Severe nephritis and renal dysfunction has been observed with nivolumab treatment (see section 4.8). Patients should be monitored for signs and symptoms of nephritis and 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 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 should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab 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 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 treatment (see section 4.8).

Patients should be monitored for clinical signs and symptoms of endocrinopathies and for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate aetiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.

For symptomatic hypothyroidism, nivolumab should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, nivolumab should be withheld and antithyroid medication should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. Nivolumab must be permanently discontinued for life-threatening hyperthyroidism or hypothyroidism.

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

For symptomatic Grade 2 or 3 hypophysitis, nivolumab 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 may be resumed after corticosteroid taper, if needed. Nivolumab 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 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 must be permanently discontinued for life-threatening diabetes.

Immune-related skin adverse reactions
Severe rash has been observed less commonly, with nivolumab as monotherapy (see section 4.8). Nivolumab should be withheld for Grade 3 rash and discontinued for Grade 4 rash. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Rare cases of SJS and TEN some of them with fatal outcome have been observed. If symptoms or signs of SJS or TEN appear, treatment with nivolumab should be discontinued and the patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab permanent discontinuation of treatment is recommended (see section 4.2).

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

Other immune-related adverse reactions
The following immune-related adverse reactions were reported in less than 1% of patients treated with nivolumab in clinical trials across doses and tumour types: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenia gravis, myasthenic syndrome, aseptic meningitis, gastritis, sarcoidosis, duodenitis, encephalitis, myositis, myocarditis and rhabdomyolysis. Cases of Vogt-Koyanagi-Harada syndrome have been reported post-marketing (see section 4.8).

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab should be withheld and corticosteroids administered. Upon improvement, nivolumab may be resumed after corticosteroid taper. Nivolumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab should be withheld or discontinued (see section 4.2), and appropriate treatment instituted.
The diagnosis of myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, nivolumab treatment should be withheld or permanently discontinued (see section 4.2).

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients.

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

Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab as monotherapy. Caution should be taken when nivolumab is administered as monotherapy. If HLH is confirmed, administration of nivolumab should be discontinued and treatment for HLH initiated.

Infusion reactions
Severe infusion reactions have been reported in clinical trials (see section 4.8). In case of a severe or life-threatening infusion reaction, the nivolumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab 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. Patients with ocular/uveal melanoma were excluded from pivotal clinical trials of melanoma. In addition, CA209037 excluded patients who have had a Grade 4 adverse reaction that was related to anti-CTLA-4 therapy (see section 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Adjuvant treatment of 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 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 benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In non-squamous NSCLC, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumour PD-L1 expression (see section 5.1).

Neoadjuvant treatment of NSCLC
Patients with a baseline performance score ≥ 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 with

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chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Renal Cell Carcinoma
Nivolumab monotherapy
Patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of nivolumab (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.

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

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

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma
Patients who had baseline ECOG performance score ≥ 2, untreated central nervous system metastases, active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in gastric, GEJ or oesophageal adenocarcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Study CA209649 excluded patients with known HER2-positive status. Patients with undetermined status were allowed in the study and represented 40.3% of patients (see section 5.1).

Patients on controlled sodium diet
Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. 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.

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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 embryofoetal toxicity (see section 5.3). Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore nivolumab has the potential to be transmitted from the mother to the developing foetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab.

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

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

4.7 Effects on ability to drive and use machines

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
In the pooled dataset of nivolumab as monotherapy across tumour types (n = 4122) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥10%) were fatigue (45%), musculoskeletal pain (31%), diarrhoea (26%), cough (24%) rash (24%), nausea (23%), pruritus (19%), decreased appetite (18%), constipation (17%), dyspnoea (17%), abdominal pain (16%), upper respiratory tract infection (16%), arthralgia (14%), pyrexia (14%), vomiting (14%), headache (13%), and oedema (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). With a minimum of 63 months follow-up in NSCLC, no new safety signals were identified.

Adjuvant treatment of melanoma
In the dataset of nivolumab 3 mg/kg as monotherapy for the adjuvant treatment of melanoma (n = 452), the most frequent adverse reactions (≥ 10%) were fatigue (46%), rash (29%), diarrhoea

(24%), pruritus (23%), nausea (15%), arthralgia (13%), musculoskeletal pain (11%), and hypothyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Tabulated summary of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 4122) 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); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 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	lymphopaenia[b], anaemia[b,j], leucopoenia[b],neutropaenia[a,b] thrombocytopaenia[b]
Uncommon	eosinophilia
Not known	haemophagocytic lymphohistiocytosis
Immune system disorders	
Common	infusion related reaction,[c] hypersensitivity[c] (including anaphylactic reaction)[c]
Uncommon	sarcoidosis
Not known	solid organ transplant rejection[g]
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism, thyroiditis
Uncommon	adrenal insufficiency[k], hypopituitarism, hypophysitis~~,~~, diabetes mellitus
Rare	diabetic ketoacidosis, hypoparathyroidism
Metabolism and nutrition disorders	
Very common	decreased appetite, hyperglycaemia[b,c], hypoglycaemia[b]
Common	Dehydration, weight decreased
Uncommon	metabolic acidosis
Not known	tumour lysis syndrome[h]
Nervous system disorders	
Very common	headache
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,c,l]
Eye disorders	
Common	blurred vision, dry eye
Uncommon	uveitis
Not known	Vogt-Koyanagi-Harada syndrome[g]

Cardiac disorders	
Common	tachycardia, atrial fibrillation
Uncommon	myocarditis[a,e], pericardial disorders[i], arrhythmia (including ventricular arrhythmia)
Vascular disorders	
Common	hypertension
Rare	vasculitis
Respiratory, thoracic and mediastinal disorders	
Very common	dyspnoea[a], cough
Common	pneumonitis[a,c], 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[c], cholestasis
Skin and subcutaneous tissue disorders	
Very common	rash [d], pruritus
Common	vitiligo, dry skin, erythema, alopecia, urticaria
Uncommon	psoriasis, rosacea, erythema multiforme
Rare	toxic epidermal necrolysis[a,c], Stevens-Johnson syndrome[a]
Not known	lichen sclerosus[h], other lichen disorders
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[f], arthralgia
Common	arthritis
Uncommon	polymyalgia rheumatica
Rare	Sjogren's syndrome, myopathy, myositis (including polymyositis)[a], rhabdomyolysis[a,c]
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)[a,c]
Rare	tubulointerstitial nephritis, cystitis noninfective[h]
General disorders and administration site conditions	
Very common	fatigue, pyrexia, oedema[m]
Common	pain, chest pain
Investigations[b]	
Very common	increased AST, hyponatraemia, hypoalbuminaemia, increased alkaline phosphatase, increased creatinine, increased ALT, increased lipase, hyperkalaemia, increased amylase, hypocalcaemia, hypomagnesaemia, hypokalaemia, hypercalcaemia.
Common	increased total bilirubin, hypernatraemia, hypermagnesaemia,

Adverse reaction frequencies presented in Table 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] Life-threatening cases have been reported in completed or ongoing clinical studies.

[d] 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.

[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] Post-marketing event (also see section 4.4)
[h] Reported in clinical studies and in the post-marketing setting.
[i] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.
[j] 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.
[k] Includes adrenal insufficiency, adrenocortical insufficiency acute, and secondary adrenocortical insufficiency.
[l] Includes encephalitis and limbic encephalitis.
[m] Oedema is a composite term which includes generalised oedema, oedema peripheral, peripheral swelling and swelling.

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

Nivolumab in combination with other therapeutic agents (see section 4.2)

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

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 = 958), with a minimum follow-up of 12.1 months for gastric, GEJ or oesophageal adenocarcinoma or following 3 cycles of treatment for resectable NSCLC, the most frequent adverse reactions were nausea (46%), peripheral neuropathy (45%), fatigue (41%), diarrhoea (34%), vomiting (28%), decreased appetite (27%), constipation (26%), abdominal pain (23%), rash (18%), musculoskeletal pain (17%), pyrexia (17%), stomatitis (15%), hypoalbuminaemia (13%), cough (12%), palmar-plantar erythrodysaesthesia syndrome (11%), and oedema (including peripheral oedema) (11%). Incidences of Grade 3-5 adverse reactions were 69% for nivolumab in combination with chemotherapy. Median duration of therapy was 6.75 months (95% CI: 6.11, 7.36) for nivolumab in combination with chemotherapy and 4.86 months (95% CI: 4.47, 5.29) for chemotherapy for gastric, GEJ or oesophageal adenocarcinoma. Ninety-three percent (93%) of patients received 3 cycles of nivolumab for resectable NSCLC.

Tabulated summary of adverse reactions
Adverse reactions reported in the dataset for patients treated with nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma or resectable NSCLC (n = 958) 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), not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

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

	Nivolumab in combination with chemotherapy
Infections and infestations	
Common	upper respiratory tract infection, pneumonia
Blood and lymphatic system disorders	
Common	febrile neutropaenia
Uncommon	eosinophilia
Immune system disorders	
Common	hypersensitivity, infusion related reaction
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism
Uncommon	hypopituitarism, adrenal insufficiency, thyroiditis, hypophysitis, diabetes mellitus
Metabolism and nutrition disorders	
Very common	decreased appetite
Nervous system disorders	
Very common	peripheral neuropathy
Common	headache, paraesthesia, dizziness
Uncommon	Guillain-Barré syndrome
Eye disorders	
Common	dry eye, blurred vision
Uncommon	uveitis
Cardiac disorders	

Common	tachycardia
Uncommon	atrial fibrillation, myocarditis
Vascular disorders	
Common	thrombosis, hypertension
Uncommon	vasculitis
Respiratory, thoracic and mediastinal disorders	
Very common	cough
Common	pneumonitis[f], dyspnoea
Gastrointestinal disorders	
Very common	diarrhoea, stomatitis, vomiting, nausea, abdominal pain, constipation
Common	colitis, dry mouth
Uncommon	pancreatitis
Hepatobiliary disorders	
Common	
Uncommon	hepatitis
Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthaesia syndrome, rash[a]
Common	pruritus, skin hyperpigmentation, alopecia, dry skin, erythema
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[b]
Common	arthralgia, muscular weakness
Renal and urinary disorders	
Common	renal failure
Uncommon	nephritis, cystitis noninfective[e]
General disorders and administration site conditions	
Very common	fatigue, pyrexia, oedema (including peripheral oedema)
Common	malaise
Investigations	
Very common	anaemia[c,d], thrombocytopaenia[c], leucopoenia[c], lymphopaenia[c], neutropaenia[c], increased transaminases[c], increased total bilirubin[c], increased creatinine[c], hyponatraemia[c], hyperkalaemia[c], hypokalaemia[c], hypocalcaemia[c], hypoglycaemia[c], hyperglycaemia[c], increased lipase, increased alkaline phosphatase, increased amylase
Common	hypernatraemia[c], hypercalcaemia[c]

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

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

[c] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See “Description of selected adverse reactions; laboratory abnormalities” below.

[d] Anaemia is a composite term which includes iron deficiency anaemia, and haemoglobin decreased.

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

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

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Nivolumab in combination with cabozantinib (see section 4.2)

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

RCC
In the dataset of nivolumab 240 mg every 2 weeks in combination with cabozantinib 40 mg once daily in RCC (n =320), with a minimum follow-up of 16.0 months, the most frequent adverse reactions (≥ 10%) were diarrhoea (64.7%), fatigue (51.3%), palmar-plantar erythrodysaesthesia syndrome (40.0%), stomatitis (38.8%), musculoskeletal pain (37.5%), hypertension (37.2%), rash (36.3%), hypothyroidism (35.6%), decreased appetite (30.3%), nausea (28.8%), abdominal pain (25.0%), dysguesia (23.8%), upper respiratory tract infection (20.6%), cough (20.6%), pruritus (20.6%), arthralgia (19.4%), vomiting (18.4%), dysphonia (17.8%), headache (16.3%), dyspepsia (15.9%), dizziness (14.1%), constipation (14.1%), pyrexia (14.1%), oedema (13.4%), muscle spasm (12.2%), dyspnoea (11.6%), proteinuria (10.9%) and hyperthyroidism (10.0%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Tabulated summary of adverse reactions
Adverse reactions reported in the dataset for patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg (n = 320) are presented in Table 54. 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. Not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 54: Adverse reactions with nivolumab in combination with cabozantinib

Infections and infestations	
Very Common	upper respiratory tract infection
Common	pneumonia
Blood and lymphatic system disorders	
Very common	anaemia[c], thrombocytopaenia[c], leucopoenia[c], lymphopaenia[c], neutropaenia[c],
Common	eosinophilia
Immune system disorders	
Common	hypersensitivity (including anaphylactic reaction)
Uncommon	infusion related hypersensitivity reaction
Endocrine disorders	
Very common	hypothyroidism, hyperthyroidism
Common	adrenal insufficiency
Uncommon	hypophysitis, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite, hypoglycaemia[c], hyperglycaemia[c], weight decreased
Common	dehydration
Nervous system disorders	
Very common	dysgeusia, dizziness, headache
Common	peripheral neuropathy
Uncommon	encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Ear and labyrinth disorders	
Common	tinnitus
Eye disorders	
Common	dry eye, blurred vision
Uncommon	uveitis
Cardiac disorders	
Common	atrial fibrillation, tachycardia
Uncommon	myocarditis
Vascular disorders	
Very common	hypertension
Common	thrombosis[a]
Respiratory, thoracic and mediastinal disorders	
Very common	dysphonia, dyspnoea, cough
Common	pneumonitis, pulmonary embolism, pleural effusion, epistaxis
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia
Common	colitis, gastritis, oral pain, dry mouth, haemorrhoids
Uncommon	pancreatitis, small intestine perforation[b], glossodynia
Hepatobiliary disorders	
Common	hepatitis
Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus
Common	alopecia, dry skin, erythema, hair colour change
Uncommon	psoriasis, urticaria
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[d], arthralgia, muscle spasm
Common	arthritis
Uncommon	myopathy, osteonecrosis of the jaw, fistula
Renal and urinary disorders	
Very common	proteinuria

Common	renal failure, acute kidney injury
Uncommon	nephritis
Rare	cystitis noninfective[f]
General disorders and administration site conditions	
Very common	fatigue, pyrexia, oedema
Common	pain, chest pain
Investigations[e]	
Very common	increased alkaline phosphatase, increased ALT, increased AST, increased total bilirubin, increased creatinine, increased amylase, increased lipase, hypokalaemia, hypomagnesaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hypophosphataemia, hyperkalaemia, hypermagnesaemia, hypernatraemia,
Common	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 54 may not be fully attributable to nivolumab alone but may contain contributions from the underlying disease or from medicinal product used in combination.

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

[b] Fatal cases have been reported.

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

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

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

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

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Description of selected adverse reactions

Data for the following immune-related adverse reactions are based on patients who received nivolumab 3 mg/kg as monotherapy and combination with cabozantinib. The management guidelines for these adverse reactions are described in section 4.4.

Immune-related pneumonitis

In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.6% (147/4122). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (38/4122) and 1.8% (74/4122) of patients respectively. Grade 3 and 4 cases were reported in 0.8% (32/4122) and <0.1% (1/4122) of patients respectively. Grade 5 cases were reported in < 0.1% (2/4122) of patients in these studies. Median time to onset was 14.4 weeks (range: 0.7-85.1). Resolution occurred in 100 patients (68.0%) with a median time to resolution of 6.6 weeks (range: 0.1^{+}-109.1^{+}); $^{+}$ denotes a censored observation.

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

Commented [SMP4]: Content adapted from approved EuSmPC

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC the incidence of pneumonitis including interstitial lung disease was 5.6% (18/320). Grade 2 and Grade 3 cases were reported in 1.9% (6/320) and 1.6% (5/320), of patients, respectively. 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, or frequent bowel movements was 15.3% (631/4122). The majority of cases were Grade 1 or 2 in severity reported in 9.9% (409/4122) and 3.9% (160/4122) of patients respectively. Grade 3 and 4 cases were reported in 1.5% (61/4122) and <0.1% (1/4122) of patients respectively. Median time to onset was 7.9 weeks (range: 0.1-115.6). Resolution occurred in 565 patients (90.5%) with a median time to resolution of 2.4 weeks (range: 0.1-124.4+).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of diarrhoea or colitis was 28.4% (272/958). Grade 2, Grade 3, and Grade 4 cases were reported in 8.5% (81/958), 4.1% (39/958), and 0.5% (5/958) of patients, respectively. Median time to onset was 4.1 weeks (range: 0.1-93.6). Resolution occurred in 237 patients (87.8%) with a median time to resolution of 1.4 weeks (range: 0.1-117.6+).

Commented [SMP5]: Content adapted from approved EuSmPC

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of diarrhoea, colitis, frequent bowel movements or enteritis was 59.1% (189/320). Grade 2 and Grade 3 cases were reported in 25.6% (82/320) and 6.3% (20/320) of patients, respectively. Grade 4 were reported in 0.6% (2/320). 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 7.4% (306/4122). The majority of cases were Grade 1 or 2 in severity reported in 4.0% (165/4122) and 1.7% (70/4122) of patients respectively. Grade 3 and 4 cases were reported in 1.4% (59/4122) and 0.3% (12/4122) of patients, respectively. Median time to onset was 10.0 weeks(range: 0.1-120.0). Resolution occurred in 240 patients (79.5%) with a median time to resolution of 6.1 weeks (range: 0.1-126.4+).

In patients treated with nivolumab 240 mg or 360 mg in combination chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of liver function test abnormalities was 23% (217/958). Grade 2 and Grade 3 cases were reported in 7.4% (71/958) and 3.0% (29/958) of patients, respectively. Median time to onset was 7 weeks (range: 0.1-61.3). Resolution occurred in 170 patients (79.4%) with a median time to resolution of 9.4 weeks (range: 0.4-150.6+).

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In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of liver function test abnormalities was 41.6% (133/320). Grade 2, Grade 3, and Grade 4 cases were reported in 14.7% (47/320), 10.3% (33/320), and 0.6% (2/320) of patients, respectively. 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 or renal dysfunction was 2.7% (112/4122). The majority of cases were Grade 1 or 2 in severity reported in 1.6% (66/4122) and 0.7% (28/4122) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (17/4122) and <0.1% (1/4122) of patients, respectively. Median time to onset was 11.3 weeks (range: 0.1-79.1). Resolution occurred in 74 patients (69.2%) with a median time to resolution of 8.0 weeks (range: 0.3-79.1+).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of nephritis or renal dysfunction was 4.1% (39/958). Grade 2, Grade 3, and Grade 4 cases were reported in 1% (10/958), 0.6% (6/958), and 0.1% (1/958) of patients, respectively. Median time to onset was 9 weeks (range: 0.9-59.4). Resolution occurred in 29 patients (74.4%) with a median time to resolution of 2.9 weeks (range: 0.1-140.7[+]).

Commented [SMP7]: Content adapted from approved EuSmPC

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of nephritis, immune mediated nephritis, renal failure, acute kidney injury, blood creatinine increased or blood urea increased was 10.0% (32/320). Grade 2 and Grade 3 cases were reported in 3.4% (11/320), and 1.3% (4/320) of patients, respectively. 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 or hyperthyroidism, was 12.5% (516/4122). The majority of cases were Grade 1 or 2 in severity reported in 6.1% (253/4122) and 6.2% (256/4122) of patients respectively. Grade 3 thyroid disorders were reported in 0.2% (7/4122) of patients. Hypophysitis (3 Grade 1, 5 Grade 2, 7 Grade 3, and 1 Grade 4), hypopituitarism (5 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency and adrenocortical insufficiency acute) (1 Grade 1, 17 Grade 2, and 8 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) (1 Grade 1, 4 Grade 2 and 5 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 278 patients (49.8%). Median time to resolution was 44.1 weeks (ranged from 0.4 to 204.4[+]).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of thyroid disorders was 11% (105/958). Grade 2 thyroid disorder was reported in 5% (48/958) patients. Grade 3 hypophysitis occurred in 0.1% (1/958) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (2/958) and 0.2% (2/958) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 0.3% (3/958) and 0.1% (1/958) of patients, respectively. Grade 2 and Grade 3 diabetes mellitus including Type 1 diabetes mellitus were reported in 0.3% (3/958) of patients. Median time to onset of these endocrinopathies was 13 weeks (range: 2.0-124.3). Resolution occurred in 53 patients (45.3%). Time to resolution ranged from 0.4 to 169.1[+] weeks.

Commented [SMP8]: Content adapted from approved EuSmPC

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of thyroid disorders was 43.1% (138/320). Grade 2 and Grade 3 thyroid disorders were reported in 23.1% (74/320) and 0.9% (3/320) of patients, respectively. Hypophysitis occurred in 0.6% (2/320) of patients, all Grade 2. Adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 4.7% (15/320) of patients. Grade 2 and Grade 3 adrenal insufficiency cases were reported in 2.2% (7/320) and 1.9% (6/320) of patients, respectively. 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 was 29.5% (1215/4122). The majority of cases were Grade 1 in severity reported in 22.4% (924/4122) of patients. Grade 2 and Grade 3 cases were reported in 5.7% (235/4122) and 1.4% (56/4122) of patients respectively. Median time to onset was 6.3 weeks (range: 0.1-121.1). Resolution occurred in 779 patients (64.6%) with a median time to resolution of 18.1 weeks (0.1-192.7[+]).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, or resectable NSCLC, the incidence of rash was 26.4% (253/958). Grade 2 and Grade 3 cases were reported in 6.8% (65/958), and 3.1% (30/958) of patients,

Commented [SMP9]: Content adapted from approved EuSmPC

respectively. Median time to onset was 7 weeks (range: 0.1-97.4). Resolution occurred in 161 patients (63.6%) with a median time to resolution of 15.7 weeks (range: 0.1-153.6+).

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of rash was 62.8% (201/320). Grade 2 and Grade 3 cases were reported in 23.1% (74/320) and 10.6% (34/320) of patients, respectively. 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 was 3.9% (160/4122), including 9 Grade 3 and 3 Grade 4 cases.

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

Commented [SMP10]: Content adapted from approved EuSmPC

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of hypersensitivity/infusion reactions was 2.5% (8/320). All 8 patients were Grade 1 or 2 in severity. Grade 2 cases were reported in 0.3% (1/320) of patients.

Elevated liver enzymes when nivolumab is combined with cabozantinib in RCC
In a clinical study of previously untreated patients with RCC receiving nivolumab in combination with cabozantinib, a higher incidence of Grades 3 and 4 ALT increased (10.1%) and AST increased (8.2%) were observed relative to nivolumab monotherapy in patients with advanced RCC. In patients with Grade ≥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 OPDIVO, 4 patients receiving cabozantinib, and 8 patients receiving both OPDIVO and cabozantinib.

Laboratory abnormalities
In patients treated with nivolumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.9% for anaemia (all Grade 3), 0.7% for thrombocytopaenia, 0.8% for leucopoenia, 9.6% for lymphopaenia, 1.0% for neutropaenia, 1.9% for increased alkaline phosphatase, 2.7% for increased AST, 2.4% for increased ALT, 0.9% for increased total bilirubin, 0.7% for increased creatinine, 2.7% for hyperglycaemia, 1.2% for hypoglycaemia, 4.2% for increased amylase, 7.4% for increased lipase, 5.2% for hyponatraemia, 1.7% for hyperkalaemia, 1.4% for hypokalaemia, 1.2% for hypercalcaemia, 0.7% for hypermagnesaemia, 0.4% for hypomagnesaemia, 0.7% for hypocalcaemia, 0.9% for hypoalbuminaemia and <0.1% for hypernatraemia.

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, or resectable NSCLC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 12% for anaemia, 6.1% for thrombocytopaenia, 10.6% leucopaenia, 10.8% for lymphopaenia, 27.9% neutropaenia, 3.7% for increased AST, 2.8% for increased ALT, 2.5% for increased bilirubin, 0.9% for increased creatinine, 0.4% for hypernatraemia, 5.5% for hyponatraemia, 1.4% for hyperkalaemia,

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5.4% for hypokalaemia, 0.2% for hypercalcaemia, 1.4% for hypocalcaemia, 1.7% for hypomagnesaemia, 4.4% for hyperglycaemia, and 0.6% for hypoglycaemia.

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

Immunogenicity
Of the 3529 patients who were treated with nivolumab monotherapy 3 mg/kg or 240mg 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, 8.8% tested positive for treatment emergent anti-product-antibodies with 0.3% tested positive for neutralising antibodies.

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.

Elderly
No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from NSCLC and adjuvant melanoma patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1).
For patients treated with nivolumab in combination with cabozantinib, data from RCC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1).

Hepatic or renal impairment
In the non-squamous NSCLC study (CA209057), the safety profile in patients with baseline renal or hepatic impairment was comparable to that in the overall population. These results should be interpreted with caution due to the small sample size within the subgroups.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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: L01XC17.

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.

Clinical efficacy and safety

Melanoma

Treatment of advanced melanoma

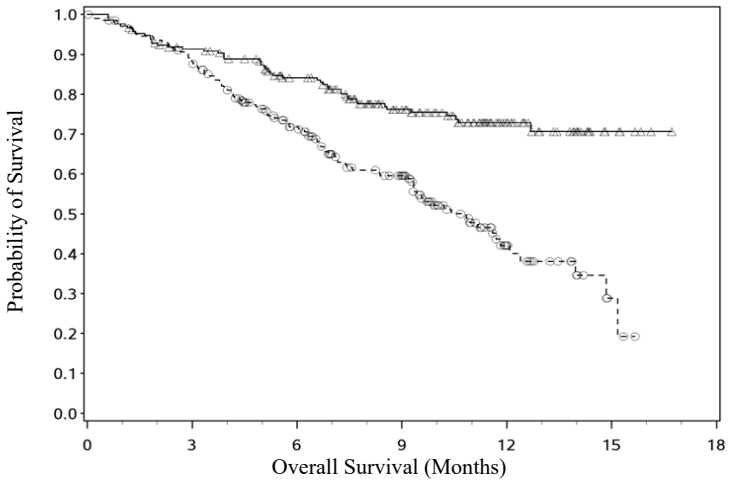
Randomised phase 3 study vs. dacarbazine (CA209066)
The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209066). The study included adult patients (18 years or older) with confirmed,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

A total of 418 patients were randomised to receive either nivolumab (n = 210) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine (n = 208) at 1000 mg/m^2 every 3 weeks. Randomisation was stratified by PD-L1 status and M stage (M0/M1a/M1b versus M1c). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse effects with the study drug, as determined by the investigator. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed progression-free survival (PFS) and objective response rate (ORR).

Baseline characteristics were balanced between the two groups. The median age was 65 years (range: 18-87), 59% were men, and 99.5% were white. Most patients had ECOG performance score of 0 (64%) or 1 (34%). Sixty-one percent of patients had M1c stage disease at study entry. Seventy-four percent of patients had cutaneous melanoma, and 11% had mucosal melanoma; 35% of patients had PD-L1 positive melanoma (≥5% tumour cell membrane expression). Sixteen percent of patients had received prior adjuvant therapy; the most common adjuvant treatment was interferon (9%). Four percent of patients had a history of brain metastasis, and 37% of patients had a baseline LDH level greater than ULN at study entry.

The Kaplan-Meier curves for OS are shown in Figure 1.

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



Number of Subjects at Risk

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

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

The observed OS benefit was consistently demonstrated across subgroups of patients including baseline ECOG performance status, M stage, history of brain metastases, and baseline LDH level. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 5% or 10%).

Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Efficacy results are shown in Table 6~~5~~.

Table 65: 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)	NA
Confirmed 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 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~~6~~.

Table 7~~6~~: 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)

Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Updated analysis (24-month follow-up)
Among all randomised patients, the ORR was 27.2% (95% CI: 22.0, 32.9) in the nivolumab group and 9.8% (95% CI: 5.3, 16.1) in the chemotherapy group. Median durations of response were 31.9 months (range: 1.4^{+}-31.9) and 12.8 months (range: 1.3^{+}-13.6^{+}), respectively. The PFS HR for nivolumab vs. chemotherapy was 1.03 (95% CI: 0.78, 1.36). The ORR and PFS were assessed by IRRC per RECIST version 1.1.

There was no statistically significant difference between nivolumab and chemotherapy in the final OS analysis. The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies and differences in baseline factors. More patients in the nivolumab arm had poor prognostic factors (elevated LDH and brain metastases) than in the chemotherapy arm.

Efficacy by BRAF status: Objective responses to nivolumab (according to the definition of the co-primary endpoint) were observed in patients with or without BRAF mutation-positive melanoma. The

ORRs in the BRAF mutation-positive subgroup were 17% (95% CI: 8.4, 29.0) for nivolumab and 11% (95% CI: 2.4, 29.2) for chemotherapy, and in the BRAF wild-type subgroup were 30% (95% CI: 24.0, 36.7) and 9% (95% CI: 4.6, 16.7), respectively.

The PFS HRs for nivolumab vs. chemotherapy were 1.58 (95% CI: 0.87, 2.87) for BRAF mutation-positive patients and 0.82 (95% CI: 0.60, 1.12) for BRAF wild-type patients. The OS HRs for nivolumab vs. chemotherapy were 1.32 (95% CI: 0.75, 2.32) for BRAF mutation-positive patients and 0.83 (95% CI: 0.62, 1.11) for BRAF wild-type patients.

Efficacy by tumour PD-L1 expression: Objective responses to nivolumab were observed regardless of tumour PD-L1 expression. However, the role of this biomarker (tumour PD-L1 expression) has not been fully elucidated.

In patients with tumour PD-L1 expression ≥1%, ORR was 33.5% for nivolumab (n=179; 95% CI: 26.7, 40.9) and 13.5% for chemotherapy (n=74; 95% CI: 6.7, 23.5). In patients with tumour PD-L1 expression <1%, ORR per IRRC was 13.0% (n=69; 95% CI: 6.1, 23.3) and 12.0% (n=25; 95% CI: 2.5, 31.2), respectively.

The PFS HRs for nivolumab vs. chemotherapy were 0.76 (95% CI: 0.54, 1.07) in patients with tumour PD-L1 expression ≥1% and 1.92 (95% CI: 1.05, 3.5) in patients with tumour PD-L1 expression <1%.

The OS HRs for nivolumab vs. chemotherapy were 0.69 (95% CI: 0.49, 0.96) in patients with tumour PD-L1 expression ≥1% and 1.52 (95% CI: 0.89, 2.57) in patients with tumour PD-L1 expression <1%.

These subgroup analyses should be interpreted with caution given the small size of the subgroups and lack of statistically significant difference in OS in the all randomised population.

Open-label phase 1 dose-escalation study (MDX1106-03)
The safety and tolerability of nivolumab were investigated in a phase 1, open-label dose-escalation study in various tumour types, including malignant melanoma. Of the 306 previously treated patients enrolled in the study, 107 had melanoma and received nivolumab at a dose of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg for a maximum of 2 years. In this patient population, objective response was reported in 33 patients (31%) with a median duration of response of 22.9 months (95% CI: 17.0, NR). The median PFS was 3.7 months (95% CI: 1.9, 9.3). The median OS was 17.3 months (95% CI: 12.5, 37.8), and the estimated OS rates were 42% (95% CI: 32, 51) at 3 years, 35% (95% CI: 26, 44) at 4 years, and 34% (95% CI: 25, 43) at 5 years (minimum follow-up of 45 months).

Adjuvant treatment of melanoma

Randomised phase 3 study of nivolumab vs ipilimumab 10 mg/kg (CA209238)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study (CA209238). The study included adult patients, who had an ECOG performance status score of 0 or 1, with Stage IIIB/C or Stage IV American Joint Committee on Cancer (AJCC), 7th edition, histologically confirmed melanoma that is completely surgically resected. Per the AJCC 8th edition, this corresponds to patients with lymph node involvement or metastases. Patients were enrolled regardless of their tumour PD-L1 status. Patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 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 randomisation) prior therapy with, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways), were excluded from the study.

A total of 906 patients were randomised to receive either nivolumab 3 mg/kg (n = 453) administered every 2 weeks or ipilimumab 10 mg/kg (n = 453) administered every 3 weeks for 4 doses then every 12 weeks beginning at week 24 for up to 1 year. Randomisation was stratified by tumour PD-L1 expression (≥ 5% vs. < 5%/indeterminate), and stage of disease per the AJCC staging system. Tumour assessments were conducted every 12 weeks for the first 2 years then every 6 months thereafter. The primary endpoint was recurrence-free survival (RFS). RFS, assessed by investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death due to any cause, whichever occurred first.

Baseline characteristics were generally balanced between the two groups. The median age was 55 years (range: 18-86), 58% were men, and 95% were white. Baseline ECOG performance status score was 0 (90%) or 1 (10%). The majority of patients had AJCC Stage III disease (81%), and 19% had Stage IV disease. Forty-eight percent of patients had macroscopic lymph nodes and 32% had tumour ulceration. Forty-two percent of patients were BRAF V600 mutation positive while 45% were BRAF wild type and 13% BRAF were status unknown. For tumour PD-L1 expression, 34% of patients had PD-L1 expression ≥ 5% and 62% had < 5% as determined by clinical trial assay. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the treatment groups. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Minimum follow-up was approximately 24 months. OS was not mature at the time of this analysis. RFS results are shown in Table 87 and Figure 2 (all randomised population).

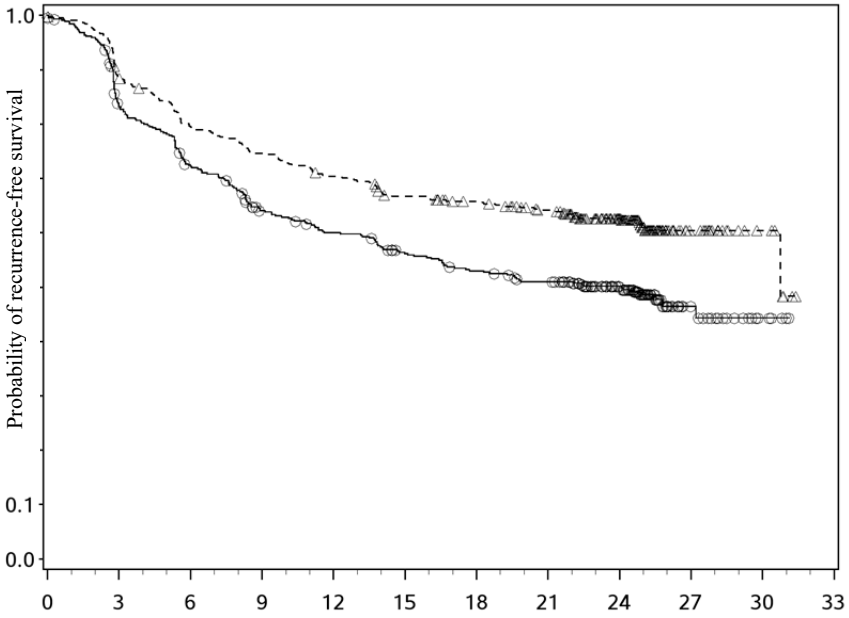
Table 87: Efficacy results (CA209238)

	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	Not Available[b]		24.08 (16.56, NR)
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 proportional hazards model.

[b] Not available as median unstable due to low number of patients and censoring with 24 months of follow-up

Figure 2: Recurrence-free survival (CA209238)



Number of subjects at risk

Nivolumab											
453	394	353	331	311	291	280	264	205	28	7	0
Ipilimumab											
453	363	314	270	251	230	216	204	149	23	5	0

- - - Δ- - - Nivolumab —❍— Ipilimumab

The trial demonstrated a statistically significant improvement in RFS for patients randomised to the nivolumab arm compared with the ipilimumab 10 mg/kg arm. RFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF status, and stage of disease.

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*)*

Squamous NSCLC

Randomised phase 3 study vs. docetaxel (CA209017)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209017). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an 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

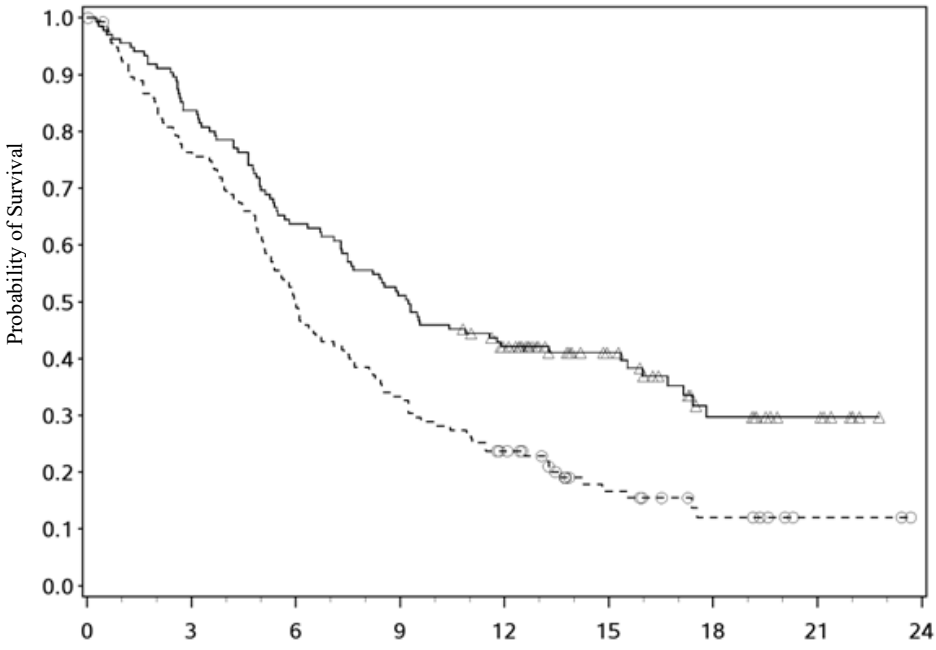
neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

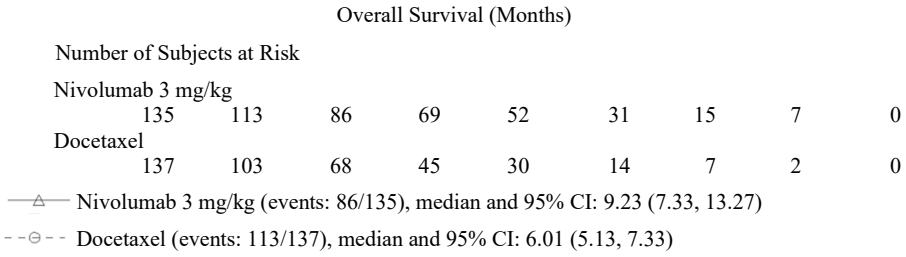
A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (N = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m^2 every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour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

Figure 3: Kaplan-Meier curves of OS (CA209017)





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. With a minimum of 24.2 months follow up, OS benefit remains consistently demonstrated across subgroups.

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 ~~9~~8.

Table 28: Efficacy results (CA209017)

	nivolumab (n = 135)	docetaxel (n = 137)
Primary analysis Minimum follow-up: 10.6 months		
Overall survival		
Events	86 (63.7)	113 (82.5)
Hazard ratio	0.59	
96.85% CI	(0.43, 0.81)	
p-value	0.0002	
Median (95% CI) 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)
Updated analysis Minimum follow-up: 24.2 months		
Overall survival[a]		
Events	110 (81.4%)	128 (93.4%)
Hazard ratio	0.62	
95% CI	(0.47, 0.80)	
Rate (95% CI) at 24 months	22.9 (16.2, 30.3)	8 (4.3, 13.3)
Confirmed objective response	20.0%	8.8%
(95% CI)	(13.6, 27.7)	(4.6, 14.8)
Median duration of response		
Months (range)	25.2 (2.9-30.4)	8.4 (1.4+-18.0+)
Progression-free survival		
Rate (95% CI) at 24 months	15.6 (9.7, 22.7)	All patients had either progressed, were censored, or lost to follow-up
Updated analysis		

Minimum follow-up: 62.6 months			
Overall survival[a]			
Events	118 (87.4%)		133 (97.1%)
Hazard ratio		0.62	
95% CI		(0.48, 0.79)	
Rate (95% CI) at 60 months	12.3 (7.4, 18.5)		3.6 (1.4, 7.8)
Confirmed objective response (95% CI)	20.0% (13.6, 27.7)		8.8% (4.6, 14.8)
Median duration of response Months (range)	25.2 (2.9-70.6+)		7.5 (0.0+-18.0+)
Progression-free survival Rate (95% CI) at 60 months	9.4 (4.8, 15.8)		All patients had either progressed, were censored, or lost to follow-up

[a] Six patients (4%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
"+" Denotes a censored observation.

The rate of disease-related symptom improvement, as measured by LCSS, was similar between the nivolumab group (18.5%) and the docetaxel group (21.2%). The average 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%.

Non-squamous NSCLC

Randomized 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, randomized, open-label study (CA209057). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen which may have included maintenance therapy and who had an ECOG performance status score of 0 or 1. An additional line of TKI therapy was allowed for patients with known EGFR mutation or ALK translocation. Patients were enrolled regardless of their PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active 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.

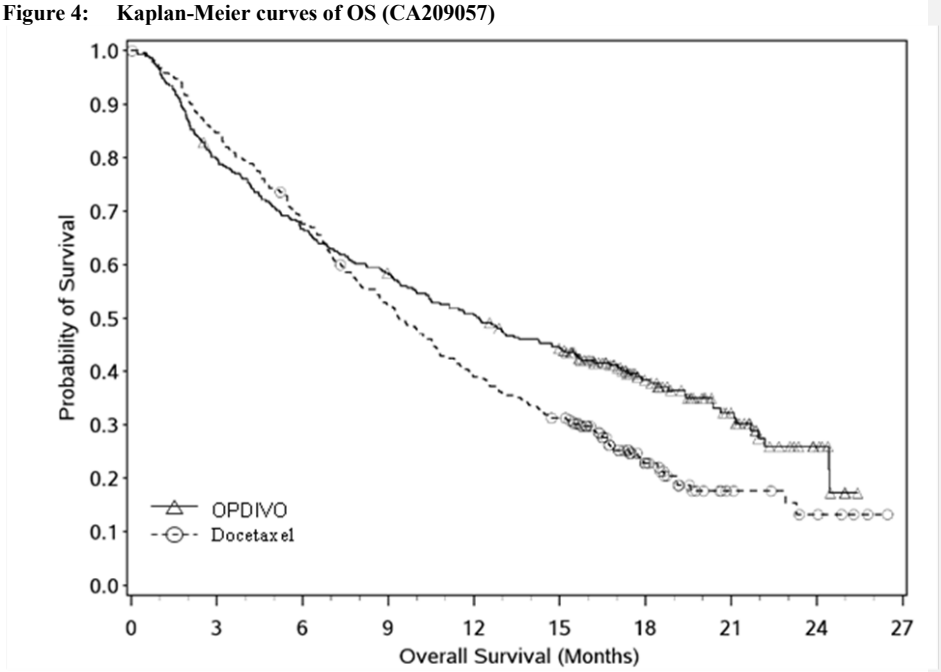
A total of 582 patients were randomized to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks (n = 292) or docetaxel 75 mg/m2 every 3 weeks (n = 290). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to RECIST, version 1.1. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. Additional prespecified subgroup analyses were conducted to evaluate the efficacy of tumour PD-L1 expression at predefined levels of 1%, 5% and 10%. Assessment according to discrete PD-L1 expression intervals were not included in the prespecified analyses due to the small sample sizes within the intervals.

Pre-study tumour tissue specimens were systematically collected prior to randomisation in order to conduct pre-planned analyses of efficacy according to tumour PD-L1 expression. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

The median age was 62 years (range: 21 to 85) with 34% ≥65 years of age and 7% ≥75 years of age. The majority of patients were white (92%) and male (55%). Baseline ECOG performance status was 0 (31%) or 1 (69%). Seventy-nine percent of patients were former/current smokers.

The Kaplan-Meier curves for OS are shown in Figure 4.

Figure 4: 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

——Δ—— Nivolumab 3 mg/kg (events: 190/292), median and 95% CI: 12.19 (9.66, 14.98)
- - -❍- - - Docetaxel (events: 223/290), median and 95% CI: 9.36 (8.05, 10.68)

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 10~~9~~.

Table 109: Efficacy Results (CA209057)

	nivolumab (n = 292)	docetaxel (n = 290)
Prespecified interim analysis Minimum follow-up: 13.2 months		
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) months	12.19 (9.66, 14.98)	9.36 (8.05, 10.68)
Rate (95% CI) at 12 months	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)
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) (months)	2.33 (2.17, 3.32)	4.21 (3.45, 4.86)
Rate (95% CI) at 12 months	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)
Updated analysis Minimum follow-up: 24.2 months		
Overall survival[c]		
Events	228 (78.1%)	247 (85.1%)
Hazard ratio[a]	0.75	
(95% CI)	(0.63, 0.91)	
Rate (95% CI) at 24 months	28.7 (23.6, 34.0)	15.8 (11.9, 20.3)
Confirmed objective response	19.2%	12.4%
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-33.7+)	5.6 (1.2+-16.8)
Progression-free survival		
Rate (95% CI) at 24 months	11.9 (8.3, 16.2)	1.0 (0.2, 3.3)
Updated analysis Minimum follow-up: 62.7 months		
Overall survival[d]		
Events	250 (85.6%)	279 (96.2%)
Hazard ratio[a]	0.70	

(95% CI)		(0.58, 0.83)
Rate (95% CI) at 60 months	14.0 (10.2, 18.3)	2.1 (0.9, 4.4)
Confirmed objective response	19.5%	12.4%
(95% CI)	(15.1, 24.5)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-70.4[+])	5.6 (0.0[+]-33.4)
Progression-free survival		
Rate (95% CI) at 60 months	7.5 (4.5, 11.4)	All patients had either progressed, were censored, or lost to follow-up

[a] Derived from a stratified proportional hazards model.
[b] P-value is derived from a log-rank test stratified by prior maintenance therapy and line of therapy; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0408.
[c] Sixteen patients (6%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
[d] Seventeen patients (6%) randomised to docetaxel crossed over at any time to receive nivolumab treatment.
"+" Denotes a censored observation.

Quantifiable tumour PD-L1 expression was measured in 79% of patients in the nivolumab group and 77% of patients in the docetaxel group.

Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs docetaxel) at each of the predefined PD-L1 expression levels of ≥1% (53% vs 55%), ≥5% (41% vs 38%), or ≥10% (37% vs 35%).

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of enhanced survival compared to docetaxel, whereas survival was similar to docetaxel in patients with no PD-L1 expression. In terms of ORR, increasing PD-L1 expression was associated with larger ORR. Comparable to the overall population, median duration of response was increased with nivolumab vs. docetaxel for patients with no PD-L1 expression (18.3 months vs. 5.6 months) and for patients with PD-L1 expression (16.0 months vs. 5.6 months).

Table 11~~0~~ summarises results of ORR and OS by tumour PD-L1 expression.

Table 110: ORR and OS by tumour PD-L1 expression (CA209057)

PD-L1 Expression	nivolumab	docetaxel	
	ORR by tumour PD-L1 expression Minimum follow-up: 13.2 months		
			Odds Ratio (95% CI)
< 1%	10/108 (9.3%) 95% CI: 4.5, 16.4	15/101 (14.9%) 95% CI: 8.6, 23.3	0.59 (0.22, 1.48)
≥ 1%	38/123 (30.9%) 95% CI: 22.9, 39.9	15/123 (12.2%) 95% CI: 7.0, 19.3	3.22 (1.60, 6.71)
≥ 1% to < 10%[a]	6/37 (16.2%) 95% CI: 6.2, 32.0	5/ 44 (11.4%) 95% CI: 3.8, 24.6	1.51 (0.35, 6.85)
≥ 10% to < 50%[a]	5/20 (25.0%) 95% CI: 8.7, 49.1	7/33 (21.2%) 95% CI: 9.0, 38.9	1.24 (0.26, 5.48)
≥ 50%[a]	27/66 (40.9%) 95% CI: 29.0, 53.7	3/46 (6.5%) 95% CI: 1.4, 17.9	9.92 (2.68, 54.09)
	OS by tumour PD-L1 expression Minimum follow-up: 13.2 months		
	Number of events (number of patients)		**Unstratified Hazard Ratio (95% CI)**
< 1%	77 (108)	75 (101)	0.90 (0.66, 1.24)
≥ 1%	68 (123)	93 (123)	0.59 (0.43, 0.82)
≥ 1% to < 10%[a]	27 (37)	30 (44)	1.33 (0.79, 2.24)
≥ 10% to < 50%[a]	11 (20)	26 (33)	0.61 (0.30, 1.23)
≥ 50%[a]	30 (66)	37 (46)	0.32 (0.20, 0.53)
	Updated analysis Minimum follow-up: 24.2 months		
< 1%	91 (108)	86 (101)	0.91 (0.67, 1.22)
≥ 1%	87 (123)	103 (123)	0.62 (0.47, 0.83)
	Updated analysis Minimum follow-up: 62.7 months		
< 1%	100 (109)	96 (101)	0.87 (0.66, 1.16)
≥1%	96 (122)	119 (123)	0.55 (0.42, 0.73)

[a] Post-hoc analysis; results should be interpreted with caution as the subgroup samples sizes are small and, at the time of the analysis, the PD-L1 IHC 28-8 pharmDx assay was not analytically validated at the 10% or 50% expression levels.

A higher proportion of patients experienced death within the first 3 months in the nivolumab arm (59/292, 20.2%) as compared to the docetaxel arm (44/290, 15.2%). Results of a post-hoc, exploratory multivariate analysis indicated that nivolumab-treated patients with poorer prognostic features and/or aggressive disease when combined with lower (e.g., < 50%) or no tumour PD-L1 expression may be at higher risk of death within the first 3 months.

In subgroup analyses, survival benefit compared to docetaxel was not shown for patients who were never-smokers or whose tumours harboured EGFR activating mutations; however, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

Neoadjuvant treatment of NSCLC

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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 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 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 49% had 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 12 and Figure 5.

Table 12: Efficacy results (CA209816)

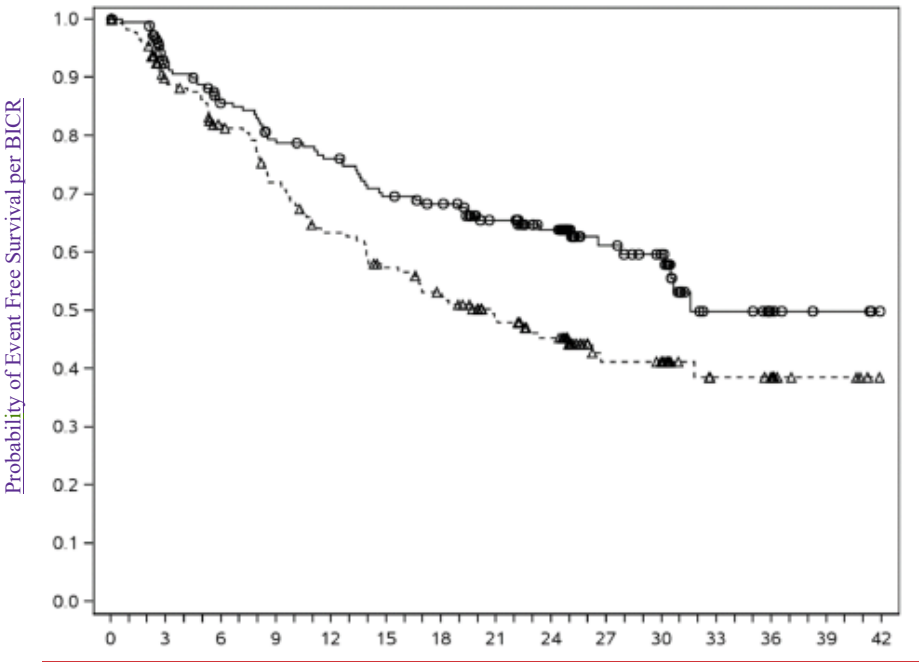
	nivolumab + chemotherapy (n = 179)	**chemotherapy (n = 179)**
Event free survival per BICR		
Events	64 (35.8%)	87 (48.6%)

Table 12: Efficacy results (CA209816)

	nivolumab + chemotherapy (n = 179)		chemotherapy (n = 179)
Hazard ratio[a]		0.63	
(97.38% CI)		(0.43, 0.91)	
Stratified log-rank p-value[b]		0.0052	
Median (months)[c]	31.6		20.8
(95% CI)	(30.2, NR)		(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 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 (CMH) 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 5: 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: 08-Sept-2021, minimum follow-up of 21 months

In descriptive, exploratory analyses, EFS and pCR favoured nivolumab in combination with chemotherapy relative to chemotherapy across key subgroups (including PD-L1, disease stage, histology).

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.

Renal Cell Carcinoma (RCC)

Randomised, open-labeled, phased 3 study vs. everolimus (CA209025)

The safety and efficacy of nivolumab 3mg/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.

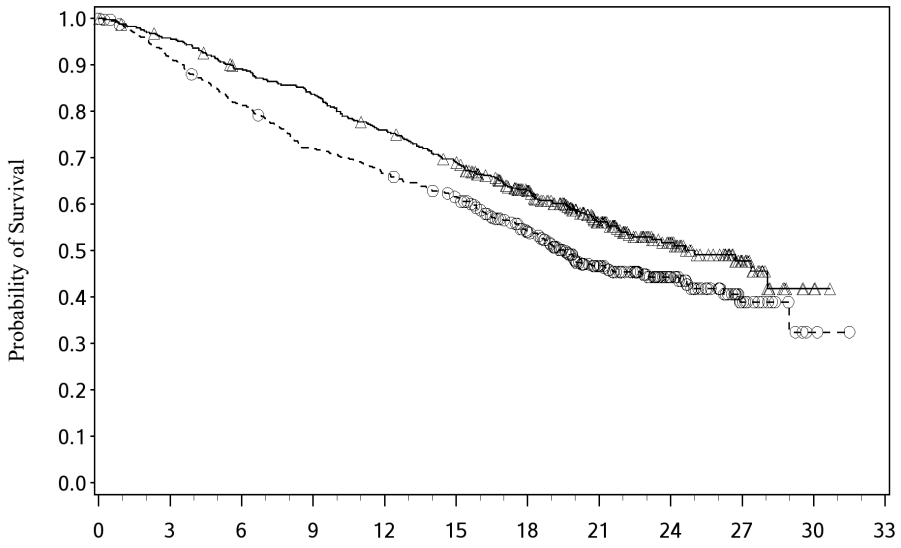
A total of 821 patients were randomized to receive either nivolumab 3 mg/kg (n=410) administered intravenously over 60 minutes every 2 weeks or everolimus (n=411) 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. 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.

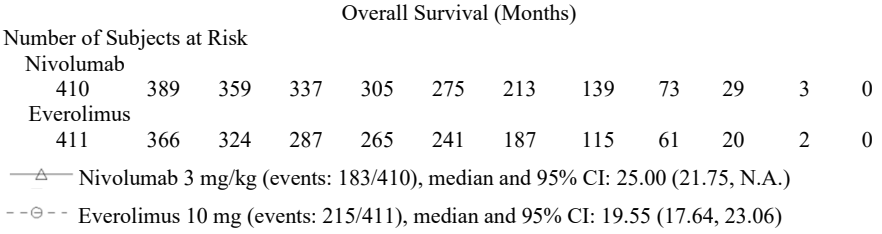
Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and white (88%), all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups were represented, 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 6~~5~~.

Figure 6~~5~~: Kaplan-Meier curves of OS (CA209025)





The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 13~~11~~ and Figure 6~~5~~). OS benefit was observed regardless of PD-L1 expression level.

Efficacy results are shown in Table 13~~1~~.

Table 13~~1~~: 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.

NE = non-estimable

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

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

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 1~~4~~2.

Table 142: 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

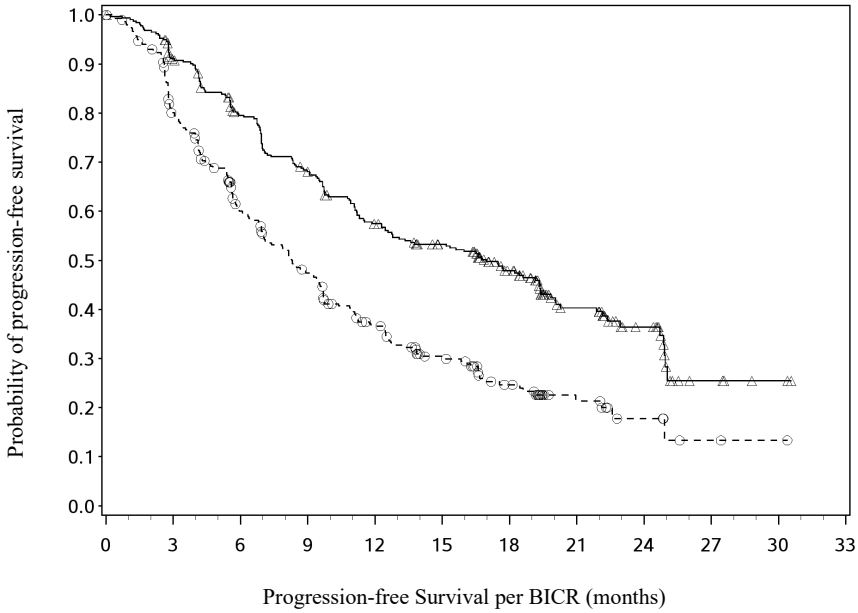
The primary analysis of PFS included censoring for new anti-cancer treatment (Table 142). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

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 7~~6~~ and 8~~7~~). 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 7~~6~~: Kaplan-Meier curves of PFS (CA2099ER)



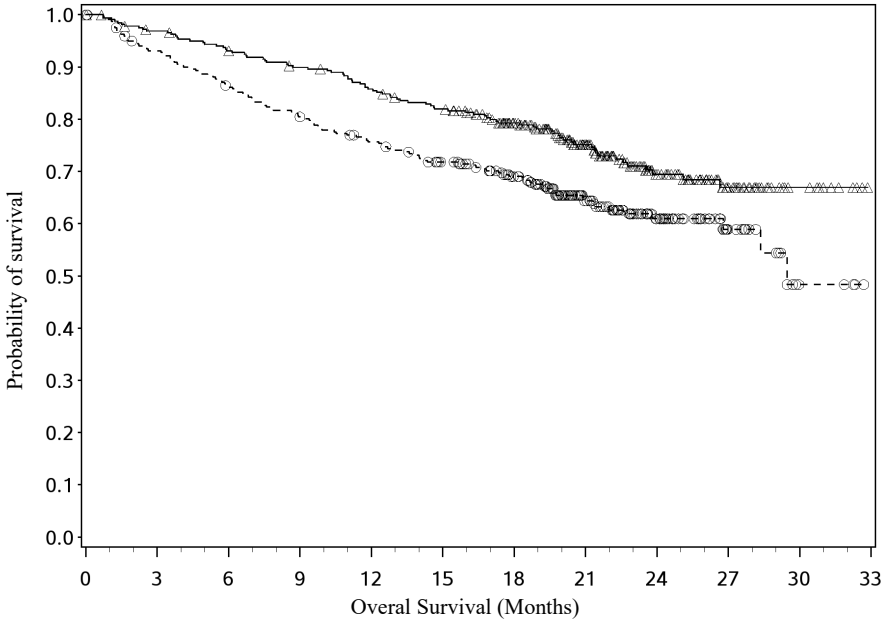
Number of subjects at risk

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 87: 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)

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

The safety and efficacy of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy (dose and schedule of nivolumab selected depending on the chemotherapy regimen used, see below) was evaluated in a phase 3, randomised, open-label study (CA209649). The study included adult patients (18 years or older) with previously untreated advanced or metastatic gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma, no prior systemic treatment (including HER2 inhibitors), and ECOG performance status score 0 or 1. Patients were enrolled regardless of their tumour cell PD-L1 status, and tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. A retrospective re-scoring of a patient's tumour PD-L1 status using CPS was conducted using the PD-L1-stained tumour specimens used for randomisation. Patients with known HER2-positive tumours, who had baseline ECOG performance score ≥ 2, untreated central nervous system metastases, or who had active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. A total of 643 patients with HER2-undetermined status (40.3% of the study population) were included in the study. Randomisation was stratified by tumour cell PD-L1 status (≥ 1% vs. < 1% or indeterminate), region (Asia vs. US vs. rest of world), ECOG performance status (0 vs. 1), and chemotherapy regimen. Chemotherapy consisted of FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

A total of 1581 patients were randomised to receive either nivolumab in combination with chemotherapy or chemotherapy. Of these, 955 patients had PD-L1 CPS ≥ 5; 473 in the nivolumab plus chemotherapy arm and 482 in the chemotherapy arm. Patients in the nivolumab plus chemotherapy arm received either nivolumab 240 mg by intravenous infusion over 30 minutes in combination with FOLFOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and fluorouracil 400 mg/m^2 intravenously on day 1 and fluorouracil 1200 mg/m^2 intravenously by continuous infusion over 24 hours daily or per local standard on days 1 and 2) every 2 weeks, or nivolumab 360 mg by intravenous infusion over 30 minutes in combination with CapeOX (oxaliplatin 130 mg/m^2 intravenously on day 1 and capecitabine 1000 mg/m^2 orally twice daily on days 1-14) every 3 weeks. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months for nivolumab only. In patients who received nivolumab plus chemotherapy and in whom chemotherapy was discontinued, nivolumab monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks or 480 mg every 4 weeks up to 24 months after treatment initiation. Tumour assessments were performed every 6 weeks up to and including week 48, then every 12 weeks thereafter.

Baseline characteristics were generally balanced across treatment groups. In patients with PD-L1 CPS ≥ 5, the median age was 62 years (range: 18-90), 11% were ≥ 75 years of age, 71% were male, 25% were Asian and 69% were white. Baseline ECOG performance status was 0 (42%) or 1 (58%). Tumour locations were distributed as gastric (70%), GEJ (18%) and oesophagus (12%).

Primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with PD-L1 CPS ≥ 5 based on the PD-L1 IHC 28-8 pharmDX. Secondary endpoints per the pre-specified hierarchical testing were OS in patients with PD-L1 CPS ≥ 1 and in all randomised patients; further endpoints included ORR (BICR) in PD-L1 CPS ≥ 5 and all randomised patients. At the primary pre-specified analysis, with a minimum follow-up of 12.1 months, the study demonstrated a statistically significant improvement in OS and PFS in patients with PD-L1 CPS ≥ 5. Median OS was 14.4 months (95% CI: 13.1, 16.2) for nivolumab in combination with chemotherapy vs. 11.1 months (95% CI: 10.0, 12.1) for chemotherapy (HR = 0.71; 98.4% CI: 0.59, 0.86; p-value <0.0001). Median PFS was 7.69 months (95% CI: 7.03, 9.17) for nivolumab in combination with chemotherapy vs. 6.05 months (95% CI: 5.55, 6.90) for chemotherapy (HR = 0.68; 98% CI: 0.56, 0.81; p-value <0.0001). The ORR was 60% (95% CI: 55, 65) for nivolumab in combination with chemotherapy vs. 45% (95% CI: 40, 50) for chemotherapy.

At an updated descriptive analysis with a minimum follow-up of 19.4 months, OS improvements were consistent with the primary analysis. Efficacy results are shown in Table 15 and Figures 9, and 10.

Table 15 Efficacy results in patients with PD-L1 CPS ≥ 5 (CA209649)

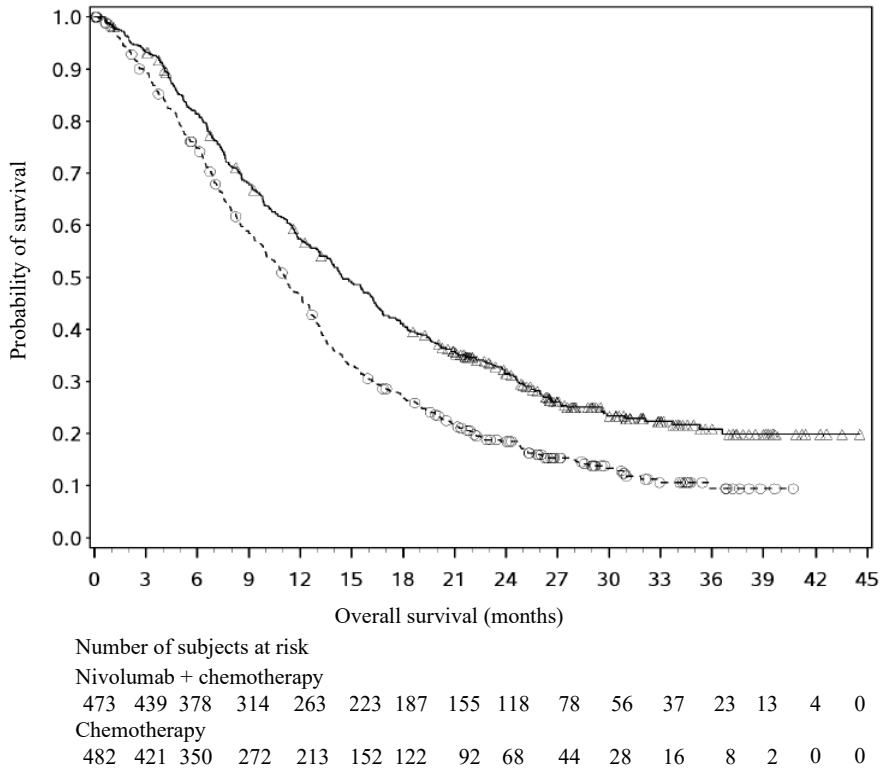
	nivolumab + chemotherapy (n = 473)		**chemotherapy (n = 482)**
	Minimum follow-up 19.4 months[a]		
Overall survival			
Events	344 (73%)		397 (82%)
Hazard ratio (95% CI)[b]		0.69 (0.60, 0.81)	
Median (95% CI) (months)[c]	14.4 (13.1, 16.3)		11.1 (10.0, 12.1)
Rate (95% CI) at 12 months	57.3 (52.6, 61.6)		46.4 (41.8, 50.8)
Progression-free survival[d]			
Events	342 (72.3%)		366 (75.9%)
Hazard ratio (CI)[b]		0.68 (0.59, 0.79)	
Median (95% CI) (months)[c]	8.31 (7.03, 9.26)		6.05 (5.55, 6.90)
Rate (95% CI) at 12 months	36.3 (31.7, 41.0)		21.9 (17.8, 26.1)
Objective response rate, n[d,e]	227/378 (60%)		176/390 (45%)
(95% CI)	(54.9, 65.0)		(40.1, 50.2)
Complete response	12.2%		6.7%
Partial response	47.9%		38.5%
Duration of response[d,e]			

Table 15 Efficacy results in patients with PD-L1 CPS ≥ 5 (CA209649)

	nivolumab + chemotherapy (n = 473)	chemotherapy (n = 482)
Median (95% CI) (months)[c]	9.69 (8.25, 12.22)	6.97 (5.62, 7.85)

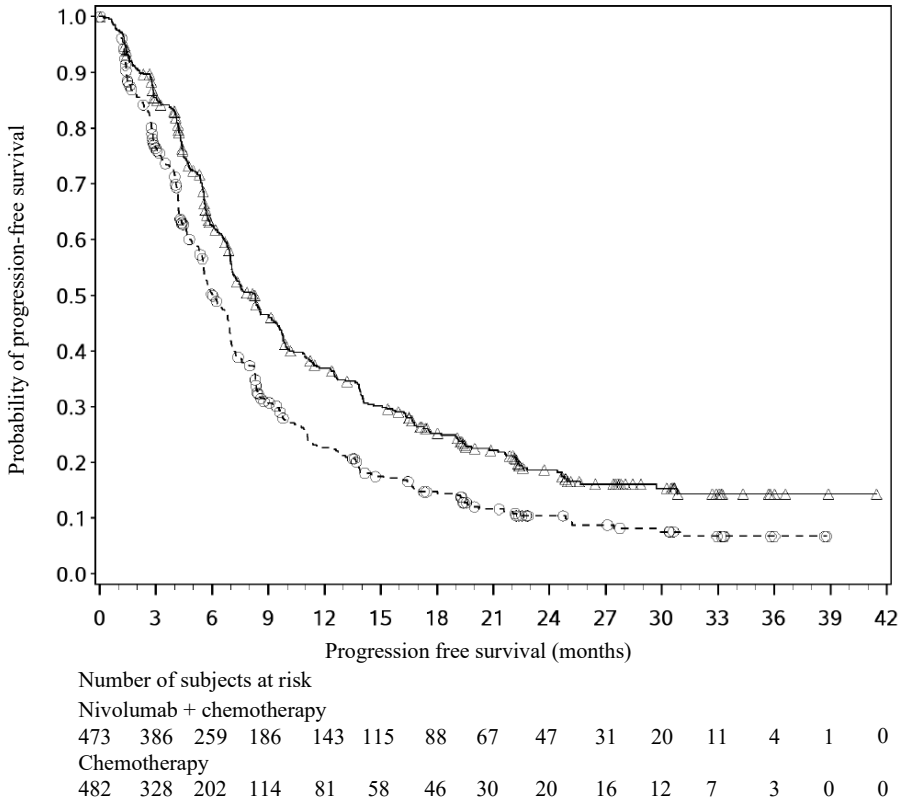
[a] Descriptive analysis based on data cut-off: 04-Jan-2021.
[b] Based on stratified long Cox proportional hazard model.
[c] Kaplan-Meier estimate.
[d] Confirmed by BICR.
[e] Based on patients with measurable disease at baseline.

Figure 9: Kaplan-Meier curves of OS in patients with PD-L1 CPS ≥ 5 (CA209649)



Minimum follow-up of 19.4 months

Figure 10: Kaplan-Meier curves of PFS in patients with PD-L1 CPS ≥ 5 (CA209649)



Minimum follow-up of 19.4 months

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 patients 75 years of age or older are too limited to draw conclusions on this population.

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 7.9 mL/h, 25.0 days, and 86.6 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.

Special populations

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

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

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

5.3 Preclinical safety data

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

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

Fertility studies have not been performed with nivolumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
3 years.

After opening
From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused 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 24 hours 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 24 hours 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 12 mL vial (Type I glass) with a stopper (coated butyl rubber) and a blue 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
The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given. More than one vial of OPDIVO concentrate may be needed to give the total dose for the patient.

- 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).

Nivolumab in combination with chemotherapy
The prescribed dose for the patient is 360 mg or 240 mg given regardless of body weight.

Nivolumab in combination with cabozantinib
The prescribed dose for the patient is nivolumab 240 mg or 480 mg given regardless of body weight.

Preparing the infusion
Take care to ensure aseptic handling when you prepare the infusion.

OPDIVO can be used for intravenous administration either:
- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting according to the following instructions:
  - the final infusion concentration should range between 1 and 10 mg/mL.
  - the total volume of infusion must not exceed 160 mL.

OPDIVO concentrate may be diluted with either:
- sodium chloride 9 mg/mL (0.9%) solution for injection; or
- 50 mg/mL (5%) glucose solution for injection.

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

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

Administration
OPDIVO infusion must not be administered as an intravenous push or bolus injection.
Administer the OPDIVO infusion intravenously over a period of 30 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 and polyolefin containers, glass bottles, PVC infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

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

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

7. MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
DKSH Malaysia Sdn Bhd
B-11-01, The Ascent, Paradigm
No.1, Jalan SS7/26A, Kelana Jaya
47301 Petaling Jaya, Selangor, Malaysia.

Manufacturer
Bristol-Myers Squibb Holdings Pharma, Ltd.
Liability Company
Road 686 Km 2.3
Bo. Tierras Nuevas
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USA

Vetter Pharma-Fertigung GmbH & Co. KG
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Batch releaser
Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics
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Mulhuddart, Dublin 15, Ireland

8. DATE OF REVISION OF THE TEXT

~~August~~ July 2023 ~~2022~~