ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.
One vial of 4 mL contains 40 mg of nivolumab.
One vial of 10 mL contains 100 mg of nivolumab.
One vial of 24 mL contains 240 mg of nivolumab.

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

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

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

Adjuvant treatment of melanoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults 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 in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

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

Renal cell carcinoma (RCC)

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

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

Classical Hodgkin lymphoma (cHL)

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

Squamous cell cancer of the head and neck (SCCHN)

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

Urothelial carcinoma

OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

Oesophageal squamous cell carcinoma (OSCC)

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

4.2 Posology and method of administration

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

Posology

OPDIVO as monotherapy
The recommended dose of OPDIVO is either nivolumab 240 mg every 2 weeks **or** 480 mg every 4 weeks (see section 5.1) depending on the indication, as presented in Table 1.

Table 1: Recommended dose and infusion time for intravenous administration of nivolumab monotherapy

Indication*	**Recommended dose and infusion time**
Melanoma (advanced or adjuvant treatment) Renal cell carcinoma	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Non-small cell lung cancer Classical Hodgkin lymphoma Squamous cell cancer of the head and neck Urothelial carcinoma Oesophageal squamous cell carcinoma	240 mg every 2 weeks over 30 minutes

*As per monotherapy indication in section 4.1.

If melanoma or RCC patients need to be switched from the 240 mg every 2 weeks schedule to the 480 mg every 4 weeks schedule, the first 480 mg dose should be administered two weeks after the last 240 mg dose. Conversely, if patients need to be switched from the 480 mg every 4 weeks schedule to the 240 mg every 2 weeks schedule, the first 240 mg dose should be administered four weeks after the last 480 mg dose.

OPDIVO in combination with ipilimumab

Melanoma
The recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks, as presented in Table 2. For the monotherapy phase, the first dose of nivolumab should be administered;

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

Table 2: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for melanoma

	Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	1 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Ipilimumab	3 mg/kg over 90 minutes	-

Renal cell carcinoma
The recommended dose is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks, as presented in Table 3. For the monotherapy phase, the first dose of nivolumab should be administered;

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

Table 3: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for RCC

	Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	3 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Ipilimumab	1 mg/kg over 30 minutes	-

OPDIVO in combination with ipilimumab and chemotherapy

Non-small cell lung cancer
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab administered intravenously every 3 weeks in combination with 1 mg/kg ipilimumab every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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

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

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

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 4. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 4: Recommended treatment modifications for OPDIVO or OPDIVO in combination with ipilimumab

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis - OPDIVO monotherapy	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	- OPDIVO+ipilimumab[a]	Permanently discontinue treatment
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	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

Table 4: Recommended treatment modifications for OPDIVO or OPDIVO in combination with ipilimumab

Immune-related adverse reaction	Severity	Treatment modification
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[b] as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[c]
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3 ; persistent Grade 2 or 3 despite treatment modification; inability to reduce 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] During administration of the second phase of treatment (nivolumab monotherapy) following combination treatment, permanently discontinue treatment if Grade 3 diarrhoea or colitis occurs.

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

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

OPDIVO or OPDIVO in combination with ipilimumab should be permanently discontinued for:

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

Patients treated with OPDIVO must be given the patient alert card and be informed about the risks of OPDIVO (see also package leaflet).

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

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 section 5.2).
Data from SCCHN, adjuvant melanoma and first-line RCC patients 75 years of age or older are too limited to draw conclusions on this population (see sections 4.8 and 5.1).

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

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

Method of administration

OPDIVO is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30 or 60 minutes depending on the dose (see Tables 1, 2 and 3). The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm.

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

The total dose of OPDIVO required can be infused directly as a 10 mg/mL solution or can be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection (see section 6.6).

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Immune-related adverse reactions
When nivolumab is administered in combination, refer to the Summary of Product Characteristics of the other combination therapy components prior to initiation of treatment. Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Most immune-related adverse reactions

improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see section 4.2).

Cardiac and pulmonary adverse reactions including pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions (see section 4.2).

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

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

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

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

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

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

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

Immune-related colitis
Severe diarrhoea or colitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Infectious and other aetiologies of diarrhoea should be ruled out, therefore appropriate laboratory tests and additional examinations must be performed. If diagnosis of

corticosteroid-refractory immune-related colitis is confirmed addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered.

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

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

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

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

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

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

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

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

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

initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Infusion reactions
Severe infusion reactions have been reported in clinical trials of nivolumab or nivolumab in combination with ipilimumab (see section 4.8). In case of a severe or life-threatening infusion reaction, the nivolumab or nivolumab in combination with ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may

receive nivolumab or nivolumab in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Disease-specific precautions

Advanced melanoma
Patients with a baseline performance score ≥ 2, active brain metastases or leptomeningeal metastases, autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of nivolumab or nivolumab in combination with ipilimumab (see sections 4.5 and 5.1). Patients with ocular/uveal melanoma were excluded from pivotal clinical trials of melanoma. In addition, CA209037 excluded patients who have had a Grade 4 adverse reaction that was related to anti-CTLA-4 therapy (see section 5.1). Patients with baseline performance score of 2, treated leptomeningeal metastases, ocular/uveal melanoma, autoimmune disease and patients who have had a Grade 3-4 adverse reaction that was related to prior anti-CTLA-4 therapy were included in study CA209172 (see section 5.1). In the absence of data for patients who had been receiving systemic immunosuppressants prior to study entry, and for patients with active brain or leptomeningeal metastases, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Relative to nivolumab monotherapy, an increase in PFS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. The improvement in OS was similar between nivolumab in combination with ipilimumab and nivolumab monotherapy in patients with high tumour PD-L1 expression (PD-L1 ≥ 1%). Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy (see sections 4.8 and 5.1).

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

Adjuvant treatment of melanoma
There are no data on adjuvant treatment in patients with melanoma with the following risk factors (see sections 4.5 and 5.1):
- patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 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
First-line treatment of NSCLC
Patients with active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, active (untreated) brain metastasis, who received prior systemic treatment for advanced disease, or who had sensitising EGFR mutations or ALK translocations were excluded from the pivotal trial in first-line treatment of NSCLC (see sections 4.5 and 5.1). Limited data are available in elderly patients (≥ 75 years) (see section 5.1). In these patients, nivolumab in combination with ipilimumab and chemotherapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

Treatment of NSCLC after prior chemotherapy
Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of NSCLC (see sections 4.5 and 5.1). Patients with baseline performance score of 2 were included in study CA209171 (see section 5.1). In the absence of data for patients with autoimmune disease, symptomatic interstitial lung disease, active brain metastases and patients who had been receiving systemic immunosuppressants prior to study entry, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.
Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In non-squamous NSCLC, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumour PD-L1 expression (see section 5.1).

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

Classical Hodgkin lymphoma
Patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL (see section 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

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

In patients treated with nivolumab after allogeneic HSCT, rapid-onset and severe GVHD, some with fatal outcome, have been reported in the post-marketing setting. Treatment with nivolumab may increase the risk of severe GVHD and death in patients who have had prior allogeneic HSCT, mainly in those with prior history of GVHD. The benefit of treatment with nivolumab versus the possible risk should be considered in these patients (see section 4.8).

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

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In head and neck cancer, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were ECOG performance status, fast progressive disease on prior platinum therapy and high tumour burden.

Urothelial carcinoma
Patients with a baseline performance score ≥2, active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were

excluded from the clinical trials of urothelial carcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Oesophageal squamous cell carcinoma
The majority of clinical data available in oesophageal squamous cell carcinoma are in patients of Asian origin (see section 5.1).
Patients with a baseline performance score ≥ 2, brain metastases that were symptomatic or required treatment, apparent tumour invasion in organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in OSCC (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with OSCC. A higher number of deaths within 2.5 months after randomisation was observed with nivolumab compared to chemotherapy. No specific factor(s) associated with early deaths could be identified (see section 5.1).

Patients on controlled sodium diet
Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. This medicinal product contains 10 mg sodium per 4 ml vial, 25 mg sodium per 10 ml vial or 60 mg sodium per 24 ml vial, which is equivalent to 0.5%, 1.25% or 3% respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Patient alert card
All prescribers of OPDIVO must be familiar with the physician information and management guidelines. The prescriber must discuss the risks of OPDIVO therapy with the patient. The patient will be provided with the patient alert card with each prescription.

4.5 Interaction with other medicinal products and other forms of interaction

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

Other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of nivolumab in pregnant women. Studies in animals have shown 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

Nivolumab or nivolumab in combination with ipilimumab may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as fatigue (see section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that nivolumab does not adversely affect them.

4.8 Undesirable effects

Nivolumab as monotherapy (see section 4.2)

Summary of the safety profile
In the pooled dataset of nivolumab as monotherapy across tumour types (n = 2787) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (29%), rash (17%), pruritus (13%), diarrhoea (13%), and nausea (12%). 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 = 2787) are presented in Table 5. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); 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 5: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Infections and infestations	
Common	upper respiratory tract infection
Uncommon	pneumonia[a], bronchitis
Not known	aseptic meningitis[h]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Very common	neutropaenia[a,b]
Uncommon	eosinophilia
Not known	haemophagocytic lymphohistiocytosis
Immune system disorders	
Common	infusion related reaction[c], hypersensitivity[c]
Rare	anaphylactic reaction[c]
Not known	solid organ transplant rejection[h], sarcoidosis[h]
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism
Uncommon	adrenal insufficiency[l], hypopituitarism, hypophysitis, thyroiditis, diabetes mellitus
Rare	diabetic ketoacidosis
Not known	hypoparathyroidism[h]
Metabolism and nutrition disorders	
Common	decreased appetite
Uncommon	dehydration, metabolic acidosis
Not known	tumour lysis syndrome[i]
Nervous system disorders	
Common	peripheral neuropathy, headache, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,c,m]
Eye disorders	
Uncommon	uveitis, blurred vision, dry eye
Not known	Vogt-Koyanagi-Harada syndrome[h]
Cardiac disorders	
Uncommon	tachycardia, pericardial disorders[j]
Rare	arrhythmia (including ventricular arrhythmia)[d], atrial fibrillation, myocarditis[a,f]
Vascular disorders	
Common	hypertension
Rare	vasculitis
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis[a,c], dyspnoea[a], cough
Uncommon	pleural effusion
Rare	lung infiltration
Gastrointestinal disorders	
Very common	diarrhoea, nausea
Common	colitis[a], stomatitis, vomiting, abdominal pain, constipation, dry mouth
Uncommon	pancreatitis, gastritis
Rare	duodenal ulcer
Hepatobiliary disorders	

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

[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] The frequency of adverse reactions in the cardiac disorders system organ class regardless of causality was higher in the nivolumab group than in the chemotherapy group in post-CTLA4/BRAF inhibitor metastatic melanoma population. Incidence rates per 100 person-years of exposure were 9.3 vs. 0; serious cardiac events were reported by 4.9% patients in the nivolumab group vs. 0 in the investigator´s choice group. The frequency of cardiac adverse reactions was lower in the nivolumab group than in the dacarbazine group in the metastatic melanoma without prior treatment population. All were considered not related to nivolumab by investigators except arrhythmia (atrial fibrillation, tachycardia and ventricular arrhythmia).

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

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

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

[h] Post-marketing event (also see section 4.4).

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

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

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

[l] Includes adrenal insufficiency and secondary adrenocortical insufficiency.

[m] Includes encephalitis and limbic encephalitis.

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 ipilimumab (see section 4.2)

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

Melanoma
In the pooled dataset of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n = 448) with minimum follow-up ranging from 6 to 28 months, the most frequent adverse reactions (≥ 10%) were rash (52%), fatigue (46%), diarrhoea (43%), pruritus (36%), nausea (26%), pyrexia (19%), decreased appetite (16%), hypothyroidism (16%), colitis (15%), vomiting (14%), arthralgia (13%), abdominal pain (13%), headache (11%), and dyspnoea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Among the patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in CA209067, 154/313 (49%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 147 patients in this group who continued treatment in the single-agent phase, 47 (32%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase. With a minimum of 60 months follow-up from study CA209067, no new safety signals were identified.

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

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

Tabulated summary of adverse reactions
Adverse reactions reported in the pooled dataset for patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg (n = 448) and for patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg (n = 547) are presented in Table 6. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 6: Adverse reactions with nivolumab in combination with ipilimumab

	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg*	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg**
Infections and infestations		
Common	pneumonia, upper respiratory tract infection	pneumonia, upper respiratory tract infection, conjunctivitis
Uncommon	bronchitis	bronchitis, aseptic meningitis
Not known	aseptic meningitis[h]	
Blood and lymphatic system disorders		
Common	eosinophilia	
Uncommon		eosinophilia
Not known	haemophagocytic lymphohistiocytosis	haemophagocytic lymphohistiocytosis
Immune system disorders		
Common	infusion related reaction, hypersensitivity	infusion-related reaction, hypersensitivity
Uncommon	sarcoidosis	
Not known	solid organ transplant rejection[h]	
Endocrine disorders		
Very common	hypothyroidism	hypothyroidism, hyperthyroidism
Common	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis	adrenal insufficiency[c], hypophysitis[c], thyroiditis, diabetes mellitus[c]
Uncommon	diabetic ketoacidosis[c], diabetes mellitus[c]	diabetic ketoacidosis[c], hypopituitarism
Not known	hypoparathyroidism[h]	hypoparathyroidism[h]
Metabolism and nutrition disorders		
Very common	decreased appetite	decreased appetite
Common	dehydration	dehydration
Uncommon		metabolic acidosis
Not known	tumour lysis syndrome[i]	
Nervous system disorders		
Very common	headache	
Common	peripheral neuropathy, dizziness	headache, peripheral neuropathy, dizziness
Uncommon	Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis[c]	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis[c]
Eye disorders		
Common	uveitis, blurred vision	blurred vision
Uncommon		uveitis
Not known	Vogt-Koyanagi-Harada syndrome[h]	
Cardiac disorders		
Common	tachycardia	tachycardia
Uncommon	arrhythmia (including ventricular arrhythmia)[a,d], atrial fibrillation, myocarditis[a,f]	arrhythmia (including ventricular arrhythmia), myocarditis[c]
Not known	pericardial disorders[j]	
Vascular disorders		
Common	hypertension	hypertension
Respiratory, thoracic and mediastinal disorders		
Very common	dyspnoea	

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

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

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

[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] The frequency of adverse reactions in the cardiac disorders system organ class regardless of causality was higher in the nivolumab group than in the chemotherapy group in post-CTLA4/BRAF inhibitor metastatic melanoma population. Incidence rates per 100 person-years of exposure were 9.3 vs. 0; serious cardiac events were reported by 4.9% patients in the nivolumab group vs. 0 in the investigator´s choice group. The frequency of cardiac adverse reactions was lower in the nivolumab group than in the dacarbazine group in the metastatic melanoma without prior treatment population. All were considered not related to nivolumab by investigators except arrhythmia (atrial fibrillation, tachycardia and ventricular arrhythmia).

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

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

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

[h] Post-marketing event (also see section 4.4)

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

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

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

Nivolumab in combination with ipilimumab and chemotherapy (see section 4.2)

Summary of the safety profile

When nivolumab is administered in combination, refer to the Summary of Product Characteristics for the respective combination therapy components prior to initiation of treatment.

In the dataset of nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of chemotherapy in NSCLC (n = 358), with a minimum follow-up of 6.5 months, the most frequent adverse reactions were fatigue (36%), nausea (26%), rash (25%), diarrhoea (20%), pruritus (18%), decreased appetite (16%), hypothyroidism (15%), and vomiting (13%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Median duration of therapy was 6.1 months (95% CI 4.93, 7.06) for nivolumab in combination with ipilimumab and chemotherapy and 2.4 months (95% CI 2.30, 2.83) for chemotherapy.

Tabulated summary of adverse reactions

Adverse reactions reported in the dataset for patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of chemotherapy in NSCLC (n = 358) are presented in Table 7. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 7: Adverse reactions with nivolumab in combination with ipilimumab and chemotherapy

Infections and infestations	
Common	conjunctivitis, pneumonia, respiratory tract infection
Blood and lymphatic system disorders	
Common	febrile neutropaenia
Uncommon	eosinophilia
Immune system disorders	
Common	infusion-related reaction, hypersensitivity
Endocrine disorders	
Very common	hypothyroidism
Common	hyperthyroidism, adrenal insufficiency, hypophysitis, thyroiditis
Uncommon	hypopituitarism, hypoparathyroidism
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration, hypoalbunaemia, hypophosphataemia
Nervous system disorders	
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis
Eye disorders	
Common	dry eye
Uncommon	blurred vision, episcleritis
Cardiac disorders	
Uncommon	tachycardia, atrial fibrillation, bradycardia
Vascular disorders	
Uncommon	hypertension
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis, dyspnoea, cough
Uncommon	pleural effusion
Gastrointestinal disorders	
Very common	nausea, diarrhoea, vomiting
Common	constipation, stomatitis, abdominal pain, colitis, dry mouth, pancreatitis
Hepatobiliary disorders	
Common	hepatitis
Skin and subcutaneous tissue disorders	
Very common	rash[a], pruritus
Common	alopecia, dry skin, erythema, urticaria
Uncommon	psoriasis, Stevens-Johnson syndrome, vitligo
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain[b], arthralgia, arthritis
Uncommon	muscular weakness, muscle spasms, polymyalgia rheumatica
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)
Uncommon	nephritis
General disorders and administration site conditions	
Very common	fatigue
Common	pyrexia, oedema (including peripheral oedema)
Uncommon	chills, chest pain
Investigations	

Very common	anaemia[c,d], thrombocytopaenia[c], leucopoenia[c], lymphopaenia[c], neutropaenia[c], increased alkaline phophatases[c], increased transaminases[c], increased creatinine[c], increased amylase[c], increased lipase[c], hypokalaemia[c], hypomagnesaemia[c], hyponatraemia[c]
Common	increased total bilirubin[c], increased thyroid stimulating hormone
Uncommon	increased gamma-glutamyltransferase

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

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

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

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

Description of selected adverse reactions

Nivolumab or nivolumab in combination is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment was required in a greater proportion of patients receiving nivolumab in combination with ipilimumab than in those receiving nivolumab monotherapy. Table 8 presents the percentage for immune-related adverse reactions who were permanently discontinued from treatment by dosing regimen. Additionally, for patients who experienced an event, Table 8 presents the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents) by dosing regimen. The management guidelines for these adverse reactions are described in section 4.4.

Table 8: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen

	Nivolumab 3 mg/kg or 240 mg monotherapy %	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC %	Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %
Immune-related adverse reaction leading to permanent discontinuation				
Pneumonitis	1.4	2.0	2.2	2.2
Colitis	0.8	16	4.0	4.2
Hepatitis	1.0	9	4.4	3.4
Nephritis and renal dysfunction	0.3	1.1	1.3	1.4
Endocrinopathies	0.2	2.7	2.9	2.0
Skin	0.4	0.9	1.5	1.1
Hypersensitivity/Infusion reaction	0.2	0	0	0.6
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]				
Pneumonitis	67	63	59	68
Colitis	14	46	26	20
Hepatitis	19	46	35	29

Table 8: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen

Nephritis and renal dysfunction	26	17	27	24
Endocrinopathies	7	27	25	8
Skin	4	7	7	10
Hypersensitivity/Infusion reaction	20	6	9	29

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

Immune-related pneumonitis
In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.6% (99/2787). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (24/2787) and 1.8% (51/2787) of patients respectively. Grade 3 and 4 cases were reported in 0.8% (21/2787) and <0.1% (1/2787) of patients respectively. Grade 5 cases were reported in < 0.1% (2/2787) of patients in these studies. Median time to onset was 3.3 months (range: 0.2-19.6). Resolution occurred in 66 patients (66.7%) with a median time to resolution of 6.6 weeks (range: 0.1^{+}-96.7^{+}); $^{+}$ denotes a censored observation.

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

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

In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of pneumonitis including interstitial lung disease was 5.3% (19/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.1% (4/358), and 0.6% (2/358) of patients, respectively. Median time to onset was 18.1 weeks (range: 0.6-52.4). Resolution occurred in 14 patients (74%) with a median time to resolution of 4.3 weeks (range: 0.7-27.9^{+}).

Immune-related colitis
In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 13% (361/2787). The majority of cases were Grade 1 or 2 in severity reported in 8.3% (230/2787) and 3.2% (88/2787) of patients respectively. Grade 3 cases were reported in 1.5% (43/2787) of patients. No Grade 4 or 5 cases were reported in these studies. Median time to onset was 1.8 months (range: 0.0-26.6). Resolution occurred in 311 patients (86.9%) with a median time to resolution of 2.1 weeks (range: 0.1-124.4^{+}).

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

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

In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of diarrhoea or colitis was 22.3% (80/358). Grade 2, Grade 3, Grade 4, and Grade 5 cases were reported in 7% (25/358), 5% (18/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively. Median time to onset was 5.1 weeks (range: 0.1-53.6). Resolution occurred in 70 patients (87.5%) with a median time to resolution of 1.4 weeks (range: 0.1-76.9^{+}).

Immune-related hepatitis
In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 6.7% (187/2787). The majority of cases were Grade 1 or 2 in severity reported in 3.5% (98/2787) and 1.4% (38/2787) of patients respectively. Grade 3 and 4 cases were reported in 1.5% (42/2787) and 0.3% (9/2787) of patients, respectively. No Grade 5 cases were reported in these studies. Median time to onset was 2.1 months (range: 0.0-27.6). Resolution occurred in 142 patients (76.3%) with a median time to resolution of 5.9 weeks (range: 0.1-94.3^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of liver function test abnormalities was 29.5% (132/448). Grade 2, Grade 3, and Grade 4 cases were reported in 6.7% (30/448), 15.4% (69/448), and 1.8% (8/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.5 months (range: 0.0-30.1). Resolution occurred in 124 patients (93.9%) with a median time to resolution of 5.1 weeks (range: 0.1-106.9).

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

In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of liver function test abnormalities was 13.4% (48/358). Grade 2, Grade 3, and Grade 4 cases were reported in 3.1% (11/358), 3.4% (12/358), and 1.1% (4/358) of patients, respectively. Median time to onset was 10.6 weeks (range: 1.1-68.3). Resolution occurred in 37 patients (80.4%) with a median time to resolution of 5 weeks (range: 0.3^{+}-45.0^{+}).

Immune-related nephritis and renal dysfunction
In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.7% (74/2787). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (41/2787) and 0.7% (20/2787) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (12/2787) and <0.1% (1/2787) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported in these studies. Median time to onset was 2.3 months (range: 0.0-18.2). Resolution occurred in 45 patients (63.4%) with a median time to resolution of 12.1 weeks (range: 0.3-79.1^{+}).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of nephritis or renal dysfunction was 5.1% (23/448). Grade 2, Grade 3, and Grade 4 cases were reported in 1.6% (7/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.6 months (range: 0.5-21.8). Resolution occurred in 21 patients (91.3%) with a median time to resolution of 2.1 weeks (range: 0.1-125.1^{+}).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of nephritis or renal dysfunction was 8.8% (48/547). Grade 2, Grade 3, and Grade 4 cases were reported in 4.4% (24/547), 0.7% (4/547), and 0.5% (3/547) of patients, respectively. No Grade 5

cases were reported. Median time to onset was 2.1 months (range: 0.0-16.1). Resolution occurred in 37 patients (77.1%) with a median time to resolution of 13.2 weeks (range: 0.1^{+}-106.0^{+}).

In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of nephritis or renal dysfunction was 7% (25/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.7% (6/358), and 0.6 (2/358) of patients, respectively. Median time to onset was 10.6 weeks (range: 0.1-51.3). Resolution occurred in 14 patients (56%) with a median time to resolution of 6.3 weeks (range: 0.1^{+}-82.9^{+}).

Immune-related endocrinopathies
In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 9.7% (270/2787). The majority of cases were Grade 1 or 2 in severity reported in 4.2% (118/2787) and 5.4% (150/2787) of patients, respectively. Grade 3 thyroid disorders were reported in < 0.1% (2/2787) of patients. Hypophysitis (1 Grade 1, 2 Grade 2, 5 Grade 3, and 1 Grade 4), hypopituitarism (5 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency) (1 Grade 1, 9 Grade 2, and 5 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus) (3 Grade 2 and 1 Grade 3), and diabetic ketoacidosis (2 Grade 3) were reported. No Grade 5 cases were reported in these studies. Median time to onset of these endocrinopathies was 2.8 months (range: 0.3-29.1). Resolution occurred in 123 patients (41.6%). Time to resolution ranged from 0.4 to 144.1^{+} weeks.

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

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

In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of thyroid disorders was 24% (86/358). Grade 2 and Grade 3 thyroid disorders were reported in 12.3% (44/358) and 0.3% (1/358) of patients, respectively. Hypophysitis occurred in 1.4% (5/358) of patients. Grade 2 and Grade 3 cases were reported in 0.6% (2/358) and 0.8% (3/358) of patients, respectively. Grade 2 hypopituitarism occurred in 0.3% (1/358) of patients. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (6/358) and 1.4% (5/358) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus was not reported. Median time to onset of these endocrinopathies was 12.1 weeks (range: 1.9-58.3). Resolution occurred in 30 patients (35.3%). Time to resolution ranged from 1.4 to 72.4^{+} weeks.

Immune-related skin adverse reactions
In patients treated with nivolumab monotherapy, the incidence of rash was 25.9% (722/2787). The majority of cases were Grade 1 in severity reported in 19.6% (546/2787) of patients. Grade 2 and Grade 3 cases were reported in 5.0% (139/2787) and 1.3% (37/2787) of patients respectively. No Grade 4 or 5 cases were reported in these studies. Median time to onset was 1.4 months (range: 0.0-27.9). Resolution occurred in 448 patients (62.8%) with a median time to resolution of 17.4 weeks (0.1-150.0^{+}).

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

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

In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of rash was 37.7% (135/358). Grade 2, Grade 3, and Grade 4 cases were reported in 11.5% (41/358), 4.2% (14/358), and 0.3% (1/358) of patients, respectively. Median time to onset was 3.3 weeks (range: 0.1-83.1). Resolution occurred in 96 patients (71.6%) with a median time to resolution of 9.4 weeks (range: 0.1^{+}-84.1^{+}).

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

Infusion reactions
In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 4.4% (123/2787), including 6 Grade 3 and 3 Grade 4 cases.

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of hypersensitivity/infusion reactions was 3.8% (17/448); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.2% (10/448) of patients. No Grade 3-5 cases were reported.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg//kg, the incidence of hypersensitivity/infusion reactions was 4.0% (22/547); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.4% (13/547) of patients. No Grade 3-5 cases were reported.

In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of hypersensitivity/infusion reactions was 4.7% (17/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively.

Complications of allogeneic HSCT in classical Hodgkin lymphoma
Rapid onset of GVHD has been reported with nivolumab use before and after allogeneic HSCT (see section 4.4).
In 49 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 13/49 patients (26.5%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in three patients (6%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (12%) within the first 6 weeks post-transplantation, with three patients responding to steroids. Hepatic veno-occlusive disease occurred in one patient, who died of GVHD and multi-organ failure. Nine of 49 patients (18.4%) died from complications of allogeneic

HSCT after nivolumab. The 49 patients had a median follow-up from subsequent allogeneic HSCT of 5.6 months (range: 0-19 months).

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: 5.4% for anaemia (all Grade 3), 0.9% for thrombocytopaenia, 1.0% for leucopoenia, 10.6% for lymphopaenia, 1.1% for neutropaenia, 2.3% for increased alkaline phosphatase, 3.0% for increased AST, 2.5% for increased ALT, 1.3% for increased total bilirubin, 0.8% for increased creatinine, 3.8% for hyperglycaemia, 1.4% for hypoglycaemia, 3.5% for increased amylase, 7.9% for increased lipase, 6.7% for hyponatraemia, 1.7% for hyperkalaemia, 1.6% for hypokalaemia, 1.6% for hypercalcaemia, 0.7% for hypermagnesaemia, 0.5% for hypomagnesaemia, 0.6% for hypocalcaemia, and 0.1% for hypernatraemia.

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

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

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

Immunogenicity
Of the 2334 patients who were treated with nivolumab monotherapy 3 mg/kg or 240 mg every 2 weeks and evaluable for the presence of anti-product-antibodies, 255 patients (10.9%) tested positive for treatment-emergent anti-product-antibodies with fifteen patients (0.6%) testing positive for neutralising antibodies.

Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26.0% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralising antibodies against nivolumab was 0.5% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 8.4% and neutralising antibodies against ipilimumab ranged from 0 to 0.3%.

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

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

Elderly
No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from SCCHN and adjuvant melanoma patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population (see section 5.1).

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

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. 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.

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

Clinical efficacy and safety

Based on modelling of dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between a nivolumab dose of 240 mg every 2 weeks or 3 mg/kg every 2 weeks. Additionally, based on these relationships, there were no clinically significant differences between a nivolumab dose of 480 mg every 4 weeks or 3 mg/kg every 2 weeks in adjuvant treatment of melanoma, advanced melanoma and advanced RCC.

Melanoma

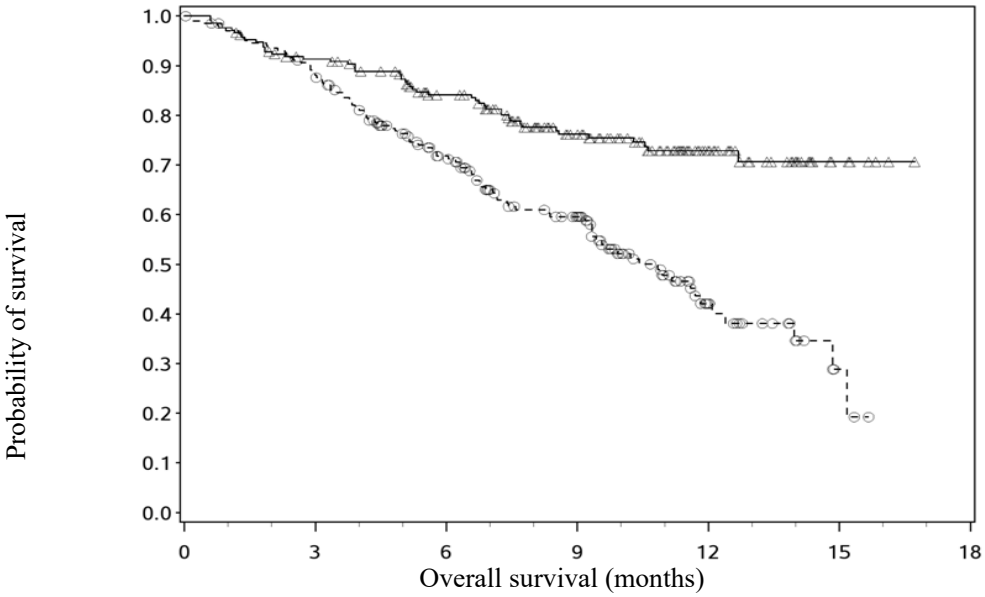
Treatment of advanced melanoma

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

A total of 418 patients were randomised to receive either nivolumab (n = 210) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine (n = 208) at 1000 mg/m^2 every 3 weeks. Randomisation was stratified by tumour PD-L1 status and M stage (M0/M1a/M1b versus M1c). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse events with the study drug, as determined by the investigator. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and objective response rate (ORR).
Baseline characteristics were balanced between the two groups. The median age was 65 years (range: 18-87), 59% were men, and 99.5% were white. Most patients had ECOG performance score of 0 (64%) or 1 (34%). Sixty-one percent of patients had M1c stage disease at study entry. Seventy-four percent of patients had cutaneous melanoma, and 11% had mucosal melanoma; 35% of patients had PD-L1 positive melanoma ($\geq$ 5% tumour cell membrane expression). Sixteen percent of patients had received prior adjuvant therapy; the most common adjuvant treatment was interferon (9%). Four percent of patients had a history of brain metastasis, and 37% of patients had a baseline LDH level greater than ULN at study entry.

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

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



Number of subjects at risk

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

──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 9.

Table 9: **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
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, active brain or leptomeningeal metastases or a known history of prior ipilimumab-related high-grade (Grade 4 per CTCAE v4.0) adverse reactions, except for resolved nausea, fatigue, infusion reactions, or endocrinopathies, were excluded from the study.

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

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

The median age was 60 years (range: 23-88). Sixty-four percent of patients were men and 98% were white. ECOG performance scores were 0 for 61% of patients and 1 for 39% of patients. The majority (75%) of patients had M1c stage disease at study entry. Seventy-three percent of patients had cutaneous melanoma and 10% had mucosal melanoma. The number of prior systemic regimen received was 1 for 27% of patients, 2 for 51% of patients, and > 2 for 21% of patients. Twenty-two percent of patients had tumours that tested BRAF mutation positive and 50% of patients had tumours that were considered PD-L1 positive. Sixty-four percent of patients had no prior clinical benefit (CR/PR or SD) on ipilimumab. Baseline characteristics were balanced between groups except for the proportions of patients who had a history of brain metastasis (19% and 13% in the nivolumab group and chemotherapy group, respectively) and patients with LDH greater than ULN at baseline (51% and 35%, respectively).

At the time of this final ORR analysis, results from 120 nivolumab-treated patients and 47 chemotherapy-treated patients who had a minimum of 6 months of follow-up were analysed. Efficacy results are presented in Table 10.

Table 10: **Best overall response, time and duration of response (CA209037)**

	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).

Single-arm phase 2 study (CA209172)
Study CA209172 was a single-arm, open label study of nivolumab monotherapy in patients with stage III (unresectable) or stage IV metastatic melanoma after prior treatment containing an anti-CTLA-4 monoclonal antibody. Safety was the primary endpoint and efficacy was a secondary endpoint. Of the 1008 treated patients, 103 (10%) had ocular/uveal melanoma, 66 (7%) had an ECOG performance score of 2, 165 (16%) had asymptomatic treated and untreated CNS metastases, 13 (1.3%) had treated leptomeningeal metastases, 25 (2%) had autoimmune disease, and 84 (8%) had Grade 3-4 immune-related AEs with prior anti-CTLA-4 therapy. No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. Efficacy results based on investigator-assessed response rates at week 12 are presented in Table 11 below.

Table 11: **Response rate at week 12 - all response evaluable patients and by subgroup (CA209172)**

	Total	Ocular/ Uveal melanoma	ECOG PS 2	CNS metastasis	Autoimmune disease	Grade 3-4 irAEs with anti-CTLA-4
N (%)[a]	161/588 (27.4)	4/61 (6.6)	4/20 (20.0)	20/73 (27.4)	3/16 (18.8)	13/46 (28.3)

[a] Responses were assessed per RECIST 1.1 for 588/1008 (58.3%) of patients who continued treatment through week 12 and had a follow-up scan at week 12.

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

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

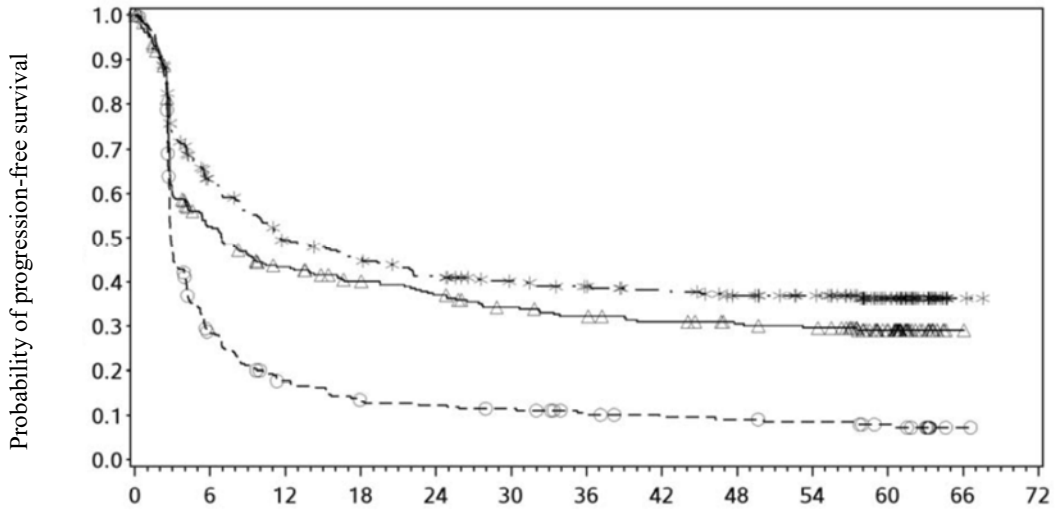
A total of 945 patients were randomised to receive nivolumab in combination with ipilimumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously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

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

At primary analysis (minimum follow-up 9 months) the median PFS was 6.9 months in the nivolumab group as compared with 2.9 months in the ipilimumab group (HR = 0.57, 99.5% CI: 0.43, 0.76; $p < 0.0001$). The median PFS was 11.5 months in the nivolumab in combination with ipilimumab group, as compared with 2.9 months in the ipilimumab group (HR = 0.42, 99.5% CI: 0.31, 0.57; $p < 0.0001$).

PFS results from descriptive analysis (with minimum follow up of 60 months) are shown in Figure 2 (all randomised population), Figure 3 (at the tumour PD-L1 5% cut off), and Figure 4 (at the tumour PD-L1 1% cut off).

Figure 2: Progression-free survival (CA209067)



Number of subjects at risk

Nivolumab + ipilimumab												
314	174	136	124	110	101	95	90	82	76	45	2	0
Nivolumab												
316	151	120	106	97	84	78	73	68	65	40	1	0
Ipilimumab												
315	78	46	34	31	28	21	18	17	15	11	1	0

- - -*- - - Nivolumab+ipilimumab (events: 182/314), median and 95% CI: 11.50 (8.74, 19.32).
PFS rate at 12 months and 95% CI: 49% (44, 55), PFS rate at 60 months and 95% CI: 36% (32, 42)

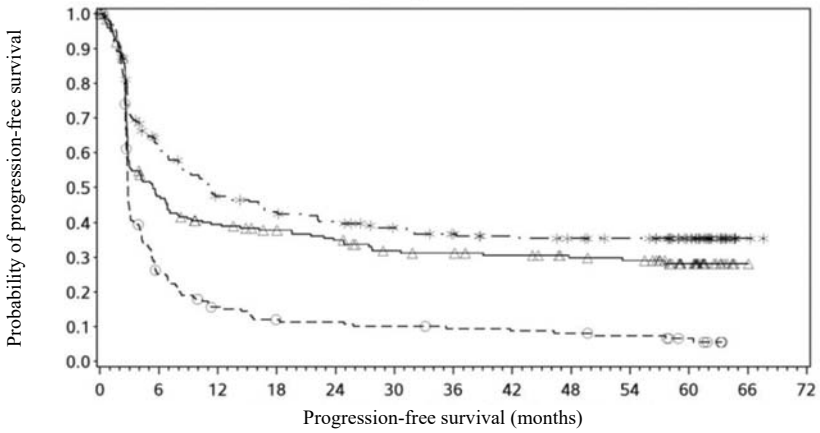
——Δ—— Nivolumab (events: 203/316), median and 95% CI: 6.93 (5.13, 10.18).
PFS rate at 12 months and 95% CI: 42% (36, 47), PFS rate at 60 months and 95% CI: 29% (24, 35)

- - -❍- - - Ipilimumab (events: 261/315), median and 95% CI: 2.86 (2.79, 3.15).
PFS rate at 12 months and 95% CI: 18% (14, 23), PFS rate at 60 months and 95% CI: 8% (5, 12)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.35, 0.51)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.53 (0.44, 0.64)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.79 (0.64, 0.96)

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

PD-L1 expression < 5%



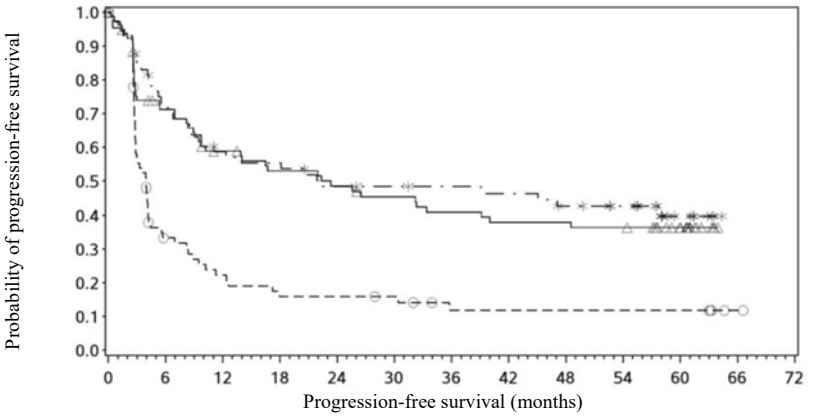
Number of subjects at risk

Nivolumab + ipilimumab												
210	113	87	78	71	64	59	55	52	49	33	2	0
Nivolumab												
208	91	73	66	60	50	48	45	40	38	23	1	0
Ipilimumab												
202	45	26	19	18	16	14	13	12	10	6	0	0

- - -*- - - Nivolumab+ipilimumab (events: 123/210), median and 95% CI: 11.17 (7.98, 17.51)
——Δ—— Nivolumab (events: 136/208), median and 95% CI: 5.39 (2.96, 7.13)
- - -O- - - Ipilimumab (events: 171/202), median and 95% CI: 2.83 (2.76, 3.02)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.33, 0.53)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.54 (0.43, 0.68)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.77 (0.60, 0.98)

PD-L1 expression ≥ 5%



Number of subjects at risk

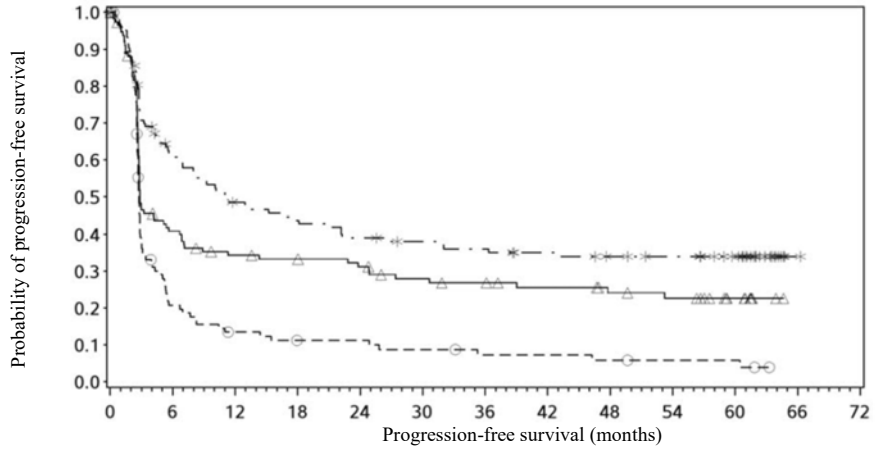
Nivolumab + ipilimumab												
68	44	35	33	28	27	26	25	22	19	7	0	0
Nivolumab												
80	52	41	36	33	30	27	25	25	24	15	0	0
Ipilimumab												
75	21	14	10	10	9	5	5	5	5	5	1	0

- - -*- - - Nivolumab+ipilimumab (events: 36/68), median and 95% CI: 22.11 (9.72, N.A.)
——Δ—— Nivolumab (events: 46/80), median and 95% CI: 22.34 (9.46, 40.02)
- - -O- - - Ipilimumab (events: 60/75), median and 95% CI: 3.94 (2.79, 4.21)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.37 (0.24, 0.56)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.28, 0.62)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.89 (0.57, 1.37)

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

PD-L1 expression < 1%



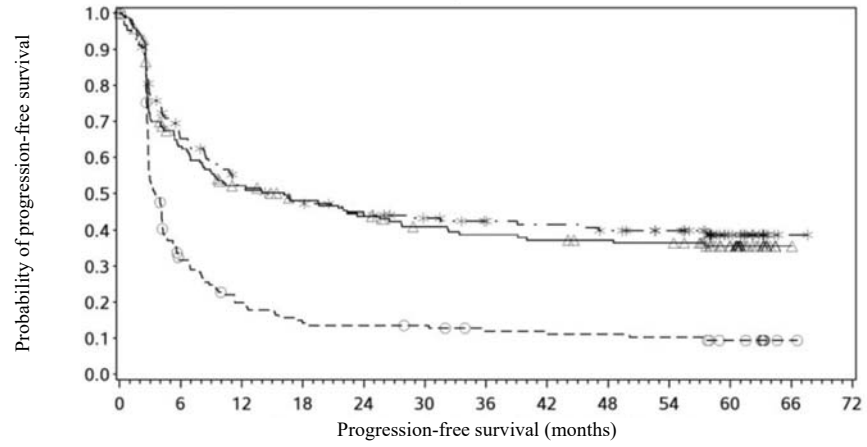
Number of subjects at risk

Nivolumab + ipilimumab												
123	65	51	46	41	38	36	33	30	28	21	1	0
Nivolumab												
117	44	35	33	30	25	23	20	17	15	8	0	0
Ipilimumab												
113	20	12	9	9	7	5	5	4	3	3	0	0

- - -*- - - Nivolumab+ipilimumab (events: 73/123), median and 95% CI: 11.17 (6.93, 22.18)
——Δ—— Nivolumab (events: 82/117), median and 95% CI: 2.83 (2.76, 5.62)
- - -❍- - - Ipilimumab (events: 94/113), median and 95% CI: 2.76 (2.66, 2.86)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.39 (0.29, 0.54)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.59 (0.44, 0.80)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.66 (0.48, 0.91)

PD-L1 expression ≥ 1%



Number of subjects at risk

Nivolumab + ipilimumab												
155	92	71	65	58	53	49	47	44	40	19	1	0
Nivolumab												
171	99	79	69	63	55	52	50	48	47	30	1	0
Ipilimumab												
164	46	28	20	19	18	14	13	13	12	8	1	0

- - -*- - - Nivolumab+ipilimumab (events: 86/155), median and 95% CI: 16.13 (8.90, 39.06)
——Δ—— Nivolumab (events: 100/171), median and 95% CI: 16.20 (8.11, 27.66)
- - -❍- - - Ipilimumab (events: 137/164), median and 95% CI: 3.48 (2.83, 4.17)

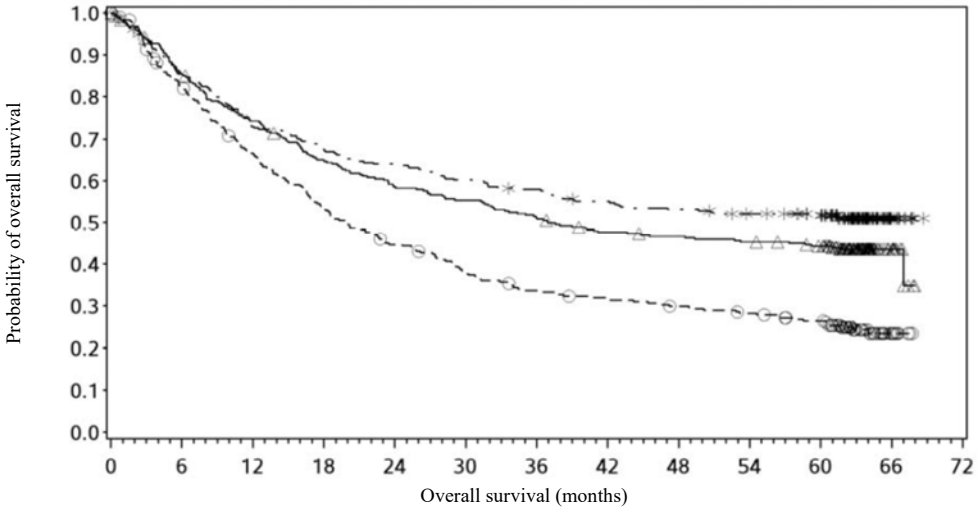
Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.41 (0.31, 0.54)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.45 (0.35, 0.58)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.91 (0.68, 1.22)

The final (primary) OS analysis occurred when all patients had a minimum follow-up of 28 months. At 28 months, median OS was not reached in the nivolumab group as compared with 19.98 months in the ipilimumab group (HR = 0.63, 98% CI: 0.48, 0.81; p-value: < 0.0001). Median OS was not reached in the nivolumab in combination with ipilimumab group as compared with the ipilimumab group (HR = 0.55, 98% CI: 0.42, 0.72; p-value: < 0.0001).

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 60 months show outcomes consistent with the original primary analysis. OS results from this follow-up analysis are shown in Figure 5 (all randomised), Figure 6 and 7 (at the tumour PD-L1 5% and 1% cut off).

The OS analysis was not adjusted to account for subsequent therapies received. Subsequent systemic therapy was received by 34.7%, 48.1%, and 65.7% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively. Subsequent immunotherapy (including anti-PD1 therapy, anti-CTLA-4 antibody, or other immunotherapy) was received by 17.5%, 33.2%, and 47.3% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively.

Figure 5: Overall survival (CA209067) - Minimum follow-up of 60 months



Number of subjects at risk

Nivolumab+ipilimumab	314	265	227	210	199	187	179	169	163	157	150	14	0
Nivolumab	316	266	231	201	181	171	158	145	141	137	130	14	0
Ipilimumab	315	253	203	163	135	113	100	94	87	81	73	12	0

- - -*- - - Nivolumab+ipilimumab (events: 152/314), median and 95% CI: N.A. (38.18, N.A.)
OS rate and 95% CI at 12 months: 73% (68, 78), 24 months: 64% (59, 69), 36 months: 58% (52, 63), and 60 months: 52% (46, 57)

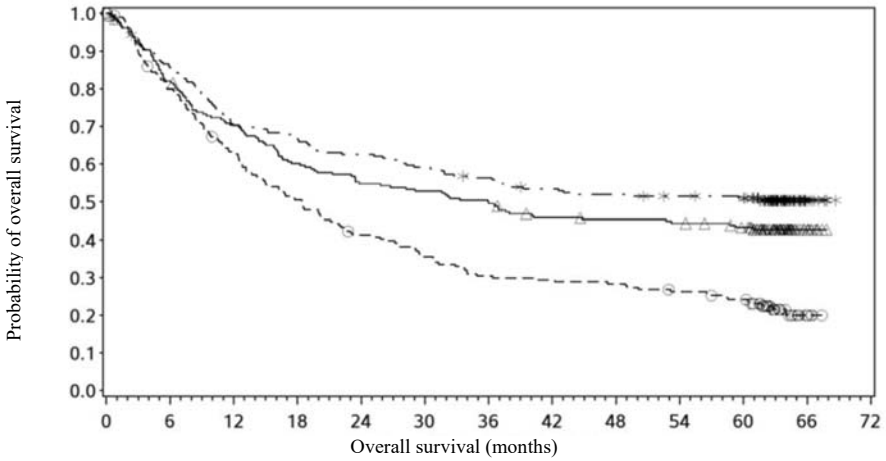
——Δ—— Nivolumab (events: 176/316), median and 95% CI: 36.93 months (28.25, 58.71)
OS rate and 95% CI at 12 months: 74% (69, 79), 24 months: 59% (53, 64), 36 months: 52% (46, 57), and 60 months: 44% (39, 50)

- - -O- - - Ipilimumab (events: 230/315), median and 95% CI: 19.94 months (16.85, 24.61)
OS rate and 95% CI at 12 months: 67% (61, 72), 24 months: 45% (39, 50), 36 months: 34% (29, 39), and 60 months: 26% (22, 31)

Nivolumab+ipilimumab vs ipilimumab - HR (95% CI): 0.63 (0.52, 0.76)
Nivolumab vs ipilimumab - HR (95% CI): 0.52 (0.42, 0.64)
Nivolumab+ipilimumab vs nivolumab - HR (95% CI): 0.83 (0.67, 1.03)

Figure 6: Overall survival by PD-L1 expression: 5% cut off (CA209067) - Minimum follow-up of 60 months

PD-L1 expression < 5%



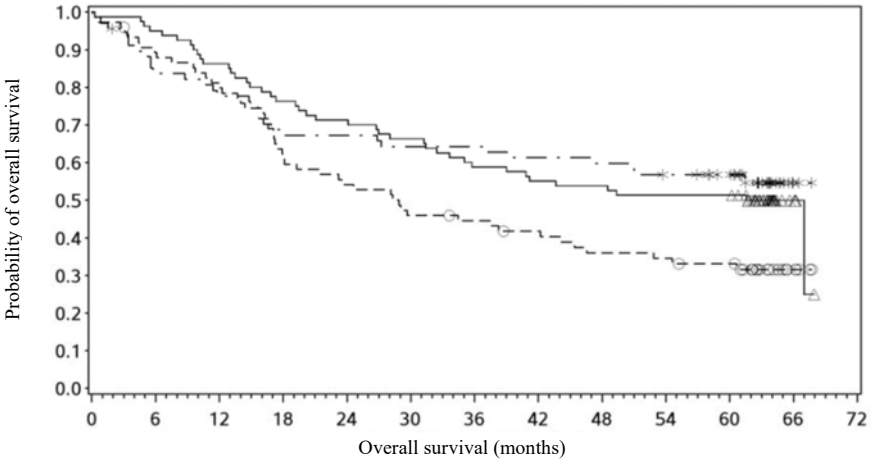
Number of subjects at risk

Nivolumab+ipilimumab												
210	178	146	139	130	123	116	109	106	103	101	9	0
Nivolumab												
208	169	144	123	112	108	102	92	90	88	82	9	0
Ipilimumab												
202	158	124	99	80	69	59	57	55	50	45	5	0

---*---- Nivolumab+ipilimumab (events: 103/210), median and 95% CI: N.A. (32.72, N.A.)
——Δ—— Nivolumab (events: 117/208), median and 95% CI: 35.94 months (23.06, 59.24.)
---O--- Ipilimumab (events: 154/202), median and 95% CI: 18.40 months (13.70, 22.51)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.50 (0.39, 0.65)
Nivolumab vs. ipilimumab - HR (95% CI): 0.62 (0.49, 0.79)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.81 (0.62, 1.06)

PD-L1 expression ≥ 5%



Number of subjects at risk

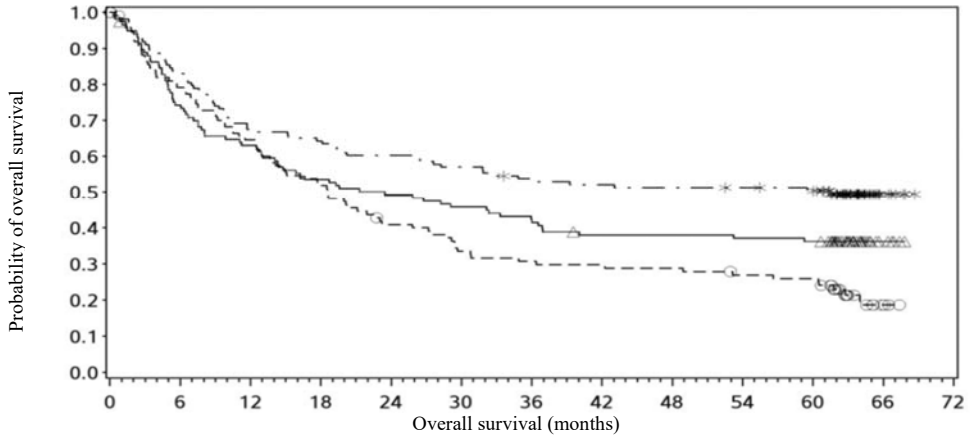
Nivolumab+ipilimumab												
68	56	52	45	45	43	43	41	40	37	33	2	0
Nivolumab												
80	76	69	61	57	53	47	44	43	41	41	5	0
Ipilimumab												
75	66	60	46	40	34	32	29	25	24	22	5	0

---*---- Nivolumab+ipilimumab (events: 30/68), median and 95% CI: N.A. (39.06, N.A.)
——Δ—— Nivolumab (events: 41/80), median and 95% CI: 61.57 months (33.64, N.A.)
---O--- Ipilimumab (events: 50/75), median and 95% CI: 28.88 months (18.10, 44.16)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.58 (0.37, 0.91)
Nivolumab vs. ipilimumab - HR (95% CI): 0.63 (0.42, 0.96)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.91 (0.657, 1.46)

Figure 7: Overall survival by PD-L1 expression: 1% cut off (CA209067) - Minimum follow-up of 60 months

PD-L1 expression < 1%



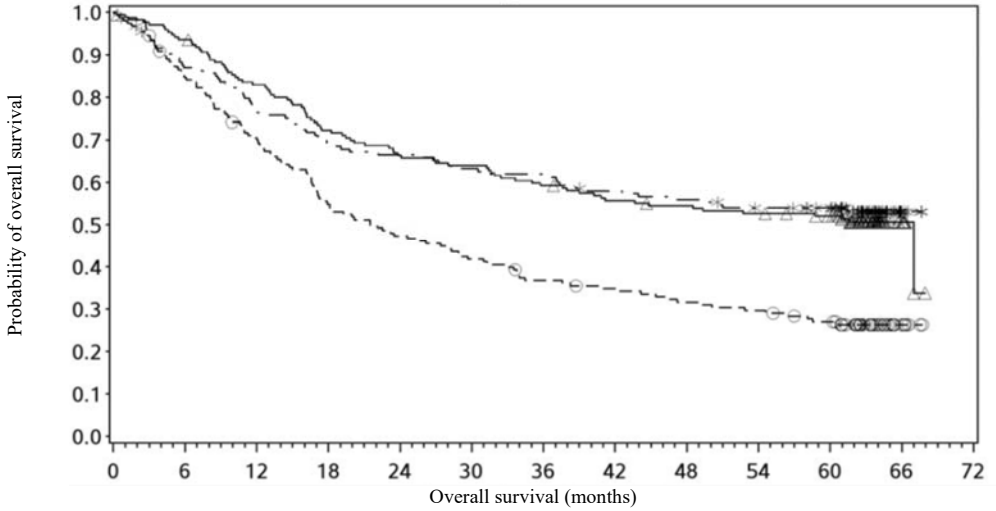
Number of subjects at risk

Nivolumab+ipilimumab												
123	102	82	79	74	70	65	63	62	61	59	6	0
Nivolumab												
117	86	73	62	57	53	49	43	43	42	41	5	0
Ipilimumab												
113	87	71	57	44	36	33	32	31	28	27	3	0

---*---- Nivolumab+ipilimumab (events: 62/123), median and 95% CI: 61.44 (26.45, N.A.)
——Δ—— Nivolumab (events: 74/117), median and 95% CI: 23.46 months (13.01, 36.53)
- - -❍- - - Ipilimumab (events: 86/113), median and 95% CI: 18.56 months (13.67, 23.20)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.53 (0.38, 0.74)
Nivolumab vs. ipilimumab - HR (95% CI): 0.77 (0.56, 1.05)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.69 (0.50, 0.97)

PD-L1 expression ≥ 1%



Number of subjects at risk

Nivolumab+ipilimumab												
155	132	116	105	101	96	94	87	84	79	75	5	0
Nivolumab												
171	159	140	122	112	108	100	93	90	87	82	9	0
Ipilimumab												
164	137	113	88	76	67	58	54	49	46	40	7	0

---*---- Nivolumab+ipilimumab (events: 71/155), median and 95% CI: N.A. (39.06, N.A.)
——Δ—— Nivolumab (events: 84/171), median and 95% CI: 66.99 months (39.00, N.A.)
- - -❍- - - Ipilimumab (events: 118/164), median and 95% CI: 21.49 months (16.85, 29.08)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.51 (0.38, 0.69)
Nivolumab vs. ipilimumab - HR (95% CI): 0.53 (0.40, 0.70)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.97 (0.70, 1.32)

Minimum follow-up for the analysis of ORR was 60 months. Responses are summarised in Table 12.

Table 12: Objective response (CA209067)

	nivolumab + ipilimumab (n = 314)	nivolumab (n = 316)	ipilimumab (n = 315)
Objective response	183 (58%)	141 (45%)	60 (19%)
(95% CI)	(52.6, 63.8)	(39.1, 50.3)	(14.9, 23.8)
Odds ratio (vs. ipilimumab)	6.35	3.5	
(95% CI)	(4.38, 9.22)	(2.46, 5.10)	
Complete response (CR)	69(22%)	60 (19%)	18 (6%)
Partial response (PR)	114 (36%)	81 (26%)	42 (13%)
Stable disease (SD)	38 (12%)	30 (10%)	69 (22%)
Duration of response			
Median (range), months	N.A. (0-65.2)	N.A. (0-63.3)	14.39 (0-61.9)
Proportion ≥12 months in duration	67%	71%	47%
Proportion ≥24 months in duration	57%	55%	36%
ORR (95% CI) by tumour PD-L1 expression			
<5%	56% (48.7, 62.5) n = 210	43% (36, 49.8) n = 208	18% (12.8, 23.8) n = 202
≥5%	72% (59.9, 82.3) n = 68	58% (45.9, 68.5) n = 80	21% (12.7, 32.3) n = 75
<1%	54% (44.4, 62.7) n = 123	36% (27.2, 45.3) n = 117	18% (11.2, 26.0) n = 113
≥1%	65% (56.4, 72) n = 155	54% (46.6, 62) n = 171	20% (13.7, 26.4) n = 164

Both nivolumab-containing arms demonstrated a significant PFS and OS benefit and greater ORR compared with ipilimumab alone. The observed PFS results at 18 months of follow-up and ORR and OS results at 28 months of follow-up were consistently demonstrated across subgroups of patients including baseline ECOG performance status, BRAF status, M stage, age, history of brain metastases, and baseline LDH level. This observation was maintained with the OS results with a minimum follow-up of 60 months.

Among 131 patients who discontinued the combination due to adverse reaction after 28 months of follow-up, the ORR was 71% (93/131) with 20% (26/131) achieving a complete response and median OS was not reached.

Both nivolumab-containing arms demonstrated greater objective response rates than ipilimumab regardless of PD-L1 expression levels. ORRs were higher for the combination of nivolumab and ipilimumab relative to nivolumab monotherapy across tumour PD-L1 expression levels (Table 12) after 60 months of follow-up, with a best overall response of complete response correlating to an improved survival rate.

After 60 months of follow-up, median durations of response for patients with tumour PD-L1 expression level ≥5% were not reached (range: 18.07-N.A.) in the combination arm, not reached (range: 26.71-N.A.) in the nivolumab monotherapy arm and 31.28 months (range: 6.08-N.A.) in the ipilimumab arm. At tumour PD-L1 expression <5%, median durations of response were not reached (range: 40.08-N.A.) in the combination arm, were not reached (range: 50.43-N.A.) in the nivolumab monotherapy arm and 12.75 months (range: 5.32-53.65) in the ipilimumab monotherapy arm.

No clear cut off for PD-L1 expression can reliably be established when considering the relevant endpoints of tumour response and PFS and OS. Results from exploratory multivariate analyses identified patient and tumour characteristics (ECOG performance status, M stage, baseline LDH, BRAF mutation status, PD-L1 status, and gender) which might contribute to the survival outcome.

Efficacy by BRAF status:
After 60 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had a median PFS of 16.76 months (95% CI: 8.28, 32.0) and 11.7 months (95% CI: 7.0, 18.14), while those in the nivolumab monotherapy arm had a median PFS of 5.6 months (95% CI: 2.79, 9.46) and 8.18 months (95% CI: 5.13, 19.55), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had a median PFS of 3.38 months (95% CI: 2.79, 5.19) and 2.83 months (95% CI: 2.76, 3.06), respectively.
After 60 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had an ORR of 67.0% (95% CI: 57.0, 75.9; n = 103) and 54.0% (95% CI: 47.1, 60.9; n = 211), while those in the nivolumab monotherapy arm had an ORR of 37.87% (95% CI: 28.2, 48.1; n = 98) and 47.7% (95% CI: 40.9, 54.6; n = 218), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had an ORR of 23.0% (95% CI: 15.2, 32.5; n = 100) and 17.2% (95% CI: 12.4, 22.9; n = 215).
After 60 months of follow-up, in BRAF [V600] mutation-positive patients median OS was not reached in the combination arm and 45.5 months in the nivolumab monotherapy arm. Median OS for BRAF [V600] mutation-positive patients in the ipilimumab monotherapy arm was 24.6 months. In BRAF wild-type patients median OS was 39.06 months in the combination arm, 34.37 months in the nivolumab monotherapy arm and 18.5 months in the ipilimumab monotherapy arm. The OS HRs for nivolumab in combination with ipilimumab vs. nivolumab monotherapy were 0.70 (95% CI: 0.46, 1.05) for BRAF[V600] mutation-positive patients and 0.89 (95% CI: 0.69, 1.15) for BRAF wild-type patients.

Randomised phase 2 study of nivolumab in combination with ipilimumab and ipilimumab (CA209069)
Study CA209069 was a randomised, Phase 2, double-blind study comparing the combination of nivolumab and ipilimumab with ipilimumab alone in 142 patients with advanced (unresectable or metastatic) melanoma with similar inclusion criteria to study CA209067 and the primary analysis in patients with BRAF wild-type melanoma (77% of patients). Investigator assessed ORR was 61% (95% CI: 48.9, 72.4) in the combination arm (n = 72) versus 11% (95% CI: 3.0, 25.4) for the ipilimumab arm (n = 37). The estimated 2 and 3 year OS rates were 68% (95% CI: 56, 78) and 61% (95% CI: 49, 71), respectively, for the combination (n = 73) and 53% (95% CI: 36, 68) and 44% (95% CI: 28, 60), respectively, for ipilimumab (n = 37).

Adjuvant treatment of melanoma

Randomised phase 3 study of nivolumab vs 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 13 and Figure 8 (all randomised population).

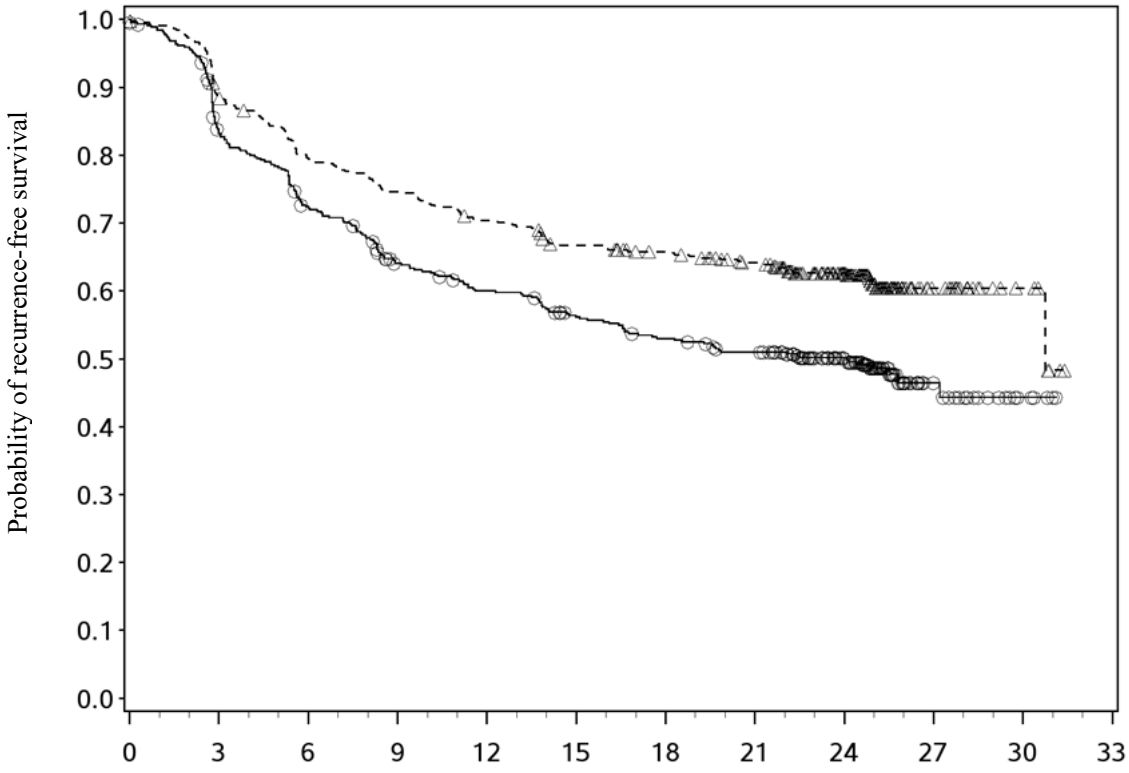
Table 13: Efficacy results (CA209238)

	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 8: 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

First-line treatment of NSCLC

Randomised phase 3 study of nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy vs. 4 cycles of platinum-based chemotherapy (CA2099LA)

The safety and efficacy of nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-based chemotherapy were evaluated in a phase 3, randomised, open-label study (CA2099LA). The study included patients (18 years or older) with histologically confirmed non-squamous or squamous Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification), ECOG performance status 0 or 1, and no

prior anticancer therapy (including EGFR and ALK inhibitors). Patients were enrolled regardless of their tumour PD-L1 status.

Patients with sensitising EGFR mutations or ALK translocations, active (untreated) brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents. Randomisation was stratified by histology (squamous vs non-squamous), tumour PD-L1 expression level (≥ 1% vs < 1%), and gender (male vs female).

A total of 719 patients were randomised to receive either nivolumab in combination with ipilimumab and platinum-based chemotherapy (n = 361) or platinum-based chemotherapy (n = 358). Patients in the nivolumab in combination with ipilimumab and platinum-based chemotherapy arm received nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-based chemotherapy administered every 3 weeks for 2 cycles. Patients in the chemotherapy arm received platinum-based chemotherapy administered every 3 weeks for 4 cycles; non-squamous patients could receive optional pemetrexed maintenance therapy.
Platinum-based chemotherapy consisted of carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m^2; or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC.

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

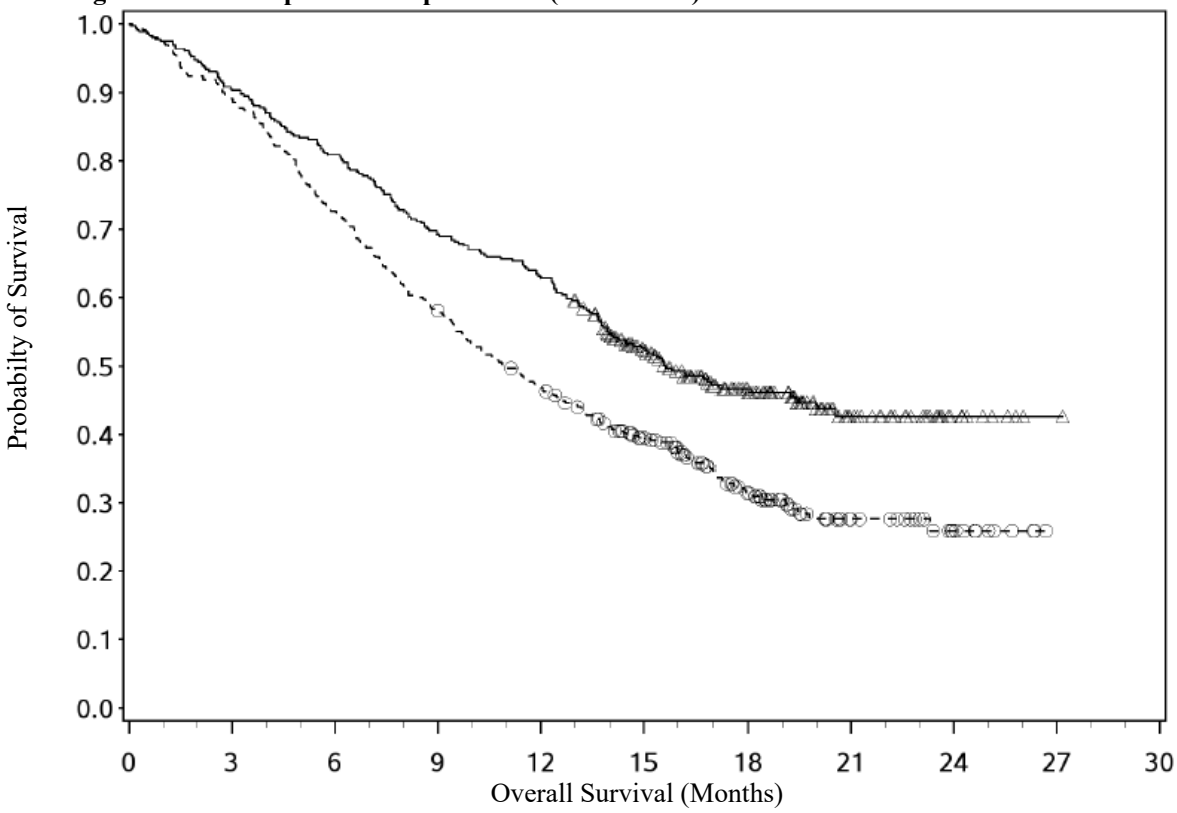
CA2099LA baseline characteristics were generally balanced across all treatment groups. The median age was 65 years (range: 26-86) with 51% ≥ 65 years of age and 10% ≥ 75 years of age. The majority of patients were white (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% of patients with PD-L1 ≥ 1% and 37% with PD-L1 < 1%, 31% had squamous and 69% had non-squamous histology, 17% had brain metastases, and 86% were former/current smokers. No patients received prior immunotherapy.

CA2099LA primary efficacy outcome measure was OS. Additional efficacy endpoints were PFS, ORR, and duration of response as assessed by BICR.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR for patients randomised to nivolumab in combination with ipilimumab and platinum-based chemotherapy as compared to platinum-based chemotherapy alone at the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis). Minimum follow-up for OS was 8.1 months.

Efficacy results are shown in Figure 9 (updated OS analysis with a minimum follow-up of 12.7 months) and Table 14 (primary analysis with a minimum follow-up of 8.1 months).
An updated efficacy analysis was performed when all patients had a minimum follow-up of 12.7 months (see Figure 9). At the time of this analysis, the hazard ratio for OS was 0.66 (95% CI: 0.55, 0.80) and the hazard ratio for PFS was 0.68 (95% CI: 0.57, 0.82).

Figure 9: Kaplan-Meier plot of OS (CA2099LA)



Number of Subjects at Risk

Nivolumab + ipilimumab + chemotherapy										
361	326	292	250	227	153	86	33	10	1	0
Chemotherapy										
358	319	260	208	166	116	67	26	11	0	0

Nivolumab + ipilimumab + chemotherapy (events: 190/361), median and 95% CI: 15.64 (13.93, 19.98)
Chemotherapy (events: 242/358), median and 95% CI: 10.91 (9.46, 12.55)

Table 14: Efficacy results (CA2099LA)

	nivolumab + ipilimumab + chemotherapy (n = 361)		**chemotherapy (n = 358)**
Overall survival			
Events	156 (43.2%)		195 (54.5%)
Hazard ratio (96.71% CI)[a]		0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]		0.0006	
Median (months) (95% CI)	14.1 (13.24, 16.16)		10.7 (9.46, 12.45)
Rate (95% CI) at 6 months	80.9 (76.4,84.6)		72.3 (67.4,76.7)
Progression-free survival			
Events	232 (64.3%)		249 (69.6%)
Hazard ratio (97.48% CI)[a]		0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]		0.0001	
Median (months)[d] (95% CI)	6.83 (5.55, 7.66)		4.96 (4.27, 5.55)

Table 14: Efficacy results (CA2099LA)

	nivolumab + ipilimumab + chemotherapy (n = 361)		chemotherapy (n = 358)
Rate (95% CI) at 6 months	51.7 (46.2, 56.8)		35.9 (30.5, 41.3)
Overall response rate[e]	136 (37.7%)		90 (25.1%)
(95% CI)	(32.7, 42.9)		(20.7, 30.0)
Stratified CMH test p-value[f]		0.0003	
Complete response (CR)	7 (1.9%)		3 (0.8%)
Partial response (PR)	129 (35.7%)		87 (24.3%)
Duration of response			
Median (months)	10.02		5.09
(95% CI)[d]	(8.21, 13.01)		(4.34, 7.00)
% with duration ≥ 6 months[g]	74		41

[a] Based on a stratified Cox proportional hazard model.
[b] p-value is compared with the allocated alpha of 0.0329 for this interim analysis.
[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.
[d] Kaplan-Meier estimate.
[e] Proportion with complete or partial response; CI based on the Clopper and Pearson Method.
[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.
[g] Based on Kaplan-Meier estimates of duration of response.
CMH = Cochran-Mantel-Haenszel

Subsequent systemic therapy was received by 28.8% and 41.1% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA4) was received by 3.9% and 27.9% of patients in the combination and chemotherapy arms, respectively.

In study CA2099LA, subgroup descriptive analysis relative to chemotherapy, OS benefit was shown in patients treated with nivolumab in combination with ipilimumab and chemotherapy with squamous histology (HR [95% CI] 0.65 [0.46, 0.93], n = 227) and in patients with non-squamous histology (HR [95% CI] 0.72 [0.55, 0.93], n = 492).

Table 15 summarises efficacy results of OS, PFS, and ORR by tumour PD-L1 expression in pre-specified subgroup analyses.

Table 15: Efficacy results by tumour PD-L1 expression (CA2099LA)

	nivolumab + ipilimumab + chemotherapy	chemo-therapy	nivolumab + ipilimumab + chemotherapy	chemo-therapy	nivolumab + ipilimumab + chemotherapy	chemo-therapy	nivolumab + ipilimumab + chemotherapy	chemo-therapy
	PD-L1 < 1% (n = 264)		**PD-L1 ≥ 1% (n = 406)**		**PD-L1 ≥ 1% to 49% (n = 233)**		**PD-L1 ≥ 50% (n = 173)**	
OS hazard ratio (95% CI)[a]	0.65 (0.46, 0.92)		0.67 (0.51, 0.89)		0.69 (0.48, 0.98)		0.64 (0.41, 1.02)	
PFS hazard ratio (95% CI)[a]	0.77 (0.57, 1.03)		0.67 (0.53, 0.85)		0.71 (0.52, 0.97)		0.59 (0.40, 0.86)	
ORR %	31.1	20.9	41.9	27.6	37.8	24.5	48.7	30.9

[a] Hazard ratio based on unstratified Cox proportional hazards model.

A total of 70 NSCLC patients aged ≥ 75 years were enrolled in study CA2099LA (37 patients in the nivolumab in combination with ipilimumab and chemotherapy arm and 33 patients in the chemotherapy arm). A HR of 1.36 (95% CI: 0.74, 2.52) in OS and a HR of 1.12 (95% CI: 0.64, 1.96) in PFS was observed for nivolumab in combination with ipilimumab and chemotherapy vs. chemotherapy within this study subgroup. ORR was 27.0% in the nivolumab in combination with ipilimumab and chemotherapy arm and 15.2% in the chemotherapy arm. Forty-three percent of patients aged ≥ 75 years discontinued treatment with nivolumab in combination with ipilimumab and chemotherapy. Efficacy and safety data of nivolumab in combination with ipilimumab and chemotherapy are limited in this patient population.

In a subgroup analysis, a reduced survival benefit for nivolumab in combination with ipilimumab and chemotherapy compared to chemotherapy was observed in patients who were never smokers. However, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

Treatment of NSCLC after prior chemotherapy
Squamous NSCLC

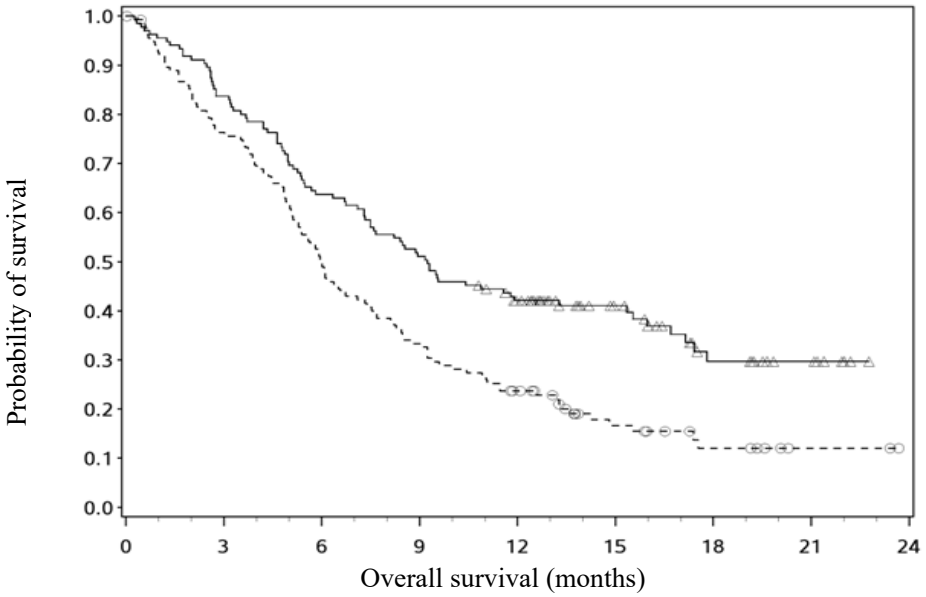
Randomised phase 3 study vs. docetaxel (CA209017)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209017). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an ECOG performance status score of 0 or 1. Patients were enrolled regardless of their tumour PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active brain metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (n = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m^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 RECIST, version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. In addition, symptom improvement and overall health status were assessed using the Lung cancer symptom score (LCSS) average symptom burden index and the EQ-5D Visual Analogue Scale (EQ-VAS), respectively.

Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 39-85) with 44% ≥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 10.

Figure 10: Kaplan-Meier curves of OS (CA209017)



Number of subjects at risk

Nivolumab 3 mg/kg								
135	113	86	69	52	31	15	7	0
Docetaxel								
137	103	68	45	30	14	7	2	0

——Δ—— Nivolumab 3 mg/kg (events: 86/135), median and 95% CI: 9.23 (7.33, 13.27)
- - -Ͻ- - - Docetaxel (events: 113/137), median and 95% CI: 6.01 (5.13, 7.33)

The observed OS benefit was consistently demonstrated across subgroups of patients. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 1%, 5% or 10%). However, the role of this biomarker (tumour PD-L1 expression) has not been fully elucidated. With a minimum of 62.6 months follow-up, OS benefit remains consistently demonstrated across subgroups.

Study CA209017 included a limited number of patients ≥ 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 16.

Table 16: **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 (95% CI)	20.0% (13.6, 27.7)		8.8% (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 ORR of 14.5% (95% CI: 8.7,22.2%), a median OS of 8.21 months (95% CI: 6.05,10.9), and a median PFS of 1.87 months (95% CI 1.77,3.15). The PFS was measured by RECIST, version 1.1. The estimated 1-year survival rate was 41%.

Single-arm phase 2 study (CA209171)
Study CA209171 was a single-arm, open label study of nivolumab monotherapy in patients with previously treated advanced or metastatic squamous NSCLC. Safety was the primary endpoint and efficacy was a secondary endpoint. Of the 811 treated patients, 103 (13%) had an ECOG performance score of 2, 686 (85%) were < 75 years old and 125 (15%) were ≥ 75 years old. No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. Efficacy results based on investigator-assessed ORR are presented in Table 17 below.

Table 17: **ORR based on response evaluable patients – total and by subgroup (CA209171)**

Results	Total	ECOG PS 2	< 75 years	≥ 75 years
N responders/ N evaluable[a] (%)	66/671 (9.8)	1/64 (6.1)	55/568 (9.7)	11/103 (10.7)
95% CI[b]	(7.7, 12.3)	(0.0, 8.4)	(7.4, 12.4)	(5.5, 18.3)

[a] includes confirmed and unconfirmed responses, scans were mandatory only at week 8/9 and week 52.
[b] CR+PR, confidence interval based on the Clopper and Pearson method

Non-squamous NSCLC

Randomised phase 3 study vs. docetaxel (CA209057)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic non-squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209057). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen which may have included maintenance therapy and who had an ECOG performance status score of 0 or 1. An additional line of TKI therapy was allowed for patients with known EGFR mutation or ALK translocation. Patients were enrolled regardless of their tumour PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active brain metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

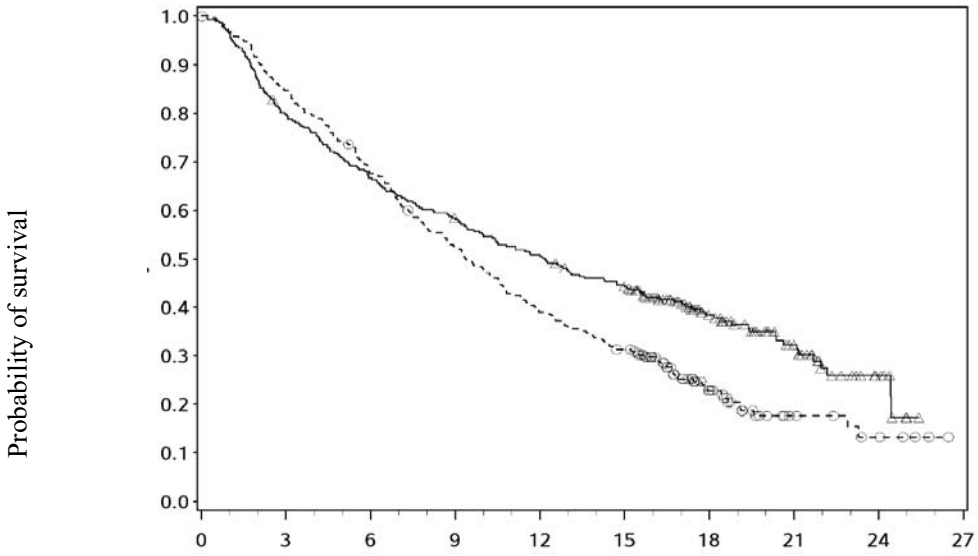
A total of 582 patients were randomised to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks (n = 292) or docetaxel 75 mg/m^2 every 3 weeks (n = 290). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour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

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

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

The Kaplan-Meier curves for OS are shown in Figure 11.

Figure 11: Kaplan-Meier curves of OS (CA209057)



Number of subjects at risk

Nivolumab 3 mg/kg									
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)
- - -O- - - 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 randomised to nivolumab as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 18.

Table 18: **Efficacy results (CA209057)**

	nivolumab (n = 292)	**docetaxel (n = 290)**
Prespecified interim analysis Minimum follow-up: 13.2 months		
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 tumour 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 improved survival compared to docetaxel, whereas survival was similar to docetaxel in patients with low or no tumour PD-L1 expression. In terms of ORR, increasing PD-L1 expression was associated with larger ORR. Comparable to the overall population, median duration of response was increased with nivolumab vs. docetaxel for patients with no PD-L1 expression (18.3 months vs. 5.6 months) and for patients with PD-L1 expression (16.0 months vs. 5.6 months).

Table 19 summarises results of ORR and OS by tumour PD-L1 expression.

Table 19: 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.

Renal cell carcinoma

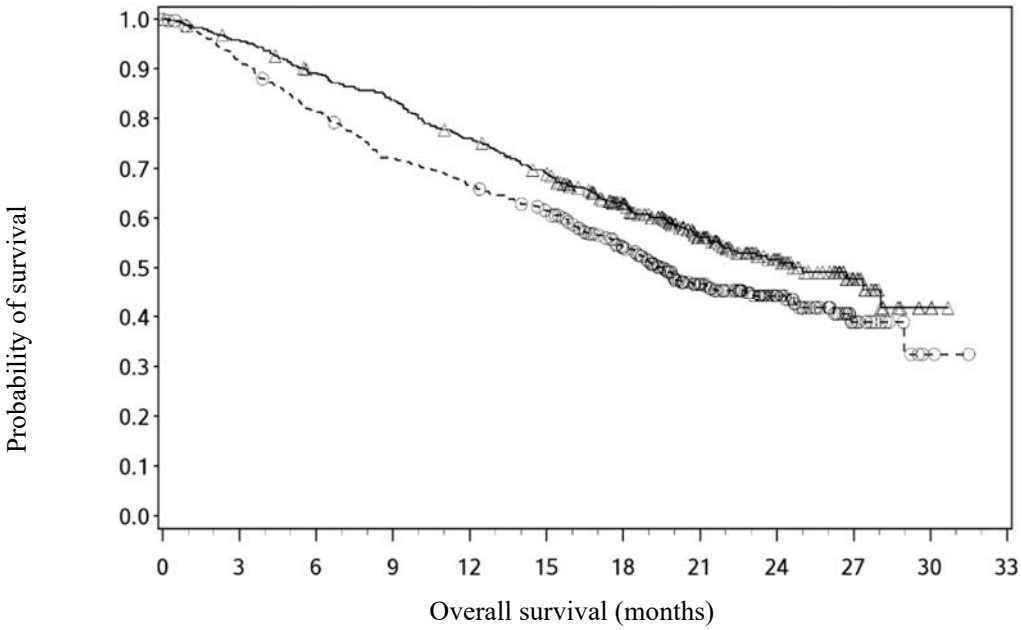
Randomised phase 3 study of nivolumab as monotherapy vs. everolimus (CA209025)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced RCC with a clear cell component was evaluated in a Phase 3, randomised, open-label study (CA209025). The study included patients (18 years or older) who have experienced disease progression during or after 1 or 2 prior anti-angiogenic therapy regimens and no more than 3 total prior systemic treatment regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥ 70%. This study included patients regardless of their tumour PD-L1 status. Patients with any history of or concurrent brain metastases, prior treatment with an mammalian target of rapamycin (mTOR) inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

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

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40% ≥ 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 randomisation was 2.6 years in both the nivolumab and everolimus groups. The median duration of treatment was 5.5 months (range: 0-29.6+ months) in nivolumab-treated patients and was 3.7 months (range: 6 days-25.7+ months) in everolimus-treated patients.
Nivolumab was continued beyond progression in 44% of patients.

The Kaplan-Meier curves for OS are shown in Figure 12.

Figure 12: Kaplan-Meier curves of OS (CA209025)



Number of subjects at risk

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

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

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

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 20 and Figure 12). OS benefit was observed regardless of tumour PD-L1 expression level.
Efficacy results are shown in Table 20.

Table 20: **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. Fourty-nine (47.6%) responders had ongoing responses with a duration ranging from 0.0-27.6^{+} months.

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

Phase 3b/4 safety study (CA209374)
Additional safety and descriptive efficacy data are available from study CA209374, an open-label Phase 3b/4 safety study of nivolumab monotherapy (treated with 240 mg every 2 weeks) for the treatment of patients with advanced or metastatic RCC (n = 142), including 44 patients with non-clear cell histology.

In subjects with non-clear cell histology, at a minimum follow-up of approximately 16.7 months ORR and median duration of response were 13.6% and 10.2 months, respectively. Clinical activity was observed regardless of tumour PD-L1 expression status.

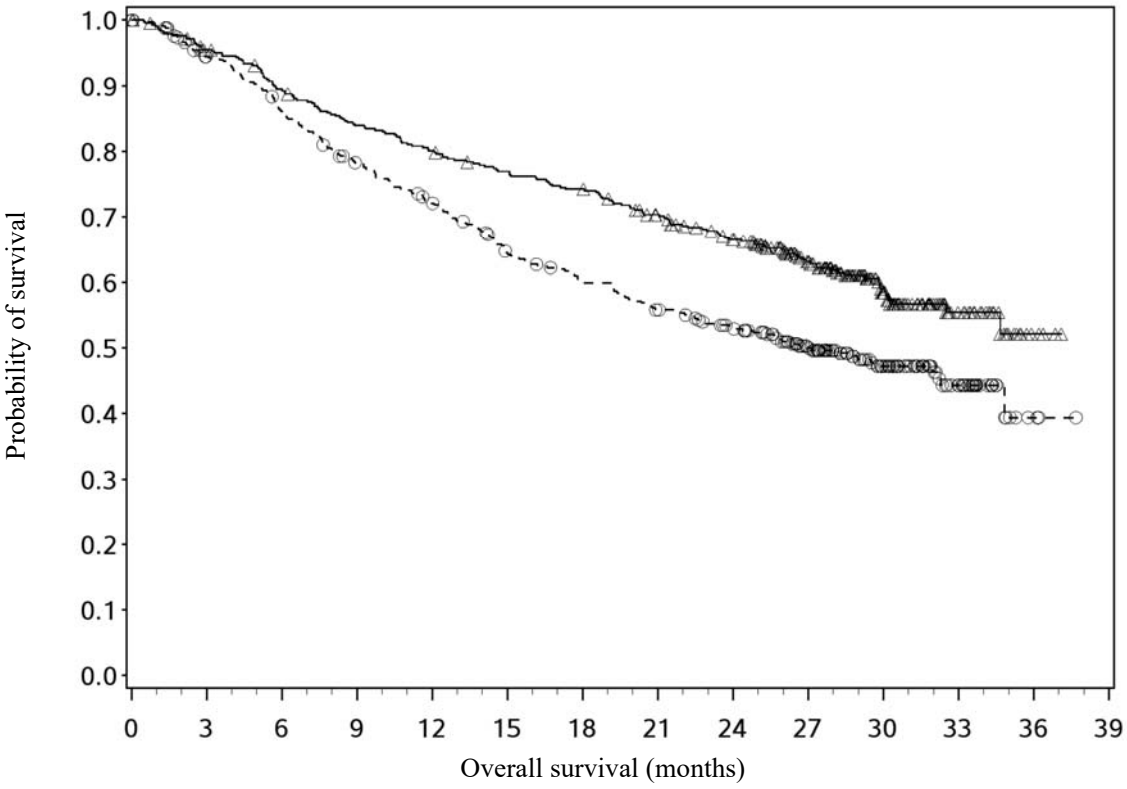
Randomised phase 3 study of nivolumab in combination with ipilimumab vs. sunitinib (CA209214)
The safety and efficacy of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA209214). The study included patients (18 years or older) with previously untreated, advanced or metastatic renal cell carcinoma with a clear-cell component. The primary efficacy population included those intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the International Metastatic RCC Database Consortium (IMDC) criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomisation, Karnofsky performance status <80%, haemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal). This study included patients regardless of their tumour PD-L1 status. Patients with Karnofsky performance status < 70% and patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were stratified by IMDC prognostic score and region.

A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either nivolumab 3 mg/kg (n = 425) administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks or sunitinib (n = 422) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off, every cycle. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 12 weeks after randomisation and continued every 6 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measures were OS, ORR and PFS as determined by a Blinded Independent Central Review (BICR) in intermediate/poor risk patients.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 21-85) with 38% ≥ 65 years of age and 8% ≥ 75 years of age. The majority of patients were male (73%) and white (87%), and 31% and 69% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The median duration of time from initial diagnosis to randomisation was 0.4 years in both the nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg and sunitinib groups. The median duration of treatment was 7.9 months (range: 1 day-21.4^{+} months) in nivolumab with ipilimumab-treated patients and was 7.8 months (range: 1 days-20.2^{+} months) in sunitinib-treated patients. Nivolumab with ipilimumab was continued beyond progression in 29% of patients.

The Kaplan-Meier curves for OS (with a minimum follow-up of 24 months) in intermediate/poor risk patients are shown in Figure 13.

Figure 13: Kaplan-Meier curves of OS in intermediate/poor risk patients (CA209214)



Number of subjects at risk

Nivolumab + ipilimumab													
425	399	372	348	332	317	306	282	257	201	102	33	4	0
Sunitinib													
422	387	352	316	288	253	233	216	196	147	87	36	3	0

Nivolumab + ipilimumab (events: 166/425), median and 95.0% CI: NA (32.49, NA)

Sunitinib (events: 209/422), median and 95.0% CI: 26.97 (22.08, 34.83)

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

CA209214 also randomised 249 favourable risk patients as per IMDC criteria to nivolumab plus ipilimumab (n = 125) or to sunitinib (n = 124). These patients were not evaluated as part of the primary efficacy population. OS in favourable risk patients receiving nivolumab plus ipilimumab compared to sunitinib had a hazard ratio of 1.13 (95% CI: 0.64, 1.99; p = 0.6710).

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

Efficacy results for the intermediate/poor risk patients from the primary analysis (minimum follow-up 17.5 months) are shown in Table 21.

Table 21: **Efficacy results in intermediate/poor risk patients (CA209214)**

	nivolumab + ipilimumab (n = 425)		sunitinib (n = 422)
Overall survival			
Events	140 (33%)		188 (45%)
Hazard ratio[a]		0.63	
99.8% CI		(0.44, 0.89)	
p-value[b, c]		< 0.0001	
Median (95% CI)	NE (28.2, NE)		25.9 (22.1, NE)
Rate (95% CI)			
At 6 months	89.5 (86.1, 92.1)		86.2 (82.4, 89.1)
At 12 months	80.1 (75.9, 83.6)		72.1 (67.4, 76.2)
Progression-free survival			
Events	228 (53.6%)		228 (54.0%)
Hazard ratio[a]		0.82	
99.1% CI		(0.64, 1.05)	
p-value[b,h]		0.0331	
Median (95% CI)	11.6 (8.71, 15.51)		8.4 (7.03, 10.81)
Confirmed objective response (BICR)	177 (41.6%)		112 (26.5%)
(95% CI)	(36.9, 46.5)		(22.4, 31.0)
Difference in ORR (95% CI)[d]		16.0 (9.8, 22.2)	
p-value[e,f]		< 0.0001	
Complete response (CR)	40 (9.4%)		5 (1.2%)
Partial response (PR)	137 (32.2%)		107 (25.4%)
Stable disease (SD)	133 (31.3%)		188 (44.5%)
Median duration of response[g]			
Months (range)	NE (1.4^{+}-25.5^{+})		18.17 (1.3^{+}-23.6^{+})
Median time to response			
Months (range)	2.8 (0.9-11.3)		3.0 (0.6-15.0)

[a] Based on a stratified proportional hazards model.
[b] Based on a stratified log-rank test.
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[d] Strata adjusted difference.
[e] Based on the stratified DerSimonian-Laird test.
[f] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[g] Computed using Kaplan-Meier method.
[h] p-value is compared to alpha 0.009 in order to achieve statistical significance.
"$^{+}$" denotes a censored observation.
NE = non-estimable

An updated OS analysis was performed when all patients had a minimum follow-up of 24 months (see figure 13). At the time of this analysis, the hazard ratio was 0.66; (99.8% CI 0.48-0.91) with 166/425 events in the combination arm and 209/422 events in the sunitinib arm. At 18 months, the OS rate was 74.3 (95% CI 69.8-78.2) for nivolumab in combination with ipilimumab and 59.9 (95% CI 54.9-64.5) for sunitinib. At 24 months, the OS rate was 66.5 (95% CI 61.8-70.9) for nivolumab in combination with ipilimumab and 52.9 (95% CI 47.9-57.7) for sunitinib.

Patients ≥ 75 years of age represented 8% of all intermediate/poor risk patients in CA209214, and the combination of nivolumab and ipilimumab showed numerically less effect on OS (HR 0.97, 95% CI: 0.48, 1.95) in this subgroup versus the overall population. Because of the small size of this subgroup, no definitive conclusions can be drawn from these data.

Classical Hodgkin lymphoma

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of relapsed or refractory cHL following ASCT was evaluated in two multi-centre, open-label, single-arm studies (CA209205 and CA209039).

CA209205 is an ongoing Phase 2, open-label, multi-cohort, single-arm study of nivolumab in cHL. It includes 243 patients who had ASCT; Cohort A included 63 (26%) patients who were brentuximab vedotin naïve; Cohort B included 80 (33%) patients who had received brentuximab vedotin after ASCT failure; and Cohort C included 100 (41%) patients who had received brentuximab vedotin before and/or after ASCT out of which 33 (14%) patients received brentuximab vedotin only prior to ASCT. All patients received nivolumab 3 mg/kg monotherapy intravenously over 60 minutes every 2 weeks. The first tumour assessments were conducted 9 weeks after the start of treatment and continued thereafter until disease progression or treatment discontinuation. The primary efficacy outcome measure was ORR as determined by an IRRC. Additional efficacy measures included duration of response, PFS and OS.

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

Data from the 80 patients from CA209205 Cohort B and from the 15 patients from CA209039 who received prior brentuximab vedotin treatment following ASCT were integrated. Additional data from 100 patients from CA209205 Cohort C who received brentuximab before and/or after ASCT are also presented. Baseline characteristics were similar across the two studies and cohorts (see Table 22 below).

Table 22: **Baseline patient characteristics in CA209205 Cohort B, Cohort C and CA209039**

	CA209205 Cohort B and CA209039 (n = 95)	**CA209205 Cohort B[a] (n = 80)**	**CA209039 (n = 15)**	**CA209205 Cohort C[b] (n = 100)**
Median age, years (range)	37.0 (18–72)	37.0 (18–72)	40.0 (24–54)	32.0 (19-69)
Gender	61 (64%) M 34 (36%) F	51 (64%) M 29 (36%) F	10 (67%) M 5 (33%) F	56 (56%) M 44 (44%) F
ECOG status				
0	49 (52%)	42 (52.5%)	7 (47%)	50 (50%)
1	46 (48%)	38 (47.5%)	8 (53%)	50 (50%)
≥ 5 prior lines of systemic therapy	49 (52%)	39 (49%)	10 (67%)	30 (30%)
Prior radiation therapy	72 (76%)	59 (74%)	13 (87%)	69 (69%)
Prior ASCT				
1	87 (92%)	74 (92.5%)	13 (87%)	100 (100%)
≥ 2	8 (8%)	6 (7.5%)	2 (13%)	0 (0%)
Years from most recent transplant to first dose of study therapy, median (min-max)	3.5 (0.2–19.0)	3.4 (0.2–19.0)	5.6 (0.5–15.0)	1.7 (0.2-17.0)

[a] 18/80 (22.5%) of the patients in CA209205 Cohort B presented B-Symptoms at baseline.
[b] 25/100 (25%) of the patients in CA209205 Cohort C presented B-Symptoms at baseline.

Efficacy from both studies was evaluated by the same IRRC. Results are shown in Table 23.

Table 23: Efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma

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

"+" denotes a censored observation.

[a] Follow-up was ongoing at the time of data submission.

[b] Data unstable due to the limited duration of response for Cohort B resulting from censoring.

NE = non-estimable

Longer follow-up data from Cohort B (minimum 20.5 months) and efficacy of Cohort C from CA209205 are presented below in Table 24.

Table 24: Updated efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma from longer follow up of study CA209205

Number (n)/ minimum follow-up (months)	CA209205 Cohort B[a] (n = 80/20.5)	CA209205 Cohort C[a] (n = 100/13.7)[b]
Objective response, n (%); (95% CI)	54 (68%); (56, 78)	73 (73%); (63, 81)
Complete remission (CR), n (%); (95% CI)	10 (13%); (6, 22)	12 (12%); (6, 20)
Partial remission (PR), n (%); (95% CI)	44 (55%); (44, 66)	61 (61%); (51, 71)
Stable disease, n (%)	17 (21)	15 (15%)
Duration of response in all responders (months)[c]		
Median (95% CI)	15.9 (7.8, 20.3)	14.5 (9.5, 16.6)
Range	0.0+-21.0+	(0.0+, 16.8+)
Duration of response in CR (months)		
Median (95% CI)	20.3 (3.8, NE)	14.5 (8.2, NE)
Range	1.6+-21.0+	(0.0+, 16.5+)
Duration of response in PR (months)		
Median (95% CI)	10.6 (6.8, 18.0)	13.2 (9.4, 16.6)
Range	0.0+-20.7+	(0.0+, 16.8+)
Median time to response		
Months (range)	2.2 (1.6-9.1)	2.1 (0.8, 8.6)
Median duration of follow-up		
Months (range)	22.7 (1.9-27.2)	16.2 (1.4, 20.4)
Progression-free survival		
Rate (95% CI) at 12 months	51 (38, 62)	49 (37, 60)
Rate (95% CI) at 18 months	47 (35, 59)	–
Overall survival		
Median	Not reached	Not reached
Rate (95% CI) at 12 months	95 (87, 98)	90 (82, 94)
Rate (95% CI) at 18 months	91 (82, 96)	–

"+" denotes a censored observation.

[a] Follow-up was ongoing at the time of data submission.

[b] Patients in Cohort C (n = 33) who have received brentuximab vedotin only prior to ASCT had ORR of 70% (95% CI: 51, 84), CR of 15% (95% CI: 5, 32), PR of 55% (95% CI: 36, 72). Median duration of response was 13.2 months (95% CI: 8.2, NE)

[c] Determined for subjects with CR or PR

NE = non-estimable

B-symptoms were present in 22% (53/243) of the patients in CA209205 at baseline. Nivolumab treatment resulted in rapid resolution of B-symptoms in 88.7% (47/53) of the patients, with a median time to resolution of 1.9 months.

In a post-hoc analysis of the 80 patients in CA209205 Cohort B, 37 had no response to prior brentuximab vedotin treatment. Among these 37 patients, treatment with nivolumab resulted in an ORR of 59.5% (22/37). The median duration of response is 18.0 months (6.6, NE) for the 22 responders to nivolumab who had failed to achieve response with prior brentuximab vedotin treatment.

Squamous cell cancer of the head and neck

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of metastatic or recurrent SCCHN were evaluated in a phase 3, randomised, open-label study (CA209141). The study included patients (18 years or older), with histologically confirmed recurrent or metastatic SCCHN

(oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) and who have experienced disease progression during or within 6 months of receiving platinum-based therapy regimen and had an ECOG performance status score of 0 or 1. Prior platinum-based therapy was administered in either the adjuvant, neo-adjuvant, primary, recurrent, or metastatic setting. Patients were enrolled regardless of their tumour PD-L1 or human papilloma virus (HPV) status. Patients with active autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or active brain or leptomeningeal metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

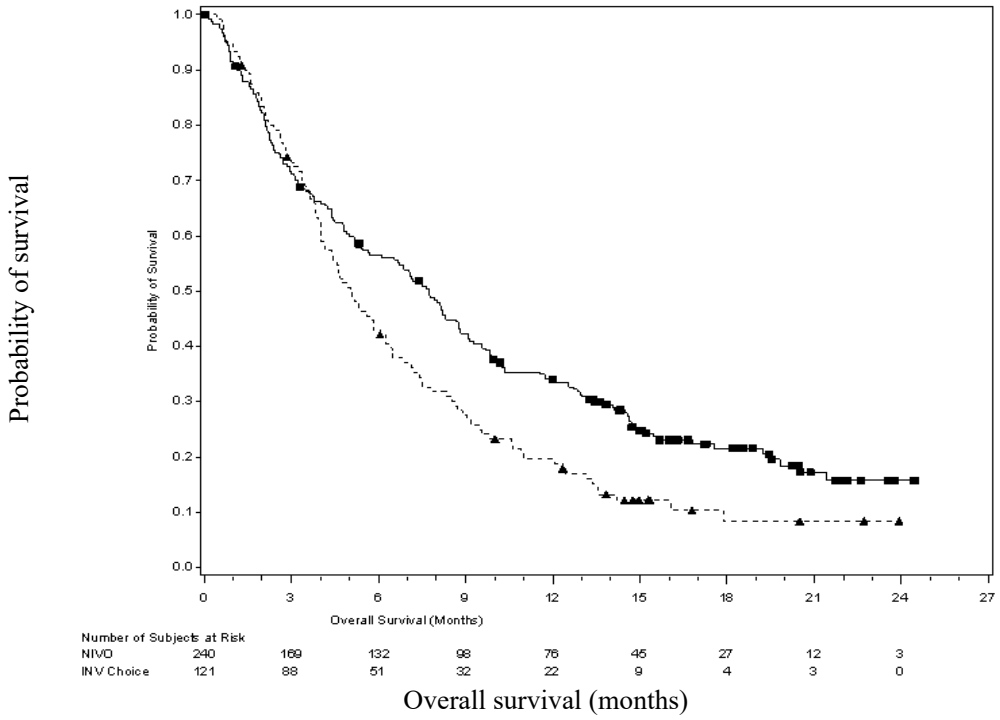
A total of 361 patients were randomised to receive either nivolumab 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n = 15), 400 mg/m^2 loading dose followed by 250 mg/m2 weekly or methotrexate (n = 52) 40 to 60 mg/m^2 weekly, or docetaxel (n = 54) 30 to 40 mg/m^2 weekly. Randomisation was stratified by prior cetuximab treatment. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to RECIST version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. Treatment beyond initial investigator-assessed RECIST version 1.1-defined progression was permitted in patients receiving nivolumab, if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and ORR. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at predefined levels of 1%, 5%, and 10%.

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

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

With a minimum follow-up of 11.4 months, the trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice. The Kaplan-Meier curves for OS are shown in Figure 14. Efficacy results are shown in Table 25.

Figure 14: Kaplan-Meier curves of OS (CA209141)



Overall survival (months)

Number of subjects at risk

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

Nivolumab 3 mg/kg (events: 184/240), median and 95% CI: 7.72 (5.68, 8.77)

Investigator's choice (events: 105/121), median and 95% CI: 5.06 (4.04, 6.24)

Table 25: **Efficacy results (CA209141)**

	nivolumab (n = 240)	investigator's choice (n = 121)
Overall survival		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio[a]	0.71	
(95% CI)	(0.55, 0.90)	
p-value[b]	0.0048	
Median (95% CI) (months)	7.72 (5.68, 8.77)	5.06 (4.04, 6.24)
Rate (95% CI) at 6 months	56.5 (49.9, 62.5)	43.0 (34.0, 51.7)
Rate (95% CI) at 12 months	34.0 (28.0, 40.1)	19.7 (13.0, 27.3)
Rate (95% CI) at 18 months	21.5 (16.2, 27.4)	8.3 (3.6, 15.7)
Progression-free survival		
Events	204 (85.0%)	104 (86.0%)
Hazard ratio	0.87	
95% CI	(0.69, 1.11)	
p-value	0.2597	
Median (95% CI) (months)	2.04 (1.91, 2.14)	2.33 (1.97, 3.12)
Rate (95% CI) at 6 months	21.0 (15.9, 26.6)	11.1 (5.9, 18.3)
Rate (95% CI) at 12 months	9.5 (6.0, 13.9)	2.5 (0.5, 7.8)
Confirmed objective response[c]	32 (13.3%)	7 (5.8%)
(95% CI)	(9.3, 18.3)	(2.4, 11.6)
Odds ratio (95% CI)	2.49 (1.07, 5.82)	
Complete response (CR)	6 (2.5%)	1 (0.8%)
Partial response (PR)	26 (10.8%)	6 (5.0%)
Stable disease (SD)	55 (22.9%)	43 (35.5%)
Median time to response		
Months (range)	2.1 (1.8-7.4)	2.0 (1.9-4.6)
Median duration of response		
Months (range)	9.7 (2.8-20.3+)	4.0 (1.5+-8.5+)

[a] Derived from a stratified proportional hazards model.

[b] P-value is derived from a log-rank test stratified by prior cetuximab; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0227.

[c] In the nivolumab group there were two patients with CRs and seven patients with PRs who had tumour PD-L1 expression < 1%.

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

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to investigator's choice. The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumour PD-L1 expression levels (see Table 26).

Table 26: OS by tumour PD-L1 expression (CA209141)

PD-L1 Expression	nivolumab	investigator's choice	
	OS by tumour PD-L1 expression		
	Number of events (number of patients)		Unstratified hazard ratio (95% CI)
< 1%	56 (73)	32 (38)	0.83 (0.54, 1.29)
≥ 1%	66 (88)	55 (61)	0.53 (0.37, 0.77)
≥ 5%	39 (54)	40 (43)	0.51 (0.32, 0.80)
≥ 10%	30 (43)	31 (34)	0.57 (0.34, 0.95)

In an exploratory post-hoc analysis using a non-validated assay, both tumour cell PD-L1 expression and tumour-associated immune cell (TAIC) PD-L1 expression were analysed in relation to the magnitude of treatment effect of nivolumab compared to investigator's choice. This analysis showed that not only tumour cell PD-L1 expression but also TAIC PD-L1 expression appeared to be associated with benefit from nivolumab relative to investigator's choice (see Table 27). Due to the small numbers of patients in the subgroups, and exploratory nature of the analysis, no definitive conclusions can be drawn from these data.

Table 27: Efficacy by tumour cell and TAIC PD-L1 expression (CA209141)

	Median OS[a] (months)		Median PFS[a] (months)		ORR (%)	
	HR[b] (95% CI)		HR[b] (95% CI)		(95% CI)[c]	
	nivolumab	investigator's choice	nivolumab	investigator's choice	nivolumab	investigator's choice
PD-L1 ≥ 1%, PD-L1+ TAIC abundant[d] (61 nivolumab, 47 investigator's choice)	9.10	4.60	3.19	1.97	19.7	0
	0.43 (0.28, 0.67)		0.48 (0.31, 0.75)		(10.6, 31.8)	(0, 7.5)
PD-L1 ≥ 1%, PD-L1+ TAIC rare[d] (27 nivolumab, 14 investigator's choice)	6.67	4.93	1.99	2.04	11.1	7.1
	0.89 (0.44, 1.80)		0.93 (0.46, 1.88)		(2.4, 29.2)	(0.2, 33.9)
PD-L1 < 1%, PD-L1+ TAIC abundant[d] (43 nivolumab, 25 investigator's choice)	11.73	6.51	2.10	2.73	18.6	12.0
	0.67 (0.38, 1.18)		0.96 (0.55, 1.67)		(8.4, 33.4)	(2.5, 31.2)
PD-L1 < 1%, PD-L1+ TAIC rare[d] (27 nivolumab, 10 investigator's choice)	3.71	4.85	1.84	2.12	3.7	10.0
	1.09 (0.50, 2.36)		1.91 (0.84, 4.36)		(< 0.1, 19.0)	(0.3, 44.5)

[a] OS and PFS were estimated using Kaplan-Meier method.

[b] Hazard ratio in each subgroup derived from a Cox proportional hazards model with treatment as the only covariate.

[c] Confidence interval for ORR calculated using the Clopper-Pearson method.

[d] PD-L1+ TAIC in the tumour microenvironment were qualitatively assessed, and characterised as "numerous", "intermediate", and "rare" based on pathologist assessments. "Numerous" and "intermediate" groups were combined to define the "abundant" group.

Patients with investigator-assessed primary site of oropharyngeal cancer were tested for HPV (determined by p16 immunohistochemistry [IHC]). OS benefit was observed regardless of HPV status (HPV-positive: HR = 0.63; 95% CI: 0.38, 1.04, HPV-negative: HR = 0.64; 95% CI: 0.40, 1.03, and HPV-unknown: HR = 0.78; 95% CI: 0.55, 1.10).

Patient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30, EORTC QLQ-H&N35, and 3-level EQ-5D. Over 15 weeks of follow-up, patients treated with nivolumab exhibited stable PROs, while those assigned to investigator's choice therapy exhibited significant declines in functioning (e.g., physical, role, social) and health status as well as increased symptomatology (e.g., fatigue, dyspnoea, appetite loss, pain, sensory problems, social contact problems). The PRO data should be interpreted in the context of the open-label study design and therefore taken cautiously.

Urothelial carcinoma

Open-label phase 2 study (CA209275)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma was evaluated in a phase 2, multicentre, open-label, single-arm study (CA209275).
The study included patients (18 years or older) who had disease progression during or following platinum-containing chemotherapy for advanced or metastatic disease or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Patients had an ECOG performance status score of 0 or 1 and were enrolled regardless of their tumour PD-L1 status. Patients with active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients that received more than 2 prior lines of chemotherapy with liver metastases were excluded.

A total of 270 patients who received nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks with a minimum follow-up of 8.3 months were evaluable for efficacy. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 8 weeks after the start of treatment and continued every 8 weeks thereafter up to 48 weeks, then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit, did not have rapid disease progression, and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was ORR as determined by BICR. Additional efficacy measures included duration of response, PFS and OS.

The median age was 66 years (range: 38 to 90) with 55% ≥65 years of age and 14% ≥75 years of age. The majority of patients were white (86%) and male (78%). Baseline ECOG performance status was 0 (54%) or 1 (46%).

Table 28: Efficacy results (CA209275)[a]

	nivolumab (n = 270)
Confirmed objective response	54 (20.0%)
(95% CI)	(15.4, 25.3)
Complete response (CR)	8 (3.0%)
Partial response (PR)	46 (17.0%)
Stable disease (SD)	60 (22.2%)
Median duration of response[b]	
Months (range)	10.4 (1.9^{+}-12.0^{+})
Median time to response	
Months (range)	1.9 (1.6, 7.2)
Progression-free survival	
Events (%)	216 (80%)
Median (95% CI) months	2.0 (1.9, 2.6)
Rate (95% CI) at 6 months	26.1 (20.9, 31.5)
Overall survival[c]	
Events (%)	154 (57%)
Median (95% CI) months	8.6 (6.05, 11.27)
Rate (95% CI) at 12 months	41.0 (34.8, 47.1)

	Tumour PD-L1 expression level	
	< 1%	**≥ 1%**
Confirmed objective response (95% CI)	16% (10.3, 22.7) n = 146	25% (17.7, 33.6) n = 124
Median duration of response Months (range)	10.4 (3.7, 12.0^{+})	Not Reached (1.9^{+}, 12.0^{+})
Progression-free survival		
Median (95% CI) months	1.9 (1.8, 2.0)	3.6 (1.9, 3.7)
Rate (95% CI) at 6 months	22.0 (15.6, 29.2)	30.8 (22.7, 39.3)
Overall survival		
Median (95% CI) months	5.9 (4.37, 8.08)	11.6 (9.10, NE)
Rate (95% CI) at 12 months	34.0 (26.1, 42.1)	49.2 (39.6, 58.1)

"+" denotes a censored observation.

[a] median follow-up 11.5 months.

[b] Data unstable due to the limited duration of response.

[c] included 4 drug-related deaths: 1 pneumonitis, 1 acute respiratory failure, 1 respiratory failure, and 1 cardiovascular failure.

NE: non-estimable

Results from post-hoc, exploratory analyses indicate that in patients with low (e.g. <1%) to no tumour PD-L1 expression, other patient characteristics (e.g. liver metastases, visceral metastases, baseline haemoglobin <10g/dL and ECOG performance status = 1) might contribute to the clinical outcome.

Open-label phase 1/2 study (CA209032)

CA209032 was a Phase 1/2 open-label multi-cohort study which included a cohort of 78 patients (including 18 subjects who received planned crossover treatment with nivolumab 3 mg/kg plus

ipilimumab 1 mg/kg combination) with similar inclusion criteria to study CA209275 treated with nivolumab monotherapy 3 mg/kg for urothelial carcinoma. At a minimum follow-up of 9 months, investigator-assessed confirmed ORR was 24.4% (95% CI: 15.3, 35.4). The median duration of response was not reached (range: 4.4-16.6^{+} months). The median OS was 9.7 months (95% CI:7.26, 16.16) and the estimated OS rates were 69.2% (CI: 57.7, 78.2) at 6 months and 45.6% (CI: 34.2, 56.3) at 12 months.

Oesophageal squamous cell carcinoma

The safety and efficacy of nivolumab 240 mg monotherapy for the treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) was evaluated in a phase 3-randomised active-controlled, open-label study (ONO-4538-24/CA209473). The study included adult patients (20 years or older) who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based combination regimen, and patients were enrolled regardless of tumour PD-L1 expression level. Patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had active autoimmune disease, medical conditions requiring systemic immunosuppression, and patients with apparent tumour invasion in organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), were excluded from the study.

A total of 419 patients were randomised 1:1 to receive either nivolumab 240 mg administered intravenously over 30 minutes every 2 weeks (n=210) or investigator's choice of taxane chemotherapy: either docetaxel (n=65) 75 mg/m^2 intravenously every 3 weeks, or paclitaxel (n=144) 100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off. Randomisation was stratified by location (Japan vs. rest of world), number of organs with metastases (≤1 vs. ≥2) and tumour PD-L1 expression (≥1% vs. <1% or indeterminate). Treatment continued until disease progression, assessed by the investigator per RECIST version 1.1, or unacceptable toxicity. Tumour assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab with no rapid progression, investigator-assessed benefit, tolerance to treatment, stable performance status, and for whom treatment beyond progression would not delay an imminent intervention to prevent serious complications associated with disease progression (e.g brain metastasis). The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at a predefined level of 1%. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

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

With a minimum follow-up of 17.6 months, the study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice taxane chemotherapy. Efficacy results are shown in Table 29 and Figure 15.

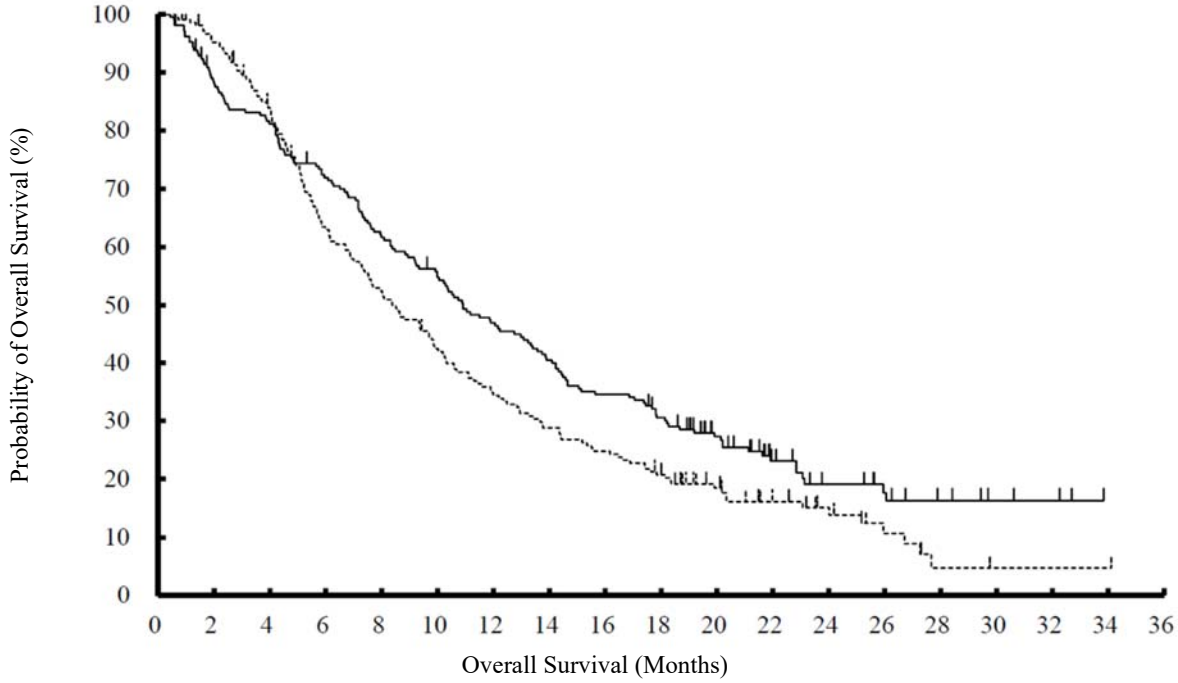
A higher proportion of patients experienced death within the first 2.5 months in the nivolumab arm (32/210, 15.2%) as compared to the chemotherapy arm (15/209, 7.2%). No specific factor(s) associated with early deaths could be identified.

Table 29: Efficacy results (ONO-4538-24/CA209473)

	nivolumab (n = 210)	investigator's choice (n = 209)
Overall Survival[a]		
Events (%)	160 (76%)	173 (83%)
Hazard ratio (95% CI)[b]	0.77 (0.62, 0.96)	
p-value[c]	0.0189	
Median (95% CI) (months)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)
Objective Response Rate[d,e]	33 (19.3%)	34 (21.5%)
(95% CI)	(13.7, 26.0)	(15.4, 28.8)
Complete response	1 (0.6%)	2 (1.3%)
Partial response	32 (18.7%)	32 (20.3%)
Stable disease	31 (18.1%)	65 (41.1%)
Median duration of response (95% CI) (months)	6.9 (5.4, 11.1)	3.9 (2.8, 4.2)
Progression-Free Survival[a]		
Events (%)	187 (89%)	176 (84%)
Median (95% CI) (months)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
Hazard ratio (95% CI)[b]	1.1 (0.9, 1.3)	

[a] Based on ITT analysis.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.
[d] Based on Response Evaluable Set (RES) analysis, n=171 in nivolumab group and n=158 in investigator's choice group.
[e] Not significant, p-value 0.6323.

Figure 15: Kaplan-Meier curves of OS (ONO-4538-24/CA209473)



Number of Subjects at Risk

Nivolumab	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
Investigator's choice	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0

——— Nivolumab - - - - - - Investigator's choice

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

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 SCCHN and adjuvant melanoma patients 75 years of age or older are too limited to draw conclusions on this population. Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with nivolumab in all subsets of the paediatric population in the treatment of malignant solid tumours, malignant neoplasms of lymphoid tissue and malignant neoplasms of the central nervous system (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Nivolumab monotherapy
The pharmacokinetics (PK) of nivolumab is linear in the dose range of 0.1 to 10 mg/kg. The geometric mean clearance (CL), terminal half-life, and average exposure at steady state at 3 mg/kg every 2 weeks of nivolumab were 7.9 mL/h, 25.0 days, and 86.6 μg/mL, respectively, based on a population PK analysis.

Nivolumab CL in cHL patients was approximately 32% lower relative to NSCLC. Nivolumab baseline CL in adjuvant melanoma patients was approximately 40% lower and steady state CL approximately 20 % lower relative to advanced melanoma. With available safety data, these decreases in CL were not clinically meaningful.

The metabolic pathway of nivolumab has not been characterised. Nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Nivolumab in combination with ipilimumab
When nivolumab 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 29% and the CL of ipilimumab was increased by 9%, which was not considered clinically relevant. When nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab was increased by 1% and the CL of ipilimumab was decreased by 1.5%, which were not considered clinically relevant.

When administered in combination with ipilimumab, the CL of nivolumab increased by 20% in the presence of anti-nivolumab antibodies and the CL of ipilimumab increased by 5.7% in the presence of anti-ipilimumab antibodies. These changes were not considered clinically relevant.

Nivolumab in combination with ipilimumab and chemotherapy
When nivolumab 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and with 2 cycles of chemotherapy, the CL of nivolumab decreased approximately 10% and the CL of ipilimumab increased approximately 22%, which were not considered clinically relevant.

Special populations

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

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 (E433)
Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
3 years

After opening
From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately.

After preparation of infusion
Chemical and physical in-use stability from the time of preparation has been demonstrated as follows (times are inclusive of the administration period):

Infusion preparation	**In-use stability**	
	Storage at 2ºC to 8ºC protected from light	**Storage at room temperature (≤ 25°C) and room light**
Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection	30 days	24 hours (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	24 hours	8 hours (of total 24 hours storage)

From a microbiological point of view the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C or 8 hours (of the total 24 hours of storage) at room temperature (≤ 25°C), unless infusion preparation has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.
The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

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

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Preparation and administration

Calculating the dose

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

Nivolumab monotherapy
The prescribed dose for the patient is 240 mg or 480 mg given regardless of body weight depending on indication (see section 4.2).

Nivolumab in combination with ipilimumab
The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given.

- 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 ipilimumab and chemotherapy
The prescribed dose for the patient is 360 mg given regardless of body weight.

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

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

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

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

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

Administration
OPDIVO infusion must not be administered as an intravenous push or bolus injection.
Administer the OPDIVO infusion intravenously over a period of 30 or 60 minutes depending on the dose.
OPDIVO infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

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

OPDIVO infusion is compatible with PVC and polyolefin containers, glass bottles, PVC infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

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

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

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/001
EU/1/15/1014/002
EU/1/15/1014/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June 2015
Date of latest renewal: 23 April 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Bristol-Myers Squibb Company
6000 Thompson Road
East Syracuse, New York 13057
USA

Lonza Biologics, Inc.
101 International Drive
Portsmouth, New Hampshire 03801
USA

Samsung Biologics Co. Ltd.
300, Songdo Bio Way (Daero)
Yeonsu-gu, Incheon, 21987
Korea

Swords Laboratories t/a Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

Name and address of the manufacturers responsible for batch release

CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale 12 Casilina, 41
03012 ANAGNI (FR)
Italy

Swords Laboratories t/a Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where OPDIVO is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use OPDIVO have access to/are provided with the patient alert card.

- **The patient alert card** shall contain the following key messages:

- That OPDIVO treatment may increase the risk of:
  - Immune-related pneumonitis
  - Immune-related colitis
  - Immune-related hepatitis
  - Immune-related nephritis and renal dysfunction
  - Immune-related endocrinopathies
  - Immune-related skin adverse reactions
  - Other immune-related ARs

- Signs or symptoms of the safety concern and when to seek attention from a HCP

- Contact details of the OPDIVO prescriber

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
1. Post authorisation efficacy study (PAES): The MAH should submit the addendum to the CA209205 Final CSR reporting the OS data and data from the discontinuation schedule in Cohort C.	30th June 2021
2. The MAH should submit the final OS data for study CA209238: A Phase 3, randomised double-blind study of OPDIVO versus Yervoy in patients who have undergone complete resection of Stage IIIb/c or Stage IV melanoma.	4Q2020

3. Post authorisation efficacy study (PAES): In order to further elucidate the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab and ipilimumab, the MAH should conduct and submit the results of a randomised, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels. This study should be conducted according to an agreed protocol.	30th September 2021

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL concentrate for solution for infusion
nivolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: sodium citrate dihydrate, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80 (E433), sodium hydroxide, hydrochloric acid, water for injections.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

40 mg/4 mL
100 mg/10 mL
240 mg/24 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/001 40 mg vial
EU/1/15/1014/002 100 mg vial
EU/1/15/1014/003 240 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL sterile concentrate
nivolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of concentrate contains 10 mg of nivolumab.
Each vial of 24 mL contains 240 mg of nivolumab.

3. LIST OF EXCIPIENTS

Excipients: sodium citrate dihydrate, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80 (E433), sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Sterile concentrate

240 mg/24 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
IV use
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

OPDIVO 10 mg/mL sterile concentrate
nivolumab
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
For single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/4 mL
100 mg/10 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

OPDIVO 10 mg/mL concentrate for solution for infusion
nivolumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the alert card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What OPDIVO is and what it is used for

OPDIVO is a medicine used to treat:
- advanced melanoma (a type of skin cancer) in adults
- melanoma after complete resection in adults (treatment after surgery is called adjuvant therapy)
- advanced non-small cell lung cancer (a type of lung cancer) in adults
- advanced renal cell carcinoma (advanced kidney cancer) in adults
- classical Hodgkin lymphoma that has come back after or has not responded to previous therapies, including an autologous stem-cell transplant (a transplant of your own blood-producing cells) in adults
- advanced cancer of the head and neck in adults
- advanced urothelial carcinoma (bladder and urinary tract cancer) in adults
- advanced oesophageal cancer (gullet cancer) in adults.

It contains the active substance nivolumab, which is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body.

Nivolumab attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the melanoma, lung, kidney, lymphoid, head and neck, bladder or oesophageal cancer cells.

OPDIVO may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflet for these other medicines. If you have any questions about these medicines, please ask your doctor.

2. What you need to know before you use OPDIVO

You should not be given OPDIVO
- if you are **allergic** to nivolumab or any of the other ingredients of this medicine (listed in section 6 "Contents of the pack and other information"). **Talk to your doctor** if you are not sure.

Warnings and precautions
Talk to your doctor before using OPDIVO as it may cause:
- **Problems with your heart** such as a change in the rhythm or rate of the heartbeat or an abnormal heart rhythm.
- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Diarrhoea** (watery, loose or soft stools) or any symptoms of **inflammation of the intestines** (colitis), such as stomach pain and mucus or blood in stool.
- **Inflammation of the liver (hepatitis).** Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, or tiredness.
- **Inflammation or problems with your kidneys.** Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.
- **Problems with your hormone producing glands** (including the pituitary, the thyroid, the parathyroid and adrenal glands) that may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache, decreased blood levels of calcium and visual disturbances.
- **Diabetes** (symptoms include excessive thirst, the passing of a greatly increased amount of urine, increase in appetite with a loss of weight, feeling tired, drowsy, weak, depressed, irritable and generally unwell) or **diabetic ketoacidosis** (acid in the blood produced from diabetes).
- **Inflammation of the skin** that can lead to severe skin reaction (known as toxic epidermal necrolysis and Stevens-Johnson syndrome). Signs and symptoms of severe skin reaction may include rash, itching, and peeling of the skin (possibly fatal).
- **Inflammation of the muscles** such as myocarditis (inflammation of the heart muscle), myositis (inflammation of the muscles) and rhabdomyolysis (stiffness in muscles and joints, muscle spasm). Signs and symptoms may include muscle pain, stiffness, weakness, chest pain, or severe fatigue.
- **Solid organ transplant rejection.**
- **Graft-versus-host disease.**
- **Haemophagocytic lymphohistiocytosis**. A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

Tell your doctor immediately if you have any of these signs or symptoms or if they get worse. **Do not try to treat your symptoms with other medicines on your own.** Your doctor may
- give you other medicines in order to prevent complications and reduce your symptoms,
- withhold the next dose of OPDIVO,
- or stop your treatment with OPDIVO altogether.

Please note that these signs and symptoms are **sometimes delayed**, and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have **blood tests** during your treatment.

Check with your doctor or nurse before you are given OPDIVO if:
- you have an **autoimmune disease** (a condition where the body attacks its own cells);
- you have **melanoma of the eye**;
- you were previously given ipilimumab, another medicine for treating melanoma, and experienced **serious side effects** because of that medicine;
- you have been told that your **cancer has spread to your brain;**
- you have any history of **inflammation of the lungs**;
- you have been taken **medicines to suppress your immune system.**

Complications of stem cell transplant that uses donor stem cells (allogeneic) after treatment with OPDIVO. These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

Children and adolescents
OPDIVO should not be used in children and adolescents below 18 years of age.

Other medicines and OPDIVO
Before you are given OPDIVO, tell your doctor if you are taking any medicines that suppress your immune system, such as corticosteroids, since these medicines may interfere with the effect of OPDIVO. However, once you are treated with OPDIVO, your doctor may give you corticosteroids to reduce any possible side effects that you may have during your treatment and this will not impact the effect of the medicine.
Tell your doctor if you are taking or have recently taken any other medicines. **Do not take any other medicines** during your treatment without talking to your doctor first.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or think you might be, if you are planning to become pregnant, or if you are breast-feeding.

Do not use OPDIVO if you are pregnant unless your doctor specifically tells you to. The effects of OPDIVO in pregnant women are not known, but it is possible that the active substance, nivolumab, could harm an unborn baby.
- You must use **effective contraception** while you are being treated with OPDIVO and for at least 5 months following the last dose of OPDIVO, if you are a woman who could become pregnant.
- If you become pregnant while using OPDIVO **tell your doctor**.

It is not known whether OPDIVO gets into breast milk. A risk to the breast-fed infant cannot be excluded. **Ask your doctor** if you can breast-feed during or after treatment with OPDIVO.

Driving and using machines
OPDIVO or OPDIVO in combination with ipilimumab may have a minor influence on the ability to drive and use machines; however, use caution when performing these activities until you are sure that OPDIVO does not adversely affect you.

OPDIVO contains sodium
Tell your doctor if you are on a low-sodium (low-salt) diet before you are given OPDIVO. This medicine contains 2.5 mg sodium (main component of cooking/table salt) in each mL of concentrate. OPDIVO contains 10 mg sodium per 4 ml vial, 25 mg sodium per 10 ml vial or 60 mg sodium per 24 ml vial, which is equivalent to 0.5%, 1.25% or 3% respectively, of the recommended maximum daily dietary intake of sodium for an adult.

You will also find key messages from this package leaflet in the patient alert card you have been given by your doctor. It is important that you keep this patient alert card and show it to your partner or caregivers.

3. How to use OPDIVO

How much OPDIVO is given
When OPDIVO is given on its own, the recommended dose is either 240 mg given every 2 weeks or 480 mg given every 4 weeks depending on indication.

When OPDIVO is given in combination with ipilimumab for the treatment of skin cancer, the recommended dose of OPDIVO is 1 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight for the

first 4 doses (combination phase). Thereafter, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab and chemotherapy for the treatment of advanced non-small cell lung cancer, the recommended dose of OPDIVO is 360 mg every 3 weeks. After completion of 2 cycles of chemotherapy, OPDIVO is given in combination with ipilimumab, the recommended dose of OPDIVO is 360 mg every 3 weeks.

Depending on your dose, the appropriate amount of OPDIVO will be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection before use. More than one vial of OPDIVO may be necessary to obtain the required dose.

How OPDIVO is given
You will receive treatment with OPDIVO in a hospital or clinic, under the supervision of an experienced doctor.

OPDIVO will be given to you as an infusion (a drip) into a vein (intravenously) over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving. Your doctor will continue giving you OPDIVO for as long as you keep benefitting from it or until you no longer tolerate the treatment.

When OPDIVO is given in combination with ipilimumab, you will be given an infusion over a period of 30 minutes, every 3 weeks for the first 4 doses (combination phase). Thereafter it will be given as an infusion over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When OPDIVO is given in combination with ipilimumab and chemotherapy for the treatment of advanced non-small cell lung cancer, you will be given an infusion over a period of 30 minutes, every 3 weeks.

If you miss a dose of OPDIVO
It is very important for you to keep all your appointments to receive OPDIVO. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop using OPDIVO
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with OPDIVO unless you have discussed this with your doctor.

If you have any further questions about your treatment or on the use of this medicine, ask your doctor.

When OPDIVO is given in combination with ipilimumab or in combination with ipilimumab and chemotherapy, you will first be given OPDIVO followed by ipilimumab and then by chemotherapy. Please refer to the package leaflet of the other anti-cancer medicines in order to understand the use of these medicines. If you have questions about these medicines, please ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

Be aware of important symptoms of inflammation. OPDIVO acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening and need treatment or withdrawal of OPDIVO.

The following side effects have been reported **with OPDIVO alone:**

Very common (may affect more than 1 in 10 people)
- Decrease in some white blood cells
- Diarrhoea (watery, loose or soft stools), nausea
- Skin rash sometimes with blisters, itching
- Feeling tired or weak

Common (may affect up to 1 in 10 people)
- Infections of the upper respiratory tract
- Allergic reaction, reactions related to the infusion of the medicine
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), headache, dizziness
- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), shortness of breath (dyspnoea), cough
- Inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), vomiting, stomach pain, constipation, dry mouth
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning
- Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)
- Fever, oedema (swelling)

Uncommon (may affect up to 1 in 100 people)
- Serious lung infection (pneumonia), bronchitis
- Increase in some white blood cells
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- Dehydration, increased acid levels in the blood
- Damage to nerves causing numbness and weakness (polyneuropathy), inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy)
- Inflammation of the eye (which causes pain and redness), blurred vision, dry eyes
- Fast heart rate, inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)
- Fluid around the lungs
- Inflammation of the pancreas (pancreatitis), inflammation of the stomach (gastritis)
- Inflammation of the liver (hepatitis)
- Severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), skin disease with thickened patches of red skin, often with silvery scales (psoriasis), skin condition of the face where the nose and cheeks are unusually red (rosacea), hives (itchy, bumpy rash)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica), inflammation of the joints (arthritis)
- Inflammation of the kidney, kidney failure (including abrupt loss of kidney function)
- Pain, chest pain

Rare (may affect up to 1 in 1000 people)
- A disease causing the inflammation or enlargement of a lymph node (Kikuchi lymphadenitis)
- Life-threatening allergic reaction
- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- A temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome), loss of the protective sheath around nerves (demyelination), a condition in which the muscles become weak and tire easily (myasthenic syndrome)

- Inflammation of the brain
- Changes in the rhythm or rate of the heartbeat, abnormal heart rhythm, inflammation of the heart muscle
- Inflammatory disease of blood vessels
- Fluid in the lungs
- Ulcer of the small intestines
- Blockage of bile ducts
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis or Stevens-Johnson syndrome)
- Disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), aching muscles, muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- Solid organ transplant rejection
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased function of the parathyroid gland
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)

The following side effects have been reported **with OPDIVO in combination** (the frequency and severity of side effects may vary with the combination of anti-cancer medicines received)**:**

Very common (may affect more than 1 in 10 people)
- Underactive thyroid gland (which can cause tiredness or weight gain),overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite
- Headache
- Shortness of breath (dyspnoea)
- Inflammation of the intestines (colitis), diarrhoea (watery, loose or soft stools), vomiting, nausea, stomach pain
- Skin rash sometimes with blisters, itching
- Pain in the joints (arthralgia), pain in the muscles and bones (musculoskeletal pain)
- Feeling tired or weak, fever

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), infections of the upper respiratory tract, inflammation of the eye (conjunctivitis)
- Increase in some white blood cells, decrease in neutrophils with fever
- Allergic reaction, reactions related to the infusion of the medicine
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- Dehydration, decreased levels of albumin and phosphate in the blood
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness
- Inflammation of the eye (which causes pain and redness), blurred vision, dry eye
- Fast heart rate

- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs, blood clots, cough
- Mouth ulcers and cold sores (stomatitis), inflammation of the pancreas (pancreatitis), constipation, dry mouth
- Inflammation of the liver
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning, hives (itchy rash)
- Inflammation of the joints (arthritis), muscle spasm, muscle weakness
- Kidney failure (including abrupt loss of kidney function)
- Oedema (swelling), pain, chest pain, chills

Uncommon (may affect up to 1 in 100 people)
- Bronchitis
- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Increased acid levels in the blood
- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- Decreased function of the parathyroid gland
- A temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome); damage to nerves causing numbness and weakness (polyneuropathy); inflammation of the nerves; foot drop (peroneal nerve palsy); inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy); muscle weakness and tiredness without atrophy (myasthenia gravis)
- Inflammation of the brain
- Changes in the rhythm or rate of the heartbeat, abnormal heart rhythm, inflammation of the heart muscle, slow heart rate
- Intestinal perforation, inflammation of the stomach (gastritis), inflammation of the duodenum
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme)
- Severe and possibly fatal peeling of the skin (Stevens-Johnson syndrome)
- Chronic disease of joints (spondyloarthropathy), disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), aching muscles, muscle tenderness of weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis), inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)
- Inflammation of the kidney

Rare (may affect up to 1 in 1000 people)
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis)

Other side effects that have been reported frequency not known (cannot be estimated from the available data):
- Solid organ transplant rejection
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)

Tell your doctor immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

Changes in test results
OPDIVO alone or in combination may cause changes in the results of tests carried out by your doctor. These include:
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- High (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- Increased or decreased amount of calcium or potassium
- Increased or decreased blood levels of magnesium or sodium
- Decrease in body weight
- Increased amount of thyroid stimulating hormone

Reporting of side effects
If you get any side effects, **talk to your doctor**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store OPDIVO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.
The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

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

6. Contents of the pack and other information

What OPDIVO contains
- The active substance is nivolumab.

Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.
Each vial contains either 40 mg (in 4 mL), 100 mg (in 10 mL) or 240 mg (in 24 mL) of nivolumab.

- The other ingredients are sodium citrate dihydrate, sodium chloride (see section 2 "OPDIVO contains sodium"), mannitol (E421), pentetic acid, polysorbate 80 (E433), sodium hydroxide, hydrochloric acid and water for injections.

What OPDIVO looks like and contents of the pack
OPDIVO concentrate for solution for infusion (sterile concentrate) is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.

It is available in packs containing either 1 vial of 4 mL, 1 vial of 10 mL or 1 vial of 24 mL.

Not all pack sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Preparation and administration of OPDIVO

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

Calculating the dose

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

Nivolumab monotherapy:
The prescribed dose for the patient is 240 mg or 480 mg given regardless of body weight depending on indication.

Nivolumab in combination with ipilimumab:
The **prescribed dose** for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given.

- 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 ipilimumab and chemotherapy:
The prescribed dose for the patient is 360 mg given regardless of body weight.

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

OPDIVO can be used for intravenous administration either:
- **without dilution,** after transfer to an infusion container using an appropriate sterile syringe;

or
- **after diluting** according to the following instructions:
  - the final infusion concentration should range between 1 and 10 mg/mL.
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kilogram of patient weight.

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

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

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

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

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

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

OPDIVO infusion is compatible with:
- PVC containers
- Polyolefin containers
- Glass bottles

- PVC infusion sets
- In-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

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

Storage conditions and shelf life
Unopened vial
OPDIVO must be **stored in a refrigerator** (2°C to 8°C). The vials must be kept in the original package in order to protect from light. OPDIVO should not be frozen.
The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

Do not use OPDIVO after the expiry date which is stated on the carton and on the vial label after EXP. The expiry date refers to the last day of that month.

OPDIVO infusion
Chemical and physical in-use stability from the time of preparation has been demonstrated as follows (times are inclusive of the administration period):

Infusion preparation	**In-use stability**	
	Storage at 2ºC to 8ºC protected from light	**Storage at room temperature (≤ 25ºC) and room light**
Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection	30 days	24 hours (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	24 hours	8 hours (of total 24 hours storage)

From a microbiological point of view the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C or 8 hours (of the total 24 hours of storage) at room temperature (≤ 25°C), unless infusion preparation has taken place in controlled and validated aseptic conditions.

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