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1. Name of the Drug Product

Nivolunix 100 Injection

2. Qualitative and Quantitative Composition

Product Name: Nivolunix 100 Injection

Each 10.0 mL Contains Nivolumab INN 100 mg.

Fill Volume per Vial: 10.50 mL

Sl. No.	Name of Materials	Specification	Quantity/ 10 mL	Used as
	ACTIVE SUBSTANCE:			
1.	Formulated Bulk of Nivolumab (10 mg/ mL)	INN	10.0 mL (Equivalent to Nivolumab INN 100 mg)	Used as API
	*** Composition of Formulated Bulk:**			
2.	Nivolumab	INN	100.000 mg	Active Material
3.	Mannitol (Injectable Grade)	BP	300.000 mg	Used as tonicity agent
4.	Pentetic Acid	BP	0.080 mg	Co-preservative (0.05%)
5.	Polysorbate 80 (Injectable Grade)	BP	2.000 mg	Used as Wetting agent (0.1–3)%
6.	Sodium Chloride (Injectable Grade)	USP	29.200 mg	Used as tonicity agent
7.	Sodium Citrate Dihydrate (Injectable Grade)	BP	58.800 mg	Used as Buffering agent
8.	Sodium Hydroxide	BP	q. s. to adjust pH	pH Adjusting Agent
9.	Hydrochloric Acid	BP	q. s. to adjust pH	pH Adjusting Agent
10.	Water for Injection	USP	q. s to 10.0 mL	Solvent

Note:

Formulated Bulk based on 100% potency

Prepared By:	Checked By:	Approved By:
08.02.20	08.02.20	08.02.20
Md. Saifuzzaman Sazib	Hasina Pervin	Dr. Parimal Talukder
Sr. Executive, PD	Manager, R&D	VP, Research & Development

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3. Pharmaceutical Form

Injection

4. Clinical particulars

4.1 Therapeutic indications

Melanoma

NIVOLUMAB 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.

Adjuvant treatment of melanoma

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

Non-Small Cell Lung Cancer (NSCLC)

NIVOLUMAB 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)

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

NIVOLUMAB in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.

Classical Hodgkin Lymphoma (cHL)

NIVOLUMAB 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)

NIVOLUMAB 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.

Urothelial Carcinoma

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

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

4.2 Posology and method of administration

NIVOLUMAB as monotherapy

The recommended dose of NIVOLUMAB is either nivolumab 240 mg every 2 weeks **or** 480 mg every 4 weeks 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)	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
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	240 mg every 2 weeks over 30 minutes
Classical Hodgkin lymphoma	240 mg every 2 weeks over 30 minutes
Squamous Cell Cancer of the Head and Neck	240 mg every 2 weeks over 30 minutes
Urothelial Carcinoma	240 mg every 2 weeks over 30 minutes

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.

NIVOLUMAB 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.

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

	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

	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	-

Duration of treatment

Treatment with NIVOLUMAB, 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.

For adjuvant therapy, the maximum treatment duration with NIVOLUMAB 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.

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

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

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	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.

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

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

• Grade 4 or recurrent Grade 3 adverse reactions;

• Persistent Grade 2 or 3 adverse reactions despite management.

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

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

Special populations

Paediatric population

The safety and efficacy of NIVOLUMAB 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).

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.

Renal impairment

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

Hepatic impairment

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Based on the population PK results, no dose adjustment is required in patients with mild hepatic impairment. Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. NIVOLUMAB 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

NIVOLUMAB 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. 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.

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

The total dose of NIVOLUMAB 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.

When administered in combination with ipilimumab, NIVOLUMAB should be given first followed by ipilimumab 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

When nivolumab is administered in combination with ipilimumab, refer to the Summary of Product Characteristics for ipilimumab 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.

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

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

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or

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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. 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. 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. 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.

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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.

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.

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Immune-related skin adverse reactions

Severe rash has been observed with nivolumab in combination with ipilimumab and, less commonly, with nivolumab as monotherapy. 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.

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.

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.

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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.

Infusion reactions

Severe infusion reactions have been reported in clinical trials of nivolumab or nivolumab in combination with ipilimumab. 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. 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.

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.

Adjuvant treatment of melanoma

There are no data on adjuvant treatment in patients with melanoma with the following risk factors.

• patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications,

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• patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥ 6 months prior to randomisation),

• patients treated with prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways),

• subjects under the age of 18 years.

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

Non-Small Cell Lung Cancer

Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of NSCLC. 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.

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

<u>Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT) in classical Hodgkin Lymphoma</u>

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.

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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.

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. 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. 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.

Patients on controlled sodium diet

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

Patient Alert Card

All prescribers of NIVOLUMAB must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of NIVOLUMAB 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 on the use of nivolumab in pregnant women. Studies in animals have shown embryofoetal toxicity. Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore, nivolumab has the potential to be transmitted from the mother to the developing foetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, nivolumab is unlikely to affect the ability to drive and use machines. Because of potential adverse reactions such as fatigue, 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

Summary of the safety profile

In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumour types (n = 2578) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (30%), 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 = 2578) 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
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, 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]
Hepatobiliary disorders	
Uncommon	hepatitis[c]
Rare	cholestasis
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]
Eye disorders	
Uncommon	uveitis, blurred vision, dry eye

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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
Uncommon	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
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], lymphopaenia, leucopoenia, thrombocytopaenia, anaemia[k], hypercalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia
Common	increased total bilirubin, hypoglycaemia, 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.

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[d] The frequency of adverse events 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 events 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.

[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

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.

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.

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
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,	adrenal insufficiency[c], hypophysitis[c],

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	hypophysitis, hyperthyroidism, thyroiditis	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]	
Hepatobiliary disorders		
Common	hepatitis[c]	hepatitis[c]
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
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,

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		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 events 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 events 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

[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.

Description of selected adverse reactions

Nivolumab or nivolumab in combination with ipilimumab 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 7 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 7 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.

Table 7: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen

	Nivolumab 3 mg/kg monotherapy %	Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg %	Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg %
Immune-related adverse reaction leading to permanent discontinuation			
Pneumonitis	1.2	2.0	2.2
Colitis	0.8	16	4.0
Hepatitis	1.0	9	4.4

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Nephritis and Renal Dysfunction	0.3	1.1	1.3
Endocrinopathies	0.1	2.7	2.9
Skin	0.3	0.9	1.5
Hypersensitivity/Infusion Reaction	0.2	0	0
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]			
Pneumonitis	69	63	59
Colitis	15	46	26
Hepatitis	21	46	35
Nephritis and Renal Dysfunction	27	17	27
Endocrinopathies	7	27	25
Skin	4	7	7
Hypersensitivity/Infusion Reaction	20	6	9

[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 3.4% (87/2578). The majority of cases were Grade 1 or 2 in severity reported in 0.8% (21/2578) and 1.7% (44/2578) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (19/2578) and <0.1% (1/2578) of patients respectively. Grade 5 cases were reported in < 0.1% (2/2578) of patients in these studies. Median time to onset was 3.6 months (range: 0.2-19.6). Resolution occurred in 63 patients (72.4%) with a median time to resolution of 6.1 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^{+}).

Immune-related colitis

In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 13.1% (339/2578). The majority of cases were Grade 1 or 2 in severity reported in 8.5% (220/2578) and 3.0% (78/2578) of patients respectively. Grade 3 cases were reported in 1.6% (41/2578) of patients. No Grade 4 or 5 cases were reported in these studies.

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Median time to onset was 1.8 months (range: 0.0-26.6). Resolution occurred in 296 patients (88.1%) 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[+]).

Immune-related hepatitis

In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 6.7% (173/2578). The majority of cases were Grade 1 or 2 in severity reported in 3.5% (91/2578) and 1.2% (32/2578) of patients respectively. Grade 3 and 4 cases were reported in 1.6% (41/2578) and 0.3% (9/2578) 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 132 patients (76.7%) with a median time to resolution of 5.9 weeks (range: 0.1-82.6[+]).

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[+]).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.8% (71/2578). The majority of cases were Grade 1 or 2 in severity reported in 1.6% (41/2578) and 0.7% (18/2578) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (11/2578) and <0.1% (1/2578) 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 42 patients (61.8%) 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^{+}).

Immune-related endocrinopathies

In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 9.6% (248/2578). The majority of cases were Grade 1 or 2 in severity reported in 4.2% (107/2578) and 5.4% (139/2578) of patients, respectively. Grade 3 thyroid disorders were reported in < 0.1% (2/2578) of patients. Hypophysitis (1 Grade 1, 2 Grade 2, 5 Grade 3, and 1 Grade 4), hypopituitarism (4 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 117 patients (42.9%). 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.

Immune-related skin adverse reactions

In patients treated with nivolumab monotherapy, the incidence of rash was 26.4% (680/2578). The majority of cases were Grade 1 in severity reported in 20.1% (518/2578) of patients. Grade 2 and

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Grade 3 cases were reported in 5.1% (131/2578) and 1.2% (31/2578) 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 428 patients (63.8%) with a median time to resolution of 17.1 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^{+}).

Rare cases of SJS and TEN some of them with fatal outcome have been observed.

Infusion reactions

In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 4.7% (121/2578), including 6 Grade 3 and 2 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.

Complications of allogeneic HSCT in classical Hodgkin Lymphoma

Rapid onset of GVHD has been reported with nivolumab use before and after allogeneic HSCT.

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: 5.2% for anaemia (all Grade 3), 1.0% for thrombocytopaenia, 1.0% for leucopoenia, 10.0% for lymphopaenia, 1.1% for

neutropaenia, 2.1% for increased alkaline phosphatase, 2.7% for increased AST, 2.2% for increased ALT, 1.2% for increased total bilirubin, 0.9% for increased creatinine, 3.8% for hyperglycaemia, 1.0% for hypoglycaemia, 3.5% for increased amylase, 7.9% for increased lipase, 6.4% for hyponatraemia, 1.8% for hyperkalaemia, 1.5% for hypokalaemia, 1.2% for hypercalcaemia, 0.7% for hypermagnesaemia, 0.5% for hypomagnesaemia, 0.7% 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 hyperkalemia, 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 hypoglycemia, 12.2% for increased amylase, 20.1% for increased lipase, 0.4% for hypocalcaemia, 1.3% for hypercalcaemia, 2.4% for hyperkalemia, 1.1% for hypermagnesaemia, 0.4% for hypomagnesaemia 1.9% for hypokalaemia, and 9.9% for hyponatraemia.

Immunogenicity

Of the 2022 patients who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks and evaluable for the presence of anti-product-antibodies, 231 patients (11.4%) tested positive for treatment-emergent anti-product-antibodies with fifteen patients (0.7 %) 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%.

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.

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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.

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.

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

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).

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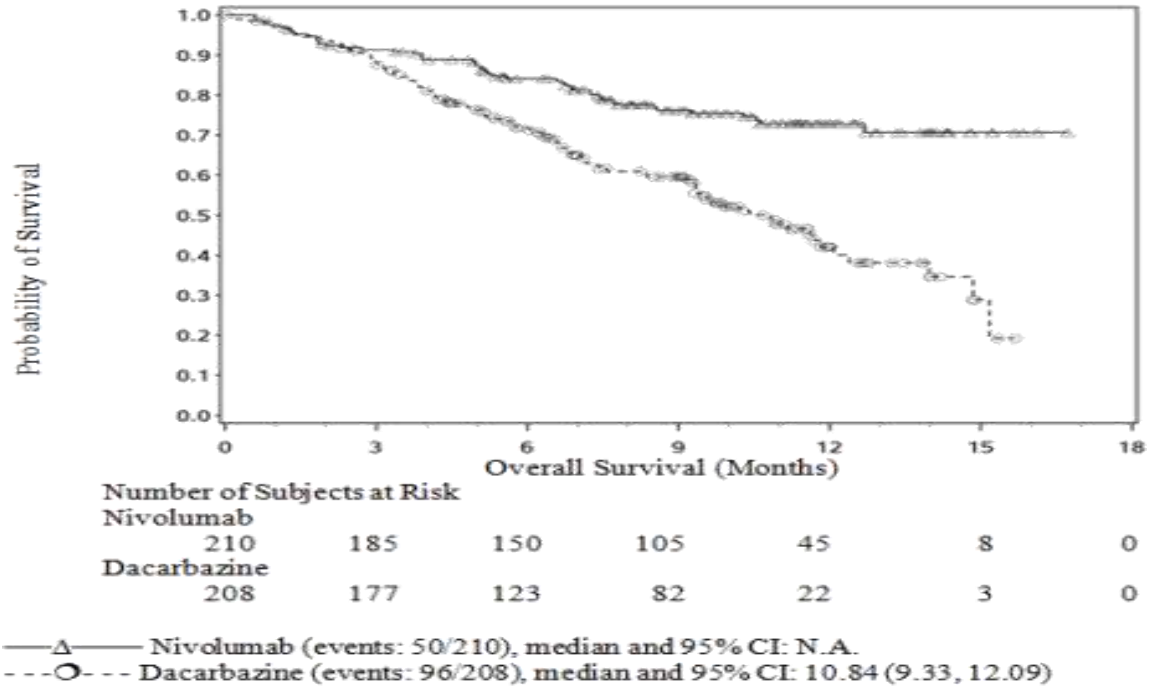
The study included adult patients (18 years or older) with confirmed, treatment-naive, Stage III or IV BRAF wild-type melanoma and an ECOG performance-status score of 0 or 1. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the 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 effects with the study drug, as determined by the investigator. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was 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 (≥ 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)**



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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 (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.

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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.

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)

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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 10 below.

Table 10: **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.

Product Name: Nivolunix 100 Injection	Generic Name: Nivolumab INN 100 mg
MODULE I: ADMINISTRETIVE PART	
Summary of Product Characteristics	

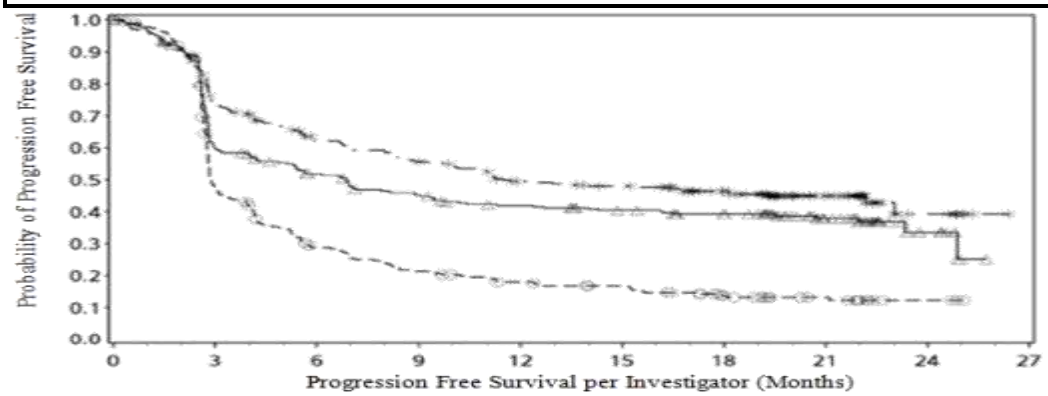
A total of 945 patients were randomised to receive nivolumab in combination with ipilimumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously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

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

PFS results (with minimum follow up of 18 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)

Product Name: Nivolunix 100 Injection	Generic Name: Nivolumab INN 100 mg
MODULE I: ADMINISTRETIVE PART	
Summary of Product Characteristics	



Number of Subjects at Risk

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

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

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

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

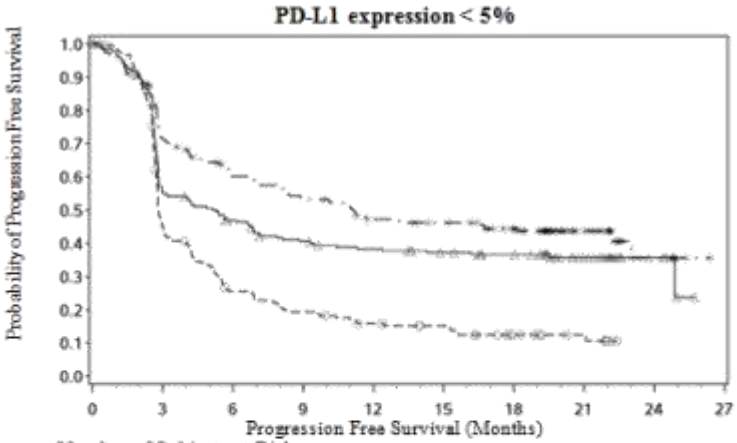
Nivolumab+ipilimumab vs. ipilimumab (primary analysis) - HR (99.5% CI): 0.42 (0.32, 0.56); p-value: < 0.0001

Nivolumab vs. ipilimumab (primary analysis) - HR (99.5% CI): 0.55 (0.42, 0.73); p-value: < 0.0001

Nivolumab+ipilimumab vs. nivolumab (descriptive analysis) - HR (95% CI): 0.76 (0.62, 0.95)

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

Product Name: Nivolunix 100 Injection	Generic Name: Nivolumab INN 100 mg
MODULE I: ADMINISTRETIVE PART	
Summary of Product Characteristics	



Number of Subjects at Risk

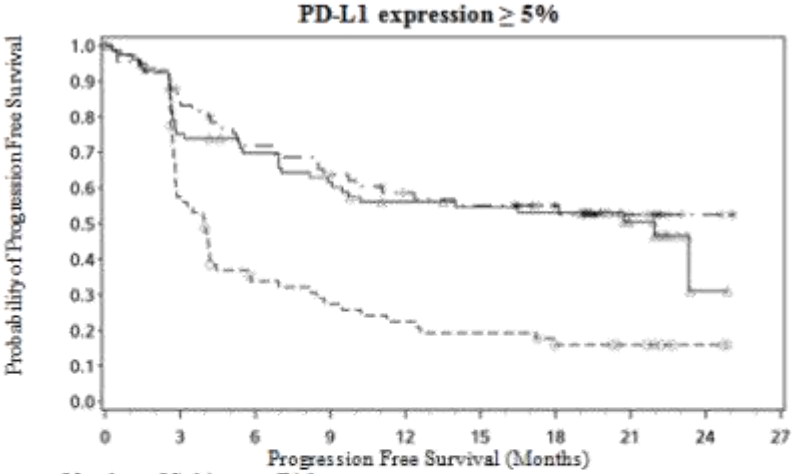
Nivolumab + Ipilimumab									
210	142	113	101	86	81	69	31	5	0
Nivolumab									
208	108	89	75	69	62	55	29	7	0
Ipilimumab									
202	82	45	34	26	22	12	7	0	0

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

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.42 (0.33, 0.54)

Nivolumab vs. Ipilimumab - hazard ratio: 0.57 (0.45, 0.72)

Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.74 (0.58, 0.96)



Number of Subjects at Risk

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

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

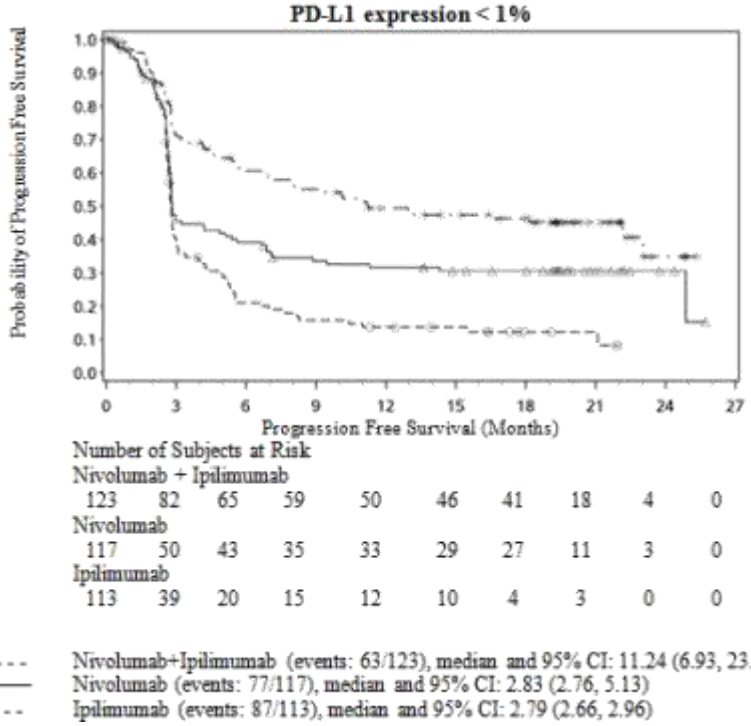
Product Name: Nivolunix 100 Injection	Generic Name: Nivolumab INN 100 mg
MODULE I: ADMINISTRETIVE PART	
Summary of Product Characteristics	

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.35 (0.22, 0.55)

Nivolumab vs. Ipilimumab - hazard ratio: 0.41 (0.27, 0.62)

Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.87 (0.54, 1.41)

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

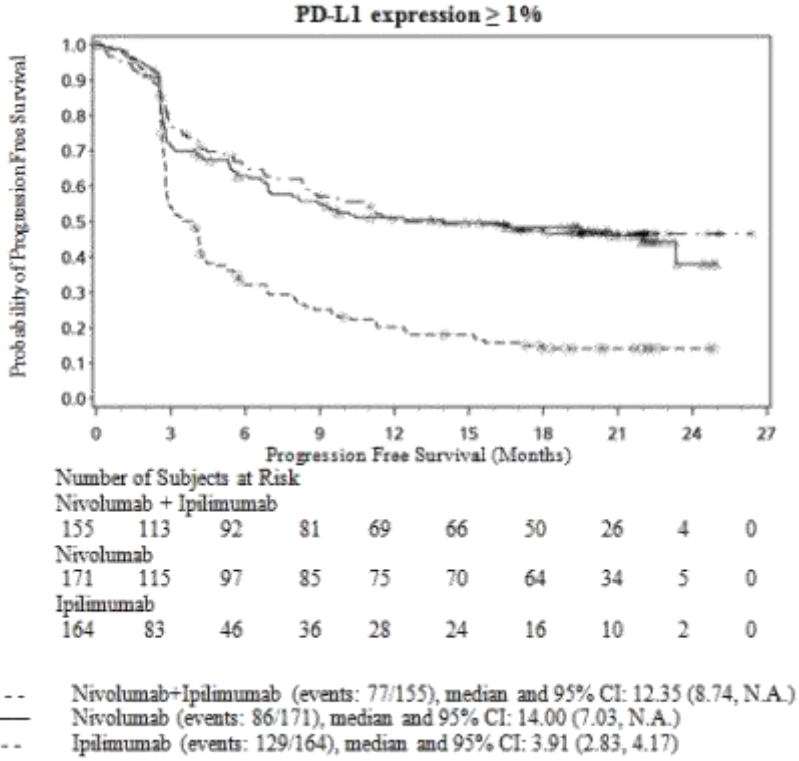


Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.39 (0.28, 0.54)

Nivolumab vs. Ipilimumab - hazard ratio: 0.65 (0.48, 0.88)

Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.60 (0.43, 0.84)

Product Name: Nivolunix 100 Injection	Generic Name: Nivolumab INN 100 mg
MODULE I: ADMINISTRETIVE PART	
Summary of Product Characteristics	



Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.42 (0.31, 0.55)

Nivolumab vs. Ipilimumab - hazard ratio: 0.44 (0.34, 0.58)

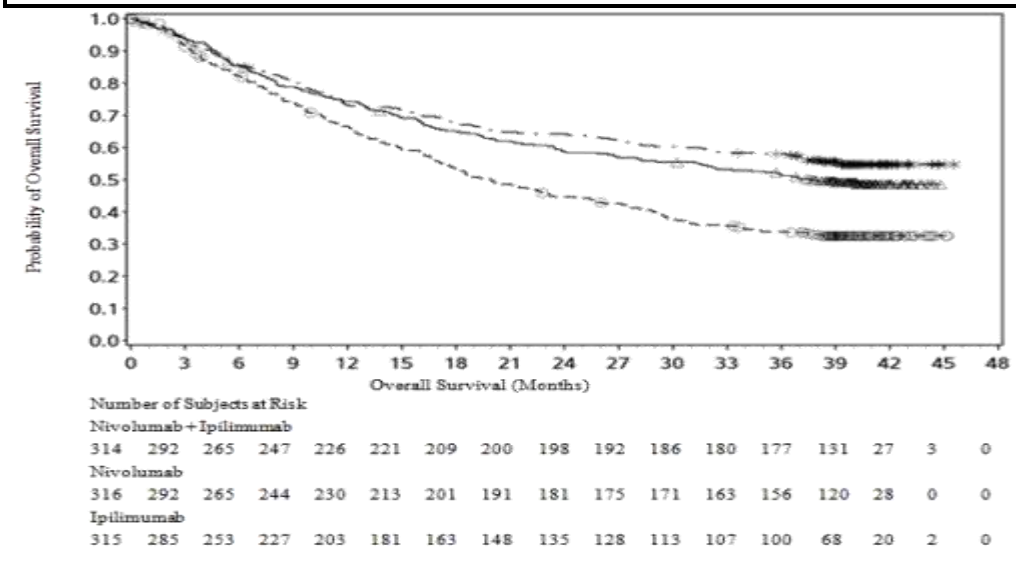
Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.94 (0.69, 1.28)

The final OS analysis occurred when all patients had a minimum follow-up of 28 months. OS results at an additional analysis undertaken at a minimum follow-up of 36 months show outcomes consistent with the original analysis. OS results from this follow-up analysis are shown in Figure 5 (all randomised), Figure 6 (at the tumour PD-L1 1% cut off), and Table 11 (at the tumour PD-L1 5% cut off).

The OS analysis was not adjusted to account for subsequent therapies received. Subsequent systemic therapy was received by 31.8%, 44.3%, and 62.2% 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 14.6%, 29.1%, and 44.1% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively.

Figure 5 Overall survival (CA209067) - Minimum follow-up of 36 months

Product Name: Nivolunix 100 Injection	Generic Name: Nivolumab INN 100 mg
MODULE I: ADMINISTRETIVE PART	
Summary of Product Characteristics	



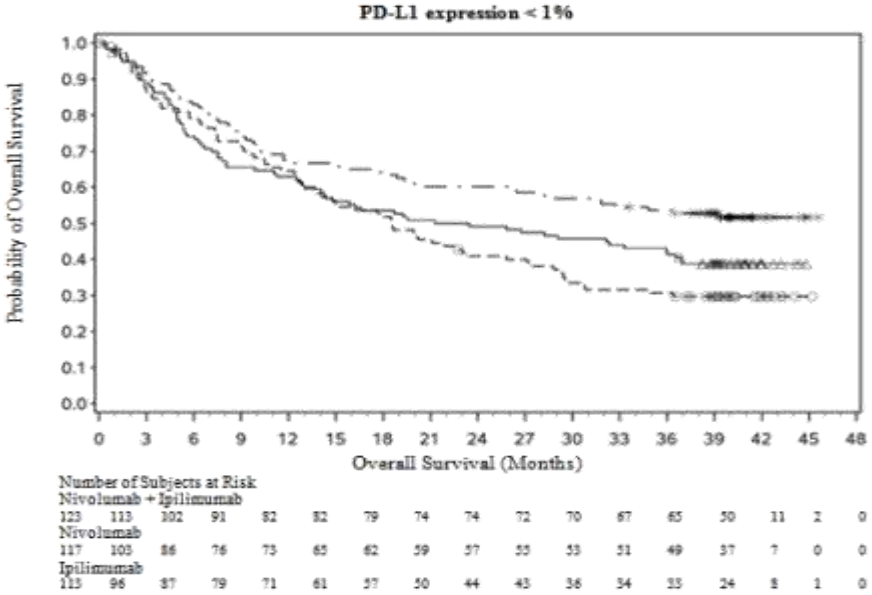
---*---- Nivolumab+ipilimumab (events: 139/314), median and 95% CI: N.A. (38.18, N.A.)
OS rate and 95% CI at 12 months: 73% (68, 78), 24 months: 64% (59, 69), and 36 months: 58% (52, 63)
—Δ— Nivolumab (events: 158/316), median and 95% CI: 37.59 months (29.08, N.A.)
OS rate and 95% CI at 12 months: 74% (69, 79), 24 months: 59% (53, 64), and 36 months: 52% (46, 57)
---O--- Ipilimumab (events: 206/315), 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), and 36 months: 34% (29, 39)

Nivolumab+ipilimumab vs ipilimumab (primary analysis) - HR (95% CI): 0.55 (0.45, 0.69); p-value: < 0.0001

Nivolumab vs ipilimumab (primary analysis) - HR (95% CI): 0.65 (0.53, 0.80); p-value: < 0.0001

Nivolumab+ipilimumab vs nivolumab (descriptive analysis) - HR (95% CI): 0.85 (0.68, 1.07)

Figure 6: Overall survival by PD-L1 expression: 1% cut off (CA209067) - Minimum follow-up of 36 months



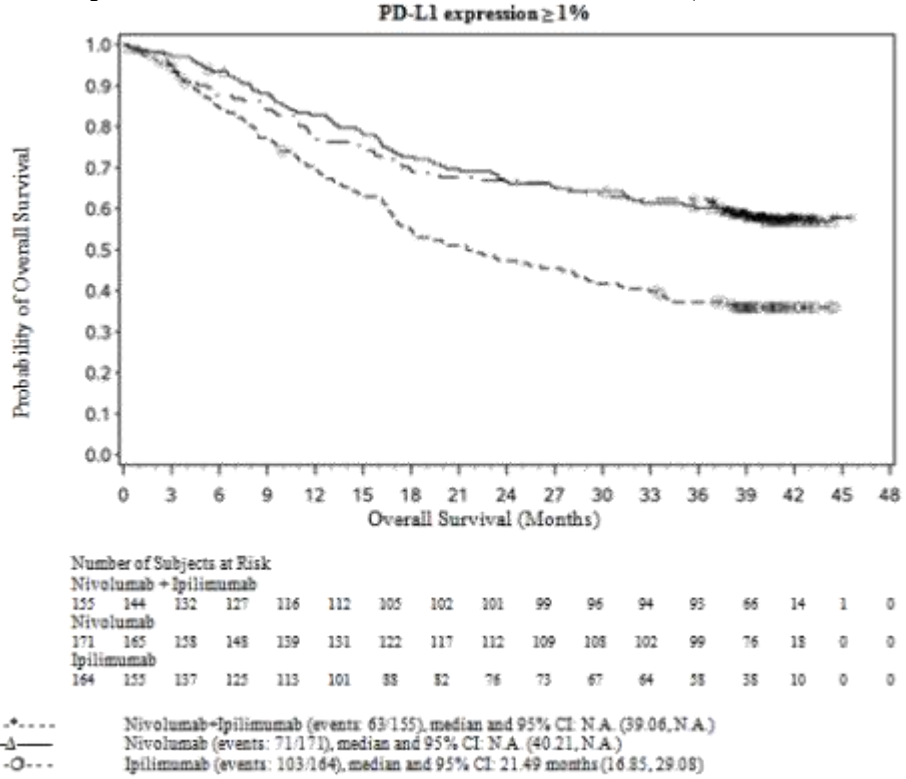
---*---- Nivolumab+Ipilimumab (events: 59/123), median and 95% CI: N.A. (26.45, N.A.)
—Δ— Nivolumab (events: 71/117), median and 95% CI: 23.46 months (13.01, 36.53)
---O--- Ipilimumab (events: 77/113), median and 95% CI: 18.56 months (13.67, 23.20)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.59 (0.42, 0.82)

Product Name: Nivolunix 100 Injection	**Generic Name: Nivolumab INN 100 mg**
MODULE I: ADMINISTRETIVE PART	
Summary of Product Characteristics	

Nivolumab vs. Ipilimumab - hazard ratio: 0.84 (0.61, 1.16)

Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.70 (0.49, 0.99)



Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.55 (0.40, 0.75)

Nivolumab vs. Ipilimumab - hazard ratio: 0.54 (0.40, 0.73)

Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 1.02 (0.73, 1.43)

Table 11: Summary of overall survival by PD-L1 expression: 5% cut off - CA209067 - Minimum follow-up of 36 months

Tumour PD-L1 expression	**n**	**nivolumab + ipilimumab Median OS (95% CI)**	**n**	**ipilimumab Median OS (95% CI)**	**Hazard Ratio (95% CI)**
<5%	210	NR (32.72, NR)	202	18.40 (13.70, 22.51)	0.56 (0.43, 0.72)
≥5%	68	NR (39.06, NR)	75	28.88 (18.10, NR)	0.59 (0.36, 0.97)
		nivolumab Median OS (95% CI)		**ipilimumab Median OS (95% CI)**	**Hazard Ratio (95% CI)**
<5%	208	35.94 (23.06, NR)	202	18.40 (13.70, 22.51)	0.68 (0.53, 0.87)
≥5%	80	NR (35.75, NR)	75	28.88 (18.10, NR)	0.60 (0.38, 0.95)
		nivolumab + ipilimumab Median OS (95% CI)		**nivolumab Median OS (95% CI)**	**Hazard Ratio (95% CI)**
<5%	210	NR (32.72, NR)	208	35.94 (23.06, NR)	0.82 (0.62, 1.08)
≥5%	68	NR (39.06, NR)	80	NR (35.75, NR)	0.99 (0.59, 1.67)

NR = not reached

Minimum follow-up for the analysis of ORR was 28 months. Responses are summarised in Table 12.

Product Name: Nivolunix 100 Injection	Generic Name: Nivolumab INN 100 mg
MODULE I: ADMINISTRETIVE PART	
Summary of Product Characteristics	

Table 12: Objective response (CA209067)

	nivolumab + ipilimumab (n=314)	nivolumab (n=316)	ipilimumab (n=315)
Objective response	185 (59%)	141 (45%)	60 (19%)
(95% CI)	(53.3, 64.4)	(39.1, 50.3)	(14.9, 23.8)
Odds ratio (vs. ipilimumab)	6.50	3.54	
(99.5% CI)	(3.81, 11.08.)	(2.10, 5.95)	
Complete response (CR)	54 (17%)	47 (15%)	14 (4%)
Partial response (PR)	131 (42%)	94 (30%)	46 (15%)
Stable disease (SD)	36 (12%)	31 (10%)	67 (21%)
Duration of response			
Median (range), months	Not reached (0^+ - 33.3^+)	31.1 (0^+ - 32.3^+)	18.2 (0^+ - 31.5^+)
Proportion ≥12 months in duration	64%	70%	53%
Proportion ≥24 months in duration	50%	49%	32%
ORR (95% CI) by tumour PD-L1 expression			
<5%	56% (49.2, 63.0) n=210	42% (35.5, 49.3) n=208	18% (12.8, 23.8) n=202
≥5%	74% (61.4, 83.5) n=68	59% (47.2, 69.6) n=80	21% (12.7, 32.3) n=75
<1%	55% (45.2, 63.5) n=123	35% (26.5, 44.4) n=117	19% (11.9, 27.0) n=113
≥1%	65% (57.1, 72.6) n=155	55% (47.2, 62.6) n=171	19% (13.2, 25.7) n=164

"+" denotes a censored observation.

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 36 months.

Among 128 patients who discontinued nivolumab in combination with ipilimumab due to adverse reaction after 18 months of follow-up, median PFS was 16.7 months (95% CI: 10.2, NA). 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 28 months of follow-up, with a best overall response of complete response correlating to an improved survival rate.

After 28 months of follow-up, median durations of response for patients with tumour PD-L1 expression level ≥5% were not reached (range: 0^+-31.6^+) in the combination arm, not reached (range: 2.8-30.6^+) in the nivolumab monotherapy arm and not reached (range: 1.4-30.6^+) in the

ipilimumab arm. At tumour PD-L1 expression <5%, median durations of response were not reached (range: 0^{+}-33.3^{+}) in the combination arm, not reached (range: 0^{+}-32.3^{+}) in the nivolumab monotherapy arm and 18.2 months (range: 0.0^{+}-31.5^{+}) 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: After18 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 15.5 months (95% CI: 8.0, NA) and 11.3 months (95% CI: 8.3, 22.2), while those in the nivolumab monotherapy arm had a median PFS of 5.6 months (95% CI: 2.8, 9.3) and 7.1 months (95% CI: 4.9, 14.3), respectively. After 28 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had an ORR of 67.6% (95% CI: 57.7, 76.6; n = 102) and 54.7% (95% CI: 47.8, 61.5; n = 212), while those in the nivolumab monotherapy arm had an ORR of 36.7% (95% CI: 27.2, 47.1; n = 98) and 48.2% (95% CI: 41.4, 55.0; n = 218), respectively. After 28 months of follow-up, median OS was not reached in either of the nivolumab containing arms regardless of BRAF status. The OS HRs for nivolumab in combination with ipilimumab vs. nivolumab monotherapy were 0.71 (95% CI: 0.45, 1.13) for BRAF[V600] mutation-positive patients and 0.97 (95% CI: 0.74, 1.28) 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), 7^{th} edition, histologically confirmed melanoma that is completely surgically resected. Per the AJCC 8^{th} 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 7 (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 7: Recurrence-free Survival (CA209238)

Product Name: Nivolunix 100 Injection	Generic Name: Nivolumab INN 100 mg
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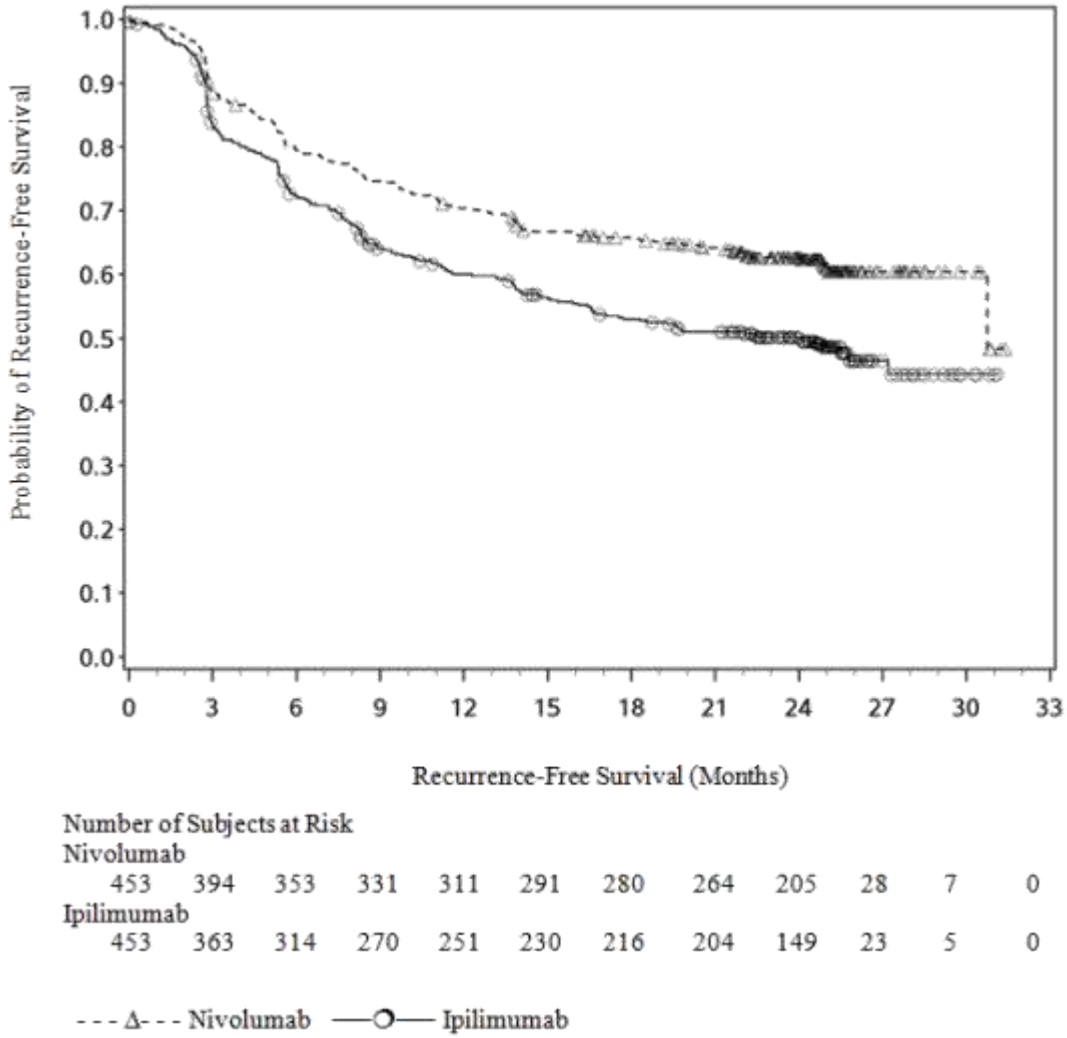

The trial demonstrated a statistically significant improvement in RFS for patients randomised to the nivolumab arm compared with the ipilimumab 10 mg/kg arm. RFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF status, and stage of disease.

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

<u>Squamous NSCLC</u>

<u>Randomised phase 3 study vs. docetaxel (CA209017)</u>

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.

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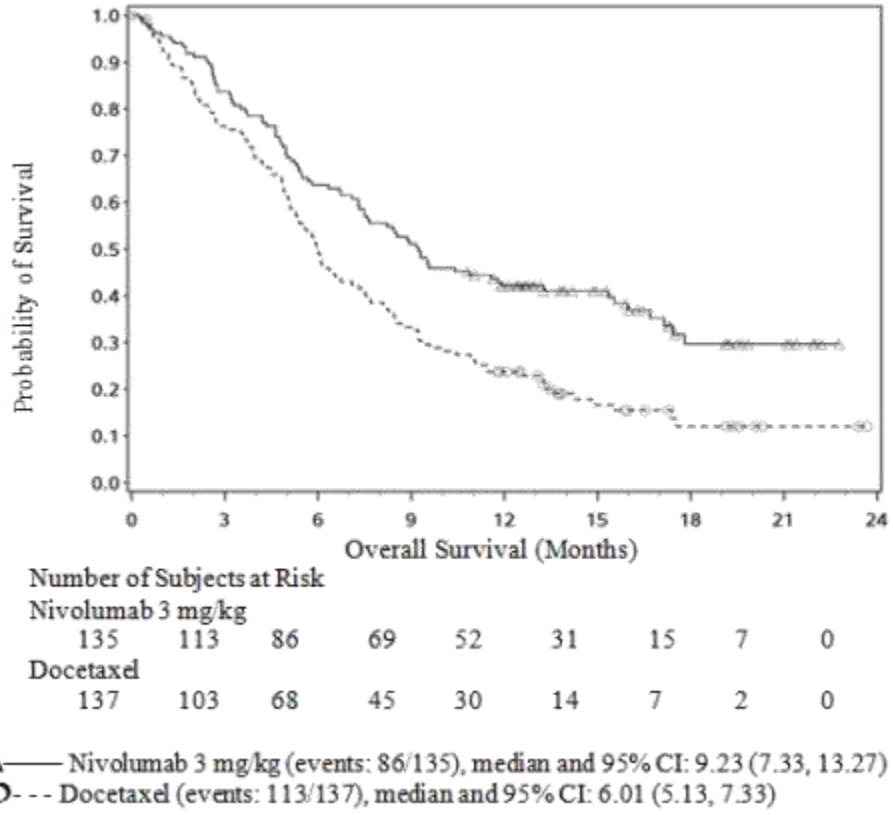
Patients with active autoimmune disease, symptomatic interstitial lung disease, or active brain metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or 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 8.

Figure 8: Kaplan-Meier curves of OS (CA209017)



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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 14.

Table 14: **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)	

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Updated analysis Minimum follow-up: 24.2 months		
Overall survival[a]		
Events	110 (81.4%)	128 (93.4%)
Hazard ratio	0.62	
95% CI	(0.47, 0.80)	
Rate (95% CI) at 24 months	22.9 (16.2, 30.3)	8 (4.3, 13.3)
Confirmed objective response	20.0%	8.8%
(95% CI)	(13.6, 27.7)	(4.6, 14.8)
Median duration of response		
Months (range)	25.2 (2.9-30.4)	8.4 (1.4^{+}-18.0^{+})
Progression-free survival		
Rate (95% CI) at 24 months	15.6 (9.7, 22.7)	All patients had either progressed, were censored, or lost to follow-up
Updated analysis Minimum follow-up: 62.6 months		
Overall survival[a]		
Events	118 (87.4%)	133 (97.1%)
Hazard ratio	0.62	
95% CI	(0.48, 0.79)	
Rate (95% CI) at 60 months	12.3 (7.4, 18.5)	3.6 (1.4, 7.8)
Confirmed objective response (95% CI)	20.0% (13.6, 27.7)	8.8% (4.6, 14.8)
Median duration of response		
Months (range)	25.2 (2.9-70.6^{+})	7.5 (0.0^{+}-18.0^{+})
Progression-free survival		
Rate (95% CI) at 60 months	9.4 (4.8, 15.8)	All patients had either progressed, were censored, or lost to follow-up

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

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

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

Single-arm phase 2 study (CA209063)

Study CA209063 was a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous NSCLC after two or more lines of therapy; otherwise similar inclusion criteria as study CA209017 were applied. Nivolumab 3 mg/kg showed an 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%.

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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 15 below.

Table 15: **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] (%) 95% CI[b]	66/671 (9.8) (7.7, 12.3)	1/64 (6.1) (0.0, 8.4)	55/568 (9.7) (7.4, 12.4)	11/103 (10.7) (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.

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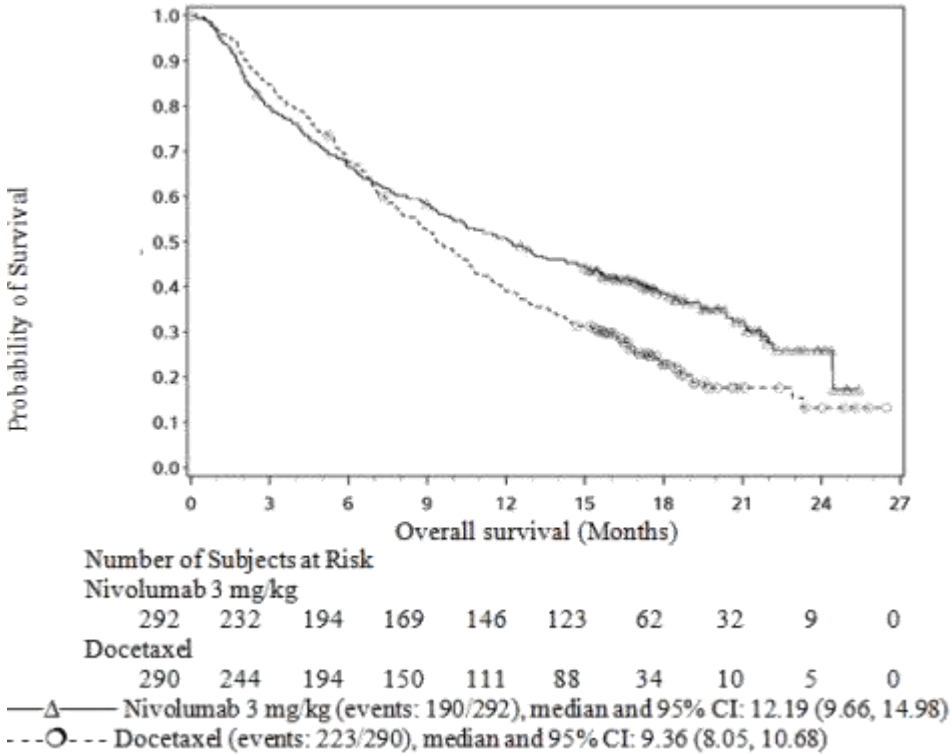
The median age was 62 years (range: 21 to 85) with 34% ≥65 years of age and 7% ≥75 years of age. The majority of patients were white (92%) and male (55%). Baseline ECOG performance status was 0 (31%) or 1 (69%). Seventy-nine percent of patients were former/current smokers.

The Kaplan-Meier curves for OS are shown in Figure 9.

Figure 9: Kaplan-Meier curves of OS (CA209057)



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 16.

Table 16: **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%)

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(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 (95% CI)	19.5% (15.1, 24.5)	12.4% (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 17 summarises results of ORR and OS by tumour PD-L1 expression.

Table 17: 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)

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≥ 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

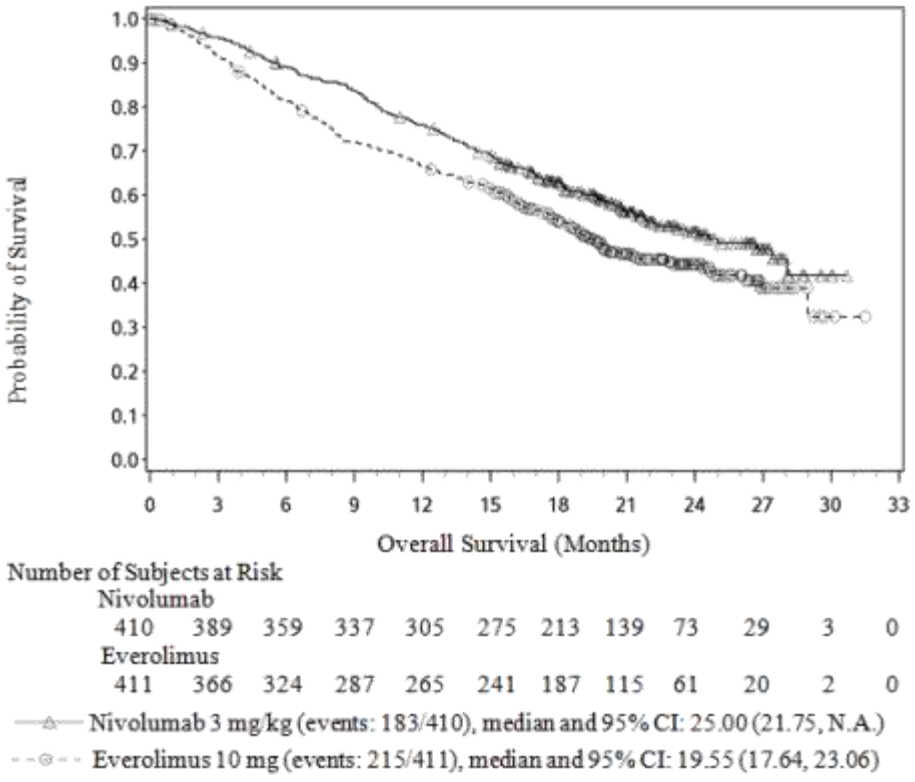
progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was OS. Secondary efficacy assessments included investigator-assessed ORR and PFS.

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 10.

Figure 10: Kaplan-Meier curves of OS (CA209025)



The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 18 and Figure 10). OS benefit was observed regardless of tumour PD-L1 expression level.

Efficacy results are shown in Table 18.

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Table 18: **Efficacy results (CA209025)**

	nivolumab (n = 410)	**everolimus (n = 411)**
Overall survival		
Events	183 (45%)	215 (52%)
Hazard ratio	0.73	
98.52% CI	(0.57, 0.93)	
p-value	0.0018	
Median (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Rate (95% CI)		
At 6 months	89.2 (85.7, 91.8)	81.2 (77.0, 84.7)
At 12 months	76.0 (71.5, 79.9)	66.7 (61.8, 71.0)
Objective response	103 (25.1%)	22 (5.4%)
(95% CI)	(21.0, 29.6)	(3.4, 8.0)
Odds ratio (95% CI)	5.98 (3.68, 9.72)	
p-value	< 0.0001	
Complete response (CR)	4 (1.0%)	2 (0.5%)
Partial response (PR)	99 (24.1%)	20 (4.9%)
Stable disease (SD)	141 (34.4%)	227 (55.2%)
Median duration of response		
Months (range)	11.99 (0.0-27.6^{+})	11.99 (0.0^{+}-22.2^{+})
Median time to response		
Months (range)	3.5 (1.4-24.8)	3.7 (1.5-11.2)
Progression-free survival		
Events	318 (77.6%)	322 (78.3%)
Hazard ratio	0.88	
95% CI	(0.75, 1.03)	
p-value	0.1135	
Median (95% CI)	4.6 (3.71, 5.39)	4.4 (3.71, 5.52)

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

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.

Product Name: Nivolunix 100 Injection	**Generic Name: Nivolumab INN 100 mg**
MODULE I: ADMINISTRETIVE PART	
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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.

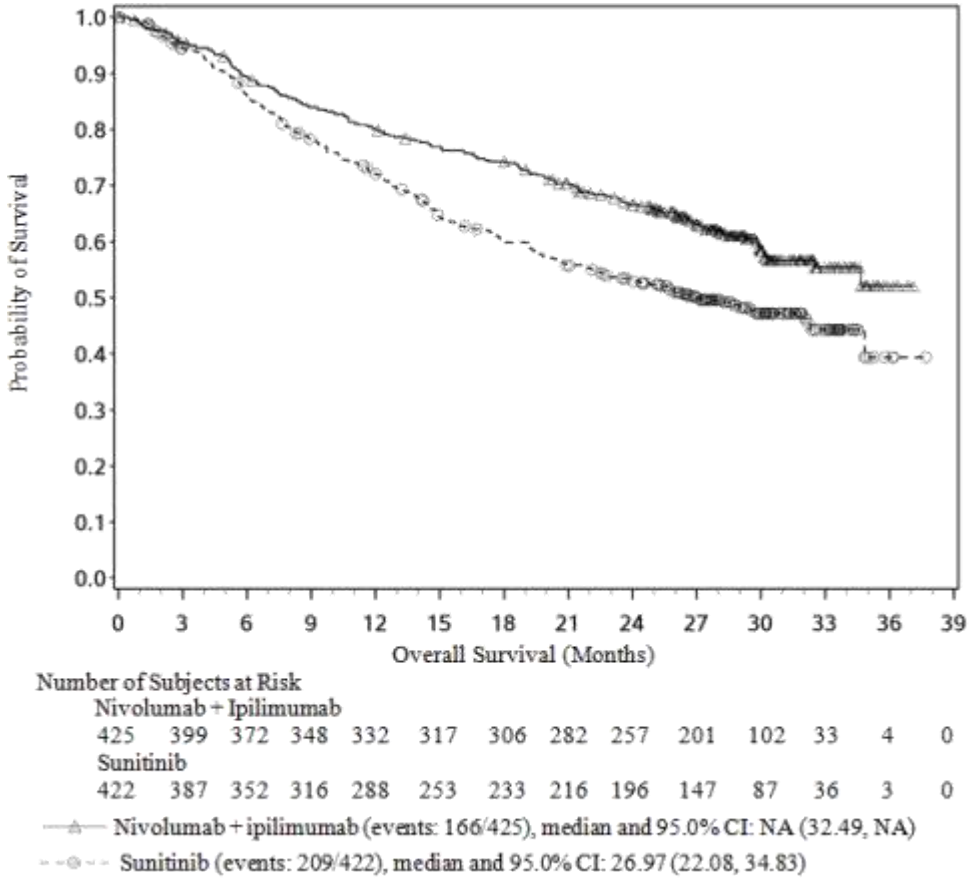
A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either nivolumab 3 mg/kg (n = 425) administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks for 4 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 11.

Figure 11: Kaplan-Meier curves of OS in intermediate/poor risk patients (CA209214)



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 19.

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

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

[a] Based on a stratified proportional hazards model.

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

[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.

[d] Strata adjusted difference.

[e] Based on the stratified DerSimonian-Laird test.

[f] p-value is compared to alpha 0.001 in order to achieve statistical significance.

[g] Computed using Kaplan-Meier method.

[h] p-value is compared to alpha 0.009 in order to achieve statistical significance.

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

NE = non-estimable

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An updated OS analysis was performed when all patients had a minimum follow-up of 24 months (see figure 11). 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 20 below).

Table 20: **Baseline patient characteristics in CA209205 Cohort B, Cohort C and CA209039**

	CA209205 Cohort B and CA209039	CA209205 Cohort B[a]	CA209039	CA209205 Cohort C[b]
	(n = 95)	(n = 80)	(n = 15)	(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	51 (64%) M	10 (67%) M	56 (56%) M

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	34 (36%) F	29 (36%) F	5 (33%) F	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 21.

Table 21: Efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma

	CA209205 Cohort B[a] and CA209039	**CA209205 Cohort B[a]**	**CA209039**
Number (n)/ minimum follow-up (months)	**(n = 95/12.0)**	**(n = 80/12.0)**	**(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 22.

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Table 22: Updated efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma from longer follow up of study CA209205

	CA209205 Cohort B[a]	CA209205 Cohort C[a]
Number (n)/ minimum follow-up (months)	**(n = 80/20.5)**	**(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

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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.

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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 12. Efficacy results are shown in Table 23.

Figure 12: Kaplan-Meier curves of OS (CA209141)

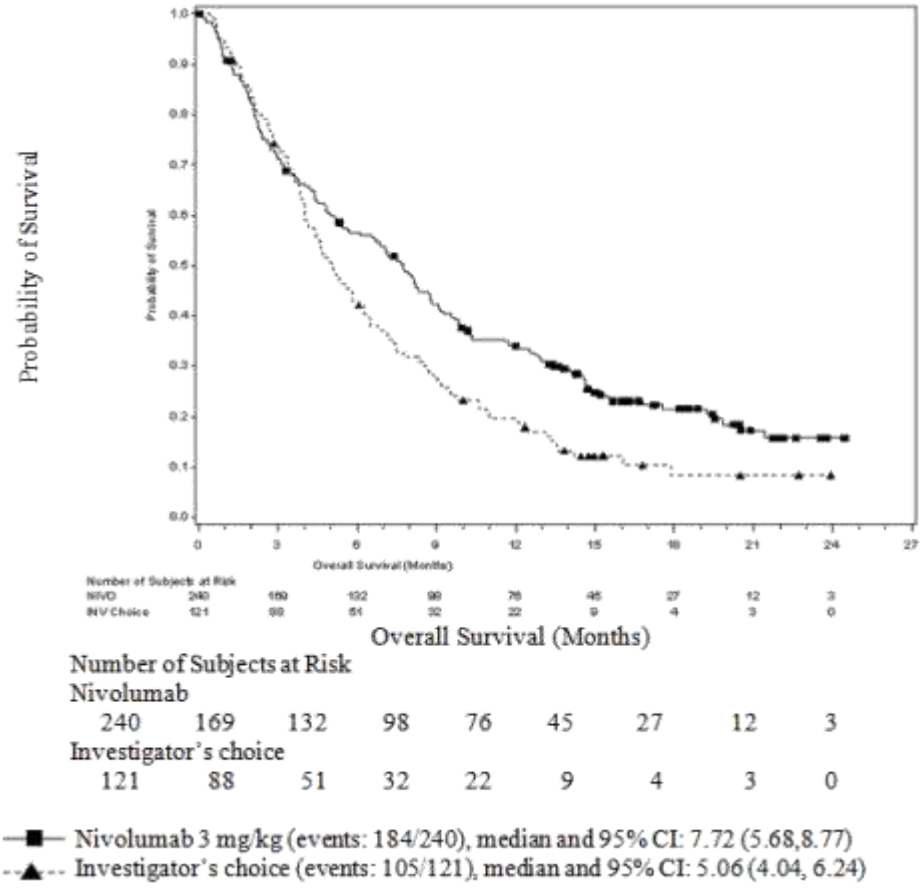

Table 23: **Efficacy results (CA209141)**

	nivolumab (n = 240)	**investigator's choice (n = 121)**
Overall survival		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio[a]	0.71	
(95% CI)	(0.55, 0.90)	
p-value[b]	0.0048	
Median (95% CI) (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%)

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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.

Table 24: 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 25). 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 25: 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

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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 26: 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)

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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.

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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

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.

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.

5.1 Pharmacodynamic properties

5.2 Pharmacokinetic properties

The pharmacokinetics of pembrolizumab was studied in 2,993 patients with metastatic or unresectable melanoma, NSCLC, or carcinoma who received doses in the range of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks.

Absorption

Pembrolizumab is administered via the intravenous route and therefore is immediately and completely bioavailable.

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Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (~6.0 L; CV: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Biotransformation

Pembrolizumab is catabolised through non-specific pathways; metabolism does not contribute to its clearance.

Elimination

Pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady-state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Linearity/non-linearity

Exposure to pembrolizumab as expressed by peak concentration (C_{max}) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3 week regimen and the systemic accumulation was 2.1-fold. The median trough concentrations (C_{min}) at steady-state were approximately 22 mcg/mL at a dose of 2 mg/kg every 3 weeks and 29 mcg/mL at a dose of 200 mg every 3 weeks. The median area under the concentration time curve at steady state over 3 weeks ($AUC_{0\text{-}3weeks}$) was 794 mcg·day/mL at a dose of 2 mg/kg every 3 weeks and 1,053 mcg·day/mL at a dose of 200 mg every 3 weeks.

Following administration of pembrolizumab 200 mg every 3 weeks in patients with cHL, the observed median C_{min} at steady-state was up to 40% higher than that in other tumour types treated with the same dosage; however, the range of trough concentrations is similar. There are no notable differences in median C_{max} between cHL and other tumour types. Based on available safety data in cHL and other tumour types, these differences are not clinically meaningful.

Special populations

The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 15-94 years), gender, race, mild or moderate renal impairment, mild hepatic impairment and tumour burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure. Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in paediatric patients (2 to 17 years) are comparable to those of adults at the same dose.

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Renal impairment

The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild or moderate renal impairment compared to patients with normal renal function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Pembrolizumab has not been studied in patients with severe renal impairment.

Hepatic impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (as defined using the US National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with moderate or severe hepatic impairment

5.3 Preclinical safety data

The safety of pembrolizumab was evaluated in a 1-month and a 6-month repeat-dose toxicity study in Cynomolgus monkeys administered intravenous doses of 6, 40 or 200 mg/kg once a week in the 1-month study and once every two weeks in the 6-month study, followed by a 4-month treatment-free period. No findings of toxicological significance were observed and the no observed adverse effect level (NOAEL) in both studies was ≥ 200 mg/kg, which produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg, respectively. The exposure multiple between the NOAEL and a human dose of 200 mg was 74.

Animal reproduction studies have not been conducted with pembrolizumab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss.

Animal fertility studies have not been conducted with pembrolizumab. In 1 month and 6 month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, many animals in these studies were not sexually mature.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet contents:

Mannitol (Injectable Grade) BP
Polysorbate 80 BP
Pentetic Acid BP
Sodium Chloride USP
Sodium Citrate Dihydrate BP

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Sodium Hydroxide BP
Hydrochloric Acid BP
Water for Injection USP

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store Nivolumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect Nivolumab from light by storing in the original package until time of use. Do not freeze or shake.

6.5 Nature and contents of container

Primary Packaging: 5 ml Clear glass vial USP type I

Secondary Packaging: Paper board carton

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 NIVOLUMAB 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 NIVOLUMAB concentrate to prepare the dose (mL) = the total dose in mg, divided by 10 (the NIVOLUMAB concentrate strength is 10 mg/mL).

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Preparing the infusion

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

NIVOLUMAB 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.

NIVOLUMAB concentrate may be diluted with either:

▪ sodium chloride 9 mg/mL (0.9%) solution for injection; or

▪ 50 mg/mL (5%) glucose solution for injection.

STEP 1

▪ Inspect the NIVOLUMAB concentrate for particulate matter or discoloration. Do not shake the vial. NIVOLUMAB concentrate is a clear to opalescent, 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 NIVOLUMAB concentrate using an appropriate sterile syringe.

STEP 2

▪ Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).

▪ If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

▪ Gently mix the infusion by manual rotation. Do not shake.

Administration

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

Administer the NIVOLUMAB infusion intravenously over a period of 30 or 60 minutes depending on the dose.

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

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

NIVOLUMAB infusion is compatible with PVC 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.

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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 authorization holder

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FACTORY

Bhaluka, Mymensingh, Bangladesh

8.Marketing authorization Number:

M.A No. 341-370-010

9. Date of first authorization/renewal of the authorization

05.11.2019/ 04.11.2024

10. Date of revision of the text

20.01.2020