

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 300 mg solution for injection

OPDIVO 600 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection contains 120 mg of nivolumab.

One vial of 2.5 mL contains 300 mg of nivolumab.

One vial of 5 mL contains 600 mg of nivolumab.

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

Excipient with known effect

Each 2.5 mL vial of this medicinal product contains 1.25 mg of polysorbate 80.

Each 5 mL vial of this medicinal product contains 2.5 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear to opalescent, colourless to yellow liquid, essentially free of visible particulates. The solution has a pH of 5.5-6.5 and an osmolality of 296-444 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

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

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults (see section 4.2).

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

Non-small cell lung cancer (NSCLC)

OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression $\geq 1\%$ (see section 5.1 for selection criteria).

OPDIVO, in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression $\geq 1\%$ (see section 5.1 for selection criteria).

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

Renal cell carcinoma (RCC)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (see sections 4.2 and 5.1).

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

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

Squamous cell cancer of the head and neck (SCCHN)

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

Urothelial carcinoma (UC)

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression $\geq 1\%$, who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1).

OPDIVO in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma (see sections 4.2 and 5.1).

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

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

OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer in the following settings:

- first-line treatment of unresectable or metastatic colorectal cancer (see sections 4.2 and 5.1);
- treatment of metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy (see sections 4.2 and 5.1).

Oesophageal squamous cell carcinoma (OSCC)

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

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

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC)

OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (see section 5.1).

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

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

Hepatocellular carcinoma (HCC)

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

4.2 Posology and method of administration

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

Patients currently receiving intravenous nivolumab monotherapy, or in combination with chemotherapy or cabozantinib, may transition to OPDIVO solution for injection.

PD-L1 testing

If specified in the indication, patient selection for treatment with OPDIVO based on the tumour expression of PD-L1 should be assessed by a CE-marked in vitro IVD medical device test. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, 4.4, and 5.1).

MSI/MMR testing

If specified in the indication, patient selection for treatment with OPDIVO based on MSI-H/dMMR tumour status should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, 4.4, and 5.1).

Posology

OPDIVO as monotherapy

The recommended dose of OPDIVO solution for injection is either nivolumab 600 mg every 2 weeks **or** 1200 mg every 4 weeks (see section 5.1).

If patients need to be switched from the 600 mg every 2 weeks schedule to the 1200 mg every 4 weeks schedule, the first 1200 mg dose should be administered two weeks after the last 600 mg dose. Conversely, if patients need to be switched from the 1200 mg every 4 weeks schedule to the 600 mg every 2 weeks schedule, the first 600 mg dose should be administered four weeks after the last 1200 mg dose.

OPDIVO in combination with ipilimumab

Melanoma

Table 1: Recommended doses and infusion times for OPDIVO solution for infusion in combination with ipilimumab followed by OPDIVO solution for injection monotherapy for melanoma (see section 5.1)

	Combination phase OPDIVO solution for infusion, intravenously (IV) and ipilimumab, for 4 dosing cycles	Monotherapy phase OPDIVO solution for injection, subcutaneously (SC)
Nivolumab	1 mg/kg every 3 weeks over 30 minutes	600 mg every 2 weeks or 1200 mg every 4 weeks The first dose should be administered: • 3 weeks after the last dose of the combination of IV nivolumab and ipilimumab if using 600 mg every 2 weeks; or • 6 weeks after the last dose of the combination of IV nivolumab and ipilimumab if using 1200 mg every 4 weeks.
Ipilimumab	3 mg/kg every 3 weeks over 30 minutes	-

Renal cell carcinoma (RCC)

Table 2: Recommended doses and infusion times for OPDIVO solution for infusion in combination with ipilimumab followed by OPDIVO solution for injection monotherapy for RCC

	Combination phase OPDIVO solution for infusion, intravenously (IV) and ipilimumab, for 4 dosing cycles	Monotherapy phase OPDIVO solution for injection, subcutaneously (SC)
Nivolumab	3 mg/kg every 3 weeks over 30 minutes	600 mg every 2 weeks or 1200 mg every 4 weeks The first dose should be administered: • 3 weeks after the last dose of the combination of IV nivolumab and ipilimumab if using 600 mg every 2 weeks; or • 6 weeks after the last dose of the combination of IV nivolumab and ipilimumab if using 1200 mg every 4 weeks.
Ipilimumab	1 mg/kg every 3 weeks over 30 minutes	-

dMMR or MSI-H colorectal cancer (CRC)

Table 3: Recommended doses and infusion times for OPDIVO solution for infusion in combination with ipilimumab followed by OPDIVO solution for injection monotherapy for dMMR or MSI-H CRC

		Combination phase, OPDIVO solution for infusion, intravenously (IV), and ipilimumab for up to 4 dosing cycles	Monotherapy phase OPDIVO solution for injection, subcutaneously (SC)
Nivolumab	First-line treatment	240 mg every 3 weeks over 30 minutes	600 mg every 2 weeks or 1200 mg every 4 weeks The first dose should be administered 3 weeks after the last dose of the combination of IV nivolumab and ipilimumab. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.
	Treatment after prior first-line fluoropyrimidine-based combination chemotherapy	3 mg/kg every 3 weeks over 30 minutes	600 mg every 2 weeks or 1200 mg every 4 weeks The first dose should be administered 3 weeks after the last dose of the combination of IV nivolumab and ipilimumab.
Ipilimumab		1 mg/kg every 3 weeks over 30 minutes	-

Hepatocellular carcinoma (HCC)

Table 4: Recommended doses and infusion times for OPDIVO solution for infusion in combination with ipilimumab followed by OPDIVO solution for injection monotherapy for the treatment of HCC (see sections 5.1 and 5.2)

	Combination phase OPDIVO solution for infusion, intravenously (IV) and ipilimumab for up to 4 dosing cycles	Monotherapy phase* OPDIVO solution for injection, subcutaneously (SC)
Nivolumab	1 mg/kg every 3 weeks over 30 minutes	600 mg every 2 weeks or 1200 mg every 4 weeks The first dose should be administered 3 weeks after the last dose of the combination of IV nivolumab and ipilimumab.
Ipilimumab	3 mg/kg every 3 weeks over 30 minutes	-

*Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months.

OPDIVO in combination with cabozantinib

Renal cell carcinoma (RCC)

Table 5: Recommended doses for OPDIVO solution for injection in combination with cabozantinib for the treatment of RCC

	Combination therapy*
Nivolumab	600 mg every 2 weeks or 1200 mg of every 4 weeks
Cabozantinib	40 mg every day, orally

*For OPDIVO in combination with cabozantinib, OPDIVO should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Cabozantinib should be continued until disease progression or unacceptable toxicity. Refer to the Summary of Product Characteristics (SmPC) for cabozantinib.

OPDIVO in combination with chemotherapy

Oesophageal squamous cell carcinoma (OSCC)

Table 6: Recommended doses for administration of OPDIVO solution for injection in combination with fluoropyrimidine- and platinum-based chemotherapy for the treatment of OSCC (see section 5.1)*

	Combination therapy
Nivolumab	600 mg every 2 weeks or 1200 mg every 4 weeks
Fluoropyrimidine- and platinum-based chemotherapy	Every 4 weeks

*Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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

Table 7: Recommended doses for administration of OPDIVO solution for injection in combination with fluoropyrimidine- and platinum-based chemotherapy for the treatment of gastric, GEJ or oesophageal adenocarcinoma (see section 5.1)*

	Combination therapy
Nivolumab	600 mg every 2 weeks or 900 mg every 3 weeks
Fluoropyrimidine- and platinum-based chemotherapy	Every 2 weeks or every 3 weeks, depending on the nivolumab regimen

*Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Urothelial carcinoma (UC)

Table 8: Recommended doses for OPDIVO solution for injection in combination with cisplatin and gemcitabine followed by OPDIVO monotherapy for UC (see section 5.1)

	Combination phase for up to 6 dosing cycles	Monotherapy phase*
Nivolumab	900 mg every 3 weeks	600 mg every 2 weeks or 1200 mg every 4 weeks
Cisplatin and gemcitabine	Every 3 weeks	-

*Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months from first dose, whichever comes first.

Neoadjuvant treatment of NSCLC

Table 9: Recommended doses for OPDIVO solution for injection in combination with platinum-based chemotherapy for neoadjuvant treatment of NSCLC (see section 5.1)

	Combination therapy for 3 cycles
Nivolumab	900 mg every 3 weeks
Platinum-based chemotherapy	Every 3 weeks

Neoadjuvant and adjuvant treatment of non-small cell lung cancer (NSCLC)

Table 10 Recommended doses for OPDIVO solution for injection in combination with platinum-based chemotherapy for neoadjuvant treatment followed by OPDIVO monotherapy for adjuvant treatment of NSCLC

	Combination phase (neoadjuvant treatment) for 4 cycles	Monotherapy phase* (adjuvant treatment)
Nivolumab	900 mg every 3 weeks	1200 mg every 4 weeks
Platinum-based chemotherapy	Every 3 weeks	-

*Treatment is recommended until disease progression or recurrence, unacceptable toxicity, or up to 13 cycles (see section 5.1).

Duration of treatment

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

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

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

Dose escalation or reduction is not recommended for OPDIVO as monotherapy or in combination with other therapeutic agents. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 10. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4. When nivolumab is administered in combination with other therapeutic agents, refer to the SmPC of these other combination therapeutic agents regarding dosing.

Table 11: Recommended treatment modifications for OPDIVO or OPDIVO in combination

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment

Immune-related adverse reaction	Severity	Treatment modification
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis OPDIVO monotherapy	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	OPDIVO+ipilimumab ^a	Permanently discontinue treatment
Immune-related hepatitis	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
	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
NOTE: for RCC patients treated with OPDIVO in combination with cabozantinib with liver enzyme elevations, see dosing guidelines following this table.	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
	Grade 3 or 4 myocarditis	Permanently discontinue treatment

Immune-related adverse reaction	Severity	Treatment modification
	Grade 3 (first occurrence)	Withhold dose(s)
Other immune-related adverse reactions	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
Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome ^d	Grade 2 Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 3 or 4 Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome	Permanently discontinue treatment

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

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

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

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

^d Presenting as an overlap of either two or all three conditions. The most severe CTCAE grade from the individual events should be considered to assess the recommended treatment modification.

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

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

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

When OPDIVO is administered intravenously 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 intravenous combination treatment or OPDIVO monotherapy administered intravenously or subcutaneously could be resumed based on the evaluation of the individual patient.

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

OPDIVO in combination with cabozantinib in RCC

When OPDIVO is used in combination with cabozantinib, the above treatment modifications in Table 10 also apply to the OPDIVO component. In addition, for liver enzyme elevations, in patients with RCC being treated with OPDIVO in combination with cabozantinib:

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

Special populations

Elderly

No dose adjustment is required for elderly patients (≥ 65 years).

Renal impairment

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

Hepatic impairment

Based on the population PK results for intravenous nivolumab, no dose adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2). Data from patients with severe hepatic impairment are too limited to draw conclusions on this populations. OPDIVO must be administered with caution in patients with severe (total bilirubin $> 3 \times$ ULN and any AST) hepatic impairment.

Paediatric population

The safety and efficacy of OPDIVO solution for injection in children below 18 years of age have not been established.

Method of administration

OPDIVO solution for injection is for subcutaneous use.

It is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and dose is being administered to the patient as prescribed.

OPDIVO solution for injection is not intended for intravenous administration and must be given by subcutaneous injection only using the doses specified. More than one vial of OPDIVO solution for injection may be needed to give the total dose for the patient. For instructions on use and handling of the OPDIVO solution for injection before administration, see section 6.6.

Administer the full contents of the syringe of OPDIVO solution for injection into the subcutaneous tissue of the abdomen or thigh over a period of 3 to 5 minutes. The dose should not be split between two syringes or between two sites of administration. Alternate injection sites for successive injections. Do not inject into areas where the skin is tender, red, or bruised, or areas where there are scars or moles. If the administration of OPDIVO solution for injection is interrupted, it can be resumed at the same site, or at an alternate site.

During the treatment course with OPDIVO solution for injection, other medicinal products for subcutaneous administration should preferably be injected at different sites.

OPDIVO solution for infusion (intravenous formulation)

The Summary of Product Characteristics (SmPC) of OPDIVO concentrate for solution for infusion should be referred to for information on dosing instructions and method of 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

Traceability

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

Assessment of PD-L1 status

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

Assessment of MSI/MMR status

When assessing the MSI-H and dMMR status of the tumour, it is important that a well-validated and robust methodology is used.

Immune-related adverse reactions

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

Immune-related adverse reactions affecting more than one body system can occur simultaneously.

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

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

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

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune-checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

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

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

Immune-related pneumonitis

Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients

should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy infiltrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

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

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

Immune-related colitis

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

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

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

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

Immune-related hepatitis

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

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

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

Immune-related nephritis and renal dysfunction

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

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

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

Immune-related endocrinopathies

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

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

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

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

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

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

Immune-related skin adverse reactions

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

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

Caution should be used when considering the use of nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anti-cancer 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, Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome, rhabdomyolysis, and myelitis. Cases of Vogt-Koyanagi-Harada syndrome, hypoparathyroidism, and cystitis noninfective have been reported post-marketing (see sections 4.2 and 4.8).

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

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued (see section 4.2), and appropriate treatment instituted.

The diagnosis of myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, nivolumab or nivolumab in combination with ipilimumab should be withheld or permanently discontinued (see section 4.2).

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

For Grade 3 or 4 Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued (see section 4.2). Corticosteroids should be initiated as clinically indicated.

For Grade 2 Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids initiated as clinically indicated (see section 4.2). Upon improvement, resumption of nivolumab may be considered after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be adjusted as clinically indicated, and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

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

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

Cases of acute graft-versus-host disease (GVHD) and transplant related mortality (TRM) have been observed from the follow-up of patients with classical Hodgkin lymphoma undergoing allogeneic haematopoietic stem cell transplant (HSCT) after previous exposure to intravenous nivolumab. Careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications should be made case-by-case. In patients treated with intravenous 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.

Infusion reactions (intravenous formulation)

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

Disease-specific precautions

Advanced melanoma

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

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

Use of nivolumab in melanoma patients with rapidly progressing disease

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

Adjuvant treatment of melanoma

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

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

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

Non-small cell lung cancer (NSCLC)

Treatment of NSCLC after prior chemotherapy

Patients with a baseline performance score ≥ 2 , active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of NSCLC (see sections 4.5 and 5.1). Patients with baseline performance score of 2 were included in study CA209171 (see section 5.1). In the absence of data for patients with autoimmune disease, symptomatic interstitial lung disease, active brain metastases and patients who had been receiving systemic immunosuppressants prior to study entry, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

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

Neoadjuvant treatment of NSCLC

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

Neoadjuvant and adjuvant treatment of NSCLC

Patients with a baseline performance score ≥ 2 , Grade 2 or greater peripheral neuropathy, active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, unresectable or metastatic disease, who received prior anti-cancer treatment for resectable disease, who had EGFR mutations or known ALK translocations, or who had brain metastasis, were excluded from the pivotal trial in neoadjuvant and adjuvant treatment of NSCLC (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Renal cell carcinoma (RCC)

Nivolumab or nivolumab in combination with ipilimumab

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

Nivolumab in combination with cabozantinib

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

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

Head and neck cancer

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

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In head and neck cancer, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors

associated with early deaths were ECOG performance status, fast progressive disease on prior platinum therapy and high tumour burden.

Urothelial carcinoma

Treatment of advanced urothelial carcinoma

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

Adjuvant treatment of urothelial carcinoma

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

dMMR or MSI-H colorectal cancer (CRC)

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 trial in dMMR or MSI-H metastatic CRC (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Oesophageal squamous cell carcinoma (OSCC)

First-line treatment of OSCC

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

Treatment of OSCC after prior first-line chemotherapy

The majority of clinical data available in oesophageal squamous cell carcinoma are in patients of Asian origin (see section 5.1).

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

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

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer

Patients with a baseline performance score ≥ 2 , who did not receive concurrent chemoradiotherapy (CRT) prior to surgery, with stage IV resectable disease, active autoimmune disease, or medical

conditions requiring systemic immunosuppression were excluded from the clinical study in oesophageal and gastro-oesophageal junction cancer (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

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

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

Hepatocellular carcinoma (HCC)

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

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

OPDIVO contains polysorbate 80 (E433)

This medicinal product contains 1.25 mg of polysorbate 80 in each 2.5 mL vial and 2.5 mg of polysorbate 80 in each 5 mL vial which is equivalent to 5 mg/10 mL. Polysorbates may cause allergic reactions.

Patient card

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Other forms of interaction

Systemic immunosuppression

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions. The preliminary results show that systemic

immunosuppression after starting nivolumab treatment does not appear to preclude the response on nivolumab.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Nivolumab as monotherapy (see section 4.2)

Summary of the safety profile

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

The safety of nivolumab administered subcutaneously was similar to the known safety profile of the intravenous formulation of nivolumab, with an additional adverse reaction of injection site reaction (7% in the subcutaneous nivolumab arm (n = 247) vs 0% in the intravenous nivolumab arm (n = 245)).

Tabulated summary of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 4646) are presented in Table 12. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$);

uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ 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 12: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Infections and infestations	
Very common	upper respiratory tract infection
Common	pneumonia ^a , bronchitis
Rare	aseptic meningitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Very common	lymphopenia ^b , anaemia ^{b,i} , leucopenia ^b , neutropenia ^{a,b} , thrombocytopenia ^b
Uncommon	eosinophilia
Not known	haemophagocytic lymphohistiocytosis
Immune system disorders	
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity (including anaphylactic reaction)
Uncommon	sarcoidosis
Not known	solid organ transplant rejection ^f
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism, thyroiditis
Uncommon	adrenal insufficiency ^j , hypopituitarism, hypophysitis, diabetes mellitus
Rare	diabetic ketoacidosis, hypoparathyroidism
Metabolism and nutrition disorders	
Very common	decreased appetite, hyperglycaemia ^b
Common	dehydration, weight decreased, hypoglycaemia ^b
Uncommon	metabolic acidosis
Not known	tumour lysis syndrome ^g
Nervous system disorders	
Very common	headache
Common	peripheral neuropathy, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome ⁿ
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis ^{a,k} , optic neuritis
Not known	myelitis (including transverse myelitis)
Eye disorders	
Common	blurred vision, dry eye
Uncommon	uveitis
Not known	Vogt-Koyanagi-Harada syndrome ^f
Cardiac disorders	
Common	tachycardia, atrial fibrillation
Uncommon	myocarditis ^a , pericardial disorders ^h , arrhythmia (including ventricular arrhythmia)
Vascular disorders	
Common	hypertension
Rare	vasculitis

	Nivolumab monotherapy
Respiratory, thoracic and mediastinal disorders	
Very common	dyspnoea ^a , cough
Common	pneumonitis ^a , pleural effusion
Uncommon	lung infiltration
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation
Common	colitis ^a , stomatitis, dry mouth
Uncommon	pancreatitis, gastritis
Rare	duodenal ulcer, pancreatic exocrine insufficiency, coeliac disease
Hepatobiliary disorders	
Uncommon	hepatitis, cholestasis
Skin and subcutaneous tissue disorders	
Very common	rash ^c , pruritus
Common	vitaligo, dry skin, erythema, alopecia
Uncommon	psoriasis, rosacea, erythema multiforme, urticaria
Rare	toxic epidermal necrolysis ^{a, d} , Stevens-Johnson syndrome ^a
Not known	lichen sclerosus ^g , other lichen disorders
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain ^e , arthralgia
Common	arthritis
Uncommon	polymyalgia rheumatica
Rare	Sjögren's syndrome, myopathy, myositis (including polymyositis) ^a , rhabdomyolysis ^{a, d}
Renal and urinary disorders	
Common	renal failure (including acute kidney injury) ^a
Rare	tubulointerstitial nephritis, cystitis noninfective
General disorders and administration site conditions	
Very common	fatigue, pyrexia
Common	pain, chest pain, oedema ^l , injection site reaction ^m
Investigations^b	
Very common	increased AST, hyponatraemia, hypoalbuminaemia, increased alkaline phosphatase, increased creatinine, increased ALT, increased lipase, hyperkalaemia, increased amylase, hypocalcaemia, hypomagnesaemia, hypokalaemia, hypercalcaemia
Common	increased total bilirubin, hypernatraemia, hypermagnesaemia

Adverse reaction frequencies presented in Table 12 may not be fully attributable to nivolumab alone but may contain contributions from the underlying disease.

^a Fatal cases have been reported in completed or ongoing clinical studies.

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

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

^d Reported also in studies outside the pooled dataset. The frequency is based on the programme-wide exposure.

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

^f Post-marketing event (also see section 4.4).

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

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

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

^j Includes adrenal insufficiency, adrenocortical insufficiency acute, and secondary adrenocortical insufficiency.

^k Includes encephalitis and limbic encephalitis.

- ^l Oedema is a composite term which includes generalised oedema, oedema peripheral, peripheral swelling and swelling.
- ^m Reported in a study outside of the pooled dataset (subcutaneous injection related). The frequency is based on exposure to OPDIVO solution for injection in CA20967T and includes injection site erythema, application site pain, injection site oedema, injection site pain, application site erythema, application site rash, injection site discolouration, injection site inflammation, and injection site pruritus.
- ⁿ Cases of Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome (presenting as an overlap of either two or all three conditions), some with fatal outcome, have been reported with nivolumab and nivolumab in combination with other therapeutic agents (see section 4.4).

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

Summary of the safety profile

When nivolumab is administered in combination, refer to the SmPC for the other therapeutic agents for additional information on the safety profile, prior to initiation of treatment.

Nivolumab in combination with ipilimumab (with or without chemotherapy)

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

Nivolumab in combination with chemotherapy

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

Nivolumab in combination with cabozantinib

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

(10.0%). The incidence of Grade 3-5 adverse reactions was 78%, with 0.3% fatal adverse reactions attributed to study drug.

Tabulated summary of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy) (n = 2626), nivolumab in combination with chemotherapy (n = 1800), and nivolumab in combination with cabozantinib (n = 320) are presented in Table 13. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\,000$ to $< 1/100$); rare ($\geq 1/10\,000$ to $< 1/1\,000$), 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 13: Adverse reactions with nivolumab in combination with other therapeutic agents

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Infections and infestations			
Very common	upper respiratory tract infection		upper respiratory tract infection
Common	pneumonia, bronchitis, conjunctivitis	upper respiratory tract infection, pneumonia ^a	pneumonia
Rare	aseptic meningitis		
Blood and lymphatic system disorders			
Very common	anaemia ^{b,j} , thrombocytopenia ^b , leucopenia ^b , lymphopenia ^b , neutropenia ^b	neutropenia ^b , anaemia ^{b,j} , leucopenia ^b , lymphopenia ^b , thrombocytopenia ^b	anaemia ^b , thrombocytopenia ^b , leucopenia ^b , lymphopenia ^b , neutropenia ^b
Common	eosinophilia	febrile neutropaenia ^a	eosinophilia
Uncommon	febrile neutropaenia	eosinophilia	
Not known	haemophagocytic lymphohistiocytosis		
Immune system disorders			
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity	hypersensitivity, infusion related reaction (including cytokine release syndrome)	hypersensitivity (including anaphylactic reaction)
Uncommon			infusion related hypersensitivity reaction
Rare	sarcoidosis		
Not known	solid organ transplant rejection ^g		

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Endocrine disorders			
Very common	hypothyroidism		hypothyroidism, hyperthyroidism
Common	hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, hypopituitarism, diabetes mellitus	hypothyroidism, hyperthyroidism, diabetes mellitus	adrenal insufficiency
Uncommon	diabetic ketoacidosis	adrenal insufficiency, thyroiditis, hypopituitarism, hypophysitis	hypophysitis, thyroiditis
Rare	hypoparathyroidism		
Metabolism and nutrition disorders			
Very common	decreased appetite, hyperglycaemia ^b , hypoglycaemia ^b	decreased appetite, hyperglycaemia ^b , hypoglycaemia ^b	decreased appetite, hypoglycaemia ^b , hyperglycaemia ^b , weight decreased
Common	dehydration, hypoalbuminaemia, hypophosphataemia, weight decreased	hypoalbuminaemia, hypophosphataemia,	dehydration
Uncommon	metabolic acidosis		
Rare		tumour lysis syndrome	
Not known	tumour lysis syndrome ^h		
Nervous system disorders			
Very common	headache	peripheral neuropathy	dysgeusia, dizziness, headache
Common	dizziness, peripheral neuropathy	paraesthesia, dizziness, headache	peripheral neuropathy
Uncommon	polyneuropathy, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis, myasthenia gravis, Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome ^l	Guillain-Barré syndrome	encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Rare	Guillain-Barré syndrome, neuritis, myelitis (including transverse myelitis), optic neuritis	encephalitis, Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome ^l	
Not known		myelitis (including transverse myelitis), optic neuritis	Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome ^l
Ear and labyrinth disorders			
Common			tinnitus

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Eye disorders			
Common	blurred vision, dry eye	dry eye, blurred vision	dry eye, blurred vision
Uncommon	uveitis, episcleritis	uveitis	uveitis
Rare	Vogt-Koyanagi-Harada syndrome		
Cardiac disorders			
Common	tachycardia, atrial fibrillation	tachycardia, atrial fibrillation	atrial fibrillation, tachycardia
Uncommon	myocarditis ^a , arrhythmia (including ventricular arrhythmia) ^a , bradycardia	myocarditis	myocarditis
Not known	pericardial disorders ⁱ		
Vascular disorders			
Very common			hypertension
Common	hypertension	thrombosis ^{a, k} , hypertension, vasculitis	thrombosis ^k
Respiratory, thoracic and mediastinal disorders			
Very common	cough, dyspnoea	cough	dysphonia, dyspnoea, cough
Common	pneumonitis ^a , pulmonary embolism ^a , pleural effusion	pneumonitis ^a , dyspnoea	pneumonitis, pulmonary embolism, pleural effusion, epistaxis
Gastrointestinal disorders			
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation	diarrhoea ^a , stomatitis, vomiting, nausea, abdominal pain, constipation	diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia
Common	colitis ^a , pancreatitis, stomatitis, gastritis, dry mouth	colitis, dry mouth	colitis, gastritis, oral pain, dry mouth, haemorrhoids
Uncommon	duodenitis	pancreatitis	pancreatitis, small intestine perforation ^a , glossodynia
Rare	intestinal perforation ^a , pancreatic exocrine insufficiency, coeliac disease		
Not known		pancreatic exocrine insufficiency, coeliac disease	pancreatic exocrine insufficiency, coeliac disease
Hepatobiliary disorders			
Common	hepatitis		hepatitis
Uncommon		hepatitis	

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Skin and subcutaneous tissue disorders			
Very common	rash ^c , pruritus	rash ^c , pruritus	palmar-plantar erythrodysesthesia syndrome, rash ^c , pruritus
Common	alopecia, vitiligo, urticaria, dry skin, erythema	palmar-plantar erythrodysesthesia syndrome, skin hyperpigmentation, alopecia, dry skin, erythema	alopecia, dry skin, erythema, hair colour change
Uncommon	Stevens-Johnson syndrome, erythema multiforme, psoriasis, other lichen disorders ^d		psoriasis, urticaria
Rare	toxic epidermal necrolysis ^{a,e} , lichen sclerosus		
Not known			lichen sclerosus, other lichen disorders
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain ^f , arthralgia	musculoskeletal pain ^f	musculoskeletal pain ^f , arthralgia, muscle spasm
Common	muscle spasms, muscular weakness, arthritis	arthralgia, muscular weakness	arthritis
Uncommon	polymyalgia rheumatica, myopathy, myositis (including polymyositis) ^a		myopathy, osteonecrosis of the jaw, fistula
Rare	spondyloarthropathy, Sjögren's syndrome, rhabdomyolysis ^a		
Renal and urinary disorders			
Very common			proteinuria
Common	renal failure (including acute kidney injury) ^a	renal failure ^a	renal failure, acute kidney injury
Uncommon	tubulointerstitial nephritis, nephritis	cystitis noninfective, nephritis	nephritis
Rare	cystitis noninfective		cystitis noninfective ^h
General disorders and administration site conditions			
Very common	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema
Common	chest pain, pain, chills	malaise	pain, chest pain

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Investigations			
Very common	increased alkaline phosphatase ^b , increased AST ^b , increased ALT ^b , increased total bilirubin ^b , increased creatinine ^b , increased amylase ^b , increased lipase ^b , hyponatraemia ^b , hyperkalaemia ^b , hypokalaemia ^b , hypercalcaemia ^b , hypocalcaemia ^b , hypomagnesaemia ^b	hypocalcaemia ^b , increased AST ^b , increased ALT ^b , hyponatraemia ^b , increased amylase ^b , hypomagnesaemia ^b , increased alkaline phosphatase ^b , hypokalaemia ^b , increased creatinine ^b , increased lipase ^b , hyperkalaemia ^b , increased total bilirubin ^b	increased alkaline phosphatase ^b , increased ALT ^b , increased AST ^b , increased total bilirubin ^b , increased creatinine ^b , increased amylase ^b , increased lipase ^b , hypokalaemia ^b , hypomagnesaemia ^b , hyponatraemia ^b , hypocalcaemia ^b , hypercalcaemia ^b , hypophosphataemia ^b , hyperkalaemia ^b , hypermagnesaemia ^b , hypernatraemia ^b
Common	hypernatraemia ^b , hypermagnesaemia ^b , increased thyroid stimulating hormone, increased gamma-glutamyltransferase	hypernatraemia ^b , hypercalcaemia ^b , hypermagnesaemia ^b	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 13 may not be fully attributable to nivolumab alone or in combination with other therapeutic agents, but may contain contributions from the underlying disease or from medicinal product used in combination.

^a Fatal cases have been reported in completed or ongoing clinical studies.

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

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

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

^e Reported also in studies outside the pooled dataset. The frequency is based on the programme-wide exposure.

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

^g Post-marketing event (also see section 4.4).

^h Reported in clinical studies and in the post-marketing setting.

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

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

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

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

Description of selected adverse reactions

Nivolumab or nivolumab in combination with other therapeutic agents is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment generally was required in a greater proportion of patients receiving nivolumab in combination with other agents than in those receiving nivolumab monotherapy. Table 14 presents the percentage of patients with immune-related adverse reactions who were permanently discontinued from treatment by dosing regimen. Additionally, for patients who experienced an event, Table 14 presents the percentage of patients who

required high-dose corticosteroids (at least 40 mg daily prednisone equivalents) by dosing regimen. The management guidelines for these adverse reactions are described in section 4.4.

Table 14: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab monotherapy, nivolumab in combination with ipilimumab (with or without chemotherapy), nivolumab in combination with chemotherapy, or nivolumab in combination with cabozantinib)

	Nivolumab monotherapy %	Nivolumab in combination with ipilimumab (with or without chemotherapy) %	Nivolumab in combination with chemotherapy %	Nivolumab in combination with cabozantinib %
Immune-related adverse reaction leading to permanent discontinuation				
Pneumonitis	1.4	2.1	2.0	2.5
Colitis	1.2	6	1.8	2.5
Hepatitis	1.1	5	0.7	4.1
Nephritis and renal dysfunction	0.3	1.1	3.1	0.6
Endocrinopathies	0.5	2.2	0.6	1.3
Skin	0.8	1.0	0.9	2.2
Hypersensitivity/Infusion reaction	0.1	0.3	1.7	0
Immune-related adverse reaction requiring high-dose corticosteroids^{a,b}				
Pneumonitis	65	59	59	56
Colitis	14	32	9	8
Hepatitis	21	39	7	23
Nephritis and renal dysfunction	22	27	9	9
Endocrinopathies	5	18	4.3	4.2
Skin	3.3	8	6	8
Hypersensitivity/Infusion reaction	18	18	22	0

^a at least 40 mg daily prednisone equivalents

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

Immune-related pneumonitis

In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.3% (155/4646). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (42/4646) and 1.7% (77/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (33/4646) and < 0.1% (1/4646) of patients respectively. Six patients (0.1%) had a fatal outcome. Median time to onset was 15.1 weeks (range: 0.7-85.1). Resolution occurred in 107 patients (69.0%) with a median time to resolution of 6.7 weeks (range: 0.1⁺-109.1⁺); ⁺ denotes a censored observation.

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

In patients treated with nivolumab in combination with chemotherapy, the incidence of pneumonitis including interstitial lung disease was 4.4% (80/1800). Grade 2, Grade 3, and Grade 4 cases were

reported in 2.2% (40/1800), 0.9% (17/1800), and 0.2% (3/1800), of patients, respectively. Three patients (0.2%) had a fatal outcome. Median time to onset was 24.6 weeks (range: 0.6-96.9). Resolution occurred in 58 patients (72.5%) with a median time to resolution of 10.4 weeks (range: 0.3⁺-171.4⁺).

In patients treated with nivolumab in combination with cabozantinib, the incidence of pneumonitis including interstitial lung disease was 5.6% (18/320). Grade 2 and Grade 3 cases were reported in 1.9% (6/320) and 1.6% (5/320) of patients, respectively. Median time to onset was 26.9 weeks (range: 12.3-74.3 weeks). Resolution occurred in 14 patients (77.8%) with a median time to resolution of 7.5 weeks (range: 2.1-60.7⁺ weeks).

Immune-related colitis

In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 15.4% (716/4646). The majority of cases were Grade 1 or 2 in severity reported in 9.9% (462/4646) and 4.0% (186/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.4% (67/4646) and < 0.1% (1/4646) of patients respectively. Median time to onset was 8.3 weeks (range: 0.1-115.6). Resolution occurred in 639 patients (90.3%) with a median time to resolution of 2.9 weeks (range: 0.1-124.4⁺).

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

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

In patients treated with nivolumab in combination with cabozantinib, the incidence of diarrhoea, colitis, frequent bowel movements or enteritis was 59.1% (189/320). Grade 2 and Grade 3 cases were reported in 25.6% (82/320) and 6.3% (20/320) of patients, respectively. Grade 4 were reported in 0.6% (2/320). Median time to onset was 12.9 weeks (range: 0.3-110.9 weeks). Resolution occurred in 143 patients (76.1%) with a median time to resolution of 12.9 weeks (range: 0.1-139.7⁺ weeks).

Immune-related hepatitis

In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 8.0% (371/4646). The majority of cases were Grade 1 or 2 in severity reported in 4.3% (200/4646) and 1.8% (82/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.6% (74/4646) and 0.3% (15/4646) of patients, respectively. Median time to onset was 10.6 weeks (range: 0.1-132.0). Resolution occurred in 298 patients (81.4%) with a median time to resolution of 6.1 weeks (range: 0.1-126.4⁺).

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

nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for HCC, the incidence of liver function test abnormalities was 34.3% including Grade 2 (8.4%), Grade 3 (14.2%), and Grade 4 (2.7%).

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

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

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.6% (121/4646). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (69/4646) and 0.7% (32/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (18/4646) and < 0.1% (2/4646) of patients, respectively. Median time to onset was 12.1 weeks (range: 0.1-79.1). Resolution occurred in 80 patients (69.0%) with a median time to resolution of 8.0 weeks (range: 0.3-79.1⁺).

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

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

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

Immune-related endocrinopathies

In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 13.0% (603/4646). The majority of cases were Grade 1 or 2 in severity reported in 6.6% (305/4646) and 6.2% (290/4646) of patients, respectively. Grade 3 thyroid disorders were reported in 0.2% (8/4646) of patients. Hypophysitis (3 Grade 1, 7 Grade 2, 9 Grade 3, and 1 Grade 4), hypopituitarism (6 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute and blood corticotrophin decreased) (2 Grade 1, 23 Grade 2, and 11 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) (1 Grade 1, 3 Grade 2 and 8 Grade 3 and 2 Grade 4), were reported. Median time to onset of these endocrinopathies was 11.1 weeks (range: 0.1-126.7). Resolution occurred in 323 patients (48.7%). Median time to resolution was 48.6 weeks (range: 0.4-204.4⁺).

In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of thyroid disorders was 23.2% (608/2626). Grade 2 and Grade 3 thyroid disorders were

reported in 12.7% (333/2626) and 1.0% (27/2626) of patients, respectively. Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 1.9% (49/2626) and 1.5% (40/2626) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.6% (16/2626) and 0.5% (13/2626) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute, blood corticotrophin decreased and immune-mediated adrenal insufficiency) occurred in 2.7% (72/2626), 1.6% (43/2626) and 0.2% (4/2626) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) occurred in < 0.1% (1/2626), 0.3% (8/2626), 0.3% (7/2626), and 0.2% (6/2626) of patients, respectively. Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-28.1). Resolution occurred in 297 patients (40.0%). Time to resolution ranged from 0.3 to 257.1⁺ weeks.

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

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

Immune-related skin adverse reactions

In patients treated with nivolumab monotherapy, the incidence of rash was 30.0% (1396/4646). The majority of cases were Grade 1 in severity reported in 22.8% (1060/4646) of patients. Grade 2 and Grade 3 cases were reported in 5.9% (274/4646) and 1.3% (62/4646) of patients respectively. Median time to onset was 6.7 weeks (range: 0.1-121.1). Resolution occurred in 896 patients (64.6%) with a median time to resolution of 20.1 weeks (0.1-192.7⁺).

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

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

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

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

Infusion reactions (intravenous formulation)

In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 4.0% (188/4646), including 9 Grade 3 and 3 Grade 4 cases.

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

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

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

Elevated liver enzymes when nivolumab is combined with cabozantinib in RCC

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

Laboratory abnormalities

In patients treated with nivolumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.4% for anaemia (all Grade 3), 0.7% for thrombocytopenia, 0.7% for leucopenia, 8.7% for lymphopenia, 0.9% for neutropenia, 1.7% for increased alkaline phosphatase, 2.6% for increased AST, 2.3% for increased ALT, 0.8% for increased total bilirubin, 0.7% for increased creatinine, 2.0% for hyperglycaemia, 0.7% for hypoglycaemia, 3.8% for increased amylase, 6.9% for increased lipase, 4.7% for hyponatraemia, 1.6% for hyperkalaemia, 1.3% for hypokalaemia, 1.1% for hypercalcaemia, 0.6% for hypermagnesaemia, 0.4% for hypomagnesaemia, 0.6% for hypocalcaemia, 0.6% for hypoalbuminaemia, and < 0.1% for hypernatraemia.

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

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

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

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

Immunogenicity

Subcutaneous formulation

Of the 202 patients who were treated with nivolumab solution for injection and evaluable for the presence of anti-nivolumab antibodies, approximately 23% (46/202) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 1% (2/202) had neutralizing antibodies against nivolumab. The incidence of treatment-emergent anti-recombinant human hyaluronidase PH20 (anti-rHuPH20) antibodies in patients treated with nivolumab solution for injection was 8.8% (19/215).

Intravenous formulation

Of the 3529 patients who were treated with nivolumab monotherapy 3 mg/kg or 240 mg every 2 weeks and evaluable for the presence of anti-product-antibodies, 328 patients (9.3%) tested positive for treatment-emergent anti-product-antibodies with 21 patients (0.6%) testing positive for neutralising antibodies.

Co-administration with chemotherapy did not affect nivolumab immunogenicity. Of the 1407 patients who were treated with nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of anti-product-antibodies, 7.2% tested positive for treatment emergent anti-product-antibodies with 0.5% tested positive for neutralising antibodies.

Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26.0% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 24.9% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralising antibodies against nivolumab was 0.8% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 1.5% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 13.7% and neutralising antibodies against ipilimumab ranged from 0 to 0.4%.

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

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

Elderly

No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from SCCHN, adjuvant melanoma, and adjuvant OC or GEJC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). Data from dMMR or MSI-H CRC patients 75 years of age or older are limited (see section 5.1). In HCC patients there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (67% and 35%, respectively) relative to all patients who received nivolumab with ipilimumab (53% and 27%, respectively).

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

Hepatic or renal impairment

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

Reporting of suspected adverse reactions

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

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PDL-1 (Programmed cell death protein 1/ death ligand 1) inhibitors. ATC code: L01FF01.

OPDIVO solution for injection contains the active substance nivolumab, which provides the therapeutic effect of this medicinal product, and recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-formulated substances when administered subcutaneously.

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

Subcutaneous formulation

Results from a simulation-based pharmacokinetic bridging analyses showed that across all solid tumour types evaluated, subcutaneous nivolumab dosing regimens (600 mg every 2 weeks and 1200 mg every 4 weeks) produced exposures that were noninferior (geometric mean ratio > 1) to those for the approved intravenous nivolumab dosing regimens (240 mg every 2 weeks and 480 mg every 4 weeks). Geometric mean exposures were also below those for intravenous nivolumab 10 mg/kg Q2W, a regimen shown to be safe in clinical studies.

The subcutaneous nivolumab clinical safety profile was comparable to intravenous nivolumab.

Melanoma

Adjuvant treatment of melanoma

Intravenous formulation

Randomised phase 3 study of nivolumab vs. placebo (CA20976K)

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

A total of 790 patients were randomised (2:1) to receive either nivolumab (n = 526) administered intravenously over 30 minutes at 480 mg every 4 weeks or placebo (n = 264) for up to 1 year or until disease recurrence or unacceptable toxicity. Randomisation was stratified by AJCC 8th edition T-category (T3b vs. T4a vs. T4b). Tumour assessments were conducted every 26 weeks during years 1-3 and every 52 weeks from 3 years to 5 years. The primary efficacy outcome measure was

recurrence-free survival (RFS). RFS, assessed by the investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first. The secondary outcome measures included OS and distant metastasis-free survival (DMFS).

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

At a primary pre-specified interim analysis (minimum follow-up 7.8 months) a statistically significant improvement in RFS was demonstrated with nivolumab compared to placebo with a HR of 0.42 (95% CI: 0.30, 0.59; $p < 0.0001$). At an updated descriptive RFS analysis (minimum follow-up of 15.6 months), nivolumab continued to demonstrate an RFS improvement with a HR of 0.53 (95% CI: 0.40, 0.71). OS was not mature. At an additional RFS descriptive analysis (minimum follow-up 26.9 months), nivolumab continued to demonstrate an RFS improvement with a HR of 0.62 (95% CI: 0.47-0.80). The median follow-up was 34.25 months for the nivolumab arm and 33.92 months for the placebo arm. The outcomes were consistent with the formal interim analysis. Results reported from the analyses with minimum follow-up of 15.6 months are summarised in Table 15 and Figure 1.

Table 15: Efficacy results (CA20976K)

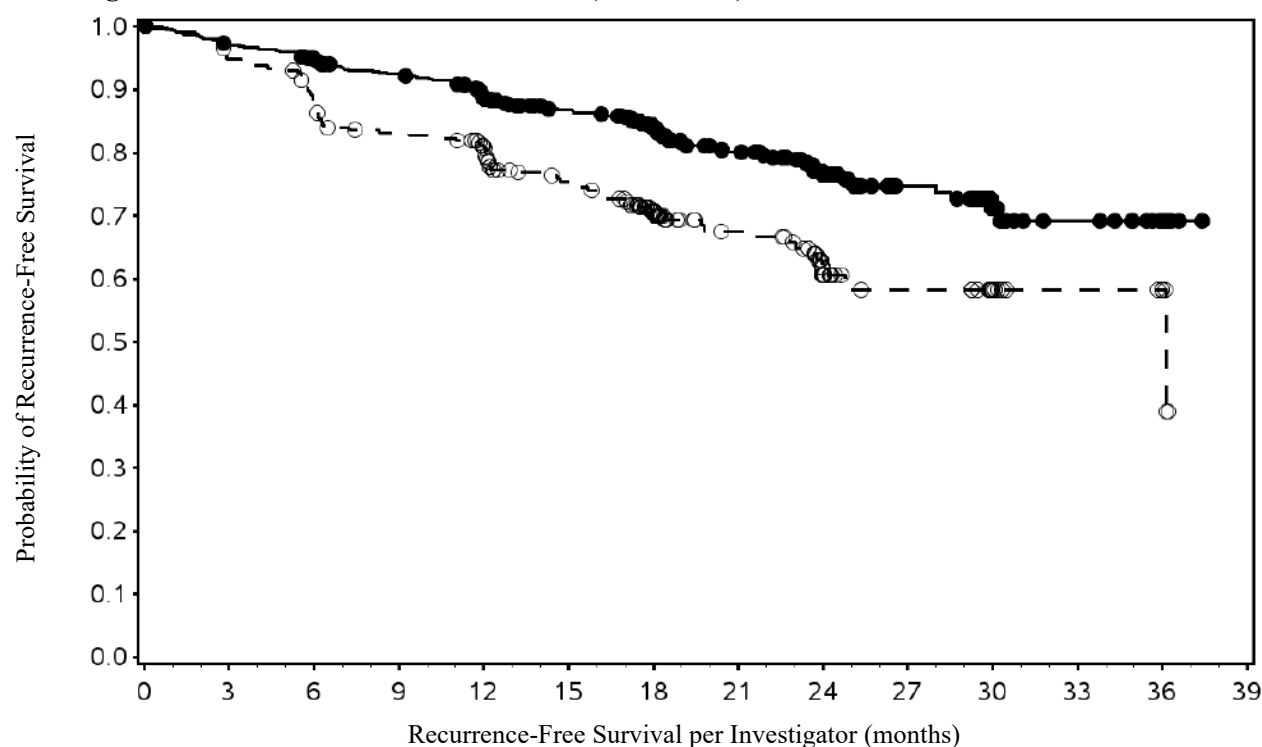
	nivolumab (n = 526)	placebo (n = 264)
Recurrence-free survival with minimum follow-up 15.6 months		
Recurrence-free survival		
Events	102 (19.4%)	84 (31.8%)
Hazard ratio ^a		0.53
95% CI		(0.40, 0.71)
Median (95% CI) months	NR	36.14 (24.77, NR)
Rate (95% CI) at 12 months ^b	88.8 (85.6, 91.2)	81.1 (75.7,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

^a Based on stratified Cox proportional hazard model.

^b Based on Kaplan-Meier estimates.

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

Figure 1: Recurrence-free survival (CA20976K)



Number of subjects at risk

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

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

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

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

Intravenous formulation

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

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study (CA209238). The study included adult patients, who had an ECOG performance status score of 0 or 1, with Stage IIIB/C or Stage IV American Joint Committee on Cancer (AJCC), 7th edition, histologically confirmed melanoma that is completely surgically resected. Per the AJCC 8th edition, this corresponds to patients with lymph node involvement or metastases. Patients were enrolled regardless of their tumour PD-L1 status. Patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥ 6 months prior to randomisation) prior therapy with, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways), were excluded from the study.

A total of 906 patients were randomised to receive either nivolumab 3 mg/kg (n = 453) administered every 2 weeks or ipilimumab 10 mg/kg (n = 453) administered every 3 weeks for 4 doses then every 12 weeks beginning at week 24 for up to 1 year. Randomisation was stratified by tumour PD-L1 expression ($\geq 5\%$ 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 $\geq 5\%$ 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.

At a primary pre-specified interim analysis (minimum follow-up 18 months) a statistically significant improvement in RFS with nivolumab compared to ipilimumab with HR of 0.65 (97.56% CI: 0.51, 0.83; stratified log-rank $p < 0.0001$) was demonstrated. At an updated descriptive RFS analysis, with minimum follow-up of 24 months RFS improvement was confirmed with HR of 0.66 (95% CI: 0.54, 0.81; $p < 0.0001$) and OS was not mature. Efficacy results with minimum follow-up of 36 months (RFS pre-specified final analysis) and 48 months (OS pre-specified final analysis) are shown in Table 16 and Figures 2 and 3 (all randomised population).

Table 16: Efficacy results (CA209238)

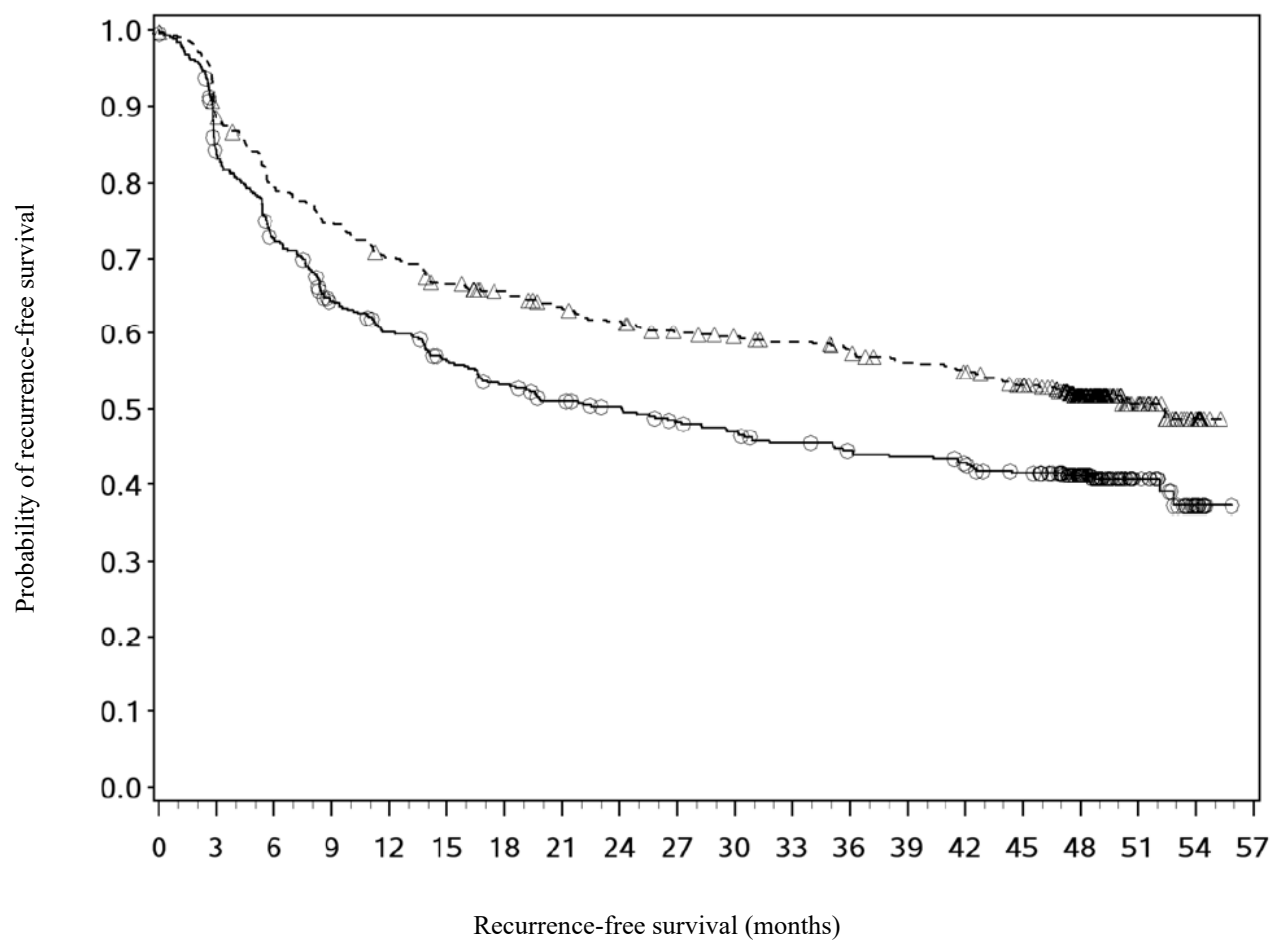
	nivolumab (n = 453)	ipilimumab 10 mg/kg (n = 453)
Final pre-specified analysis		
Recurrence-free survival with minimum follow-up 36 months		
Events	188 (41.5%)	239 (52.8%)
Hazard ratio ^a		0.68
95% CI		(0.56, 0.82)
p-value		$p < 0.0001$
Median (95% CI) months	NR (38.67, NR)	24.87 (16.62, 35.12)
Recurrence-free survival with minimum follow-up 48 months		
Events	212 (46.8%)	253 (55.8%)
Hazard ratio ^a		0.71
95% CI		(0.60, 0.86)
Median (95% CI) months	52.37 (42.51, NR)	24.08 (16.56, 35.09)
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)
Rate (95% CI) at 36 months	57.6 (52.8, 62.1)	44.4 (39.6, 49.1)
Rate (95% CI) at 48 months	51.7 (46.8, 56.3)	41.2 (36.4, 45.9)

	nivolumab (n = 453)	ipilimumab 10 mg/kg (n = 453)
Final pre-specified analysis		
Overall survival with minimum follow-up 48 months		
Events	100 (22.1%)	111 (24.5%)
Hazard ratio ^a		0.87
95.03% CI		(0.66, 1.14)
p-value		0.3148
Median (95% CI) months	Not Reached	Not Reached
Rate (95% CI) at 12 months	96.2 (93.9, 97.6)	95.3 (92.8, 96.9)
Rate (95% CI) at 18 months	91.9 (88.9, 94.1)	91.8 (88.8, 94.0)
Rate (95% CI) at 24 months	88.0 (84.6, 90.7)	87.8 (84.4, 90.6)
Rate (95% CI) at 36 months	81.7 (77.8, 85.1)	81.6 (77.6, 85.0)
Rate (95% CI) at 48 months	77.9 (73.7, 81.5)	76.6 (72.2, 80.3)

^a Derived from a stratified proportional hazards model.

With a minimum follow-up of 36 months, 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. With a minimum follow up of 48 months, shown in Figure 2, the trial continued to demonstrate improvement in RFS in the nivolumab arm compared with the ipilimumab arm. RFS benefit was sustained across all subgroups.

Figure 2: Recurrence-free survival (CA209238)



Number of subjects at risk

Nivolumab

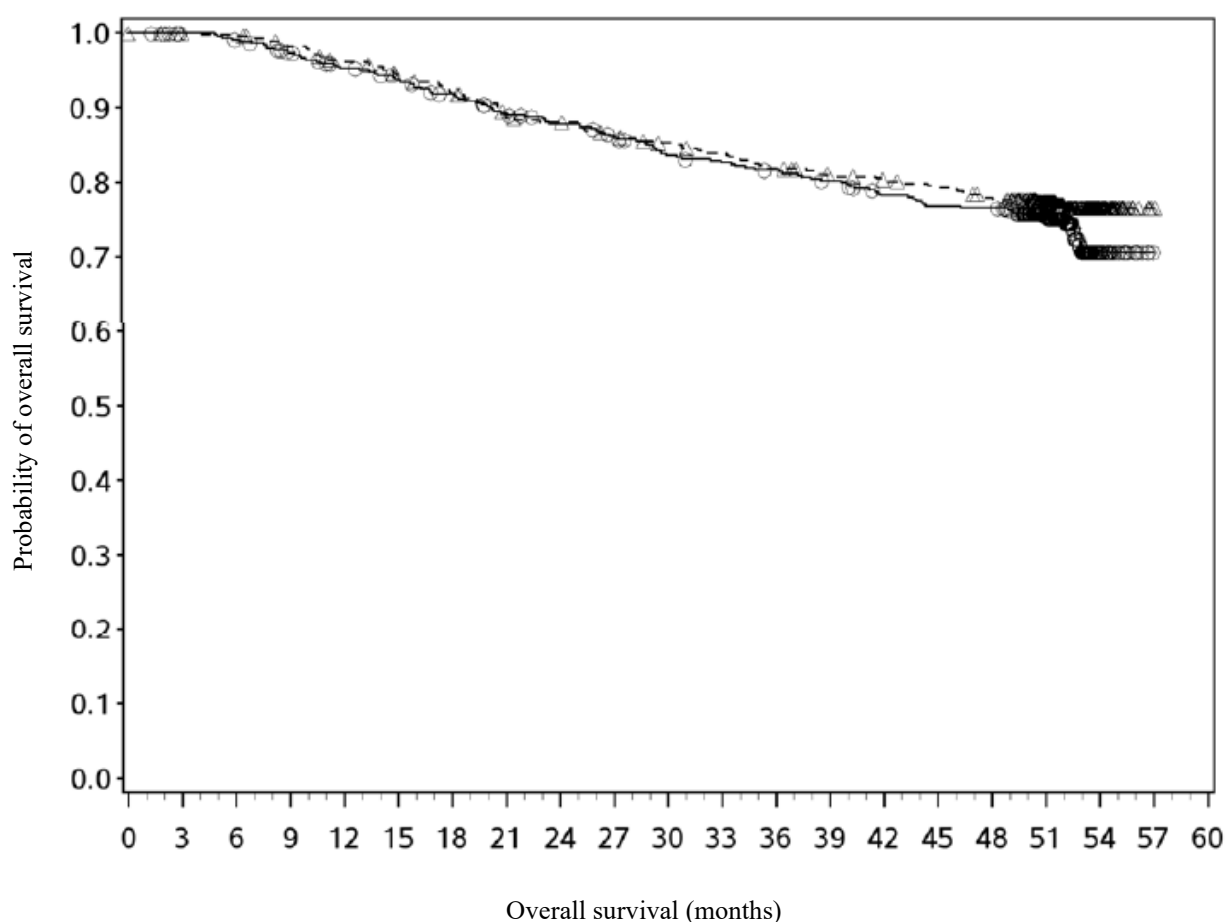
453 395 354 332 311 293 283 271 262 250 245 240 233 224 218 206 147 37 11 0

Ipilimumab

453 366 316 273 253 234 220 208 201 191 185 177 171 168 163 154 113 32 10 0

---△--- Nivolumab ---○--- Ipilimumab

Figure 3: Overall survival (CA209238)



Number of subjects at risk

Nivolumab																				
453	450	447	438	427	416	405	388	383	373	366	359	350	341	337	332	324	237	45	1	0
Ipilimumab																				
453	447	442	430	416	407	395	382	373	363	350	345	340	333	322	316	315	218	40	0	0

---△--- Nivolumab ---○--- Ipilimumab

With a minimum follow-up of 48 months, shown in Figure 3, median OS was not reached in either group (HR = 0.87, 95.03% CI: 0.66, 1.14; p-value: 0.3148). The overall survival data are confounded by the effects of effective subsequent anti-cancer therapies. Subsequent systemic therapy was received by 33% and 42% of patients in the nivolumab and ipilimumab arms, respectively. Subsequent immunotherapy (including anti-PD1 therapy, anti-CTLA-4 antibody, or other immunotherapy) was received by 23% and 34% of patients in the nivolumab and ipilimumab arms, respectively.

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 Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EQ-5D utility index and visual analog scale (VAS).

Treatment of advanced melanoma

Intravenous formulation

Randomised phase 3 study vs. dacarbazine (CA209066)

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

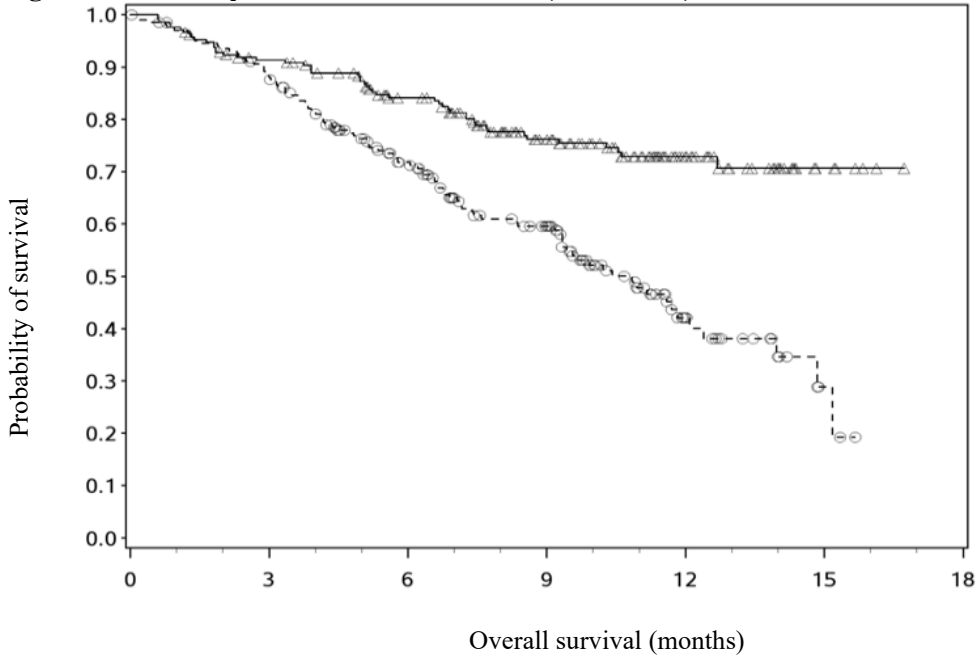
autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

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 1 000 mg/m² every 3 weeks. Randomisation was stratified by tumour PD-L1 status and M stage (M0/M1a/M1b versus M1c). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse events with the study drug, as determined by the investigator. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and objective response rate (ORR).

Baseline characteristics were balanced between the two groups. The median age was 65 years (range: 18-87), 59% were men, and 99.5% were white. Most patients had ECOG performance score of 0 (64%) or 1 (34%). Sixty-one percent of patients had M1c stage disease at study entry. Seventy-four percent of patients had cutaneous melanoma, and 11% had mucosal melanoma; 35% of patients had PD-L1 positive melanoma (≥ 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 4.

Figure 4: Kaplan-Meier curves of OS (CA209066)



Number of subjects at risk						
Nivolumab						
210	185	150	105	45	8	0
Dacarbazine						
208	177	123	82	22	3	0

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

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

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

Efficacy results are shown in Table 17.

Table 17: Efficacy results (CA209066)

	nivolumab (n = 210)	dacarbazine (n = 208)
Overall survival		
Events	50 (23.8%)	96 (46.2%)
Hazard ratio		0.42
99.79% CI		(0.25, 0.73)
95% CI		(0.30, 0.60)
p-value		< 0.0001
Median (95% CI)	Not reached	10.8 (9.33, 12.09)
Rate (95% CI)		
At 6 months	84.1 (78.3, 88.5)	71.8 (64.9, 77.6)
At 12 months	72.9 (65.5, 78.9)	42.1 (33.0, 50.9)
Progression-free survival		
Events	108 (51.4%)	163 (78.4%)
Hazard ratio		0.43
95% CI		(0.34, 0.56)
p-value		< 0.0001
Median (95% CI)	5.1 (3.48, 10.81)	2.2 (2.10, 2.40)
Rate (95% CI)		
At 6 months	48.0 (40.8, 54.9)	18.5 (13.1, 24.6)
At 12 months	41.8 (34.0, 49.3)	N.A.
Objective response		
(95% CI)	84 (40.0%) (33.3, 47.0)	29 (13.9%) (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.

Intravenous formulation

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/m² every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m² every 3 weeks). Randomisation was stratified by BRAF and tumour PD-L1 status and best response to prior ipilimumab.

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

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

At the time of this final ORR analysis, results from 120 nivolumab-treated patients and 47 chemotherapy-treated patients who had a minimum of 6 months of follow-up were analysed. Efficacy results are presented in Table 18.

Table 18: Best overall response, time and duration of response (CA209037)

	nivolumab (n = 120)	chemotherapy (n = 47)
Confirmed objective response (IRRC) (95% CI)	38 (31.7%) (23.5, 40.8)	5 (10.6%) (3.5, 23.1)
Complete response (CR)	4 (3.3%)	0
Partial response (PR)	34 (28.3%)	5 (10.6%)
Stable disease (SD)	28 (23.3%)	16 (34.0%)
Median duration of response		
Months (range)	Not reached	3.6 (Not available)
Median time to response		
Months (range)	2.1 (1.6-7.4)	3.5 (2.1-6.1)

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

Updated analysis (24-month follow-up)

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

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

Efficacy by BRAF status: Objective responses to nivolumab (according to the definition of the co-primary endpoint) were observed in patients with or without BRAF mutation-positive melanoma. The ORRs in the BRAF mutation-positive subgroup were 17% (95% CI: 8.4, 29.0) for nivolumab and 11% (95% CI: 2.4, 29.2) for chemotherapy, and in the BRAF wild-type subgroup were 30% (95% CI: 24.0, 36.7) and 9% (95% CI: 4.6, 16.7), respectively.

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

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

In patients with tumour PD-L1 expression $\geq 1\%$, 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 $\geq 1\%$ 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 $\geq 1\%$ 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.

Intravenous formulation

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).

Intravenous formulation

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 1 008 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 19 below.

Table 19: 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	161/588	4/61	4/20	20/73	3/16	13/46
(%) ^a	(27.4)	(6.6)	(20.0)	(27.4)	(18.8)	(28.3)

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

Intravenous formulation

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 anti-cancer therapy for unresectable or metastatic melanoma were enrolled. Prior adjuvant or neoadjuvant therapy was allowed if it was completed at least 6 weeks prior to randomisation. Patients with active autoimmune disease, ocular/uveal melanoma, or active brain or leptomeningeal metastases were excluded from the study.

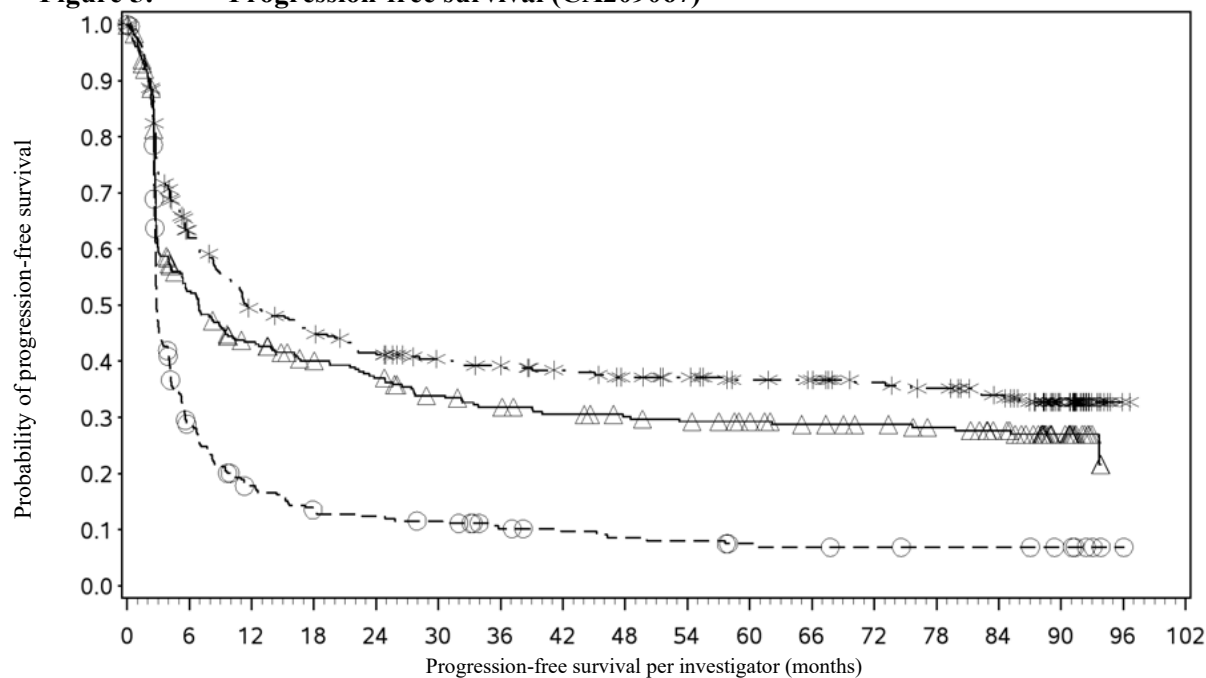
A total of 945 patients were randomised to receive nivolumab in combination with ipilimumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously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

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

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

PFS results from descriptive analysis (with minimum follow up of 90 months) are shown in Figure 5 (all randomised population), Figure 6 (at the tumour PD-L1 5% cut off), and Figure 7 (at the tumour PD-L1 1% cut off).

Figure 5: Progression-free survival (CA209067)



Number of subjects at risk

Nivolumab + ipilimumab																			
314	175	138	126	112	103	99	93	87	84	78	76	70	66	57	33	1	-		
Nivolumab																			
316	151	120	106	97	84	78	73	69	66	62	57	54	50	44	21	0	-		
Ipilimumab																			
315	78	46	34	31	28	21	18	16	15	12	11	10	9	9	7	1	-		

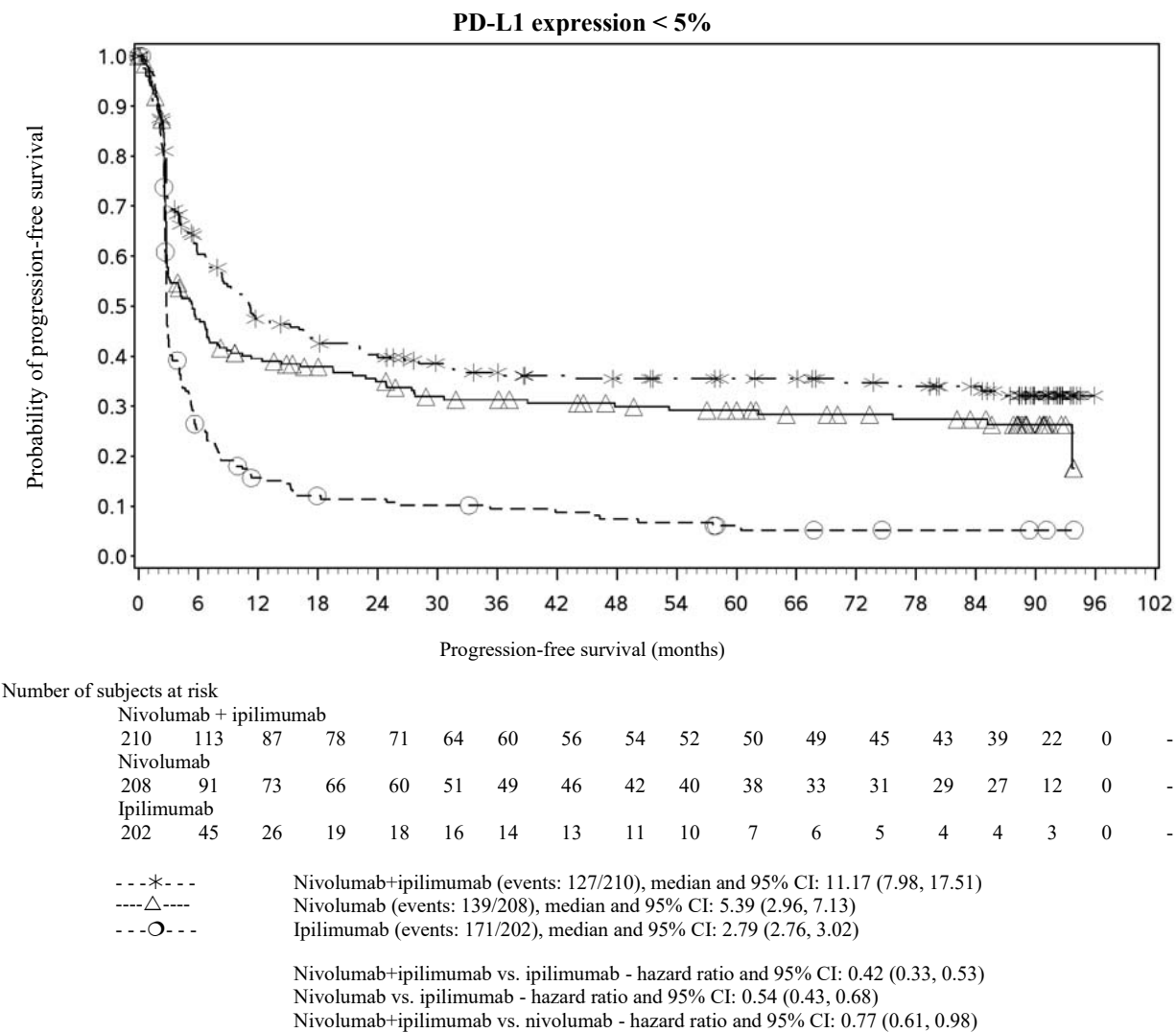
- *--- Nivolumab+ipilimumab (events: 189/314), median and 95% CI: 11.50 (8.90, 20.04).
PFS rate at 12 months and 95% CI: 49% (44, 55), PFS rate at 60 months and 95% CI: 36% (32, 42), PFS rate at 90 months and 95% CI: 33% (27, 39)
- △--- Nivolumab (events: 208/316), median and 95% CI: 6.93 (5.13, 10.18).
PFS rate at 12 months and 95% CI: 42% (36, 47), PFS rate at 60 months and 95% CI: 29% (24, 35), PFS rate at 90 months and 95% CI: 27% (22, 33)
- Ipilimumab (events: 261/315), median and 95% CI: 2.86 (2.79, 3.09).
PFS rate at 12 months and 95% CI: 18% (14, 23), PFS rate at 60 months and 95% CI: 8% (5, 12), PFS rate at 90 months and 95% CI: 7% (4, 11)

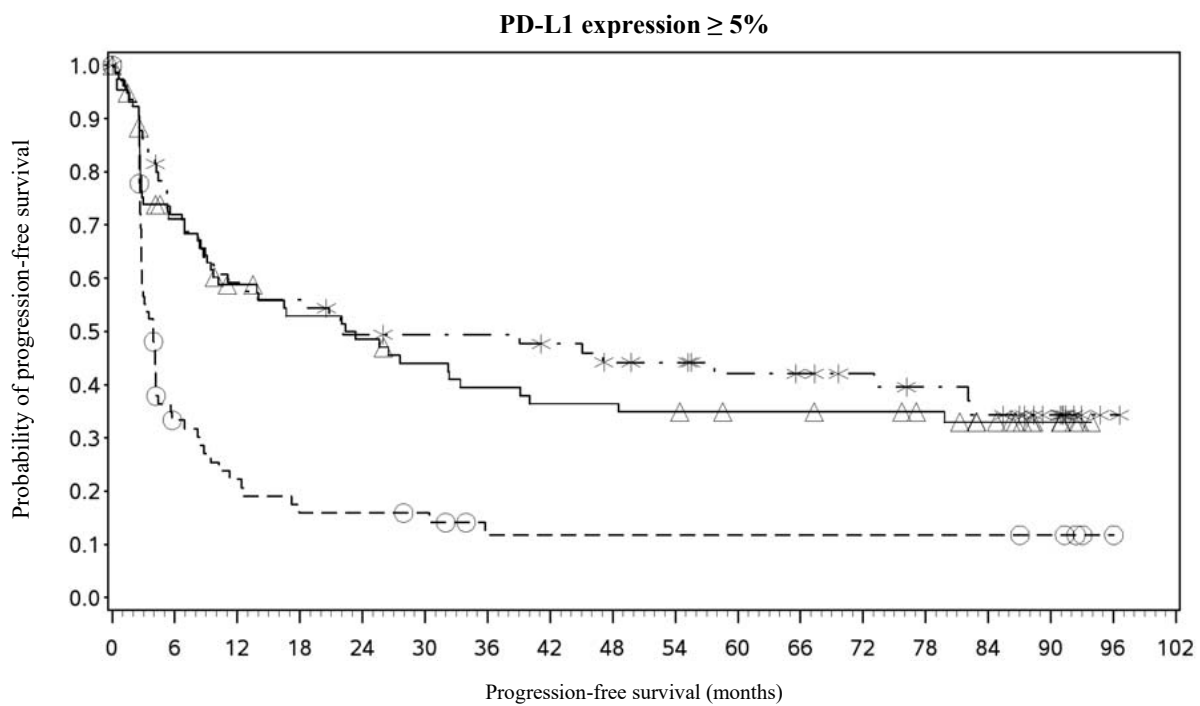
Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.35, 0.51)

Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.53 (0.44, 0.64)

Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.79 (0.65, 0.97)

Figure 6: Progression-free survival by PD-L1 expression: 5% cut off (CA209067)





Number of subjects at risk

Nivolumab + ipilimumab																
68	45	37	35	30	29	29	27	24	23	20	19	17	15	13	8	1
Nivolumab																
80	52	41	36	33	29	26	24	24	23	21	21	20	18	14	7	0
Ipilimumab																
75	21	14	10	10	9	5	5	5	5	5	5	5	5	5	4	1

---*--- Nivolumab+ipilimumab (events: 36/68), median and 95% CI: 22.11 (9.72, 82.07)

---△--- Nivolumab (events: 48/80), median and 95% CI: 22.34 (9.46, 39.13)

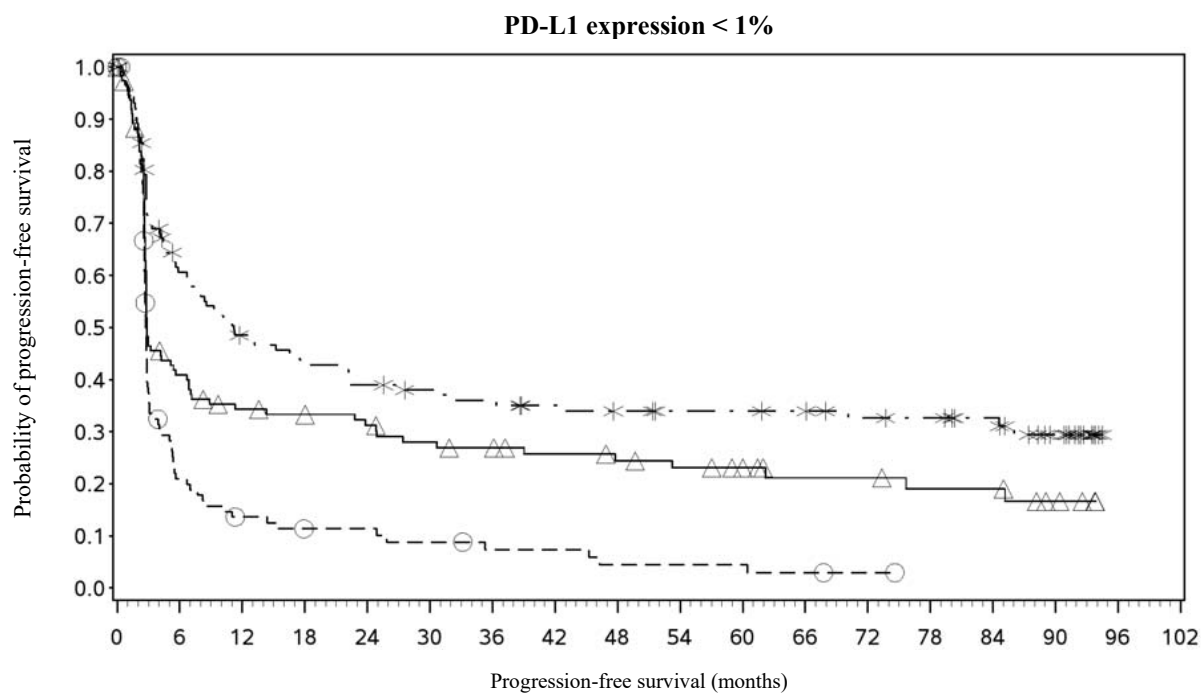
---○--- Ipilimumab (events: 60/75), median and 95% CI: 3.94 (2.79, 4.21)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.38 (0.25, 0.58)

Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.43 (0.29, 0.64)

Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.89 (0.58, 1.35)

Figure 7: Progression-free survival by PD-L1 expression: 1% cut off (CA209067)



Number of subjects at risk

Nivolumab + ipilimumab																	
123	65	51	46	41	38	36	33	31	29	29	28	25	24	21	13	0	-
Nivolumab																	
117	44	35	33	30	26	24	21	19	17	15	11	11	9	9	5	0	-
Ipilimumab																	
113	20	12	9	9	7	5	5	3	3	3	2	1	0	0	0	0	-

---*--- Nivolumab+ipilimumab (events: 76/123), median and 95% CI: 11.17 (6.93, 22.18)

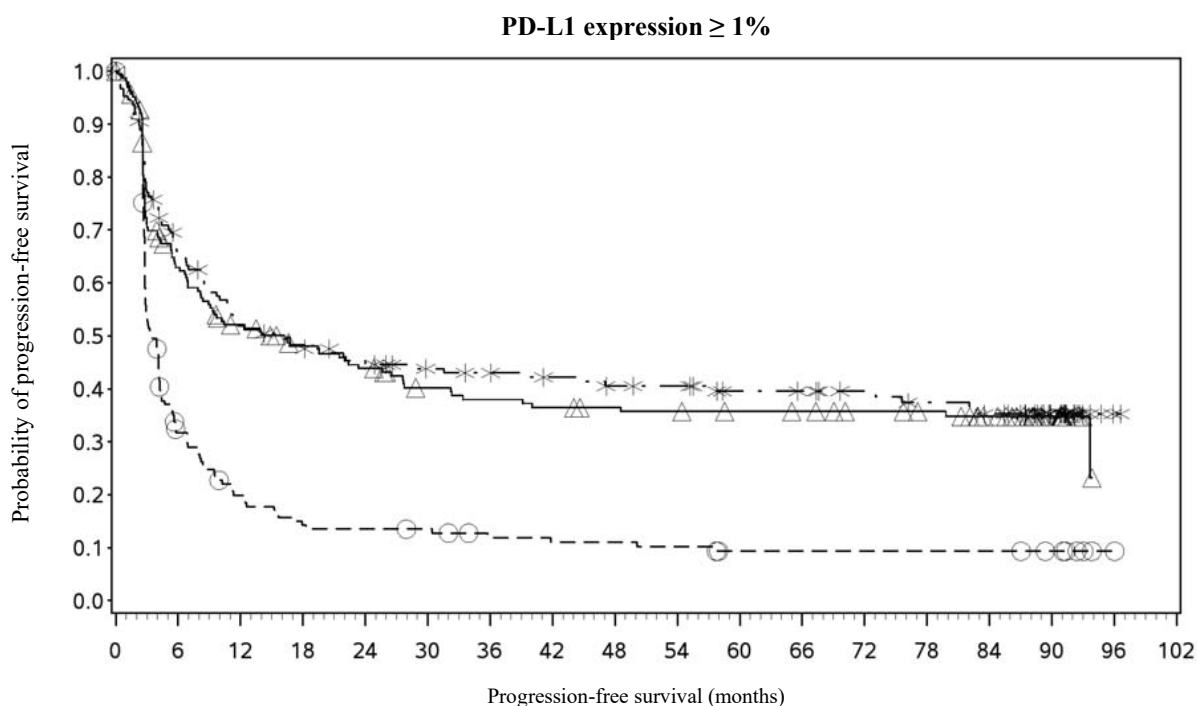
---△--- Nivolumab (events: 85/117), median and 95% CI: 2.83 (2.76, 5.62)

---○--- Ipilimumab (events: 94/113), median and 95% CI: 2.73 (2.66, 2.83)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.39 (0.28, 0.53)

Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.59 (0.44, 0.79)

Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.66 (0.48, 0.90)



Number of subjects at risk

Nivolumab + ipilimumab																
155	93	73	67	60	55	53	50	47	46	41	40	37	34	31	17	1
Nivolumab																
171	99	79	69	63	54	51	49	47	46	44	43	40	38	32	14	0
Ipilimumab																
164	46	28	20	19	18	14	13	13	12	9	9	9	9	9	7	1

---*--- Nivolumab+ipilimumab (events: 90/155), median and 95% CI: 16.13 (8.90, 45.08)

---△--- Nivolumab (events: 102/171), median and 95% CI: 16.20 (8.11, 27.60)

---○--- Ipilimumab (events: 137/164), median and 95% CI: 3.48 (2.83, 4.17)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.32, 0.55)

Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.45 (0.35, 0.59)

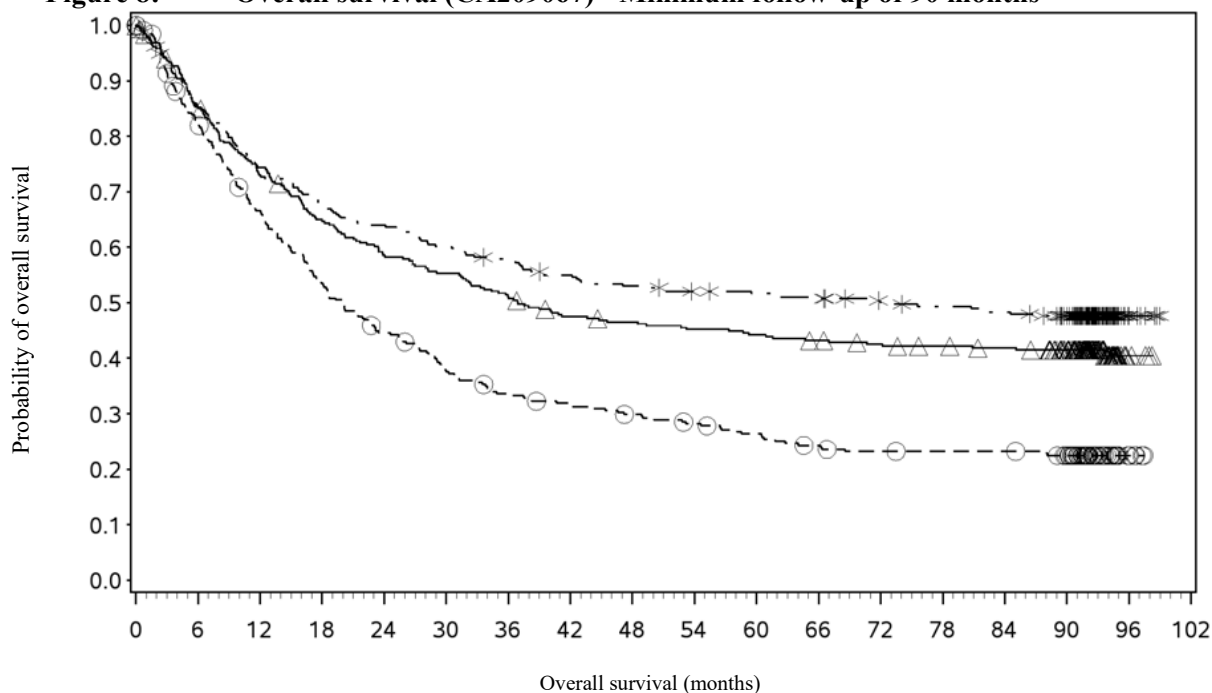
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.92 (0.69, 1.22)

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

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 90 months show outcomes consistent with the original primary analysis. OS results from this follow-up analysis are shown in Figure 8 (all randomised), Figures 9 and 10 (at the tumour PD-L1 5% and 1% cut off).

The OS analysis was not adjusted to account for subsequent therapies received. Subsequent systemic therapy was received by 36.0%, 49.1%, and 66.3% 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 19.1%, 34.2%, and 48.3% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively.

Figure 8: Overall survival (CA209067) - Minimum follow-up of 90 months



Number of subjects at risk

Nivolumab+ipilimumab																
314	265	227	210	199	187	179	169	163	158	156	153	147	144	141	129	7
Nivolumab																
316	266	231	201	181	171	158	145	141	137	134	130	126	123	120	107	4
Ipilimumab																
315	253	203	163	135	113	100	94	87	81	75	68	64	63	63	57	5

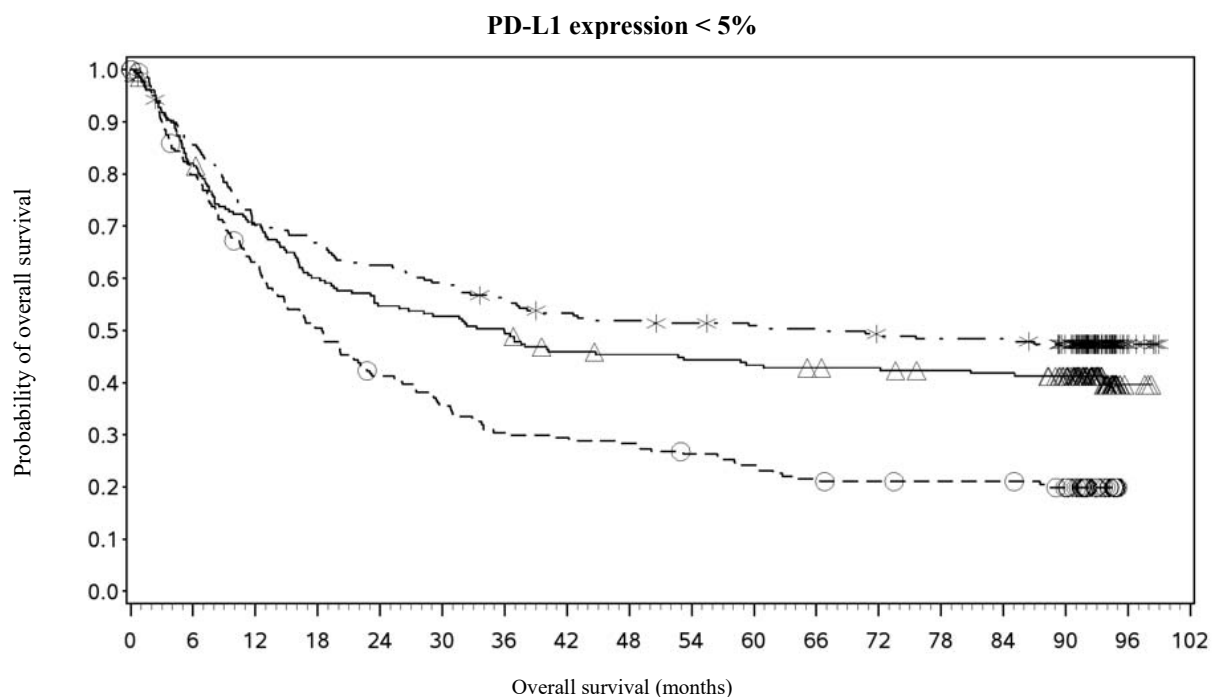
- *--- Nivolumab+ipilimumab (events: 162/314), median and 95% CI: 72.08 (38.18, N.A.)
OS rate and 95% CI at 12 months: 73% (68, 78), 24 months: 64% (59, 69), 36 months: 58% (52, 63),
60 months: 52% (46, 57), and 90 months: 48% (42, 53)
- △--- Nivolumab (events: 182/316), median and 95% CI: 36.93 months (28.25, 58.71)
OS rate and 95% CI at 12 months: 74% (69, 79), 24 months: 59% (53, 64), 36 months: 52% (46, 57),
60 months: 44% (39, 50), and 90 months: 42% (36, 47)
- Ipilimumab (events: 235/315), median and 95% CI: 19.94 months (16.85, 24.61)
OS rate and 95% CI at 12 months: 67% (61, 72), 24 months: 45% (39, 50), 36 months: 34% (29, 39),
60 months: 26% (22, 31), and 90 months: 22% (18, 27)

Nivolumab+ipilimumab vs ipilimumab - HR (95% CI): 0.53 (0.44, 0.65)

Nivolumab vs ipilimumab - HR (95% CI): 0.63 (0.52, 0.77)

Nivolumab+ipilimumab vs nivolumab - HR (95% CI): 0.84 (0.68, 1.04)

Figure 9: Overall survival by PD-L1 expression: 5% cut off (CA209067) - Minimum follow-up of 90 months



Number of subjects at risk

Nivolumab+ipilimumab

210 178 146 139 130 123 116 109 106 104 102 100 98 96 96 88 6 -

Nivolumab

208 169 144 123 112 108 102 92 90 88 86 84 83 80 79 70 3 -

Ipilimumab

202 158 124 99 80 69 59 57 55 50 46 41 39 38 38 33 0 -

---*---

Nivolumab+ipilimumab (events: 109/210), median and 95% CI: 65.94 (32.72, N.A.)

---△---

Nivolumab (events: 121/208), median and 95% CI: 35.94 months (23.06, 60.91)

---○---

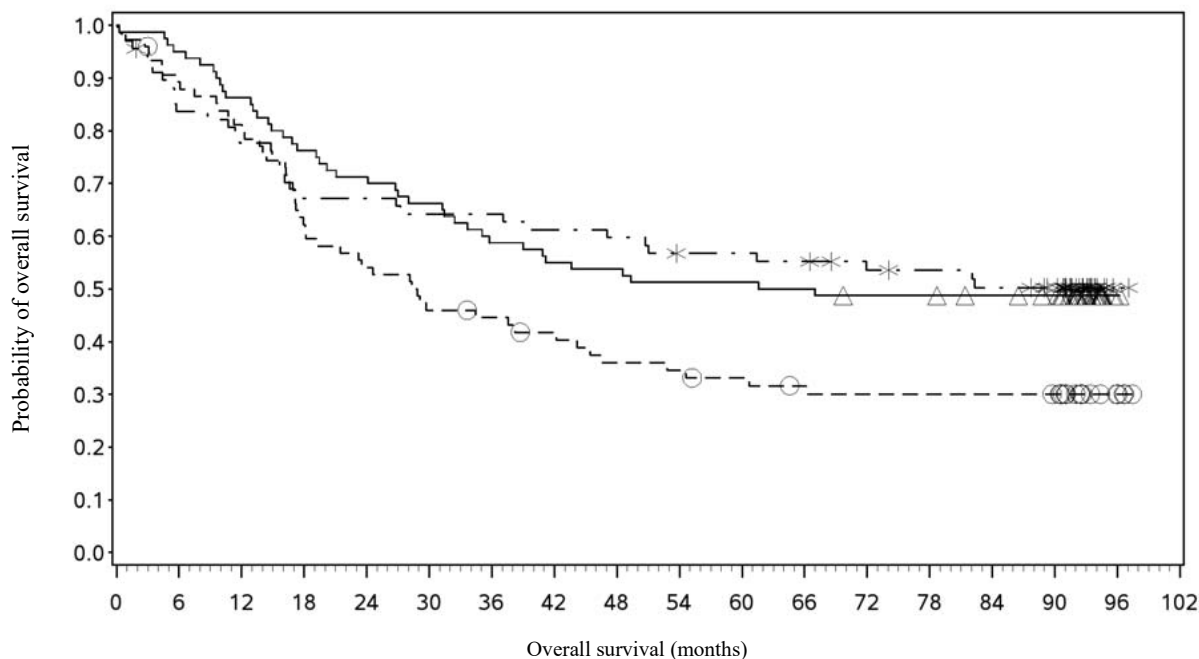
Ipilimumab (events: 157/202), median and 95% CI: 18.40 months (13.70, 22.51)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.51 (0.40, 0.66)

Nivolumab vs. ipilimumab - HR (95% CI): 0.62 (0.49, 0.79)

Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.83 (0.64, 1.07)

PD-L1 expression $\geq 5\%$



Number of subjects at risk

Nivolumab+ipilimumab																
68	56	52	45	45	43	43	41	40	37	37	36	33	32	30	27	1
Nivolumab																
80	76	69	61	57	53	47	44	43	41	41	40	38	38	36	33	1
Ipilimumab																
75	66	60	46	40	34	32	29	25	24	22	20	19	19	19	18	4

---*--- Nivolumab+ipilimumab (events: 33/68), median and 95% CI: N.A. (39.06, N.A.)

---△--- Nivolumab (events: 41/80), median and 95% CI: 64.28 months (33.64, N.A.)

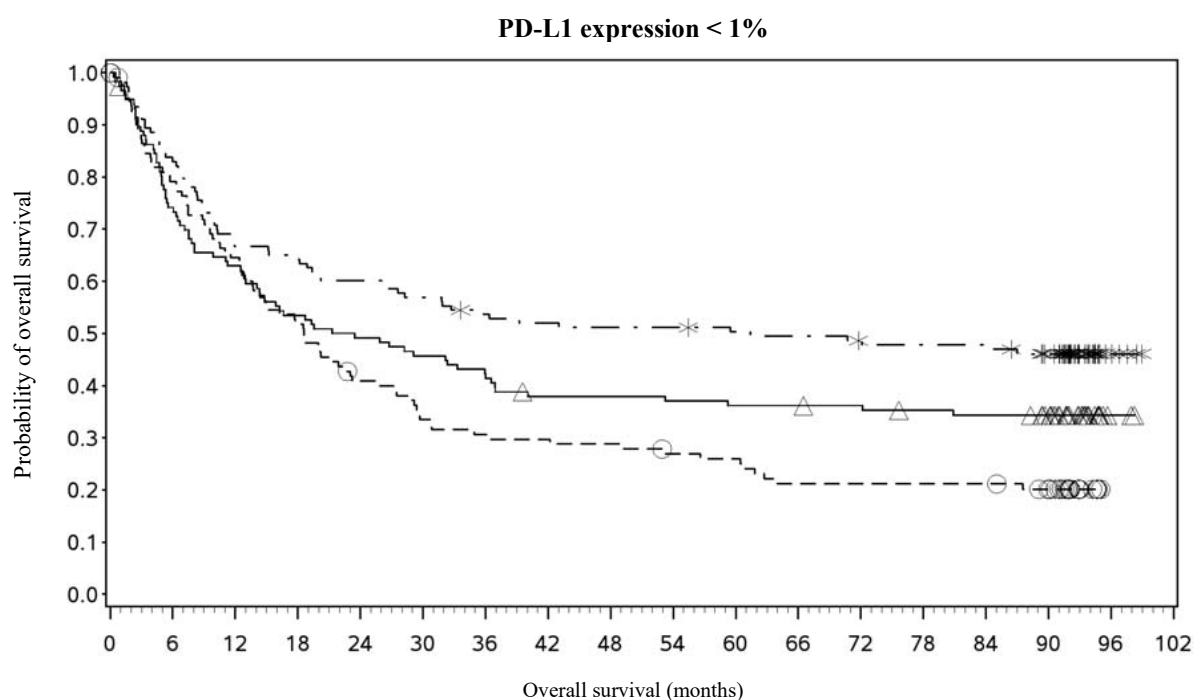
---○--- Ipilimumab (events: 51/75), median and 95% CI: 28.88 months (18.10, 44.16)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.61 (0.39, 0.94)

Nivolumab vs. ipilimumab - HR (95% CI): 0.61 (0.41, 0.93)

Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.99 (0.63, 1.57)

Figure 10: Overall survival by PD-L1 expression: 1% cut off (CA209067) - Minimum follow-up of 90 months



Number of subjects at risk

Nivolumab+ipilimumab

123	102	82	79	74	70	65	63	62	62	62	60	59	57	56	50	5	-
-----	-----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	---	---

Nivolumab

117	86	73	62	57	53	49	43	43	42	41	41	40	38	37	33	2	-
-----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	---	---

Ipilimumab

113	87	71	57	44	36	33	32	31	28	27	22	22	22	22	18	0	-
-----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	---	---

---*---

Nivolumab+ipilimumab (events: 66/123), median and 95% CI: 61.44 (26.45, N.A.)

---△---

Nivolumab (events: 76/117), median and 95% CI: 23.46 months (13.01, 36.53)

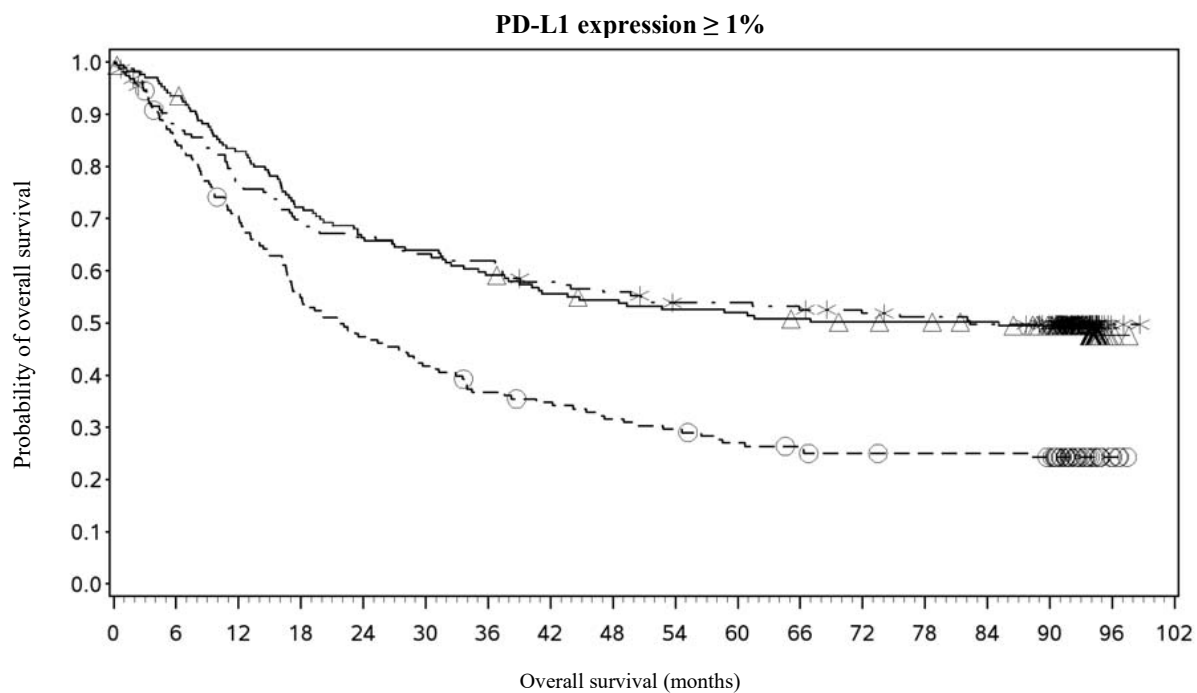
---○---

Ipilimumab (events: 87/113), median and 95% CI: 18.56 months (13.67, 23.20)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.55 (0.40, 0.76)

Nivolumab vs. ipilimumab - HR (95% CI): 0.77 (0.57, 1.05)

Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.71 (0.51, 0.99)



Number of subjects at risk

Nivolumab+ipilimumab																	
155	132	116	105	101	96	94	87	84	79	79	77	74	72	70	65	2	-
Nivolumab																	
171	159	140	122	112	108	100	93	90	87	86	83	81	80	78	70	2	-
Ipilimumab																	
164	137	113	88	76	67	58	54	49	46	41	39	36	35	35	33	4	-

---*---

Nivolumab+ipilimumab (events: 76/155), median and 95% CI: 82.30 (39.06, N.A.)

---△---

Nivolumab (events: 86/171), median and 95% CI: 85.09 months (39.00, N.A.)

---○---

Ipilimumab (events: 121/164), median and 95% CI: 21.49 months (16.85, 29.08)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.52 (0.39, 0.70)

Nivolumab vs. ipilimumab - HR (95% CI): 0.52 (0.39, 0.69)

Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 1.01 (0.74, 1.37)

Minimum follow-up for the analysis of ORR was 90 months. Responses are summarised in Table 20.

Table 20: Objective response (CA209067)

	nivolumab + ipilimumab (n = 314)	nivolumab (n = 316)	ipilimumab (n = 315)
Objective response	183 (58%)	142 (45%)	60 (19%)
(95% CI)	(52.6, 63.8)	(39.4, 50.6)	(14.9, 23.8)
Odds ratio (vs. ipilimumab)	6.35	3.5	
(95% CI)	(4.38, 9.22)	(2.49, 5.16)	
Complete response (CR)	71 (23%)	59 (19%)	19 (6%)
Partial response (PR)	112 (36%)	83 (26%)	41 (13%)
Stable disease (SD)	38 (12%)	29 (9%)	69 (22%)
Duration of response			
Median (range), months	N.A. (69.1-N.A.)	90.8 (45.7-N.A.)	19.3 (8.8-47.4)
Proportion ≥ 12 months in duration	68%	73%	44%
Proportion ≥ 24 months in duration	58%	63%	30%
ORR (95% CI) by tumour PD-L1 expression			
< 5%	56% (48.7, 62.5) n = 210	43% (36, 49.8) n = 208	18% (12.8, 23.8) n = 202
≥ 5%	72% (59.9, 82.3) n = 68	59% (47.2, 69.6) n = 80	21% (12.7, 32.3) n = 75
< 1%	54% (44.4, 62.7) n = 123	36% (27.2, 45.3) n = 117	18% (11.2, 26.0) n = 113
≥ 1%	65% (56.4, 72) n = 155	55% (47.2, 62.6) n = 171	20% (13.7, 26.4) n = 164

Both nivolumab-containing arms demonstrated a significant PFS and OS benefit and greater ORR compared with ipilimumab alone. The observed PFS results at 18 months of follow-up and ORR and OS results at 28 months of follow-up were consistently demonstrated across subgroups of patients including baseline ECOG performance status, BRAF status, M stage, age, history of brain metastases, and baseline LDH level. This observation was maintained with the OS results with a minimum follow-up of 90 months.

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

Both nivolumab-containing arms demonstrated greater objective response rates than ipilimumab regardless of PD-L1 expression levels. ORRs were higher for the combination of nivolumab and ipilimumab relative to nivolumab monotherapy across tumour PD-L1 expression levels (Table 19) after 90 months of follow-up, with a best overall response of complete response correlating to an improved survival rate.

After 90 months of follow-up, median durations of response for patients with tumour PD-L1 expression level ≥ 5% were 78.19 months (range: 18.07-N.A.) in the combination arm, 77.21 months (range: 26.25-N.A.) in the nivolumab monotherapy arm and 31.28 months (range: 6.08-N.A.) in the ipilimumab arm. At tumour PD-L1 expression < 5%, median durations of response were not reached (range: 61.93-N.A.) in the combination arm, were 90.84 months (range: 50.43-N.A.) in the nivolumab monotherapy arm and 19.25 months (range: 5.32-47.44) in the ipilimumab monotherapy arm.

No clear cut off for PD-L1 expression can reliably be established when considering the relevant endpoints of tumour response and PFS and OS. Results from exploratory multivariate analyses

identified patient and tumour characteristics (ECOG performance status, M stage, baseline LDH, BRAF mutation status, PD-L1 status, and gender) which might contribute to the survival outcome.

Efficacy by BRAF status:

After 90 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had a median PFS of 16.76 months (95% CI: 8.28, 32.0) and 11.7 months (95% CI: 7.0, 19.32), while those in the nivolumab monotherapy arm had a median PFS of 5.62 months (95% CI: 2.79, 9.46) and 8.18 months (95% CI: 5.13, 19.55), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had a median PFS of 3.09 months (95% CI: 2.79, 5.19) and 2.83 months (95% CI: 2.76, 3.06), respectively.

After 90 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to nivolumab in combination with ipilimumab had an ORR of 67.0% (95% CI: 57.0, 75.9; n = 103) and 54.0% (95% CI: 47.1, 60.9; n = 211), while those in the nivolumab monotherapy arm had an ORR of 37.87% (95% CI: 28.2, 48.1; n = 98) and 48.2% (95% CI: 41.4, 55.0; n = 218), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had an ORR of 23.0% (95% CI: 15.2, 32.5; n = 100) and 17.2% (95% CI: 12.4, 22.9; n = 215).

After 90 months of follow-up, in BRAF [V600] mutation-positive patients median OS was not reached in the combination arm and 45.5 months in the nivolumab monotherapy arm. Median OS for BRAF [V600] mutation-positive patients in the ipilimumab monotherapy arm was 24.6 months. In BRAF wild-type patients median OS was 39.06 months in the combination arm, 34.37 months in the nivolumab monotherapy arm and 18.5 months in the ipilimumab monotherapy arm. The OS HRs for nivolumab in combination with ipilimumab vs. nivolumab monotherapy were 0.66 (95% CI: 0.44, 0.98) for BRAF[V600] mutation-positive patients and 0.95 (95% CI: 0.74, 1.22) for BRAF wild-type patients.

Intravenous formulation

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).

Non-small cell lung cancer

Neoadjuvant treatment of NSCLC

Intravenous formulation

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

The safety and efficacy of nivolumab in combination with platinum-based chemotherapy for 3 cycles were evaluated in a phase 3, randomised, open-label study (CA209816). The study included patients with ECOG performance status 0 or 1, measurable disease (per RECIST, version 1.1), and whose tumours were resectable, histologically confirmed Stage IB (≥ 4 cm), II, or IIIA NSCLC (per the 7th edition AJCC/Union for International Cancer Control (UICC) staging criteria).

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of a patient population with stage II-IIIa disease according to

the 7th edition AJCC/UICC staging criteria: any patient with a tumour size ≥ 5 cm; any patient with N1 or N2 disease (regardless of primary tumour size); patients with multiple tumour nodules in either the same lobe or different ipsilateral lobes; patients with tumours that are invasive of thoracic structures (directly invade visceral pleura, parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus; or tumours that are associated with atelectasis or obstructive pneumonitis that extends to the hilar region or involves the entire lung.

The study did not include patients who had N2 status with tumours also invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

Patients with unresectable or metastatic NSCLC, known EGFR mutations or ALK translocations (testing for EGFR mutations or ALK translocations was not mandatory at study entry), Grade 2 or greater peripheral neuropathy, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Randomisation was stratified by tumour PD-L1 expression level ($\geq 1\%$ vs. $< 1\%$ or non-quantifiable), disease stage (IB/II vs. IIIA), and gender (male vs. female). Patients were enrolled regardless of their tumour PD-L1 status. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

A total of 358 patients were randomised to receive either nivolumab in combination with platinum-based chemotherapy (n = 179) or platinum-based chemotherapy (n = 179). Patients in the nivolumab in combination with chemotherapy arm received nivolumab 360 mg administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for up to 3 cycles. Patients in the chemotherapy arm received platinum-based chemotherapy administered every 3 weeks for up to 3 cycles. Platinum-based chemotherapy consisted of investigator's choice of paclitaxel 175 mg/m² or 200 mg/m² and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m² and cisplatin 75 mg/m² (non-squamous histology); or gemcitabine 1000 mg/m² or 1250 mg/m² and cisplatin 75 mg/m² (squamous histology). In the chemotherapy arm, two additional treatment regimen options included vinorelbine 25 mg/m² or 30 mg/m² and cisplatin 75 mg/m²; or docetaxel 60 mg/m² or 75 mg/m² and cisplatin 75 mg/m² (any histology).

Tumour assessments were performed at baseline, within 14 days of surgery, every 12 weeks after surgery for 2 years, then every 6 months for 3 years, and every year for 5 years until disease recurrence or progression. The primary efficacy outcome measures were event-free survival (EFS) based on BICR assessment and pathological complete response rate (pCR) by blinded-independent pathology review (BIPR). OS was a key secondary efficacy outcome measure and exploratory endpoints included feasibility of surgery.

Baseline characteristics in the ITT population were generally balanced across treatment groups. The median age was 65 years (range: 34-84) with 51% of patients ≥ 65 years and 7% of patients ≥ 75 years; 50% of patients were Asian, 47% were white, and 71% were male. Baseline ECOG performance status was 0 (67%) or 1 (33%); 50% of patients with PD-L1 $\geq 1\%$ and 43% with PD-L1 $< 1\%$; 5% had Stage IB, 17% had Stage IIA, 13% had Stage IIB, and 64% had Stage IIIA disease; 51% had squamous and 49% had non-squamous histology; and 89% were former/current smokers. Definitive surgery was performed on 83% of the patients in the nivolumab in combination with chemotherapy arm and on 75% of the patients in the chemotherapy arm. Adjuvant systemic treatment was received by 14.8% of patients in the nivolumab in combination with chemotherapy arm and by 25% of patients in the chemotherapy arm.

At the final pCR analysis and pre-specified interim EFS analysis (minimum follow-up 21 months), in all randomised patients, a statistically significant improvement was demonstrated in pCR and EFS for patients randomised to nivolumab in combination with chemotherapy as compared to chemotherapy alone. The pCR response rate was 24% in the nivolumab in combination with chemotherapy arm and 2.2% in the chemotherapy arm (difference of pCR 21.6, 99% CI: 13.0, 30.3; odds ratio of pCR 13.9, 99% CI: 3.49, 55.75; stratified p-value < 0.0001). Median EFS was 31.6 months in the nivolumab in

combination with chemotherapy arm and 20.8 months in the chemotherapy arm (HR = 0.63, 97.38% CI: 0.43, 0.91; stratified log-rank p-value 0.0052). At a pre-specified interim analysis, the HR for OS (minimum follow up 21 months) was 0.57 (99.67% CI: 0.30, 1.07) for nivolumab in combination with chemotherapy vs. chemotherapy.

At the final OS analysis with a minimum follow up of 59.9 months, the HR for OS was 0.72 (95.18% CI: 0.52, 1.00), with a statistically significant p-value of 0.0479 (stratified log-rank test) for nivolumab in combination with chemotherapy vs. chemotherapy.

Exploratory subgroup analysis by tumour PD-L1 expression and disease stage

The key efficacy results for the subgroup of patients with tumour PD-L1 expression $\geq 1\%$ and disease stage II-IIIa from an exploratory analysis with a minimum follow-up of 32.9 months are summarized in Table 21.

Table 21: Efficacy results in patients with tumour PD-L1 $\geq 1\%$ and stage II-IIIa disease* (CA209816)

	nivolumab + chemotherapy (n = 81)	chemotherapy (n = 86)
Event-free survival per BICR		
Events	22 (27.2%)	39 (45.3%)
Hazard ratio ^a (95% CI)		0.49 (0.29, 0.83)
Median (months) ^b (95% CI)	NR (44.42, NR)	26.71 (13.40, NR)
Pathologic complete response per BIPR		
Responses	26 (32.1%)	2 (2.3%)
95% CI ^c	(22.2, 43.4)	(0.3, 8.1)
Difference of pCR (95% CI) ^d		29.8% (19.0, 40.7)

^a Based on an unstratified Cox proportional hazards model.

^b Kaplan-Meier estimate.

^c Based on Clopper and Pearson method.

^d Two-sided 95% confidence interval for unweighted difference was calculated using Newcombe method.

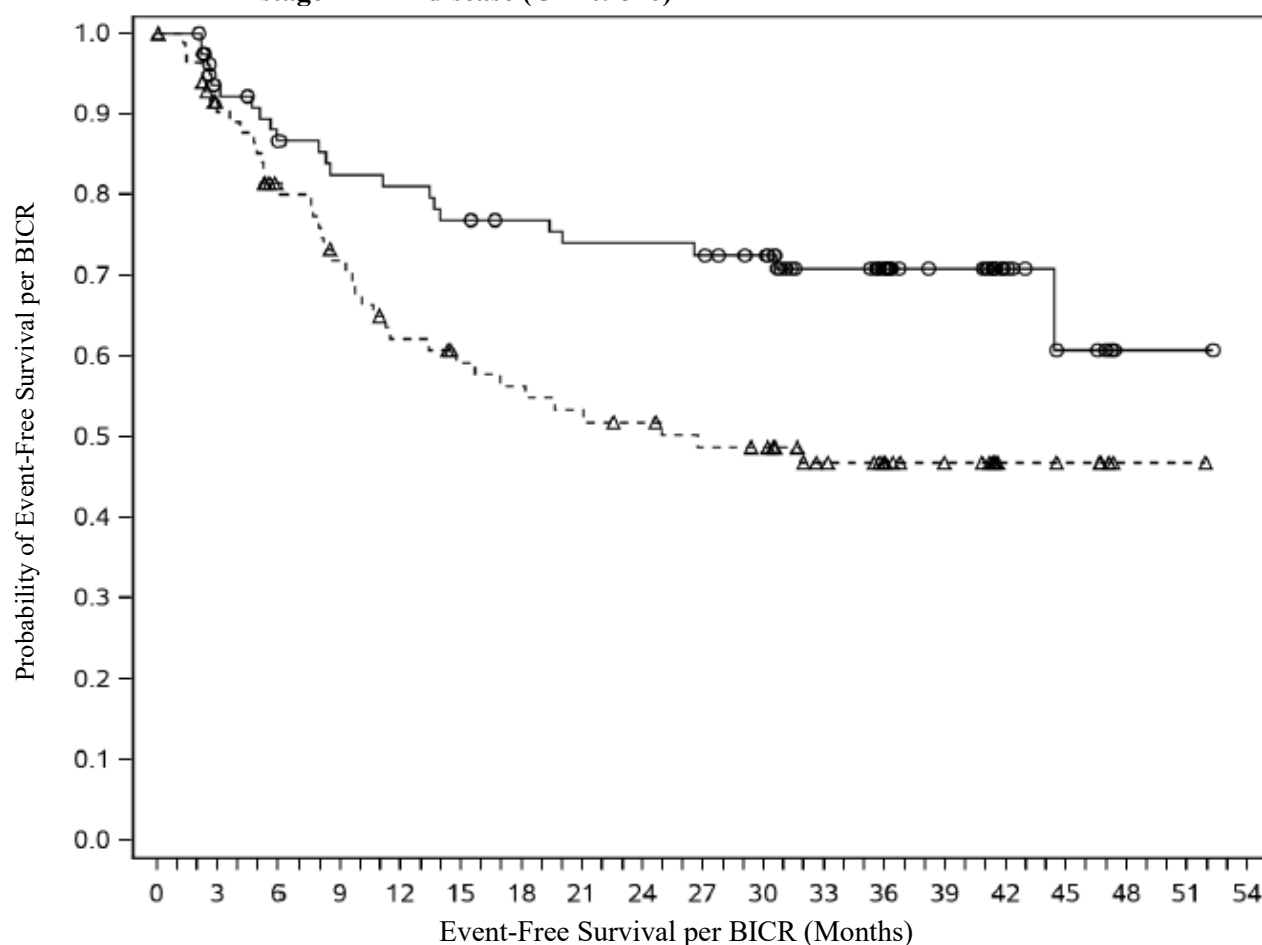
* 7th edition AJCC/UICC staging criteria.

Minimum follow-up for EFS was 32.9 months, data cut-off: 06-Sep-2022

pCR data cut-off: 28-Jul-2020

The Kaplan-Meier curves for EFS for the subgroup of patients with tumour PD-L1 expression $\geq 1\%$ and stage II-IIIa disease, with a minimum follow-up of 32.9 months, are shown in Figure 11.

Figure 11: Kaplan-Meier curves of EFS in patients with tumour PD-L1 $\geq 1\%$ and stage II-IIIa disease (CA209816)



Number of Subjects at Risk

Nivolumab + chemotherapy

81 69 62 59 58 55 53 51 51 50 47 37 32 21 10 5 1 1 0

Chemotherapy

86 71 60 52 44 40 38 36 34 31 30 23 18 14 7 6 1 1 0

—○— Nivolumab + chemotherapy (events: 22/81), median and 95% CI: NR (44.42, NR)

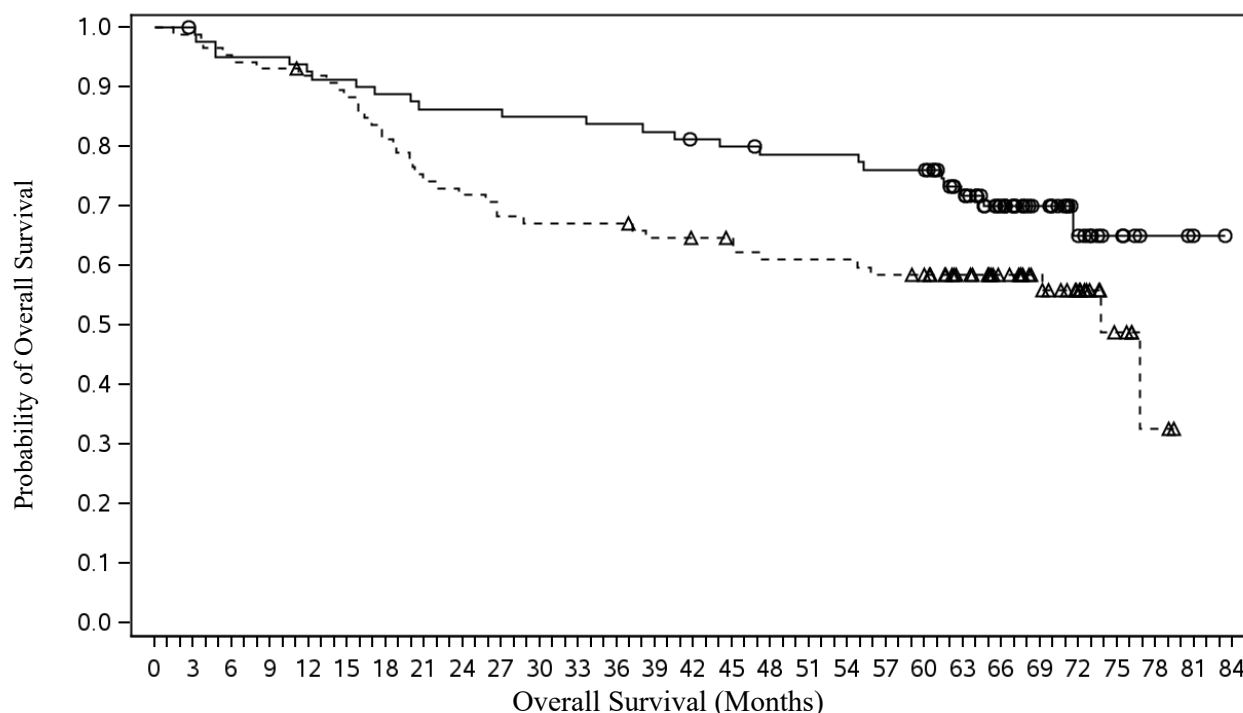
---△--- Chemotherapy (events: 39/86), median and 95% CI: 26.71 (13.40, NR)

Based on data cut-off: 06-Sep-2022, minimum follow-up of 32.9 months

At the time of the updated EFS analysis, an interim analysis for OS was performed (minimum follow-up of 32.9 months). The exploratory, descriptive HR for OS in patients with tumour PD-L1 expression $\geq 1\%$ and stage II-IIIa disease was 0.43 (95% CI: 0.22, 0.83) for nivolumab in combination with chemotherapy vs. chemotherapy.

At the final analysis (minimum follow-up of 59.9 months), the HR for OS in patients with tumour PD-L1 expression $\geq 1\%$ and stage II-IIIa disease was 0.59 (95% CI: 0.35, 0.98) for nivolumab in combination with chemotherapy vs. chemotherapy. The corresponding Kaplan-Meier curves for OS are shown in Figure 12.

Figure 12: Kaplan-Meier curves of OS in patients with tumour PD-L1 $\geq 1\%$ and stage II-IIIa disease (CA209816)



Number of Subjects at Risk

Nivolumab + chemotherapy

81 80 76 76 74 73 71 69 69 69 68 68 67 66 64 63 61 61 61 59 59 48 35 23 12 7 3 1 0

Chemotherapy

86 85 81 80 78 75 69 63 61 58 57 57 57 54 53 52 49 49 49 47 45 38 30 22 15 6 2 0 0

—○— Nivolumab + chemotherapy (events: 24/81), median and 95% CI: NR (71.59, NR)

---△--- Chemotherapy (events: 38/86), median and 95% CI: 73.72 47.34, NR)

Based on data cut-off: 23-Jan-2025, minimum follow-up of 59.9 months

Neoadjuvant and adjuvant treatment of NSCLC

Intravenous formulation

Randomised, double-blind, phase 3 study of neoadjuvant nivolumab in combination with platinum-based chemotherapy vs. platinum-based chemotherapy and adjuvant nivolumab monotherapy vs. placebo (CA20977T)

The safety and efficacy of nivolumab in combination with platinum-based chemotherapy for 4 cycles, followed by nivolumab monotherapy, were evaluated in a randomised, double-blind study (CA20977T). The study included patients with ECOG performance status 0 or 1 whose tumours were resectable, suspected or histologically confirmed Stage IIA (> 4 cm) to IIIB (T3-T4 N2) NSCLC (per the 8th edition American Joint Committee on Cancer (AJCC) Staging Manual). Patients were enrolled regardless of their tumour PD-L1 status.

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of a patient population with stage IIA-IIIB disease according to the 8th edition AJCC/UICC staging criteria: any patient with a tumour size > 4 cm; any patient with N1 or N2 disease (regardless of primary tumour size); patients with multiple tumour nodules in either the same lobe or different ipsilateral lobes; patients with tumours that are invasive of thoracic structures (directly invade visceral pleura, parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus; or tumours that are associated with atelectasis or obstructive pneumonitis that extends to the hilar region or involves the entire lung.

Patients with unresectable or metastatic NSCLC, EGFR mutations or known ALK translocations (testing for ALK translocations was not mandatory at study entry), brain metastasis, Grade 2 or greater peripheral neuropathy, interstitial lung disease or active, non-infectious pneumonitis (symptomatic and/or requiring treatment), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 461 patients were randomised to receive either nivolumab in combination with platinum-based chemotherapy followed by nivolumab monotherapy (n = 229) or platinum-based chemotherapy followed by placebo (n = 232). In the neoadjuvant phase, patients received either nivolumab 360 mg administered intravenously over 30 minutes and platinum-doublet chemotherapy administered every 3 weeks, or placebo and platinum-doublet chemotherapy administered every 3 weeks until disease progression or unacceptable toxicity, for up to 4 cycles. Patients in both treatment arms could receive post-operative radiation therapy (PORT) as standard of care. In the adjuvant phase, within 90 days after the surgery patients received either nivolumab 480 mg administered intravenously over 30 minutes every 4 weeks, or placebo administered every 4 weeks until disease progression, recurrence, or unacceptable toxicity, for up to 13 cycles. Platinum-based chemotherapy consisted of paclitaxel 175 mg/m² or 200 mg/m² and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m², and cisplatin 75 mg/m² or carboplatin AUC 5 or AUC 6 (non-squamous histology); or cisplatin 75 mg/m² and docetaxel 75 mg/m² (squamous histology).

Stratification factors for randomisation were tumour PD-L1 expression level ($\geq 1\%$ versus $< 1\%$ versus indeterminate/not evaluable), disease stage (Stage II versus Stage III), and tumour histology (squamous versus nonsquamous). Tumour PD-L1 expression levels were assessed using the PD-L1 IHC 28-8 pharmDx test. Tumour assessments were performed at baseline, within 14 days after the last dose of neoadjuvant treatment and before surgery, within 7 days prior to the start of adjuvant treatment after surgery, every 12 weeks after the first dose of adjuvant treatment for 2 years, then every 24 weeks for up to 5 years until disease recurrence or progression was confirmed by BICR.

Among the 442 patients in CA20977T, 256 (58%) had tumour PD-L1 expression $\geq 1\%$ based on the PD-L1 IHC 28-8 pharmDx test. The median age was 66 years (range: 35 to 86) with 55% of patients ≥ 65 years and 7% of patients ≥ 75 years, 69% were White, 28% were Asian, 2% were Black, and 75% were male. Baseline ECOG performance status was 0 (59%) or 1 (41%); 36% had stage II and 63% had stage III disease; 24% were N1 and 39% were N2; 25% were single-station and 14% were multistation; 61% had tumours with squamous histology and 39% had tumours with non-squamous histology; and 91% were former/current smokers.

Seventy-eight percent of patients in the neoadjuvant nivolumab in combination with platinum-doublet chemotherapy followed by adjuvant nivolumab arm had definitive surgery compared to 77% of patients in the neoadjuvant placebo and platinum-doublet chemotherapy followed by placebo arm. Approximately 5% of patients in each treatment arm received PORT.

The primary efficacy outcome measure was event-free survival (EFS) based on BICR assessment. Additional efficacy outcome measures included overall survival (OS), pathologic complete response (pCR) and major pathologic response as evaluated by blinded independent pathology review (BIPR).

In a pre-specified interim analysis in all randomised patients with a median follow-up of 25.4 months (range: 15.7-44.2 months), the study demonstrated statistically significant improvement of EFS. Median EFS was not reached (95% CI: 28.94, NE) in the nivolumab in combination with chemotherapy/nivolumab arm and 18.43 months (95% CI: 13.63, 28.06) in the placebo with chemotherapy/placebo arm (HR = 0.58, 97.36% CI: 0.42, 0.81; stratified log-rank p-value 0.00025). In a pre-specified interim analysis in all randomised patients with a median follow-up of 41 months (range: 31.3-59.8 months), median OS was not reached in both the nivolumab in combination with chemotherapy/nivolumab arm and in the placebo with chemotherapy/placebo arm (HR = 0.85, 97.63% CI: 0.58, 1.25).

Exploratory subgroup analysis by tumour PD-L1 expression

EFS for the subgroup of patients with tumour PD-L1 expression $\geq 1\%$, with a median follow-up of 41 months (range: 31.3-59.8 months), are presented in Table 22 and Figure 13.

Table 22: Efficacy results in patients with tumour PD-L1 $\geq 1\%$ (CA20977T)

	nivolumab with chemotherapy/ nivolumab (n = 128)	placebo with chemotherapy/ placebo (n = 128)
Event-free survival (EFS) per BICR		
Events (%)	47 (37%)	70 (55%)
Median (months) ^a (95% CI)	46.55 (35.81, NE)	15.08 (9.33, 31.41)
Hazard Ratio ^b (95% CI)	0.53 (0.36, 0.76)	

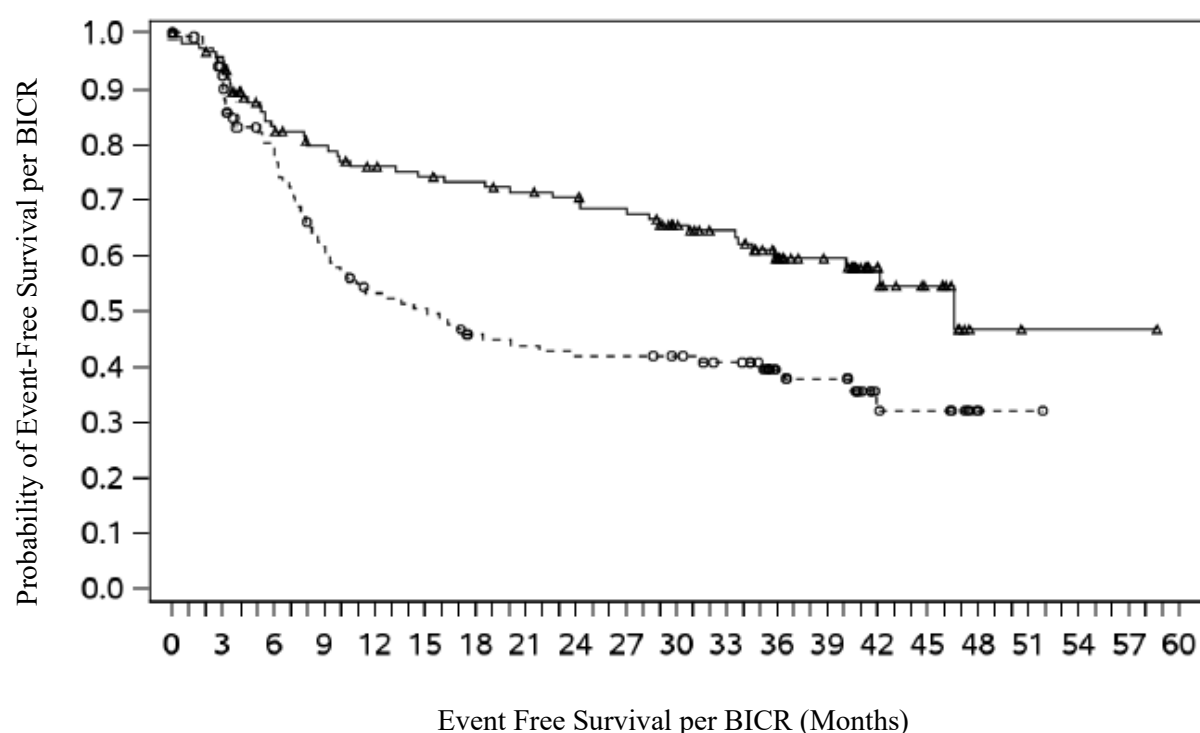
NE = non-estimable

Minimum follow-up for EFS was 31.3 months; data cut-off: 11-Nov-2024.

^a Kaplan-Meier estimate.

^b Based on an unstratified Cox proportional hazard model.

Figure 13: Kaplan-Meier curves of EFS in patients with tumour PD-L1 $\geq 1\%$ (CA20977T)



Number of Subjects at Risk

Nivolumab + chemotherapy/Nivolumab

128 119 95 89 83 80 78 75 73 70 61 55 44 35 17 11 2 1 1 1 0

Placebo + chemotherapy/Placebo

128 110 87 68 57 54 46 44 42 42 40 36 23 20 9 8 2 1 0 0 0

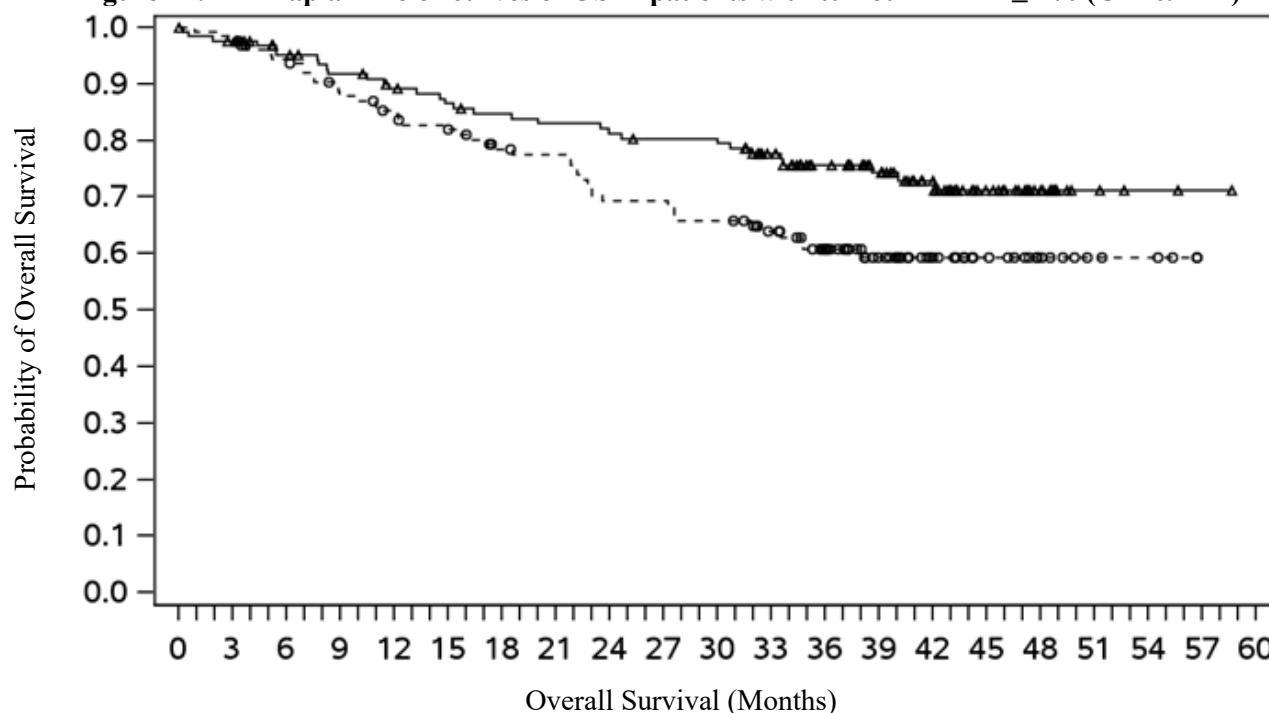
—△— Nivolumab + chemotherapy/Nivolumab (events: 47/128), median and 95% CI: 46.55 (35.81, NE)

---○--- Placebo + Chemotherapy/Placebo (events: 70/128), median and 95% CI: 15.08 (9.33, 31.41)

Based on data cut-off 11-Nov-2024, minimum follow-up of 31.3 months

At the time of the updated EFS analysis, an interim analysis for OS was performed (minimum follow-up of 31.3 months). The exploratory, descriptive HR for OS in patients with tumour PD-L1 expression $\geq 1\%$ was 0.61 (95% CI: 0.39, 0.97) for the nivolumab in combination with chemotherapy/nivolumab arm vs. the placebo with chemotherapy/placebo arm. The Kaplan-Meier curves for OS for the subgroup of patients with tumour PD-L1 expression $\geq 1\%$ are shown in Figure 14.

Figure 14: Kaplan-Meier curves of OS in patients with tumour PD-L1 $\geq 1\%$ (CA20977T)



Number of Subjects at Risk

Nivolumab + chemotherapy/Nivolumab

128 123 114 108 103 99 96 94 92 90 90 80 67 55 42 26 15 4 2 1 0

Placebo + chemotherapy/Placebo

128 126 116 106 101 96 88 86 77 77 73 65 54 36 25 17 10 5 4 0 0

—△— Nivolumab + chemotherapy/Nivolumab (events: 31/128), median and 95% CI: NR

---○--- Placebo + Chemotherapy/Placebo (events: 46/128), median and 95% CI: NR (38.08, NE)

Based on data cut-off 11-Nov-2024, minimum follow-up of 31.3 months

Treatment of NSCLC after prior chemotherapy

Squamous NSCLC

Intravenous formulation

Randomised phase 3 study vs. docetaxel (CA209017)

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

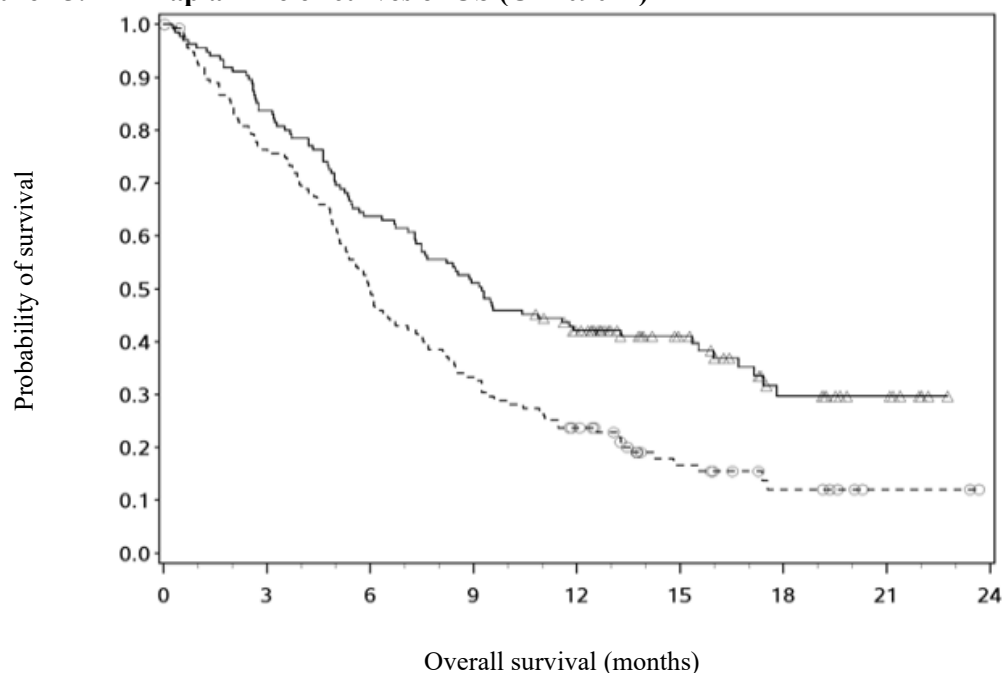
A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (n = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m² every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour 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 15.

Figure 15: Kaplan-Meier curves of OS (CA209017)



Number of subjects at risk

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

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

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

The observed OS benefit was consistently demonstrated across subgroups of patients. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 1%, 5% or 10%). However, the role of this biomarker (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 23.

Table 23: 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		
(95% CI)	27 (20.0%) (13.6, 27.7)	12 (8.8%) (4.6, 14.8)
Odds ratio (95% CI)	2.64 (1.27, 5.49)	
p-value	0.0083	
Complete response (CR)	1 (0.7%)	0
Partial response (PR)	26 (19.3%)	12 (8.8%)
Stable disease (SD)	39 (28.9%)	47 (34.3%)
Median duration of response		
Months (range)	Not reached (2.9-20.5 ⁺)	8.4 (1.4 ⁺ -15.2 ⁺)
Median time to response		
Months (range)	2.2 (1.6-11.8)	2.1 (1.8-9.5)
Progression-free survival		
Events	105 (77.8%)	122 (89.1%)
Hazard ratio	0.62	
95% CI	(0.47, 0.81)	
p-value	< 0.0004	
Median (95% CI) (months)	3.48 (2.14, 4.86)	2.83 (2.10, 3.52)
Rate (95% CI) at 12 months	20.8 (14.0, 28.4)	6.4 (2.9, 11.8)
Updated analysis		
Minimum follow-up: 24.2 months		
Overall survival^a		
Events	110 (81.4%)	128 (93.4%)
Hazard ratio	0.62	
95% CI	(0.47, 0.80)	
Rate (95% CI) at 24 months	22.9 (16.2, 30.3)	8 (4.3, 13.3)
Confirmed objective response		
(95% CI)	20.0% (13.6, 27.7)	8.8% (4.6, 14.8)
Median duration of response		
Months (range)	25.2 (2.9-30.4)	8.4 (1.4 ⁺ -18.0 ⁺)

	nivolumab (n = 135)	docetaxel (n = 137)
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.

Intravenous formulation

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%.

Intravenous formulation

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 24 below.

Table 24: ORR based on response evaluable patients – total and by subgroup (CA209171)

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

^a includes confirmed and unconfirmed responses, scans were mandatory only at week 8/9 and week 52.

^b CR+PR, confidence interval based on the Clopper and Pearson method

Non-squamous NSCLC

Intravenous formulation

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.

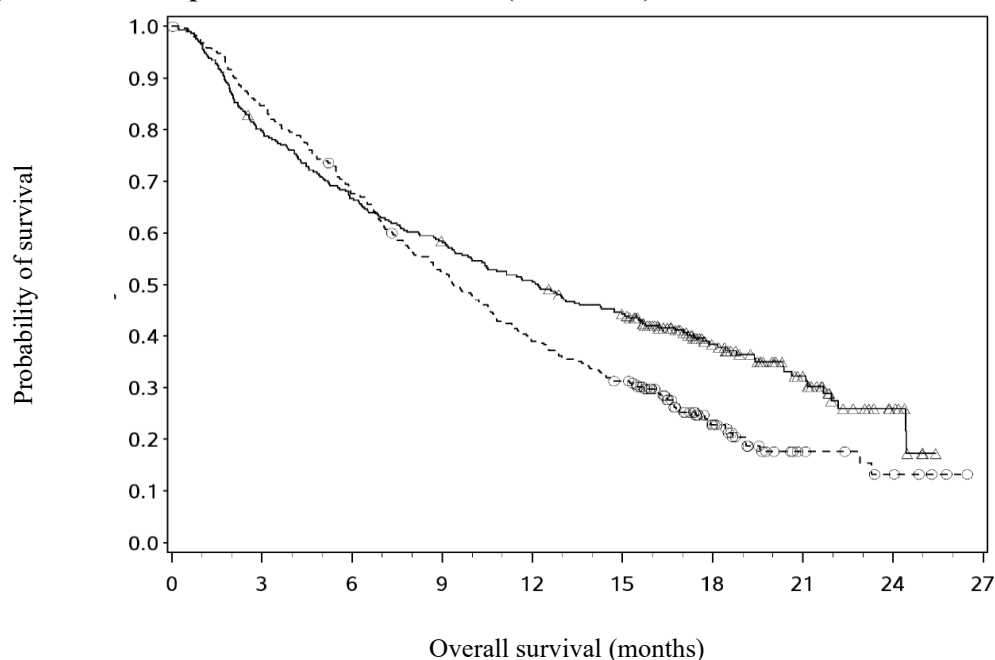
A total of 582 patients were randomised to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks (n = 292) or docetaxel 75 mg/m² every 3 weeks (n = 290). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments 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 pre-specified 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 pre-specified analyses due to the small sample sizes within the intervals.

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

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

The Kaplan-Meier curves for OS are shown in Figure 16.

Figure 16: Kaplan-Meier curves of OS (CA209057)



Number of subjects at risk

Nivolumab 3 mg/kg	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

---△--- Nivolumab 3 mg/kg (events: 190/292), median and 95% CI: 12.19 (9.66, 14.98)

---○--- Docetaxel (events: 223/290), median and 95% CI: 9.36 (8.05, 10.68)

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with docetaxel at the pre-specified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 25.

Table 25: Efficacy results (CA209057)

	nivolumab (n = 292)	docetaxel (n = 290)
Pre-specified interim analysis		
Minimum follow-up: 13.2 months		
Overall survival		
Events	190 (65.1%)	223 (76.9%)
Hazard ratio ^a (95.92% CI)		0.73 (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		
(95% CI)	56 (19.2%) (14.8, 24.2)	36 (12.4%) (8.8, 16.8)
Odds ratio (95% CI)		1.68 (1.07, 2.64)
p-value		0.0246

	nivolumab (n = 292)	docetaxel (n = 290)
Complete response (CR)	4 (1.4%)	1 (0.3%)
Partial response (PR)	52 (17.8%)	35 (12.1%)
Stable disease (SD)	74 (25.3%)	122 (42.1%)
Median duration of response		
Months (range)	17.15 (1.8-22.6 ⁺)	5.55 (1.2 ⁺ -15.2 ⁺)
Median time to response		
Months (range)	2.10 (1.2-8.6)	2.61 (1.4-6.3)
Progression-free survival		
Events	234 (80.1%)	245 (84.5%)
Hazard ratio		0.92
95% CI		(0.77, 1.11)
p-value		0.3932
Median (95% CI) (months)	2.33 (2.17, 3.32)	4.21 (3.45, 4.86)
Rate (95% CI) at 12 months	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)
Updated analysis		
Minimum follow-up: 24.2 months		
Overall survival^c		
Events	228 (78.1%)	247 (85.1%)
Hazard ratio ^a		0.75
(95% CI)		(0.63, 0.91)
Rate (95% CI) at 24 months	28.7 (23.6, 34.0)	15.8 (11.9, 20.3)
Confirmed objective response	19.2%	12.4%
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-33.7 ⁺)	5.6 (1.2 ⁺ -16.8)
Progression-free survival		
Rate (95% CI) at 24 months	11.9 (8.3, 16.2)	1.0 (0.2, 3.3)
Updated analysis		
Minimum follow-up: 62.7 months		
Overall survival^d		
Events	250 (85.6%)	279 (96.2%)
Hazard ratio ^a		0.70
(95% CI)		(0.58, 0.83)
Rate (95% CI) at 60 months	14.0 (10.2, 18.3)	2.1 (0.9, 4.4)
Confirmed objective response	19.5%	12.4%
(95% CI)	(15.1, 24.5)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-70.4 ⁺)	5.6 (0.0 ⁺ -33.4)

	nivolumab (n = 292)	docetaxel (n = 290)
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 $\geq 1\%$ (53% vs. 55%), $\geq 5\%$ (41% vs. 38%), or $\geq 10\%$ (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 26 summarises results of ORR and OS by tumour PD-L1 expression.

Table 26: 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)
$\geq 1\%$	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)
$\geq 1\%$ 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)
$\geq 10\%$ 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)
$\geq 50\%$ ^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)
$\geq 1\%$	68 (123)	93 (123)	0.59 (0.43, 0.82)
$\geq 1\%$ to < 10% ^a	27 (37)	30 (44)	1.33 (0.79, 2.24)
$\geq 10\%$ to < 50% ^a	11 (20)	26 (33)	0.61 (0.30, 1.23)
$\geq 50\%$ ^a	30 (66)	37 (46)	0.32 (0.20, 0.53)

PD-L1 expression	nivolumab	docetaxel	
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 (RCC)

Intravenous formulation

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 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% $\geq$ 65 years of age and 8% $\geq$ 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 day-20.2+ months) in sunitinib-treated patients. Nivolumab with ipilimumab was continued beyond progression in 29% of patients.

Efficacy results for the intermediate/poor risk patients are shown in Table 27 (primary analysis with a minimum follow-up of 17.5 months and with a minimum follow-up of 60 months) and in Figure 17 (minimum follow-up of 60 months).

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 60 months show outcomes consistent with the original primary analysis.

Table 27: Efficacy results in intermediate/poor risk patients (CA209214)

	nivolumab + ipilimumab (n = 425)	sunitinib (n = 422)
Primary analysis minimum follow-up: 17.5 months		
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)

	nivolumab + ipilimumab (n = 425)	sunitinib (n = 422)
Updated analysis* minimum follow-up: 60 months		
Overall survival		
Events	242 (57%)	282 (67%)
Hazard ratio ^a		0.68
95% CI		(0.58, 0.81)
Median (95% CI)	46.95 (35.35, 57.43)	26.64 (22.08, 33.54)
Rate (95% CI)		
At 24 months	66.3 (61.5, 70.6)	52.4 (47.4, 57.1)
At 36 months	54.6 (49.7, 59.3)	43.7 (38.7, 48.5)
At 48 months	49.9 (44.9, 54.6)	35.8 (31.1, 40.5)
At 60 months	43.0 (38.1, 47.7)	31.3 (26.8, 35.9)
Progression-free survival		
Events	245 (57.6%)	253 (60.0%)
Hazard ratio ^a		0.73
95% CI		(0.61, 0.87)
Median (95% CI)	11.6 (8.44, 16.63)	8.3 (7.03, 10.41)
Confirmed objective response (BICR)		
	179 (42.1%)	113 (26.8%)
(95% CI)	(37.4, 47.0)	(22.6, 31.3)
Difference in ORR (95% CI) ^{d,e}		16.2 (10.0, 22.5)
Complete response (CR)	48 (11.3%)	9 (2.1%)
Partial response (PR)	131 (30.8%)	104 (24.6%)
Stable disease (SD)	131 (30.8%)	187 (44.3%)
Median duration of response^g		
Months (range)	NE (50.89-NE)	19.38 (15.38-25.10)
Median time to response		
Months (range)	2.8 (0.9-35.0)	3.1 (0.6-23.6)

^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.

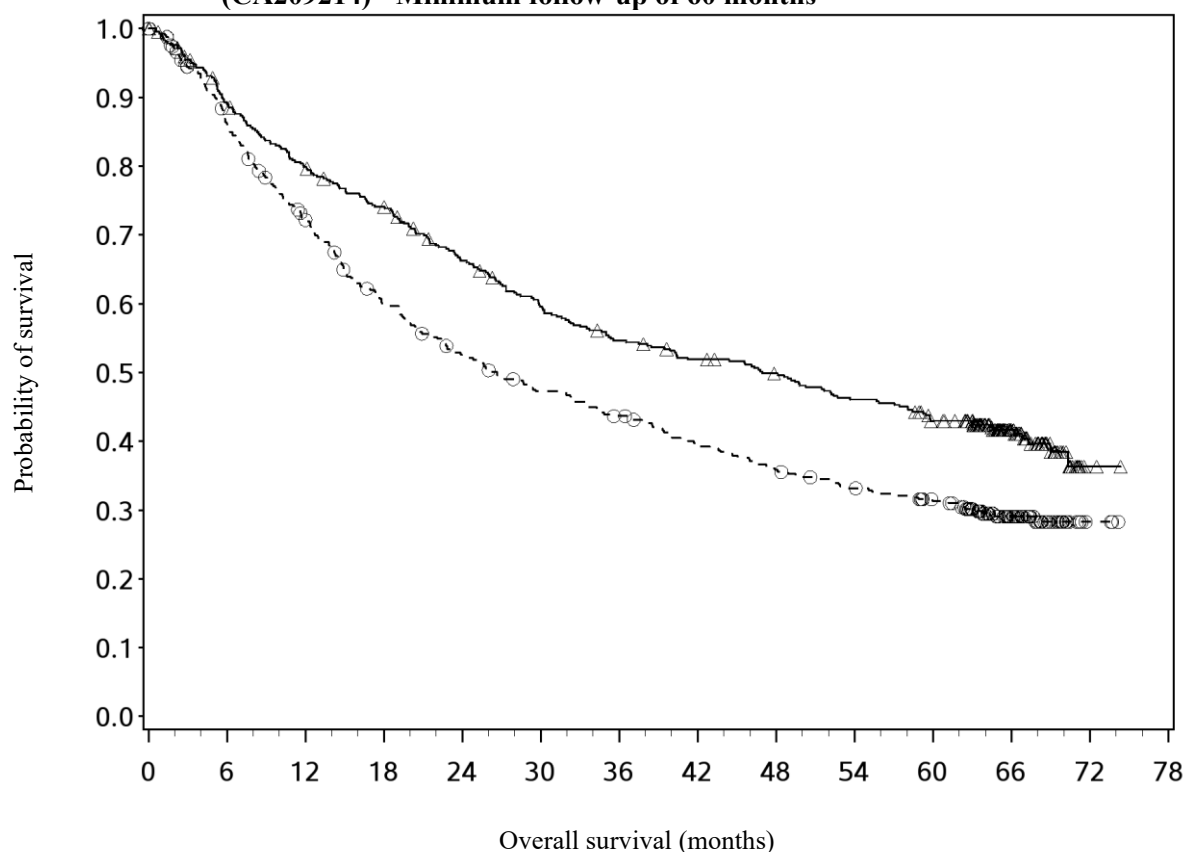
^h p-value is compared to alpha 0.009 in order to achieve statistical significance.

“+” denotes a censored observation.

NE = non-estimable

* Descriptive analysis based on data cut-off: 26-Feb-2021.

Figure 17: Kaplan-Meier curves of OS in intermediate/poor risk patients (CA209214) - Minimum follow-up of 60 months



Number of subjects at risk

Nivolumab + ipilimumab

425 372 332 306 270 241 220 207 196 181 163 79 2 0

Sunitinib

422 353 291 237 206 184 169 151 137 125 112 58 3 0

---△--- Nivolumab + ipilimumab (events: 242/425), median and 95.0% CI: 46.95 (35.35, 57.43)

---○--- Sunitinib (events: 282/422), median and 95.0% CI: 26.64 (22.08, 33.54)

An updated descriptive OS analysis was performed when all patients had a minimum follow-up of 24 months. 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. 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 $\geq 1\%$ 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. At a minimum of 24 months follow-up, 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). With 60 months minimum follow-up, the HR for OS was 0.94 (95% CI: 0.65, 1.37).

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

Patients ≥ 75 years of age represented 8% of all intermediate/poor risk patients in CA209214, and the combination of nivolumab and ipilimumab showed numerically less effect on OS (HR 0.97, 95% CI: 0.48, 1.95) in this subgroup versus the overall population at a minimum follow-up of 17.5 months. Because of the small size of this subgroup, no definitive conclusions can be drawn from these data.

Intravenous formulation

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

The safety and efficacy of nivolumab 240 mg in combination with cabozantinib 40 mg for the first-line treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA2099ER). The study included patients (18 years or older) with advanced or metastatic RCC with a clear cell component, Karnofsky Performance Status (KPS) $\geq 70\%$, and measurable disease as per RECIST, version 1.1 regardless of their PD-L1 status or IMDC risk group. The study excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression, patients who had prior treatment with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, poorly controlled hypertension despite antihypertensive therapy, active brain metastases and uncontrolled adrenal insufficiency. Patients were stratified by IMDC prognostic score, PD-L1 tumour expression, and region.

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

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

The study demonstrated a statistically significant benefit in PFS, OS, and ORR for patients randomised to nivolumab in combination with cabozantinib as compared to sunitinib. Efficacy results from the primary analysis (minimum follow-up 10.6 months; median follow-up 18.1 months) are shown in Table 28.

Table 28: Efficacy results (CA2099ER)

	nivolumab + cabozantinib (n = 323)	sunitinib (n = 328)
Progression-free survival		
Events	144 (44.6%)	191 (58.2%)
Hazard ratio ^a	0.51	
95% CI	(0.41, 0.64)	
p-value ^{b, c}	< 0.0001	
Median (95% CI) ^d	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)
Overall survival		
Events	67 (20.7%)	99 (30.2%)
Hazard ratio ^a	0.60	
98.89% CI	(0.40, 0.89)	
p-value ^{b, c, e}	0.0010	
Median (95% CI)	N.E.	N.E. (22.6, N.E.)
Rate (95% CI)		
At 6 months	93.1 (89.7, 95.4)	86.2 (81.9, 89.5)
Confirmed objective response (BICR)		
	180 (55.7%)	89 (27.1%)
(95% CI) ^f	(50.1, 61.2)	(22.4, 32.3)
Difference in ORR (95% CI) ^g	28.6 (21.7, 35.6)	
p-value ^h	< 0.0001	
Complete response (CR)	26 (8.0%)	15 (4.6%)
Partial response (PR)	154 (47.7%)	74 (22.6%)
Stable disease (SD)	104 (32.2%)	138 (42.1%)
Median duration of response^d		
Months (range)	20.17 (17.31, N.E.)	11.47 (8.31, 18.43)
Median time to response		
Months (range)	2.83 (1.0-19.4)	4.17 (1.7-12.3)
^a	Stratified Cox proportional hazards model. Hazard ratio is nivolumab and cabozantinib over sunitinib.	
^b	Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥ 1% versus < 1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.	
^c	2-sided p-values from stratified regular log-rank test.	
^d	Based on Kaplan-Meier estimates.	
^e	Boundary for statistical significance p-value < 0.0111.	
^f	CI based on the Clopper and Pearson method.	
^g	Strata adjusted difference in objective response rate (nivolumab + cabozantinib - sunitinib) based on DerSimonian and Laird.	
^h	2-sided p-value from CMH test.	
NE = non-estimable		

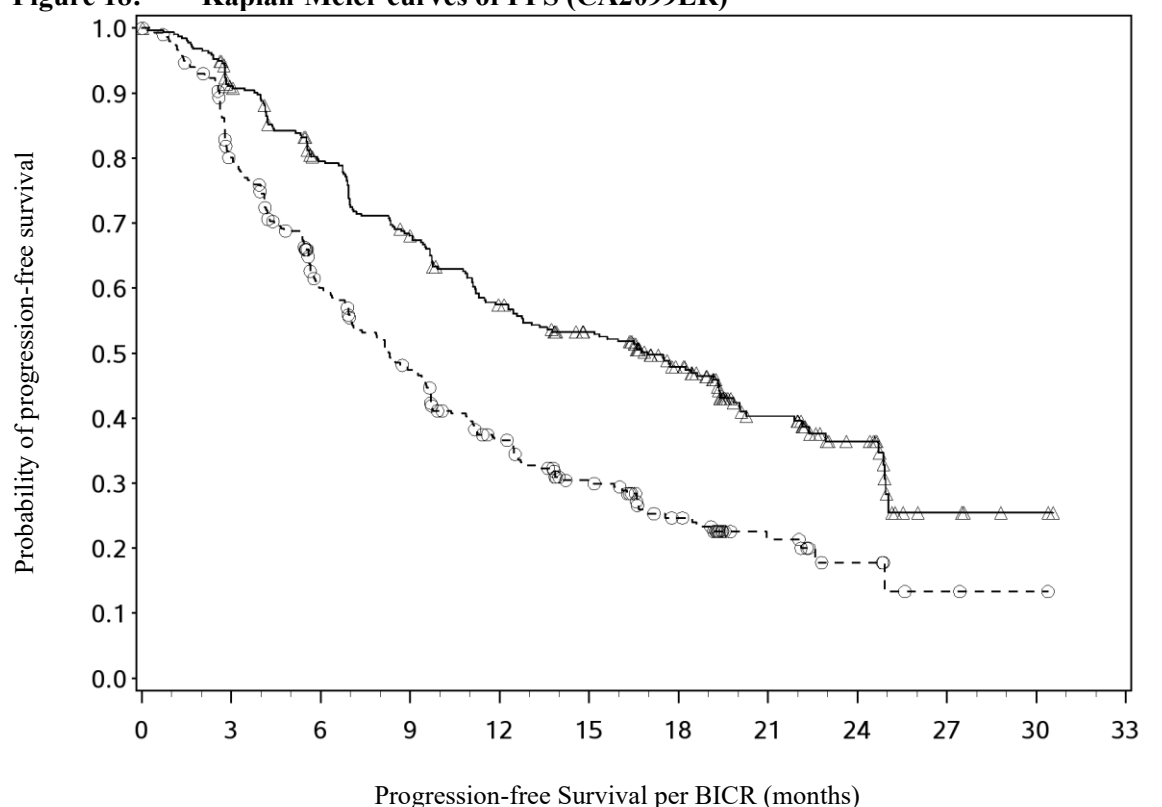
The primary analysis of PFS included censoring for new anti-cancer treatment (Table 28). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

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

PFS benefit was observed in the nivolumab in combination with cabozantinib arm vs. sunitinib regardless of tumour PD-L1 expression. Median PFS for tumour PD-L1 expression $\geq 1\%$ was 13.08 months for nivolumab in combination with cabozantinib, and was 4.67 months in the sunitinib arm (HR = 0.45; 95% CI: 0.29, 0.68). For tumour PD-L1 expression $< 1\%$, the median PFS was 19.84 months for nivolumab in combination with cabozantinib, and 9.26 months in the sunitinib arm (HR = 0.50; 95% CI: 0.38, 0.65).

An updated PFS and OS analysis were performed when all patients had a minimum follow-up of 16.0 months and a median follow-up of 23.5 months (see Figures 18 and 19). The PFS hazard ratio was 0.52 (95% CI: 0.43, 0.64). The OS hazard ratio was 0.66 (95% CI: 0.50, 0.87). Updated efficacy data (PFS and OS) in subgroups for the IMDC risk categories and PD-L1 expression levels confirmed the original results. With the updated analysis, median PFS is reached for the favourable risk group.

Figure 18: Kaplan-Meier curves of PFS (CA2099ER)

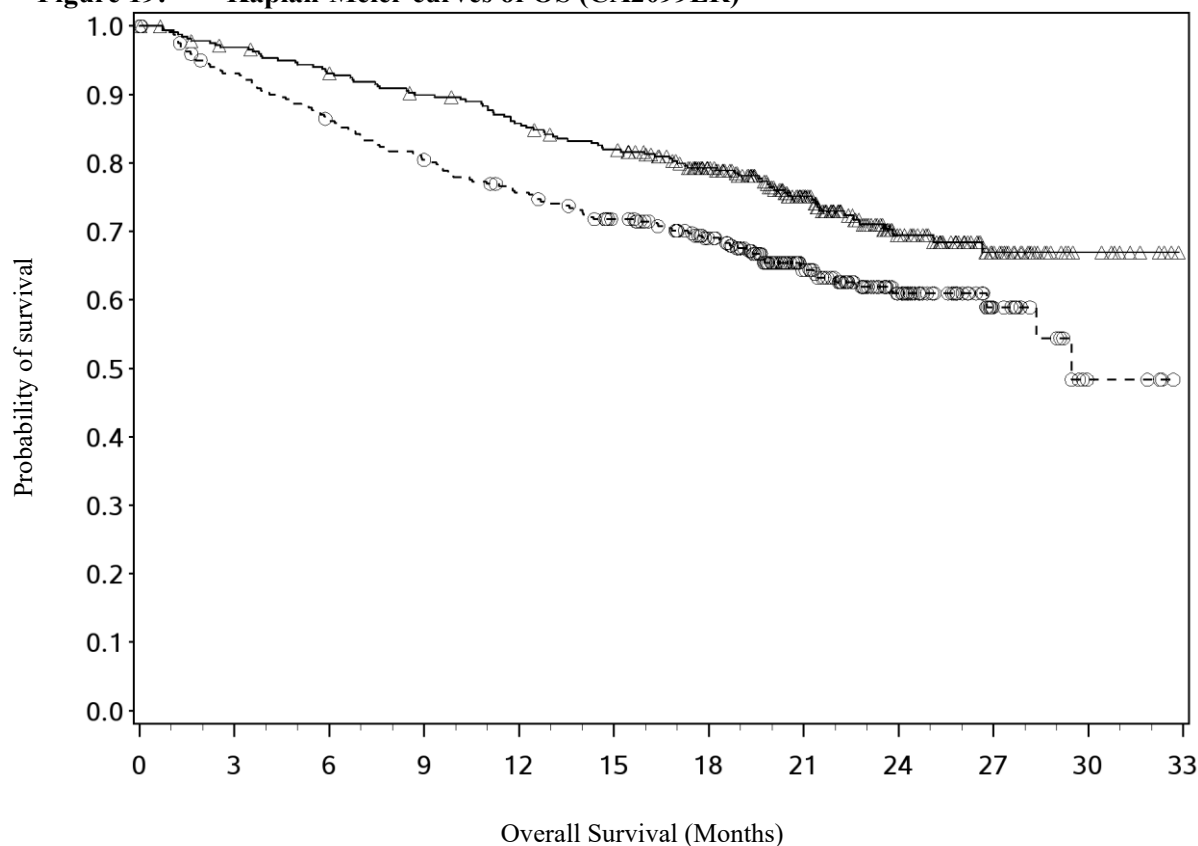


Number of subjects at risk

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

---△--- Nivolumab + cabozantinib (events: 175/323), median and 95.0% CI: 16.95 (12.58, 19.38)
 ---○--- Sunitinib (events: 206/328), median and 95.0% CI: 8.31 (6.93, 9.69)

Figure 19: Kaplan-Meier curves of OS (CA2099ER)



Number of subjects at risk

Nivolumab + cabozantinib

323 308 295 283 269 255 220 147 84 40 10 0

Sunitinib

328 295 272 254 236 217 189 118 62 22 4 0

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

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

Subcutaneous formulation

Randomised, open-label phase 3 study vs. intravenous nivolumab (CA20967T)

The safety and efficacy of nivolumab subcutaneous formulation was evaluated in a multicentre, randomised, open-label study in patients with advanced or metastatic clear cell RCC (CA20967T). Patients 18 years of age or older with histologically confirmed advanced or metastatic RCC with a clear cell component, including those with sarcomatoid features, and who received no more than 2 prior systemic treatment regimens were randomised to receive nivolumab 1200 mg every 4 weeks subcutaneously or nivolumab 3 mg/kg every 2 weeks intravenously. Patients with untreated, symptomatic CNS metastases; leptomeningeal metastases; concurrent malignancies requiring treatment or history of prior malignancy within the prior 2 years; active, known, or suspected autoimmune disease; or who received prior treatment with a checkpoint inhibitor were excluded from the study. Patients with asymptomatic, stable CNS metastases that did not require immediate treatment were eligible if there was no evidence of progression within 28 days prior to the first dose of study drug administration.

Stratification factors for randomisation were weight (< 80 kg vs ≥ 80 kg) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification (favourable vs intermediate vs poor risk).

The primary objective of the study was to demonstrate noninferiority of the serum nivolumab C_{avgd28} and C_{minss} for the subcutaneous administration of nivolumab to the intravenous administration of

nivolumab (see section 5.2). The key secondary objective of the study was to demonstrate noninferiority of the ORR for the subcutaneous administration of nivolumab to the intravenous administration of nivolumab, as assessed by blinded independent central review (BICR). Additional secondary objectives included assessing duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

A total of 495 patients were randomised to receive either subcutaneous nivolumab (n = 248) or intravenous nivolumab (n = 247). The median age was 65 years (range: 20 to 93), with 51% $\geq$ 65 years of age and 14% $\geq$ 75 years of age, 85% White, 0.8% Asian, and 0.4% Black, and 68% male. Fifty-seven percent of patients weighed $<$ 80 kg and 43% weighed $\geq$ 80 kg. Baseline Karnofsky performance status was 70 (7%), 80 (20%), 90 (34%), or 100 (39%). Patient distribution by IMDC risk categories was 21% favourable, 62% intermediate, and 17% poor.

The study demonstrated noninferiority of nivolumab 1200 mg administered subcutaneously to nivolumab 3 mg/kg administered intravenously (see section 5.2). At the primary analysis (minimum follow-up of 8 months) ORR was 24.2% (95% CI: 19.0, 30.0) for subcutaneous nivolumab and 18.2% (95% CI: 13.6, 23.6) for intravenous nivolumab. The estimate of objective response risk ratio was 1.33 (95% CI: 0.94, 1.88). To declare noninferiority, the lower bound of the two-sided 95% CI of the objective response risk ratio had to be $\geq$ 0.60. Updated efficacy results with a minimum follow-up of 14.9 months (data cut-off 21-Feb-2024) are shown in Table 29.

Table 29: Efficacy results - CA20967T

	Subcutaneous nivolumab	Intravenous nivolumab
ORR ^a per BICR % (n/N)	26.6% (66/248)	20.6% (51/247)
95% CI ^b	(21.2, 32.6)	(15.8, 26.2)
Estimate of objective response risk ratio (95% CI) ^{c, d}	1.28 (0.93, 1.77)	
DORa per BICR Median, months (95% CI) ^e	13.57 (8.57, NE)	NR (15.7, NE)

NR = not reached, NE = non-estimable

^a Descriptive analysis.

^b Confidence interval based on the Clopper and Pearson method.

^c Stratified by weight ($<$ 80 kg vs $\geq$ 80 kg) and IMDC risk group (favourable vs intermediate vs poor).

^d Strata adjusted risk ratio (subcutaneous nivolumab over intravenous nivolumab) using Mantel-Haenszel method.

^e Median computed using Kaplan-Meier method.

Intravenous formulation

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) $\geq$ 70%. This study included patients regardless of their tumour PD-L1 status. Patients with any history of or concurrent brain metastases, prior treatment with a mammalian target of rapamycin (mTOR) inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 821 patients were 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.

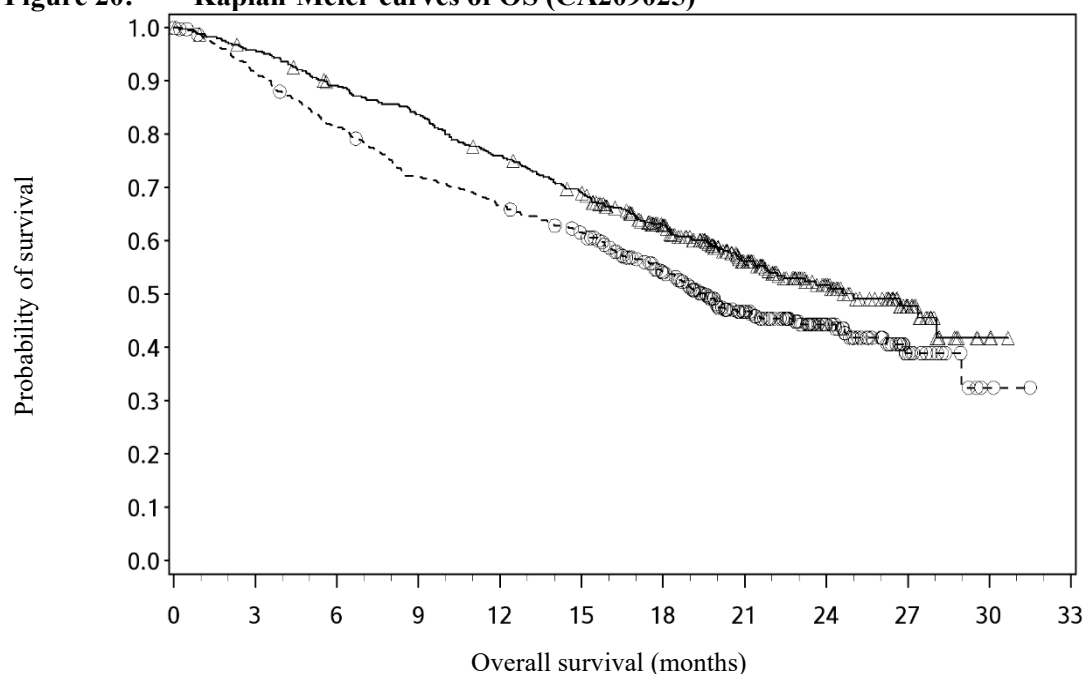
Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was OS. Secondary efficacy assessments included investigator-assessed 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 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 20.

Figure 20: Kaplan-Meier curves of OS (CA209025)



Number of subjects at risk

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

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

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

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with everolimus at the pre-specified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 30 and Figure 20). OS benefit was observed regardless of tumour PD-L1 expression level.

Efficacy results are shown in Table 30.

Table 30: 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		
(95% CI)	103 (25.1%) (21.0, 29.6)	22 (5.4%) (3.4, 8.0)
Odds ratio (95% CI)		5.98 (3.68, 9.72)
p-value		< 0.0001
Complete response (CR)	4 (1.0%)	2 (0.5%)
Partial response (PR)	99 (24.1%)	20 (4.9%)
Stable disease (SD)	141 (34.4%)	227 (55.2%)
Median duration of response		
Months (range)	11.99 (0.0-27.6 ⁺)	11.99 (0.0 ⁺ -22.2 ⁺)
Median time to response		
Months (range)	3.5 (1.4-24.8)	3.7 (1.5-11.2)
Progression-free survival		
Events	318 (77.6%)	322 (78.3%)
Hazard ratio		0.88
95% CI		(0.75, 1.03)
p-value		0.1135
Median (95% CI)	4.6 (3.71, 5.39)	4.4 (3.71, 5.52)

^{“+”} denotes a censored observation.

NE = non-estimable

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

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

Intravenous formulation

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.

Squamous cell cancer of the head and neck

Intravenous formulation

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.

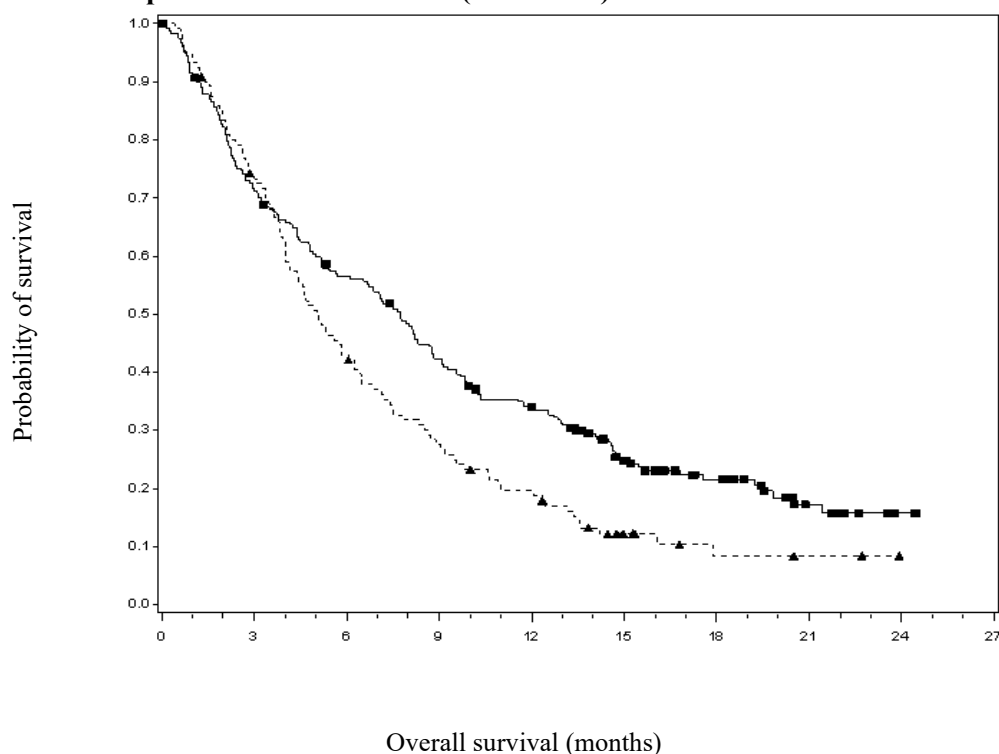
A total of 361 patients were randomised to receive either nivolumab 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n = 15), 400 mg/m² loading dose followed by 250 mg/m² weekly or methotrexate (n = 52) 40 to 60 mg/m² weekly, or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

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

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

With a minimum follow-up of 11.4 months, the trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice. The Kaplan-Meier curves for OS are shown in Figure 21. Efficacy results are shown in Table 31.

Figure 21: Kaplan-Meier curves of OS (CA209141)



Number of subjects at risk

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

—■— Nivolumab 3 mg/kg (events: 184/240), median and 95% CI: 7.72 (5.68, 8.77)
 ---▲--- Investigator's choice (events: 105/121), median and 95% CI: 5.06 (4.04, 6.24)

Table 31: Efficacy results (CA209141)

	nivolumab (n = 240)	investigator's choice (n = 121)
Overall survival		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio ^a		0.71
(95% CI)		(0.55, 0.90)
p-value ^b		0.0048
Median (95% CI) (months)	7.72 (5.68, 8.77)	5.06 (4.04, 6.24)
Rate (95% CI) at 6 months	56.5 (49.9, 62.5)	43.0 (34.0, 51.7)
Rate (95% CI) at 12 months	34.0 (28.0, 40.1)	19.7 (13.0, 27.3)
Rate (95% CI) at 18 months	21.5 (16.2, 27.4)	8.3 (3.6, 15.7)
Progression-free survival		
Events	204 (85.0%)	104 (86.0%)
Hazard ratio		0.87
95% CI		(0.69, 1.11)
p-value		0.2597

	nivolumab (n = 240)	investigator's choice (n = 121)
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 $\geq 1\%$ (55% vs. 62%), $\geq 5\%$ (34% vs. 43%), or $\geq 10\%$ (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 $\geq 1\%$, $\geq 5\%$ or $\geq 10\%$ tumour PD-L1 expression levels (see Table 32).

Table 32: 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)
$\geq 1\%$	66 (88)	55 (61)	0.53 (0.37, 0.77)
$\geq 5\%$	39 (54)	40 (43)	0.51 (0.32, 0.80)
$\geq 10\%$	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 33). 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 33: 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

Adjuvant treatment of urothelial carcinoma

Intravenous formulation

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

The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of urothelial carcinoma was evaluated in a phase 3 multicentre, randomised, placebo-controlled, double-blinded study (CA209274). The study included patients (18 years or older) who have undergone radical resection of muscle invasive urothelial carcinoma (MIUC) originating in the bladder or upper urinary tract (renal

pelvis or ureter) and are at high risk of recurrence. The MIUC pathologic staging criteria that defines high risk patients was ypT2-ypT4a or ypN⁺ for adult patients who received neoadjuvant cisplatin chemotherapy, and pT3-pT4a or pN⁺ for adult patients who did not receive neoadjuvant cisplatin chemotherapy and were not eligible or refused adjuvant cisplatin chemotherapy. The study included patients regardless of their PD-L1 status, who had an ECOG performance status score of 0 or 1 (an ECOG PS of 2 was allowed for patients ineligible for neoadjuvant cisplatin chemotherapy). Tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. The study excluded patients with active, known or suspected autoimmune disease, patients who had treatment with any chemotherapy, radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment.

A total of 709 patients were randomised to receive either nivolumab 240 mg (n = 353) every 2 weeks or placebo (n = 356) every 2 weeks until recurrence or unacceptable toxicity for a maximum treatment duration of 1 year. Of these, 282 patients had tumour cell PD-L1 expression $\geq 1\%$; 140 in the nivolumab arm and 142 in the placebo arm. Randomisation was stratified by pathologic nodal status (N⁺ vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), tumour cell PD-L1 expression ($\geq 1\%$ vs. $< 1\%$ /indeterminate), and use of cisplatin neoadjuvant chemotherapy. Tumour imaging assessments were to be performed every 12 weeks from the date of first dose to week 96, then every 16 weeks from week 96 to week 160, then every 24 weeks until non-urothelial tract recurrence or treatment was discontinued (whichever occurred later) for a maximum of 5 years. The primary efficacy outcome measures were disease-free survival (DFS) in all randomised patients and DFS in randomised patients with tumour cell PD-L1 expression $\geq 1\%$. DFS was defined as the time between the date of randomisation and the date of the first documented recurrence assessed by investigator (local urothelial tract, local non-urothelial tract or distant), or death (from any cause), whichever occurred first. Secondary efficacy outcome measures included overall survival (OS).

Baseline characteristics were generally balanced across treatment groups. In patients with tumour cell PD-L1 expression $\geq 1\%$, the median age was 66 years (range: 34-92 years), 76% were male and 76% were white. Eighty two percent had muscle invasive bladder cancer (MIBC), 18% had upper tract urothelial carcinoma (UTUC) (renal pelvis and ureter), 42% of patients received prior cisplatin in the neoadjuvant setting, 45% of patients were N⁺ at radical resection, patients had ECOG performance status of 0 (61%), 1 (37%), or 2 (2%), and 7% of patients had a haemoglobin < 10 g/dL.

At the primary pre-specified interim analysis in patients with tumour cell PD-L1 expression $\geq 1\%$ (minimum follow-up of 6.3 months and median follow-up of 22.1 months for the nivolumab arm), the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab as compared to placebo. Median DFS as determined by the investigator was not reached (95% CI: 21.19, N.R.) for nivolumab versus 8.41 months (95% CI: 5.59, 21.19) for placebo, HR 0.55 (98.72% CI: 0.35, 0.85), p-value = 0.0005. The primary analysis of DFS included censoring for new anti-cancer treatment. Results for DFS with and without censoring for new anti-cancer treatment were consistent.

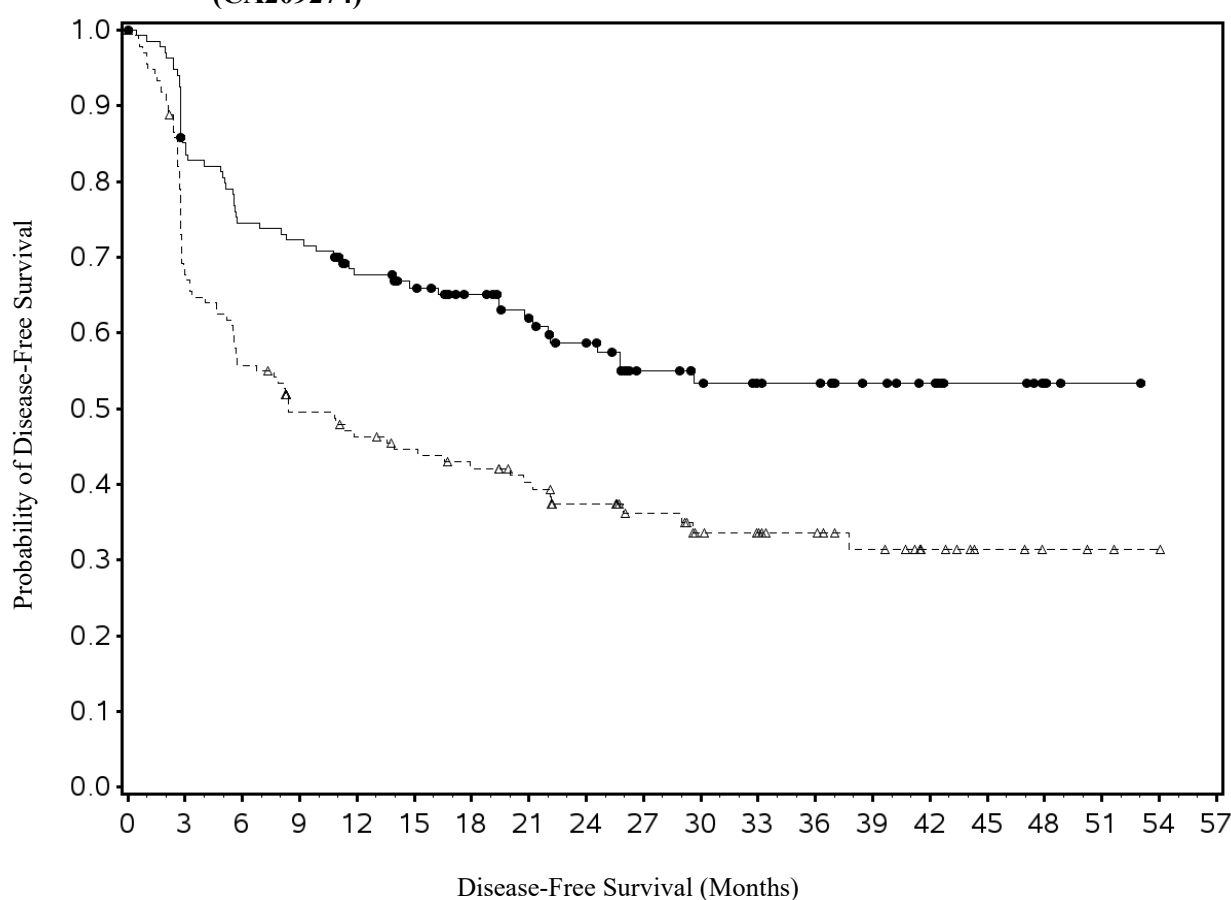
In an updated descriptive DFS analysis in patients with tumour cell PD-L1 expression $\geq 1\%$ (minimum follow-up of 11.4 months and median follow-up of 25.5 months for the nivolumab arm), DFS improvement was confirmed.

Efficacy results from this descriptive updated analysis are shown in Table 34 and Figure 22.

Table 34: Efficacy results in patients with tumour cell PD-L1 $\geq 1\%$ (CA209274)

	nivolumab (n = 140)	placebo (n = 142)
Disease-Free Survival	Minimum follow-up 11.4 months	
Events (%)	56 (40.0)	85 (59.9)
Hazard ratio (95% CI) ^a	0.53 (0.38, 0.75)	
Median (95% CI) (months) ^b	NR (22.11, NE)	8.41 (5.59, 20.04)
Rate (95% CI) at 6 months	74.5 (66.2, 81.1)	55.7 (46.8, 63.6)
Rate (95% CI) at 12 months	67.6 (59.0, 74.9)	46.3 (37.6, 54.5)
Rate (95% CI) at 24 months	58.6 (49.3, 66.9)	37.4 (29.0, 45.8)

NR: not reached, NE: non-estimable.

^a Stratified Cox proportional hazard model. Hazard Ratio is nivolumab over placebo.^b Based on Kaplan-Meier estimates.**Figure 22: Kaplan-Meier curves of DFS in patients with tumour cell PD-L1 expression $\geq 1\%$ (CA209274)**

Number of subjects at risk

Placebo	142	90	74	62	57	53	49	44	36	29	23	21	18	14	9	5	3	2	1	0
Nivolumab	140	113	99	96	85	75	67	58	50	38	33	30	29	22	19	8	3	1	0	0

---△--- Placebo (events: 85/142), median and 95% CI: 8.41 (5.59, 20.04)

—●— Nivolumab (events: 56/140), median and 95% CI: N.A. (22.11, N.A.)

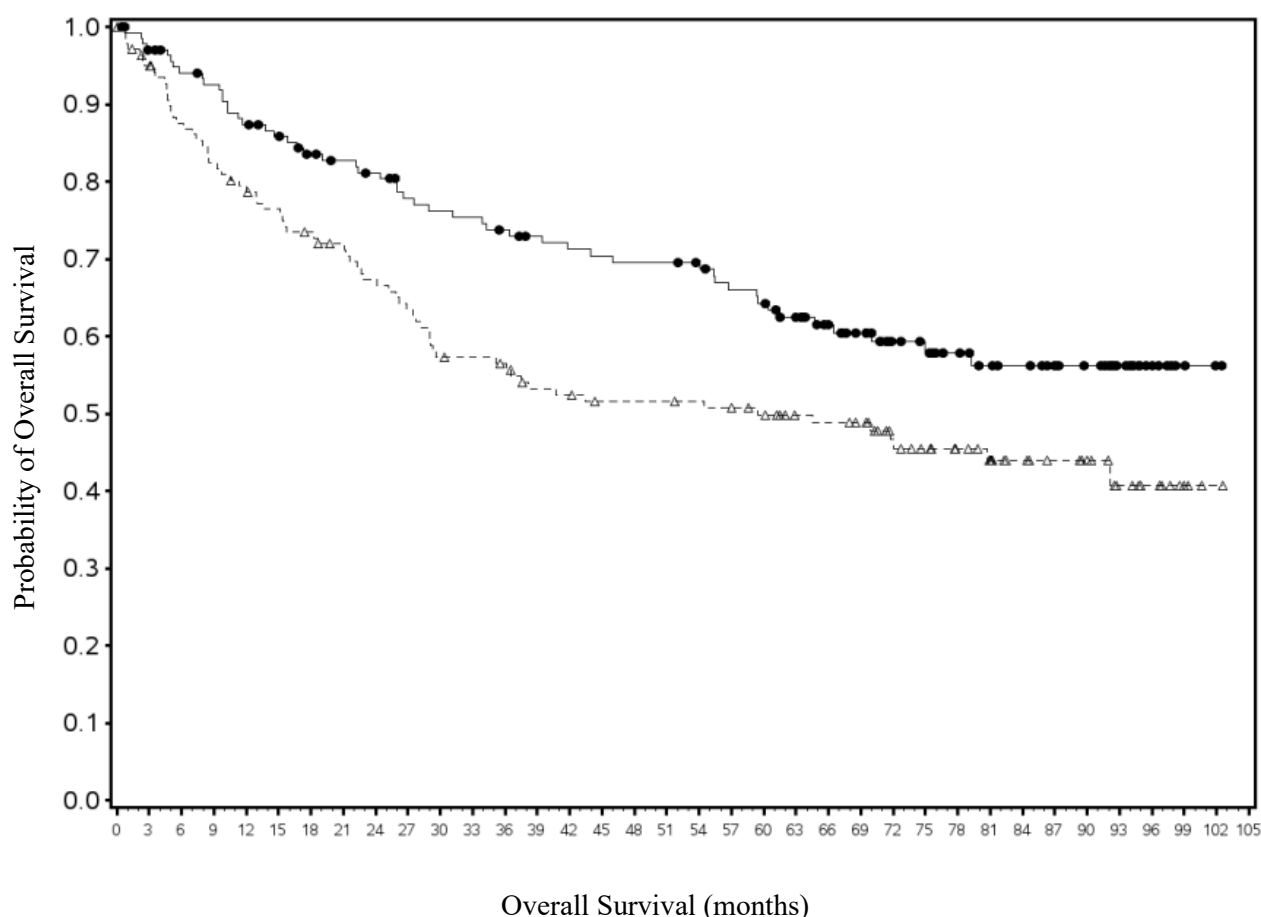
Minimum follow-up of 11.4 months

In an interim OS analysis, OS data was immature with HR = 0.63; (99.26% CI: 0.38 to 1.02; p-value = 0.0099). The median OS was not reached in the nivolumab arm, while median OS was 59.43 months (95% CI: 29.14, NA) in the control arm (see Figure 23).

Exploratory pre-specified subgroup descriptive analyses were performed in patients based on prior cisplatin treatment in the neoadjuvant setting.

In the subgroup of patients with tumour cell PD-L1 expression $\geq 1\%$ who received prior cisplatin in the neoadjuvant setting (n = 118), the DFS HR was 0.37 (95% CI: 0.22, 0.64) with median DFS not reached and 8.41 months for the nivolumab and placebo arms, respectively. In the subgroup of patients with tumour cell PD-L1 expression $\geq 1\%$ who did not receive prior cisplatin in the neoadjuvant setting (n = 164), the DFS HR was 0.69 (95% CI: 0.44, 1.08) with median DFS of 29.67 and 11.37 months for the nivolumab and placebo arms, respectively.

Figure 23: Kaplan-Meier curves of Overall Survival in patients with PD-L1 Expression $\geq 1\%$ (CA209274)



Number of subjects at risk

Placebo

142 131 119 112 107 102 97 93 87 82 74 73 71 65 64 61 61 61 60 59 56 51 50 48 40 36 31 27 22 19 16 11 8 3 1 0

Nivolumab

140 133 127 124 117 113 107 104 101 95 93 92 89 86 84 83 82 82 80 75 73 67 60 54 45 43 36 32 30 26 23 17 9 4 1 0

---△--- Placebo

—●— Nivolumab

Minimum follow-up of 52.9 months

Treatment of advanced urothelial carcinoma

Intravenous formulation

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

The safety and efficacy of nivolumab in combination with cisplatin and gemcitabine followed by nivolumab monotherapy were evaluated in a randomised open-label study CA209901 in cisplatin-

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

A total of 608 patients were randomised to receive either nivolumab in combination with cisplatin and gemcitabine (n = 304) or cisplatin and gemcitabine (n = 304). Randomisation was stratified by tumour PD-L1 status ($\geq 1\%$ vs. $< 1\%$ or indeterminate) and liver metastasis (yes vs. no). The median age was 65 years of age (range: 32 to 86) with 51% of patients ≥ 65 years of age and 12% of patients ≥ 75 years of age, 23% were Asian, 72% were White, 0.3% were Black; 77% were male, 23% were female. Baseline ECOG performance status was 0 (53%) or 1 (46%). Patients in the nivolumab in combination with cisplatin and gemcitabine arm were treated with nivolumab 360 mg every three weeks, in combination with cisplatin and gemcitabine for up to 6 cycles, after which patients received nivolumab monotherapy 480 mg every 4 weeks for a total of up to 24 months. Patients received gemcitabine dosed at 1000 mg/m² IV over 30-minutes on Days 1 and 8 of the 3 week treatment cycle and cisplatin dosed at 70 mg/m² IV over 30 to 120-minutes on Day 1 of the 3 week treatment cycle. A total of 92 patients (49 in the nivolumab in combination with cisplatin and gemcitabine arm and 43 in the cisplatin and gemcitabine arm) switched from cisplatin to carboplatin after at least one cycle of cisplatin.

The study demonstrated a statistically significant benefit in OS and PFS for patients randomised to nivolumab in combination with cisplatin and gemcitabine compared to cisplatin and gemcitabine alone. Efficacy results are presented in Table 35 and Figures 24 and 25.

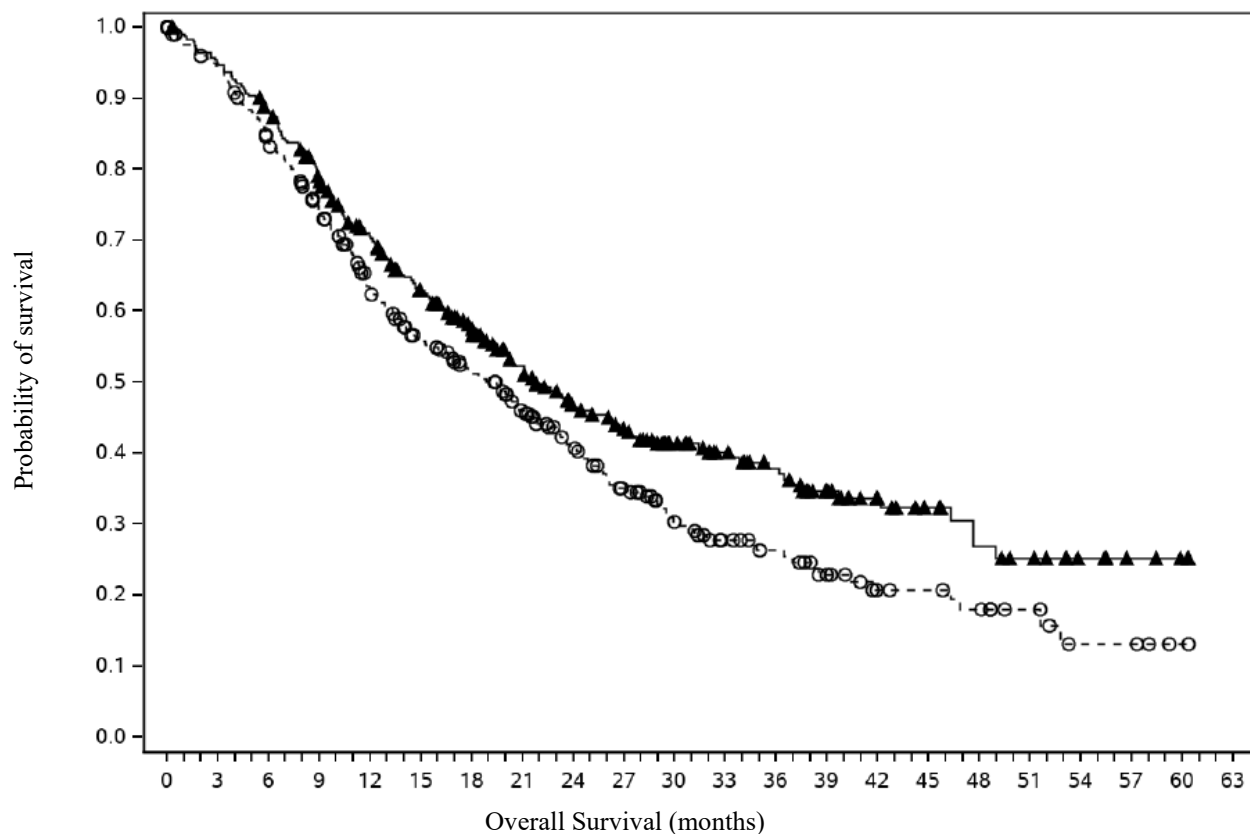
Table 35: Efficacy Results (CA209901)

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

^a Based on Kaplan-Meier Estimates

- ^b Stratified Cox proportional hazard model.
^c 2 sided p-value from stratified log-rank test.

Figure 24: Kaplan Meier curves of OS (CA209901)



Number of subjects at risk

Nivolumab + gemcitabine-cisplatin chemotherapy

304 286 264 228 196 167 142 119 97 84 69 58 48 36 25 20 15 12 7 4 2 0

Gemcitabine-cisplatin chemotherapy

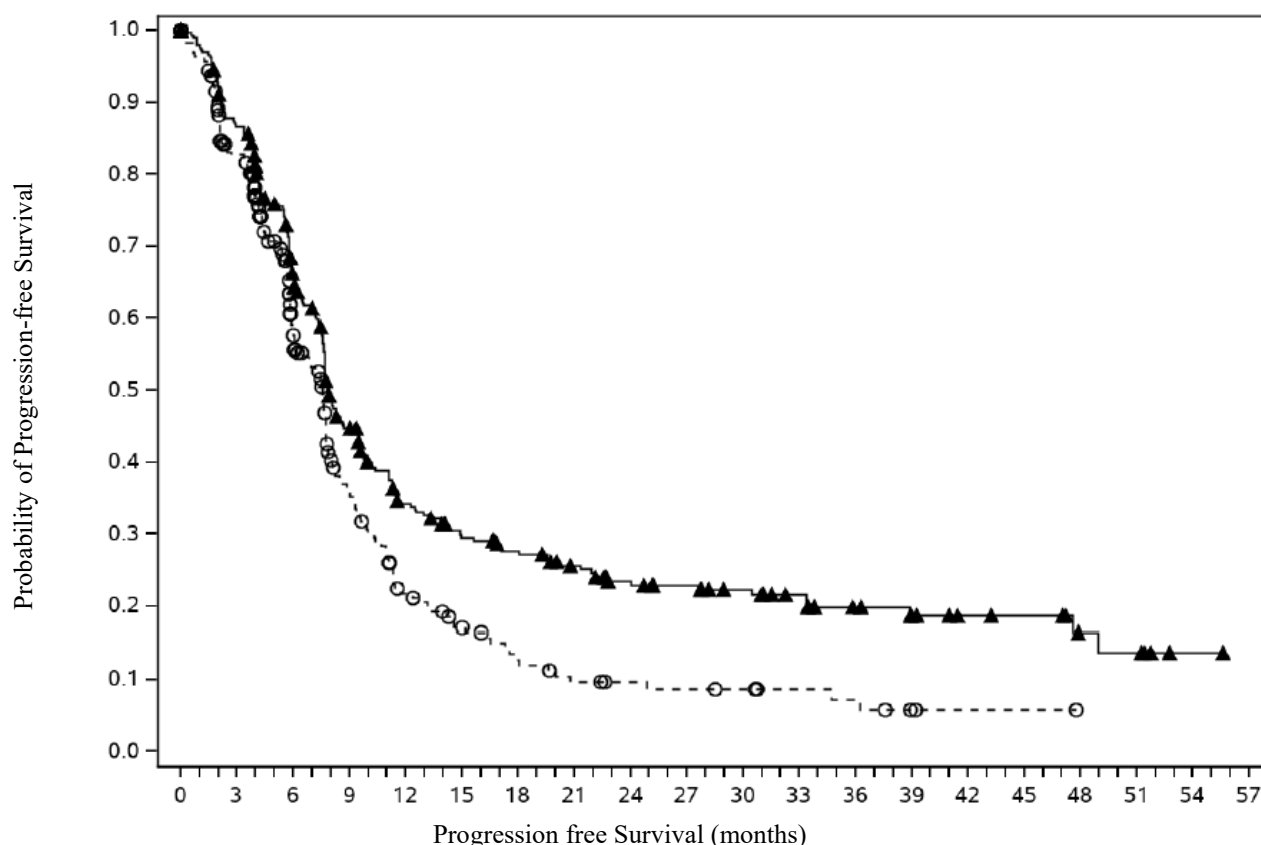
304 277 242 208 166 140 122 102 82 65 49 39 33 24 17 16 13 9 4 4 1 0

—▲— Nivolumab + gemcitabine-cisplatin chemotherapy (events: 172/304), median and 95% CI: 21.72 (18.63, 26.38)

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

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

Figure 25: Kaplan Meier curves of PFS (CA209901)



Number of subjects at risk

Nivolumab + gemcitabine-cisplatin chemotherapy

304 253 179 116 82 65 57 49 41 36 31 26 19 14 11 10 10 6 5 1 0

Gemcitabine-cisplatin chemotherapy

304 223 119 63 35 25 17 12 12 10 9 8 6 5 2 1 1 0 0 0 0

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

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

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

The primary analysis of PFS included censoring for new anti-cancer treatment before disease progression (Table 33). Results for PFS with and without censoring for new anti-cancer treatment before disease progression were consistent.

Intravenous formulation

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 (see Table 36).

The median age was 66 years (range: 38 to 90) with 55% $\geq$ 65 years of age and 14% $\geq$ 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 36: Efficacy results (CA209275)^a

nivolumab (n = 270)	
Confirmed objective response	54 (20.0%)
(95% CI)	(15.4, 25.3)
Complete response (CR)	8 (3.0%)
Partial response (PR)	46 (17.0%)
Stable disease (SD)	60 (22.2%)
Median duration of response^b	
Months (range)	10.4 (1.9 ⁺ -12.0 ⁺)
Median time to response	
Months (range)	1.9 (1.6, 7.2)
Progression-free survival	
Events (%)	216 (80)
Median (95% CI) months	2.0 (1.9, 2.6)
Rate (95% CI) at 6 months	26.1 (20.9, 31.5)
Overall survival^c	
Events (%)	154 (57)
Median (95% CI) months	8.6 (6.05, 11.27)
Rate (95% CI) at 12 months	41.0 (34.8, 47.1)
Tumour PD-L1 expression level	
< 1%	≥ 1%
Confirmed objective response	
(95% CI)	
16% (10.3, 22.7) n = 146	25% (17.7, 33.6) n = 124
Median duration of response	
Months (range)	
10.4 (3.7, 12.0 ⁺)	Not Reached (1.9 ⁺ , 12.0 ⁺)
Progression-free survival	
Median (95% CI) months	3.6 (1.9, 3.7)
Rate (95% CI) at 6 months	30.8 (22.7, 39.3)
Overall survival	
Median (95% CI) months	11.6 (9.10, NE)
Rate (95% CI) at 12 months	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.

Intravenous formulation

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.

dMMR or MSI-H colorectal cancer

Intravenous formulation

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

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

A total of 303 previously untreated patients, in the metastatic setting, were randomised to study, including 202 patients to nivolumab in combination with ipilimumab and 101 patients to chemotherapy. Among them 255 had centrally confirmed MSI-H/dMMR status, 171 in the nivolumab in combination with ipilimumab arm and 84 in the chemotherapy arm. Patients in the nivolumab plus ipilimumab arm received nivolumab 240 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks. Patients in the chemotherapy arm received: mFOLFOX6 (oxaliplatin, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m², leucovorin 400 mg/m², and fluorouracil 400 mg/m² bolus followed by fluorouracil 2400 mg/m² over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m² administered prior to mFOLFOX6 every 2 weeks; or FOLFIRI (irinotecan, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m², leucovorin 400 mg/m², and fluorouracil 400 mg/m² bolus and fluorouracil 2400 mg/m² over 46 hours every 2 weeks. Bevacizumab 5 mg/kg on or cetuximab 500 mg/m² administered prior to FOLFIRI every 2 weeks. Treatment continued until disease progression, unacceptable toxicity, or for nivolumab in combination with ipilimumab up to

24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Tumour assessments per RECIST version 1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter until week 96, then every 16 weeks thereafter until week 146, and then every 24 weeks.

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

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

The study met the primary endpoint, at the planned interim analysis, demonstrating a statistically significant improvement in BICR assessed-PFS for patients with centrally confirmed MSI-H/dMMR in the nivolumab in combination with ipilimumab arm compared with the chemotherapy arm. The BICR-assessed PFS results are presented in Table 37 and Figure 26. At the time of this interim analysis, the other endpoints, including the data from nivolumab monotherapy arm, were not tested, due to testing hierarchy.

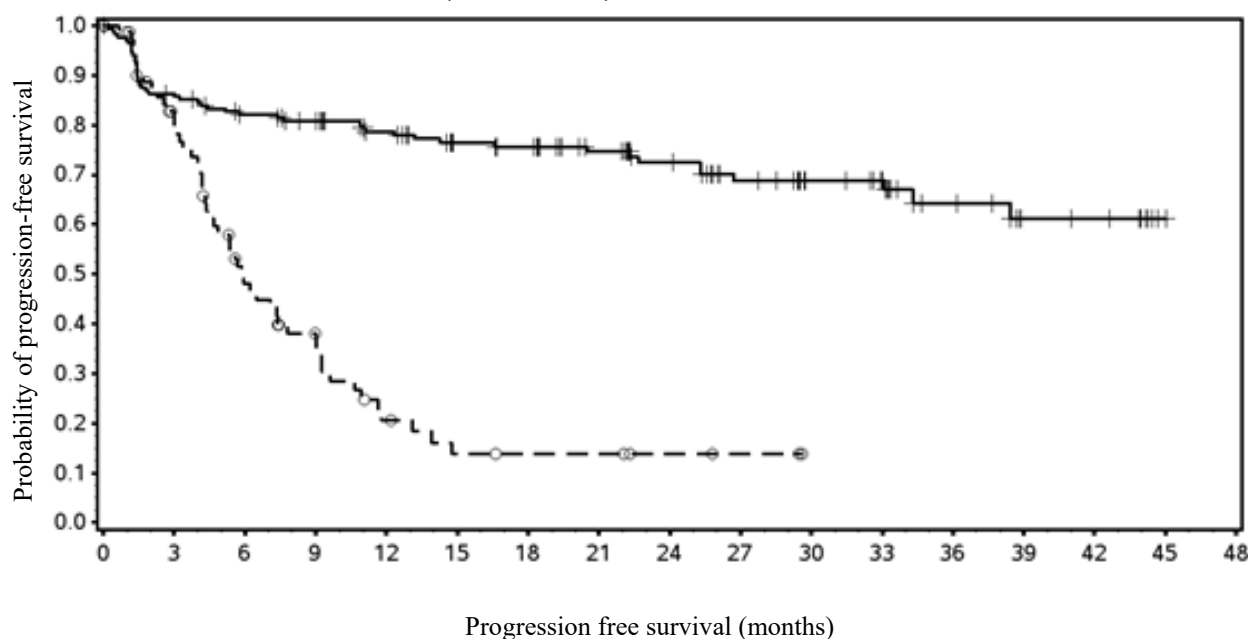
Table 37: Efficacy results in first-line MSI-H/dMMR centrally confirmed CRC (CA2098HW)^a

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

^a Median follow-up of 31.5 months (range: 6.1 to 48.4 months).

^b Based on stratified 2-sided log-rank test.

Figure 26: Kaplan-Meier curve of PFS in first-line patients with MSI-H/dMMR centrally confirmed CRC (CA2098HW)



Number of subjects at risk

Nivolumab + ipilimumab

171 144 132 122 108 95 92 77 64 53 42 37 22 10 9 1 0

Chemotherapy

84 53 29 20 10 6 5 5 3 2 0 0 0 0 0 0 0

—+— Nivolumab + ipilimumab (events: 48/171), median and 95% CI: N.A. (38.44, N.A.)

---O--- Chemotherapy (events: 52/84), median and 95% CI: 5.85 (4.37, 7.79)

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

The safety and efficacy of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the treatment of dMMR or MSI-H metastatic CRC was evaluated in a phase 2, multi-centre, open-label, single-arm study (CA209142).

The study included patients (18 years or older) with locally determined dMMR or MSI-H status, who had disease progression during, after, or were intolerant to, prior therapy with fluoropyrimidine and oxaliplatin or irinotecan. Patients who had their most recent prior treatment in the adjuvant setting should have progressed on or within 6 months of completion of adjuvant 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, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 119 patients were treated with nivolumab 3 mg/kg administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments according to RECIST, version 1.1 were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The primary outcome measure was investigator-assessed ORR. Secondary outcome measures were BICR-assessed ORR and disease control rate. Analysis of ORR included duration of and time to response. Exploratory outcome measures included PFS and OS.

The median age was 58 years (range: 21-88) with 32% ≥ 65 years of age and 9% ≥ 75 years of age, 59% were male and 92% were white. Baseline ECOG performance status was 0 (45%) or 1 (55%), 25% of patients had BRAF mutations, 37% had KRAS mutations, and 12% were unknown. Of the

119 treated patients, 109 had received prior fluoropyrimidine- based chemotherapy in the metastatic setting and 9 in the adjuvant setting. Before study enrolment, of the 119 treated patients, 118 (99%) had received fluorouracil, 111 (93%) had received oxaliplatin, 87 (73%) had received irinotecan as part of prior therapies; 82 (69%) had received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Twenty three percent, 36%, 24%, and 16% received 1, 2, 3, or 4 or more prior therapies respectively, and 29% of patients had received an EGFR inhibitor.

Efficacy results (minimum follow-up 46.9 months; median follow-up 51.1 months) are shown in Table 38.

Table 38: Efficacy results (CA209142)*

	nivolumab + ipilimumab (n = 119)
Confirmed objective response, n (%)	77 (64.7)
(95% CI)	(55.4, 73.2)
Complete response (CR), n (%)	15 (12.6)
Partial response (PR), n (%)	62 (52.1)
Stable disease (SD), n (%)	25 (21.0)
Duration of response	
Median (range) months	NR (1.4, 58.0+)
Median time to response	
Months (range)	2.8 (1.1, 37.1)

* per investigator assessment

“+” denotes a censored observation.

NR = not reached

The BICR-assessed ORR was 61.3% (95% CI: 52.0, 70.1), including CR rate of 20.2% (95% CI: 13.4, 28.5), PR rate of 41.2% (95% CI: 32.2, 50.6) and stable disease reported in 22.7%. BICR assessments were generally consistent with the investigator assessment. Confirmed responses were observed regardless of BRAF or KRAS mutation status, and tumour PD-L1 expression levels.

Of 119 patients 11 (9.2%) patients were ≥ 75 years. The investigator assessed ORR in patients ≥ 75 years was 45.5% (95% CI: 16.7, 76.6).

Oesophageal squamous cell carcinoma

Intravenous formulation

Randomised phase 3 study of nivolumab in combination with ipilimumab vs. chemotherapy and nivolumab in combination with chemotherapy vs. chemotherapy as first-line treatment (CA209648)

The safety and efficacy of nivolumab in combination with ipilimumab and nivolumab in combination with chemotherapy were evaluated in a randomised, active-controlled, open-label study (CA209648). The study included adult patients (18 years or older) with previously untreated, unresectable advanced, recurrent or metastatic OSCC. Patients were enrolled regardless of their tumour PD-L1 status, and tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. Patients were required to have squamous cell carcinoma or adenosquamous cell carcinoma of oesophagus, not amenable to chemoradiation and/or surgery. Prior adjuvant, neoadjuvant, or definitive chemotherapy, radiotherapy or chemoradiotherapy was permitted if given as part of curative intent regimen prior to trial enrollment. Patients who had a baseline performance score ≥ 2 , had brain metastases that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the study. Randomisation was stratified by tumour cell PD-L1 status ($\geq 1\%$ vs. $< 1\%$ or indeterminate), region (East Asia vs. rest of Asia vs. rest of world), ECOG performance status (0 vs. 1), and number of organs with metastases (≤ 1 vs. ≥ 2).

A total of 970 patients were randomised to receive either nivolumab in combination with ipilimumab, (n = 325), nivolumab in combination with chemotherapy (n = 321) or chemotherapy (n = 324). Of these, 473 patients had tumour cell PD-L1 expression $\geq 1\%$, 158 in the nivolumab plus ipilimumab arm, 158 in the nivolumab plus chemotherapy arm, and 157 in the chemotherapy arm. Patients in the nivolumab plus ipilimumab arm received nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks, and patients in the nivolumab plus chemotherapy arm received nivolumab 240 mg every 2 weeks on days 1 and 15, fluorouracil 800 mg/m²/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m² intravenously on day 1 (of a 4-week cycle). Patients in the chemotherapy arm received fluorouracil 800 mg/m²/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m² intravenously on day 1 (of a 4-week cycle). Treatment continued until disease progression, unacceptable toxicity, or up to 24 months. Patients in the nivolumab plus ipilimumab arm who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Patients in the nivolumab plus chemotherapy arm in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued.

Baseline characteristics were generally balanced across treatment groups. In patients with tumour cell PD-L1 expression $\geq 1\%$, the median age was 63 years (range: 26-85), 8.2% were ≥ 75 years of age, 81.8% were male, 73.1% were Asian, and 23.3% were white. Patients had histological confirmation of squamous cell carcinoma (98.9%) or adenosquamous cell carcinoma (1.1%) in the oesophagus. Baseline ECOG performance status was 0 (45.2%) or 1 (54.8%).

Nivolumab in combination with chemotherapy vs. chemotherapy

The primary efficacy outcome measures were PFS (by BICR) and OS in patients with tumour cell PD-L1 expression $\geq 1\%$. Secondary endpoints per the pre-specified hierarchical testing included OS, PFS (by BICR), and ORR (by BICR) in all randomised patients. The tumour assessments per RECIST version 1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

At the primary pre-specified analysis, with a minimum follow-up of 12.9 months the study demonstrated a statistically significant improvement in OS and PFS in patients with tumour cell PD-L1 expression $\geq 1\%$. Efficacy results are shown in Table 39.

Table 39: Efficacy results in patients with tumour cell PD-L1 $\geq 1\%$ (CA209648)

	nivolumab + chemotherapy (n = 158)	chemotherapy ^a (n = 157)
Overall survival		
Events	98 (62.0%)	121 (77.1%)
Hazard ratio (99.5% CI) ^b	0.54 (0.37, 0.80)	
p-value ^c	< 0.0001	
Median (95% CI) (months) ^d	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months ^d	58.0 (49.8, 65.3)	37.1 (29.2, 44.9)
Progression-free survival^e		
Events	117 (74.1%)	100 (63.7%)
Hazard ratio (98.5% CI) ^b	0.65 (0.46, 0.92)	
p-value ^c	0.0023	
Median (95% CI) (months) ^d	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)
Rate (95% CI) at 12 months ^d	25.4 (18.2, 33.2)	10.5 (4.7, 18.8)
Overall response rate, n (%)^e	84 (53.2)	31 (19.7)
(95% CI)	(45.1, 61.1)	(13.8, 26.8)
Complete response	26 (16.5)	8 (5.1)
Partial response	58 (36.7)	23 (14.6)

	nivolumab + chemotherapy (n = 158)	chemotherapy ^a (n = 157)
Duration of response^e		
Median (95% CI) (months) ^d	8.38 (6.90, 12.35)	5.68 (4.40, 8.67)
Range	1.4 ⁺ , 34.6	1.4 ⁺ , 31.8 ⁺

^a Fluorouracil and cisplatin.

^b Based on stratified Cox proportional hazard model.

^c Based on stratified 2-sided log-rank test.

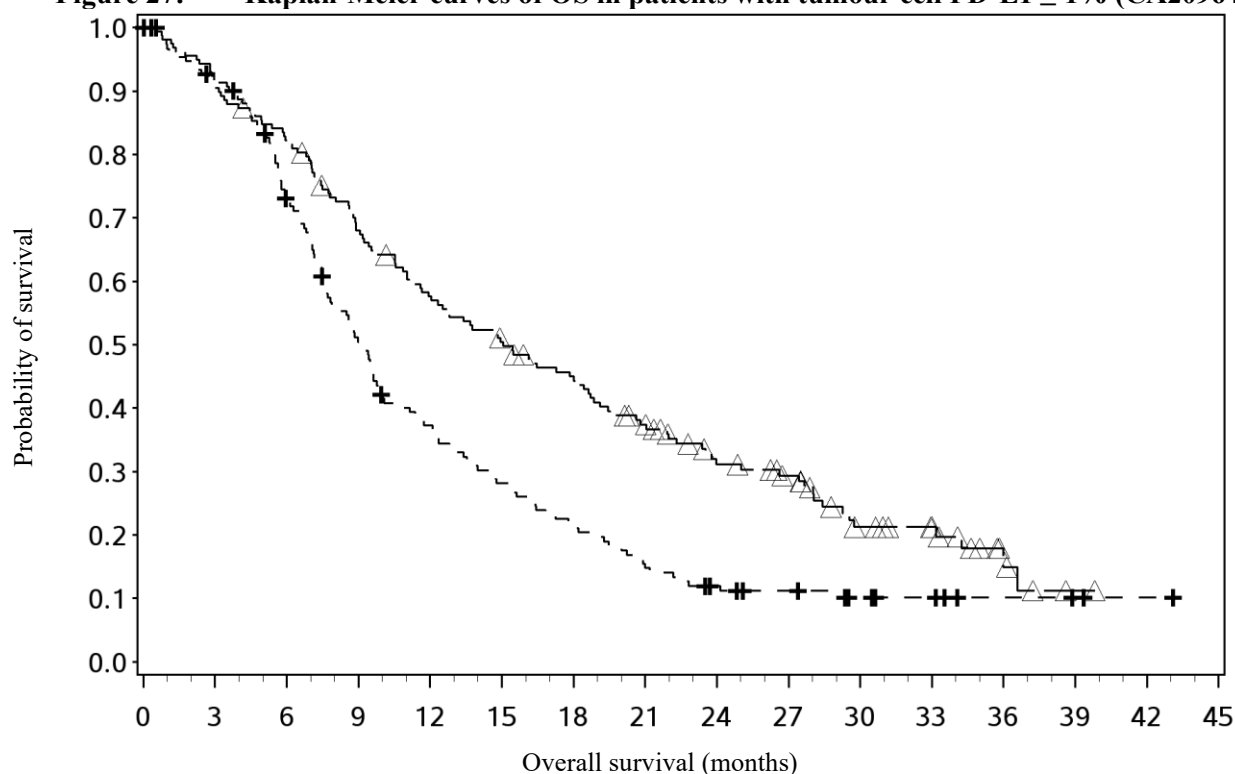
^d Based on Kaplan-Meier estimates.

^e Assessed by BICR.

At an updated descriptive analysis with a minimum follow-up of 20 months, OS improvements were consistent with the primary analysis. Median OS was 15.05 months (95% CI: 11.93, 18.63) for nivolumab plus chemotherapy vs. 9.07 months (95% CI: 7.69, 10.02) for chemotherapy (HR = 0.59; 95% CI: 0.46, 0.76). Median PFS was 6.93 months (95% CI: 5.68, 8.35) for nivolumab plus chemotherapy vs. 4.44 months (95% CI: 2.89, 5.82) for chemotherapy (HR = 0.66; 95% CI: 0.50, 0.87). The ORR was 53.2% (95% CI: 45.1, 61.1) for nivolumab plus chemotherapy vs. 19.7% (95% CI: 13.8, 26.8) for chemotherapy.

The Kaplan-Meier curves for OS and PFS with a minimum follow-up of 20 months are shown in Figures 27 and 28.

Figure 27: Kaplan-Meier curves of OS in patients with tumour cell PD-L1 $\geq 1\%$ (CA209648)



Number of subjects at risk

Nivolumab + chemotherapy

158 143 129 105 88 76 66 52 38 32 19 15 5 1 0 0

Chemotherapy

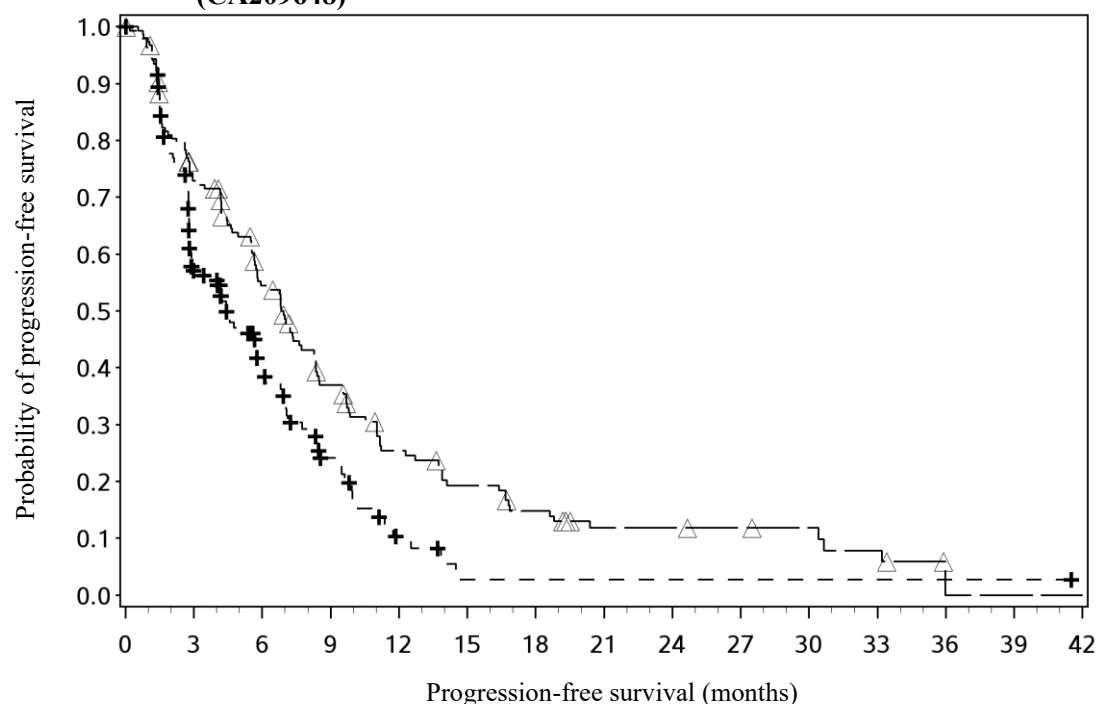
157 137 107 73 53 40 30 21 15 12 8 6 3 2 1 0

---△--- Nivolumab + chemotherapy (events: 118/158), median and 95% CI: 15.05 (11.93, 18.63)

---+--- Chemotherapy (events: 130/157), median and 95% CI: 9.07 (7.69, 10.02)

Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

Figure 28: Kaplan-Meier curves of PFS in patients with tumour cell PD-L1 $\geq 1\%$ (CA209648)



Number of subjects at risk

Nivolumab + chemotherapy

158 107 75 47 30 22 16 10 10 7 6 4 0 0 0

Chemotherapy

157 68 36 17 5 1 1 1 1 1 1 1 1 1 0

---△--- Nivolumab + chemotherapy (events: 123/158), median and 95% CI: 6.93 (5.65, 8.35)

---+--- Chemotherapy (events: 101/157), median and 95% CI: 4.44 (2.89, 5.82)

Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

Intravenous formulation

Randomised phase 3 study of nivolumab monotherapy in previously treated patients (ONO-4538-24/CA209473)

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

A total of 419 patients were randomised 1:1 to receive either nivolumab 240 mg administered intravenously over 30 minutes every 2 weeks (n = 210) or investigator's choice of taxane chemotherapy: either docetaxel (n = 65) 75 mg/m² intravenously every 3 weeks, or paclitaxel (n = 144) 100 mg/m² intravenously once a week for 6 weeks followed by 1 week off. Randomisation was stratified by location (Japan vs. rest of world), number of organs with metastases (≤ 1 vs. ≥ 2) and tumour PD-L1 expression ($\geq 1\%$ vs. $<1\%$ or indeterminate). Treatment continued until disease progression, assessed by the investigator per RECIST, version 1.1, or unacceptable toxicity. Tumour assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab with no

rapid progression, investigator-assessed benefit, tolerance to treatment, stable performance status, and for whom treatment beyond progression would not delay an imminent intervention to prevent serious complications associated with disease progression (e.g. brain metastasis). The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. Additional pre-specified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at a predefined level of 1%. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

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

With a minimum follow-up of 17.6 months, the study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice taxane chemotherapy. Efficacy results are shown in Table 40 and Figure 29.

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

Table 40: Efficacy results (ONO-4538-24/CA209473)

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

^a Based on ITT analysis.

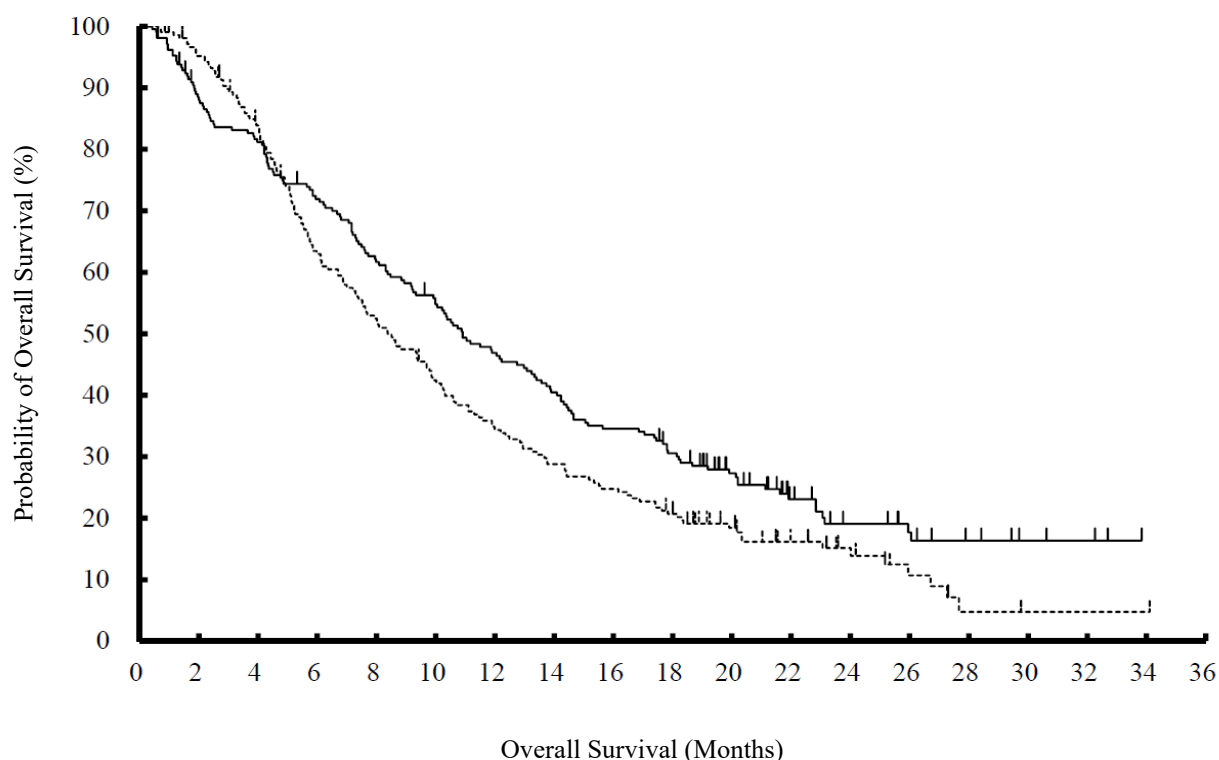
^b Based on a stratified proportional hazards model.

^c Based on a stratified log-rank test.

^d Based on Response Evaluable Set (RES) analysis, n = 171 in nivolumab group and n = 158 in investigator's choice group.

^e Not significant, p-value 0.6323.

Figure 29: Kaplan-Meier curves of OS (ONO-4538-24/CA209473)



Number of subjects at risk

Nivolumab

210 182 167 147 126 111 95 82 70 60 43 25 17 13 7 4 3 0 0

Investigator's choice

209 196 169 126 105 84 68 57 49 40 27 17 12 6 2 1 1 1 0

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

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

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer

Intravenous formulation

The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer was evaluated in a phase 3 multicentre, randomised, placebo-controlled, double-blinded study (CA209577). The study included adult patients who had received CRT, followed by complete surgical resection of carcinoma within 16 weeks prior to randomisation, and who had residual pathologic disease as confirmed by the investigator, with at least ypN1 or ypT1. Patients with a baseline performance score ≥ 2 , who did not receive concurrent CRT prior to surgery, with stage IV resectable disease, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were enrolled regardless of tumour PD-L1 expression level.

A total of 794 patients were randomised 2:1 to receive either nivolumab 240 mg (n = 532) or placebo (n = 262). Patients were administered nivolumab intravenously over 30 minutes every 2 weeks for 16 weeks followed by 480 mg infused over 30 minutes every 4 weeks beginning at week 17. Patients were administered placebo over 30 minutes with the same dosing schedule as nivolumab.

Randomisation was stratified by tumour PD-L1 status ($\geq 1\%$ vs. $< 1\%$ or indeterminate or non-evaluable), pathologic lymph node status (positive $\geq$ ypN1 vs. negative ypN0), and histology (squamous vs. adenocarcinoma). Treatment continued until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. The primary efficacy outcome measure was disease-free survival (DFS), as assessed by the investigator, defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant from the primary resected site) or death from any cause, whichever occurred first. Patients on treatment underwent imaging for tumour recurrence every 12 weeks for 2 years, and a minimum of one scan every 6 to 12 months for years 3 to 5.

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 26-86) with $36\% \geq 65$ years of age and $5\% \geq 75$ years of years. The majority of patients were white (82%) and male (85 %). Baseline ECOG performance status was 0 (58%) or 1 (42%).

At the primary pre-specified interim analysis (minimum of 6.2 months and a median of 24.4 months follow-up), the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab compared with placebo. Median DFS as determined by the investigator was 22.41 months (95% CI: 16.62, 34.00) for nivolumab versus 11.04 months (95% CI: 8.34, 14.32) for placebo, HR 0.69 (96.4% CI: 0.56, 0.86), p-value < 0.0003 . The primary analysis of DFS included censoring for new anti-cancer treatment. Results for DFS with and without censoring for new anti-cancer treatment were consistent. In an updated descriptive DFS analysis with minimum of 14 months and median of 32.2 months follow-up, DFS improvement was confirmed. Efficacy results from this descriptive secondary analysis are shown in Table 41 and Figure 30.

Table 41: Efficacy results (CA209577)

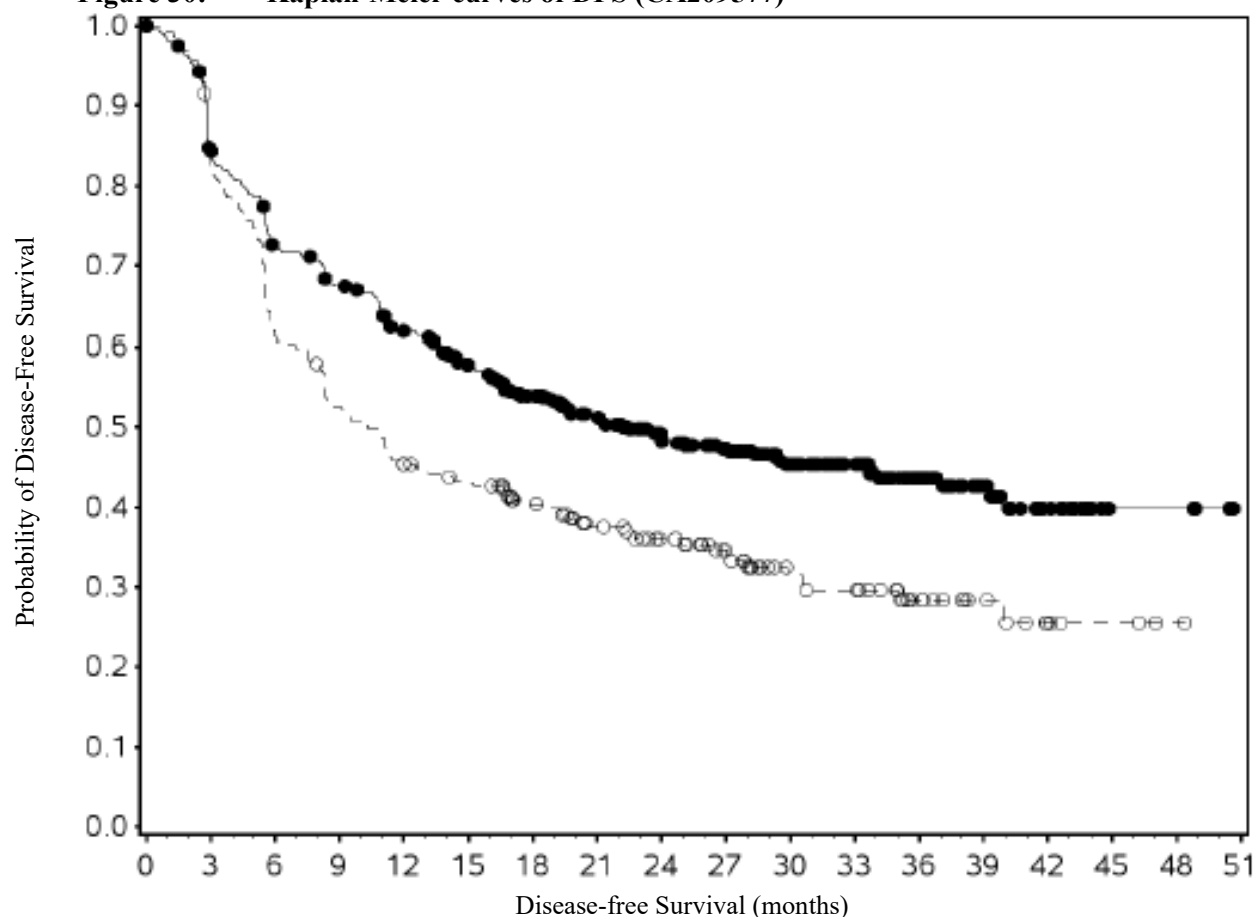
	nivolumab (n = 532)	placebo (n = 262)
Disease-free Survival^a with minimum follow-up 14 months^c		
Events (%)	268 (50)	171 (65)
Hazard ratio (95% CI) ^b	0.67 (0.55, 0.81)	
Median (95% CI) (months)	22.4 (17.0, 33.6)	10.4 (8.3, 13.9)
Rate (95% CI) at 6 months	72.6 (68.5, 76.3)	61.5 (55.3, 67.1)
Rate (95% CI) at 12 months	61.8 (57.4, 65.8)	45.5 (39.3, 51.4)
Rate (95% CI) at 24 months	48.3 (43.7, 52.8)	36.0 (29.9, 42.0)

^a Based on all randomised patients.

^b Based on a stratified cox proportional hazards model.

^c Descriptive analysis based on data cut-off: 18-Feb-2021.

Figure 30: Kaplan-Meier curves of DFS (CA209577)



Number of subjects at risk

Nivolumab

532 433 371 342 307 272 228 194 160 137 106 84 57 34 19 4 4 0

Placebo

262 211 158 134 114 107 88 73 62 50 33 30 18 11 5 3 1 0

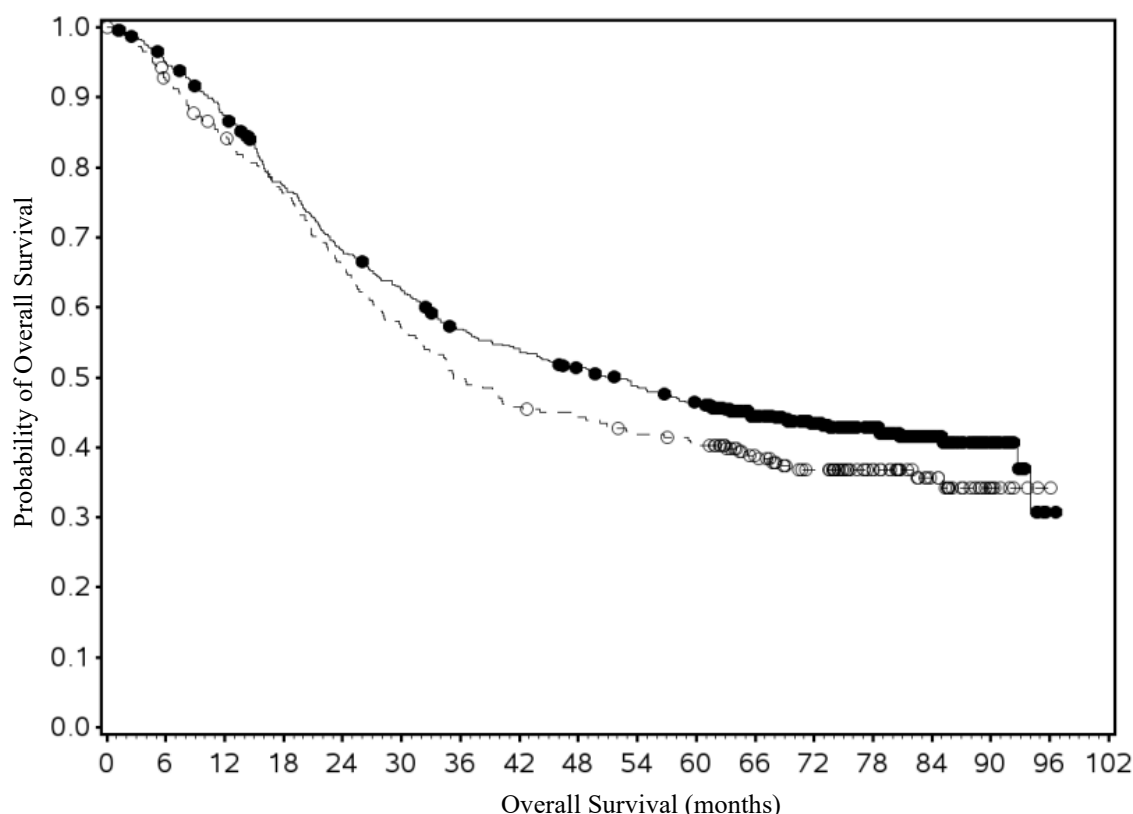
—●— Nivolumab (events: 268/532), median and 95% CI: 22.41 (16.95, 33.64)

- - -○- - - Placebo (events: 171/262), median and 95% CI: 10.35 (8.31, 13.93)

Based on data cut-off: 18-Feb-2021, minimum follow-up of 14 months

At the final OS analysis with a minimum follow up of 60 months, the HR for OS was 0.85 (95.87% CI: 0.70, 1.04), p-value = 0.1064. Median OS was 51.71 (95% CI: 41.03, 61.63) months in the nivolumab arm compared with 35.25 (95% CI: 30.72, 48.76) months in the placebo arm. The Kaplan-Meier curves for OS with a minimum follow-up of 60 months are shown in Figure 31.

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



Nivolumab
532 501 460 402 354 325 292 278 261 244 230 185 150 111 59 22 1 0

Placebo
262 239 217 195 168 146 127 117 112 105 101 80 64 46 26 8 1 0

—●— Nivolumab (events: 299/532), median and 95% CI: 51.71 (41.03, 61.63)
- - -○- - - Placebo (events: 162/262), median and 95% CI: 35.25 (30.72, 48.76)

Based on data cut-off: 17-Dec-2024, minimum follow-up of 60 months

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

Intravenous formulation

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

A total of 1581 patients were randomised to receive either nivolumab in combination with chemotherapy or chemotherapy. Of these, 955 patients had PD-L1 CPS ≥ 5 ; 473 in the nivolumab plus chemotherapy arm and 482 in the chemotherapy arm. Patients in the nivolumab plus chemotherapy arm received either nivolumab 240 mg by intravenous infusion over 30 minutes in combination with FOLFOX (oxaliplatin 85 mg/m², leucovorin 400 mg/m² and fluorouracil 400 mg/m² intravenously on day 1 and fluorouracil 1200 mg/m² intravenously by continuous infusion over 24 hours daily or per local standard on days 1 and 2) every 2 weeks, or nivolumab 360 mg by intravenous infusion over 30 minutes in combination with CapeOX (oxaliplatin 130 mg/m² intravenously on day 1 and capecitabine 1000 mg/m² orally twice daily on days 1-14) every 3 weeks. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months for nivolumab only. In patients who received nivolumab plus chemotherapy and in whom chemotherapy was discontinued, nivolumab monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks or 480 mg every 4 weeks up to 24 months after treatment initiation. Tumour assessments were performed every 6 weeks up to and including week 48, then every 12 weeks thereafter.

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

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

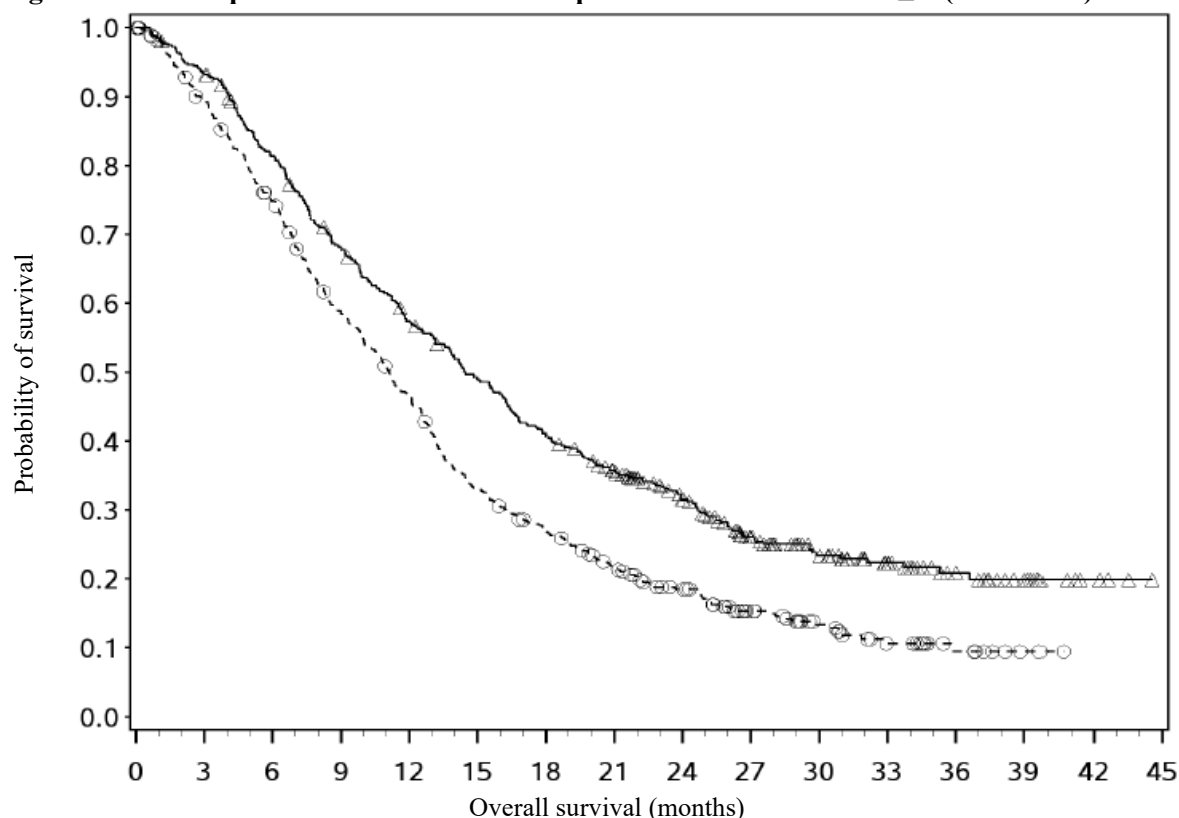
At an updated descriptive analysis with a minimum follow-up of 19.4 months, OS improvements were consistent with the primary analysis. Efficacy results are shown in Table 42, and Figures 32 and 33.

Table 42: Efficacy results in patients with PD-L1 CPS ≥ 5 (CA209649)

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

	nivolumab + chemotherapy (n = 473)	chemotherapy (n = 482)
Duration of response^{d,e}		
Median (95% CI) (months) ^c	9.69 (8.25, 12.22)	6.97 (5.62, 7.85)
^a	Descriptive analysis based on data cut-off: 04-Jan-2021.	
^b	Based on stratified long Cox proportional hazard model.	
^c	Kaplan-Meier estimate.	
^d	Confirmed by BICR.	
^e	Based on patients with measurable disease at baseline.	

Figure 32: Kaplan-Meier curves of OS in patients with PD-L1 CPS ≥ 5 (CA209649)



Number of subjects at risk

Nivolumab + chemotherapy

473 439 378 314 263 223 187 155 118 78 56 37 23 13 4 0

Chemotherapy

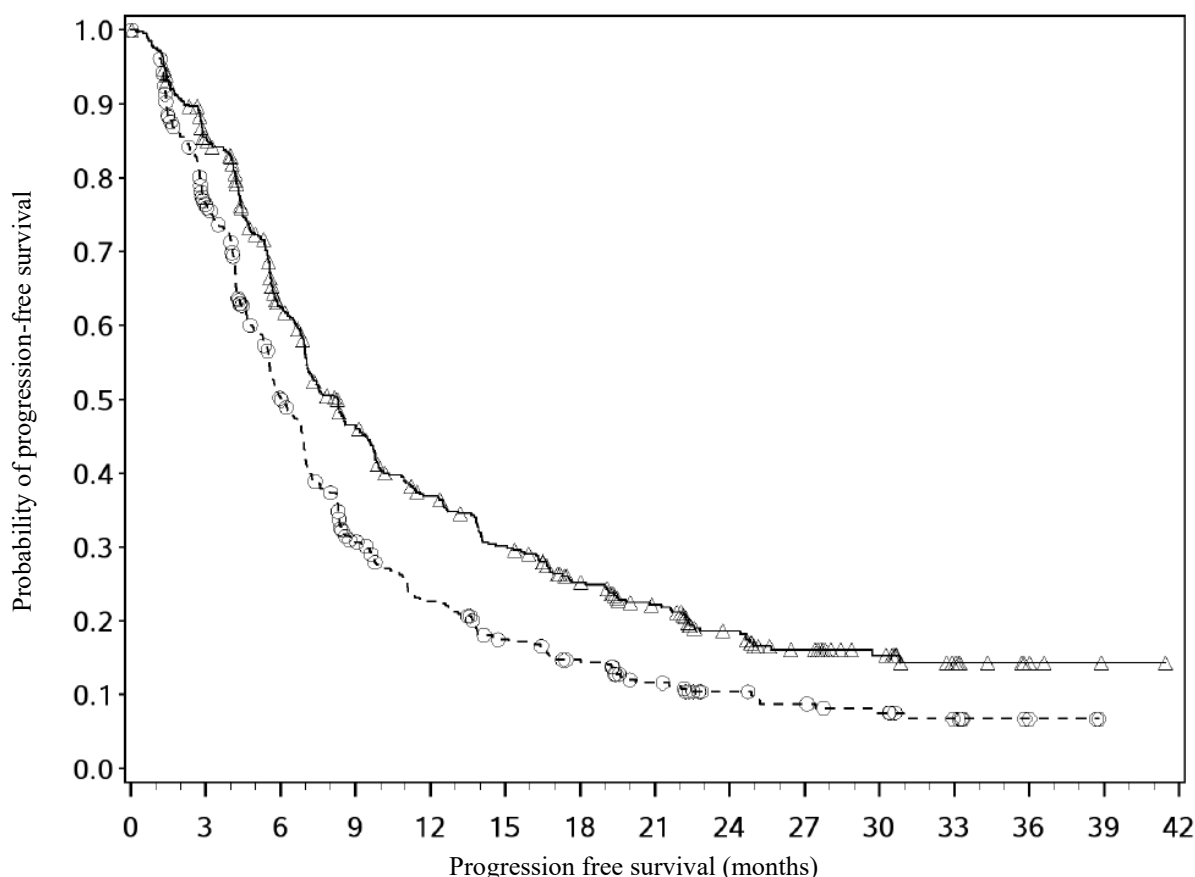
482 421 350 272 213 152 122 92 68 44 28 16 8 2 0 0

—△— Nivolumab + chemotherapy (events: 344/473), median and 95% CI: 14.42 (13.14, 16.26)

---○--- Chemotherapy (events: 397/482), median and 95% CI: 11.10 (10.02, 12.09)

Minimum follow-up of 19.4 months

Figure 33: Kaplan-Meier curves of PFS in patients with PD-L1 CPS ≥ 5 (CA209649)



Number of subjects at risk

Nivolumab + chemotherapy

473 386 259 186 143 115 88 67 47 31 20 11 4 1 0

Chemotherapy

482 328 202 114 81 58 46 30 20 16 12 7 3 0 0

—△— Nivolumab + chemotherapy (events: 342/473), median and 95% CI: 8.31 (7.03, 9.26)

---○--- Chemotherapy (events: 397/482), median and 95% CI: 6.05 (5.55, 6.90)

Minimum follow-up of 19.4 months

Hepatocellular carcinoma

Intravenous formulation

The safety and efficacy of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks in the first-line treatment of unresectable or advanced hepatocellular carcinoma (HCC) were evaluated in a phase 3, randomised, active-controlled, open-label study (CA2099DW). The study included adult patients (18 years or older) with histologically confirmed HCC, Child Pugh Class A, ECOG performance status 0 or 1, and no prior systemic therapy for advanced disease.

Esophagogastroduodenoscopy was not mandated prior to enrolment. The study enrolled adults whose disease was not amenable to or progressed after surgical and/or locoregional therapies. Prior neo-adjuvant or adjuvant systemic therapy was permitted. Patients with active autoimmune disease, brain or leptomeningeal metastases, prior liver transplant, a history of hepatic encephalopathy (within 12 months of randomisation), clinically significant ascites, medical conditions requiring systemic immunosuppression, infection with HIV, or active co infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV) were excluded from the study.

Randomisation was stratified by aetiology (HBV vs. HCV vs. non-viral), macrovascular invasion and/or extrahepatic spread (present or absent), and alpha-fetoprotein levels (≥ 400 or < 400 ng/mL).

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

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

The study demonstrated a statistically significant benefit in OS and ORR for patients randomised to nivolumab in combination with ipilimumab compared to investigator's choice of lenvatinib or sorafenib. Efficacy results are presented in Table 43 and Figure 34.

Table 43: Efficacy results in first-line HCC (CA2099DW)^a

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

^a Minimum follow-up of 26.8 months. Median follow up of 35.2 months.

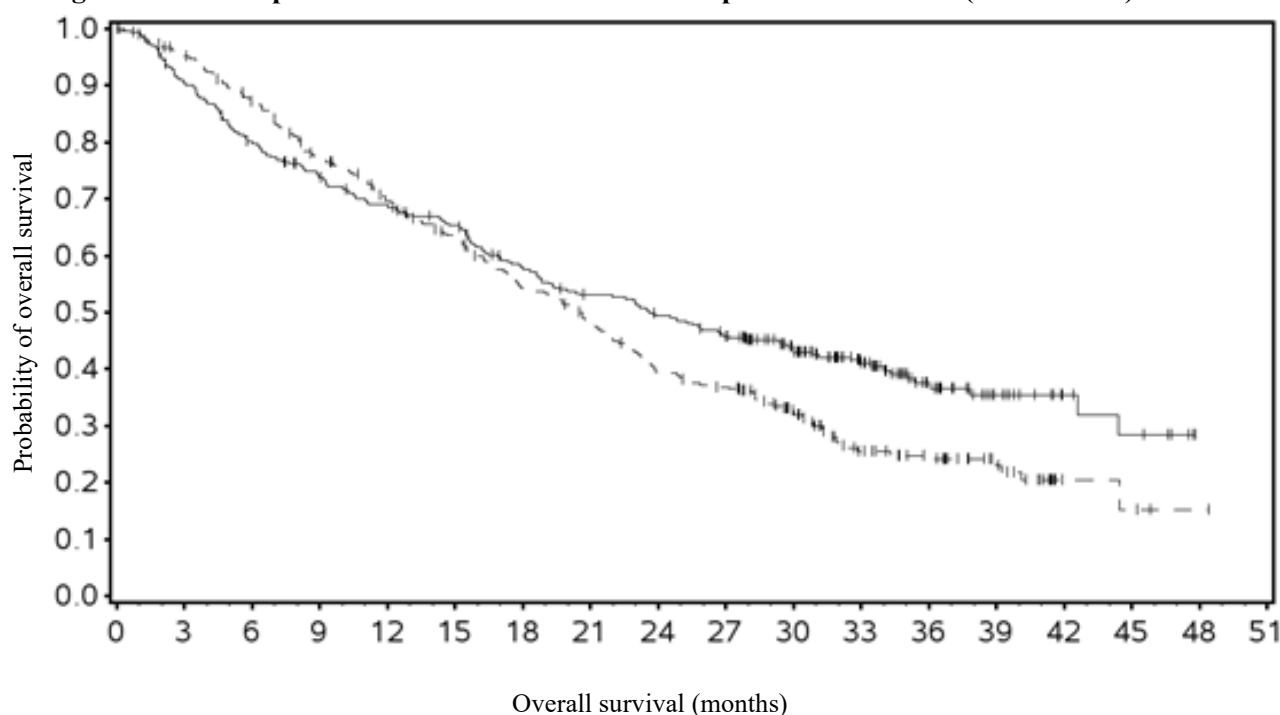
^b Based on stratified Cox proportional hazard model.

^c Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value ≤ 0.0257.

^d Assessed by BICR using RECIST, version 1.1.

^e Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: p-value ≤ 0.025.

Figure 34: Kaplan-Meier curve of OS in first-line patients with HCC (CA2099DW)



Number of subjects at risk

Nivolumab + ipilimumab

335 300 264 239 220 206 179 162 150 137 104 71 42 24 11 8 0 0

Investigator's choice

333 310 280 245 216 194 164 144 116 106 76 44 34 20 4 3 1 0

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

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

Paediatric population

Subcutaneous formulation

No dedicated studies of OPDIVO solution for injection have been conducted in paediatric patients.

The European Medicines Agency has waived the obligation to submit the results of studies with OPDIVO solution for injection for subcutaneous use in all subsets of the paediatric population in the treatment of malignant neoplasms (except central nervous system neoplasms, haematopoietic and lymphoid tissue neoplasms other than Hodgkin lymphoma) (see section 4.2 for information on paediatric use).

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, adjuvant melanoma, and adjuvant OC or GEJC patients 75 years of age or older are too limited to draw conclusions on this population.

5.2 Pharmacokinetic properties

Nivolumab solution for injection pharmacokinetics (PK) were assessed using a population PK approach. The PK was studied at a dose of 1200 mg administered as multiple doses every 4 weeks.

Nivolumab time-averaged serum concentration over 28 days (C_{avgd28}) showed non-inferiority of subcutaneous nivolumab (77.4 mcg/mL) to intravenous nivolumab (36.9 mcg/mL), with a geometric mean ratio of 2.098 (90% CI: 2.001, 2.200). Nivolumab minimum serum concentration at steady state

($C_{\min ss}$) showed non-inferiority of subcutaneous nivolumab (122.2 mcg/mL) to intravenous nivolumab (68.9 mcg/mL), with a geometric mean ratio of 1.774 (90% CI: 1.633, 1.927).

Absorption

The mean absorption rate constant (K_a) and bioavailability (F) of nivolumab solution for injection are 0.0123 hr⁻¹ (or 0.295 Day⁻¹) and 78.8%, respectively. Peak concentrations occurred by around 6 days.

Distribution

The geometric mean (CV%) volume of distribution at steady state (V_{ss}) is 6.32 L (21.3%).

Elimination

Nivolumab solution for injection human clearance (CL) decreases over time, with a mean maximal reduction from baseline values (CV%) of 24.6% (15.8%) resulting in a geometric mean (CV%) steady-state clearance (CL_{ss}) of 7.18 mL/h (52.3%) in patients with RCC; the decrease in CL_{ss} is not considered clinically relevant.

The geometric mean (CV%) elimination half-life ($t_{1/2}$) is 26.5 days (32.1%).

Special populations

The following factors had no clinically important effect on the bioavailability of nivolumab solution for injection: sex and performance status. The following factors had no clinically important effect on the clearance of nivolumab solution for injection: body weight (35 to 153 kg), sex, eGFR (24 to 124 mL/min/1.73 m²), or performance status.

Renal impairment

In population PK analyses for intravenous nivolumab, the effect of renal impairment on the CL of nivolumab was evaluated in patients with mild ($GFR < 90$ and ≥ 60 mL/min/1.73 m²; $n = 379$), moderate ($GFR < 60$ and ≥ 30 mL/min/1.73 m²; $n = 179$), or severe ($GFR < 30$ and ≥ 15 mL/min/1.73 m²; $n = 2$) renal impairment compared to patients with normal renal function ($GFR \geq 90$ mL/min/1.73 m²; $n = 342$). 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

In population PK analyses for intravenous nivolumab, the effect of hepatic impairment on the CL of nivolumab was evaluated in patients with different tumour types (NSCLC, SCLC, melanoma, RCC, SCCHN, UC, GC, and cHL) with mild hepatic impairment (total bilirubin $1.0 \times$ to $1.5 \times$ ULN or $AST > ULN$ as defined using the National Cancer Institute criteria of hepatic dysfunction; $n = 351$) and in patients with moderate hepatic impairment (total bilirubin $> 1.5 \times$ to $3 \times$ ULN and any AST ; $n = 10$) compared to patients with normal hepatic function (total bilirubin and $AST \leq ULN$; $n = 3096$). No clinically important differences in the CL of nivolumab were found between patients with mild or moderate hepatic impairment and normal hepatic function. Similar results were observed in patients with HCC (mild hepatic impairment: $n = 152$; moderate hepatic impairment: $n = 13$). Nivolumab has not been studied in patients with severe hepatic impairment (total bilirubin $> 3 \times$ ULN and any AST) (see section 4.2).

5.3 Preclinical safety data

Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to increase foetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels either 8 or 35 times higher than those observed

at the clinical dose of 3 mg/kg of nivolumab (based on AUC). There was a dose-dependent increase in foetal losses and increased neonatal mortality beginning in the third trimester.

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

Fertility studies have not been performed with nivolumab.

Subcutaneous formulation

Hyaluronidase is found in most tissues of the human body. Non-clinical data for recombinant human hyaluronidase reveal no special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints. Reproductive toxicology studies with rHuPH20 revealed embryofoetal toxicity in mice at high systemic exposure but did not show teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)

Histidine

Histidine hydrochloride monohydrate

Sucrose

Pentetic acid

Polysorbate 80 (E433)

Methionine

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

3 years

Storage in syringe

From a microbiological point of view, once transferred from the vial to the syringe, the medicinal product should be used immediately since the medicinal product does not contain any antimicrobial preservative or bacteriostatic agents. If not used immediately, OPDIVO solution for injection transferred to the syringe can be stored in the refrigerator at 2°C to 8°C, protected from light for up to 7 days and/or at room temperature 20°C to 25°C and room light for up to 8 hours. Discard if storage time exceeds these limits. Aseptic handling should be ensured during the preparation of the syringe for injection.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

Store in the original package in order to protect from light.

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

6.5 Nature and contents of container

OPDIVO 300 mg solution for injection: Type I glass vial with a butyl rubber stopper and an aluminium seal with a plastic violet flip-off cap containing 2.5 mL of solution for injection.

OPDIVO 600 mg solution for injection: Type I glass vial with a butyl rubber stopper and an aluminium seal with a plastic orange flip-off cap containing 5 mL of solution for injection.

Pack of one vial.

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 of the syringe

OPDIVO solution for injection is for single use only and is ready to use.

OPDIVO solution for injection should NOT be diluted or mixed with other medicinal products.

OPDIVO solution for injection is compatible with polypropylene, polycarbonate, polyethylene, polyurethane, polyvinyl chloride, fluorinated ethylene propylene, and stainless steel.

OPDIVO solution for injection should be a clear to opalescent, colourless to yellow solution. Prior to use, visually inspect and discard if discoloured or contains extraneous particulate matter other than a few translucent-to-white particles.

Do not shake the vial.

Calculate the appropriate number of vials of OPDIVO solution for injection needed based on the prescribed dose.

Allow vial(s) to reach room temperature before withdrawing the dose.

A syringe and a transfer needle are needed to withdraw the medicinal product from the vial. OPDIVO solution for injection may be administered subcutaneously using a 23G-25G hypodermic injection needle or subcutaneous administration set (e.g., winged/butterfly).

Withdraw the required volume either 5 mL (600 mg), 7.5 mL (900 mg), or 10 mL (1200 mg), according to the recommended dose.

The hypodermic injection needle must be attached to the syringe immediately prior to administration to avoid clogging.

It is recommended to use the prepared dose immediately.

If storage is required (see section 6.3), apply a syringe tip cap prior to storage.

If stored in the refrigerator, allow the solution to reach ambient temperature before administration.

Disposal

Discard any unused solution remaining in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/005
EU/1/15/1014/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

23 July 2026

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