ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.
One vial of 4 mL contains 40 mg of nivolumab.
One vial of 10 mL contains 100 mg of nivolumab.
One vial of 12 mL contains 120 mg of nivolumab.
One vial of 24 mL contains 240 mg of nivolumab.

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

Excipient with known effect

Each mL of concentrate contains 0.1 mmol (or 2.5 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older.

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

Adjuvant treatment of melanoma

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

Non-small cell lung cancer (NSCLC)

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

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

Neoadjuvant treatment of 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 ≥ 1% (see section 5.1 for selection criteria).

Neoadjuvant and adjuvant treatment of NSCLC

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 ≥ 1% (see section 5.1 for selection criteria).

Malignant pleural mesothelioma (MPM)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Renal cell carcinoma (RCC)

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

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

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

Classical Hodgkin lymphoma (cHL)

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

Squamous cell cancer of the head and neck (SCCHN)

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

Urothelial carcinoma

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

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

Adjuvant treatment of urothelial carcinoma

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

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;
- treatment of metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy (see section 5.1).

Oesophageal squamous cell carcinoma (OSCC)

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

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

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

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.

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 is either nivolumab 240 mg every 2 weeks **or** 480 mg every 4 weeks depending on the indication and population (see sections 5.1 and 5.2), as presented in Table 1.

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

Indication*	**Recommended dose and infusion time**
Melanoma (advanced or adjuvant treatment)	Adults and adolescents (12 years of age and older and weighing at least 50 kg): 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes or over 30 minutes (adjuvant melanoma, see section 5.1)
	Adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes
Renal cell carcinoma Muscle invasive urothelial carcinoma (MIUC) (adjuvant treatment)	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Oesophageal or gastro-oesophageal junction cancer (adjuvant treatment)	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks, followed by 480 mg every 4 weeks over 30 minutes
Non-small cell lung cancer Classical Hodgkin lymphoma Squamous cell cancer of the head and neck Urothelial carcinoma Oesophageal squamous cell carcinoma	240 mg every 2 weeks over 30 minutes

*As per monotherapy indication in section 4.1.

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

OPDIVO in combination with ipilimumab

Melanoma
In adults and adolescents 12 years of age and older and weighing at least 50 kg, the recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks (see sections 5.1 and 5.2), as presented in Table 2. For the monotherapy phase, the first dose of nivolumab should be administered:

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

In adolescents 12 years of age and older and weighing less than 50 kg, the recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every

3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 3 mg/kg every 2 weeks **or** 6 mg/kg every 4 weeks (see sections 5.1 and 5.2), as presented in Table 2. For the monotherapy phase, the first dose of nivolumab should be administered:

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

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

	Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	Adults and adolescents 12 years of age and older: 1 mg/kg over 30 minutes	Adults and adolescents (12 years of age and older and weighing at least 50 kg): 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes Adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes
Ipilimumab	Adults and adolescents 12 years of age and older: 3 mg/kg over 30 minutes	-

Malignant pleural mesothelioma

The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks. Treatment is continued for up to 24 months in patients without disease progression.

Renal cell carcinoma

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

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

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

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

dMMR or MSI-H colorectal cancer

The recommended dose for first-line treatment of dMMR or MSI-H CRC is 240 mg of nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for a maximum of 4 doses, followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks, as presented in Table 4. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab

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

The recommended dose in patients who received prior fluoropyrimidine-based combination chemotherapy for dMMR or MSI-H CRC is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab monotherapy administered intravenously 240 mg every 2 weeks, as presented in Table 4. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab.

Table 4: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for dMMR or MSI-H CRC

		Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	First-line	240 mg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes
	After prior fluoropyrimidine-based combination chemotherapy	3 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes
Ipilimumab		1 mg/kg over 30 minutes	-

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

Hepatocellular carcinoma
The recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for up to 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks (see sections 5.1 and 5.2), as presented in Table 5. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months. For the monotherapy phase, the first dose of nivolumab should be administered:

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

Table 5: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for HCC

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

OPDIVO in combination with cabozantinib

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

Table 6: Recommended doses and infusion times for intravenous administration of nivolumab in combination with oral administration of cabozantinib for RCC

	Combination phase
Nivolumab	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Cabozantinib	40 mg once daily

OPDIVO in combination with ipilimumab and chemotherapy

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

OPDIVO in combination with chemotherapy

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

Neoadjuvant and adjuvant treatment of non-small cell lung cancer
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for 4 cycles in the neoadjuvant phase, followed by adjuvant treatment with nivolumab 480 mg as monotherapy every 4 weeks. Treatment is recommended until disease progression or recurrence, unacceptable toxicity, or up to 13 cycles (see section 5.1).

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

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

First-line treatment of unresectable or metastatic urothelial carcinoma
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks over 30 minutes **or** at 480 mg every 4 weeks over 30 minutes (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months from first dose, whichever comes first.

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

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

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.

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 7. 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 7: Recommended treatment modifications for OPDIVO or OPDIVO in combination

Immune-related adverse reaction	**Severity**	**Treatment modification**
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis - OPDIVO monotherapy	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	- OPDIVO+ipilimumab[a]	Permanently discontinue treatment
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis without HCC **NOTE:** for RCC patients treated with **OPDIVO in combination with cabozantinib** with liver enzyme elevations, see dosing guidelines following this table.	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment

Immune-related adverse reaction	Severity	Treatment modification
Immune-related hepatitis with HCC	If AST/ALT is within normal limits at baseline and increases to > 3 and ≤ 10 times ULN or Baseline AST/ALT is > 1 and ≤ 3 times ULN and increases to > 5 and ≤ 10 times ULN or Baseline AST/ALT is > 3 and ≤ 5 times ULN and increases to > 8 and ≤ 10 times ULN.	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	AST/ALT increases to > 10 times ULN or Total bilirubin increases to > 3 times ULN	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[b] as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[c]
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment

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

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

[b] Recommendation for the use of hormone replacement therapy is provided in section 4.4.
[c] The safety of re-initiating nivolumab or nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known.

OPDIVO 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 alert card and be informed about the risks of OPDIVO (see also package leaflet).

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

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 7 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

Paediatric population
The safety and efficacy of OPDIVO in children below 18 years of age have not been established except in adolescents 12 years of age and older with melanoma. Currently available data of OPDIVO as monotherapy or in combination with ipilimumab are described in sections 4.2, 4.8, 5.1 and 5.2.

Elderly
No dose adjustment is required for elderly patients (≥ 65 years) (see section 5.2).

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

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

Method of administration

OPDIVO is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30 or 60 minutes depending on the dose (see Tables 1, 2, 3, 4 and 5). The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 μm.

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

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

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

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 filtrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

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

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

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

immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered.

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

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

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

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

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

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

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

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

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

methylprednisolone equivalents, and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

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

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

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

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

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

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

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

Rare cases of SJS and TEN some of them with fatal outcome have been observed. If symptoms or signs of SJS or TEN appear, treatment with nivolumab or nivolumab in combination with ipilimumab

should be discontinued and the patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab or nivolumab in combination with ipilimumab, permanent discontinuation of treatment is recommended (see section 4.2).

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

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

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.

<u>Infusion reactions</u>

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

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

Disease-specific precautions

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

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

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

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

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

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

Non-small cell lung cancer
First-line treatment of NSCLC
Patients with active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, active (untreated) brain metastasis, who received prior systemic treatment for advanced disease, or who had sensitising EGFR mutations or ALK translocations were excluded from the pivotal trial in first-line treatment of NSCLC (see sections 4.5 and 5.1). Limited data are available in elderly patients (≥ 75 years) (see section 5.1). In these patients, nivolumab in combination with ipilimumab and chemotherapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

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

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

Malignant pleural mesothelioma
Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the pivotal trial in first-line treatment of MPM (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with ipilimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Renal cell carcinoma
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).

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

Complications of allogeneic haematopoietic stem cell transplant (HSCT) in classical Hodgkin lymphoma
Cases of acute graft-versus-host disease (GVHD) and transplant related mortality (TRM) have been observed from the follow-up of patients with cHL undergoing allogeneic HSCT after previous exposure to nivolumab. Careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications should be made case-by-case (see section 4.8).

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

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

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

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

In the first-line OSCC trial, a higher number of deaths within 4 months was observed with nivolumab in combination with ipilimumab compared to chemotherapy. Physicians should consider the delayed onset of effect of nivolumab in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease (see section 5.1).

Treatment of OSCC after prior first-line chemotherapy
The majority of clinical data available in oesophageal squamous cell carcinoma are in patients of Asian origin (see section 5.1).
Patients with a baseline performance score ≥ 2, brain metastases that were symptomatic or required treatment, apparent tumour invasion 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
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.

Patients on controlled sodium diet

Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. This medicinal product contains 10 mg sodium per 4 mL vial, 25 mg sodium per 10 mL vial, 30 mg sodium per 12 mL vial or 60 mg sodium per 24 mL vial, which is equivalent to 0.5%, 1.25%, 1.5% or 3% respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult. Sodium intake could vary in case sodium chloride is used for the dilution steps.

Patient alert card

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Nivolumab as monotherapy (see section 4.2)

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

Tabulated summary of adverse reactions
Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 4646) are presented in Table 8. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 8: 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)

	Nivolumab monotherapy
Blood and lymphatic system disorders	
Very common	lymphopaenia[b], anaemia[b,i], leucopoenia[b], neutropaenia[a,b], thrombocytopaenia[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)
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
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

	Nivolumab monotherapy
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus
Common	vitiligo, dry skin, erythema, alopecia
Uncommon	psoriasis, rosacea, erythema multiforme, urticaria
Rare	toxic epidermal necrolysis[a, d], Stevens-Johnson syndrome[a]
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	Sjogren's syndrome, myopathy, myositis (including polymyositis)[a,], rhabdomyolysis[a,d]
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)[a]
Rare	tubulointerstitial nephritis, cystitis noninfective
General disorders and administration site conditions	
Very common	fatigue, pyrexia
Common	pain, chest pain, oedema[l]
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 8 may not be fully attributable to nivolumab alone but may contain contributions from the underlying disease.

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

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

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

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

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

[f] 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.

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 (≥ 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 ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate. Among patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy for NSCLC, anaemia (32%) and neutropaenia (15%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate.

Nivolumab in combination with chemotherapy
In the pooled dataset of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy across tumour types (n = 1800), with a minimum follow-up ranging from 7.4 to 23.6 months, or following 3 cycles of treatment for resectable NSCLC, the most frequent adverse reactions (≥ 10%) were nausea (48%), fatigue (40%), peripheral neuropathy (33%), decreased appetite (31%), constipation (31%), diarrhoea (28%), vomiting (24%), rash (19%), abdominal pain (18%), stomatitis (18%), musculoskeletal pain (18%), pyrexia (16%), cough (13%), 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 240 mg every 2 weeks in combination with cabozantinib 40 mg once daily in RCC (n =320), with a minimum follow -up of 16.0 months, the most frequent adverse reactions (≥ 10%) were diarrhoea (64.7%), fatigue (51.3%), -palmar plantar erythrodysaesthesia syndrome (40.0%), stomatitis (38.8%), musculoskeletal pain (37.5%), hypertension (37.2%), rash (36.3%), hypothyroidism (35.6%), decreased appetite (30.3%), nausea (28.8%), abdominal pain (25.0%), dysgeusia (23.8%), upper respiratory tract infection (20.6%), cough (20.6%), pruritus (20.6%), arthralgia (19.4%), vomiting (18.4%), dysphonia (17.8%), headache (16.3%), dyspepsia (15.9%), dizziness (14.1%), constipation (14.1%), pyrexia (14.1%), oedema (13.4%), muscle spasm (12.2%), dyspnoea (11.6%), proteinuria (10.9%) and hyperthyroidism (10.0%). The 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 9. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000), 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 9: 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], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]	neutropaenia[b], anaemia[b,j], leucopoenia[b], lymphopaenia[b], thrombocytopaenia[b]	anaemia[b], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[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]		
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		

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
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	Guillain-Barré syndrome	encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Rare	Guillain-Barré syndrome, neuritis, myelitis (including transverse myelitis), optic neuritis	encephalitis	
Not known		myelitis (including transverse myelitis), optic neuritis	
Ear and labyrinth disorders			
Common			tinnitus
Eye disorders			
Common	blurred vision, dry eye	dry eye, blurred vision	dry eye, blurred vision
Uncommon	uveitis, episcleritis	uveitis	uveitis
Rare	Vogt Koyanagi Harada syndrome		
Cardiac disorders			
Common	tachycardia, atrial fibrillation	tachycardia, atrial fibrillation	atrial fibrillation, tachycardia
Uncommon	myocarditis[a], arrhythmia (including ventricular arrhythmia)[a], bradycardia	myocarditis	myocarditis
Not known	pericardial disorders[i]		
Vascular disorders			
Very common			hypertension
Common	hypertension	thrombosis[a, k], hypertension, vasculitis	thrombosis[k]

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
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	
Skin and subcutaneous tissue disorders			
Very common	rash[c], pruritus	rash[c], pruritus	palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus
Common	alopecia, vitiligo, urticaria, dry skin, erythema,	palmar-plantar erythrodysaesthesia 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

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[f], arthralgia	musculoskeletal pain[f]	musculoskeletal pain[f], arthralgia, muscle spasm
Common	muscle spasms, muscular weakness, arthritis	arthralgia, muscular weakness	arthritis
Uncommon	polymyalgia rheumatica, myopathy, myositis (including polymyositis)[a]		myopathy, osteonecrosis of the jaw, fistula
Rare	spondyloarthropathy, Sjogren's syndrome, rhabdomyolysis[a]		
Renal and urinary disorders			
Very common			proteinuria
Common	renal failure (including acute kidney injury)[a]	renal failure[a]	renal failure, acute kidney injury
Uncommon	tubulointerstitial nephritis, nephritis	cystitis noninfective, nephritis	nephritis
Rare	cystitis noninfective		cystitis noninfective[h]
General disorders and administration site conditions			
Very common	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema
Common	chest pain, pain, chills	malaise	pain, chest pain
Investigations			
Very common	increased alkaline phosphatase[b], increased AST[b], increased ALT[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hyponatraemia[b], hyperkalaemia[b], hypokalaemia[b], hypercalcaemia[b], hypocalcaemia[b]	hypocalcaemia[b], increased AST[b], increased ALT[b], hyponatraemia[b], increased amylase[b], hypomagnesaemia[b], increased alkaline phosphatase[b], hypokalaemia[b], increased creatinine[b], increased lipase[b], hyperkalaemia[b], increased total bilirubin[b]	increased alkaline phosphatase[b], increased ALT[b], increased AST[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hypokalaemia[b], hypomagnesaemia[b], hyponatraemia[b], hypocalcaemia[b], hypercalcaemia[b], hypophosphataemia[b], hyperkalaemia[b], hypermagnesaemia[b], hypernatraemia[b]
Common	hypernatraemia[b], hypermagnesaemia[b], increased thyroid stimulating hormone, increased gamma-glutamyltransferase	hypernatraemia[b], hypercalcaemia[b], hypermagnesaemia[b]	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 9 may not be fully attributable to nivolumab alone or in combination with other therapeutic agents, but may contain contributions from the underlying disease or from medicinal product used in combination.

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

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

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

[d] Lichen disorders is a composite term which includes lichen keratosis and lichen planus.
[e] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.
[f] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, and spinal pain.
[g] 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.

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 10 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 10 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 10: 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

	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 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 patients, respectively. Median time to onset was 0.7 months (range: 0.0-33.8). Resolution occurred in 843 patients (70%) with a median time to resolution of 12.1 weeks (range: 0.1-268.7^{+}). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma, the incidence of rash was 65.2%, including Grade 2 (20.3%) and Grade 3 (7.8%).

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

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

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

Infusion reactions
In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions 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.

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

Elevated liver enzymes when 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 thrombocytopaenia, 0.7% for leucopoenia, 8.7% for lymphopaenia, 0.9% for neutropaenia, 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 thrombocytopaenia, 2.2% for leucopoenia, 6.9% for lymphopaenia, 3.3% for neutropaenia, 2.7% for increased alkaline phosphatase, 9.8% for increased AST, 9.3% for increased ALT, 2.3% for increased total bilirubin, 1.8% for increased creatinine, 1.4% for hypoalbuminaemia, 7.1% for hyperglycaemia, 0.7% for hypoglycaemia, 7.8% for increased amylase, 16.3% for increased lipase, 0.8% for hypocalcaemia, 0.2% for hypernatraemia, 0.8% for hypercalcaemia, 2.0% for hyperkalaemia, 0.8% for hypermagnesaemia, 0.4% for hypomagnesaemia, 3.0% for hypokalaemia, and 8.7% for hyponatraemia.

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

In patients treated with nivolumab in combination with chemotherapy, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows:

14.7% for anaemia, 6.2% for thrombocytopaenia, 11.7% leukopaenia, 13.6% for lymphopaenia, 26.3% neutropaenia, 2.0% for increased alkaline phosphatase, 3.3% for increased AST, 2.6% for increased ALT, 1.9% for increased bilirubin, 1.3% for increased creatinine, 4.5% for increased amylase, 5.2% for increased lipase, 0.4% for hypernatraemia, 8.1% for hyponatraemia, 1.8% for hyperkalaemia, 5.1% for hypokalaemia, 0.7% for hypercalcaemia, 1.8% for hypocalcaemia, 1.5% for hypermagnesaemia, 2.9% for hypomagnesaemia, 3.7% for hyperglycaemia, and 0.6% for hypoglycaemia.

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

Immunogenicity
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.

Paediatric population

The safety of nivolumab as monotherapy (3 mg/kg every 2 weeks) and in combination with ipilimumab (nivolumab 1 mg/kg or 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks) was evaluated in

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

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

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

No new safety signals were observed in clinical study CA209908 of 151 paediatric patients with high-grade primary central nervous system (CNS) malignancies (see section 5.1), relative to data available in adult studies across indications.

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). Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population (see section 5.1). In MPM patients, there was a higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older (68% and 35%, respectively) relative to all patients who received nivolumab in combination with ipilimumab (54% and 28%, respectively). In HCC patients there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (67% and 35%, respectively) relative to all patients who received nivolumab with ipilimumab (53% and 27%, respectively).

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

Hepatic or renal impairment

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

Reporting of suspected adverse reactions

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

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

Clinical efficacy and safety

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

Melanoma

Treatment of advanced melanoma

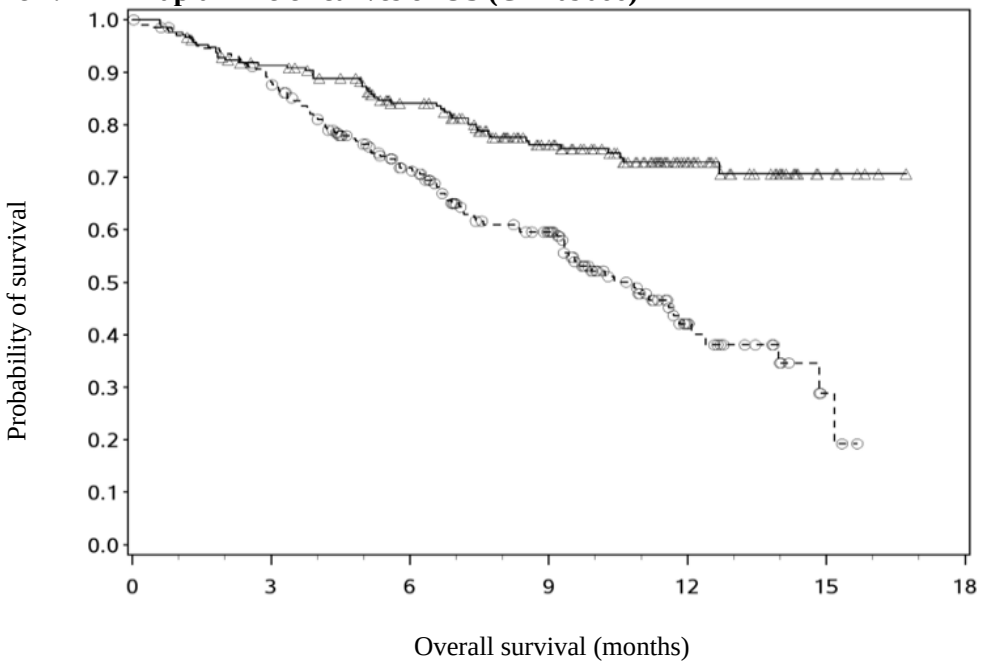
Randomised phase 3 study vs. dacarbazine (CA209066)
The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209066). The study included adult patients (18 years or older) with confirmed,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

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

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

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

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



Number of subjects at risk

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

—△—— 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 11.

Table 11: Efficacy results (CA209066)

	nivolumab (n = 210)		dacarbazine (n = 208)
Overall survival			
Events	50 (23.8%)		96 (46.2%)
Hazard ratio		0.42	
99.79% CI		(0.25, 0.73)	
95% CI		(0.30, 0.60)	
p-value		< 0.0001	
Median (95% CI)	Not reached		10.8 (9.33, 12.09)
Rate (95% CI)			
At 6 months	84.1 (78.3, 88.5)		71.8 (64.9, 77.6)
At 12 months	72.9 (65.5, 78.9)		42.1 (33.0, 50.9)
Progression-free survival			
Events	108 (51.4%)		163 (78.4%)
Hazard ratio		0.43	
95% CI		(0.34, 0.56)	
p-value		< 0.0001	
Median (95% CI)	5.1 (3.48, 10.81)		2.2 (2.10, 2.40)
Rate (95% CI)			
At 6 months	48.0 (40.8, 54.9)		18.5 (13.1, 24.6)
At 12 months	41.8 (34.0, 49.3)		NA
Objective response	84 (40.0%)		29 (13.9%)
(95% CI)	(33.3, 47.0)		(9.5, 19.4)
Odds ratio (95% CI)		4.06 (2.52, 6.54)	
p-value		< 0.0001	
Complete response (CR)	16 (7.6%)		2 (1.0%)
Partial response (PR)	68 (32.4%)		27 (13.0%)
Stable disease (SD)	35 (16.7%)		46 (22.1%)
Median duration of response			
Months (range)	Not reached (0^+-12.5^+)		6.0 (1.1-10.0^+)
Median time to response			
Months (range)	2.1 (1.2-7.6)		2.1 (1.8-3.6)

"+" denotes a censored observation.

Randomised phase 3 study vs. chemotherapy (CA209037)

The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, open-label study (CA209037). The study included adult patients who had progressed on or after ipilimumab and if BRAF V600 mutation positive had also progressed on or after BRAF kinase inhibitor therapy. Patients with active autoimmune disease, ocular melanoma, active brain or leptomeningeal metastases or a known history of prior ipilimumab-related high-grade (Grade 4 per CTCAE v4.0) adverse reactions, except for resolved nausea, fatigue, infusion reactions, or endocrinopathies, were excluded from the study.

A total of 405 patients were randomised to receive either nivolumab (n = 272) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or chemotherapy (n = 133) which consisted of the investigator's choice of either dacarbazine (1000 mg/m^2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks). Randomisation was stratified by BRAF and tumour PD-L1 status and best response to prior ipilimumab.

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

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

At the time of this final ORR analysis, results from 120 nivolumab-treated patients and 47 chemotherapy-treated patients who had a minimum of 6 months of follow-up were analysed. Efficacy results are presented in Table 12.

Table 12: Best overall response, time and duration of response (CA209037)

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

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

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

There was no statistically significant difference between nivolumab and chemotherapy in the final OS analysis. The primary OS analysis was not adjusted to account for subsequent therapies, with

54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies and differences in baseline factors. More patients in the nivolumab arm had poor prognostic factors (elevated LDH and brain metastases) than in the chemotherapy arm.

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

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

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

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

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

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

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

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

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

Table 13: 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 1.1 for 588/1008 (58.3%) of patients who continued treatment through week 12 and had a follow-up scan at week 12.

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

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

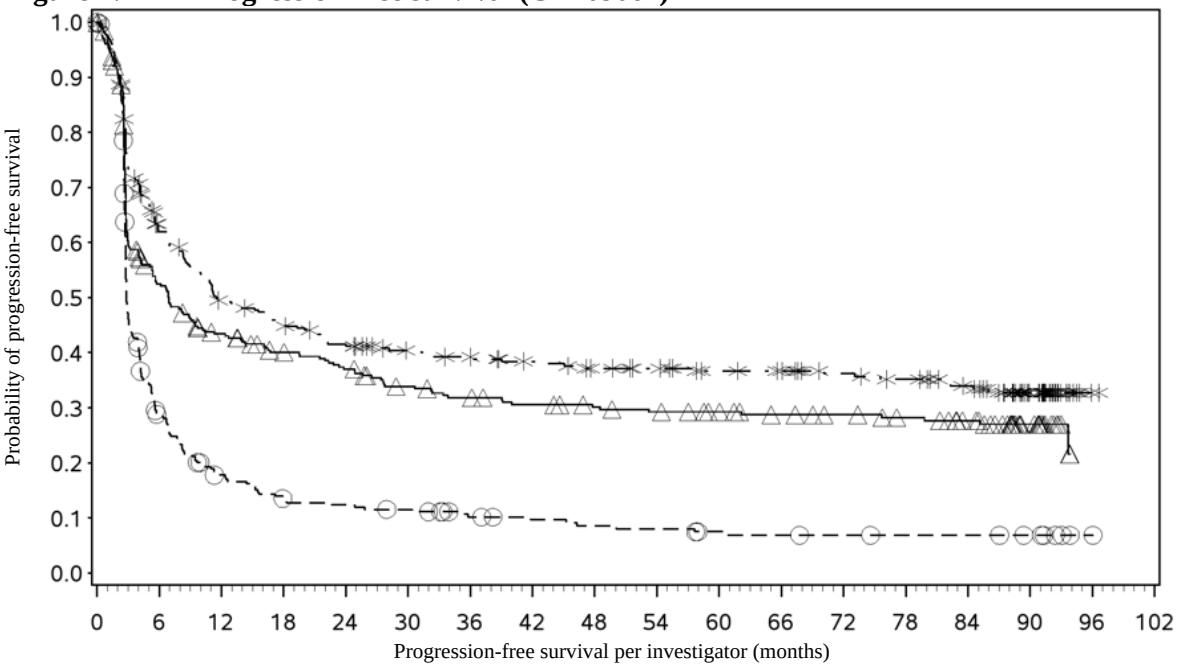
A total of 945 patients were randomised to receive nivolumab in combination with ipilimumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously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

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

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

PFS results from descriptive analysis (with minimum follow up of 90 months) are shown in Figure 2 (all randomised population), Figure 3 (at the tumour PD-L1 5% cut off), and Figure 4 (at the tumour PD-L1 1% cut off).

Figure 2: Progression-free survival (CA209067)



Number of subjects at risk

Nivolumab + ipilimumab																
314	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)

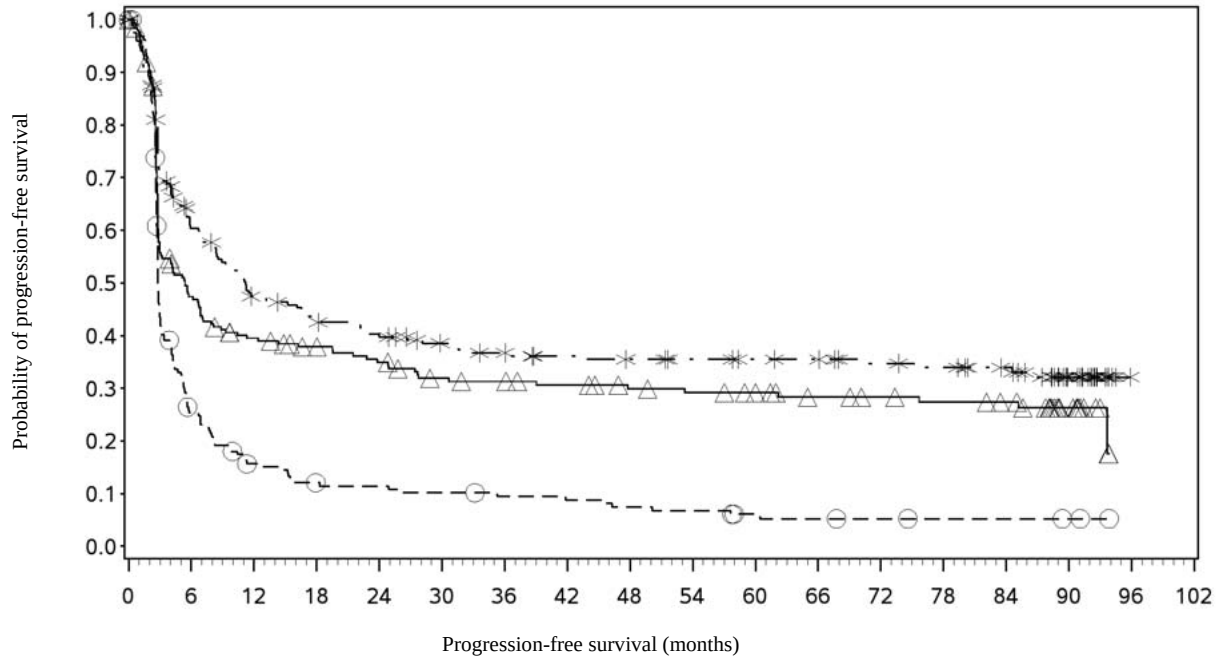
——△——— Nivolumab (events: 208/316), median and 95% CI: 6.93 (5.13, 10.18).
PFS rate at 12 months and 95% CI: 42% (36, 47), PFS rate at 60 months and 95% CI: 29% (24, 35), PFS rate at 90 months and 95% CI: 27% (22, 33)

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

PD-L1 expression < 5%



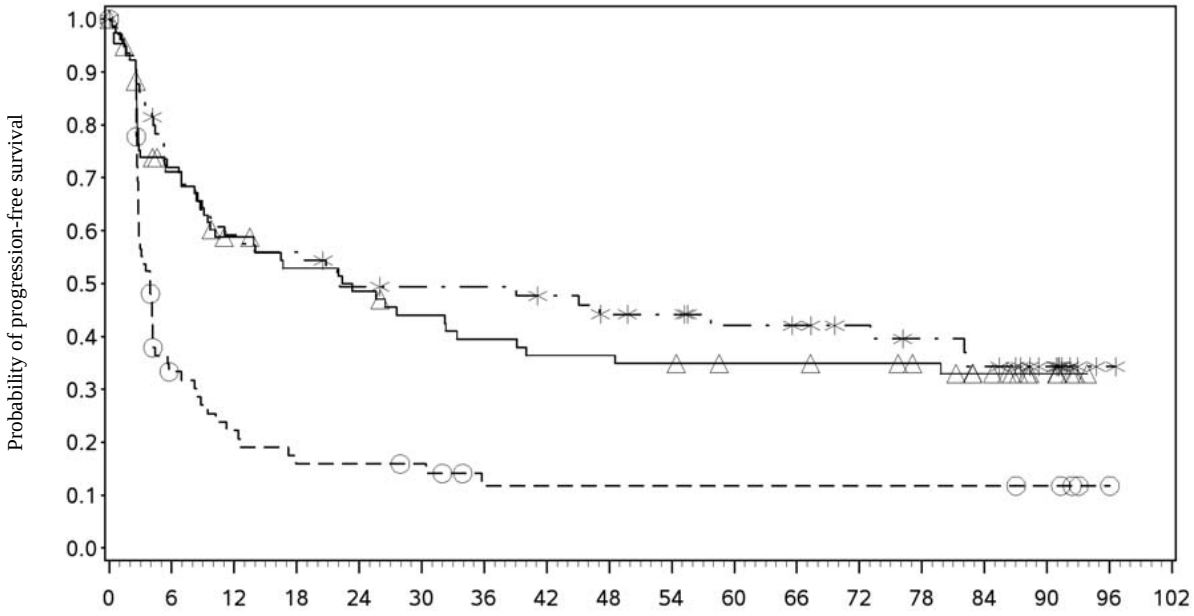
Number of subjects at risk

Nivolumab + ipilimumab																	
210	113	87	78	71	64	60	56	54	52	50	49	45	43	39	22	0	-
Nivolumab																	
208	91	73	66	60	51	49	46	42	40	38	33	31	29	27	12	0	-
Ipilimumab																	
202	45	26	19	18	16	14	13	11	10	7	6	5	4	4	3	0	-

- - -✳- - - Nivolumab+ipilimumab (events: 127/210), median and 95% CI: 11.17 (7.98, 17.51)
—△—— Nivolumab (events: 139/208), median and 95% CI: 5.39 (2.96, 7.13)
- - -❍- - - Ipilimumab (events: 171/202), median and 95% CI: 2.79 (2.76, 3.02)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.33, 0.53)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.54 (0.43, 0.68)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.77 (0.61, 0.98)

PD-L1 expression ≥ 5%



Number of subjects at risk

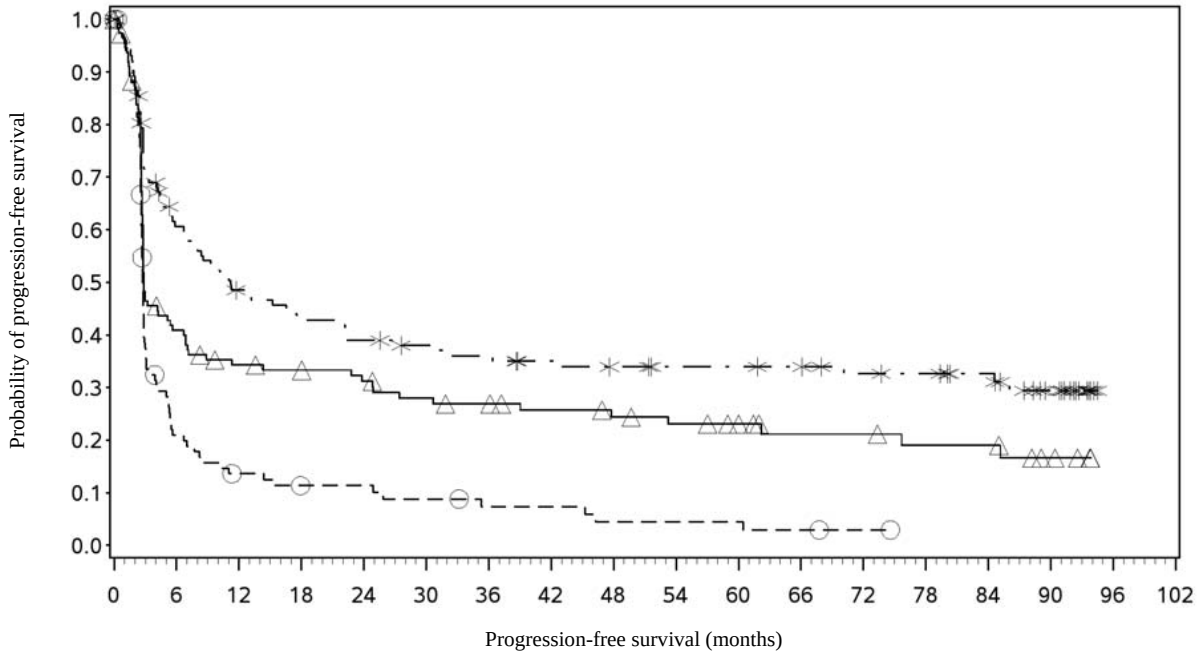
Nivolumab + ipilimumab																	
68	45	37	35	30	29	29	27	24	23	20	19	17	15	13	8	1	-
Nivolumab																	
80	52	41	36	33	29	26	24	24	23	21	21	20	18	14	7	0	-
Ipilimumab																	
75	21	14	10	10	9	5	5	5	5	5	5	5	5	5	4	1	-

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

PD-L1 expression < 1%



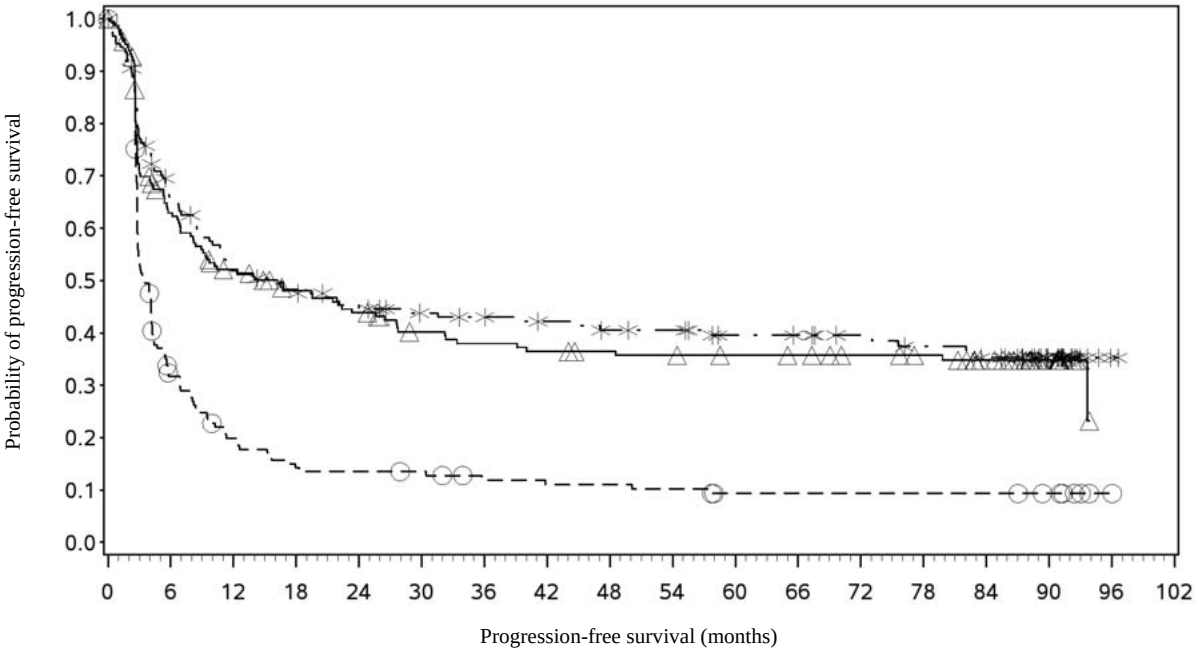
Number of subjects at risk

Nivolumab + ipilimumab																	
123	65	51	46	41	38	36	33	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)

PD-L1 expression ≥ 1%



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)

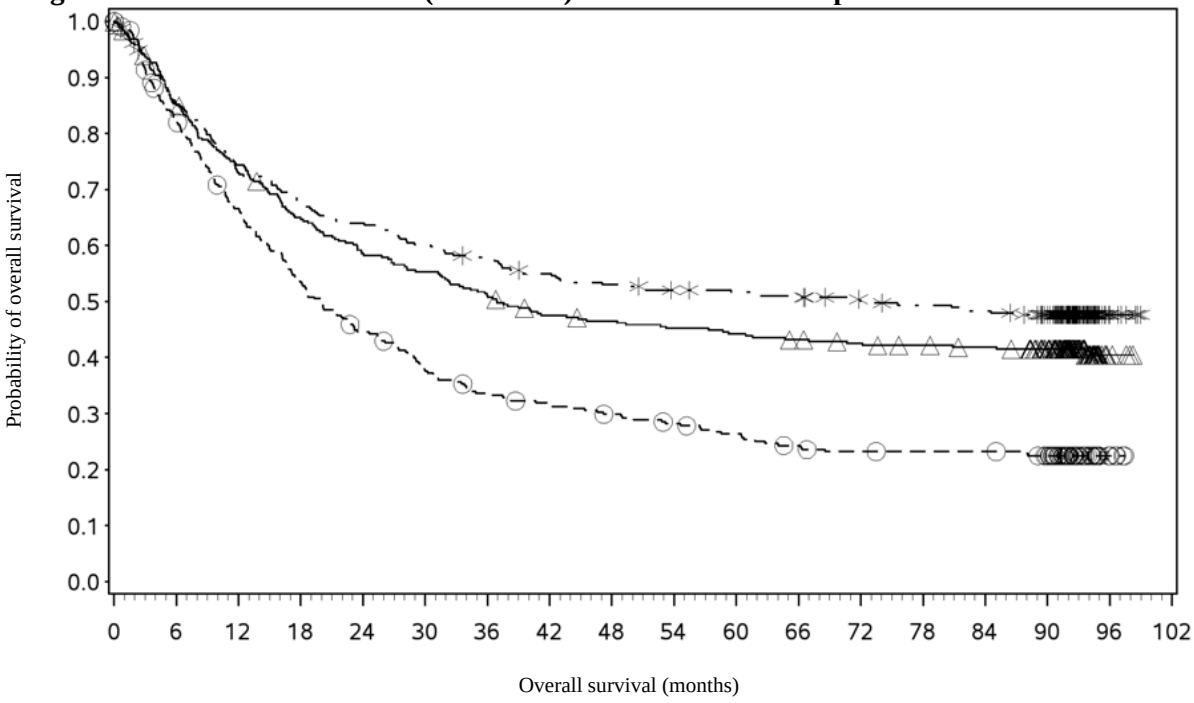
Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.32, 0.55)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.45 (0.35, 0.59)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.92 (0.69, 1.22)

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 5 (all randomised), Figure 6 and 7 (at the tumour PD-L1 5% and 1% cut off).

The OS analysis was not adjusted to account for subsequent therapies received. Subsequent systemic therapy was received by 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 5: 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)

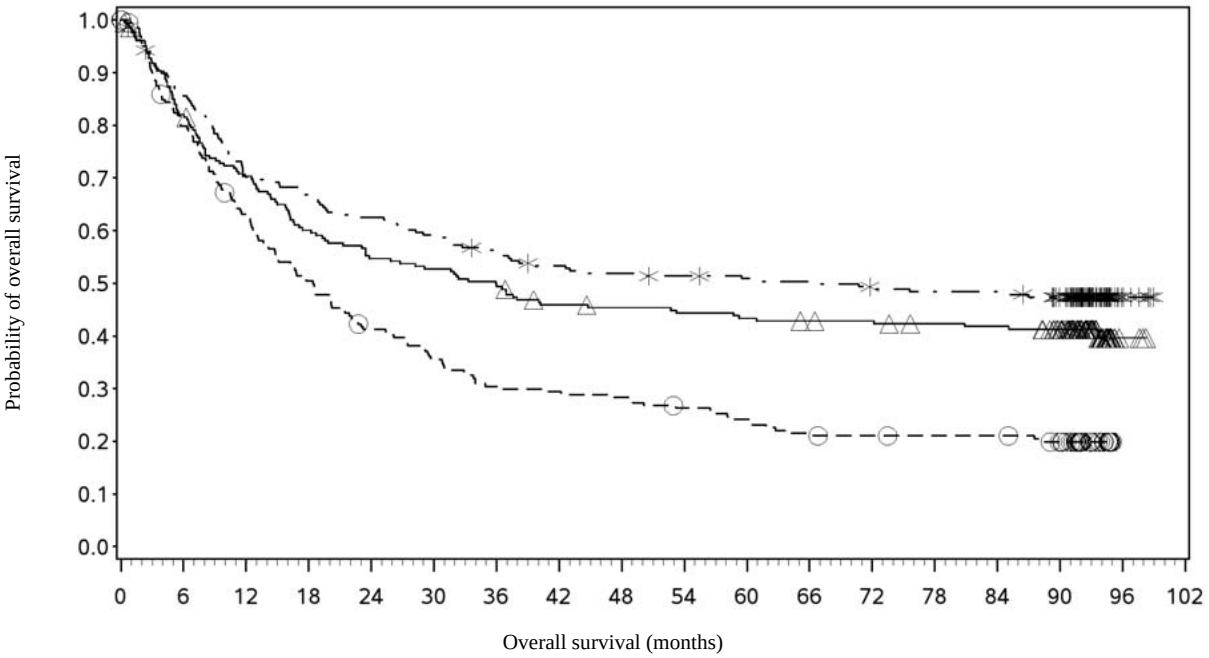
Nivolumab+ipilimumab vs ipilimumab - HR (95% CI): 0.53 (0.44, 0.65)

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

PD-L1 expression < 5%



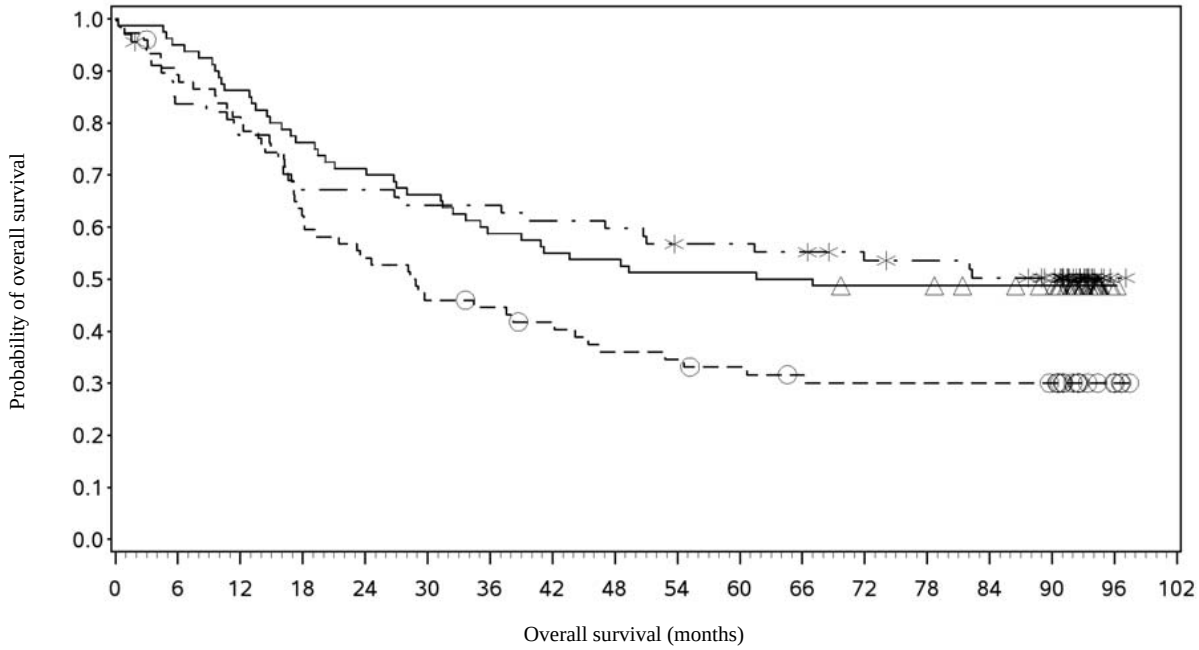
Number of subjects at risk

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 ≥ 5%



Number of subjects at risk

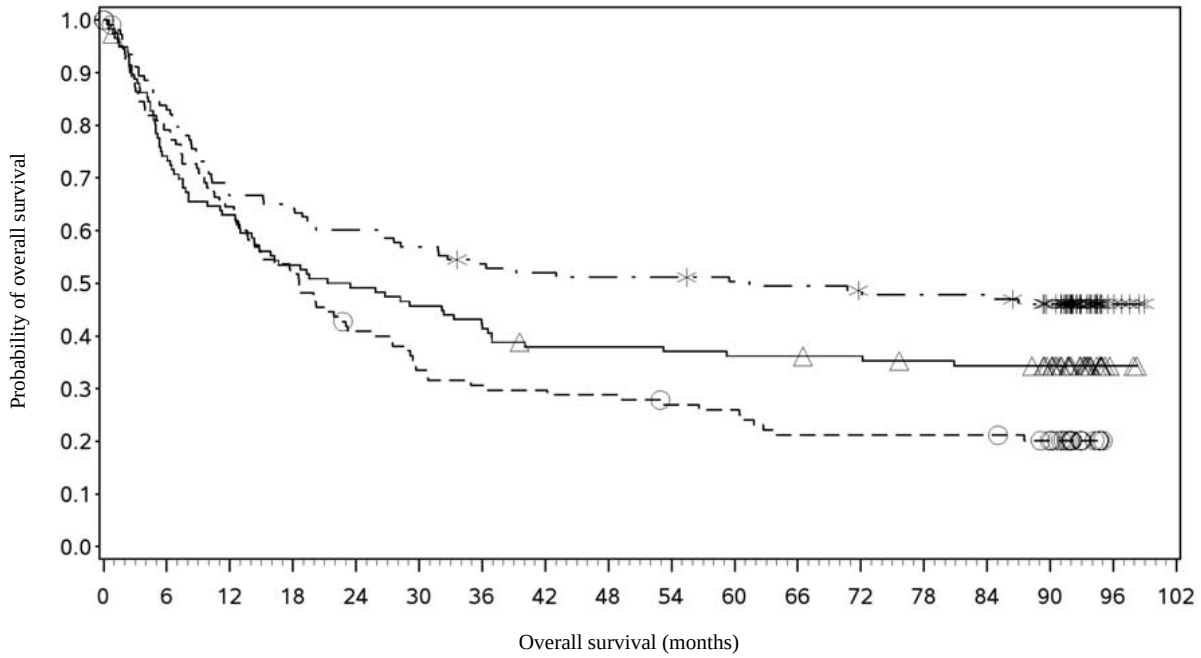
Nivolumab+ipilimumab																	
68	56	52	45	45	43	43	41	40	37	37	36	33	32	30	27	1	-
Nivolumab																	
80	76	69	61	57	53	47	44	43	41	41	40	38	38	36	33	1	-
Ipilimumab																	
75	66	60	46	40	34	32	29	25	24	22	20	19	19	19	18	4	-

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

PD-L1 expression < 1%



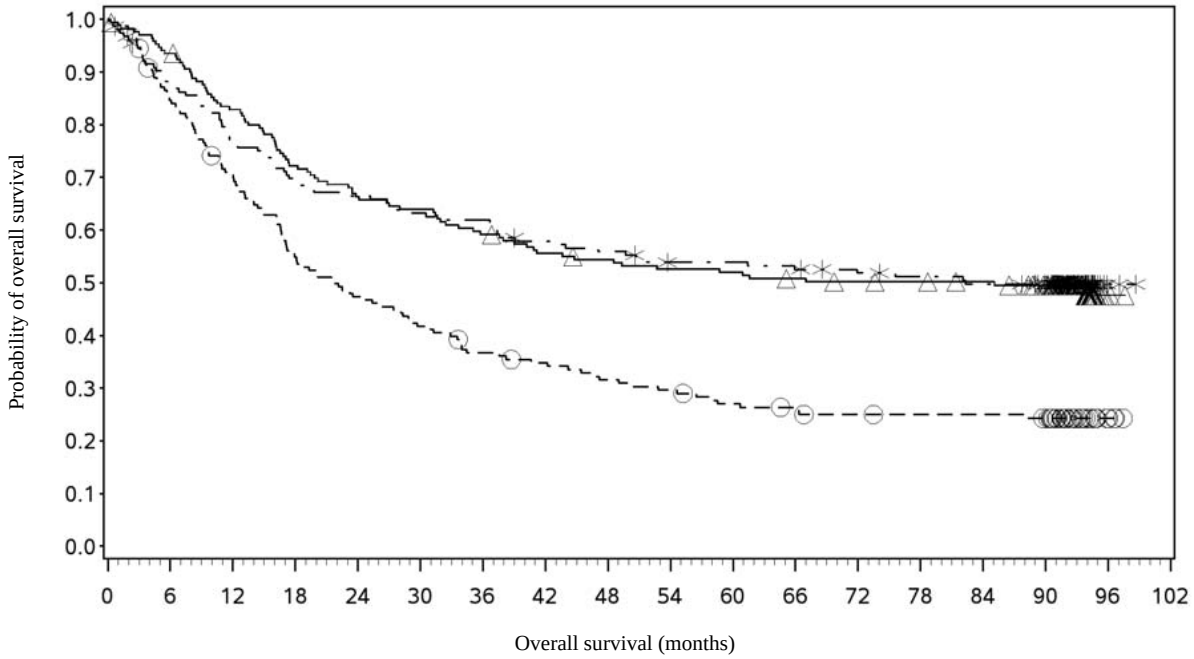
Number of subjects at risk

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)

PD-L1 expression ≥ 1%



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 14.

Table 14: 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 14) 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.

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

Adjuvant treatment of melanoma

Randomised phase 3 study of nivolumab vs. 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 8.

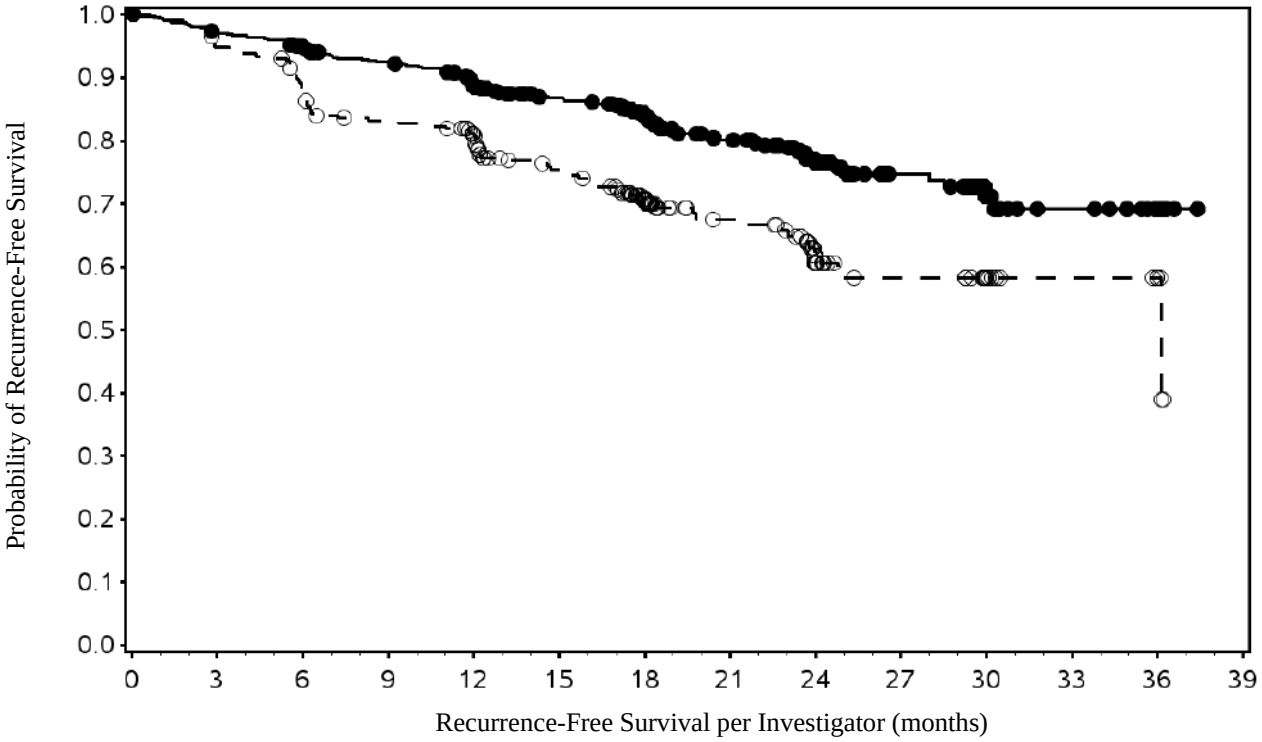
Table 15: Efficacy results (CA20976K)

	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 8: Recurrence-free survival (CA20976K)



Number of subjects at risk

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

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

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

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

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

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

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

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

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% Cl: 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 Figure 9 and 10 (all randomised population).

Table 16: Efficacy results (CA209238)

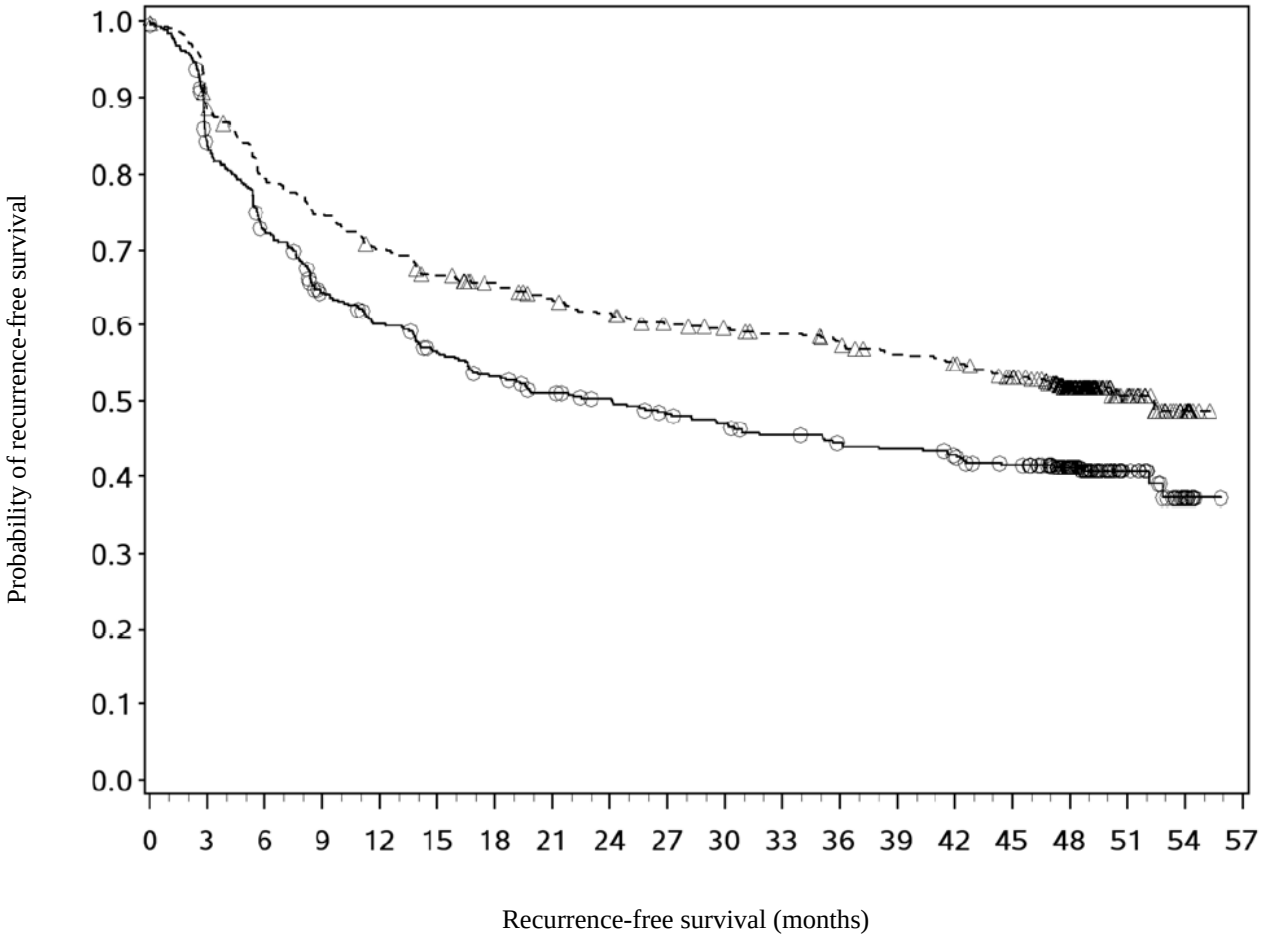
	nivolumab (n = 453)	**ipilimumab 10 mg/kg (n = 453)**
Final pre-specified analysis Recurrence-free survival with minimum follow-up 36 months		
Events	188 (41.5%)	239 (52.8%)
Hazard ratio[a]	0.68	
95% CI	(0.56, 0.82)	
p-value	p < 0.0001	
Median (95% CI) months	NR (38.67, NR)	24.87 (16.62, 35.12)
Recurrence-free 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 9, 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 9: Recurrence-free survival (CA209238)

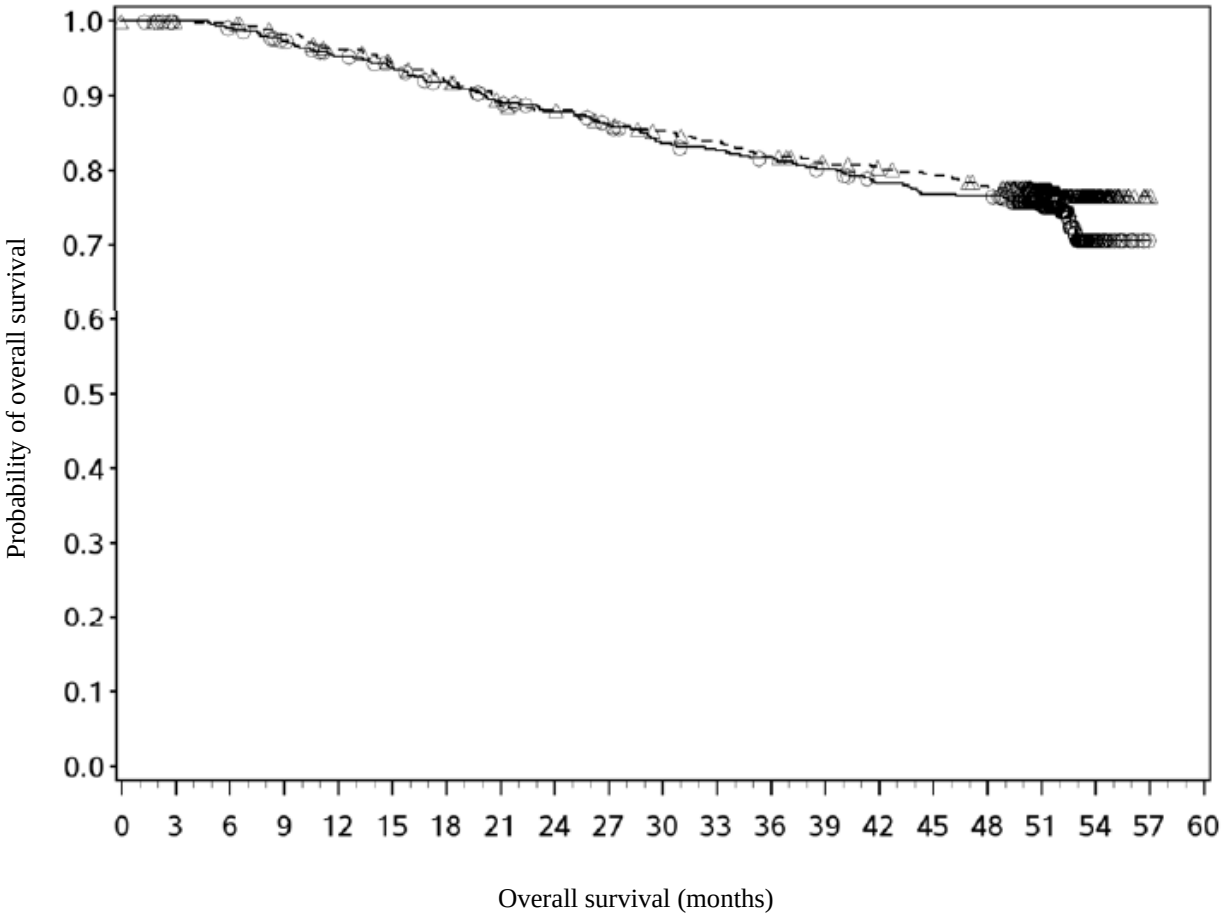


Number of subjects at risk

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 10: 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 10, 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).

Non-small cell lung cancer

Neoadjuvant treatment of NSCLC

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

The safety and efficacy of nivolumab 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 (≥ 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/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (non-squamous histology); or gemcitabine 1000 mg/m^2 or 1250 mg/m^2 and cisplatin 75 mg/m^2 (squamous histology). In the chemotherapy arm, two additional treatment regimen options included vinorelbine 25 mg/m^2 or 30 mg/m^2 and cisplatin 75 mg/m^2; or docetaxel 60 mg/m^2 or 75 mg/m^2 and cisplatin 75 mg/m^2 (any histology).

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

Baseline characteristics 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 ≥ 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 ≥ 1% and disease stage II-IIIA from an exploratory analysis with a minimum follow-up of 32.9 months are summarized in Table 17.

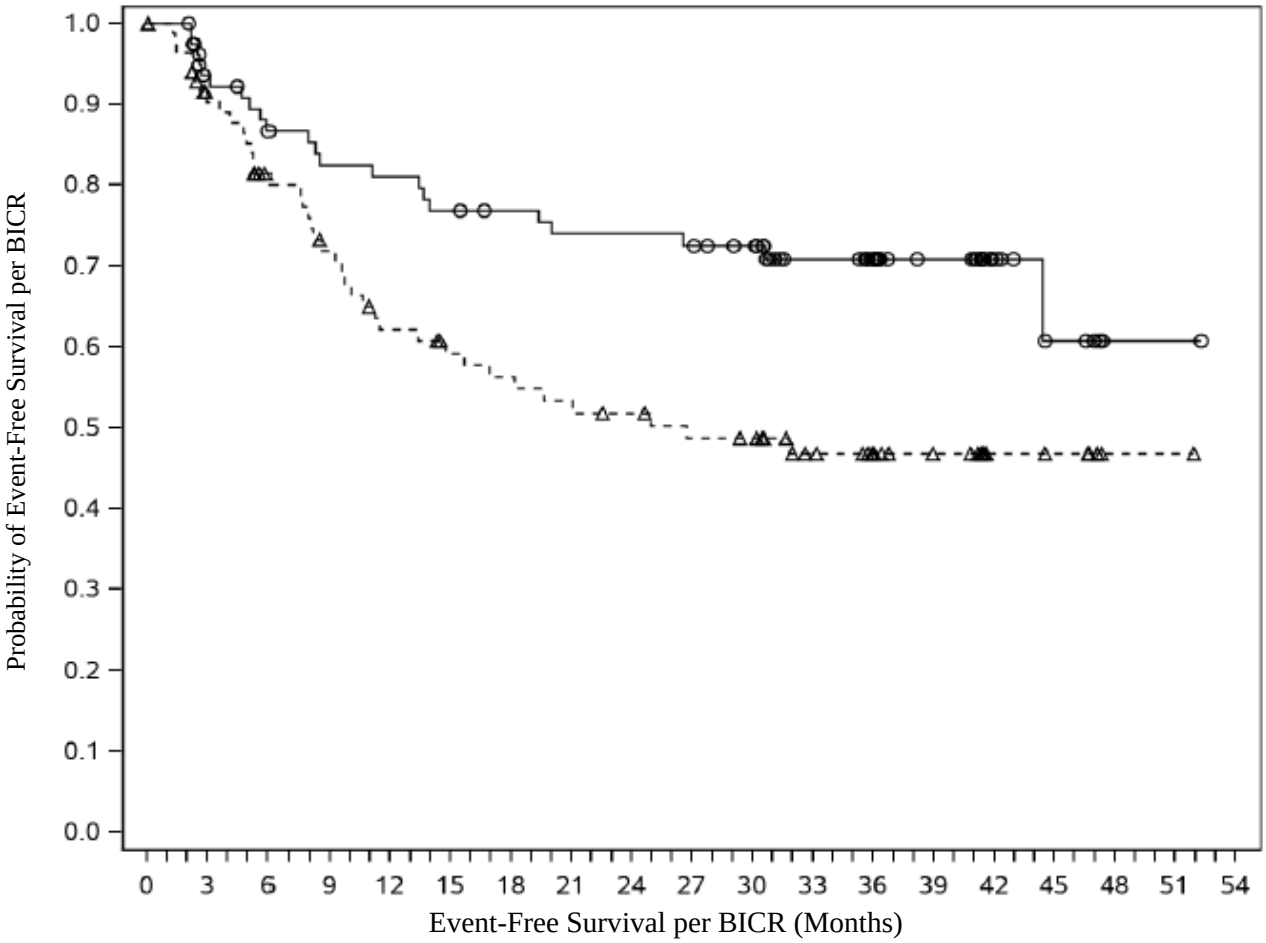
Table 17: Efficacy results in patients with tumour PD-L1 ≥ 1% and stage II-IIIA disease* (CA209816)

	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 ≥ 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 ≥ 1% and stage II-IIIA disease (CA209816)



Number of Subjects at Risk

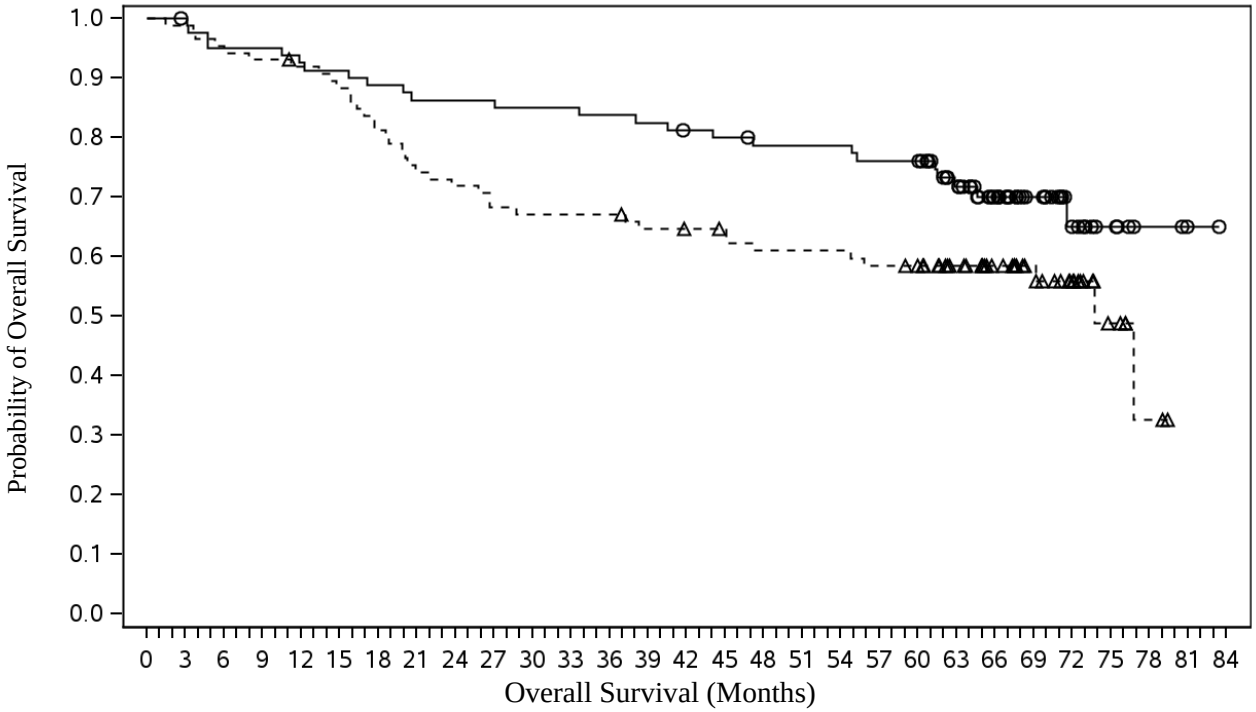
Nivolumab + chemotherapy																		
81	69	62	59	58	55	53	51	51	50	47	37	32	21	10	5	1	1	0
Chemotherapy																		
86	71	60	52	44	40	38	36	34	31	30	23	18	14	7	6	1	1	0

—❍—— 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 ≥ 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 ≥ 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 ≥ 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

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 for until disease progression, recurrence, or unacceptable toxicity, for up to 13 cycles. Platinum-based chemotherapy consisted of paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m^2, and cisplatin 75 mg/m^2 or carboplatin AUC 5 or AUC 6 (non-squamous histology); or cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 (squamous histology).

Stratification factors for randomisation were tumour PD-L1 expression level (≥ 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 ≥ 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).

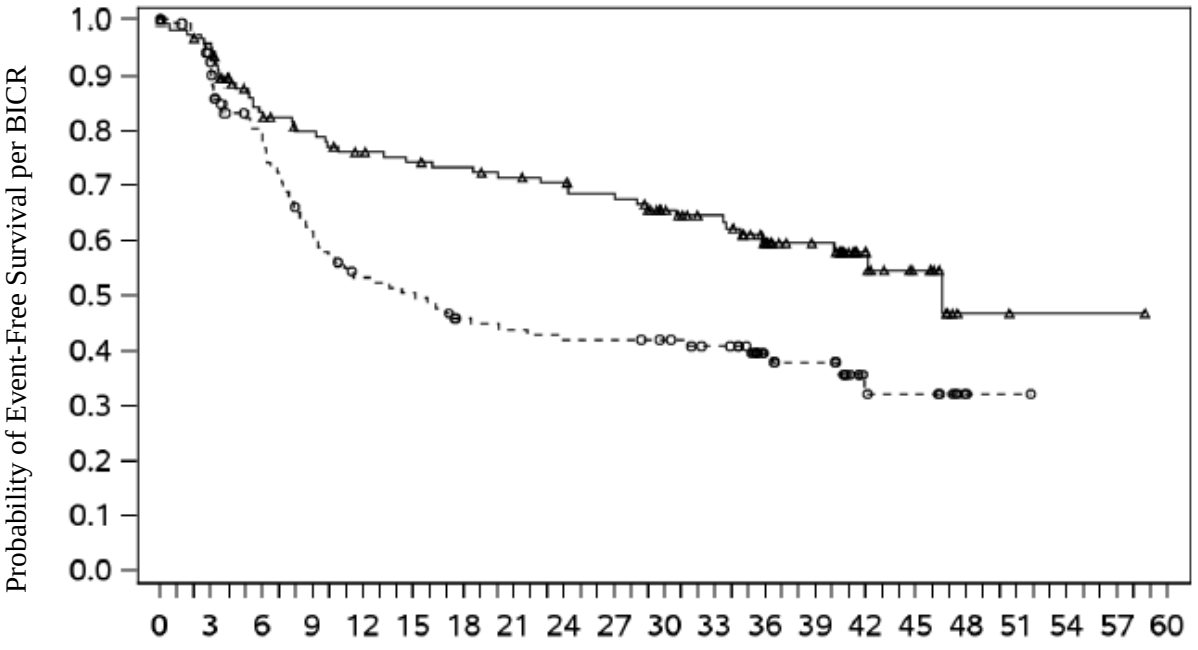
Exploratory subgroup analysis by tumour PD-L1 expression
EFS for the subgroup of patients with tumour PD-L1 expression ≥ 1%, with a median follow-up of 41 months (range: 31.3-59.8 months), are presented in Table 18 and Figure 13.

Table 18: Efficacy results in patients with tumour PD-L1 ≥ 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 ≥ 1% (CA20977T)



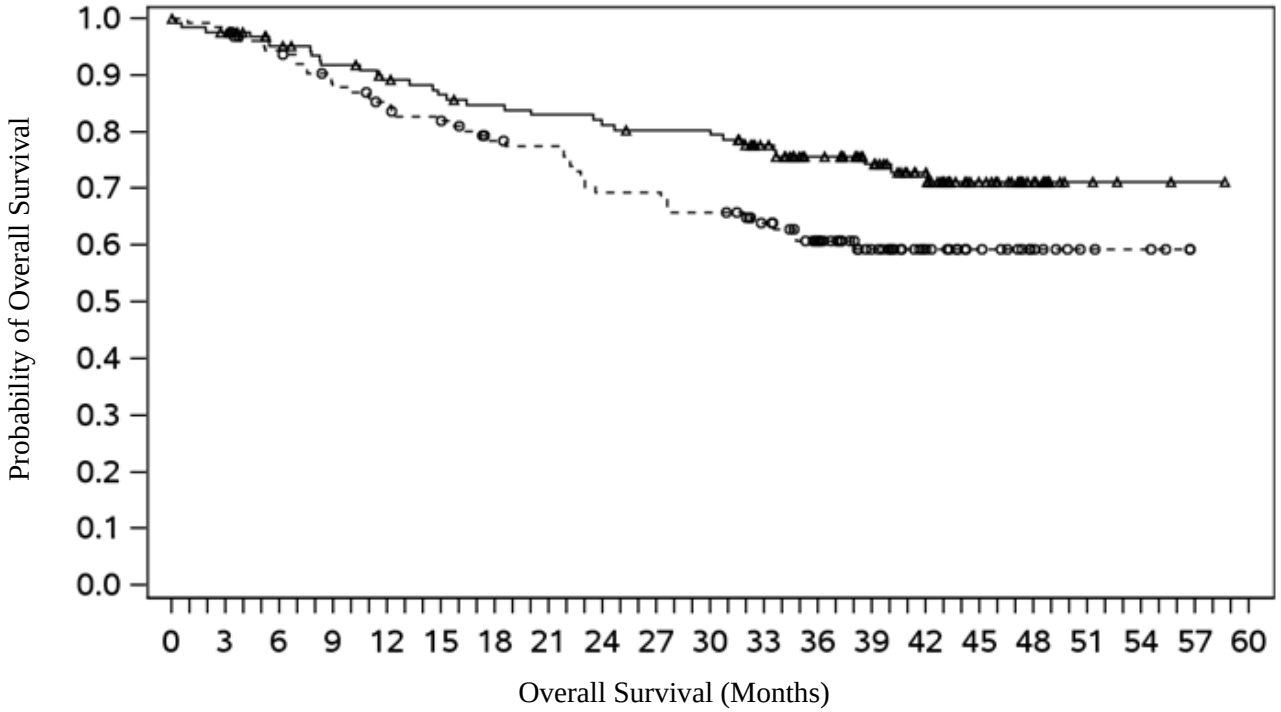
Number of Subjects at Risk

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 ≥ 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 ≥ 1% are shown in Figure 14.

Figure 14: Kaplan-Meier curves of OS in patients with tumour PD-L1 ≥ 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

First-line treatment of NSCLC

Randomised phase 3 study of nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy vs. 4 cycles of platinum-based chemotherapy (CA2099LA)
The safety and efficacy of nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-based chemotherapy were evaluated in a phase 3, randomised, open-label study (CA2099LA). The study included patients (18 years or older) with histologically confirmed non-squamous or squamous Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors). Patients were enrolled regardless of their tumour PD-L1 status.

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

A total of 719 patients were randomised to receive either nivolumab in combination with ipilimumab and platinum-based chemotherapy (n = 361) or platinum-based chemotherapy (n = 358). Patients in the nivolumab in combination with ipilimumab and platinum-based chemotherapy arm received nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-based

chemotherapy administered every 3 weeks for 2 cycles. Patients in the chemotherapy arm received platinum-based chemotherapy administered every 3 weeks for 4 cycles; non-squamous patients could receive optional pemetrexed maintenance therapy.

Platinum-based chemotherapy consisted of carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m^2; or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC.

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

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

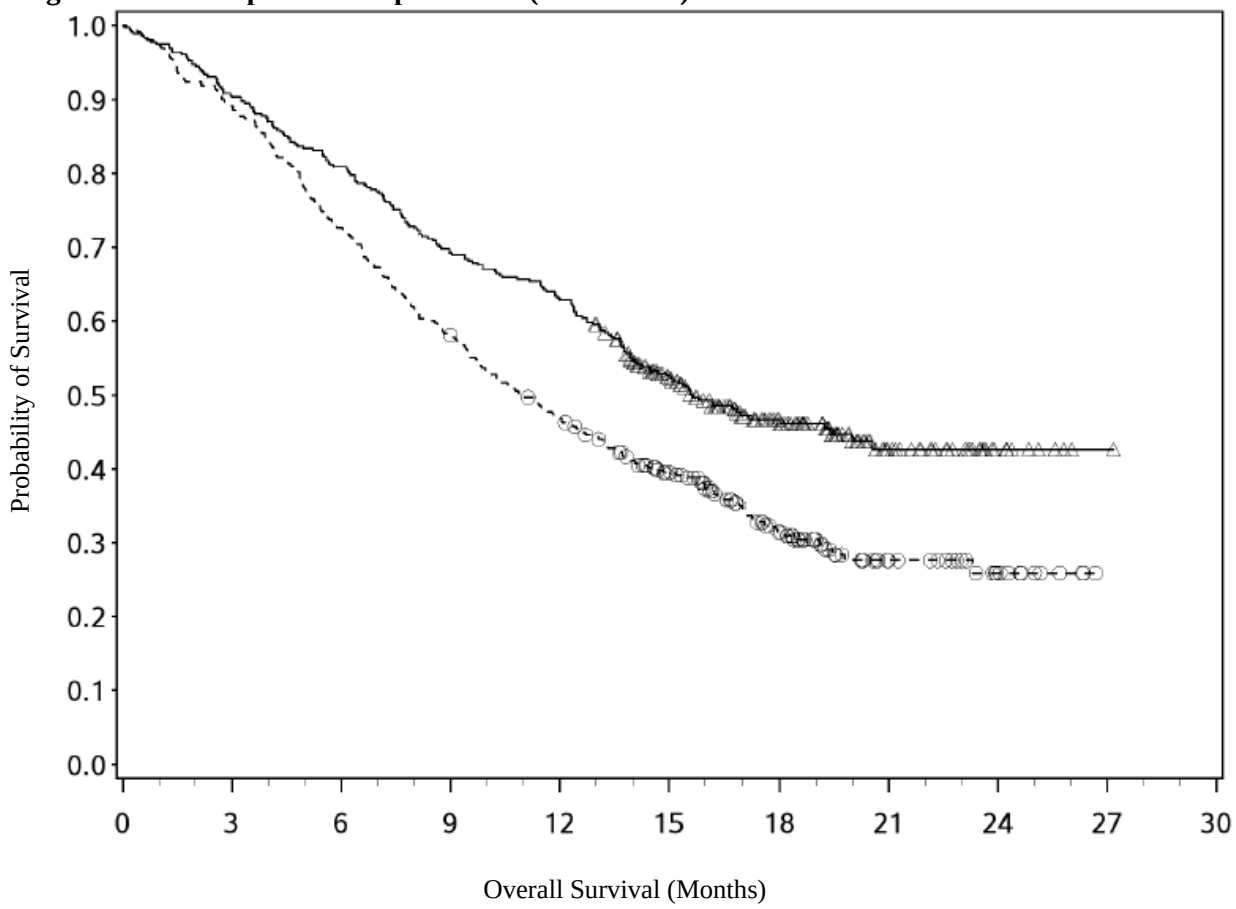
CA2099LA primary efficacy outcome measure was OS. Additional efficacy endpoints were PFS, ORR, and duration of response as assessed by BICR.

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

Efficacy results are shown in Figure 15 (updated OS analysis with a minimum follow-up of 12.7 months) and Table 19 (primary analysis with a minimum follow-up of 8.1 months).

An updated efficacy analysis was performed when all patients had a minimum follow-up of 12.7 months (see Figure 15). At the time of this analysis, the hazard ratio for OS was 0.66 (95% CI: 0.55, 0.80) and the hazard ratio for PFS was 0.68 (95% CI: 0.57, 0.82).

Figure 15: Kaplan-Meier plot of OS (CA2099LA)



Number of subjects at risk

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

—△—— Nivolumab + ipilimumab + chemotherapy (events: 190/361), median and 95% CI: 15.64 (13.93, 19.98)

- - -❍- - - Chemotherapy (events: 242/358), median and 95% CI: 10.91 (9.46, 12.55)

Table 19: Efficacy results (CA2099LA)

	nivolumab + ipilimumab + chemotherapy (n = 361)		**chemotherapy (n = 358)**
Overall survival			
Events	156 (43.2%)		195 (54.5%)
Hazard ratio (96.71% CI)[a]		0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]		0.0006	
Median (months) (95% CI)	14.1 (13.24, 16.16)		10.7 (9.46, 12.45)
Rate (95% CI) at 6 months	80.9 (76.4,84.6)		72.3 (67.4,76.7)

	nivolumab + ipilimumab + chemotherapy (n = 361)		chemotherapy (n = 358)
Progression-free survival			
Events	232 (64.3%)		249 (69.6%)
Hazard ratio (97.48% CI)[a]		0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]		0.0001	
Median (months)[d] (95% CI)	6.83 (5.55, 7.66)		4.96 (4.27, 5.55)
Rate (95% CI) at 6 months	51.7 (46.2, 56.8)		35.9 (30.5, 41.3)
Overall response rate[e]	136 (37.7%)		90 (25.1%)
(95% CI)	(32.7, 42.9)		(20.7, 30.0)
Stratified CMH test p-value[f]		0.0003	
Complete response (CR)	7 (1.9%)		3 (0.8%)
Partial response (PR)	129 (35.7%)		87 (24.3%)
Duration of response			
Median (months) (95% CI)[d]	10.02 (8.21, 13.01)		5.09 (4.34, 7.00)
% with duration ≥ 6 months[g]	74		41

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

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

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

Table 20 summarises efficacy results of OS, PFS, and ORR by tumour PD-L1 expression in pre-specified subgroup analyses.

Table 20: Efficacy results by tumour PD-L1 expression (CA2099LA)

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

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

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

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

Treatment of NSCLC after prior chemotherapy

Squamous NSCLC

Randomised phase 3 study vs. docetaxel (CA209017)

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

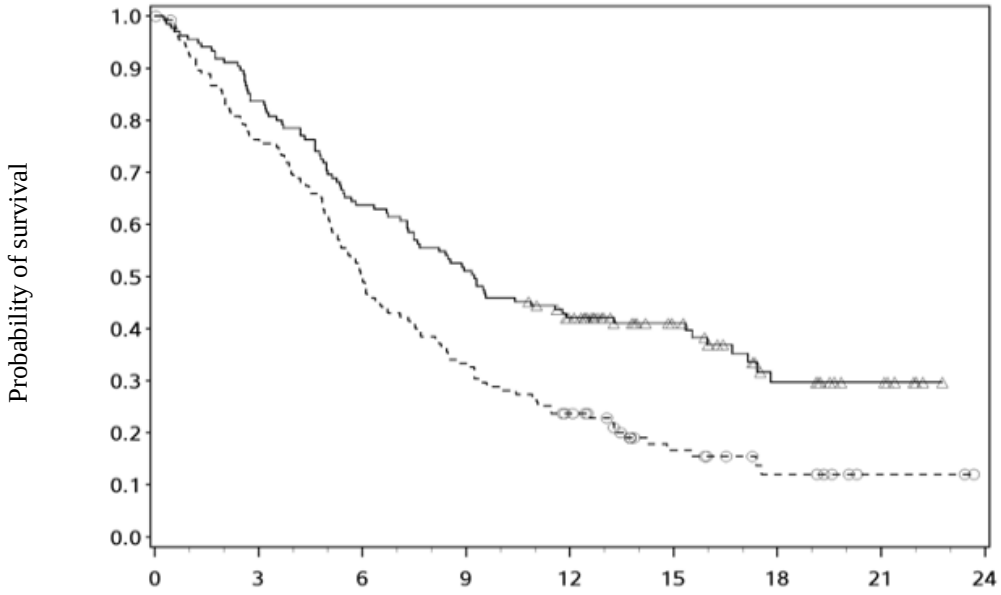
A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (n = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m^2 every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to the RECIST, version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. In addition, symptom improvement and overall health status were assessed using the Lung cancer symptom score

(LCSS) average symptom burden index and the EQ-5D Visual Analogue Scale (EQ-VAS), respectively.

Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 39-85) with 44% ≥ 65 years of age and 11% ≥ 75 years of age. The majority of patients were white (93%) and male (76%). Thirty-one percent had progressive disease reported as the best response to their most recent prior regimen and 45% received nivolumab within 3 months of completing their most recent prior regimen. Baseline ECOG performance status score was 0 (24%) or 1 (76%).

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

Figure 16: 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 21.

Table 21: Efficacy results (CA209017)

	nivolumab (n = 135)		docetaxel (n = 137)
Primary analysis Minimum follow-up: 10.6 months			
Overall survival			
Events	86 (63.7%)		113 (82.5%)
Hazard ratio		0.59	
96.85% CI		(0.43, 0.81)	
p-value		0.0002	
Median (95% CI) months	9.23 (7.33, 13.27)		6.01 (5.13, 7.33)
Rate (95% CI) at 12 months	42.1 (33.7, 50.3)		23.7 (16.9, 31.1)
Confirmed objective response	27 (20.0%)		12 (8.8%)
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Odds ratio (95% CI)		2.64 (1.27, 5.49)	
p-value		0.0083	
Complete response (CR)	1 (0.7%)		0
Partial response (PR)	26 (19.3%)		12 (8.8%)
Stable disease (SD)	39 (28.9%)		47 (34.3%)
Median duration of response			
Months (range)	Not reached (2.9-20.5^{+})		8.4 (1.4^{+}-15.2^{+})
Median time to response			
Months (range)	2.2 (1.6-11.8)		2.1 (1.8-9.5)
Progression-free survival			
Events	105 (77.8%)		122 (89.1%)
Hazard ratio		0.62	
95% CI		(0.47, 0.81)	
p-value		< 0.0004	
Median (95% CI) (months)	3.48 (2.14, 4.86)		2.83 (2.10, 3.52)
Rate (95% CI) at 12 months	20.8 (14.0, 28.4)		6.4 (2.9, 11.8)
Updated analysis Minimum follow-up: 24.2 months			
Overall survival[a]			
Events	110 (81.4%)		128 (93.4%)
Hazard ratio		0.62	
95% CI		(0.47, 0.80)	
Rate (95% CI) at 24 months	22.9 (16.2, 30.3)		8 (4.3, 13.3)
Confirmed objective response	20.0%		8.8%
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Median duration of response			
Months (range)	25.2 (2.9-30.4)		8.4 (1.4^{+}-18.0^{+})

	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	20.0%	8.8%
(95% CI)	(13.6, 27.7)	(4.6, 14.8)
Median duration of response		
Months (range)	25.2 (2.9-70.6+)	7.5 (0.0+-18.0+)
Progression-free survival		
Rate (95% CI) at 60 months	9.4 (4.8, 15.8)	All patients had either progressed, were censored, or lost to follow-up

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

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

Single-arm phase 2 study (CA209063)
Study CA209063 was a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous NSCLC after two or more lines of therapy; otherwise similar inclusion criteria as study CA209017 were applied. Nivolumab 3 mg/kg showed an ORR of 14.5% (95% CI: 8.7,22.2), a median OS of 8.21 months (95% CI: 6.05,10.9), and a median PFS of 1.87 months (95% CI 1.77,3.15). The PFS was measured by RECIST, version 1.1. The estimated 1-year survival rate was 41%.

Single-arm phase 2 study (CA209171)
Study CA209171 was a single-arm, open label study of nivolumab monotherapy in patients with previously treated advanced or metastatic squamous NSCLC. Safety was the primary endpoint and efficacy was a secondary endpoint. Of the 811 treated patients, 103 (13%) had an ECOG performance score of 2, 686 (85%) were < 75 years old and 125 (15%) were ≥ 75 years old. No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. Efficacy results based on investigator-assessed ORR are presented in Table 22 below.

Table 22: 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	1/64	55/568	11/103
(%)	(9.8)	(6.1)	(9.7)	(10.7)
95% CI[b]	(7.7, 12.3)	(0.0, 8.4)	(7.4, 12.4)	(5.5, 18.3)

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

Non-squamous NSCLC

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

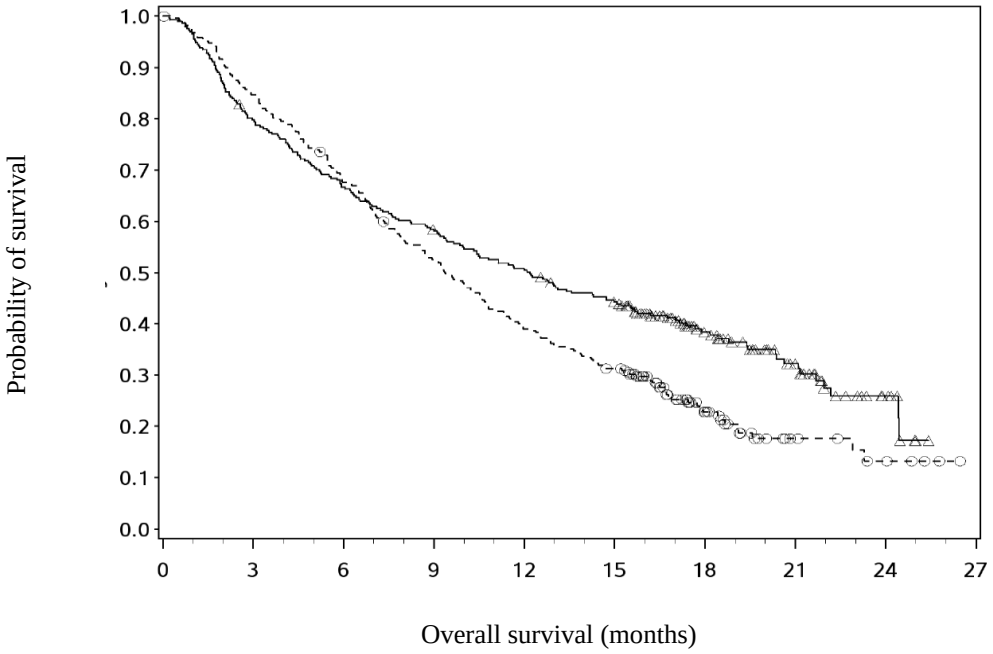
A total of 582 patients were randomised to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks (n = 292) or docetaxel 75 mg/m^2 every 3 weeks (n = 290). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour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

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

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

The Kaplan-Meier curves for OS are shown in Figure 17.

Figure 17: 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 prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 23.

Table 23: Efficacy results (CA209057)

	nivolumab (n = 292)	**docetaxel (n = 290)**
Prespecified interim analysis Minimum follow-up: 13.2 months		
Overall survival		
Events	190 (65.1%)	223 (76.9%)
Hazard ratio[a]	0.73	
(95.92% CI)	(0.59, 0.89)	
p-value[b]	0.0015	
Median (95% CI) months	12.19 (9.66, 14.98)	9.36 (8.05, 10.68)
Rate (95% CI) at 12 months	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)

	nivolumab (n = 292)	docetaxel (n = 290)
Confirmed objective response	56 (19.2%)	36 (12.4%)
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Odds ratio (95% CI)	1.68 (1.07, 2.64)	
p-value	0.0246	
Complete response (CR)	4 (1.4%)	1 (0.3%)
Partial response (PR)	52 (17.8%)	35 (12.1%)
Stable disease (SD)	74 (25.3%)	122 (42.1%)
Median duration of response		
Months (range)	17.15 (1.8-22.6+)	5.55 (1.2+-15.2+)
Median time to response		
Months (range)	2.10 (1.2-8.6)	2.61 (1.4-6.3)
Progression-free survival		
Events	234 (80.1%)	245 (84.5%)
Hazard ratio	0.92	
95% CI	(0.77, 1.11)	
p-value	0.3932	
Median (95% CI) (months)	2.33 (2.17, 3.32)	4.21 (3.45, 4.86)
Rate (95% CI) at 12 months	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)
Updated analysis Minimum follow-up: 24.2 months		
Overall survival[c]		
Events	228 (78.1%)	247 (85.1%)
Hazard ratio[a]	0.75	
(95% CI)	(0.63, 0.91)	
Rate (95% CI) at 24 months	28.7 (23.6, 34.0)	15.8 (11.9, 20.3)
Confirmed objective response	19.2%	12.4%
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-33.7+)	5.6 (1.2+-16.8)
Progression-free survival		
Rate (95% CI) at 24 months	11.9 (8.3, 16.2)	1.0 (0.2, 3.3)

	nivolumab (n = 292)	docetaxel (n = 290)
Updated analysis Minimum follow-up: 62.7 months		
Overall survival[d]		
Events	250 (85.6%)	279 (96.2%)
Hazard ratio[a]	0.70	
(95% CI)	(0.58, 0.83)	
Rate (95% CI) at 60 months	14.0 (10.2, 18.3)	2.1 (0.9, 4.4)
Confirmed objective response	19.5%	12.4%
(95% CI)	(15.1, 24.5)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-70.4+)	5.6 (0.0+-33.4)
Progression-free survival		
Rate (95% CI) at 60 months	7.5 (4.5, 11.4)	All patients had either progressed, were censored, or lost to follow-up

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

Quantifiable tumour PD-L1 expression was measured in 79% of patients in the nivolumab group and 77% of patients in the docetaxel group. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. docetaxel) at each of the predefined tumour PD-L1 expression levels of ≥ 1% (53% vs. 55%), ≥ 5% (41% vs. 38%), or ≥ 10% (37% vs. 35%).

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

Table 24 summarises results of ORR and OS by tumour PD-L1 expression.

Table 24: ORR and OS by tumour PD-L1 expression (CA209057)

PD-L1 expression	nivolumab	docetaxel	
ORR by tumour PD-L1 expression Minimum follow-up: 13.2 months			
			Odds ratio (95% CI)
< 1%	10/108 (9.3%) 95% CI: 4.5, 16.4	15/101 (14.9%) 95% CI: 8.6, 23.3	0.59 (0.22, 1.48)
≥ 1%	38/123 (30.9%) 95% CI: 22.9, 39.9	15/123 (12.2%) 95% CI: 7.0, 19.3	3.22 (1.60, 6.71)
≥ 1% to < 10%[a]	6/37 (16.2%) 95% CI: 6.2, 32.0	5/44 (11.4%) 95% CI: 3.8, 24.6	1.51 (0.35, 6.85)
≥ 10% to < 50%[a]	5/20 (25.0%) 95% CI: 8.7, 49.1	7/33 (21.2%) 95% CI: 9.0, 38.9	1.24 (0.26, 5.48)
≥ 50%[a]	27/66 (40.9%) 95% CI: 29.0, 53.7	3/46 (6.5%) 95% CI: 1.4, 17.9	9.92 (2.68, 54.09)

PD-L1 expression	nivolumab	docetaxel	
	OS by tumour PD-L1 expression		
	Minimum follow-up: 13.2 months		
	Number of events (number of patients)		**Unstratified hazard ratio (95% CI)**
< 1%	77 (108)	75 (101)	0.90 (0.66, 1.24)
≥ 1%	68 (123)	93 (123)	0.59 (0.43, 0.82)
≥ 1% to < 10%[a]	27 (37)	30 (44)	1.33 (0.79, 2.24)
≥ 10% to < 50%[a]	11 (20)	26 (33)	0.61 (0.30, 1.23)
≥ 50%[a]	30 (66)	37 (46)	0.32 (0.20, 0.53)
	Updated analysis		
	Minimum follow-up: 24.2 months		
< 1%	91 (108)	86 (101)	0.91 (0.67, 1.22)
≥ 1%	87 (123)	103 (123)	0.62 (0.47, 0.83)
	Updated analysis		
	Minimum follow-up: 62.7 months		
< 1%	100 (109)	96 (101)	0.87 (0.66, 1.16)
≥1%	96 (122)	119 (123)	0.55 (0.42, 0.73)

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

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

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

Malignant pleural mesothelioma

Randomised phase 3 study of nivolumab in combination with ipilimumab vs. chemotherapy (CA209743)

The safety and efficacy of nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks were evaluated in a phase 3, randomised, open-label study (CA209743). The study included patients (18 years or older) with histologically confirmed and previously untreated malignant pleural mesothelioma of epithelioid or non-epithelioid histology, ECOG performance status 0 or 1, and no palliative radiotherapy within 14 days of first study therapy. Patients were enrolled regardless of their tumour PD-L1 status.

Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the trial. Randomisation was stratified by histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and gender (male vs. female).

A total of 605 patients were randomised to receive either nivolumab in combination with ipilimumab (n = 303) or chemotherapy (n = 302). Patients in the nivolumab in combination with ipilimumab arm received nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks in combination

with ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years. Patients in the chemotherapy arm received chemotherapy for up to 6 cycles (each cycle was 21 days). Chemotherapy consisted of cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 or carboplatin 5 AUC and pemetrexed 500 mg/m^2.

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

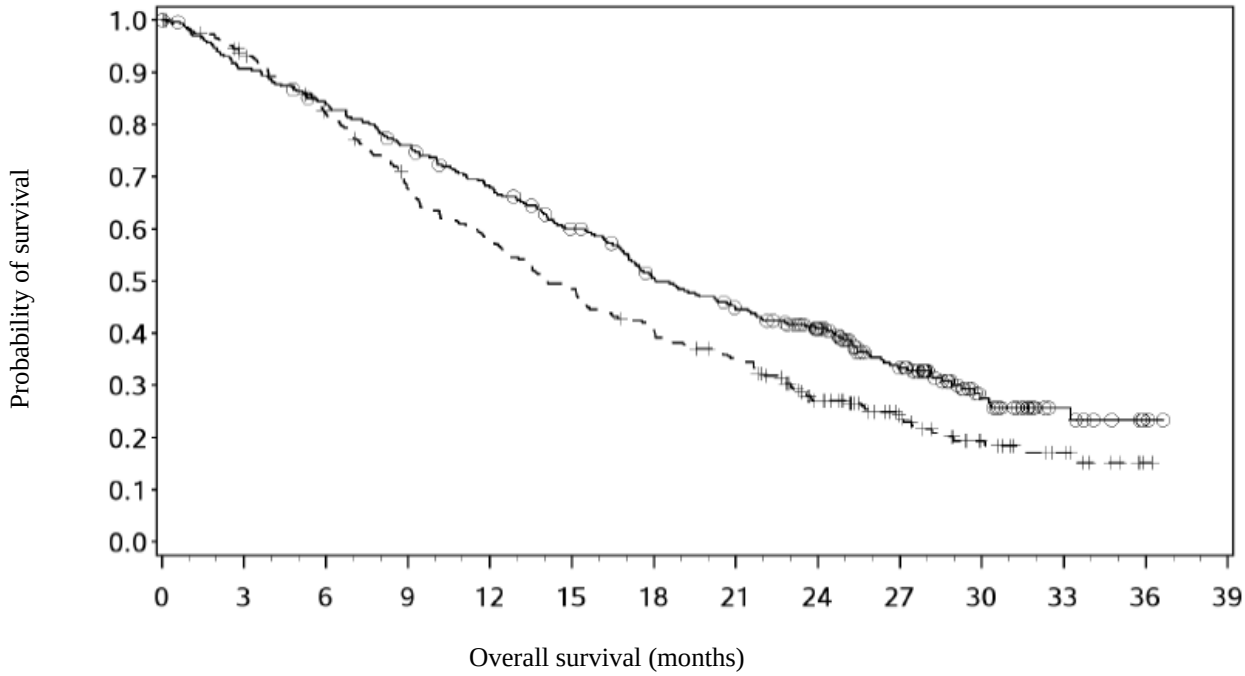
CA209743 baseline characteristics were generally balanced across all treatment groups. The median age was 69 years (range: 25-89) with 72% ≥ 65 years of age and 26% ≥ 75 years of age. The majority of patients were white (85%) and male (77%). Baseline ECOG performance status was 0 (40%) or 1 (60%), 80% of patients with PD-L1 ≥ 1% and 20% with PD-L1 < 1%, 75% had epithelioid and 25% had non-epithelioid histology.

CA209743 primary efficacy outcome measure was OS. Key secondary efficacy endpoints were PFS, ORR, and duration of response as assessed by Blinded Independent Central Review (BICR) utilising modified RECIST criteria for pleural mesothelioma. Descriptive analyses for these secondary endpoints are presented in Table 25.

The study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab in combination with ipilimumab as compared to chemotherapy at the prespecified interim analysis when 419 events were observed (89% of the planned number of events for final analysis). Minimum follow-up for OS was 22 months.

Efficacy results are shown in Figure 18 and Table 25.

Figure 18: Kaplan-Meier curves of OS (CA209743)



Number of subjects at risk

Nivolumab + ipilimumab													
303	273	251	226	200	173	143	124	101	65	30	11	2	0
Chemotherapy													
302	268	233	190	162	136	113	95	62	38	20	11	1	0

- - -❍- - - Nivolumab + ipilimumab (events: 200/303), median and 95% CI: 18.07 (16.82, 21.45)
- - -┼- - - Chemotherapy (events: 219/302), median and 95% CI: 14.09 (12.45, 16.23)

Table 25: Efficacy results (CA209743)

	nivolumab + ipilimumab (n = 303)		**chemotherapy (n = 302)**
Overall survival			
Events	200 (66%)		219 (73%)
Hazard ratio (96.6% CI)[a]		0.74 (0.60, 0.91)	
Stratified log-rank p-value[b]		0.002	
Median (months)[c] (95% CI)	18.1 (16.8, 21.5)		14.1 (12.5, 16.2)
Rate (95% CI) at 24 months[c]	41% (35.1, 46.5)		27% (21.9, 32.4)
Progression-free survival			
Events	218 (72%)		209 (69%)
Hazard ratio (95% CI)[a]		1.0 (0.82, 1.21)	
Median (months)[c] (95% CI)	6.8 (5.6, 7.4)		7.2 (6.9, 8.1)

	nivolumab + ipilimumab (n = 303)	chemotherapy (n = 302)
Overall response rate	40%	43%
(95% CI)	(34.1, 45.4)	(37.1, 48.5)
Complete response (CR)	1.7%	0
Partial response (PR)	38%	43%
Duration of response		
Median (months)[c]	11.0	6.7
(95% CI)	(8.1, 16.5)	(5.3, 7.1)

[a] Stratified Cox proportional hazard model.
[b] p-value is compared with the allocated alpha of 0.0345 for this interim analysis.
[c] Kaplan-Meier estimate.

Subsequent systemic therapy was received by 44.2% and 40.7% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA-4) was received by 3.3% and 20.2% of patients in the combination and chemotherapy arms, respectively.

Table 26 summarises efficacy results of OS, PFS, and ORR by histology in prespecified subgroup analyses.

Table 26: Efficacy results by histology (CA209743)

	Epithelioid (n = 471)		Non-epithelioid (n = 134)	
	nivolumab + ipilimumab (n = 236)	chemotherapy (n = 235)	nivolumab + ipilimumab (n = 67)	chemotherapy (n = 67)
Overall survival				
Events	157	164	43	55
Hazard ratio (95% CI)[a]	0.85 (0.68, 1.06)		0.46 (0.31, 0.70)	
Median (months) (95% CI)	18.73 (17.05, 21.72)	16.23 (14.09, 19.15)	16.89 (11.83, 25.20)	8.80 (7.62, 11.76)
Rate (95% CI) at 24 months	41.2 (34.7, 47.6)	31.8 (25.7, 38.1)	39.5 (27.5, 51.2)	9.7 (3.8, 18.9)
Progression-free survival				
Hazard ratio (95% CI)[a]	1.14 (0.92, 1.41)		0.58 (0.38, 0.90)	
Median (months) (95% CI)	6.18 (5.49, 7.03)	7.66 (7.03, 8.31)	8.31 (3.84, 11.01)	5.59 (5.13, 7.16)
Overall response rate (95% CI)[b]	38.6% (32.3, 45.1)	47.2% (40.7, 53.8)	43.3% (31.2, 56.0)	26.9% (16.8, 39.1)
Duration of response Median (months) (95% CI)[c]	8.44 (7.16, 14.59)	6.83 (5.59, 7.13)	24.02 (8.31, N.A.)	4.21 (2.79, 7.03)

[a] Hazard ratio based on unstratified Cox proportional hazards model.
[b] Confidence interval based on the Clopper and Pearson method
[c] Median computed using Kaplan-Meier method

Table 27 summarises efficacy results of OS, PFS, and ORR by baseline tumour PD-L1 expression in prespecified subgroup analyses.

Table 27: Efficacy results by tumour PD-L1 expression (CA209743)

	PD-L1 < 1% (n = 135)		PD-L1 ≥ 1% (n = 451)	
	nivolumab + ipilimumab (n = 57)	**chemotherapy (n = 78)**	**nivolumab + ipilimumab (n = 232)**	**chemotherapy (n = 219)**
Overall survival				
Events	40	58	150	157
Hazard ratio (95% CI)[a]	0.94 (0.62, 1.40)		0.69 (0.55, 0.87)	
Median (months) (95% CI)[b]	17.3 (10.1, 24.3)	16.5 (13.4, 20.5)	18.0 (16.8, 21.5)	13.3 (11.6, 15.4)
Rate (95% CI) at 24 months	38.7 (25.9, 51.3)	24.6 (15.5, 35.0)	40.8 (34.3, 47.2)	28.3 (22.1, 34.7)
Progression-free survival				
Hazard ratio (95% CI)[a]	1.79 (1.21, 2.64)		0.81 (0.64, 1.01)	
Median (months) (95% CI)[b]	4.1 (2.7, 5.6)	8.3 (7.0, 11.1)	7.0 (5.8, 8.5)	7.1 (6.2, 7.6)
Overall response rate	21.1%	38.5%	43.5%	44.3%
(95% CI)[c]	(11.4, 33.9)	(27.7, 50.2)	(37.1, 50.2)	(37.6, 51.1)

[a] Hazard ratio based on unstratified Cox proportional hazards model.
[b] Median computed using Kaplan-Meier method.
[c] Confidence interval based on the Clopper and Pearson method.

A total of 157 MPM patients aged ≥ 75 years were enrolled in study CA209743 (78 in the nivolumab in combination with ipilimumab arm and 79 in the chemotherapy arm). A HR of 1.02 (95% CI: 0.70, 1.48) in OS was observed for nivolumab in combination with ipilimumab vs. chemotherapy within this study subgroup. A higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older relative to all patients who received nivolumab in combination with ipilimumab was shown (see section 4.8). However, due to the exploratory nature of this subgroup analysis, no definitive conclusions can be drawn.

Renal cell carcinoma

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

A total of 821 patients were randomised to receive either nivolumab 3 mg/kg (n = 410) administered intravenously over 60 minutes every 2 weeks or everolimus (n = 411) 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour assessments were conducted 8 weeks after randomisation and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after

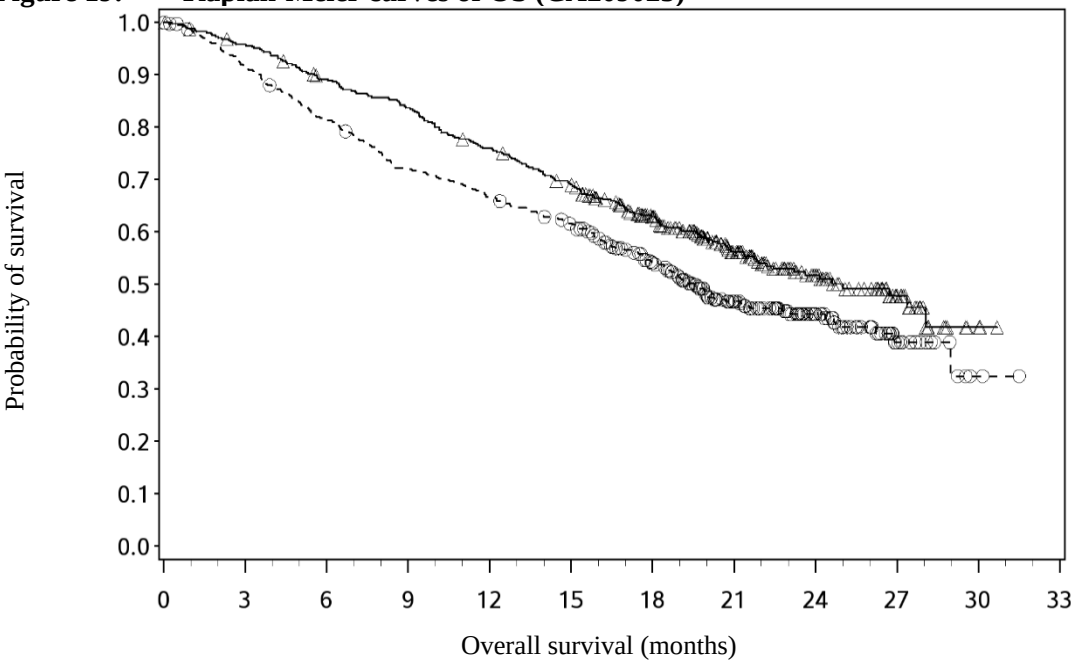
treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was OS. Secondary efficacy assessments included investigator-assessed ORR and PFS.

Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40% ≥ 65 years of age and 9% ≥ 75 years of age. The majority of patients were male (75%) and white (88%), all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups were represented, and 34% and 66% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The majority of patients (72%) were treated with one prior anti-angiogenic therapy. The median duration of time from initial diagnosis to randomisation was 2.6 years in both the nivolumab and everolimus groups. The median duration of treatment was 5.5 months (range: 0-29.6+ months) in nivolumab-treated patients and was 3.7 months (range: 6 days-25.7+ months) in everolimus-treated patients.

Nivolumab was continued beyond progression in 44% of patients.

The Kaplan-Meier curves for OS are shown in Figure 19.

Figure 19: Kaplan-Meier curves of OS (CA209025)



Number of subjects at risk

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

—△—— Nivolumab 3 mg/kg (events: 183/410), median and 95% CI: 25.00 (21.75, N.A.)
- - -❍- - - Everolimus 10 mg (events: 215/411), median and 95% CI: 19.55 (17.64, 23.06)

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 28 and Figure 19). OS benefit was observed regardless of tumour PD-L1 expression level.
Efficacy results are shown in Table 28.

Table 28: Efficacy results (CA209025)

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

"$^{+}$" denotes a censored observation.
NE = non-estimable

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

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

Phase 3b/4 safety study (CA209374)
Additional safety and descriptive efficacy data are available from study CA209374, an open-label Phase 3b/4 safety study of nivolumab monotherapy (treated with 240 mg every 2 weeks) for the

treatment of patients with advanced or metastatic RCC (n = 142), including 44 patients with non-clear cell histology.

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

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

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

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

Efficacy results for the intermediate/poor risk patients are shown in Table 29 (primary analysis with a minimum follow-up of 17.5 months and with a minimum follow-up of 60 months) and in Figure 20 (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.

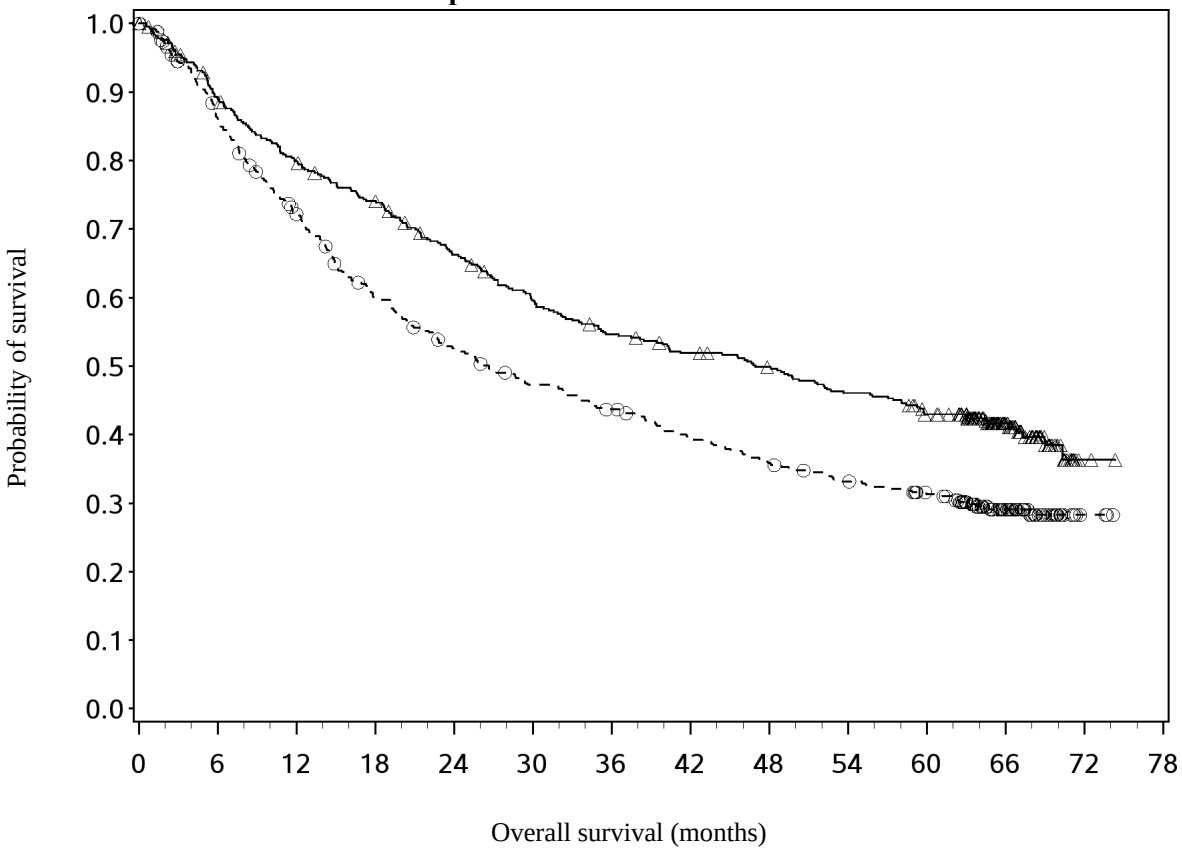
Table 29: Efficacy results in intermediate/poor risk patients (CA209214)

	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)
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)

	nivolumab + ipilimumab (n = 425)		sunitinib (n = 422)
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 20: 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 ≥ 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.

Randomised phase 3 study of nivolumab in combination with cabozantinib vs. sunitinib (CA2099ER)
The safety and efficacy of nivolumab 240 mg in combination with cabozantinib 40 mg for the first-line treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA2099ER). The study included patients (18 years or older) with advanced or metastatic RCC with a clear cell component, Karnofsky Performance Status (KPS) ≥ 70%, and measurable disease as per RECIST v1.1 regardless of their PD-L1 status or IMDC risk group. The study excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression, patients who had prior treatment with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, poorly controlled hypertension despite antihypertensive therapy, active brain metastases and uncontrolled adrenal insufficiency. Patients were stratified by IMDC prognostic score, PD-L1 tumour expression, and region.

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

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

The study demonstrated a statistically significant benefit in PFS, OS, and ORR for patients randomised to nivolumab in combination with cabozantinib as compared to sunitinib. Efficacy results from the primary analysis (minimum follow-up 10.6 months; median follow-up 18.1 months) are shown in Table 30.

Table 30: 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)

	nivolumab + cabozantinib (n = 323)		sunitinib (n = 328)
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

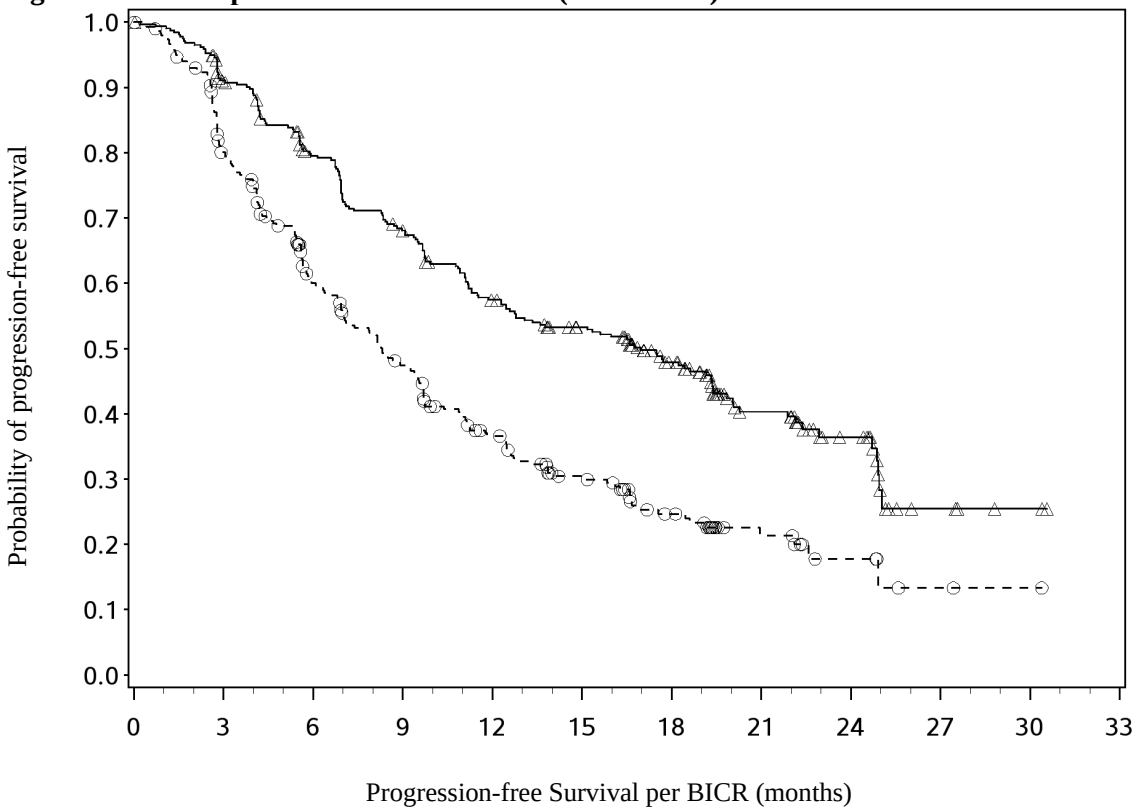
The primary analysis of PFS included censoring for new anti-cancer treatment (Table 30). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

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

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

An updated PFS and OS analysis were performed when all patients had a minimum follow-up of 16.0 months and a median follow-up of 23.5 months (see Figures 21 and 22). 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 21: Kaplan-Meier curves of PFS (CA2099ER)

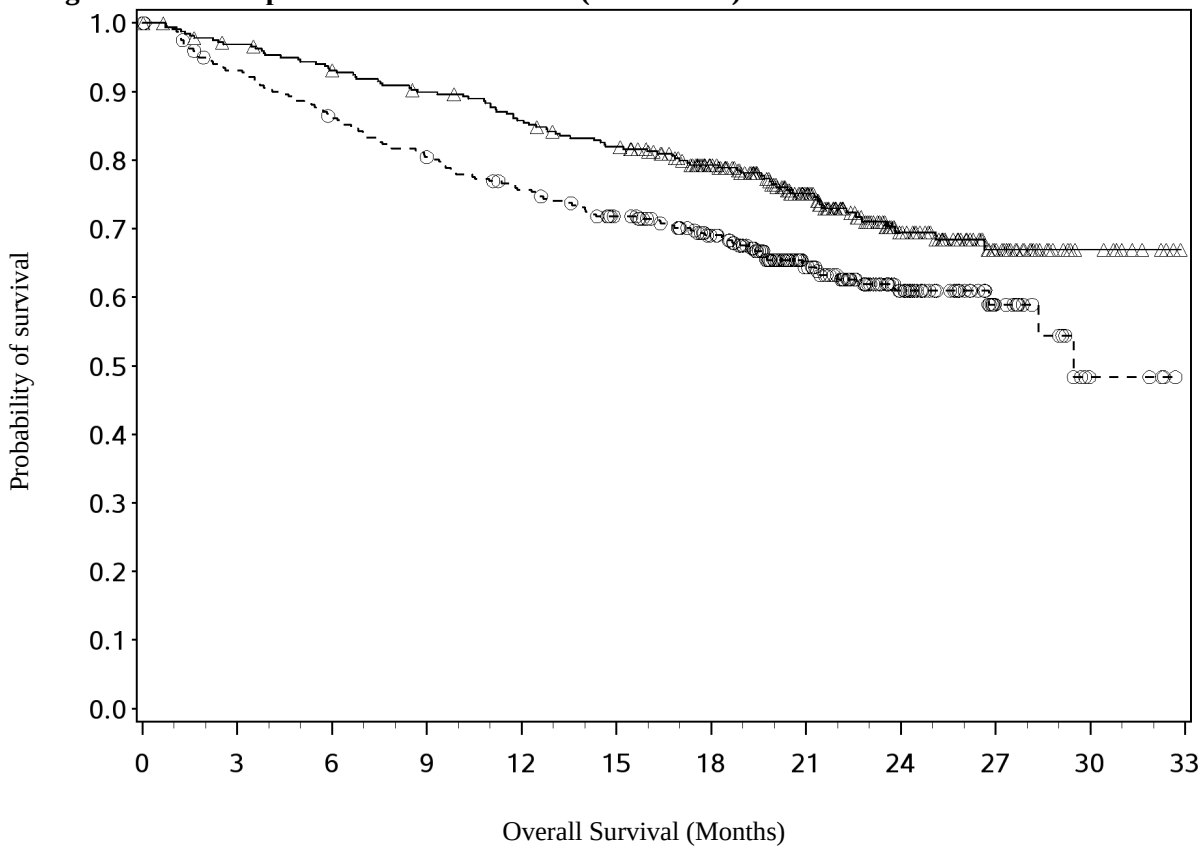


Number of subjects at risk

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 22: 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)

Classical Hodgkin lymphoma

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

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

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

disease progression or treatment discontinuation. Efficacy assessments included investigator-assessed ORR, retrospectively evaluated by an IRRC, and duration of response.

Data from the 80 patients from CA209205 Cohort B and from the 15 patients from CA209039 who received prior brentuximab vedotin treatment following ASCT were integrated. Additional data from 100 patients from CA209205 Cohort C who received brentuximab before and/or after ASCT are also presented. Baseline characteristics were similar across the two studies and cohorts (see Table 31 below).

Table 31: Baseline patient characteristics in CA209205 Cohort B, Cohort C and CA209039

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

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

Efficacy from both studies was evaluated by the same IRRC. Results are shown in Table 32.

Table 32: Efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma

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

"+" denotes a censored observation.
[a] Follow-up was ongoing at the time of data submission.
[b] Data unstable due to the limited duration of response for Cohort B resulting from censoring.
NE = non-estimable

Updated efficacy results from longer follow-up data of Cohort B (minimum 68.7 months) and Cohort C (minimum 61.9 months) from CA209205 are presented below in Table 33.

Table 33: Updated efficacy results in patients with relapsed/refractory classical Hodgkin lymphoma from longer follow-up of study CA209205

Number (n)/ minimum follow-up (months)	CA209205 Cohort B (n = 80/68.7)	CA209205 Cohort C (n = 100/61.9)[a]
Objective response, n (%); (95% CI)	57 (71%); (60, 81)	75 (75%); (65, 83)
Complete remission (CR), n (%); (95% CI)	11 (14%); (7, 23)	21 (21%); (14, 30)
Partial remission (PR), n (%); (95% CI)	46 (58%); (46, 69)	54 (54%); (44, 64)
Stable disease, n (%)	14 (18%)	12 (12%)
Duration of response in all responders (months)[b]		
Median (95% CI)	16.6 (9.3, 25.7)	18.2 (11.6, 30.9)
Range	0.0^{+}-71.0^{+}	0.0^{+}-59.8^{+}
Duration of response in CR (months)		
Median (95% CI)	30.3 (2.4, NE)	26.4 (7.1, NE)
Range	0.7^{+}-50.0^{+}	0.0^{+}-55.7^{+}
Duration of response in PR (months)		
Median (95% CI)	10.6 (7.5, 25.3)	14.7 (9.4, 30.4)
Range	0.0^{+}-67.9^{+}	0.0^{+}-55.9^{+}
Median time to response		
Months (range)	2.2 (1.6-11.1)	2.1 (0.8, 17.9)
Median duration of follow-up		
Months (range)	58.5 (1.9-74.3)	53.5 (1.4-70.4)
Progression-free survival		
Median (95% CI)	14.8 (11.0, 19.8)	15.1 (11.1, 19.1)
Rate (95% CI) at 12 months	52 (39, 63)	53 (42, 64)
Rate (95% CI) at 24 months	36 (24, 48)	37 (25, 48)
Rate (95% CI) at 60 months	16 (6, 29)	15 (6, 28)
Overall survival		
Median	Not reached	Not reached
Rate (95% CI) at 12 months	95 (87, 98)	90 (82, 94)
Rate (95% CI) at 24 months	87 (77, 93)	86 (77, 91)
Rate (95% CI) at 60 months	72 (60, 81)	67 (56, 75)

"+" denotes a censored observation.

[a] Patients in Cohort C (n = 33) who have received brentuximab vedotin only prior to ASCT had ORR of 73% (95% CI: 55, 87), CR of 21% (95% CI: 9, 39), PR of 52% (95% CI: 34, 69). Median duration of response was 13.5 months (95% CI: 9.4, 30.9).

[b] Determined for subjects with CR or PR.

NE = non-estimable

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

In a post-hoc analysis of the 80 patients in CA209205 Cohort B, 37 had no response to prior brentuximab vedotin treatment. Among these 37 patients, treatment with nivolumab resulted in an ORR of 62.2% (23/37). The median duration of response is 25.6 months (10.6, 56.5) for the 23 responders to nivolumab who had failed to achieve response with prior brentuximab vedotin treatment.

Squamous cell cancer of the head and neck

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of metastatic or recurrent SCCHN were evaluated in a phase 3, randomised, open-label study (CA209141). The study included patients (18 years or older), with histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) and who have experienced disease progression during or within 6 months of receiving platinum-based therapy regimen and had an ECOG performance status score of 0 or 1. Prior platinum-based therapy was administered in either the adjuvant, neo-adjuvant, primary, recurrent, or metastatic setting. Patients were enrolled regardless of their tumour PD-L1 or human papilloma virus (HPV) status. Patients with active autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or active brain or leptomeningeal metastases were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

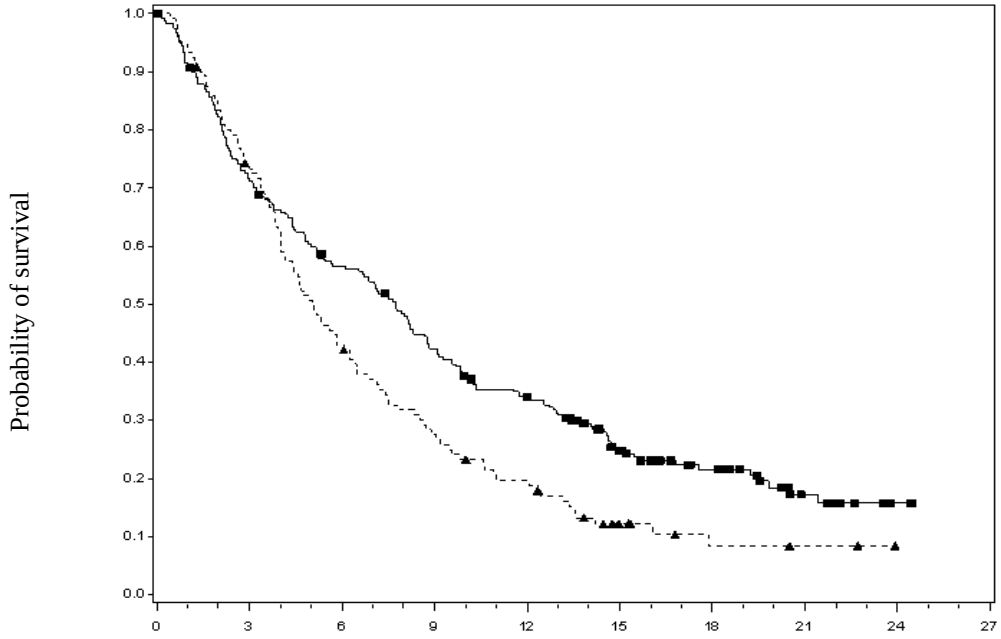
A total of 361 patients were randomised to receive either nivolumab 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n = 15), 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly or methotrexate (n = 52) 40 to 60 mg/m^2 weekly,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

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

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

With a minimum follow-up of 11.4 months, the trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice. The Kaplan-Meier curves for OS are shown in Figure 23. Efficacy results are shown in Table 34.

Figure 23: Kaplan-Meier curves of OS (CA209141)



Overall survival (months)

Number of subjects at risk

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

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

Table 34: Efficacy results (CA209141)

	nivolumab (n = 240)	**investigator's choice (n = 121)**
Overall survival		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio[a]	0.71	
(95% CI)	(0.55, 0.90)	
p-value[b]	0.0048	
Median (95% CI) (months)	7.72 (5.68, 8.77)	5.06 (4.04, 6.24)
Rate (95% CI) at 6 months	56.5 (49.9, 62.5)	43.0 (34.0, 51.7)
Rate (95% CI) at 12 months	34.0 (28.0, 40.1)	19.7 (13.0, 27.3)
Rate (95% CI) at 18 months	21.5 (16.2, 27.4)	8.3 (3.6, 15.7)
Progression-free survival		
Events	204 (85.0%)	104 (86.0%)
Hazard ratio	0.87	
95% CI	(0.69, 1.11)	
p-value	0.2597	
Median (95% CI) (months)	2.04 (1.91, 2.14)	2.33 (1.97, 3.12)
Rate (95% CI) at 6 months	21.0 (15.9, 26.6)	11.1 (5.9, 18.3)
Rate (95% CI) at 12 months	9.5 (6.0, 13.9)	2.5 (0.5, 7.8)

	nivolumab (n = 240)	investigator's choice (n = 121)
Confirmed objective response[c]	32 (13.3%)	7 (5.8%)
(95% CI)	(9.3, 18.3)	(2.4, 11.6)
Odds ratio (95% CI)	2.49 (1.07, 5.82)	
Complete response (CR)	6 (2.5%)	1 (0.8%)
Partial response (PR)	26 (10.8%)	6 (5.0%)
Stable disease (SD)	55 (22.9%)	43 (35.5%)
Median time to response		
Months (range)	2.1 (1.8-7.4)	2.0 (1.9-4.6)
Median duration of response		
Months (range)	9.7 (2.8-20.3+)	4.0 (1.5+-8.5+)

[a] Derived from a stratified proportional hazards model.
[b] P-value is derived from a log-rank test stratified by prior cetuximab; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0227.
[c] In the nivolumab group there were two patients with CRs and seven patients with PRs who had tumour PD-L1 expression < 1%.

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

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to investigator's choice. The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumour PD-L1 expression levels (see Table 35).

Table 35: OS by tumour PD-L1 expression (CA209141)

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

In an exploratory post-hoc analysis using a non-validated assay, both tumour cell PD-L1 expression and tumour-associated immune cell (TAIC) PD-L1 expression were analysed in relation to the magnitude of treatment effect of nivolumab compared to investigator's choice. This analysis showed that not only tumour cell PD-L1 expression but also TAIC PD-L1 expression appeared to be associated with benefit from nivolumab relative to investigator's choice (see Table 36). 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 36: Efficacy by tumour cell and TAIC PD-L1 expression (CA209141)

	Median OS[a] (months) HR[b] (95% CI)		Median PFS[a] (months) HR[b] (95% CI)		ORR (%) (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.

Advanced urothelial carcinoma

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

The safety and efficacy of nivolumab in combination with cisplatin and gemcitabine followed by nivolumab monotherapy were evaluated in a randomised open-label study CA209901 in cisplatin-eligible patients with unresectable or metastatic urothelial carcinoma. The study included subjects (18 years or older) with histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra, who were eligible for cisplatin and gemcitabine. Minor histologic variants (< 50% overall) were acceptable (TCC must have been the dominant histology). All subjects were required to have

measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria. No prior systemic anti-cancer therapy for metastatic or surgically unresectable urothelial carcinoma was permitted. Prior neoadjuvant chemotherapy or prior adjuvant platinum-based chemotherapy following radical cystectomy were permitted as long as the disease recurrence took place ≥ 12 months from completion of therapy. Prior intravesical therapy was permitted if completed at least 4 weeks prior to initiation of study treatment. Radiation therapy (with or without chemotherapy) with curative intent was permitted if treatment was completed ≥ 12 months before enrolment. Palliative radiotherapy was permitted as long as it was completed at least 2 weeks prior to therapy.

A total of 608 patients were randomised to receive either nivolumab in combination with cisplatin and gemcitabine (n = 304) or cisplatin and gemcitabine (n = 304). Randomisation was stratified by tumour PD-L1 status (≥ 1% vs. < 1% or indeterminate) and liver metastasis (yes vs. no). The median age was 65 years of age (range: 32 to 86) with 51% of patients ≥ 65 years of age and 12% of patients ≥ 75 years of age, 23% were Asian, 72% were White, 0.3% were Black; 77% were male, 23% were female. Baseline ECOG performance status was 0 (53%) or 1 (46%). Patients in the nivolumab in combination with cisplatin and gemcitabine arm were treated with nivolumab 360 mg every three weeks, in combination with cisplatin and gemcitabine for up to 6 cycles, after which patients received nivolumab monotherapy 480 mg every 4 weeks for a total of up to 24 months. Patients received gemcitabine dosed at 1000 mg/m^2 IV over 30-minutes on Days 1 and 8 of the 3 week treatment cycle and cisplatin dosed at 70 mg/m^2 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.

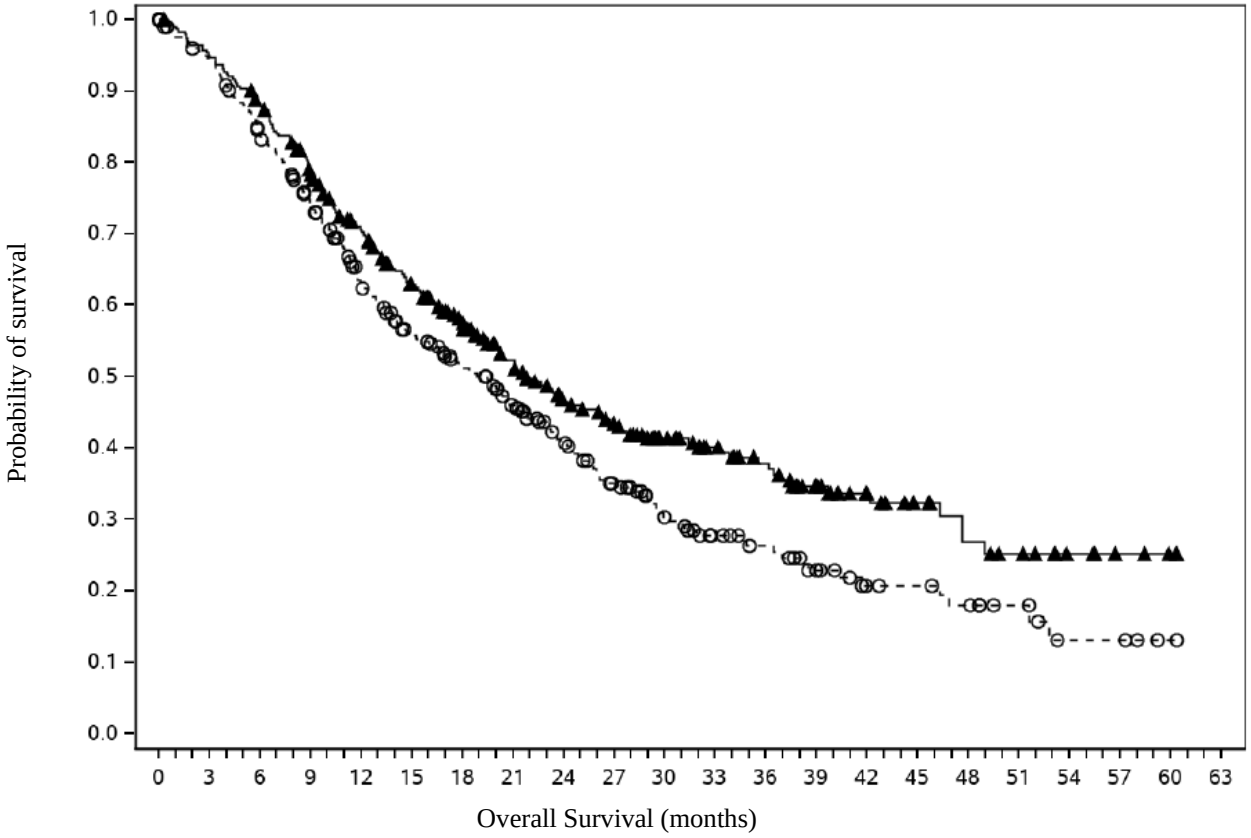
The study demonstrated a statistically significant benefit in OS and PFS for patients randomised to nivolumab in combination with cisplatin and gemcitabine compared to cisplatin and gemcitabine alone. Efficacy results are presented in Table 37 and Figures 24 and 25.

Table 37: 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

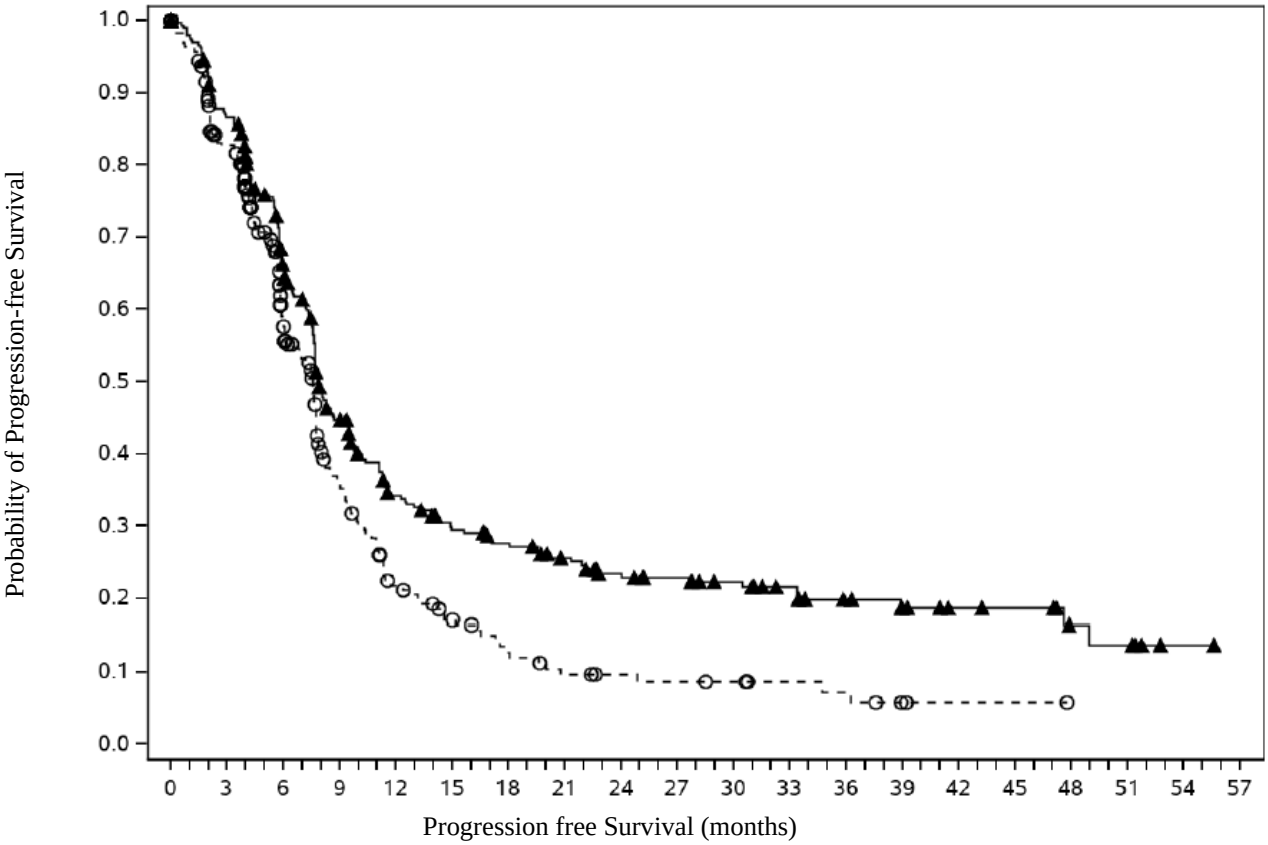
304 277 242 208 166 140 122 102 82 65 49 39 33 24 17 16 13 9 4 4 1 0

- - -▲- - - 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 37). Results for PFS with and without censoring for new anti-cancer treatment before disease progression were consistent.

Open-label phase 2 study (CA209275)

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma was evaluated in a phase 2, multicentre, open-label, single-arm study (CA209275).

The study included patients (18 years or older) who had disease progression during or following platinum-containing chemotherapy for advanced or metastatic disease or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Patients had an ECOG performance status score of 0 or 1 and were enrolled regardless of their tumour PD-L1 status. Patients with active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients that received more than 2 prior lines of chemotherapy with liver metastases were excluded.

A total of 270 patients who received nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks with a minimum follow-up of 8.3 months were evaluable for efficacy. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first

tumour assessments were conducted 8 weeks after the start of treatment and continued every 8 weeks thereafter up to 48 weeks, then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit, did not have rapid disease progression, and was tolerating study drug as determined by the investigator. The primary efficacy outcome measure was ORR as determined by BICR. Additional efficacy measures included duration of response, PFS and OS.

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

Table 38: Efficacy results (CA209275)[a]

	nivolumab (n = 270)	
Confirmed objective response	54 (20.0%)	
(95% CI)	(15.4, 25.3)	
Complete response (CR)	8 (3.0%)	
Partial response (PR)	46 (17.0%)	
Stable disease (SD)	60 (22.2%)	
Median duration of response[b]		
Months (range)	10.4 (1.9^+-12.0^+)	
Median time to response		
Months (range)	1.9 (1.6, 7.2)	
Progression-free survival		
Events (%)	216 (80)	
Median (95% CI) months	2.0 (1.9, 2.6)	
Rate (95% CI) at 6 months	26.1 (20.9, 31.5)	
Overall survival[c]		
Events (%)	154 (57)	
Median (95% CI) months	8.6 (6.05, 11.27)	
Rate (95% CI) at 12 months	41.0 (34.8, 47.1)	
	Tumour PD-L1 expression level	
	< 1%	**≥ 1%**
Confirmed objective response (95% CI)	16% (10.3, 22.7) n = 146	25% (17.7, 33.6) n = 124
Median duration of response Months (range)	10.4 (3.7, 12.0^+)	Not Reached (1.9^+, 12.0^+)
Progression-free survival		
Median (95% CI) months	1.9 (1.8, 2.0)	3.6 (1.9, 3.7)
Rate (95% CI) at 6 months	22.0 (15.6, 29.2)	30.8 (22.7, 39.3)
Overall survival		
Median (95% CI) months	5.9 (4.37, 8.08)	11.6 (9.10, NE)
Rate (95% CI) at 12 months	34.0 (26.1, 42.1)	49.2 (39.6, 58.1)

"+" denotes a censored observation.

[a] median follow-up 11.5 months.

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

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

NE: non-estimable

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

Open-label phase 1/2 study (CA209032)
CA209032 was a Phase 1/2 open-label multi-cohort study which included a cohort of 78 patients (including 18 subjects who received planned crossover treatment with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg combination) with similar inclusion criteria to study CA209275 treated with nivolumab monotherapy 3 mg/kg for urothelial carcinoma. At a minimum follow-up of 9 months, investigator-assessed confirmed ORR was 24.4% (95% CI: 15.3, 35.4). The median duration of response was not reached (range: 4.4-16.6^{+} months). The median OS was 9.7 months (95% CI: 7.26, 16.16) and the estimated OS rates were 69.2% (CI: 57.7, 78.2) at 6 months and 45.6% (CI: 34.2, 56.3) at 12 months.

Adjuvant treatment of urothelial carcinoma

Randomised phase 3 study of adjuvant nivolumab vs. placebo (CA209274)
The safety and efficacy of nivolumab monotherapy for the adjuvant treatment of urothelial carcinoma was evaluated in a phase 3 multicentre, randomised, placebo-controlled, double-blinded study (CA209274). The study included patients (18 years or older) who have undergone radical resection of muscle invasive urothelial carcinoma (MIUC) originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence. The MIUC pathologic staging criteria that defines high risk patients was ypT2-ypT4a or ypN^{+} for adult patients who received 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 ≥ 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 (≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 39 and Figure 26.

Table 39: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209274)

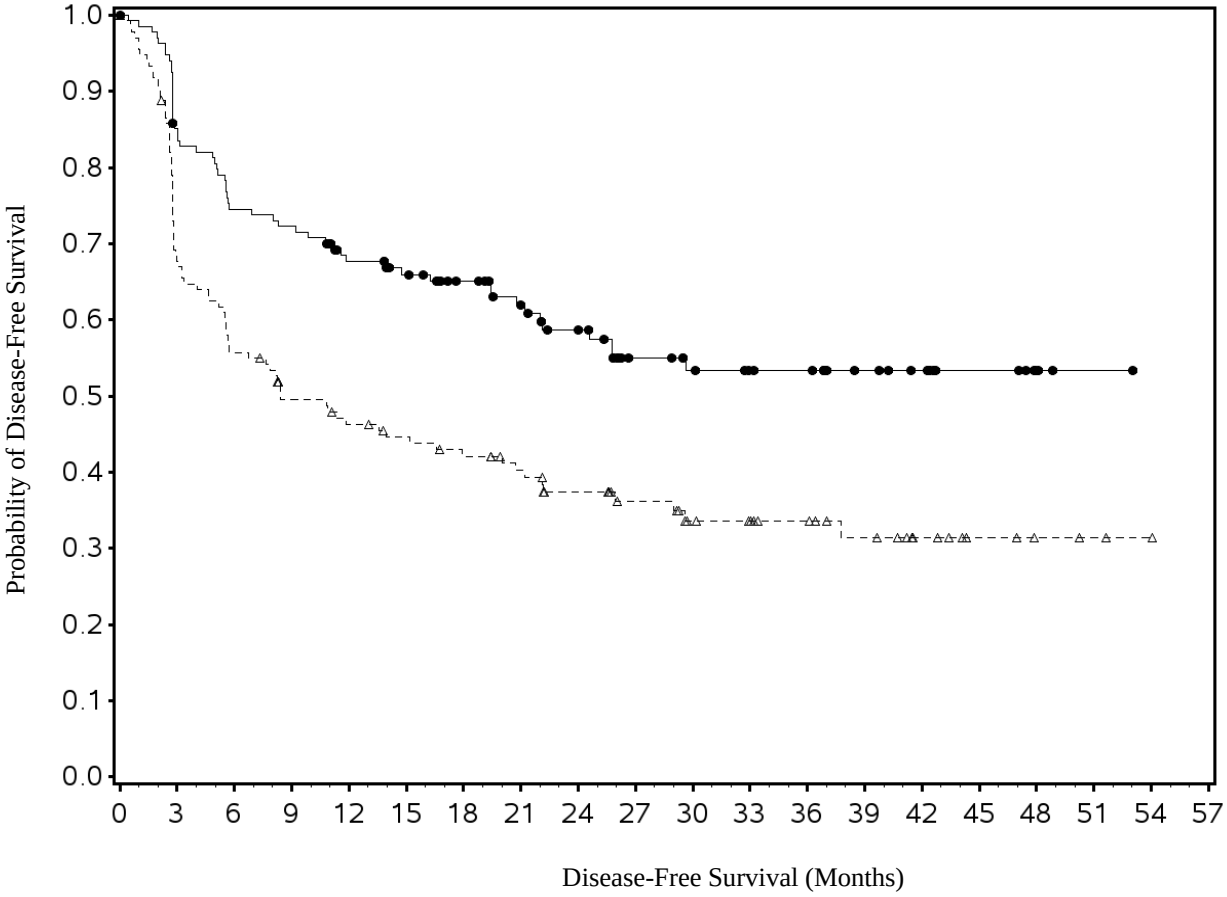
	nivolumab (n = 140)	**placebo** (n = 142)
Disease-Free Survival	Minimum follow-up 11.4 months	
Events (%)	56 (40.0)	85 (59.9)
Hazard ratio (95% CI)[a]	0.53 (0.38, 0.75)	
Median (95% CI) (months)[b]	NR (22.11, NE)	8.41 (5.59, 20.04)
Rate (95% CI) at 6 months	74.5 (66.2, 81.1)	55.7 (46.8, 63.6)
Rate (95% 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 26: Kaplan-Meier curves of DFS in patients with tumour cell PD-L1 expression ≥ 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

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 ≥ 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 ≥ 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.

dMMR or MSI-H colorectal cancer

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 randomized, multi-arm, phase 3, open-label study (CA2098HW). Study treatment arms included nivolumab monotherapy, nivolumab in combination with ipilimumab, or investigator's

choice of chemotherapy. MSI-H or dMMR tumour status was determined in accordance with local standard of practice using PCR, NGS or IHC, assays. Central assessment of MSI-H status using PCR (Idylla MSI) test and dMMR status using IHC (Omnis MMR) test was conducted retrospectively on patient tumour specimens used for local MSI-H/dMMR status determination. Patients with confirmed MSI-H/dMMR status by either central test comprised the primary efficacy population. Patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors were excluded from the study. Randomisation was stratified by tumour location (right vs left). Patients randomized to the chemotherapy arm could receive nivolumab plus ipilimumab combination upon progression assessed by BICR.

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

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

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

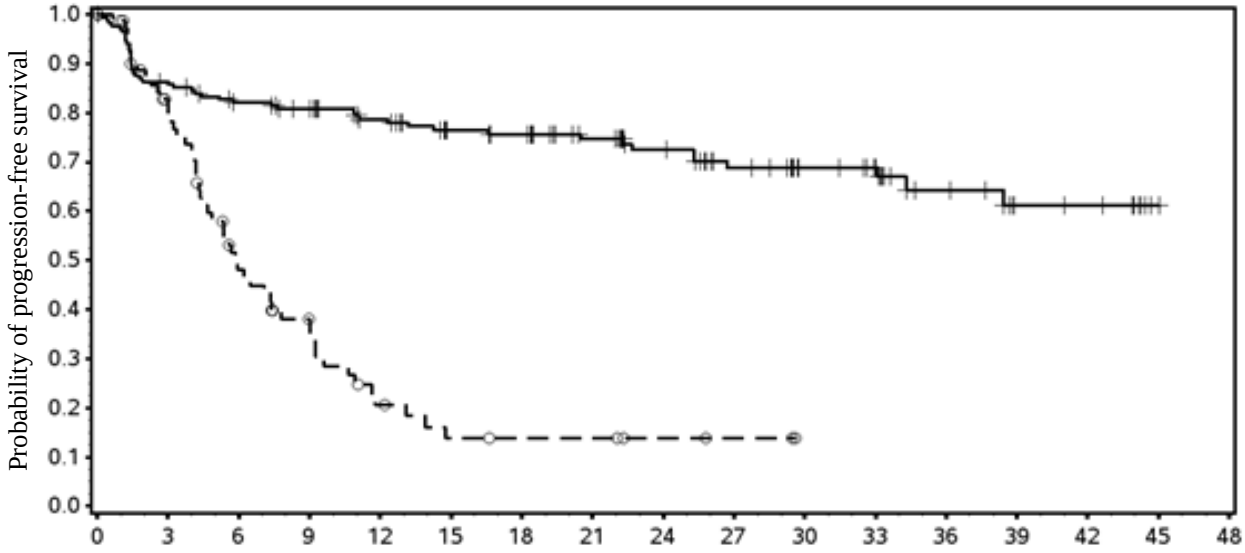
The study met the primary endpoint, at the planned interim analysis, demonstrating a statistically significant improvement in BICR assessed-PFS for patients with centrally confirmed MSI-H/dMMR in the nivolumab in combination with ipilimumab arm compared with the chemotherapy arm. The BICR-assessed PFS results are presented in Table 40 and Figure 27. 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 40: 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 27: Kaplan-Meier curve of PFS in first-line patients with MSI-H/dMMR centrally confirmed CRC (CA2098HW)



Number of subjects at risk

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

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

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

The safety and efficacy of nivolumab 3 mg/kg 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 41.

Table 41: 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

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

Baseline characteristics were generally balanced between the two groups. The median age was 65 years (range: 33-87), 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 42 and Figure 28.

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.

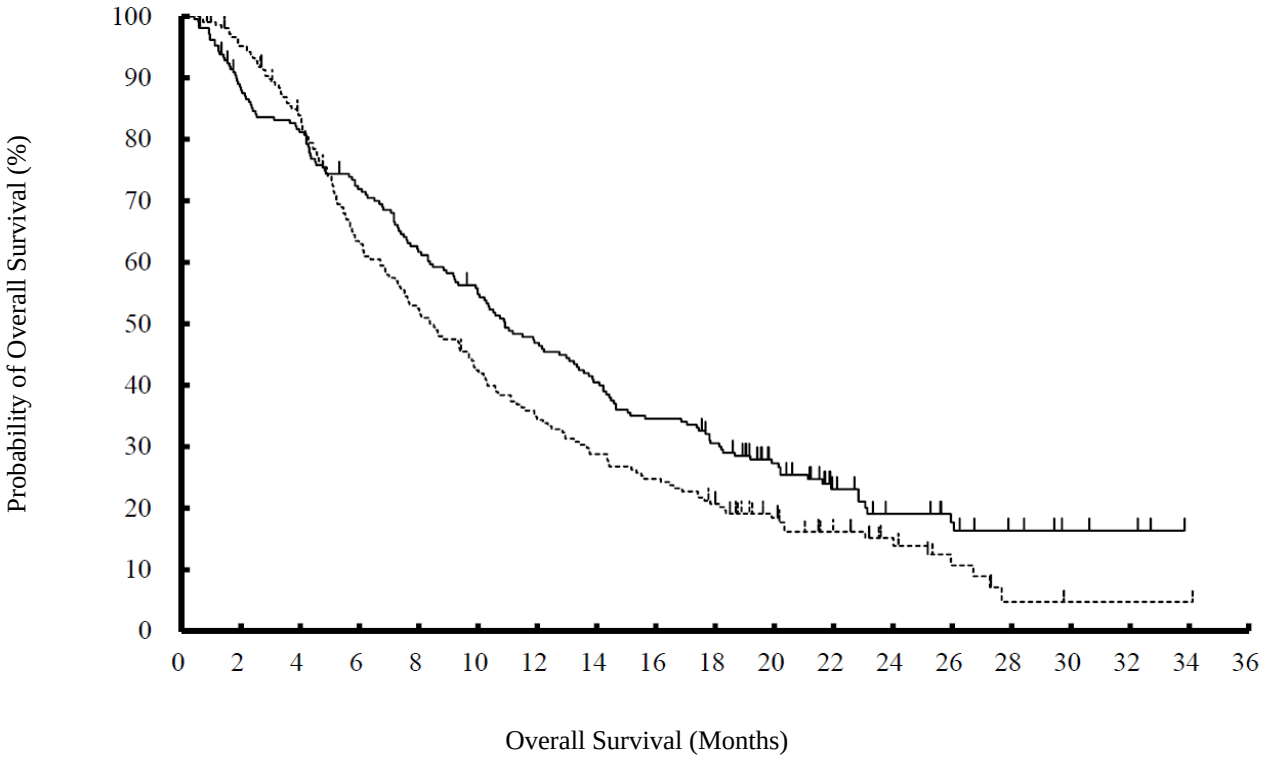
Table 42: Efficacy results (ONO-4538-24/CA209473)

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

[a] Based on ITT analysis.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.

[d] Based on Response Evaluable Set (RES) analysis, n=171 in nivolumab group and n=158 in investigator's choice group.
[e] Not significant, p-value 0.6323.

Figure 28: Kaplan-Meier curves of OS (ONO-4538-24/CA209473)



Number of subjects at risk

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

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

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

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 (≥ 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 ≥ 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/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle). Patients in the chemotherapy arm received fluorouracil 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 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 ≥ 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 ipilimumab vs. chemotherapy

The primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with tumour cell PD-L1 expression ≥ 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 v1.1 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 13.1 months, the study demonstrated a statistically significant improvement in OS in patients with tumour cell PD-L1 expression ≥ 1%. Efficacy results are shown in Table 43.

Table 43: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209648)

	nivolumab + ipilimumab (n = 158)	**chemotherapy[a] (n = 157)**
Overall survival		
Events	106 (67.1%)	121 (77.1%)
Hazard ratio (98.6% CI)[b]	0.64 (0.46, 0.90)	
p-value[c]	0.0010	
Median (95% CI) (months)[d]	13.70 (11.24, 17.02)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months[d]	57.1 (49.0, 64.4)	37.1 (29.2, 44.9)
Progression-free survival[e]		
Events	123 (77.8%)	100 (63.7%)
Hazard ratio (98.5% CI)[b]	1.02 (0.73, 1.43)	
p-value[c]	0.8958	
Median (95% CI) (months)[d]	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)
Rate (95% CI) at 12 months[d]	26.4 (19.5, 33.9)	10.5 (4.7, 18.8)

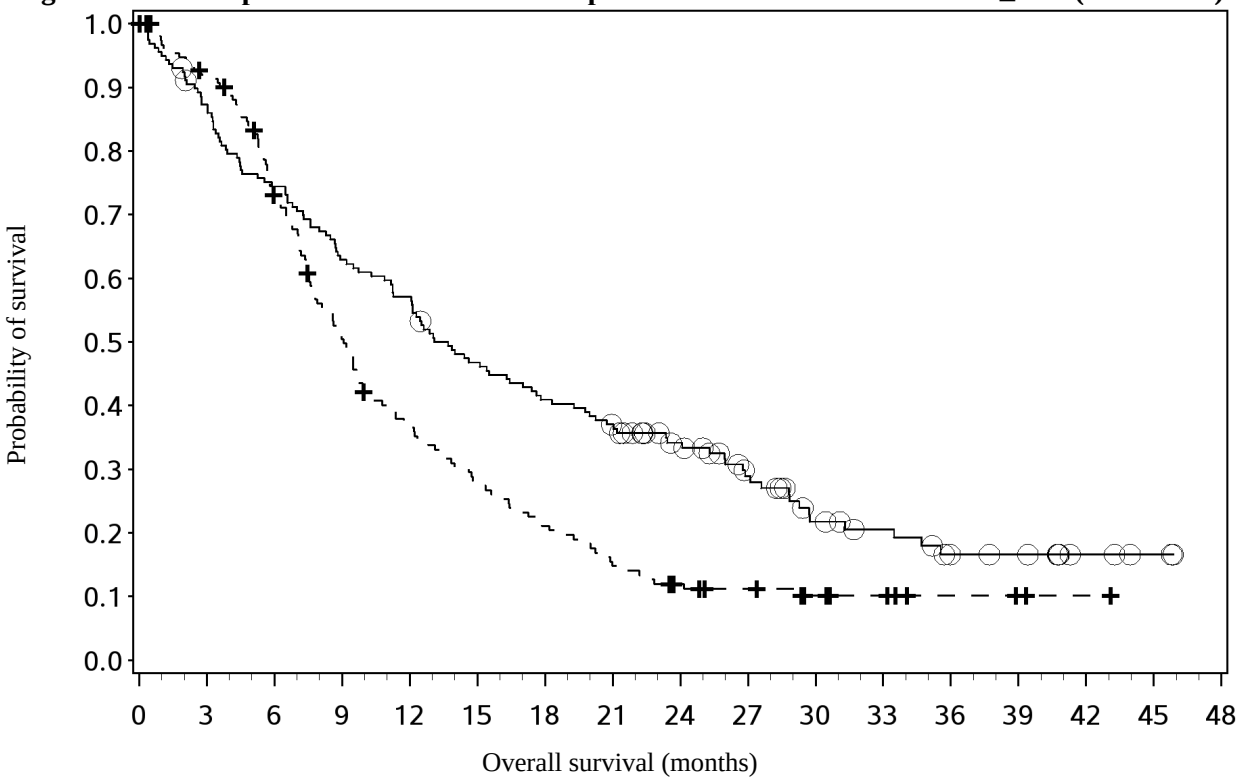
	nivolumab + ipilimumab (n = 158)	chemotherapy[a] (n = 157)
Overall response rate, n (%)[e]	56 (35.4)	31 (19.7)
(95% CI)	(28.0, 43.4)	(13.8, 26.8)
Complete response	28 (17.7)	8 (5.1)
Partial response	28 (17.7)	23 (14.6)
Duration of response[e]		
Median (95% CI) (months)[d]	11.83 (7.10, 27.43)	5.68 (4.40, 8.67)
Range	1.4^{+}, 34.5^{+}	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 13.70 months (95% CI: 11.24, 17.41) for nivolumab plus ipilimumab vs. 9.07 months (95% CI: 7.69, 10.02) for chemotherapy (HR = 0.63; 95% CI: 0.49, 0.82). Median PFS was 4.04 months (95% CI: 2.40, 4.93) for nivolumab plus ipilimumab vs. 4.44 months (95% CI: 2.89, 5.82) for chemotherapy (HR = 1.02; 95% CI: 0.77, 1.34). The ORR was 35.4% (95% CI: 28.0, 43.4) for nivolumab plus ipilimumab vs. 19.7% (95% CI: 13.8, 26.8) for chemotherapy.

The Kaplan-Meier curves for OS with a minimum follow-up of 20 months are shown in Figure 29.

Figure 29: Kaplan-Meier curves of OS in patients with tumour cell PD-L1 ≥ 1% (CA209648)



Number of subjects at risk

Nivolumab + ipilimumab																
158	136	116	98	89	72	63	55	43	31	20	16	10	9	4	2	0
Chemotherapy																
157	137	107	73	53	40	30	21	15	12	8	6	3	2	1	0	0

—❍—— Nivolumab + ipilimumab (events: 119/158), median and 95% CI: 13.70 (11.24, 17.41)
- - - + - - - 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

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 ≥ 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 v1.1 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 ≥ 1%. Efficacy results are shown in Table 44.

Table 44: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209648)

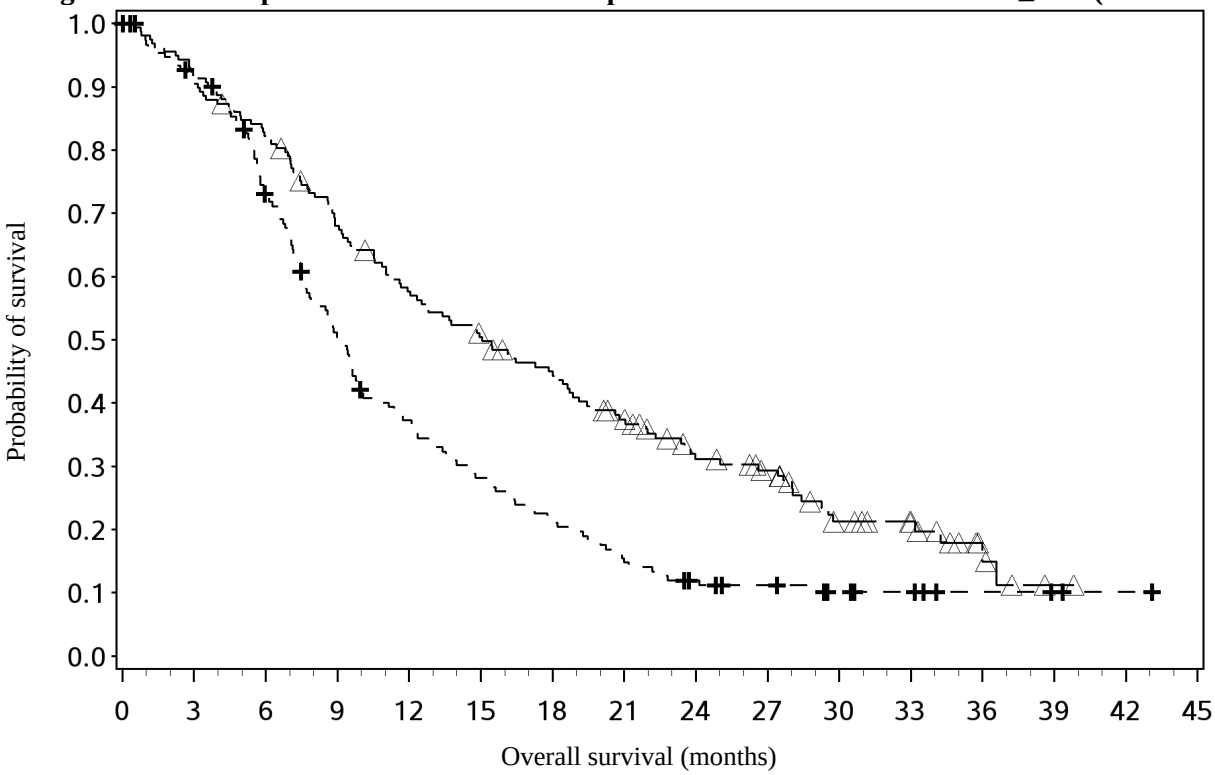
	nivolumab + chemotherapy (n = 158)	**chemotherapy[a] (n = 157)**
Overall survival		
Events	98 (62.0%)	121 (77.1%)
Hazard ratio (99.5% CI)[b]	0.54 (0.37, 0.80)	
p-value[c]	< 0.0001	
Median (95% CI) (months)[d]	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months[d]	58.0 (49.8, 65.3)	37.1 (29.2, 44.9)

	nivolumab + chemotherapy (n = 158)	chemotherapy[a] (n = 157)
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)
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 30 and 31.

Figure 30: Kaplan-Meier curves of OS in patients with tumour cell PD-L1 ≥ 1% (CA209648)



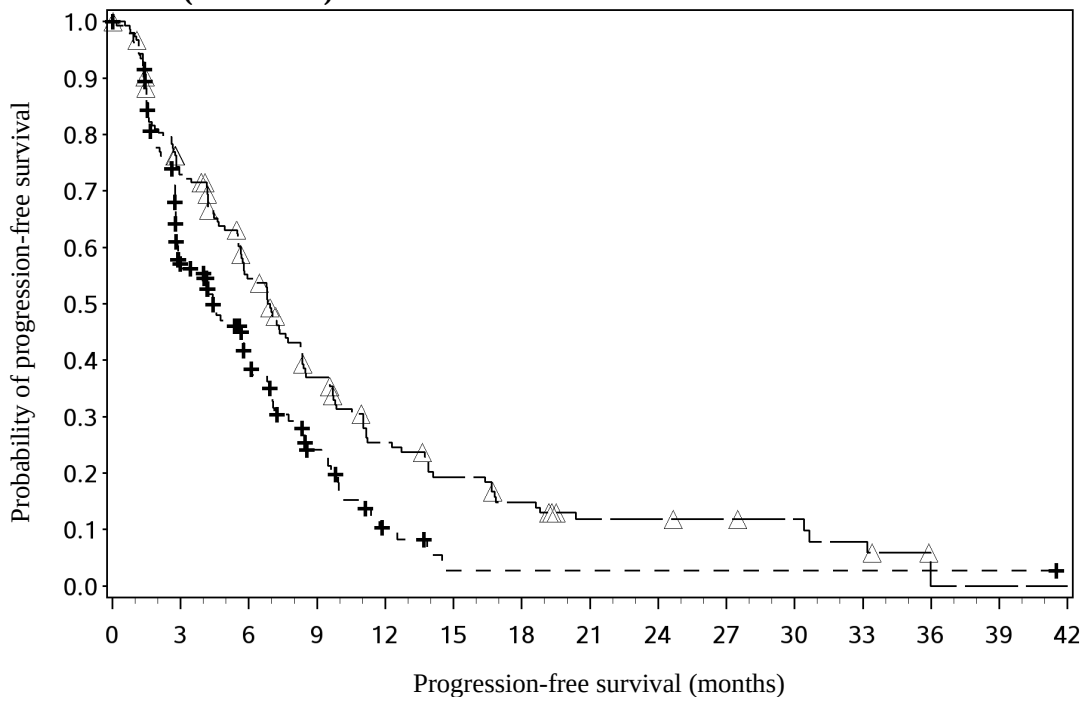
Number of subjects at risk

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 31: Kaplan-Meier curves of PFS in patients with tumour cell PD-L1 ≥ 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

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer

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 (≥ 1% vs. < 1% or indeterminate or non-evaluable), pathologic lymph node status (positive ≥ 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% ≥ 65 years of age and 5% ≥ 75 years of years. The majority of patients were white (82%) and male (85 %). Baseline ECOG performance status was 0 (58%) or 1 (42%).

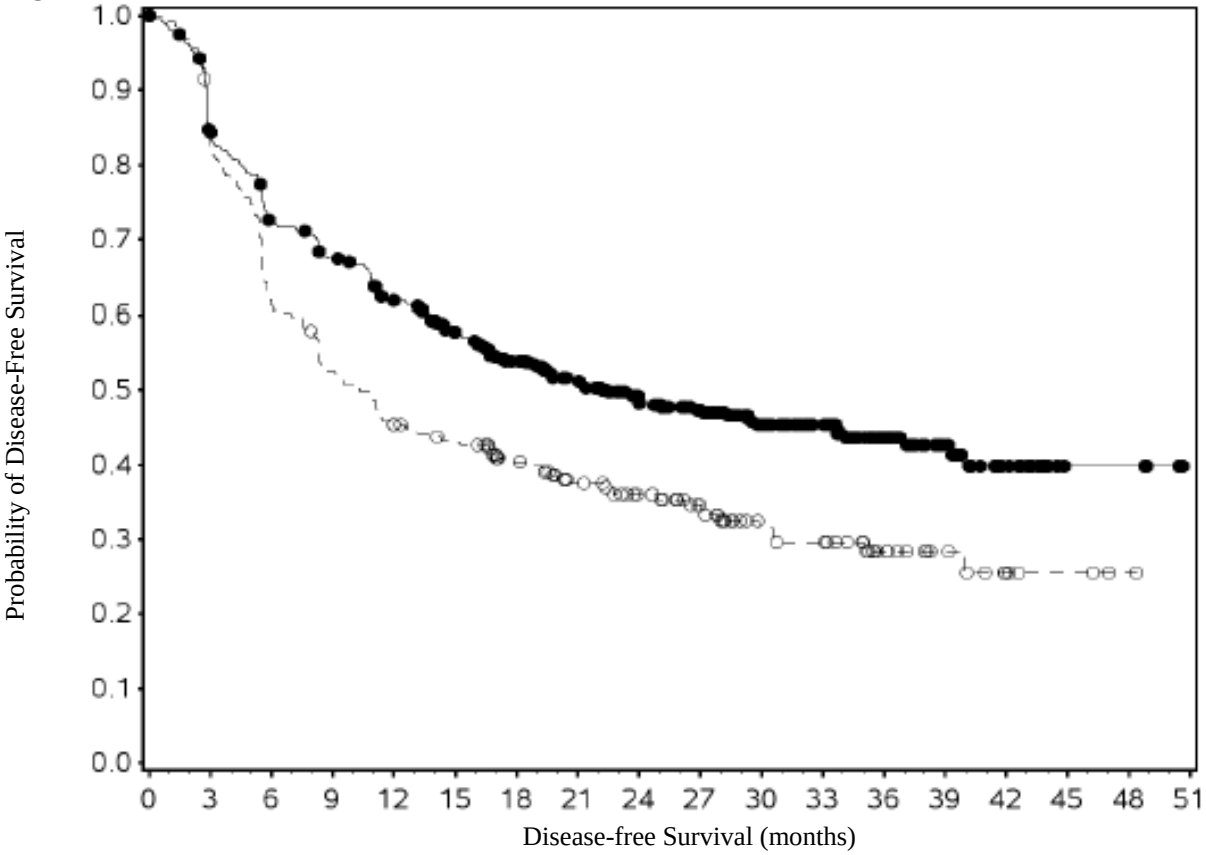
At the primary pre-specified interim analysis (minimum of 6.2 months and a median of 24.4 months follow-up), the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab compared with placebo. Median DFS as determined by the investigator was 22.41 months (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 45 and Figure 32.

Table 45: 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 32: 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

DFS benefit was observed regardless of histology and PD-L1 expression.

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

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

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

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

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

At an updated descriptive analysis with a minimum follow-up of 19.4 months, OS improvements were consistent with the primary analysis. Efficacy results are shown in Table 46, and Figures 33, and 34.

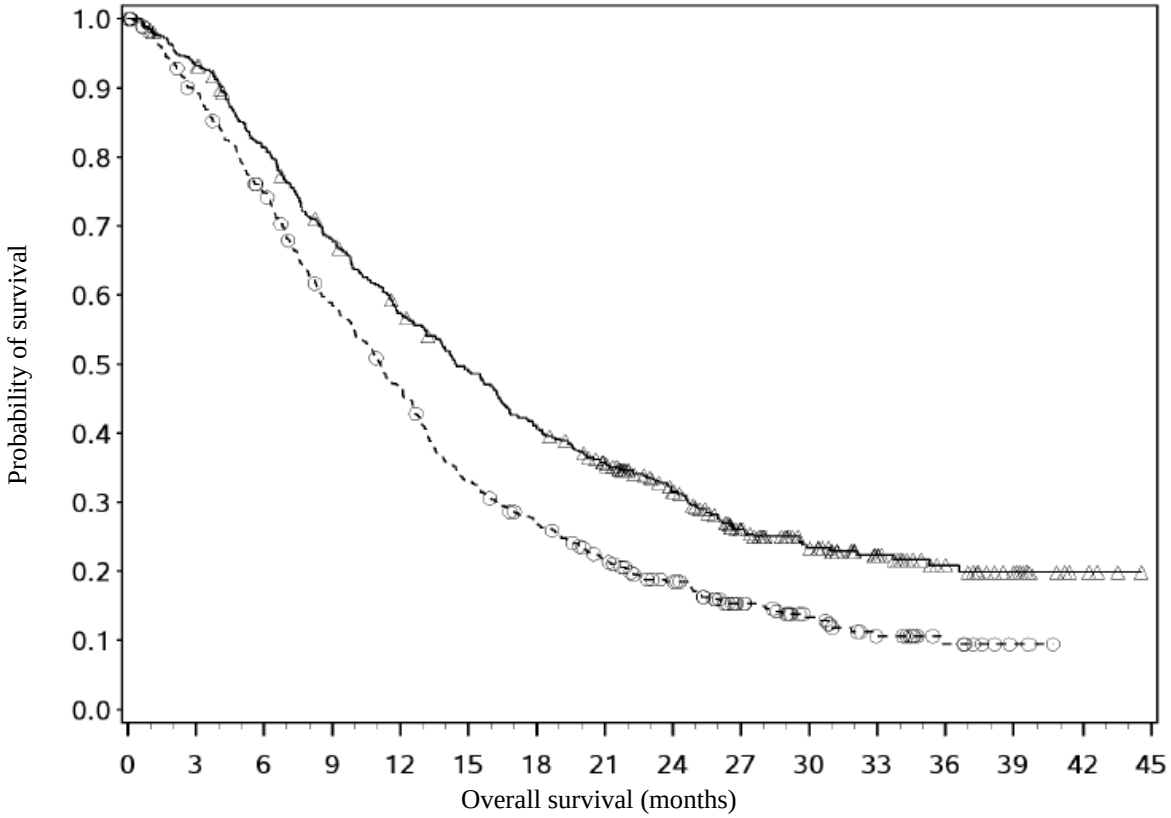
Table 46: Efficacy results in patients with PD-L1 CPS ≥ 5 (CA209649)

	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)

	nivolumab + chemotherapy (n = 473)	chemotherapy (n = 482)
Objective response rate, n[d,e]	227/378 (60%)	176/390 (45%)
(95% CI)	(54.9, 65.0)	(40.1, 50.2)
Complete response	12.2%	6.7%
Partial response	47.9%	38.5%
Duration of response[d,e]		
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 33: Kaplan-Meier curves of OS in patients with PD-L1 CPS ≥ 5 (CA209649)

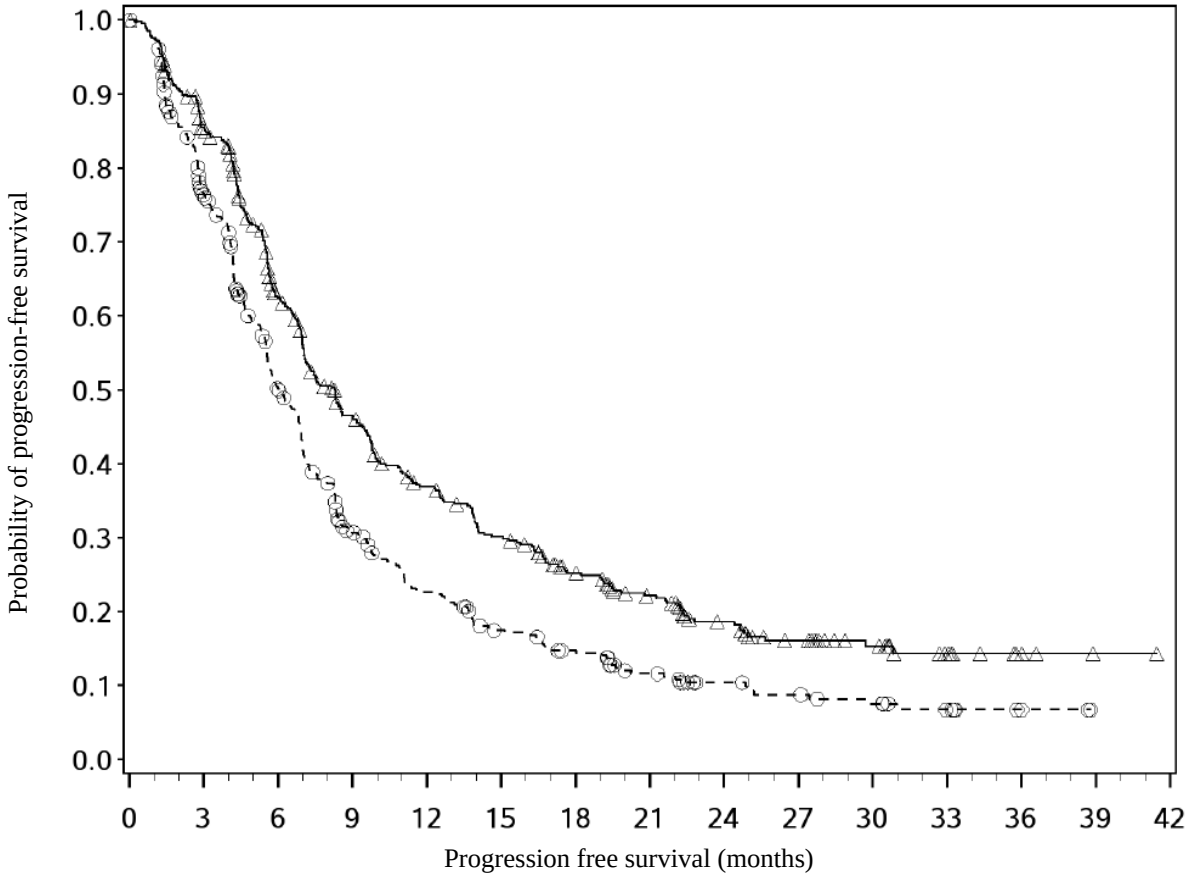


Number of subjects at risk

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 34: 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

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.

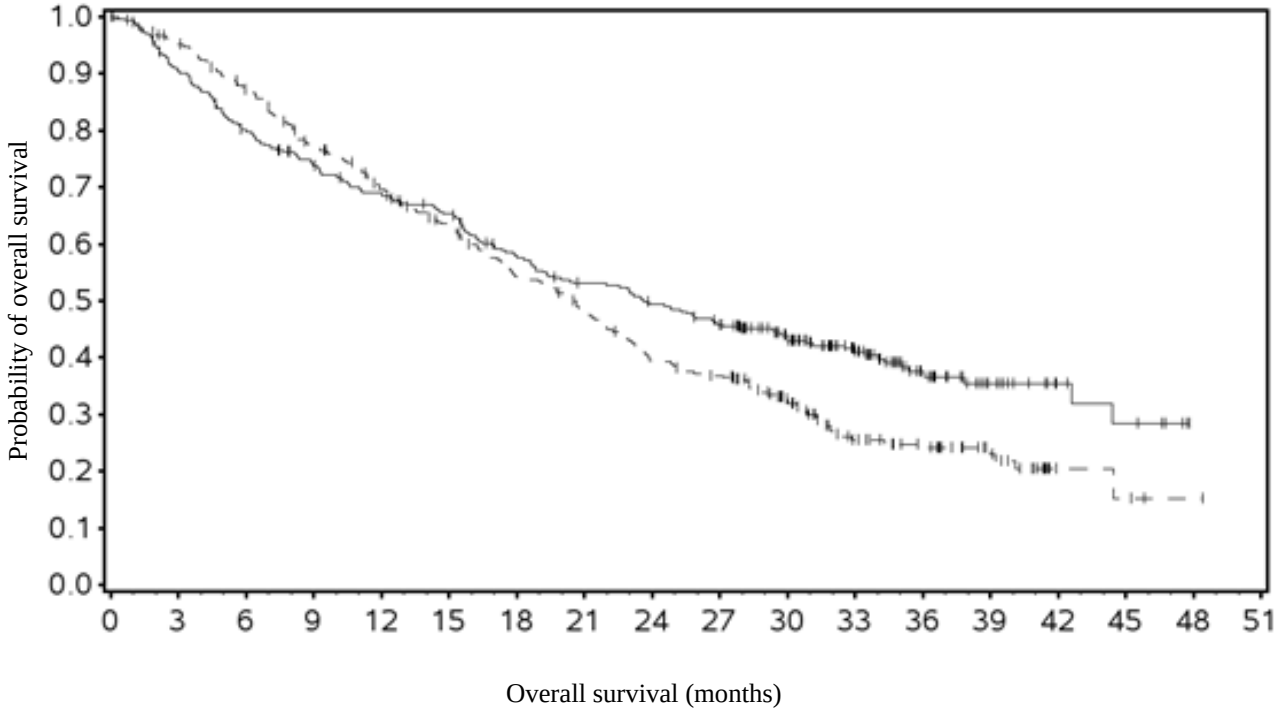
The study demonstrated a statistically significant benefit in OS and ORR for patients randomised to nivolumab in combination with ipilimumab compared to investigator's choice of lenvatinib or sorafenib. Efficacy results are presented in Table 47 and Figure 35.

Table 47: 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]	121 (36.1)	44 (13.2)
(95% CI)	(31.0, 41.5)	(9.8, 17.3)
p-value[e]	< 0.0001	
Complete response (%)	23 (6.9)	6 (1.8)
Partial response (%)	98 (29.3)	38 (11.4)
Duration of Response (months)[d]		
Median	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 1.1.
[e] Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: p-value ≤ 0.025.

Figure 35: 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

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

Among the 64 paediatric patients treated with nivolumab monotherapy, 60 were response-evaluable patients (melanoma n = 1, solid tumours n = 47 and haematological tumours n = 12). In the 48 response-evaluable paediatric patients with melanoma or solid tumours, no objective responses were observed. In the 12 response-evaluable paediatric patients with haematological tumours, ORR was 25.0% (95% CI: 5.5, 57.2), including 1 complete response in cHL and 2 partial responses, one in cHL and another one in NHL. In the descriptive analyses for the 64 paediatric patients treated with nivolumab monotherapy, the median OS was 6.67 months (95% CI: 5.98, NA); 6.14 months

(95% CI: 5.39, 24.67) for patients with melanoma or solid tumours, and not reached for patients with haematological tumours.

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

Open label phase 1b/2 study (CA209908)
Study CA209908 was an open-label, sequential-arm, phase 1b/2 clinical study of nivolumab monotherapy and nivolumab in combination with ipilimumab in paediatric and young adult patients with high-grade primary CNS malignancies, including diffuse intrinsic pontine glioma (DIPG), high-grade glioma, medulloblastoma, ependymoma and other recurrent subtypes of high-grade CNS malignancy (e.g., pineoblastoma, atypical teratoid/rhabdoid tumour, and embryonal CNS tumours). Of the 151 paediatric patients (from ≥ 6 months to < 18 years old) enrolled in the study, 77 were treated with nivolumab monotherapy (3 mg/kg every 2 weeks) and 74 were treated with nivolumab in combination with ipilimumab (3 mg/kg nivolumab followed by 1 mg/kg ipilimumab, every 3 weeks for 4 doses, followed by nivolumab monotherapy 3 mg/kg every 2 weeks). The primary efficacy outcome measures were OS in the DIPG cohort and investigator-assessed PFS, based on RANO criteria, for all other tumour types. The median OS in the DIPG cohort was 10.97 months (80% CI: 9.92, 12.16) in patients treated with nivolumab monotherapy and 10.50 months (80% CI: 9.10, 12.32) in patients treated with nivolumab in combination with ipilimumab. For all other studied CNS paediatric tumour types, the median PFS ranged from 1.23 to 2.35 months in patients treated with nivolumab monotherapy and from 1.45 to 3.09 months in patients treated with nivolumab in combination with ipilimumab. There were no objective responses observed in the study with the exception of one ependymoma patient treated with nivolumab monotherapy who had a partial response. Results for OS, PFS, and ORR observed in study CA209908 do not suggest clinically meaningful benefit over what may be expected in these patient populations.

The European Medicines Agency has deferred the obligation to submit the results of studies with nivolumab in all subsets of the paediatric population in the treatment of malignant neoplasms of lymphoid tissue (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. Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population. Data from MPM patients showed a higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older (68% and 35%, respectively) relative to all patients who received nivolumab in combination with ipilimumab (54% and 28%, respectively).

5.2 Pharmacokinetic properties

Nivolumab monotherapy

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

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

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

Nivolumab in combination with ipilimumab

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

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

Nivolumab in combination with ipilimumab and chemotherapy

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

Special populations

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

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

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

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

Hepatic impairment
The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with different tumour types (NSCLC, SCLC, melanoma, RCC, SCCHN, UC, GC, and cHL) with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 351) and in patients with moderate hepatic impairment (total bilirubin > 1.5 × to 3 × ULN and any AST; n = 10) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 3096) in a population PK analysis. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate

hepatic impairment and normal hepatic function. Similar results were observed in patients with HCC (mild hepatic impairment: n = 152; moderate hepatic impairment: n = 13). Nivolumab has not been studied in patients with severe hepatic impairment (total bilirubin > 3 × ULN and any AST) (see section 4.2).

5.3 Preclinical safety data

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

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

Fertility studies have not been performed with nivolumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
Sodium chloride
Mannitol (E421)
Pentetic acid (diethylenetriaminepentaacetic acid)
Polysorbate 80 (E433)
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

3 years

After preparation of infusion

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

Infusion preparation	**Chemical and physical in-use stability**	
	Storage at 2ºC to 8ºC protected from light	**Storage at room temperature (≤ 25°C) and room light**
Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection	30 days	24 hours (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	7 days	8 hours (of total 7 days storage)

From a microbiological point of view the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2°C to 8°C or 8 hours (of the total 7 days of storage) at room temperature (≤ 25°C). Aseptic handling should be ensured during the preparation of infusion (see section 6.6).

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Preparation and administration

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

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

Melanoma (advanced or adjuvant treatment) in adolescents. The prescribed dose for adolescents 12 years of age and older weighing at least 50 kg is 240 mg or 480 mg. For adolescents 12 years of age and older and weighing less than 50 kg, the prescribed dose is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given.

- The total nivolumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The volume of OPDIVO concentrate to prepare the dose (mL) = the total nivolumab dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

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

Nivolumab in combination with ipilimumab in MPM
The prescribed dose for the patient is 360 mg given regardless of body weight.

Nivolumab in combination with ipilimumab in advanced colorectal cancer
The prescribed dose for the patient can be based on body weight (3 mg/kg) or can be 240 mg given regardless of body weight.

Nivolumab in combination with ipilimumab in OSCC
The prescribed dose for the patient can be based on body weight (3 mg/kg) or 360 mg given regardless of body weight.

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

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

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

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

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

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

OPDIVO can be used for intravenous administration either:

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

OPDIVO concentrate may be diluted with either:

- sodium chloride 9 mg/mL (0.9%) solution for injection; or
- 50 mg/mL (5%) glucose solution for injection.

STEP 1

- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake the vial. OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid. Discard the vial

if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of OPDIVO concentrate using an appropriate sterile syringe.

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

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

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

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

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/001
EU/1/15/1014/002
EU/1/15/1014/003
EU/1/15/1014/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

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 5 mL contains 600 mg of nivolumab.

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

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 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).

Adjuvant treatment of 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).

Non-small cell lung cancer (NSCLC)

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

Renal cell carcinoma (RCC)

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

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

Squamous cell cancer of the head and neck (SCCHN)

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

Urothelial carcinoma

OPDIVO 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.

Adjuvant treatment of urothelial carcinoma

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

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 ≥ 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.

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
Intravenous administration - OPDIVO combination phase
The recommended dose of OPDIVO solution for infusion is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously over 30 minutes every 3 weeks for the first 4 doses.

Subcutaneous administration - OPDIVO monotherapy phase
The recommended dose of OPDIVO solution for injection is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks (see section 5.1). For the monotherapy phase, the first dose of nivolumab should be administered;
- 3 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab if using 600 mg every 2 weeks; or
- 6 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab if using 1200 mg every 4 weeks.

Renal cell carcinoma
Intravenous administration - OPDIVO combination phase
The recommended dose of OPDIVO solution for infusion is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 3 weeks for the first 4 doses.

Subcutaneous administration - OPDIVO monotherapy phase
The recommended dose of OPDIVO solution for injection is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks. For the monotherapy phase, the first dose of nivolumab should be administered;
- 3 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab if using 600 mg every 2 weeks; or
- 6 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab if using 1200 mg every 4 weeks.

dMMR or MSI-H colorectal cancer

First-line treatment of dMMR or MSI-H CRC
Intravenous administration - OPDIVO combination phase
The recommended dose is 240 mg of nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for a maximum of 4 doses.

Subcutaneous administration - OPDIVO monotherapy phase
The recommended dose of OPDIVO solution for injection is 600 mg every 2 weeks **or** 1200 mg every 4 weeks. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Treatment of dMMR or MSI-H CRC after prior first-line fluoropyrimidine-based combination chemotherapy
Intravenous administration - OPDIVO combination phase
The recommended dose is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses.

Subcutaneous administration - OPDIVO monotherapy phase
The recommended dose of OPDIVO solution for injection is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the intravenous combination of nivolumab and ipilimumab.

OPDIVO in combination with cabozantinib

Renal cell carcinoma
The recommended dose of OPDIVO solution for injection is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks in combination with 40 mg cabozantinib administered orally every day.

OPDIVO in combination with chemotherapy

Oesophageal squamous cell carcinoma
The recommended dose of OPDIVO solution for injection is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks administered in combination with fluoropyrimidine- and platinum-based chemotherapy (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma
The recommended dose of OPDIVO solution for injection is 600 mg in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 2 weeks (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

First-line treatment of unresectable or metastatic urothelial carcinoma
Intravenous administration - OPDIVO combination phase
The recommended dose of OPDIVO solution for infusion is 360 mg administered intravenously over 30 minutes in combination with cisplatin and gemcitabine every 3 weeks for up to 6 cycles.

Subcutaneous administration - OPDIVO monotherapy phase
The recommended dose of OPDIVO solution for injection is 600 mg every 2 weeks **or** 1200 mg every 4 weeks (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months from first dose, whichever comes first.

Duration of treatment
Treatment with OPDIVO, either as 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.

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.

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 1. 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 1: Recommended treatment modifications for OPDIVO or OPDIVO in combination

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

Immune-related adverse reaction	Severity	Treatment modification
Immune-related hepatitis **NOTE:** for RCC patients treated with **OPDIVO in combination with cabozantinib** with liver enzyme elevations, see dosing guidelines following this table.	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[b] as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[c]
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment

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

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

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

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

OPDIVO 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 alert 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 1 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

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

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 hepatic impairment (see section 5.2). Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. OPDIVO must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment.

Method of administration

OPDIVO 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 filtrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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 ≥ 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

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

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

Renal cell carcinoma

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
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

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).

OPDIVO contains polysorbate 80 (E433)
This medicinal product contains 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 alert card
All prescribers of OPDIVO must be familiar with the physician information and management guidelines. The prescriber must discuss the risks of OPDIVO therapy with the patient. The patient will be provided with the patient alert card with each prescription.

4.5 Interaction with other medicinal products and other forms of interaction

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

Other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

It is unknown whether nivolumab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from

nivolumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Nivolumab as monotherapy (see section 4.2)

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

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 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions with nivolumab monotherapy

	Nivolumab monotherapy
Infections and infestations	
Very common	upper respiratory tract infection
Common	pneumonia[a], bronchitis
Rare	aseptic meningitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Very common	lymphopaenia[b], anaemia[b,i], leucopoenia[b], neutropaenia[a,b], thrombocytopaenia[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)
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
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	vitiligo, 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	Sjogren's syndrome, myopathy, myositis (including polymyositis)[a], rhabdomyolysis[a,d]
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)[a]
Rare	tubulointerstitial nephritis, cystitis noninfective
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 2 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.

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 = 2294) with minimum follow-up ranging from 6 to 47 months, the most frequent adverse reactions (≥ 10%) were fatigue (49%), diarrhoea (37%), rash (37%), nausea (30%), pruritus (29%), musculoskeletal pain (27%), pyrexia (24%), decreased appetite (23%), cough (22%), vomiting (19%), constipation (19%), arthralgia (19%), abdominal pain (19%), dyspnoea (18%), hypothyroidism (16%), headache (15%), upper respiratory tract infection (15%), oedema (13%), and dizziness (10%). The incidence of Grade 3-5 adverse reactions was 67% for nivolumab in combination with ipilimumab (with or without chemotherapy), with 0.7% fatal adverse reactions

attributed to study drug. Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, fatigue (62%), rash (57%), diarrhoea (52%), nausea (42%), pruritus (40%), pyrexia (36%), and headache (26%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate. Among patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy, anaemia (32%) and neutropaenia (15%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate.

Nivolumab in combination with chemotherapy
In the pooled dataset of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy across tumour types (n = 1572), with a minimum follow-up ranging from 7.4 to 20 months for gastric, GEJ or oesophageal adenocarcinoma, OSCC, or urothelial carcinoma, or following 3 cycles of treatment for resectable NSCLC, the most frequent adverse reactions (≥ 10%) were nausea (51%), fatigue (41%), peripheral neuropathy (34%), decreased appetite (32%), constipation (31%), diarrhoea (30%), vomiting (26%), stomatitis (19%), abdominal pain (19%), rash (19%), musculoskeletal pain (18%), pyrexia (17%), oedema (including peripheral oedema) (13%), cough (12%), and hypoalbuminaemia (10%). Incidences of Grade 3-5 adverse reactions were 72% for nivolumab in combination with chemotherapy, with 1.3% fatal adverse reactions attributed to nivolumab in combination with chemotherapy. Median duration of therapy was 6.44 months (95% CI: 5.95, 6.80) for nivolumab in combination with chemotherapy, 4.34 months (95% CI: 4.04, 4.70) for chemotherapy for gastric, GEJ or oesophageal adenocarcinoma, or OSCC, and 7.39 months (95% CI: 7.06, 8.38) for urothelial carcinoma. 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 (≥ 10%) were diarrhoea (64.7%), fatigue (51.3%), palmar-plantar erythrodysaesthesia syndrome (40.0%), stomatitis (38.8%), musculoskeletal pain (37.5%), hypertension (37.2%), rash (36.3%), hypothyroidism (35.6%), decreased appetite (30.3%), nausea (28.8%), abdominal pain (25.0%), dysgeusia (23.8%), upper respiratory tract infection (20.6%), cough (20.6%), pruritus (20.6%), arthralgia (19.4%), vomiting (18.4%), dysphonia (17.8%), headache (16.3%), dyspepsia (15.9%), dizziness (14.1%), constipation (14.1%), pyrexia (14.1%), oedema (13.4%), muscle spasm (12.2%), dyspnoea (11.6%), proteinuria (10.9%) and hyperthyroidism (10.0%). The 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 = 2294), nivolumab in combination with chemotherapy (n = 1572), and nivolumab in combination with cabozantinib (n = 320) are presented in Table 3. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000), not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions with nivolumab in combination with other therapeutic agents

	Combination with ipilimumab (with or without chemotherapy)	**Combination with chemotherapy**	**Combination with cabozantinib**
Infections and infestations			
Very common	upper respiratory tract infection		upper respiratory tract infection
Common	pneumonia, bronchitis, conjunctivitis	upper respiratory tract infection, pneumonia[a]	pneumonia
Rare	aseptic meningitis		
Blood and lymphatic system disorders			
Very common	anaemia[b,i], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]	neutropaenia[b], anaemia[b,i], leucopoenia[b], lymphopaenia[b], thrombocytopaenia[b]	anaemia[b], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]
Common	eosinophilia	febrile neutropaenia[a]	eosinophilia
Uncommon	febrile 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[f]		
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		

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Metabolism and nutrition disorders			
Very common	decreased appetite, hyperglycaemia[b], hypoglycaemia[b]	decreased appetite, hypoalbuminaemia, hyperglycaemia[b], hypoglycaemia[b]	decreased appetite, hypoglycaemia[b], hyperglycaemia[b], weight decreased
Common	dehydration, hypoalbuminaemia, hypophosphataemia, weight decreased	hypophosphataemia	dehydration
Uncommon	metabolic acidosis		
Rare		tumour lysis syndrome	
Not known	tumour lysis syndrome[g]		
Nervous system disorders			
Very common	headache, dizziness	peripheral neuropathy	dysgeusia, dizziness, headache
Common	peripheral neuropathy	paraesthesia, dizziness, headache	peripheral neuropathy
Uncommon	polyneuropathy, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis, myasthenia gravis		encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Rare	Guillain-Barré syndrome, neuritis, myelitis (including transverse myelitis), optic neuritis	Guillain-Barré syndrome, encephalitis	
Not known		myelitis (including transverse myelitis), optic neuritis	
Ear and labyrinth disorders			
Common			tinnitus
Eye disorders			
Common	blurred vision, dry eye	dry eye, blurred vision	dry eye, blurred vision
Uncommon	uveitis, episcleritis	uveitis	uveitis
Rare	Vogt-Koyanagi-Harada syndrome		
Cardiac disorders			
Common	tachycardia, atrial fibrillation	tachycardia, atrial fibrillation	atrial fibrillation, tachycardia
Uncommon	myocarditis[a], arrhythmia (including ventricular arrhythmia)[a], bradycardia	myocarditis	myocarditis
Not known	pericardial disorders[h]		
Vascular disorders			
Very common			hypertension
Common	hypertension	thrombosis[a, j], hypertension, vasculitis	thrombosis[j]

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
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	
Skin and subcutaneous tissue disorders			
Very common	rash[c], pruritus	rash[c], pruritus	palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus
Common	alopecia, vitiligo, urticaria, dry skin, erythema,	palmar-plantar erythrodysaesthesia syndrome, skin hyperpigmentation, alopecia, dry skin, erythema	alopecia, dry skin, erythema, hair colour change
Uncommon	Stevens-Johnson syndrome, erythema multiforme, psoriasis, other lichen disorders		psoriasis, urticaria
Rare	toxic epidermal necrolysis[a,d,] lichen sclerosus		
Not known			lichen sclerosus, other lichen disorders

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[e], arthralgia	musculoskeletal pain[e]	musculoskeletal pain[e], arthralgia, muscle spasm
Common	muscle spasms, muscular weakness, arthritis	arthralgia, muscular weakness	arthritis
Uncommon	polymyalgia rheumatica, myopathy, myositis (including polymyositis)[a]		myopathy, osteonecrosis of the jaw, fistula
Rare	spondyloarthropathy, Sjogren's syndrome, rhabdomyolysis[a]		
Renal and urinary disorders			
Very common			proteinuria
Common	renal failure (including acute kidney injury)[a]	renal failure[a]	renal failure, acute kidney injury
Uncommon	tubulointerstitial nephritis, nephritis	cystitis noninfective, nephritis	nephritis
Rare	cystitis noninfective		cystitis noninfective[g]
General disorders and administration site conditions			
Very common	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue, pyrexia, oedema
Common	chest pain, pain, chills	malaise	pain, chest pain
Investigations			
Very common	increased alkaline phosphatase[b], increased AST[b], increased ALT[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hyponatraemia[b], hyperkalaemia[b], hypokalaemia[b], hypercalcaemia[b], hypocalcaemia[b]	hypocalcaemia[b], increased AST[b], increased ALT[b], hyponatraemia[b], increased amylase[b], hypomagnesaemia[b], increased alkaline phosphatase[b], hypokalaemia[b], increased creatinine[b], increased lipase[b], hyperkalaemia[b], increased total bilirubin[b]	increased alkaline phosphatase[b], increased ALT[b], increased AST[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hypokalaemia[b], hypomagnesaemia[b], hyponatraemia[b], hypocalcaemia[b], hypercalcaemia[b], hypophosphataemia[b], hyperkalaemia[b], hypermagnesaemia[b], hypernatraemia[b]
Common	hypernatraemia[b], hypermagnesaemia[b], increased thyroid stimulating hormone, increased gamma-glutamyltransferase	hypernatraemia[b], hypercalcaemia[b], hypermagnesaemia[b]	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 3 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] 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] 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.

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 4 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 4 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 4: 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	2.4	1.8	2.5
Colitis	1.2	6	1.8	2.5
Hepatitis	1.1	5	0.8	4.1
Nephritis and renal dysfunction	0.3	1.2	3.3	0.6
Endocrinopathies	0.5	2.3	0.6	1.3
Skin	0.8	1.0	1.0	2.2
Hypersensitivity/Infusion reaction	0.1	0.3	1.8	0
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]				
Pneumonitis	65	59	58	56
Colitis	14	31	8	8
Hepatitis	21	36	8	23
Nephritis and renal dysfunction	22	27	7	9
Endocrinopathies	5	19	5	4.2
Skin	3.3	8	6	8
Hypersensitivity/Infusion reaction	18	16	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 6.5% (150/2294). Grade 2, Grade 3, and Grade 4 cases were reported in 3.2% (74/2294), 1.1% (26/2294), and 0.3% (8/2294) 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 124 patients (82.7%) 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 4.3% (67/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 2.1% (33/1572), 0.9% (14/1572), and 0.2% (3/1572), of patients, respectively. Two patients (0.1%) had a fatal outcome. Median time to onset was 25 weeks (range: 1.6-96.9). Resolution occurred in 48 patients (71.6%) with a median time to resolution of 10.4 weeks (range: 0.3^{+}-121.3^{+}).

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 27.3% (626/2294). Grade 2, Grade 3, and Grade 4 cases were reported in 8.5% (194/2294), 6.5% (150/2294), and 0.2% (4/2294), of patients, respectively. One patient (< 0.1%) had a fatal outcome. Median time to onset was 1.4 months (range: 0.0-48.9). Resolution occurred in 567 patients (91%) with a median time to resolution of 2.7 weeks (range: 0.1-159.4^{+}). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, 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 24.0% (377/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 7.3% (115/1572), 3.2% (51/1572), and 0.4% (6/1572) 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 329 patients (87.7%) 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 19.3% (442/2294). Grade 2, Grade 3, and Grade 4 cases were reported in 4.5% (104/2294), 7.5% (171/2294), and 1.1% (25/2294) of patients, respectively. Median time to onset was 2 months (range: 0.0-36.6). Resolution occurred in 388 patients (88.2%) with a median time to resolution of 5.4 weeks (range: 0.1-175.9^{+}). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of liver function test abnormalities was 30.1% including Grade 2 (6.9%), Grade 3 (15.8%), and Grade 4 (1.8%).

In patients treated with nivolumab in combination with chemotherapy, the incidence of liver function test abnormalities was 18.6% (293/1572). Grade 2, Grade 3 and Grade 4 cases were reported in 5.6% (88/1572), 2.9% (45/1572) and < 0.1% (1/1572) of patients, respectively. Median time to onset was 7.7 weeks (range: 0.1-99.0). Resolution occurred in 231 patients (79.9%) 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 5.9% (135/2294). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (50/2294), 0.9% (20/2294), and 0.5% (11/2294) 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 104 patients (75.8%) with a median time to resolution of 6.1 weeks (range: 0.1-172.1^{+}).

In patients treated with nivolumab in combination with chemotherapy, the incidence of nephritis or renal dysfunction was 10.8% (170/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 4.1% (64/1572), 1.5% (24/1572), and 0.1% (2/1572) of patients, respectively. Two patients (0.1%) had a fatal outcome. Median time to onset was 6.9 weeks (range: 0.1-60.7). Resolution occurred in 111 patients (65.3%) with a median time to resolution of 11.6 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 22.9% (526/2294). Grade 2 and Grade 3 thyroid disorders were reported in 12.2% (281/2294) and 1.0% (24/2294) of patients, respectively.
Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 2.0% (45/2294) and 1.6% (37/2294) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.7% (16/2294) and 0.5% (11/2294) 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% (62/2294), 1.7% (39/2294) and 0.2% (4/2294) 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% (1/2294), 0.3% (8/2294), 0.2% (5/2294), and 0.3% (6/2294) of patients, respectively. Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-28.1). Resolution occurred in 254 patients (39.1%). 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 12.7% (199/1572). Grade 2 thyroid disorder was reported in 6.2% (97/1572) patients. Grade 3 hypophysitis occurred in 0.1% (2/1572) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (3/1572) and 0.3% (4/1572) of patients, respectively. Grade 2, Grade 3 and Grade 4 adrenal insufficiency occurred in 0.6% (9/1572), 0.2% (3/1572) and < 0.1% (1/1572) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus, fulminant Type 1 diabetes mellitus, and diabetic ketoacidosis (3 Grade 2, 2 Grade 3, and 1 Grade 4) were reported. Median time to onset of these endocrinopathies was 14.7 weeks (range: 1.1-124.3). Resolution occurred in 81 patients (37.2%). Time to resolution ranged from 0.4 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 45.2% (1038/2294). Grade 2, Grade 3, and Grade 4 cases were reported in 13.6% (312/2294), 4.4% (102/2294), and < 0.1% (2/2294) of patients, respectively. Median time to onset was 0.8 months (range: 0.0-33.8). Resolution occurred in 724 patients (70%) with a median time

to resolution of 11.3 weeks (range: 0.1-268.7[+]). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, 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 25.6% (402/1572). Grade 2 and Grade 3 cases were reported in 6.2% (97/1572) and 2.5% (39/1572) of patients, respectively. Median time to onset was 7.0 weeks (range: 0.1-97.4). Resolution occurred in 273 patients (68.1%) with a median time to resolution of 12.3 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 4.8% (110/2294). Grade 1, Grade 2, Grade 3, and Grade 4 cases were reported in 2.0% (47/2294), 2.5% (57/2294), 0.2% (5/2294), and < 0.1% (1/2294) 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 8.5% (134/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (76/1572), 1.1% (18/1572), and 0.2% (3/1572) 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 thrombocytopaenia, 0.7% for leucopoenia, 8.7% for lymphopaenia, 0.9% for neutropaenia, 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, 1.4% for thrombocytopaenia, 2.1% for leucopoenia, 7.0% for lymphopaenia, 3.2% for neutropaenia, 2.8% for increased alkaline phosphatase, 7.0% for increased AST, 8.1% for increased ALT, 1.3% for increased total bilirubin, 1.7% for increased creatinine, 5.8% for hyperglycaemia, 0.7% for hypoglycaemia, 8.2% for increased amylase, 16.3% for increased lipase, 0.7% for hypocalcaemia, 0.2% for hypernatraemia, 0.9% for hypercalcaemia, 1.9% for hyperkalaemia, 0.5% for hypermagnesaemia, 0.4% for hypomagnesaemia, 3.2% for hypokalaemia, and 9.2% for hyponatraemia.

Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, 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: 15.8% for anaemia, 6.9% for thrombocytopaenia, 12.2% leukopaenia, 14.6% for lymphopaenia, 27.6% neutropaenia, 2.4% for increased alkaline phosphatase, 3.4% for increased AST, 2.6% for increased ALT, 2.0% for increased bilirubin, 1.4% for increased creatinine, 4.5% for increased amylase, 5.2% for increased lipase, 0.5% for hypernatraemia, 8.8% for hyponatraemia, 1.9% for hyperkalaemia, 5.6% for hypokalaemia, 0.8% for hypercalcaemia, 1.9% for hypocalcaemia, 1.5% for hypermagnesaemia, 2.9% for hypomagnesaemia, 3.5% for hyperglycaemia, and 0.7% for hypoglycaemia.

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

Immunogenicity

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 patients who were treated with nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of anti-product-antibodies, 7.5% tested positive for treatment emergent anti-product-antibodies with 0.5% tested positive for neutralising antibodies.

Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26.0% 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).

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

Hepatic or renal impairment

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

Reporting of suspected adverse reactions

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies 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

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-naive, Stage III or IV BRAF wild-type melanoma and an ECOG performance-status score of 0 or 1. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

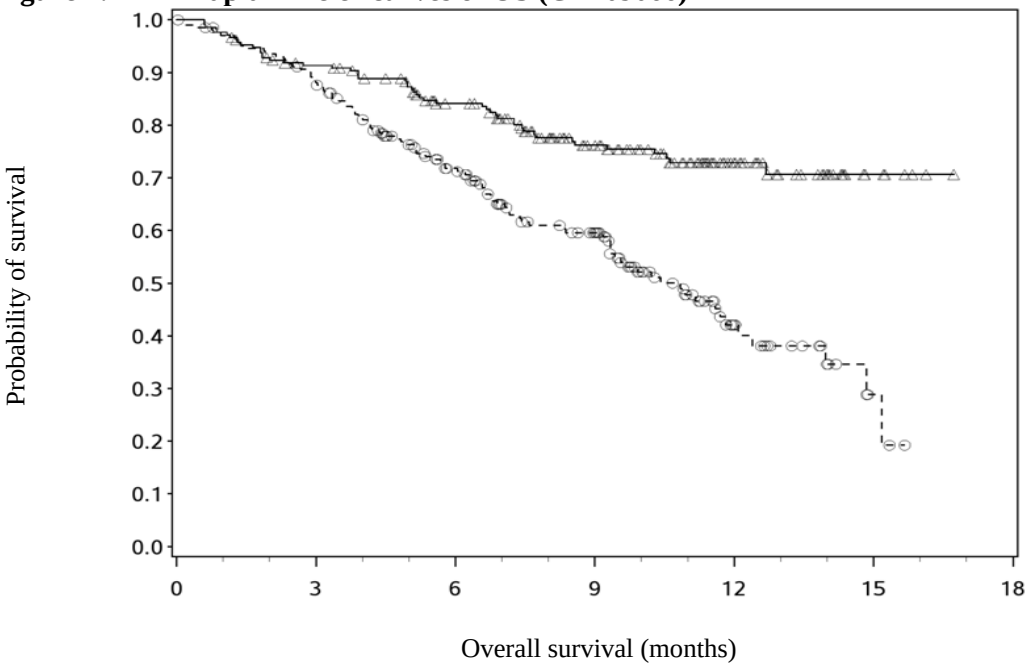
A total of 418 patients were randomised to receive either nivolumab (n = 210) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine (n = 208) at 1 000 mg/m^2

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

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

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

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



Number of subjects at risk

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

----△---- 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 5.

Table 5: Efficacy results (CA209066)

	nivolumab (n = 210)		dacarbazine (n = 208)
Overall survival			
Events	50 (23.8%)		96 (46.2%)
Hazard ratio		0.42	
99.79% CI		(0.25, 0.73)	
95% CI		(0.30, 0.60)	
p-value		< 0.0001	
Median (95% CI)	Not reached		10.8 (9.33, 12.09)
Rate (95% CI)			
At 6 months	84.1 (78.3, 88.5)		71.8 (64.9, 77.6)
At 12 months	72.9 (65.5, 78.9)		42.1 (33.0, 50.9)
Progression-free survival			
Events	108 (51.4%)		163 (78.4%)
Hazard ratio		0.43	
95% CI		(0.34, 0.56)	
p-value		< 0.0001	
Median (95% CI)	5.1 (3.48, 10.81)		2.2 (2.10, 2.40)
Rate (95% CI)			
At 6 months	48.0 (40.8, 54.9)		18.5 (13.1, 24.6)
At 12 months	41.8 (34.0, 49.3)		NA
Objective response	84 (40.0%)		29 (13.9%)
(95% CI)	(33.3, 47.0)		(9.5, 19.4)
Odds ratio (95% CI)		4.06 (2.52, 6.54)	
p-value		< 0.0001	
Complete response (CR)	16 (7.6%)		2 (1.0%)
Partial response (PR)	68 (32.4%)		27 (13.0%)
Stable disease (SD)	35 (16.7%)		46 (22.1%)
Median duration of response			
Months (range)	Not reached	(0^+-12.5^+)	6.0 (1.1-10.0^+)
Median time to response			
Months (range)	2.1 (1.2-7.6)		2.1 (1.8-3.6)

"+" denotes a censored observation.

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/m^2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks). Randomisation was stratified by BRAF and tumour PD-L1 status and best response to prior ipilimumab.

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

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

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

Table 6: Best overall response, time and duration of response (CA209037)

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

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

Updated analysis (24-month follow-up)
Among all randomised patients, the ORR was 27.2% (95% CI: 22.0, 32.9) in the nivolumab group and 9.8% (95% CI: 5.3, 16.1) in the chemotherapy group. Median durations of response were 31.9 months

(range: 1.4^{+}-31.9) and 12.8 months (range: 1.3^{+}-13.6^{+}), respectively. The PFS HR for nivolumab vs. chemotherapy was 1.03 (95% CI: 0.78, 1.36). The ORR and PFS were assessed by IRRC per RECIST version 1.1.

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

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

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

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

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

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

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

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

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 7 below.

Table 7: Response rate at week 12 - all response evaluable patients and by subgroup (CA209172)

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

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

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

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

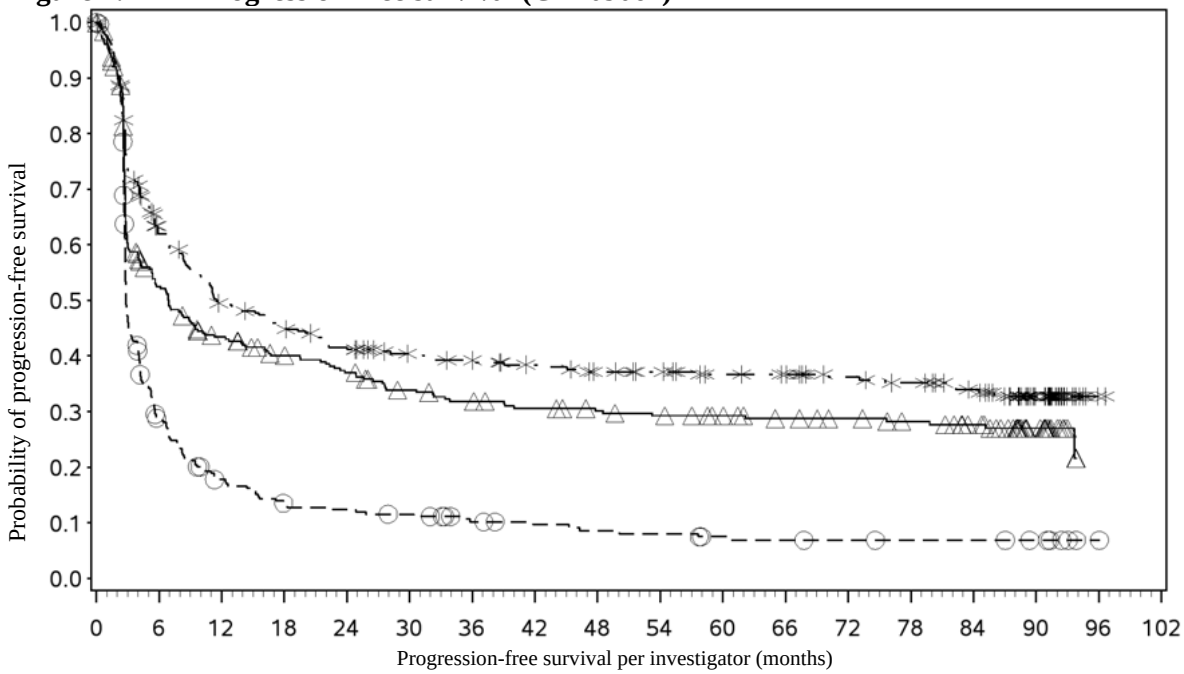
Baseline characteristics were balanced across the three treatment groups. The median age was 61 years (range: 18 to 90 years), 65% of patients were men, and 97% were white. ECOG performance status score was 0 (73%) or 1 (27%). The majority of the patients had AJCC Stage IV disease (93%); 58% had M1c disease at study entry. Twenty-two percent of patients had received prior adjuvant therapy.

Thirty-two percent of patients had BRAF mutation-positive melanoma; 26.5% of patients had PD-L1 ≥ 5% tumour cell membrane expression. Four percent of patients had a history of brain metastasis, and 36% of patients had a baseline LDH level greater than ULN at study entry. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the three treatment groups. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

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

PFS results from descriptive analysis (with minimum follow up of 90 months) are shown in Figure 2 (all randomised population), Figure 3 (at the tumour PD-L1 5% cut off), and Figure 4 (at the tumour PD-L1 1% cut off).

Figure 2: Progression-free survival (CA209067)



Number of subjects at risk

Nivolumab + ipilimumab																	
314	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)

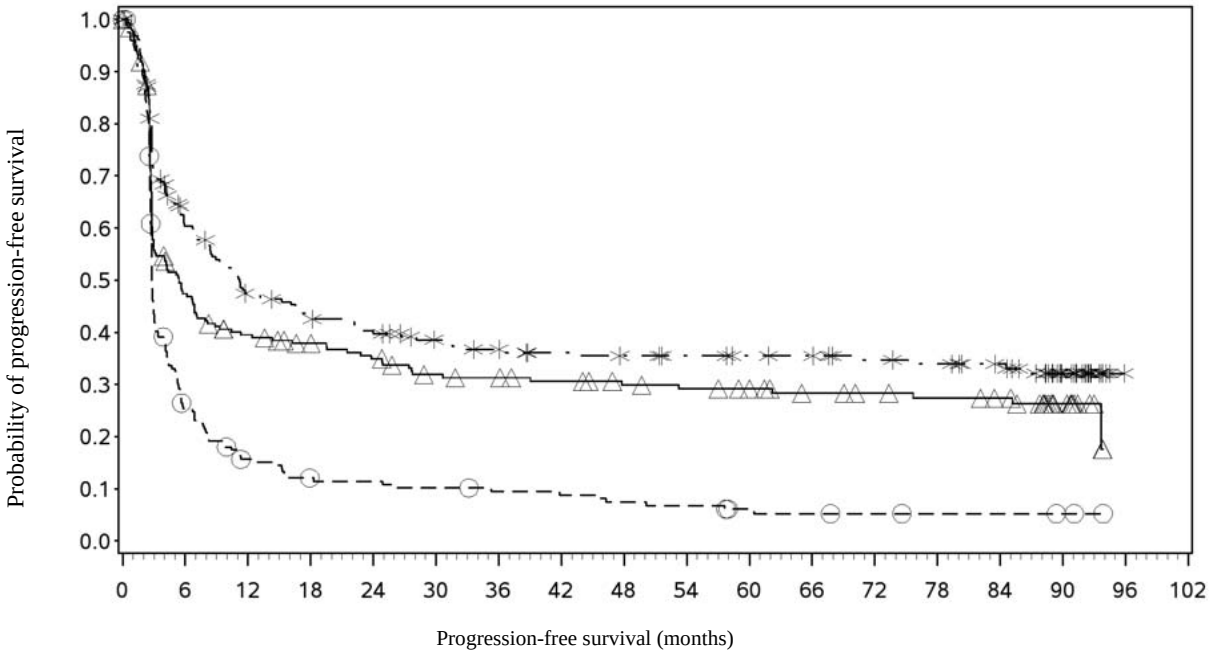
----△---- Nivolumab (events: 208/316), median and 95% CI: 6.93 (5.13, 10.18).
PFS rate at 12 months and 95% CI: 42% (36, 47), PFS rate at 60 months and 95% CI: 29% (24, 35), PFS rate at 90 months and 95% CI: 27% (22, 33)

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

PD-L1 expression < 5%



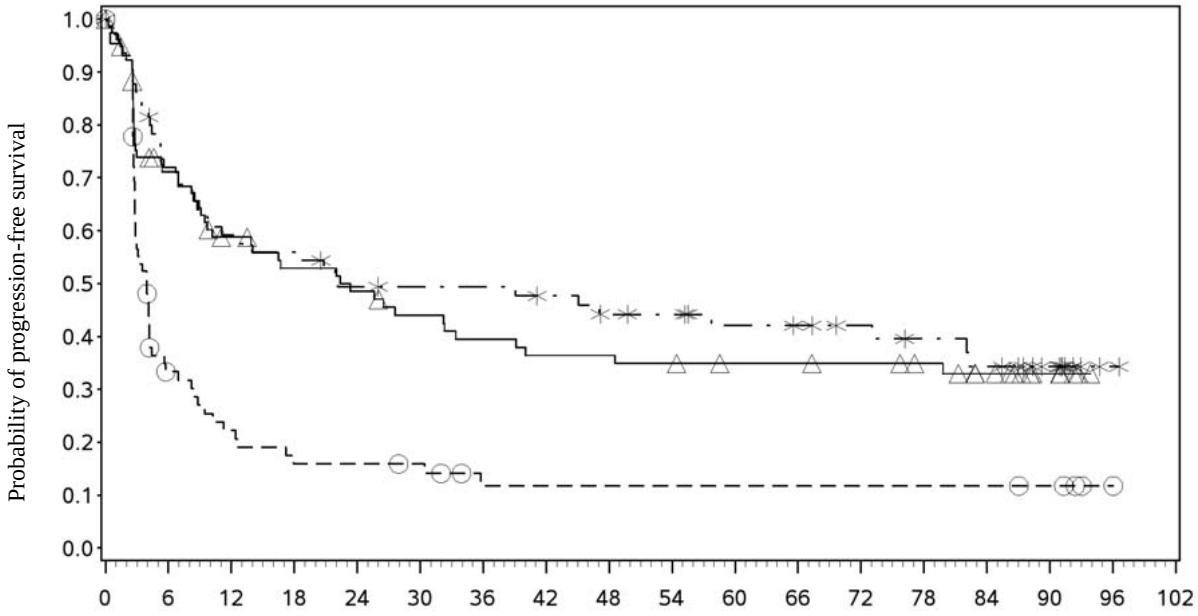
Number of subjects at risk

Nivolumab + ipilimumab																	
210	113	87	78	71	64	60	56	54	52	50	49	45	43	39	22	0	-
Nivolumab																	
208	91	73	66	60	51	49	46	42	40	38	33	31	29	27	12	0	-
Ipilimumab																	
202	45	26	19	18	16	14	13	11	10	7	6	5	4	4	3	0	-

- - -✳- - - Nivolumab+ipilimumab (events: 127/210), median and 95% CI: 11.17 (7.98, 17.51)
----△---- Nivolumab (events: 139/208), median and 95% CI: 5.39 (2.96, 7.13)
- - -❍- - - Ipilimumab (events: 171/202), median and 95% CI: 2.79 (2.76, 3.02)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.33, 0.53)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.54 (0.43, 0.68)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.77 (0.61, 0.98)

PD-L1 expression ≥ 5%



Number of subjects at risk

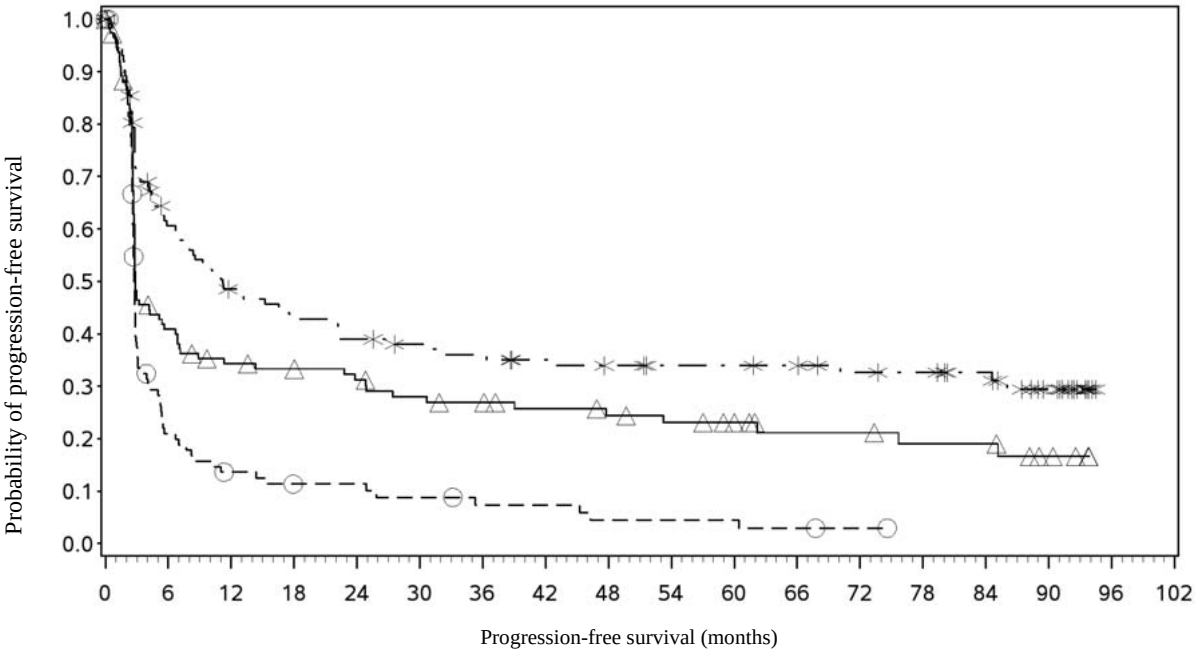
Nivolumab + ipilimumab																	
68	45	37	35	30	29	29	27	24	23	20	19	17	15	13	8	1	-
Nivolumab																	
80	52	41	36	33	29	26	24	24	23	21	21	20	18	14	7	0	-
Ipilimumab																	
75	21	14	10	10	9	5	5	5	5	5	5	5	5	5	4	1	-

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

PD-L1 expression < 1%



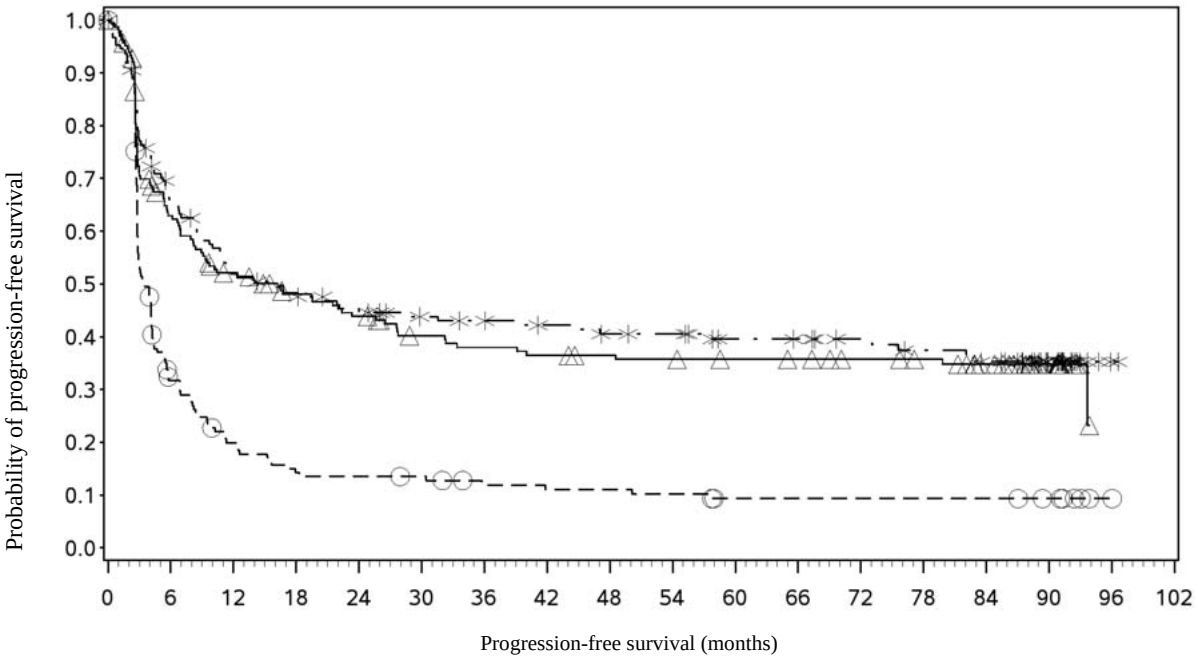
Number of subjects at risk

Nivolumab + ipilimumab																	
123	65	51	46	41	38	36	33	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)

PD-L1 expression ≥ 1%



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)

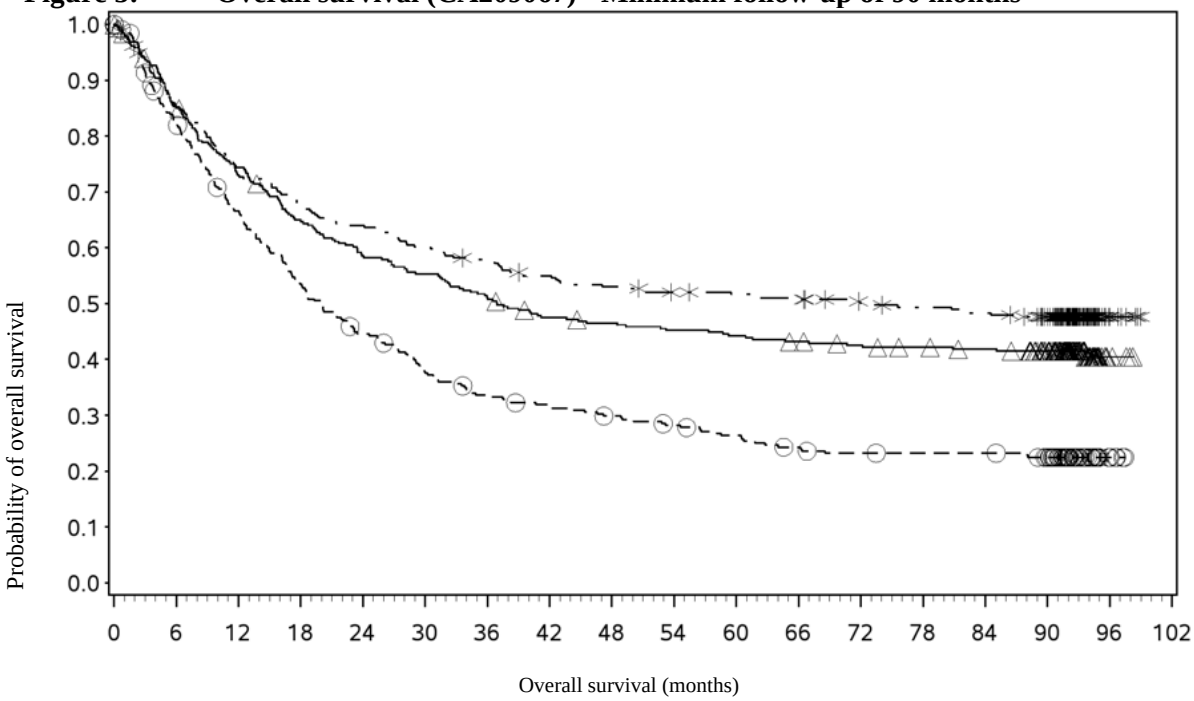
Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.32, 0.55)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.45 (0.35, 0.59)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.92 (0.69, 1.22)

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 5 (all randomised), Figures 6 and 7 (at the tumour PD-L1 5% and 1% cut off).

The OS analysis was not adjusted to account for subsequent therapies received. Subsequent systemic therapy was received by 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 5: 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)

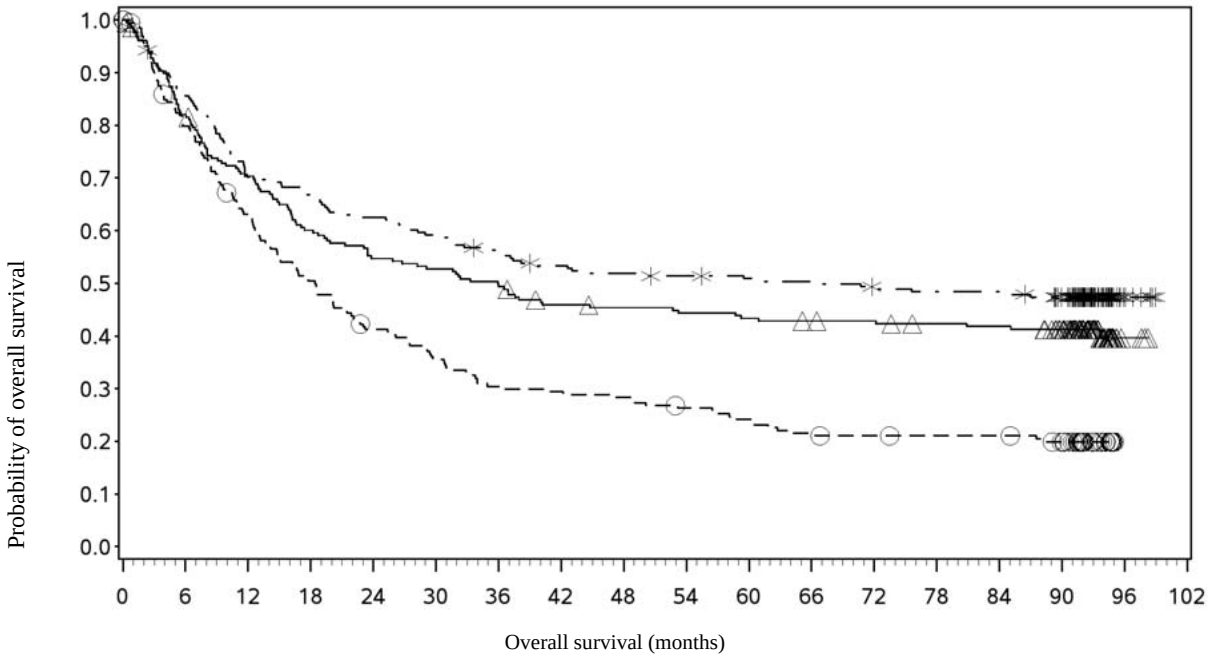
Nivolumab+ipilimumab vs ipilimumab - HR (95% CI): 0.53 (0.44, 0.65)

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

PD-L1 expression < 5%



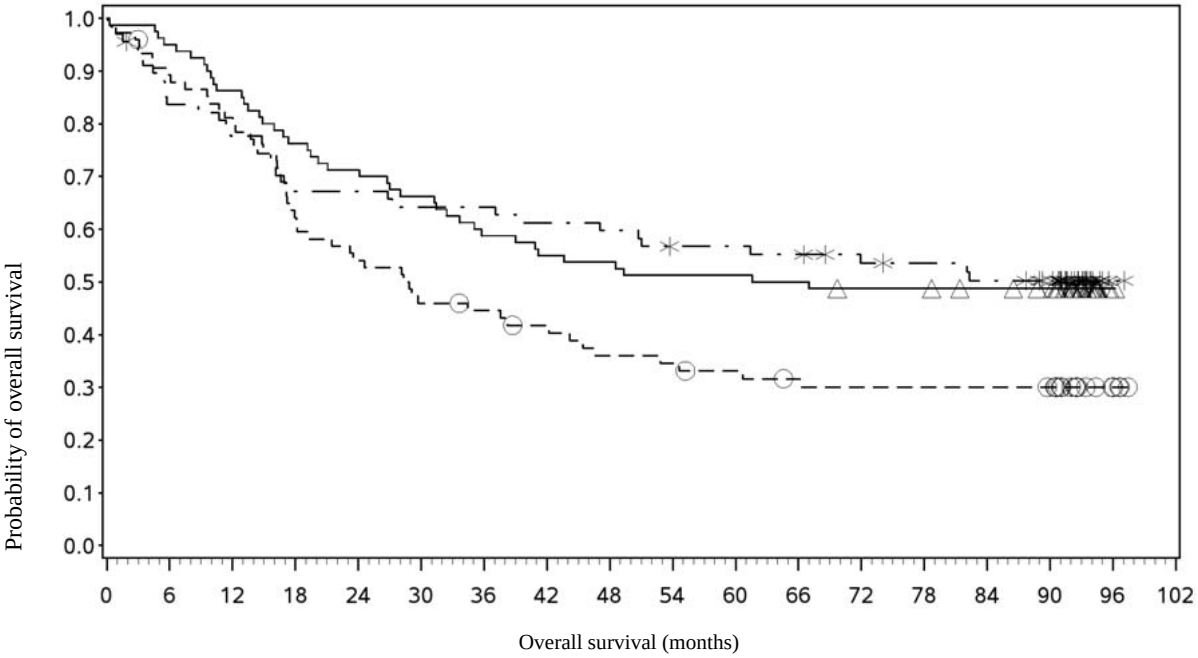
Number of subjects at risk

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 ≥ 5%



Number of subjects at risk

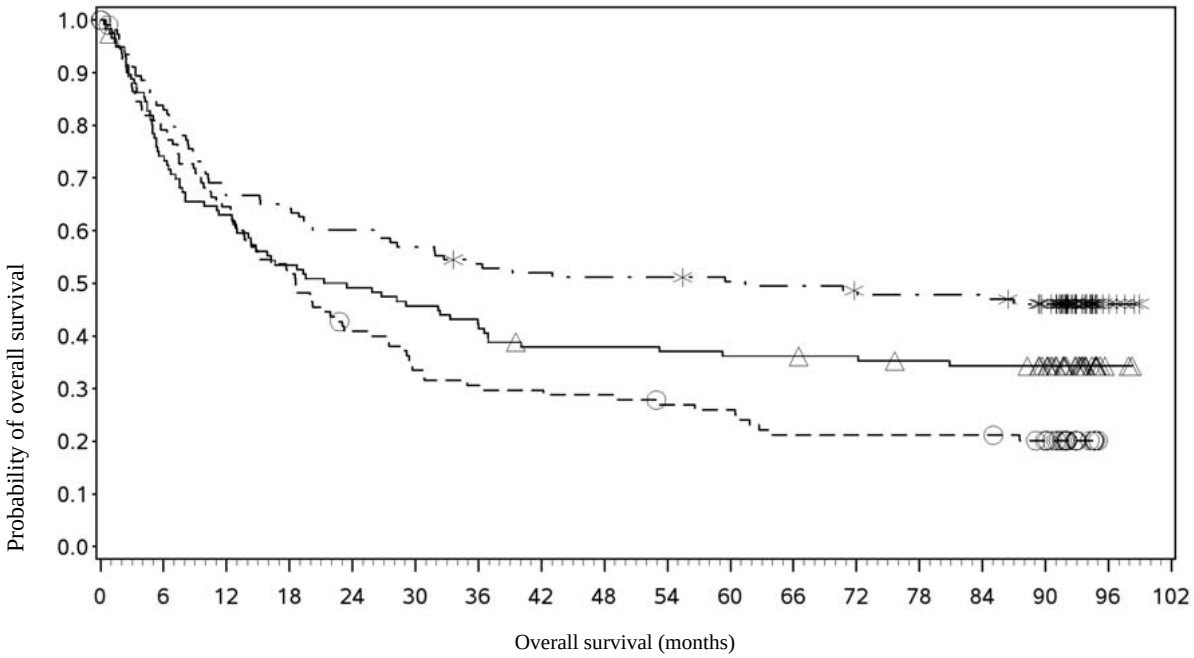
Nivolumab+ipilimumab																
68	56	52	45	45	43	43	41	40	37	37	36	33	32	30	27	1	-
Nivolumab																
80	76	69	61	57	53	47	44	43	41	41	40	38	38	36	33	1	-
Ipilimumab																
75	66	60	46	40	34	32	29	25	24	22	20	19	19	19	18	4	-

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

PD-L1 expression < 1%



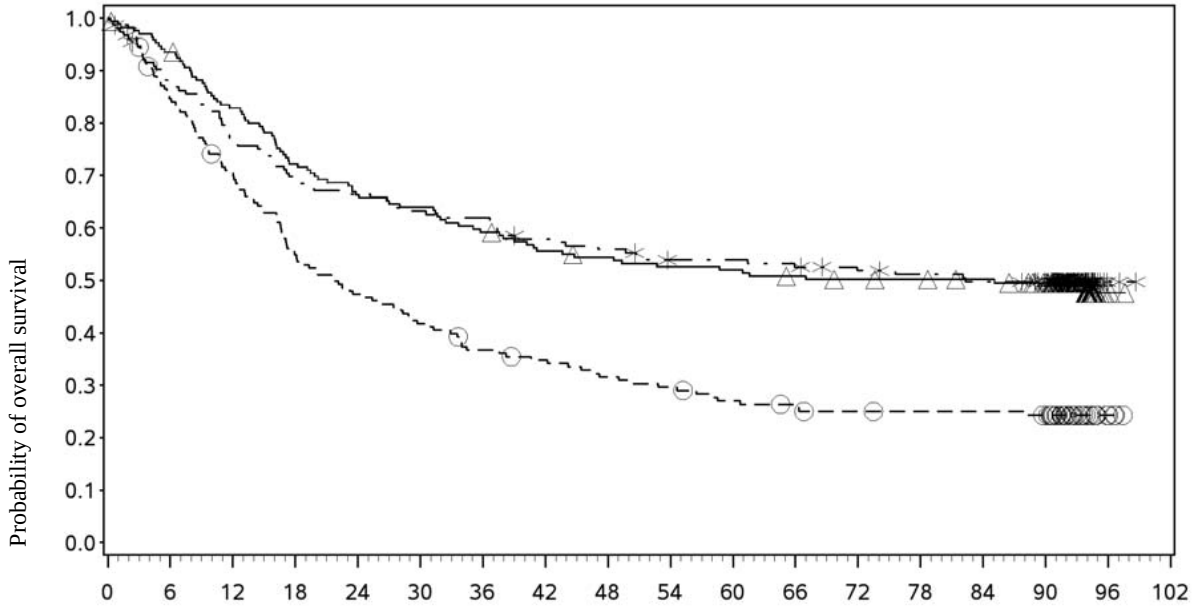
Number of subjects at risk

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)

PD-L1 expression ≥ 1%



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 8.

Table 8: 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 8) 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).

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 9 and Figure 8.

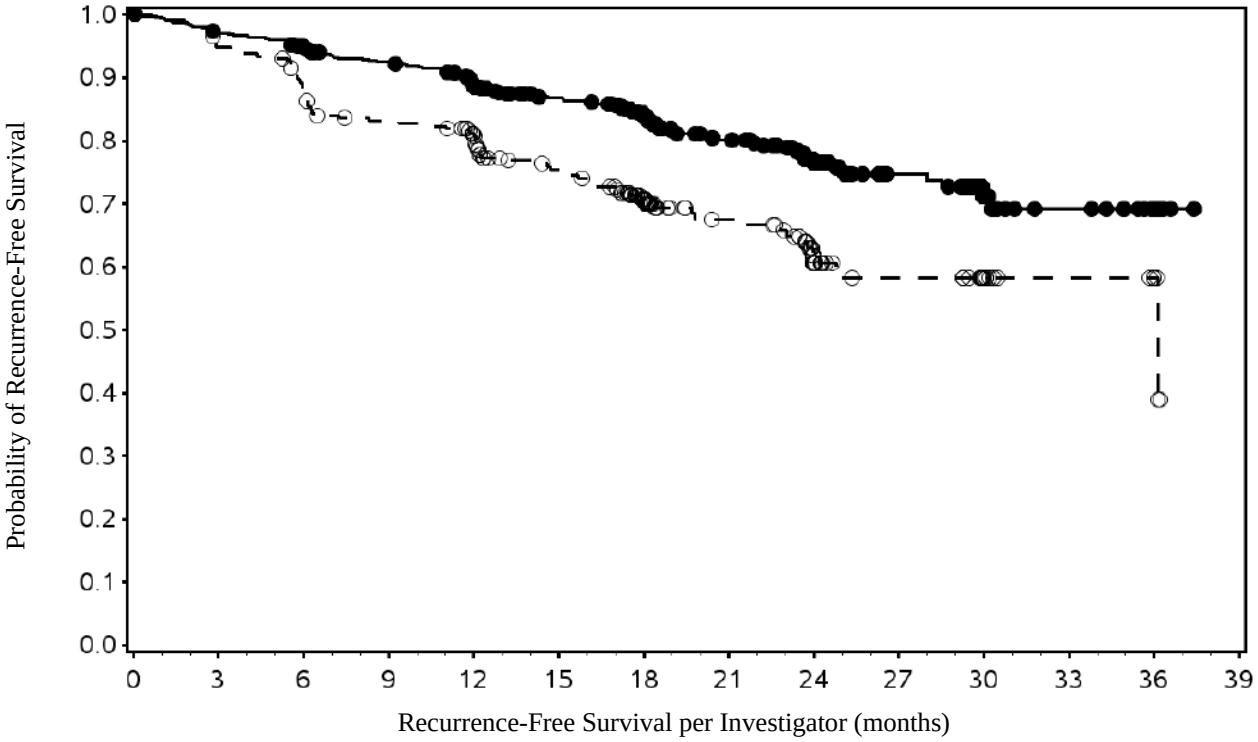
Table 9: Efficacy results (CA20976K)

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

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

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

Figure 8: Recurrence-free survival (CA20976K)



Number of subjects at risk

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

----●---- Nivolumab (events 102/526), median and 95% CI: NR
- - -❍- - - Placebo (events: 84/264), median and 95% CI: 36.14 (24.77, NR)
Nivolumab vs. Placebo – HR (95% CI): 0.53 (0.40, 0.71)
Based on data cut-off: 21-February-2023, minimum follow-up of 15.6 months

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

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 (≥ 5% vs. < 5%/indeterminate), and stage of disease per the AJCC staging system. Tumour assessments were conducted every 12 weeks for the first 2 years then every 6 months thereafter. The primary endpoint was recurrence-free survival (RFS). RFS, assessed by investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death due to any cause, whichever occurred first.

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

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% Cl: 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 10 and Figures 9 and 10 (all randomised population).

Table 10: Efficacy results (CA209238)

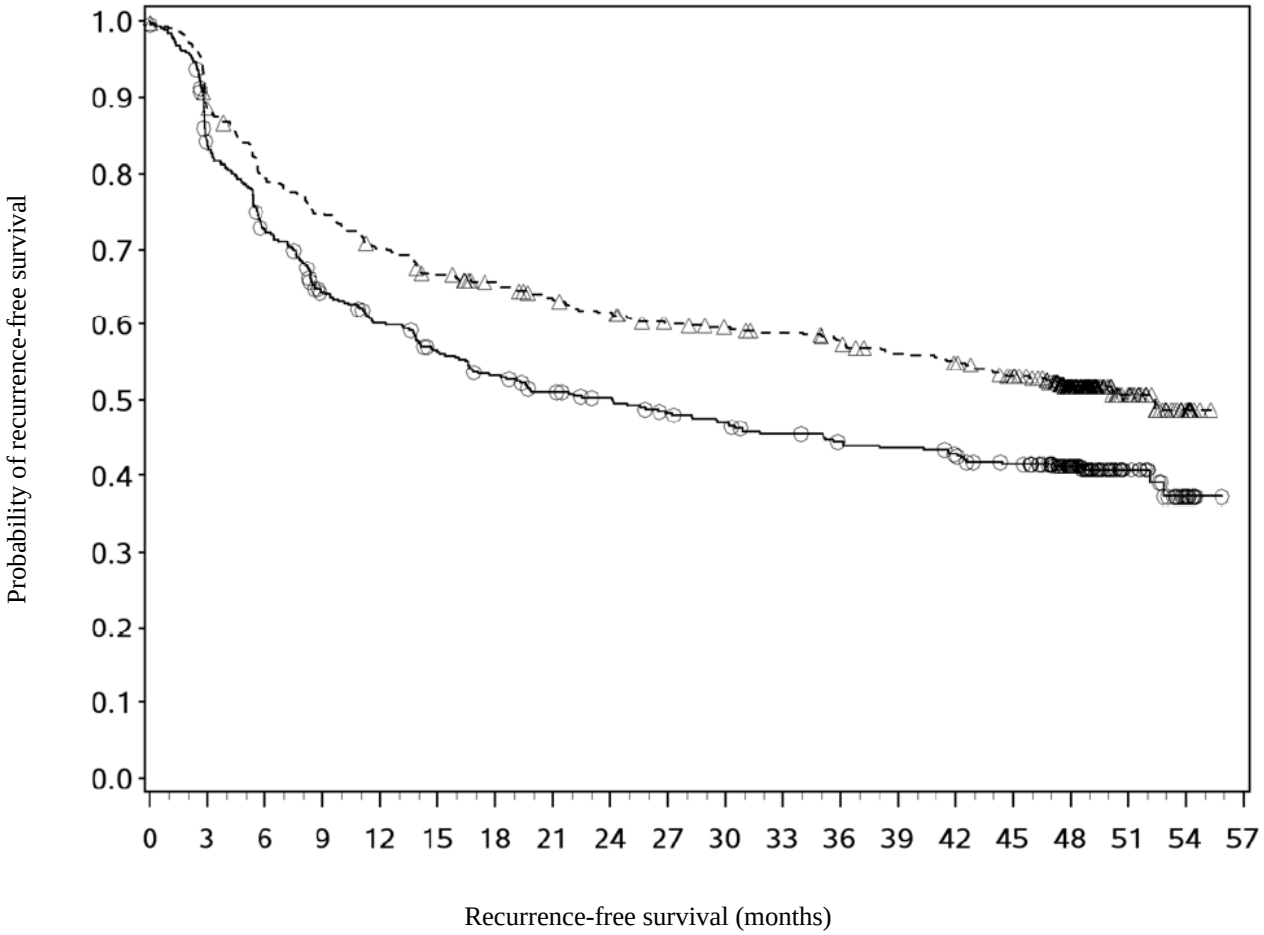
	nivolumab (n = 453)	**ipilimumab 10 mg/kg (n = 453)**
Final pre-specified analysis Recurrence-free survival with minimum follow-up 36 months		
Events	188 (41.5%)	239 (52.8%)
Hazard ratio[a]	0.68	
95% CI	(0.56, 0.82)	
p-value	p < 0.0001	
Median (95% CI) months	NR (38.67, NR)	24.87 (16.62, 35.12)
Recurrence-free 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 9, 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 9: Recurrence-free survival (CA209238)

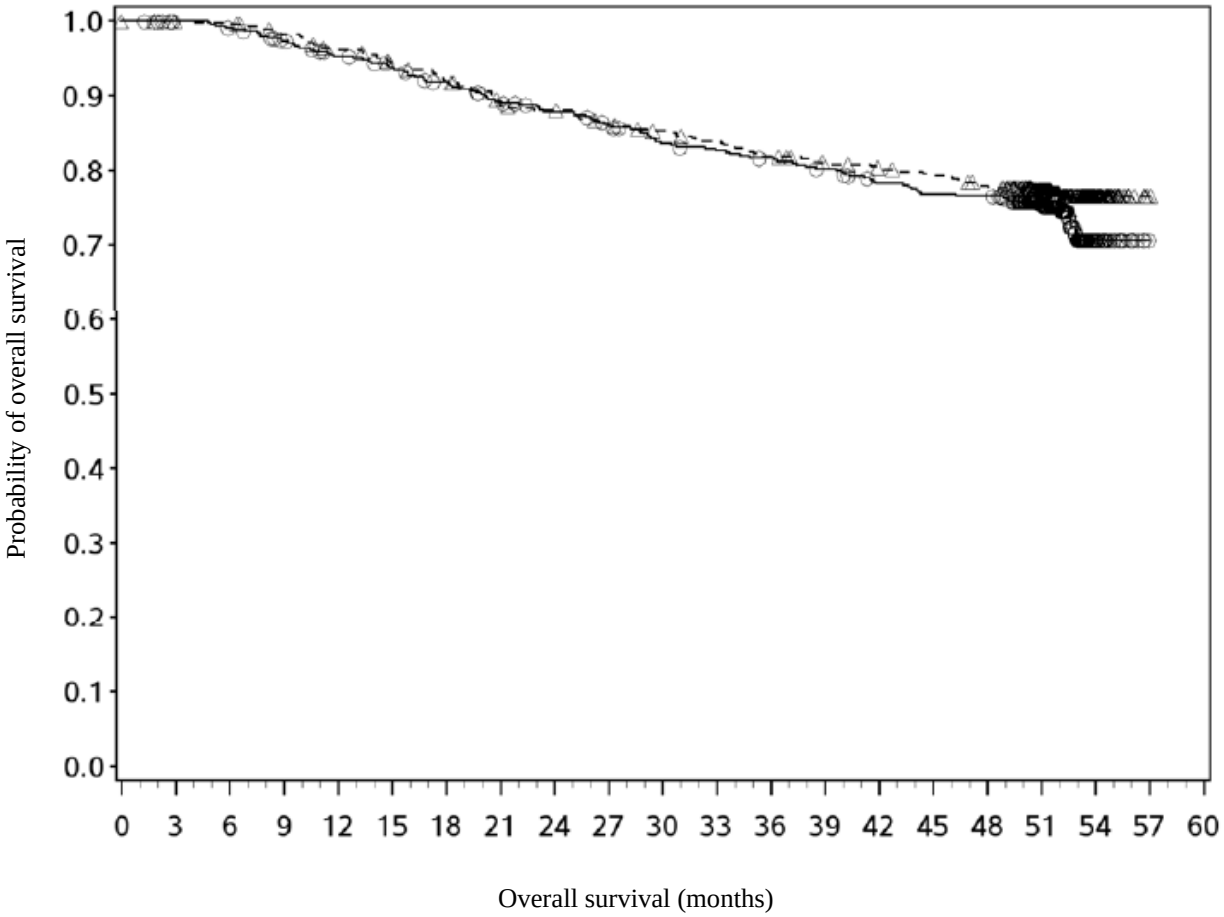


Number of subjects at risk

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 10: 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 10, 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).

Non-small cell lung cancer

Treatment of NSCLC after prior chemotherapy

Squamous NSCLC

Intravenous formulation

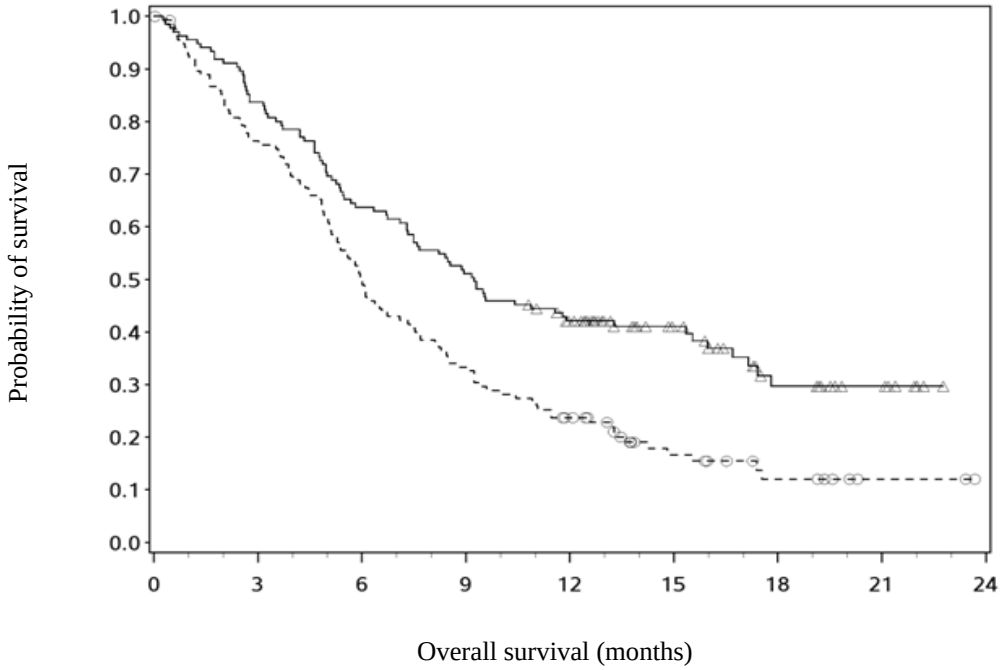
Randomised phase 3 study vs. docetaxel (CA209017)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209017). The study included patients (18 years or older) who have experienced 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/m^2 every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to the RECIST, version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. In addition, symptom improvement and overall health status were assessed using the Lung cancer symptom score (LCSS) average symptom burden index and the EQ-5D Visual Analogue Scale (EQ-VAS), respectively.

Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 39-85) with 44% ≥ 65 years of age and 11% ≥ 75 years of age. The majority of patients were white (93%) and male (76%). Thirty-one percent had progressive disease reported as the best response to their most recent prior regimen and 45% received nivolumab within 3 months of completing their most recent prior regimen. Baseline ECOG performance status score was 0 (24%) or 1 (76%).

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

Figure 11: 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 11.

Table 11: Efficacy results (CA209017)

	nivolumab (n = 135)		docetaxel (n = 137)
Primary analysis Minimum follow-up: 10.6 months			
Overall survival			
Events	86 (63.7%)		113 (82.5%)
Hazard ratio		0.59	
96.85% CI		(0.43, 0.81)	
p-value		0.0002	
Median (95% CI) months	9.23 (7.33, 13.27)		6.01 (5.13, 7.33)
Rate (95% CI) at 12 months	42.1 (33.7, 50.3)		23.7 (16.9, 31.1)
Confirmed objective response	27 (20.0%)		12 (8.8%)
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Odds ratio (95% CI)		2.64 (1.27, 5.49)	
p-value		0.0083	
Complete response (CR)	1 (0.7%)		0
Partial response (PR)	26 (19.3%)		12 (8.8%)
Stable disease (SD)	39 (28.9%)		47 (34.3%)
Median duration of response			
Months (range)	Not reached (2.9-20.5^{+})		8.4 (1.4^{+}-15.2^{+})
Median time to response			
Months (range)	2.2 (1.6-11.8)		2.1 (1.8-9.5)
Progression-free survival			
Events	105 (77.8%)		122 (89.1%)
Hazard ratio		0.62	
95% CI		(0.47, 0.81)	
p-value		< 0.0004	
Median (95% CI) (months)	3.48 (2.14, 4.86)		2.83 (2.10, 3.52)
Rate (95% CI) at 12 months	20.8 (14.0, 28.4)		6.4 (2.9, 11.8)
Updated analysis Minimum follow-up: 24.2 months			
Overall survival[a]			
Events	110 (81.4%)		128 (93.4%)
Hazard ratio		0.62	
95% CI		(0.47, 0.80)	
Rate (95% CI) at 24 months	22.9 (16.2, 30.3)		8 (4.3, 13.3)
Confirmed objective response	20.0%		8.8%
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Median duration of response			
Months (range)	25.2 (2.9-30.4)		8.4 (1.4^{+}-18.0^{+})

	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	20.0%	8.8%
(95% CI)	(13.6, 27.7)	(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 12 below.

Table 12: 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	1/64	55/568	11/103
(%)	(9.8)	(6.1)	(9.7)	(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.

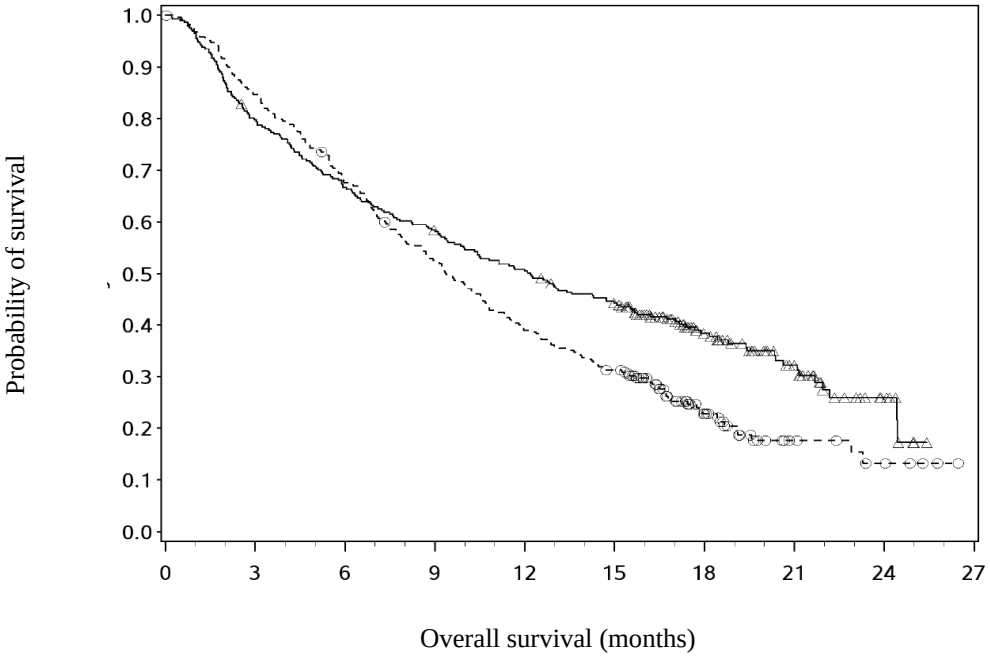
A total of 582 patients were randomised to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks (n = 292) or docetaxel 75 mg/m^2 every 3 weeks (n = 290). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour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

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

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

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

Figure 12: 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 prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 13.

Table 13: Efficacy results (CA209057)

	nivolumab (n = 292)	**docetaxel (n = 290)**
Prespecified interim analysis Minimum follow-up: 13.2 months		
Overall survival		
Events	190 (65.1%)	223 (76.9%)
Hazard ratio[a]	0.73	
(95.92% CI)	(0.59, 0.89)	
p-value[b]	0.0015	
Median (95% CI) months	12.19 (9.66, 14.98)	9.36 (8.05, 10.68)
Rate (95% CI) at 12 months	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)

	nivolumab (n = 292)	docetaxel (n = 290)
Confirmed objective response	56 (19.2%)	36 (12.4%)
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Odds ratio (95% CI)	1.68 (1.07, 2.64)	
p-value	0.0246	
Complete response (CR)	4 (1.4%)	1 (0.3%)
Partial response (PR)	52 (17.8%)	35 (12.1%)
Stable disease (SD)	74 (25.3%)	122 (42.1%)
Median duration of response		
Months (range)	17.15 (1.8-22.6+)	5.55 (1.2+-15.2+)
Median time to response		
Months (range)	2.10 (1.2-8.6)	2.61 (1.4-6.3)
Progression-free survival		
Events	234 (80.1%)	245 (84.5%)
Hazard ratio	0.92	
95% CI	(0.77, 1.11)	
p-value	0.3932	
Median (95% CI) (months)	2.33 (2.17, 3.32)	4.21 (3.45, 4.86)
Rate (95% CI) at 12 months	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)
Updated analysis Minimum follow-up: 24.2 months		
Overall survival[c]		
Events	228 (78.1%)	247 (85.1%)
Hazard ratioa	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)

	nivolumab (n = 292)	docetaxel (n = 290)
Confirmed objective response	19.5%	12.4%
(95% CI)	(15.1, 24.5)	(8.8, 16.8)
Median duration of response		
Months (range)	17.2 (1.8-70.4[+])	5.6 (0.0[+]-33.4)
Progression-free survival		
Rate (95% CI) at 60 months	7.5 (4.5, 11.4)	All patients had either progressed, were censored, or lost to follow-up

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

Quantifiable tumour PD-L1 expression was measured in 79% of patients in the nivolumab group and 77% of patients in the docetaxel group. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. docetaxel) at each of the predefined tumour PD-L1 expression levels of ≥ 1% (53% vs. 55%), ≥ 5% (41% vs. 38%), or ≥ 10% (37% vs. 35%).

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

Table 14 summarises results of ORR and OS by tumour PD-L1 expression.

Table 14: ORR and OS by tumour PD-L1 expression (CA209057)

PD-L1 expression	nivolumab	docetaxel	
	ORR by tumour PD-L1 expression Minimum follow-up: 13.2 months		
			Odds ratio (95% CI)
< 1%	10/108 (9.3%) 95% CI: 4.5, 16.4	15/101 (14.9%) 95% CI: 8.6, 23.3	0.59 (0.22, 1.48)
≥ 1%	38/123 (30.9%) 95% CI: 22.9, 39.9	15/123 (12.2%) 95% CI: 7.0, 19.3	3.22 (1.60, 6.71)
≥ 1% to < 10%[a]	6/37 (16.2%) 95% CI: 6.2, 32.0	5/44 (11.4%) 95% CI: 3.8, 24.6	1.51 (0.35, 6.85)
≥ 10% to < 50%[a]	5/20 (25.0%) 95% CI: 8.7, 49.1	7/33 (21.2%) 95% CI: 9.0, 38.9	1.24 (0.26, 5.48)
≥ 50%[a]	27/66 (40.9%) 95% CI: 29.0, 53.7	3/46 (6.5%) 95% CI: 1.4, 17.9	9.92 (2.68, 54.09)

PD-L1 expression	nivolumab	docetaxel	
	OS by tumour PD-L1 expression		
	Minimum follow-up: 13.2 months		
	Number of events (number of patients)		**Unstratified hazard ratio (95% CI)**
< 1%	77 (108)	75 (101)	0.90 (0.66, 1.24)
≥ 1%	68 (123)	93 (123)	0.59 (0.43, 0.82)
≥ 1% to < 10%[a]	27 (37)	30 (44)	1.33 (0.79, 2.24)
≥ 10% to < 50%[a]	11 (20)	26 (33)	0.61 (0.30, 1.23)
≥ 50%[a]	30 (66)	37 (46)	0.32 (0.20, 0.53)
	Updated analysis		
	Minimum follow-up: 24.2 months		
< 1%	91 (108)	86 (101)	0.91 (0.67, 1.22)
≥ 1%	87 (123)	103 (123)	0.62 (0.47, 0.83)
	Updated analysis		
	Minimum follow-up: 62.7 months		
< 1%	100 (109)	96 (101)	0.87 (0.66, 1.16)
≥1%	96 (122)	119 (123)	0.55 (0.42, 0.73)

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

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

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

Renal cell carcinoma (RCC)

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% ≥ 65 years of age and 14% ≥ 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 ≥ 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 ≥ 0.60. Updated efficacy results with a minimum follow-up of 14.9 months (data cut-off 21-Feb-2024) are shown in Table 15.

Table 15: 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 ≥ 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) ≥ 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

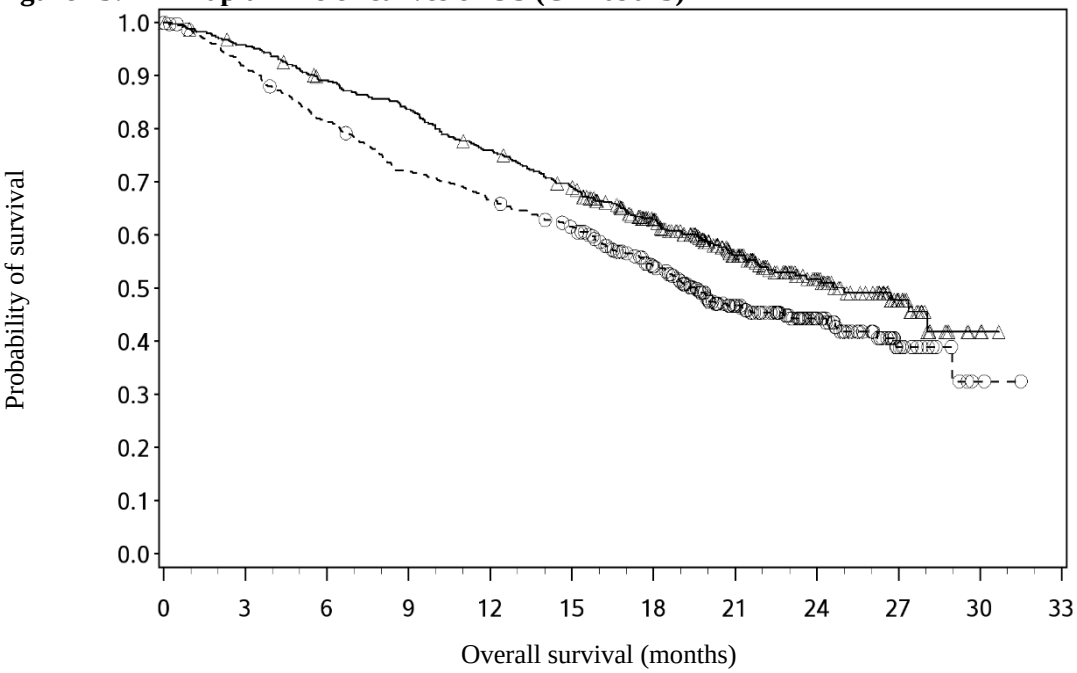
longer tolerated. The first tumour assessments were conducted 8 weeks after randomisation and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation 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 (MSKCC) risk groups were represented, and 34% and 66% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The majority of patients (72%) were treated with one prior anti-angiogenic therapy. The median duration of time from initial diagnosis to randomisation was 2.6 years in both the nivolumab and everolimus groups. The median duration of treatment was 5.5 months (range: 0-29.6+ months) in nivolumab-treated patients and was 3.7 months (range: 6 days-25.7+ months) in everolimus-treated patients.

Nivolumab was continued beyond progression in 44% of patients.

The Kaplan-Meier curves for OS are shown in Figure 13.

Figure 13: Kaplan-Meier curves of OS (CA209025)



Number of subjects at risk

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

----△---- Nivolumab 3 mg/kg (events: 183/410), median and 95% CI: 25.00 (21.75, N.A.)
- - -❍- - - Everolimus 10 mg (events: 215/411), median and 95% CI: 19.55 (17.64, 23.06)

The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 16 and Figure 13). OS benefit was observed regardless of tumour PD-L1 expression level.

Efficacy results are shown in Table 16.

Table 16: Efficacy results (CA209025)

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

"+" denotes a censored observation.
NE = non-estimable

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

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

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.

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

Efficacy results for the intermediate/poor risk patients are shown in Table 17 (primary analysis with a minimum follow-up of 17.5 months and with a minimum follow-up of 60 months) and in Figure 14 (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.

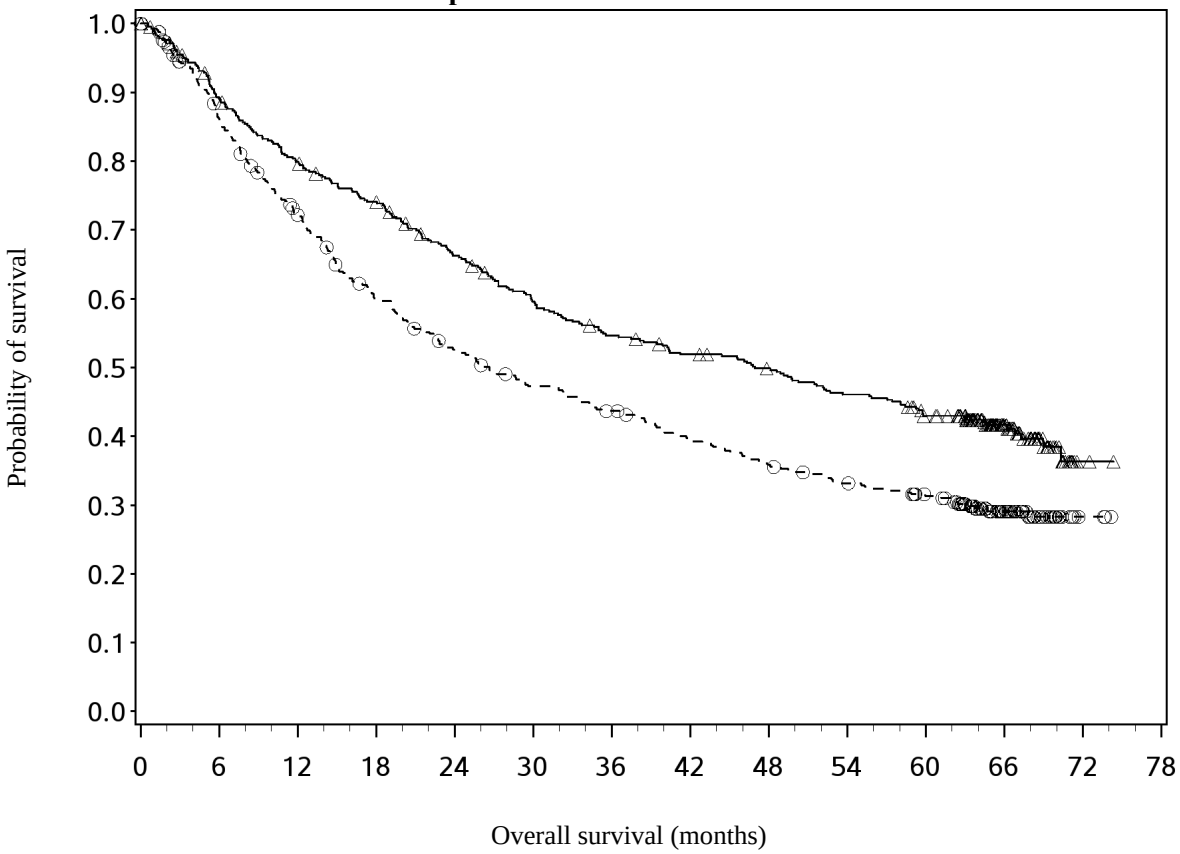
Table 17: Efficacy results in intermediate/poor risk patients (CA209214)

	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)
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)

	nivolumab + ipilimumab (n = 425)		sunitinib (n = 422)
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 14: 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 ≥ 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) ≥ 70%, and measurable disease as per RECIST v1.1 regardless of their PD-L1 status or IMDC risk group. The study excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression, patients who had prior treatment with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, poorly controlled hypertension despite antihypertensive therapy, active brain metastases and uncontrolled adrenal insufficiency. Patients were stratified by IMDC prognostic score, PD-L1 tumour expression, and region.

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

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

The study demonstrated a statistically significant benefit in PFS, OS, and ORR for patients randomised to nivolumab in combination with cabozantinib as compared to sunitinib. Efficacy results from the primary analysis (minimum follow-up 10.6 months; median follow-up 18.1 months) are shown in Table 18.

Table 18: 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	

	nivolumab + cabozantinib (n = 323)	sunitinib (n = 328)
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

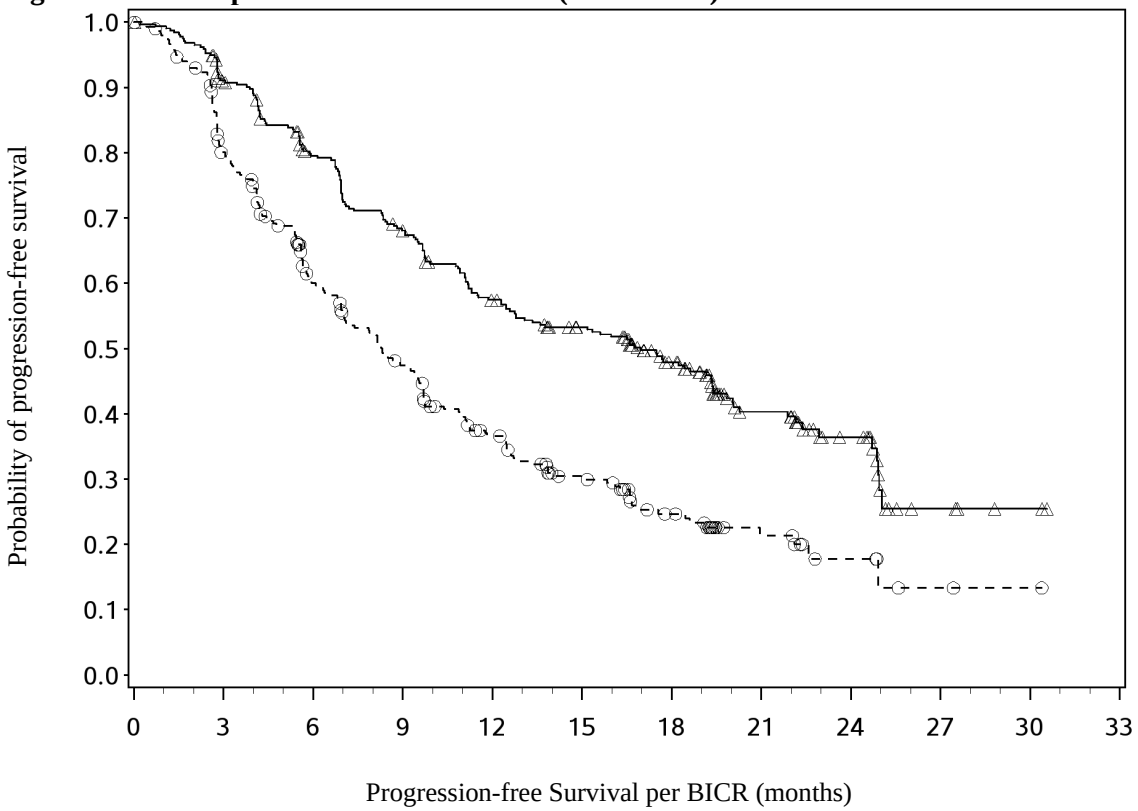
The primary analysis of PFS included censoring for new anti-cancer treatment (Table 18). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

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 ≥ 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 15 and 16). 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 15: Kaplan-Meier curves of PFS (CA2099ER)

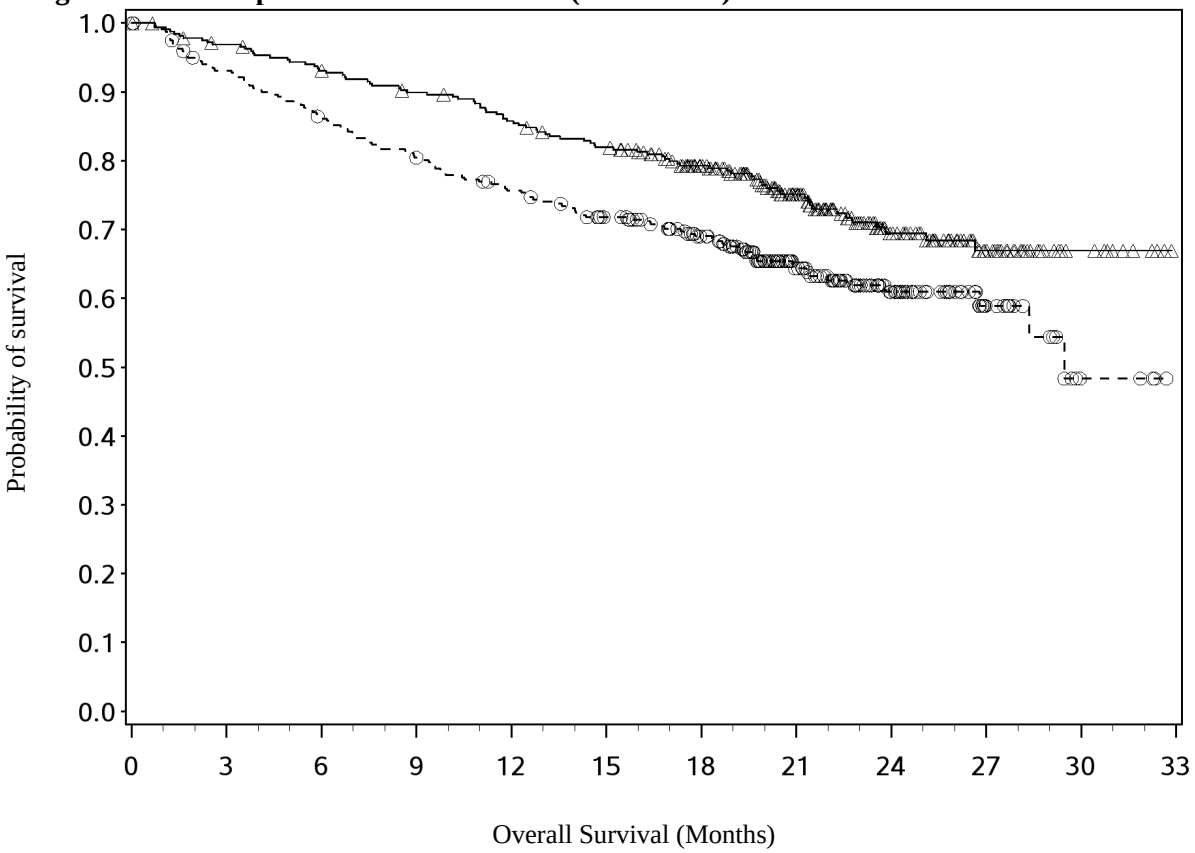


Number of subjects at risk

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 16: 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)

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),

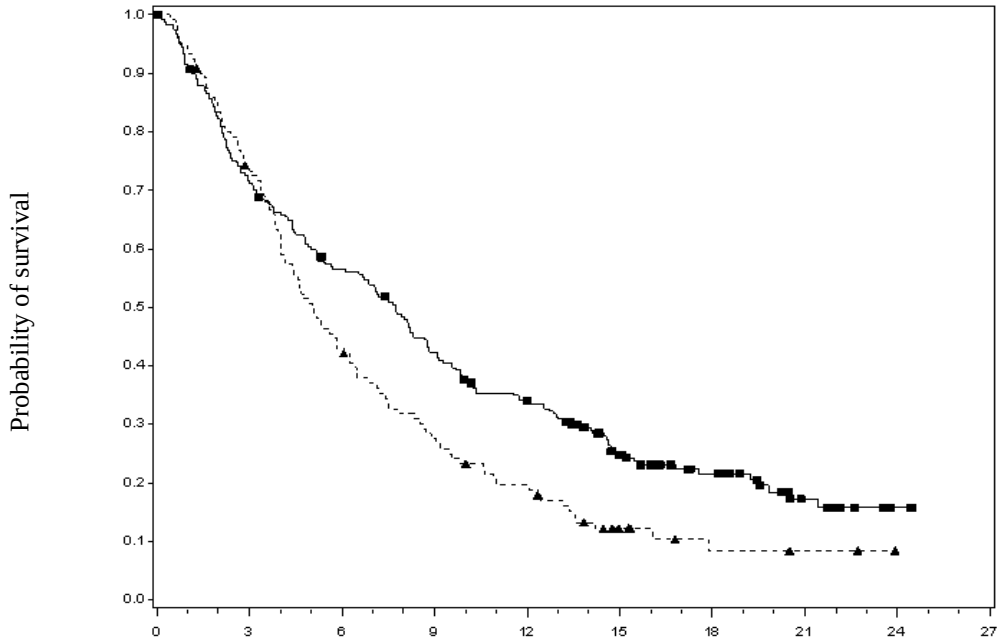
400 mg/m^2 loading dose followed by 250 mg/m^2 weekly or methotrexate (n = 52) 40 to 60 mg/m^2 weekly, or docetaxel (n = 54) 30 to 40 mg/m^2 weekly. Randomisation was stratified by prior cetuximab treatment. Treatment was continued as long as clinical benefit was observed or until treatment was no longer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

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

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

With a minimum follow-up of 11.4 months, the trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice. The Kaplan-Meier curves for OS are shown in Figure 17. Efficacy results are shown in Table 19.

Figure 17: Kaplan-Meier curves of OS (CA209141)



Overall survival (months)

Number of subjects at risk

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

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

Table 19: Efficacy results (CA209141)

	nivolumab (n = 240)	**investigator's choice (n = 121)**
Overall survival		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio[a]	0.71	
(95% CI)	(0.55, 0.90)	
p-value[b]	0.0048	
Median (95% CI) (months)	7.72 (5.68, 8.77)	5.06 (4.04, 6.24)
Rate (95% CI) at 6 months	56.5 (49.9, 62.5)	43.0 (34.0, 51.7)
Rate (95% CI) at 12 months	34.0 (28.0, 40.1)	19.7 (13.0, 27.3)
Rate (95% CI) at 18 months	21.5 (16.2, 27.4)	8.3 (3.6, 15.7)
Progression-free survival		
Events	204 (85.0%)	104 (86.0%)
Hazard ratio	0.87	
95% CI	(0.69, 1.11)	
p-value	0.2597	
Median (95% CI) (months)	2.04 (1.91, 2.14)	2.33 (1.97, 3.12)
Rate (95% CI) at 6 months	21.0 (15.9, 26.6)	11.1 (5.9, 18.3)
Rate (95% CI) at 12 months	9.5 (6.0, 13.9)	2.5 (0.5, 7.8)

	nivolumab (n = 240)	investigator's choice (n = 121)
Confirmed objective response[c]	32 (13.3%)	7 (5.8%)
(95% CI)	(9.3, 18.3)	(2.4, 11.6)
Odds ratio (95% CI)	2.49 (1.07, 5.82)	
Complete response (CR)	6 (2.5%)	1 (0.8%)
Partial response (PR)	26 (10.8%)	6 (5.0%)
Stable disease (SD)	55 (22.9%)	43 (35.5%)
Median time to response		
Months (range)	2.1 (1.8-7.4)	2.0 (1.9-4.6)
Median duration of response		
Months (range)	9.7 (2.8-20.3+)	4.0 (1.5+-8.5+)

[a] Derived from a stratified proportional hazards model.
[b] P-value is derived from a log-rank test stratified by prior cetuximab; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0227.
[c] In the nivolumab group there were two patients with CRs and seven patients with PRs who had tumour PD-L1 expression < 1%.

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

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to investigator's choice. The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumour PD-L1 expression levels (see Table 20).

Table 20: OS by tumour PD-L1 expression (CA209141)

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

In an exploratory post-hoc analysis using a non-validated assay, both tumour cell PD-L1 expression and tumour-associated immune cell (TAIC) PD-L1 expression were analysed in relation to the magnitude of treatment effect of nivolumab compared to investigator's choice. This analysis showed that not only tumour cell PD-L1 expression but also TAIC PD-L1 expression appeared to be associated with benefit from nivolumab relative to investigator's choice (see Table 21). 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 21: Efficacy by tumour cell and TAIC PD-L1 expression (CA209141)

	Median OS[a] (months) HR[b] (95% CI)		Median PFS[a] (months) HR[b] (95% CI)		ORR (%) (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

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 1.1 criteria. No prior systemic anti-cancer therapy for metastatic or surgically unresectable urothelial carcinoma was permitted. Prior neoadjuvant chemotherapy or prior adjuvant platinum-based chemotherapy following radical cystectomy were permitted as long as the disease recurrence took place ≥ 12 months from completion of therapy. Prior intravesical therapy was permitted if completed at least 4 weeks prior to initiation of study treatment. Radiation therapy (with or without chemotherapy) with curative intent was permitted if treatment was completed ≥ 12 months before enrolment. Palliative radiotherapy was permitted as long as it was completed at least 2 weeks prior to therapy.

A total of 608 patients were randomised to receive either nivolumab in combination with cisplatin and gemcitabine (n = 304) or cisplatin and gemcitabine (n = 304). Randomisation was stratified by tumour PD-L1 status (≥ 1% vs. < 1% or indeterminate) and liver metastasis (yes vs. no). The median age was 65 years of age (range: 32 to 86) with 51% of patients ≥ 65 years of age and 12% of patients ≥ 75 years of age, 23% were Asian, 72% were White, 0.3% were Black; 77% were male, 23% were female. Baseline ECOG performance status was 0 (53%) or 1 (46%). Patients in the nivolumab in combination with cisplatin and gemcitabine arm were treated with nivolumab 360 mg every three weeks, in combination with cisplatin and gemcitabine for up to 6 cycles, after which patients received nivolumab monotherapy 480 mg every 4 weeks for a total of up to 24 months. Patients received gemcitabine dosed at 1000 mg/m^2 IV over 30-minutes on Days 1 and 8 of the 3 week treatment cycle and cisplatin dosed at 70 mg/m^2 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 22 and Figures 18 and 19.

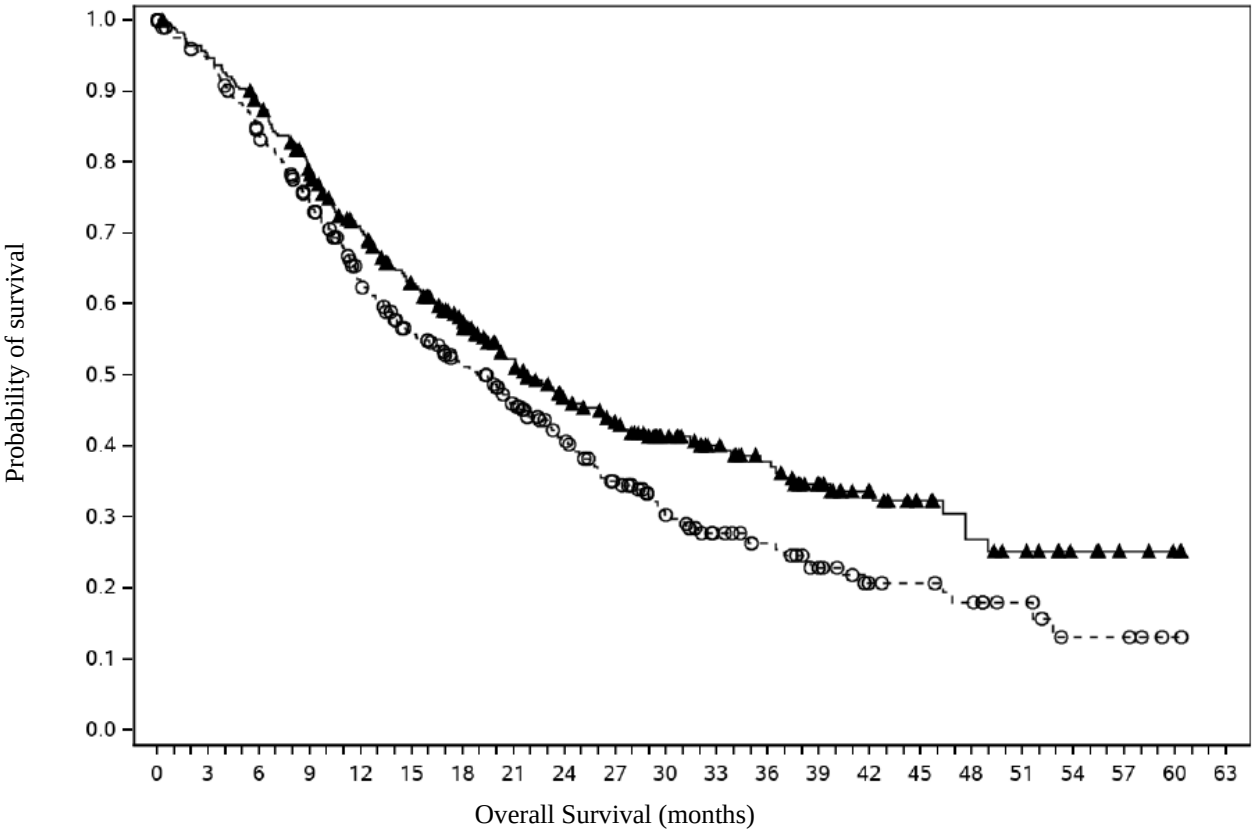
Table 22: Efficacy Results (CA209901)

	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 18: Kaplan Meier curves of OS (CA209901)



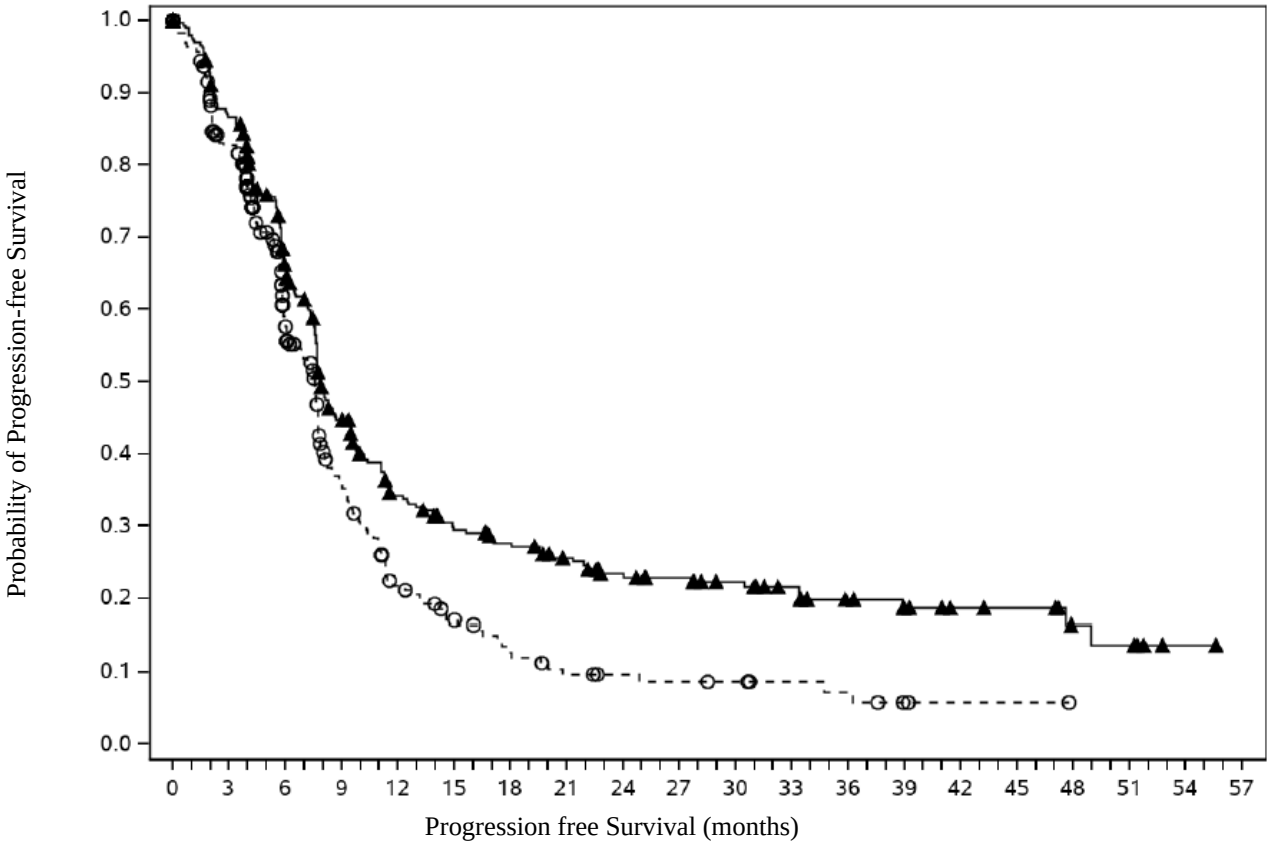
Number of subjects at risk

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 19: 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 22). 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.

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

Table 23: Efficacy results (CA209275)[a]

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

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

"+" denotes a censored observation.

[a] median follow-up 11.5 months.

[b] Data unstable due to the limited duration of response.
[c] included 4 drug-related deaths: 1 pneumonitis, 1 acute respiratory failure, 1 respiratory failure, and 1 cardiovascular failure.
NE: non-estimable

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

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.

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 ≥ 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 (≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 24 and Figure 20.

Table 24: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209274)

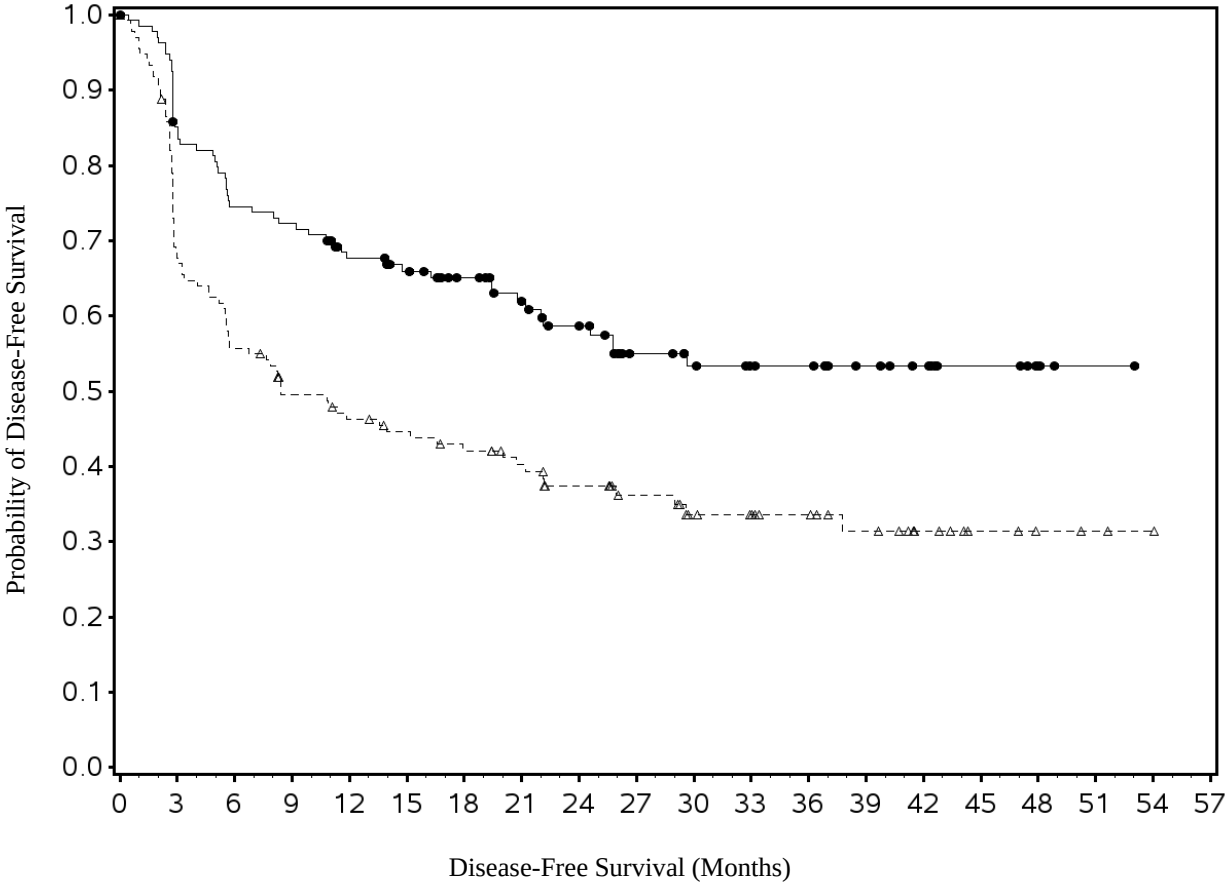
	nivolumab (n = 140)	**placebo** (n = 142)
Disease-Free Survival	Minimum follow-up 11.4 months	
Events (%)	56 (40.0)	85 (59.9)
Hazard ratio (95% CI)[a]	0.53 (0.38, 0.75)	
Median (95% CI) (months)[b]	NR (22.11, NE)	8.41 (5.59, 20.04)
Rate (95% CI) at 6 months	74.5 (66.2, 81.1)	55.7 (46.8, 63.6)
Rate (95% 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 20: Kaplan-Meier curves of DFS in patients with tumour cell PD-L1 expression ≥ 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

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 ≥ 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 ≥ 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.

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/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus followed by fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m^2 administered prior to mFOLFOX6 every 2 weeks; or FOLFIRI (irinotecan, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus and fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg on or cetuximab 500 mg/m^2 administered prior to FOLFIRI every 2 weeks. Treatment continued until disease progression, unacceptable toxicity, or for nivolumab in combination with ipilimumab up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Tumour assessments per RECIST v1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter until week 96, then every 16 weeks thereafter until week 146, and then every 24 weeks.

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

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

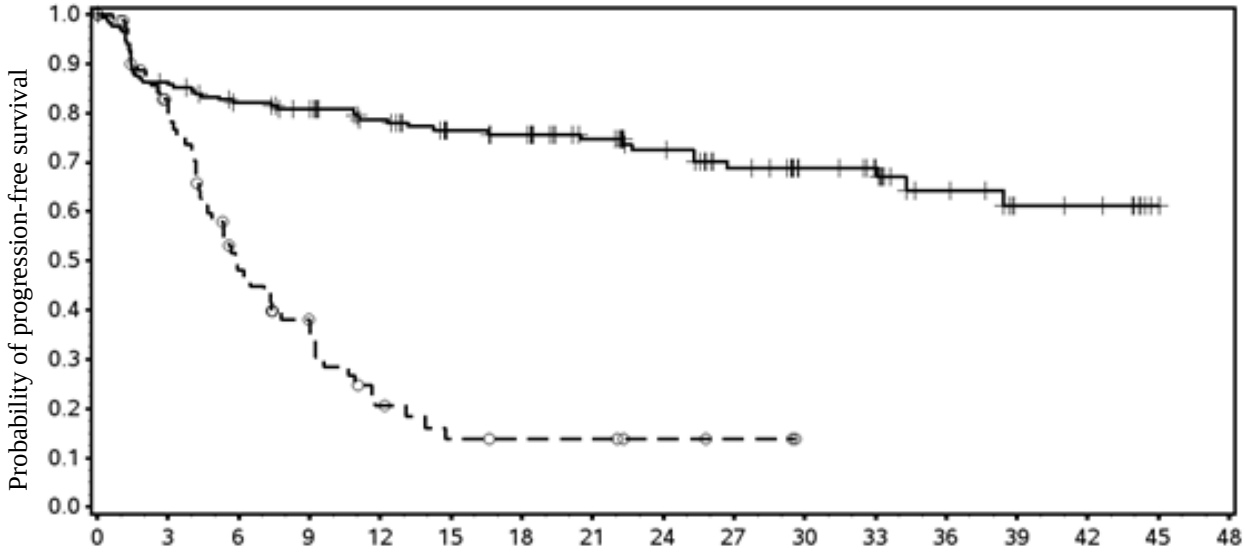
The study met the primary endpoint, at the planned interim analysis, demonstrating a statistically significant improvement in BICR assessed-PFS for patients with centrally confirmed MSI-H/dMMR in the nivolumab in combination with ipilimumab arm compared with the chemotherapy arm. The BICR-assessed PFS results are presented in Table 25 and Figure 21. 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 25: 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 21: Kaplan-Meier curve of PFS in first-line patients with MSI-H/dMMR centrally confirmed CRC (CA2098HW)



Number of subjects at risk

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

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

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

The safety and efficacy of nivolumab 3 mg/kg 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 26.

Table 26: 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 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/m^2 intravenously every 3 weeks, or paclitaxel (n = 144) 100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off. Randomisation was stratified by location (Japan vs. rest of world), number of organs with metastases (≤ 1 vs. ≥ 2) and tumour PD-L1 expression (≥ 1% vs. <1% or indeterminate). Treatment continued until disease progression, assessed by the investigator per RECIST version 1.1, or unacceptable toxicity. Tumour assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab with no rapid progression, investigator-assessed benefit, tolerance to treatment, stable performance status, and for whom treatment beyond progression would not delay an imminent intervention to prevent serious complications associated with disease progression (e.g. brain metastasis). The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed ORR and PFS. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at a predefined level of 1%. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Baseline characteristics were generally balanced between the two groups. The median age was 65 years (range: 33-87), 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 27 and Figure 22.

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.

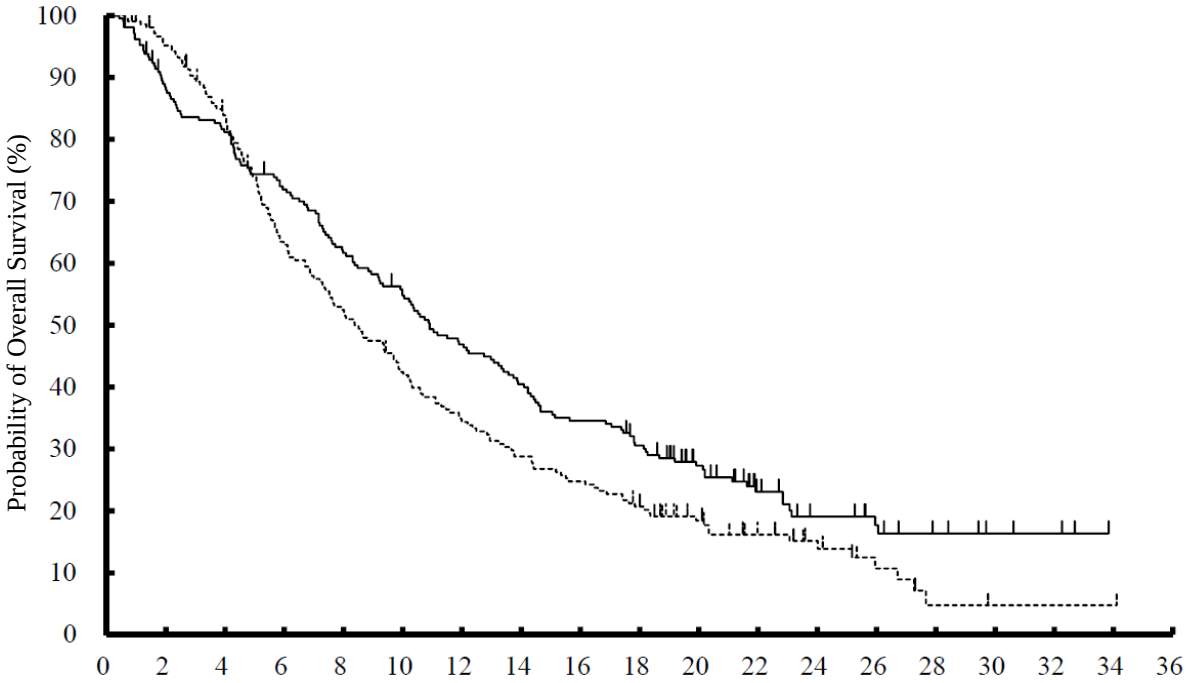
Table 27: Efficacy results (ONO-4538-24/CA209473)

	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)

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

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

Figure 22: Kaplan-Meier curves of OS (ONO-4538-24/CA209473)



Number of subjects at risk

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

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

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

negative OSCC subgroup, the HR for OS was 0.84 (95% CI: 0.62, 1.14) with median survivals of 10.9 and 9.3 months for the nivolumab and chemotherapy arms, respectively.

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 (≥ 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 ≥ 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/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle). Patients in the chemotherapy arm received fluorouracil 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 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 ≥ 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 ≥ 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 v1.1 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 ≥ 1%. Efficacy results are shown in Table 28.

Table 28: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209648)

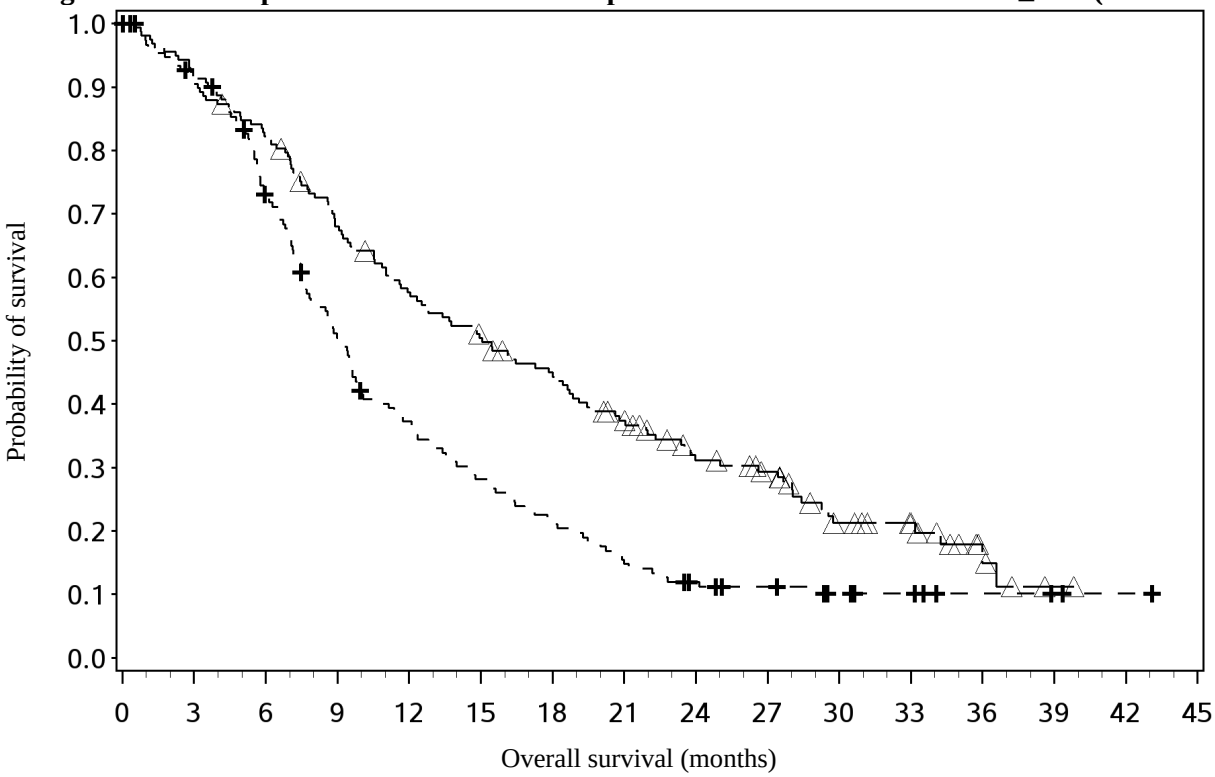
	nivolumab + chemotherapy (n = 158)	chemotherapy[a] (n = 157)
Overall survival		
Events	98 (62.0%)	121 (77.1%)
Hazard ratio (99.5% CI)[b]	0.54 (0.37, 0.80)	
p-value[c]	< 0.0001	
Median (95% CI) (months)[d]	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months[d]	58.0 (49.8, 65.3)	37.1 (29.2, 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)
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 23 and 24.

Figure 23: Kaplan-Meier curves of OS in patients with tumour cell PD-L1 ≥ 1% (CA209648)



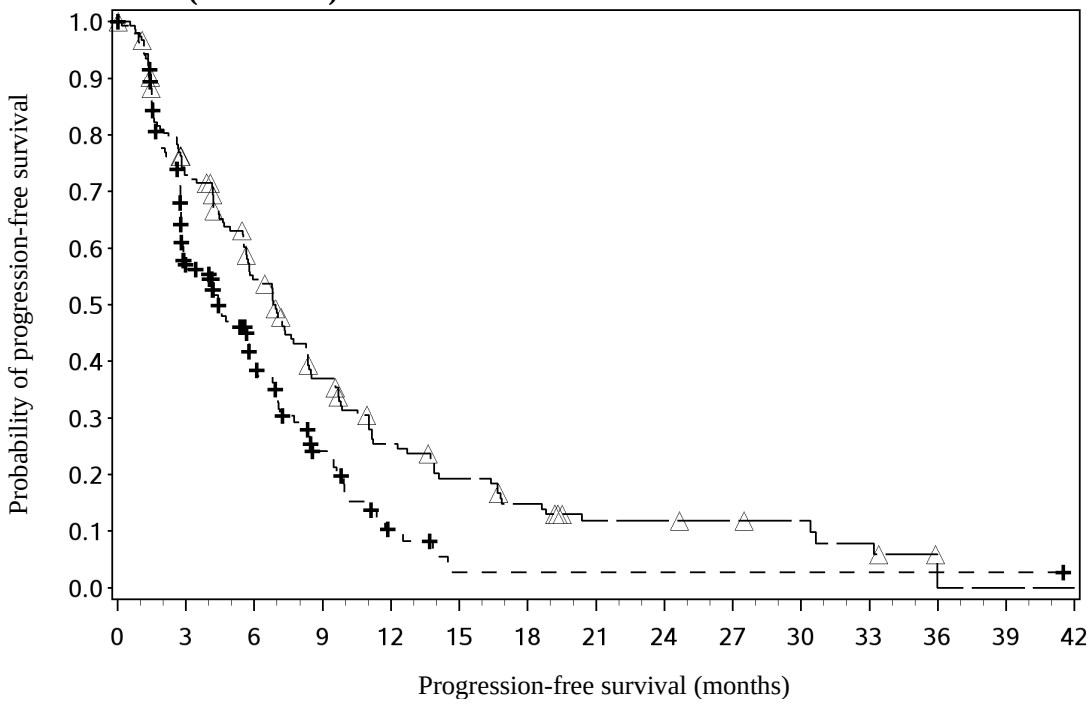
Number of subjects at risk

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 24: Kaplan-Meier curves of PFS in patients with tumour cell PD-L1 ≥ 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

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 (≥ 1% vs. < 1% or indeterminate or non-evaluable), pathologic lymph node status (positive ≥ 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% ≥ 65 years of age and 5% ≥ 75 years of years. The majority of patients were white (82%) and male (85 %). Baseline ECOG performance status was 0 (58%) or 1 (42%).

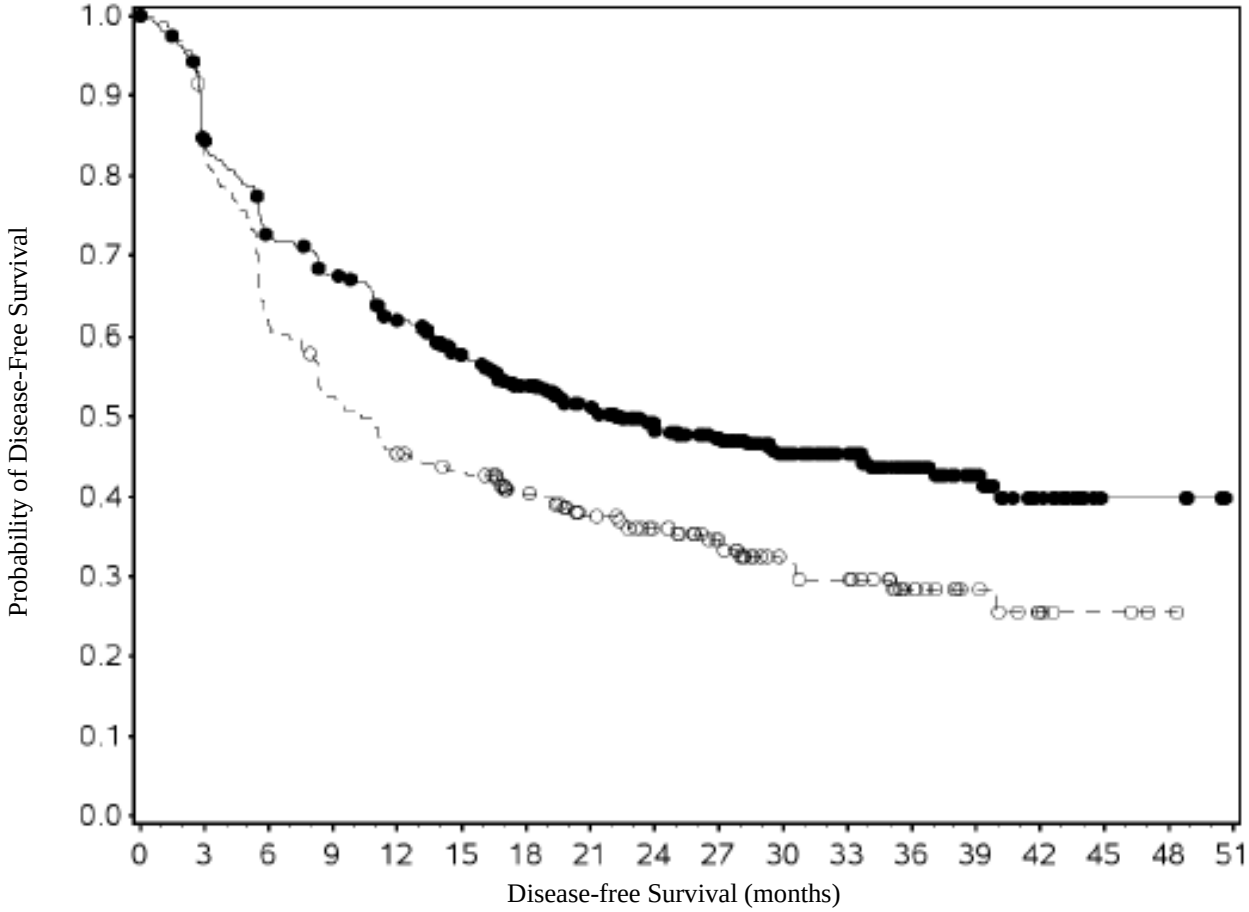
At the primary pre-specified interim analysis (minimum of 6.2 months and a median of 24.4 months follow-up), the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab compared with placebo. Median DFS as determined by the investigator was 22.41 months (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 29 and Figure 25.

Table 29: 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 25: 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

DFS benefit was observed regardless of histology and PD-L1 expression.

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 (≥ 1% vs. < 1% or indeterminate),

region (Asia vs. US vs. rest of world), ECOG performance status (0 vs. 1), and chemotherapy regimen. Chemotherapy consisted of FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

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

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

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

At an updated descriptive analysis with a minimum follow-up of 19.4 months, OS improvements were consistent with the primary analysis. Efficacy results are shown in Table 30, and Figures 26 and 27.

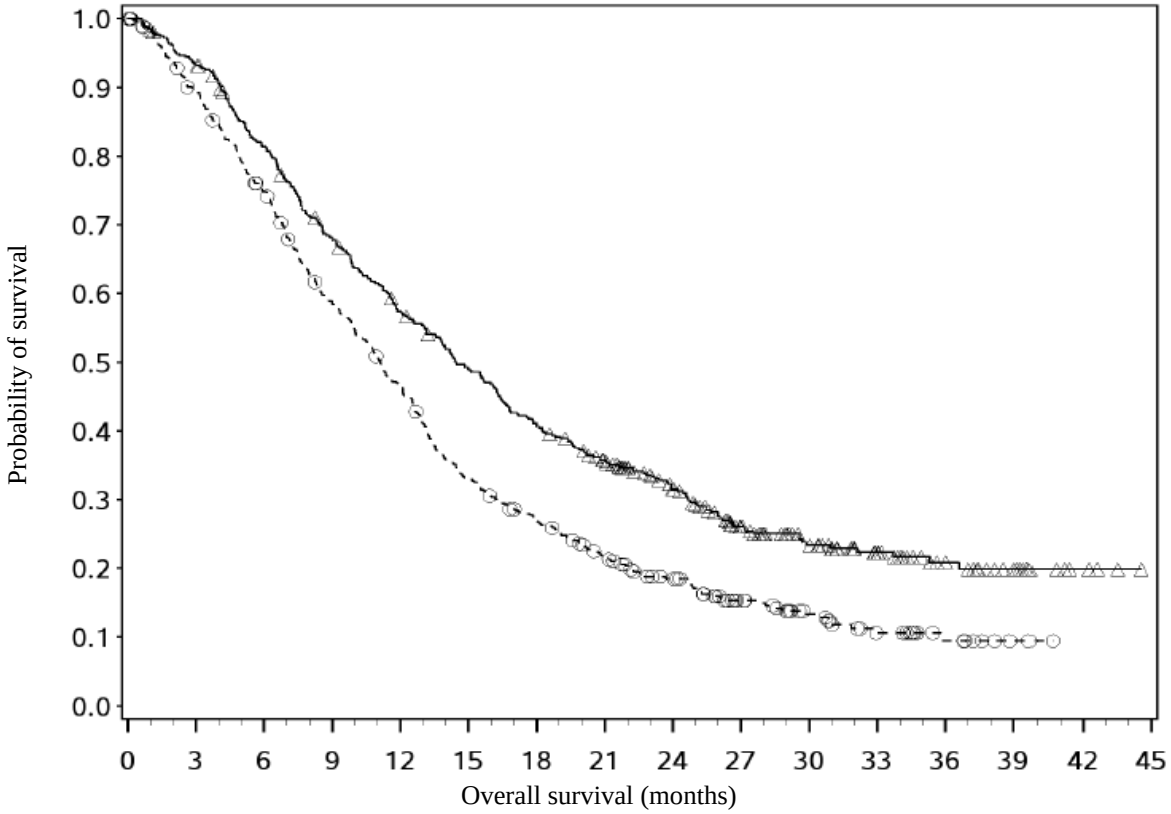
Table 30: Efficacy results in patients with PD-L1 CPS ≥ 5 (CA209649)

	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)

	nivolumab + chemotherapy (n = 473)	chemotherapy (n = 482)
Objective response rate, n[d,e]	227/378 (60%)	176/390 (45%)
(95% CI)	(54.9, 65.0)	(40.1, 50.2)
Complete response	12.2%	6.7%
Partial response	47.9%	38.5%
Duration of response[d,e]		
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 26: Kaplan-Meier curves of OS in patients with PD-L1 CPS ≥ 5 (CA209649)

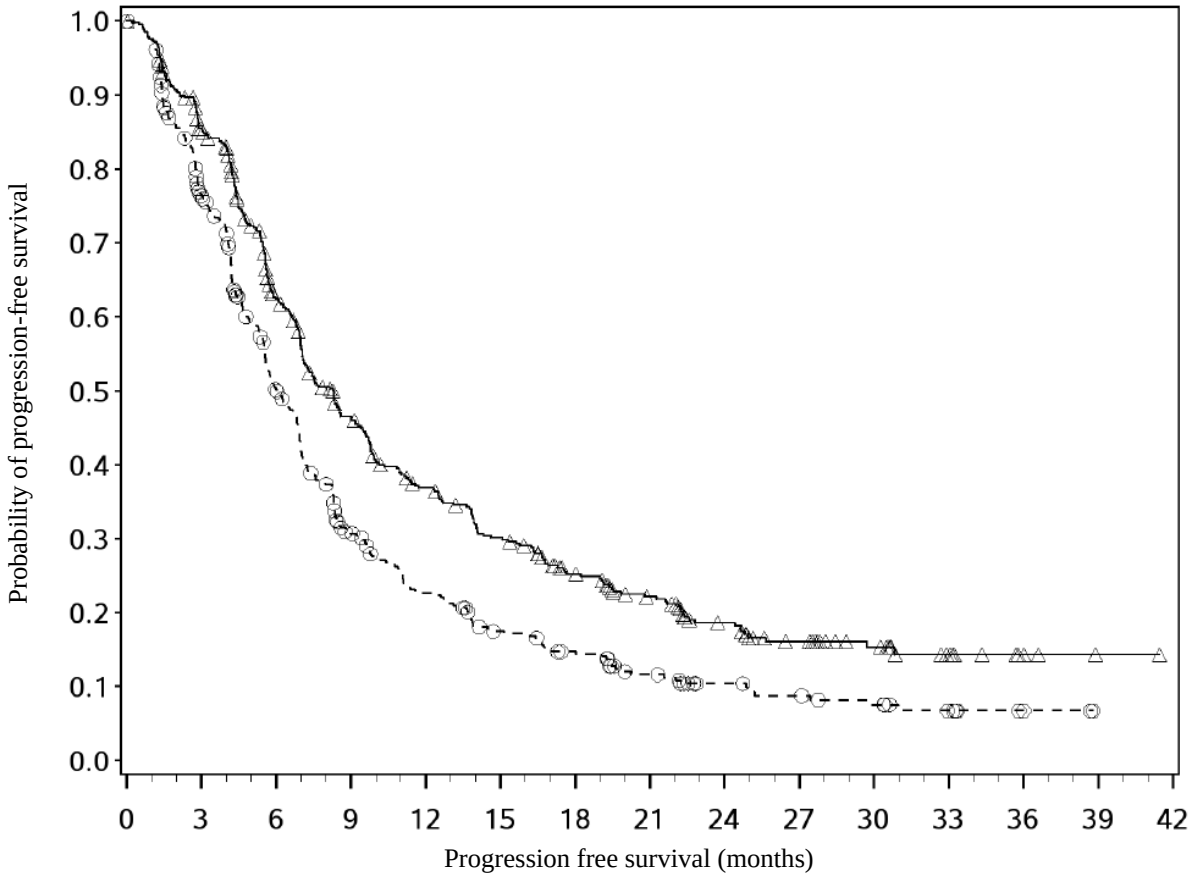


Number of subjects at risk

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 27: 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

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 (Cavgd28) 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_{minss}) 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 (Ka) 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 (Vss) 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 (CLss) of 7.18 mL/h (52.3%) in patients with RCC; the decrease in CLss is not considered clinically relevant.

The geometric mean (CV%) elimination half-life (t1/2) 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 m^2), 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 m^2; n = 379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 m^2; n = 179), or severe (GFR < 30 and ≥ 15 mL/min/1.73 m^2; n = 2) renal impairment compared to patients with normal renal function (GFR ≥ 90 mL/min/1.73 m^2; n = 342). 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 mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 92) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 804). No clinically important differences in the CL of nivolumab were found between patients with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in patients with moderate (total bilirubin > 1.5 × to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST) (see section 4.2).

5.3 Preclinical safety data

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

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

Fertility studies have not been performed with nivolumab.

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 injection

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

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.

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).

If a dose of 600 mg is to be administered, allow 1 vial to reach room temperature, then withdraw 5 mL of OPDIVO solution for injection into the syringe.

If a dose of 1200 mg is to be administered, allow 2 vials to reach room temperature, then withdraw 10 mL of OPDIVO solution for injection into the syringe.

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer of the biological active substance

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

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

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

- **Additional risk minimisation measures**

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

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

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

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

- Contact details of the OPDIVO prescriber

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

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

Description	Due date
1. Post authorisation efficacy study (PAES): In order to further elucidate the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab and ipilimumab, the MAH should conduct and submit the results of a randomised, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels. This study should be conducted according to an agreed protocol.	By 28th February 2027
2. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer, the MAH should submit the OS data from the second interim analysis and the final OS analysis of the Phase III study CA209577.	By 30th June 2025
3. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adults with muscle invasive urothelial carcinoma, the MAH should submit the OS data from the 2nd IA and the final OS analysis of the Phase 3 CA209274 study in the PD-L1 ≥ 1% population.	By 31st December 2027
4. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or stage IIC melanoma, the MAH should submit the OS data from the first interim OS analysis of the Phase III study CA20976K.	By 31st March 2029
5. Post authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of OPDIVO in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%, the MAH should submit the results of the final OS analysis from study CA20977T, a phase III, randomised, double-blind study.	By 30th June 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL concentrate for solution for infusion
nivolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of concentrate contains 10 mg of nivolumab.
Each vial of 4 mL contains 40 mg of nivolumab.
Each vial of 10 mL contains 100 mg of nivolumab.
Each vial of 12 mL contains 120 mg of nivolumab.
Each vial of 24 mL contains 240 mg of nivolumab.

3. LIST OF EXCIPIENTS

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

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

40 mg/4 mL
100 mg/10 mL
120 mg/12 mL
240 mg/24 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/001 40 mg vial
EU/1/15/1014/002 100 mg vial
EU/1/15/1014/003 240 mg vial
EU/1/15/1014/004 120 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 600 mg solution for injection
Nivolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 600 mg of nivolumab in 5 mL solution.
Each mL of solution for injection contains 120 mg of nivolumab.

3. LIST OF EXCIPIENTS

Excipients: recombinant human hyaluronidase (rHuPH20), histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80, methionine, water for injection. See leaflet for further information before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

600 mg/5 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use only.
For single use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL sterile concentrate
nivolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of concentrate contains 10 mg of nivolumab.
Each vial of 12 mL contains 120 mg of nivolumab.
Each vial of 24 mL contains 240 mg of nivolumab.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Sterile concentrate

120 mg/12 mL
240 mg/24 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/003 240 mg vial
EU/1/15/1014/004 120 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

OPDIVO 10 mg/mL sterile concentrate
nivolumab
IV use

2. METHOD OF ADMINISTRATION

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

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/4 mL
100 mg/10 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

OPDIVO 600 mg solution for injection
Nivolumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

600 mg/5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

OPDIVO 10 mg/mL concentrate for solution for infusion
nivolumab

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

What is in this leaflet

1. What OPDIVO is and what it is used for

OPDIVO is a medicine used to treat:
- advanced melanoma (a type of skin cancer) in adults and adolescents 12 years of age and older
- melanoma after complete resection in adults and adolescents 12 years of age and older (treatment after surgery is called adjuvant therapy)
- advanced non-small cell lung cancer (a type of lung cancer) in adults
- non-small cell lung cancer (a type of lung cancer) prior to resection in adults (treatment prior to surgery is called neoadjuvant therapy)
- non-small cell lung cancer (a type of lung cancer) prior to resection and after resection in adults (treatment prior to surgery is called neoadjuvant therapy; treatment after surgery is called adjuvant therapy)
- malignant pleural mesothelioma (a type of cancer that affects the lining of the lung) in adults
- advanced renal cell carcinoma (advanced kidney cancer) in adults
- classical Hodgkin lymphoma that has come back after or has not responded to previous therapies, including an autologous stem-cell transplant (a transplant of your own blood-producing cells) in adults
- advanced cancer of the head and neck in adults
- advanced urothelial carcinoma (bladder and urinary tract cancer) in adults
- urothelial carcinoma after complete resection in adults
- advanced colorectal cancer (colon or rectal cancer) in adults
- advanced oesophageal cancer (gullet cancer) in adults
- oesophageal (gullet) or gastro-oesophageal junction cancer with residual pathologic disease after chemoradiation followed by surgery in adults
- advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (stomach or gullet cancer) in adults
- unresectable or advanced hepatocellular carcinoma (liver cancer) in adults.

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

Nivolumab attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching

off your T cells. This helps increase their activity against the melanoma, lung, kidney, lymphoid, head and neck, bladder, colon, rectal, stomach, oesophageal or gastro-oesophageal junction cancer cells.

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

2. What you need to know before you use OPDIVO

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

Warnings and precautions
Talk to your doctor before using OPDIVO as it may cause:
- **Problems with your heart** such as a change in the rhythm or rate of the heartbeat or an abnormal heart rhythm.
- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Diarrhoea** (watery, loose or soft stools) or any symptoms of **inflammation of the intestines** (colitis), such as stomach pain and mucus or blood in stool.
- **Inflammation of the liver (hepatitis).** Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, or tiredness.
- **Inflammation or problems with your kidneys.** Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.
- **Problems with your hormone producing glands** (including the pituitary, the thyroid, the parathyroid and adrenal glands) that may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache, decreased blood levels of calcium and visual disturbances.
- **Diabetes** including a serious, sometimes life-threatening problem due to acid in the blood produced from diabetes (diabetic ketoacidosis). Symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, feeling tired or having difficulty thinking clearly, breath that smells sweet or fruity, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, feeling sick or being sick, stomach pain, and deep or fast breathing.
- **Inflammation of the skin** that can lead to severe skin reaction (known as toxic epidermal necrolysis and Stevens-Johnson syndrome). Signs and symptoms of severe skin reaction may include rash, itching, and peeling of the skin (possibly fatal).
- **Inflammation of the muscles** such as myocarditis (inflammation of the heart muscle), myositis (inflammation of the muscles) and rhabdomyolysis (stiffness in muscles and joints, muscle spasm). Signs and symptoms may include muscle pain, stiffness, weakness, chest pain, or severe fatigue.
- **Solid organ transplant rejection.**
- **Graft-versus-host disease.**
- **Haemophagocytic lymphohistiocytosis**. A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

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

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

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

OPDIVO acts on your immune system. It may cause inflammation in parts of your body. Your risk of these side effects may be higher if you already have an autoimmune disease (a condition where the body attacks its own cells). You may also experience frequent flares of your autoimmune disease, which in the majority of cases are mild.

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

Children and adolescents
OPDIVO should not be used in children and adolescents below 18 years of age except for adolescents 12 years of age and older with melanoma.

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

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

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

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

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

OPDIVO contains sodium
Tell your doctor if you are on a low-sodium (low-salt) diet before you are given OPDIVO. This medicine contains 2.5 mg sodium (main component of cooking/table salt) in each mL of concentrate. OPDIVO contains 10 mg sodium per 4 mL vial, 25 mg sodium per 10 mL vial, 30 mg sodium per 12 mL vial or 60 mg sodium per 24 mL vial, which is equivalent to 0.5%, 1.25%, 1.5% or 3% respectively, of the recommended maximum daily dietary intake of sodium for an adult.

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

3. How to use OPDIVO

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

When OPDIVO is given on its own, for the treatment of skin cancer in adolescents 12 years of age and older and weighing at least 50 kg, the recommended dose is either 240 mg given every 2 weeks or 480 mg given every 4 weeks. For adolescents 12 years of age and older and weighing less than 50 kg, the recommended dose is either 3 mg of nivolumab per kilogram of your body weight given every 2 weeks or 6 mg of nivolumab per kilogram of your body weight given every 4 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of skin cancer in adults and adolescents 12 years of age and older, the recommended dose of OPDIVO is 1 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter the recommended dose of OPDIVO (single-agent phase) is 240 mg given every 2 weeks or 480 mg given every 4 weeks in adults and adolescents 12 years of age and older and weighing at least 50 kg or 3 mg of nivolumab per kilogram of your body weight given every 2 weeks or 6 mg of nivolumab per kilogram of your body weight given every 4 weeks for adolescents 12 years of age and older and weighing less than 50 kg.

When OPDIVO is given in combination with ipilimumab for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced colon or rectal cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight or 240 mg for the first 4 doses (combination phase) depending on your treatment. Thereafter, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg every 4 weeks (single-agent phase) depending on your treatment.

When OPDIVO is given in combination with ipilimumab for the treatment of malignant pleural mesothelioma, the recommended dose of OPDIVO is 360 mg every 3 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of advanced oesophageal cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight every 2 weeks or 360 mg every 3 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of unresectable or advanced liver cancer, the recommended dose of OPDIVO is 1 mg of nivolumab per kilogram of your body weight for up to 4 doses (combination phase) depending on your treatment. Thereafter, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg every 4 weeks (single agent phase) depending on your treatment.

When OPDIVO is given in combination with chemotherapy for the neoadjuvant treatment of non-small cell lung cancer, the recommended dose of OPDIVO is 360 mg every 3 weeks.

When OPDIVO is given in combination with chemotherapy for the neoadjuvant and adjuvant treatment of non-small cell lung cancer, the recommended dose of OPDIVO is 360 mg every 3 weeks prior to resection and 480 mg every 4 weeks after surgery.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced oesophageal cancer, the recommended dose of OPDIVO is 240 mg every 2 weeks or 480 mg every 4 weeks.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the recommended dose of OPDIVO is 360 mg every 3 weeks or 240 mg every 2 weeks.

When OPDIVO is given in combination with chemotherapy for the treatment of urothelial carcinoma, the recommended dose of OPDIVO is 360 mg nivolumab every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks.

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

When OPDIVO is given in combination with cabozantinib for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg given every 4 weeks.

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

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

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

When OPDIVO is given in combination with ipilimumab for the treatment of skin, advanced kidney advanced colon or rectal cancer, or unresectable or advanced liver cancer you will be given an infusion over a period of 30 minutes, every 3 weeks for up to 4 doses (combination phase) depending on your treatment. Thereafter it will be given as an infusion over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of malignant pleural mesothelioma, you will be given an infusion over a period of 30 minutes, every 3 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of advanced oesophageal cancer, you will be given an infusion over a period of 30 minutes, every 2 or 3 weeks, depending on the dose you are receiving.

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

When OPDIVO is given after surgery as adjuvant treatment of non-small cell lung cancer, you will be given an infusion over a period of 30 minutes, every 4 weeks.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced oesophageal cancer, you will be given an infusion over a period of 30 minutes, every 2 or 4 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, you will be given an infusion over a period of 30 minutes every 3 weeks or every 2 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with chemotherapy for the treatment of urothelial carcinoma, you will be given an infusion over a period of 30 minutes every 2, 3 or 4 weeks, depending on the dose you are receiving.

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

When OPDIVO is given in combination with cabozantinib, you will be given an infusion over a period of 30 minutes or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving.

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

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

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

When OPDIVO is given in combination with other anti-cancer medicines, you will first be given OPDIVO followed by the other medicine.

Please refer to the package leaflet of these other medicines in order to understand the use of these medicines. If you have questions about them, please ask your doctor.

4. Possible side effects

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

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

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

Very common (may affect more than 1 in 10 people)
- Infections of the upper respiratory tract
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- Decreased appetite, high sugar levels in the blood (hyperglycaemia)
- Headache
- Shortness of breath (dyspnoea), cough

- Diarrhoea (watery, loose or soft stools), vomiting, nausea, stomach pain, constipation
- Skin rash sometimes with blisters, itching
- Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)
- Feeling tired or weak, fever

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), bronchitis
- Reactions related to the infusion of the medicine, allergic reaction (including life-threatening allergic reaction)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss), swelling of the thyroid gland
- Dehydration, decrease in body weight, low sugar levels in the blood (hypoglycaemia)
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness
- Blurred vision, dry eyes
- Fast heart rate, abnormal heart rhythm
- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs
- Inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), dry mouth
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning
- Inflammation of the joints (arthritis)
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, oedema (swelling)

Uncommon (may affect up to 1 in 100 people)
- Increase in some white blood cells
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, diabetes
- Increased acid levels in the blood (metabolic acidosis)
- Damage to nerves causing numbness and weakness (polyneuropathy), inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy)
- Inflammation of the eye (which causes pain and redness)
- Inflammation of the heart muscle, inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders), changes in the rhythm or rate of the heartbeat
- Fluid in the lungs
- Inflammation of the pancreas (pancreatitis), inflammation of the stomach (gastritis)
- Inflammation of the liver (hepatitis), blockage of bile ducts (cholestasis)
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis), skin condition of the face where the nose and cheeks are unusually red (rosacea), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), hives (itchy, bumpy rash)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)

Rare (may affect up to 1 in 1000 people)
- A temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- A disease causing the inflammation or enlargement of a lymph node (Kikuchi lymphadenitis)
- Acid in the blood produced from diabetes (diabetic ketoacidosis), decreased function of the parathyroid gland

- A temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome), loss of the protective sheath around nerves (demyelination), a condition in which the muscles become weak and tire easily (myasthenic syndrome), inflammation of the brain
- An inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Inflammatory disease of blood vessels
- Ulcer of the small intestines
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis or Stevens-Johnson syndrome)
- Disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), aching muscles, muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus or other lichen disorders)

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

Very common (may affect more than 1 in 10 people)
- Infections of the upper respiratory tract
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite, decrease in body weight, decreased levels of albumin in the blood, high (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), headache, dizziness, altered sense of taste
- High blood pressure (hypertension)
- Shortness of breath (dyspnoea), cough, abnormal speaking sound (dysphonia)
- Diarrhoea (watery, loose or soft stools), constipation, vomiting, nausea, stomach pain, mouth ulcers and cold sores (stomatitis), indigestion (dyspepsia)

- Skin rash sometimes with blisters, itching, pain of the hands or soles of the feet: rash or redness of the skin, tingling and tenderness developing to symmetrical redness, swelling and pain primarily on the palm of the hand and sole of the foot (palmar-plantar erythrodysaesthaesia syndrome)
- Pain in the joints (arthralgia), pain in the muscles and bones (musculoskeletal pain), muscle spasm
- Excess protein in urine
- Feeling tired or weak, fever, oedema (swelling)

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), bronchitis, inflammation of the eye (conjunctivitis)
- Increase in some white blood cells, decrease in neutrophils with fever
- Allergic reaction, reactions related to the infusion of the medicine
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- Dehydration, decreased levels of phosphate in the blood
- Sensations like numbness and tingling (paraesthesia)
- Hearing a persistent sound in your ear when no sound exists (tinnitus)
- Blurred vision, dry eye
- Fast heart rate, abnormal heart rhythm, inflammatory disease of blood vessels
- Formation of a blood clot within a blood vessel (thrombosis)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs, blood clots, nose bleeding
- Inflammation of the intestines (colitis), inflammation of the pancreas (pancreatitis), dry mouth, inflammation of the stomach (gastritis), oral pain, haemorrhoids (piles)
- Inflammation of the liver
- Skin colour change in patches (including vitiligo), redness of the skin, unusual hair loss or thinning, hair colour change, hives (itchy rash), discolouration or abnormal darkening of the skin (skin hyperpigmentation), dry skin
- Inflammation of the joints (arthritis), muscle weakness, aching muscles
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, chills
- Feeling generally unwell (malaise)

Uncommon (may affect up to 1 in 100 people)
- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- Increased acid levels in the blood
- A temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome); damage to nerves causing numbness and weakness (polyneuropathy); foot drop (peroneal nerve palsy); inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy); muscle weakness and tiredness without atrophy (myasthenia gravis or syndrome)
- Inflammation of the brain
- Inflammation of the eye (which causes pain and redness)
- Changes in the rhythm or rate of the heartbeat, slow heart rate, inflammation of the heart muscle
- Intestinal perforation, inflammation of the duodenum, burning or painful sensation in the tongue (glossodynia)
- Severe and possibly fatal peeling of the skin (Stevens-Johnson syndrome), skin disease with thickened patches of red skin, often with silvery scales (psoriasis), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (other lichen disorders)
- Muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, inflammation of the muscles causing pain or

stiffness (polymyalgia rheumatica), bone damage in the jaw, abnormal opening between two body parts, such as an organ or blood vessel and another structure (fistula)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

Rare (may affect up to 1 in 1000 people)
- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased function of the parathyroid gland
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- An inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Inflammation of the nerves
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus)
- Chronic disease of joints (spondyloarthropathy), disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), muscle spasm (rhabdomyolysis)
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)

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

Changes in test results
OPDIVO alone or in combination may cause changes in the results of tests carried out by your doctor. These include:
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- Increased or decreased amount of calcium or potassium
- Increased or decreased blood levels of magnesium or sodium

- Increased amount of thyroid stimulating hormone
- Increase in blood triglyceride levels in the blood
- Increase in cholesterol levels in the blood

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

5. How to store OPDIVO

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

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

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

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

6. Contents of the pack and other information

What OPDIVO contains
- The active substance is nivolumab.

Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.
Each vial contains either 40 mg (in 4 mL), 100 mg (in 10 mL), 120 mg (in 12 mL) or 240 mg (in 24 mL) of nivolumab.

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

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

It is available in packs containing either 1 vial of 4 mL, 1 vial of 10 mL, 1 vial of 12 mL or 1 vial of 24 mL.

Not all pack sizes may be marketed.

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

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

This leaflet was last revised in

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

The following information is intended for healthcare professionals only:

Preparation and administration of OPDIVO

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

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

Nivolumab monotherapy

The prescribed dose for adults is 240 mg or 480 mg given regardless of body weight depending on indication.

Melanoma (advanced or adjuvant treatment) in adolescents. The prescribed dose for adolescents 12 years of age and older weighing at least 50 kg is 240 mg or 480 mg. For adolescents 12 years of age and older and weighing less than 50 kg the prescribed dose is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given.

- The **total nivolumab dose** in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The **volume of OPDIVO concentrate** to prepare the dose (mL) = the total nivolumab dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

Nivolumab in combination with ipilimumab

The **prescribed dose** for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given (please see above).

Nivolumab in combination with ipilimumab in malignant pleural mesothelioma

The prescribed dose for the patient is 360 mg given regardless of body weight.

Nivolumab in combination with ipilimumab in advanced colorectal cancer

The prescribed dose for the patient can be based on body weight (3 mg/kg) or can be 240 mg given regardless of body weight.

Nivolumab in combination with ipilimumab in advanced oesophageal cancer

The prescribed dose for the patient can be based on body weight (3 mg/kg) or is 360 mg given regardless of body weight.

Nivolumab in combination with ipilimumab in unresectable or advanced liver cancer

The prescribed dose for the patient is based on body weight (1 mg/kg).

Nivolumab in combination with chemotherapy in resectable non-small cell lung cancer

The prescribed dose for the patient is 360 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in advanced oesophageal cancer

The prescribed dose for the patient is 240 mg or 480 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

The prescribed dose for the patient is 360 mg or 240 mg given regardless of body weight.

Nivolumab in combination with ipilimumab and chemotherapy

The prescribed dose for the patient is 360 mg given regardless of body weight.

Nivolumab in combination with cabozantinib

The prescribed dose for the patient is nivolumab 240 mg or 480 mg given regardless of body weight.

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

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

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

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

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

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

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

Administer the OPDIVO infusion **intravenously over a period of 30 or 60 minutes depending on the dose and the indication**.

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

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

OPDIVO infusion is compatible with:
- PVC containers
- Polyolefin containers
- Glass bottles
- PVC infusion sets
- In-line filters with polyethersulfone membranes with pore sizes of 0.2 μm to 1.2 μm.

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

Storage conditions and shelf life

Unopened vial

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

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

OPDIVO infusion

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

Infusion preparation	**Chemical and physical in-use stability**	
	Storage at 2ºC to 8ºC protected from light	**Storage at room temperature (≤ 25°C) and room light**
Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection	30 days	24 hours (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	7 days	8 hours (of total 7 days storage)

From a microbiological point of view the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2°C to 8°C or 8 hours (of the total 7 days of storage) at room temperature (≤ 25°C). Aseptic handling should be ensured during the preparation of infusion.

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

Package leaflet: Information for the user

OPDIVO 600 mg solution for injection
nivolumab

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

What is in this leaflet

1. What OPDIVO is and what it is used for

OPDIVO is a medicine used to treat:
- advanced melanoma (a type of skin cancer) in adults
- melanoma after complete resection in adults (treatment after surgery is called adjuvant therapy)
- advanced non-small cell lung cancer (a type of lung cancer) in adults
- advanced renal cell carcinoma (advanced kidney cancer) in adults
- advanced cancer of the head and neck in adults
- advanced urothelial carcinoma (bladder and urinary tract cancer) in adults
- urothelial carcinoma after complete resection in adults
- advanced colorectal cancer (colon or rectal cancer) in adults
- advanced oesophageal cancer (gullet cancer) in adults
- oesophageal (gullet) or gastro-oesophageal junction cancer with residual pathologic disease after chemoradiation followed by surgery in adults
- advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (stomach or gullet cancer) in adults.

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

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

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

2. What you need to know before you use OPDIVO

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

Warnings and precautions
Talk to your doctor before using OPDIVO as it may cause:
- **Problems with your heart** such as a change in the rhythm or rate of the heartbeat or an abnormal heart rhythm.
- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Diarrhoea** (watery, loose or soft stools) or any symptoms of **inflammation of the intestines** (colitis), such as stomach pain and mucus or blood in stool.
- **Inflammation of the liver (hepatitis).** Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, or tiredness.
- **Inflammation or problems with your kidneys.** Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.
- **Problems with your hormone producing glands** (including the pituitary, the thyroid, the parathyroid and adrenal glands) that may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache, decreased blood levels of calcium and visual disturbances.
- **Diabetes** including a serious, sometimes life-threatening problem due to acid in the blood produced from diabetes (diabetic ketoacidosis). Symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, feeling tired or having difficulty thinking clearly, breath that smells sweet or fruity, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, feeling sick or being sick, stomach pain, and deep or fast breathing.
- **Inflammation of the skin** that can lead to severe skin reaction (known as toxic epidermal necrolysis and Stevens-Johnson syndrome). Signs and symptoms of severe skin reaction may include rash, itching, and peeling of the skin (possibly fatal).
- **Inflammation of the muscles** such as myocarditis (inflammation of the heart muscle), myositis (inflammation of the muscles) and rhabdomyolysis (stiffness in muscles and joints, muscle spasm). Signs and symptoms may include muscle pain, stiffness, weakness, chest pain, or severe fatigue.
- **Solid organ transplant rejection.**
- **Graft-versus-host disease.**
- **Haemophagocytic lymphohistiocytosis**. A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

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

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

Check with your doctor or nurse before you are given OPDIVO if:
- you have an **autoimmune disease** (a condition where the body attacks its own cells);
- you have **melanoma of the eye**;

- you were previously given ipilimumab, another medicine for treating melanoma, and experienced **serious side effects** because of that medicine;
- you have been told that your **cancer has spread to your brain;**
- you have any history of **inflammation of the lungs**;
- you have been taking **medicines to suppress your immune system.**

OPDIVO acts on your immune system. It may cause inflammation in parts of your body. Your risk of these side effects may be higher if you already have an autoimmune disease (a condition where the body attacks its own cells). You may also experience frequent flares of your autoimmune disease, which in the majority of cases are mild.

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

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

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

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

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

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

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

OPDIVO contains polysorbate 80 (E433)
This medicine contains 2.5 mg of polysorbate 80 in each 5 mL vial which is equivalent to 5 mg/10 mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

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

3. How to use OPDIVO

How much OPDIVO is given
When OPDIVO is given on its own as an injection under your skin (subcutaneous injection), the recommended dose is either 600 mg given every 2 weeks or 1200 mg given every 4 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of skin cancer, the recommended dose of OPDIVO given as an infusion into a vein is 1 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter, the recommended dose of OPDIVO given as an injection under your skin is 600 mg every 2 weeks or 1200 mg every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced kidney cancer, the recommended dose of OPDIVO given as an infusion into a vein is 3 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter, the recommended dose of OPDIVO given as an injection under your skin is 600 mg every 2 weeks or 1200 mg every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced colon or rectal cancer, the recommended dose of OPDIVO given as an infusion into a vein is 3 mg of nivolumab per kilogram of your body weight or 240 mg for the first 4 doses (combination phase) depending on your treatment. Thereafter, the recommended dose of OPDIVO given as an injection under your skin is 600 mg every 2 weeks or 1200 mg every 4 weeks (single-agent phase) depending on your treatment.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced oesophageal cancer, the recommended dose of OPDIVO is 600 mg every 2 weeks or 1200 mg every 4 weeks as an injection under your skin.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the recommended dose of OPDIVO is 600 mg every 2 weeks as an injection under your skin.

When OPDIVO is given in combination with chemotherapy for the treatment of urothelial carcinoma, the recommended dose of OPDIVO given as an infusion into a vein is 360 mg nivolumab every 3 weeks for up to 6 cycles (combination phase). Thereafter, the recommended dose of OPDIVO given as an injection under your skin is either 600 mg every 2 weeks **or** 1200 mg every 4 weeks (single-agent phase).

When OPDIVO is given in combination with cabozantinib for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 600 mg given every 2 weeks or 1200 mg given every 4 weeks as an injection under your skin.

How OPDIVO is given
You will receive treatment with OPDIVO under the supervision of an experienced doctor. More than one vial of OPDIVO may be necessary to obtain the required dose.

OPDIVO is given as an injection under the skin of the abdomen or thigh over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving. Treatment with OPDIVO will continue for as long as you keep benefitting from it or until you no longer tolerate the treatment.

When OPDIVO is given in combination with ipilimumab for the treatment of skin, advanced kidney or advanced colon or rectal cancer, you will be given an infusion over a period of 30 minutes, every 3 weeks for the first 4 doses (combination phase). Thereafter, it will be given as an injection under the skin of the abdomen or thigh over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with chemotherapy for the treatment of advanced oesophageal cancer, it will be given over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving.

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, it will be given over a period of 3 to 5 minutes every 2 weeks.

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with chemotherapy for the treatment of urothelial carcinoma, it will be given over a period of 3 to 5 minutes every 2 or 4 weeks, depending on the dose you are receiving.

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with cabozantinib, it will be given over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving.

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

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

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

When OPDIVO is given in combination with other anti-cancer medicines, you will first be given OPDIVO followed by the other medicine.

Please refer to the package leaflet of these other medicines in order to understand the use of these medicines. If you have questions about them, please ask your doctor.

4. Possible side effects

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

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

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

Very common (may affect more than 1 in 10 people)
- Infections of the upper respiratory tract
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- Decreased appetite, high sugar levels in the blood (hyperglycaemia)
- Headache
- Shortness of breath (dyspnoea), cough
- Diarrhoea (watery, loose or soft stools), vomiting, nausea, stomach pain, constipation
- Skin rash sometimes with blisters, itching
- Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)
- Feeling tired or weak, fever

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), bronchitis
- Reactions related to the infusion of the medicine, allergic reaction, (including life-threatening allergic reaction)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss), swelling of the thyroid gland
- Dehydration, decrease in body weight, low sugar levels in the blood (hypoglycaemia)
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness
- Blurred vision, dry eyes
- Fast heart rate, abnormal heart rhythm
- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs
- Inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), dry mouth
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning
- Inflammation of the joints (arthritis)
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, oedema (swelling)
- Reaction at site of injection

Uncommon (may affect up to 1 in 100 people)
- Increase in some white blood cells
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, diabetes
- Increased acid levels in the blood (metabolic acidosis)
- Damage to nerves causing numbness and weakness (polyneuropathy), inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy)
- Inflammation of the eye (which causes pain and redness)
- Inflammation of the heart muscle, inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders), changes in the rhythm or rate of the heartbeat
- Fluid in the lungs
- Inflammation of the pancreas (pancreatitis), inflammation of the stomach (gastritis)
- Inflammation of the liver (hepatitis), blockage of bile ducts (cholestasis)
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis), skin condition of the face where the nose and cheeks are unusually red (rosacea), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), hives (itchy, bumpy rash)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)

Rare (may affect up to 1 in 1 000 people)
- A temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- A disease causing the inflammation or enlargement of a lymph node (Kikuchi lymphadenitis)
- Acid in the blood produced from diabetes (diabetic ketoacidosis), decreased function of the parathyroid gland
- A temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome), loss of the protective sheath around nerves (demyelination), a condition in which the muscles become weak and tire easily (myasthenic syndrome), inflammation of the brain

- An inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Inflammatory disease of blood vessels
- Ulcer of the small intestines
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis or Stevens-Johnson syndrome)
- Disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), aching muscles, muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus or other lichen disorders)

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

Very common (may affect more than 1 in 10 people)
- Infections of the upper respiratory tract
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite, decrease in body weight, decreased levels of albumin in the blood, high (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), headache, dizziness, altered sense of taste
- High blood pressure (hypertension)
- Shortness of breath (dyspnoea), cough, abnormal speaking sound (dysphonia)
- Diarrhoea (watery, loose or soft stools), constipation, vomiting, nausea, stomach pain, mouth ulcers and cold sores (stomatitis), indigestion (dyspepsia)
- Skin rash sometimes with blisters, itching, pain of the hands or soles of the feet: rash or redness of the skin, tingling and tenderness developing to symmetrical redness, swelling and pain primarily on the palm of the hand and sole of the foot (palmar-plantar erythrodysaesthaesia syndrome)

- Pain in the joints (arthralgia), pain in the muscles and bones (musculoskeletal pain), muscle spasm
- Excess protein in urine
- Feeling tired or weak, fever, oedema (swelling)

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), bronchitis, inflammation of the eye (conjunctivitis)
- Increase in some white blood cells, decrease in neutrophils with fever
- Allergic reaction, reactions related to the infusion of the medicine
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- Dehydration, decreased levels of phosphate in the blood
- Sensations like numbness and tingling (paraesthesia)
- Hearing a persistent sound in your ear when no sound exists (tinnitus)
- Blurred vision, dry eye
- Fast heart rate, abnormal heart rhythm, inflammatory disease of blood vessels
- Formation of a blood clot within a blood vessel (thrombosis)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs, blood clots, nose bleeding
- Inflammation of the intestines (colitis), inflammation of the pancreas (pancreatitis), dry mouth, inflammation of the stomach (gastritis), oral pain, haemorrhoids (piles)
- Inflammation of the liver
- Skin colour change in patches (including vitiligo), redness of the skin, unusual hair loss or thinning, hair colour change, hives (itchy rash), discolouration or abnormal darkening of the skin (skin hyperpigmentation), dry skin
- Inflammation of the joints (arthritis), muscle weakness, aching muscles
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, chills
- Feeling generally unwell (malaise)

Uncommon (may affect up to 1 in 100 people)
- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- Increased acid levels in the blood
- A temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome); damage to nerves causing numbness and weakness (polyneuropathy); foot drop (peroneal nerve palsy); inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy); muscle weakness and tiredness without atrophy (myasthenia gravis or syndrome), inflammation of the brain
- Inflammation of the eye (which causes pain and redness)
- Changes in the rhythm or rate of the heartbeat, slow heart rate, inflammation of the heart muscle
- Intestinal perforation, inflammation of the duodenum, burning or painful sensation in the tongue (glossodynia)
- Severe and possibly fatal peeling of the skin (Stevens-Johnson syndrome), skin disease with thickened patches of red skin, often with silvery scales (psoriasis), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (other lichen disorders)
- Muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica), bone damage in the jaw, abnormal opening between two body parts, such as an organ or blood vessel and another structure (fistula)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

Rare (may affect up to 1 in 1 000 people)
- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Decreased function of the parathyroid gland
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- An inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Inflammation of the nerves
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus)
- Chronic disease of joints (spondyloarthropathy), disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), muscle spasm (rhabdomyolysis)
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)

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

Changes in test results
OPDIVO alone or in combination may cause changes in the results of tests carried out by your doctor. These include:
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- Increased or decreased amount of calcium or potassium
- Increased or decreased blood levels of magnesium or sodium
- Increased amount of thyroid stimulating hormone
- Increase in blood triglyceride levels in the blood
- Increase in cholesterol levels in the blood

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

5. How to store OPDIVO

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

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

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

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

6. Contents of the pack and other information

What OPDIVO contains
- The active substance is nivolumab.

Each mL of solution for injection contains 120 mg of nivolumab.
Each vial contains 600 mg (in 5 mL) of nivolumab.

The other ingredients are recombinant human hyaluronidase (rHuPH20), histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80 (E433), methionine, and water for injection (see section 2 “OPDIVO contains polysorbate 80 (E433)”).

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

It is available in packs containing 1 glass vial of 5 mL.

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

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

This leaflet was last revised in

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

The following information is intended for healthcare professionals only:

To prevent medication errors, it is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) is being given to the patient as prescribed.

Preparation and administration of OPDIVO

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

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

Nivolumab monotherapy
The prescribed dose for the patient is 600 mg or 1200 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in advanced oesophageal cancer
The prescribed dose for the patient is 600 mg or 1200 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma
The prescribed dose for the patient is 600 mg given regardless of body weight.

Nivolumab in combination with cabozantinib
The prescribed dose for the patient is nivolumab 600 mg or 1200 mg given regardless of body weight.

Preparing the injection
- Inspect the vial of OPDIVO solution for injection for particulate matter or discolouration. Do not shake the vial. OPDIVO solution for injection is a clear to opalescent, colourless to yellow liquid. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Allow the vial or vials (depending on the prescribed dose) to reach room temperature.
- Withdraw the required volume of OPDIVO solution for injection using an appropriate sterile syringe and transfer needle.

Administration
OPDIVO solution for injection must not be administered intravenously.

Administer the OPDIVO solution for injection subcutaneously via a 23G-25G hypodermic needle or subcutaneous administration set (e.g., winged/butterfly) **over a period of 3 to 5 minutes** into the subcutaneous tissue of the abdomen or thigh.

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 is interrupted, continue administering at the same site, or at an alternate site.

Do not administer other subcutaneous medicines at the same site used for OPDIVO solution for injection.

OPDIVO solution for injection is compatible with:
- Polypropylene
- Polycarbonate
- Polyethylene
- Polyurethane
- Polyvinyl chloride
- Fluorinated ethylene propylene
- Stainless steel

Storage conditions and shelf life

Unopened vial

OPDIVO must be **stored in a refrigerator** (2°C to 8°C). The vials must be kept in the original package in order to protect from light. OPDIVO should not be frozen.

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

Storage in the syringe

From a microbiological point of view, once transferred from the vial to the syringe, the medicinal product should be used immediately since the medicine 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.

Disposal

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