AUSTRALIAN PRODUCT INFORMATION
OPDIVO® SC (NIVOLUMAB)

1 NAME OF THE MEDICINE

Nivolumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL vial of OPDIVO SC contains 600 mg nivolumab.

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

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear to very opalescent, colourless to yellow liquid. Essentially free of visible particulates. The solution has a pH of 5.5-6.5.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MELANOMA

OPDIVO SC, as monotherapy, is indicated for the adjuvant treatment of adult patients with completely resected Stage IIB, IIC, III or IV melanoma.

OPDIVO SC, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic melanoma.

OPDIVO SC, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic melanoma following treatment with intravenous OPDIVO and ipilimumab combination therapy. The approval of this indication is based on a pre-specified comparison to ipilimumab monotherapy. All analyses comparing nivolumab monotherapy with the nivolumab/ipilimumab combination are descriptive.

NON-SMALL CELL LUNG CANCER (NSCLC)

OPDIVO SC, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of adult patients with resectable non-small cell lung cancer (NSCLC).

OPDIVO SC, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of adult patients with resectable (tumours ≥4cm or node positive) non-small cell lung cancer and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by OPDIVO SC as a single agent in the adjuvant setting after surgical resection.

OPDIVO SC, as monotherapy, is indicated for the treatment of adult patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy.

OPDIVO SC, as monotherapy, is indicated for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, OPDIVO SC should be used after progression on or after targeted therapy.

RENAL CELL CARCINOMA (RCC)

OPDIVO SC, as monotherapy, is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma following combination treatment with intravenous OPDIVO and ipilimumab.

OPDIVO SC, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma.

OPDIVO SC, as monotherapy, is indicated for the treatment of adult patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy.

SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)

OPDIVO SC, as monotherapy, is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adult patients progressing on or after platinum based therapy.

UROTHELIAL CARCINOMA (UC)

OPDIVO SC, as monotherapy, is indicated for the adjuvant treatment of adult patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC.

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

OPDIVO SC, as monotherapy, is indicated for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval of this indication is based on objective response rate and duration of response in a single arm study.

HEPATOCELLULAR CARCINOMA (HCC)

OPDIVO SC, as monotherapy, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma following combination treatment with intravenous OPDIVO and ipilimumab.

OPDIVO SC, as monotherapy, is indicated for the treatment of adult patients with hepatocellular carcinoma after prior sorafenib therapy. This indication is approved based on objective response rate and duration of response in a single arm study. An improvement in survival or disease-related symptoms has not been established.

OESOPHAGEAL SQUAMOUS CELL CARCINOMA (OSCC)

OPDIVO SC, 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% as determined by a validated test.

OPDIVO SC, 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 chemotherapy.

ADJUVANT OESOPHAGEAL CANCER (OC) OR GASTRO-OESOPHAGEAL JUNCTION CANCER (GOJC)

OPDIVO SC, as monotherapy, is indicated for the adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer in adult patients who have received neoadjuvant chemoradiotherapy.

GASTRIC CANCER (GC), GASTRO-OESOPHAGEAL JUNCTION CANCER (GOJC), OR OESOPHAGEAL ADENOCARCINOMA (OAC)

OPDIVO SC, 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 or gastro-oesophageal junction or oesophageal adenocarcinoma.

MICROSATELLITE INSTABILITY HIGH (MSI-H) OR MISMATCH REPAIR DEFICIENT (DMMR) COLORECTAL CANCER (CRC)

OPDIVO SC, as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic colorectal cancer (CRC) that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) as determined by a validated test following combination treatment with intravenous OPDIVO and ipilimumab.

4.2 DOSE AND METHOD OF ADMINISTRATION

OPDIVO SC has different dosage and administration instructions than intravenous nivolumab.

OPDIVO SC is for subcutaneous use only in the abdomen or thigh.

OPDIVO SC is to be administered by a healthcare professional only.

Do not administer intravenously.

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

Adult patients currently receiving intravenous OPDIVO monotherapy, or in combination with chemotherapy or cabozantinib, may transition to OPDIVO SC.

OPDIVO SC is not indicated in combination with ipilimumab. After completion of a maximum of four doses of intravenous OPDIVO and ipilimumab combination therapy, patients may transition to OPDIVO SC as a single agent.

If specified in the indication, patient selection for treatment with OPDIVO SC based on the relevant biomarker (tumour cell PD-L1 expression/MSI-H/dMMR status) should be confirmed by a validated test (see Sections 4.1, 4.4, and 5.1).

Dose escalation or reduction is not recommended for OPDIVO SC. Guidelines for permanent discontinuation or withholding of doses are described in Table 3. Detailed guidelines for the management of immune-related adverse reactions are described in Section 4.4 Special warnings and precautions for use.

Nivolumab was originally developed using an every-two-weeks monotherapy dosing regimen (see Section 5.1 Pharmacodynamic Properties – Clinical Trials). Subsequent approval of the every-four-weeks monotherapy dosing regimen was based on pharmacokinetic and exposure-response modelling and simulations, with supporting clinical safety data. Data from randomised controlled trials of every-two-weeks versus every-four-weeks dosing of nivolumab, with sufficient sample size to demonstrate non-inferiority using clinical endpoint data (such as PFS or OS), is not available.

RECOMMENDED DOSES

The recommended doses of OPDIVO SC as a single agent are presented in Table 1.

Table 1 Recommended Doses for OPDIVO SC as Monotherapy

<table>
<tr><th>Indication^</th><th>Recommended OPDIVO SC Dosage</th><th>Duration of Therapy</th></tr>
<tr><td rowspan="2">Unresectable or metastatic melanoma</td><td>As monotherapy:
600 mg nivolumab* every 2 weeks
or
1200 mg nivolumab* every 4 weeks</td><td>Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated.</td></tr>
<tr><td>As monotherapy following 4 doses of intravenous OPDIVO and ipilimumab combination therapy:
600 mg nivolumab* every 2 weeks†
or
1200 mg nivolumab* every 4 weeks†</td><td>After completing 4 doses of intravenous OPDIVO and ipilimumab combination therapy, administer OPDIVO SC as single agent as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.</td></tr>
<tr><td>Locally advanced or metastatic squamous non-small cell lung cancer</td><td rowspan="6">600 mg nivolumab* every 2 weeks
or
1200 mg nivolumab* every 4 weeks</td><td rowspan="6">Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated.</td></tr>
<tr><td>Locally advanced or metastatic non-squamous non-small cell lung cancer</td></tr>
<tr><td>Recurrent or metastatic squamous cell carcinoma of the head and neck</td></tr>
<tr><td>Unresectable or metastatic urothelial carcinoma</td></tr>
<tr><td>Previously treated hepatocellular carcinoma</td></tr>
<tr><td>Oesophageal squamous cell carcinoma</td></tr>
<tr><td rowspan="2">Advanced renal cell carcinoma</td><td>As monotherapy:
600 mg nivolumab* every 2 weeks
or
1200 mg nivolumab* every 4 weeks</td><td>Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated.</td></tr>
<tr><td>As monotherapy following 4 doses of intravenous OPDIVO and ipilimumab combination therapy:
600 mg nivolumab* every 2 weeks
or
1200 mg nivolumab* every 4 weeks</td><td>After completing 4 doses of intravenous OPDIVO and ipilimumab combination therapy, administer OPDIVO SC as single agent as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.</td></tr>
</table>

Indication^	Recommended OPDIVO SC Dosage	Duration of Therapy
Unresectable or metastatic hepatocellular carcinoma	600 mg nivolumab* every 2 weeks or 1200 mg nivolumab* every 4 weeks	After completing a maximum 4 doses of intravenous OPDIVO and ipilimumab combination therapy, administer OPDIVO SC as a single agent until disease progression, is no longer tolerated, or up to 2 years.
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) Colorectal Cancer	600 mg nivolumab* every 2 weeks# or 1200 mg nivolumab* every 4 weeks#	
Adjuvant treatment of melanoma	600 mg nivolumab* every 2 weeks or 1200 mg nivolumab* every 4 weeks	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated to maximum duration of 12 months.
Adjuvant treatment of muscle invasive urothelial carcinoma		
Adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer	600 mg nivolumab* every 2 weeks or 1200 mg nivolumab* every 4 weeks	After completing 16 weeks of therapy, administer OPDIVO SC as 1200 mg every 4 weeks until disease progression or unacceptable toxicity for a total treatment duration of 1 year

^ As per monotherapy indications in Section 4.1 Therapeutic Indications.
* Administer via subcutaneous injection over approximately 3-5 minutes.
† Following the last dose of the combination of intravenous OPDIVO and ipilimumab, the first dose of OPDIVO SC monotherapy should be administered after 3 weeks when using 600 mg or 6 weeks when using 1200 mg.
# Following the last dose of the combination of intravenous OPDIVO and ipilimumab, the first dose of OPDIVO SC monotherapy should be administered after 3 weeks when using 600 mg or 1200 mg.

The recommended doses of OPDIVO SC in combination with other therapeutic agents are presented in Table 2. Refer to the respective Product Information for each therapeutic agent administered in combination with OPDIVO SC for the recommended dose information, as appropriate.

Table 2 Recommended Doses of OPDIVO SC in Combination with Other Therapeutic Agents

Indication^	Recommended OPDIVO SC Dosage	Duration of Therapy
Neoadjuvant treatment of resectable non-small cell lung cancer	900 mg nivolumab* every 3 weeks with platinum-doublet chemotherapy on the same day every 3 weeks	In combination with platinum-doublet chemotherapy for 3 cycles
Neoadjuvant and adjuvant treatment of resectable non-small cell lung cancer	Neoadjuvant: 900 mg nivolumab* every 3 weeks with platinum-doublet chemotherapy on the same day every 3 weeks	Neoadjuvant: in combination with platinum-doublet chemotherapy until disease progression or unacceptable toxicity, for up to 4 cycles
	Adjuvant:	Adjuvant: following neoadjuvant therapy and surgery, administer as a single agent until disease progression,

Indication^	Recommended OPDIVO SC Dosage	Duration of Therapy
	600 mg nivolumab* every 2 weeks or 1200 mg nivolumab* every 4 weeks	recurrence, or unacceptable toxicity, for up to 13 cycles (up to 1 year)
Unresectable or metastatic urothelial carcinoma	900 mg nivolumab* every 3 weeks Administer OPDIVO SC in combination with cisplatin-based chemotherapy on the same day every 3 weeks.	In combination with cisplatin-based chemotherapy for up to 6 cycles
	600 mg nivolumab* every 2 weeks or 1200 mg nivolumab* every 4 weeks	After completing up to 6 cycles of combination therapy, administer as single agent until disease progression, unacceptable toxicity, or up to 2 years from first dose in patients without disease progression
Advanced renal cell carcinoma	600 mg nivolumab* every 2 weeks or 1200 mg nivolumab* every 4 weeks Administer OPDIVO SC in combination with cabozantinib 40 mg orally once daily. Patients should be instructed to not eat anything for at least 2 hours before and 1 hour after taking cabozantinib.	OPDIVO SC: Treatment should be continued as long as clinical benefit is observed, until treatment is no longer tolerated by the patient, or up to 2 years in patients without disease progression. Cabozantinib: Until disease progression or unacceptable toxicity
Oesophageal squamous cell carcinoma	600 mg nivolumab* every 2 weeks or 1200 mg nivolumab* every 4 weeks Administer OPDIVO SC in combination with fluoropyrimidine- and platinum-containing chemotherapy	OPDIVO SC: Until disease progression, is no longer tolerated, or up to 2 years in patients without disease progression Chemotherapy: Until disease progression or until treatment is no longer tolerated by the patient.
Gastric cancer, gastro-oesophageal junction cancer, or oesophageal adenocarcinoma	600 mg nivolumab* with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks or 900 mg nivolumab* with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks	Treatment should be continued until disease progression, is no longer tolerated or up to 2 years in patients without disease progression.

^ As per combination indications in Section 4.1 Therapeutic Indications.
* Administer via subcutaneous injection over approximately 3-5 minutes.

RECOMMENDED TREATMENT MODIFICATIONS FOR OPDIVO SC AS MONOTHERAPY AND OPDIVO SC IN COMBINATION WITH OTHER THERAPEUTIC AGENTS

Dose escalation or reduction is not recommended for OPDIVO SC as monotherapy or in combination with other therapeutic agents. Dosing delay or discontinuation may be required based on individual

safety and tolerability. When nivolumab is administered in combination, refer to the Product Information of the other combination therapy agents regarding dosing.

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.

When OPDIVO SC is administered in combination with chemotherapy, refer to the Product Information of the other combination therapy agents regarding dosing. Dose escalation or reduction is not recommended for OPDIVO SC. If any agents are withheld, the other agents may be continued. If dosing is resumed after a delay, either the combination treatment, OPDIVO SC monotherapy or chemotherapy alone could be resumed based on the evaluation of the individual patient.

Table 3 Recommended treatment modifications for OPDIVO SC as monotherapy or OPDIVO SC in combination with other therapeutic agents

Immune-related adverse reaction	Severity of Adverse Reaction[a]	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.
	Grade 3 diarrhoea or colitis - OPDIVO+ipilimumab Grade 4 diarrhoea or colitis	Permanently discontinue treatment.
Immune-related hepatitis	*Patients with normal AST/ALT/bilirubin at baseline:* 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.
	HCC patients with elevated AST/ALT at baseline: Grade 1 elevation in AST/ALT at baseline (>1 to 3 times upper limit of normal [ULN]) and on-treatment AST/ALT elevation at >5-10 times the ULN. Grade 2 elevation in AST/ALT at baseline (>3 to 5 times ULN) and on-treatment AST/ALT elevation at >8-10 times ULN.	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete.

Immune-related adverse reaction	Severity of Adverse Reaction[a]	Treatment modification
	AST/ALT >10 time ULN or Grade 3 or 4 elevation in 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. OPDIVO 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.
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s).
	Grade 4 rash Confirmed SJS/TEN	Permanently discontinue treatment.
Immune-related neurological adverse reactions	New onset moderate or severe neurologic signs or symptoms	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete.
	Immune-related encephalitis Immune-related myasthenic syndrome/myasthenia gravis	Permanently discontinue treatment.
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete. Retreatment may be considered after recovery.
	Grade 3 myocarditis	Permanently discontinue treatment.
Other immune-related adverse reactions	Other Grade 3 adverse reaction First occurrence	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete.
	Recurrence of same Grade 3 adverse reaction	Permanently discontinue treatment.
	Grade 3 myotoxicity	Permanently discontinue treatment.

Immune-related adverse reaction	Severity of Adverse Reaction[a]	Treatment modification
	Life-threatening or Grade 4 adverse reaction Inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day Persistent Grade 2 or 3 adverse reactions despite treatment modification	Permanently discontinue treatment.

[a] Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).
[b] Recommendation for the use of hormone replacement therapy is provided in Section 4.4 Precautions.

OPDIVO SC in combination with cabozantinib in RCC

For RCC patients treated with OPDIVO SC in combination with cabozantinib, see the Product Information regarding treatment modifications of cabozantinib.

For liver enzyme elevations, in patients with RCC being treated with OPDIVO SC in combination with cabozantinib:

If ALT or AST > 3 times ULN but ≤10 times ULN without concurrent total bilirubin ≥ 2 times ULN, both OPDIVO SC 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 Product Information.

If ALT or AST > 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both OPDIVO SC and cabozantinib should be permanently discontinued and corticosteroid therapy may be considered.

SPECIAL POPULATIONS

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. Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Hepatic impairment

Based on the population PK results for intravenous nivolumab, no dose adjustment is required in patients with mild or moderate hepatic impairment, although data in moderate hepatic impairment are limited (see Section 5.2 Pharmacokinetic properties). OPDIVO SC has not been studied in patients with severe hepatic impairment or cirrhosis of Child-Pugh B or C severity and OPDIVO SC must be administered with caution in these patients (see Section 4.4 Special warnings and precautions for use).

Paediatric and adolescent use

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

Use in the elderly

No dose adjustment is required for elderly patients (≥ 65 years) (see Section 5.2 Pharmacokinetic properties).

METHOD OF ADMINISTRATION

OPDIVO SC subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only.

Administer OPDIVO SC solution for subcutaneous injection into the subcutaneous tissue of the abdomen or thigh over approximately 3 to 5 minutes, alternating injection sites each cycle.

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 SC is interrupted, it can be resumed at the same site or at an alternate site.

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

Preparation of the syringe

To prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is OPDIVO SC for subcutaneous use and NOT intravenous nivolumab. **Do NOT administer OPDIVO SC intravenously.** OPDIVO SC should be administered by a healthcare professional.

OPDIVO SC is a single-use, ready-to-use solution for injection. It should not be diluted.

Prior to use, visually inspect for particulate matter and discoloration. OPDIVO SC is a clear to opalescent, colourless to yellow solution. Discard if the solution is discoloured or contains extraneous particulate matter other than a few translucent-to-white particles. Do not shake the vial.

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

A syringe, a transfer needle, and a hypodermic injection needle are needed to withdraw OPDIVO SC solution from the vial and inject it subcutaneously. OPDIVO SC may be injected using a 23G-25G (3/8”-5/8”) hypodermic injection needle.

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

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

If a dose of 900 mg is to be administered, allow 2 vials to reach room temperature, then withdraw 7.5 mL of OPDIVO SC 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 SC into the syringe.

If the dose is to be used immediately, attach a 23G-25G (3/8”-5/8”) hypodermic injection needle to the syringe. If the dose is not to be used immediately, attach a tip cap to the syringe prior to storage. To avoid clogging of the hypodermic injection needle, attach the needle to the syringe immediately prior to administration.

If storage is required (see Section 6.4 Special precautions for storage), apply a syringe tip cap prior to storage.

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

Discard partially used or empty vials of OPDIVO SC.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

When assessing the PD-L1 status of the tumour, it is important that a validated test is used.

Early identification of adverse reactions and appropriate intervention are an important part of the safe use of OPDIVO SC.

OPDIVO SC monotherapy is associated with immune related adverse reactions. In clinical trials, almost all immune-related adverse reactions have occurred at higher frequencies when intravenous OPDIVO was administered in combination with ipilimumab compared with intravenous OPDIVO as a monotherapy. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and dose modifications.

Patients should be monitored continuously, as an immune-related adverse reaction with OPDIVO SC may occur at any time during or after discontinuation of therapy. The majority of these initially manifested during treatment; however, a minority occurred weeks to months after discontinuation.

Clinicians should consider immune-related adverse reactions for all unexplained illnesses. Adequate evaluation should be performed to confirm aetiology or exclude other causes.

Based on the severity of the adverse reaction, OPDIVO SC should be withheld (see Section 4.2 Dose and method of administration) and corticosteroids administered.

If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least one 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.

OPDIVO SC 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.

OPDIVO SC must be permanently discontinued for any severe immune related adverse reaction that recurs and for any life threatening immune related adverse reaction (see Section 4.2 Dose and method of administration).

IMMUNE-RELATED PNEUMONITIS

Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with nivolumab monotherapy, nivolumab in combination with ipilimumab or nivolumab in combination with chemotherapy.

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, OPDIVO SC 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, OPDIVO SC should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, OPDIVO SC 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 OPDIVO SC must be permanently discontinued.

IMMUNE-RELATED COLITIS

Severe diarrhoea or colitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab. Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Infectious and disease-related aetiologies should be ruled out. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid refractory immune-related colitis. Stool infections work-up (including CMV, other viral aetiology, culture, Clostridium difficile, ova, and parasite) should be performed upon presentation of diarrhoea or colitis to exclude infectious or other alternate aetiologies.

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

OPDIVO SC 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, OPDIVO SC may be resumed (after corticosteroid taper). If worsening or no improvement occurs despite initiation of corticosteroids, OPDIVO SC must be permanently discontinued.

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

The experience from clinical trials on the management of corticosteroid refractory diarrhoea or colitis is limited. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded (including CMV infection/reactivation evaluated with viral PCR on biopsy, and other viral, bacterial, and parasitic aetiology).

IMMUNE-RELATED HEPATITIS

Severe hepatitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab. Infectious and disease-related aetiologies should be ruled out.

Elevations in liver function tests may develop in the absence of clinical symptoms. Monitor patients for abnormal liver tests prior to and periodically during treatment as indicated based on clinical evaluation.

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

Management of transaminase elevation in patients with HCC (see also Section 4.2 Dose and method of administration).

In patients with HCC, OPDIVO SC should be withheld or permanently discontinued based on the following criteria and corticosteroids initiated at a dose of 1 to 2 mg/kg methylprednisolone equivalent.

- For Grade 1 transaminase levels at baseline (>1 to 3 times ULN) and on-treatment transaminase elevation at >5 to 10 times ULN, treatment should be withheld
- For Grade 2 transaminase levels at baseline (> 3 to 5 times ULN) and on-treatment transaminase elevation at >8 to 10 times ULN, treatment should be withheld
- Regardless of baseline transaminase levels, treatment must be permanently discontinued for on-treatment transaminase increases > 10 times ULN or Grade 3 or 4 total bilirubin increases.

IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION

Severe nephritis and renal dysfunction have been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab. Disease related aetiologies should be ruled out.

Creatinine elevations may develop in the absence of clinical symptoms. Monitor patients for elevated serum creatinine prior to and periodically during treatment as indicated based on clinical evaluation.

For Grade 4 serum creatinine elevation, OPDIVO SC 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, OPDIVO SC should be withheld and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, OPDIVO SC 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 OPDIVO SC must be permanently discontinued.

IMMUNE-RELATED ENDOCRINOPATHIES

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

Patients should be monitored for clinical signs and symptoms of endocrinopathies and for 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, hypotension, or other nonspecific symptoms which may resemble those associated with 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, OPDIVO SC should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, OPDIVO SC should be withheld and an antithyroid medicine 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, OPDIVO SC may be resumed (after corticosteroid taper). Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. OPDIVO SC should be permanently discontinued for life-threatening (Grade 4) hypothyroidism or hyperthyroidism.

For symptomatic Grade 2 adrenal insufficiency, OPDIVO SC should be withheld, and physiologic corticosteroid replacement should be initiated as needed. OPDIVO SC 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, OPDIVO SC 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, OPDIVO SC may be resumed (after corticosteroid taper). OPDIVO SC 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, OPDIVO SC should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. OPDIVO SC should be permanently discontinued for life-threatening (Grade 4) diabetes.

IMMUNE-RELATED SKIN ADVERSE REACTIONS

Patients should be monitored for rash. Severe rash has been observed with nivolumab in combination with ipilimumab and less commonly with nivolumab monotherapy. OPDIVO SC should be withheld for Grade 3 rash and permanently discontinued for Grade 4 rash. Severe rash should be managed with high-dose corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Rare cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been observed. If symptoms or signs of SJS or TEN appear, OPDIVO SC should be withheld and the patient referred for specialist assessment and treatment. If the patient has confirmed SJS or TEN, permanent discontinuation of OPDIVO SC is recommended.

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

IMMUNE-RELATED NEUROLOGICAL ADVERSE REACTIONS

The following adverse events have been observed across clinical trials of nivolumab or nivolumab in combination with ipilimumab: demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis and encephalitis.

Withhold OPDIVO SC in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. Evaluation may include consultation with a neurologist, brain MRI, and lumbar puncture. While other aetiologies are being ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents, followed by corticosteroid taper.

Permanently discontinue OPDIVO SC for immune-related encephalitis and myasthenic syndrome/myasthenia gravis.

COMPLICATIONS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT AFTER TREATMENT WITH PD-1/PD-L1 INHIBITORS

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1 receptor blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause) (see Section 4.8 Adverse effects). These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody prior to or after an allogeneic HSCT.

OTHER IMMUNE-RELATED ADVERSE REACTIONS

Other clinically significant immune-related adverse reactions, including some with fatal outcome, have been observed across clinical trials of intravenous OPDIVO or intravenous OPDIVO in combination with ipilimumab investigating various doses across tumour types, and in OPDIVO SC (see Section 4.8 Adverse effects).

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, OPDIVO SC should be withheld and corticosteroids administered. Upon improvement, OPDIVO SC may be resumed after corticosteroid taper. OPDIVO SC 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 Dose and method of administration), and appropriate treatment instituted.

Some cases of myocarditis can be asymptomatic, so a diagnosis of myocarditis requires a high index of suspicion. Therefore, patients with cardiac or cardio-pulmonary symptoms should undergo a prompt diagnostic workup to evaluate for myocarditis with close monitoring. Troponin is a sensitive but not diagnostic marker of 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 including electrocardiogram, troponin, and echocardiogram should be initiated. Additional testing may be warranted, as guided by the cardiologist, and may include cardiac

magnetic resonance imaging. Once a diagnosis is established, nivolumab or nivolumab in combination with ipilimumab should be withheld. For grade 3 myocarditis, nivolumab or nivolumab in combination with ipilimumab therapy should be permanently discontinued (see Section 4.2 Dose and method of administration).

Cases of haemolytic anaemia and aplastic anaemia have been observed during treatment with immune checkpoint inhibitors. Patients should be monitored for signs and symptoms indicative of these immune-mediated adverse reactions.

Cases of autoimmune haemolytic anaemia some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab (see Section 4.8 Adverse effects (undesirable effects)). Patients with signs and symptoms of anaemia should undergo a prompt diagnostic workup to evaluate for autoimmune haemolytic anaemia.

Cases of Vogt-Koyanagi-Harada syndrome have been reported during post approval use of nivolumab or nivolumab in combination with ipilimumab (see Section 4.8 Adverse effects - Postmarketing Experience).

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1/PD-L1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with nivolumab versus the risk of possible organ rejection in these patients.

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

Cases of myocarditis-myositis-myasthenia gravis overlap syndrome (presenting as an overlap of either two or all three conditions), some with fatal outcome, have been reported with nivolumab and nivolumab in combination with ipilimumab. Early recognition and aggressive management are essential to address associated morbidity and risk of mortality.

PATIENTS WITH PRE-EXISTING AUTOIMMUNE DISEASE (AID)

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.

INFUSION REACTION (INTRAVENOUS FORMULATION)

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

INTRAVENOUS OPDIVO IN COMBINATION WITH CABOZANTINIB

When nivolumab is given with cabozantinib, higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC (see Section 4.8 Adverse effects). 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 Dose and method of administration and refer to the Product Information for cabozantinib).

INTRAVENOUS OPDIVO AND EGFR TKIS IN NSCLC

OPDIVO SC is not approved for combination with epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) use in NSCLC. Serious adverse events, including deaths (one case of pneumonitis and one case of toxic epidermal necrolysis), have been reported in a Phase II non- randomised trial of nivolumab in combination with an investigational 3rd generation TKI.

In patients transitioning from an EGFR TKI to OPDIVO SC monotherapy, a sufficient wash-out period should be observed to minimise the risk of adverse events occurring from the combination. Clinical judgement should be used to determine if any serious or clinically relevant adverse events occurring from an EGFR TKI are resolved prior to initiation of OPDIVO SC.

INCREASED MORTALITY IN PATIENTS WITH MULTIPLE MYELOMA (NOT AN APPROVED INDICATION) WHEN A PD-1 BLOCKING ANTIBODY IS ADDED TO A THALIDOMIDE ANALOGUE AND DEXAMETHASONE

In randomised clinical trials in patients with multiple myeloma, the addition of a PD-1 blocking antibody, including nivolumab, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

PATIENT COUNSELLING INFORMATION

Patients should be advised to report immediately any signs or symptoms suggestive of adverse reactions (as described in Section 4.4 Special warnings and precautions for use). The importance of reporting any worsening of symptoms or severity should be emphasised. Patients should be strongly advised not to treat any of these symptoms with over-the-counter medications without consultation with a health care provider.

PATIENT CARD

All prescribers of OPDIVO SC must be familiar with the immune-related adverse reactions. The prescriber must discuss the risks of OPDIVO SC therapy with the patient. Each patient must be provided with the OPDIVO patient card.

SPECIAL POPULATIONS

Populations excluded from registrational clinical trials

Populations excluded from clinical studies of nivolumab or nivolumab in combination with other therapeutic agents are listed in Table 4 according to studied indication. In the absence of data, OPDIVO SC should be used with caution in these populations after careful consideration of the potential benefit-risk on an individual basis (see also Section 5.1 Pharmacodynamic properties - Clinical Trials).

Table 4 Populations excluded from registrational clinical trials

Indication	Excluded populations
All	• Patients with autoimmune disease • Patients with active brain metastases (or leptomeningeal metastases) • Patients with Eastern Cooperative Oncology Group (ECOG) performance score ≥2 or Karnofsky performance score (KPS) <70% • Patients receiving systemic immunosuppressants prior to study entry
Adjuvant melanoma	• Patients with prior therapy for melanoma except surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥ 6 months prior to randomisation
Melanoma	• Patients with ocular/uveal melanoma • CA209037 only: patients who had a Grade 4 adverse reaction related to anti-CTLA-4 therapy (except for resolved nausea, fatigue, infusion reaction or endocrinopathy controlled by hormone replacement)
NSCLC	• Patients with symptomatic interstitial lung disease *Previously untreated NSCLC*

Indication	Excluded populations
	• Patients with sensitising EGFR mutations or ALK translocations *Resectable NSCLC* • *Neoadjuvant Treatment* - Patients who received prior anticancer treatments for resectable disease, patients with known EGFR mutations or ALK translocations. • *Neoadjuvant and adjuvant treatment* - patients who received prior anti-cancer treatment for resectable disease, with sensitising EGFR mutations or known ALK translocations, with Grade 2 or greater peripheral neuropathy.
SCCHN	• Patients with carcinoma of the nasopharynx or salivary gland as the primary tumour site
HCC	*Unresectable or metastatic HCC* • Patients with a Child-Pugh score other than A, 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). *Previously treated metastatic HCC* • Patients with a Child-Pugh score other than A, any history of hepatic encephalopathy, clinically significant ascites on physical exam, infection with HIV, active coinfection with HBV/HCV or HBV/HDV, or history of concurrent brain metastases.
OSCC	• Patients with apparent tumour invasion on organs located adjacent to the oesophageal disease (eg the aorta or respiratory tract).
Adjuvant OC, GOJC	• Patients who did not receive concurrent chemoradiotherapy (CRT) prior to surgery, stage IV resectable disease, autoimmune disease, any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications.
GC, GOJC or OAC	• Patients positive for human epidermal growth factor receptor 2 (HER2)
Adjuvant MIUC	• 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

USE IN RENAL IMPAIRMENT

The safety and efficacy of OPDIVO SC have not been studied in patients with severe renal impairment. See Section 4.2 Dose and method of administration – renal impairment.

USE IN HEPATIC IMPAIRMENT

The safety and efficacy of OPDIVO SC have not been studied in patients with severe hepatic impairment or with cirrhosis of Child-Pugh B or C severity. OPDIVO SC must be administered with caution in these patients. Data in patients with moderate hepatic impairment are limited (see Section 5.2 Pharmacokinetic properties, 4.2 Dose and method of administration - hepatic impairment and 4.7 Adverse effects (undesirable effects) – Description of selected immune-related adverse reactions – Immune-related hepatitis).

USE IN THE ELDERLY

See Section 4.2 Dose and method of administration.

PAEDIATRIC USE

The safety and efficacy of OPDIVO SC in children below 18 years have not been established. The use of OPDIVO SC in children or adolescents is not recommended.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacokinetic interaction studies have not been conducted. Nivolumab is a human monoclonal antibody. 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. Nivolumab is not expected to have an effect on CYP or other drug metabolising enzymes in terms of inhibition or induction.

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 use of systemic immunosuppression after starting nivolumab treatment does not appear to impair the efficacy of nivolumab.

4.6 FERTILITY, PREGNANCY AND LACTATION

EFFECTS ON 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.

USE IN PREGNANCY (CATEGORY D)

OPDIVO SC is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO SC for at least 5 months following the last dose of OPDIVO SC.

There are no data on the use of OPDIVO SC in pregnant women. 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 fetus.

Based on its mechanism of action and data from animal studies, OPDIVO SC can cause fetal harm when administered during pregnancy. The PD-1/PD-L1 pathway is involved in maintaining immune tolerance to a fetus. Blockade of the PD-1/PD-L1 pathway has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss.

The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab intravenously at 10 and 50 mg/kg twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels 4 and 18 times, respectively, those predicted at steady-state for the clinical dose of 600 mg every 2 weeks OPDIVO SC (based on AUC). There was a dose-dependent increase in fetal losses and increased neonatal mortality mainly in the 3rd trimester of pregnancy and after birth.

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.

USE IN LACTATION

It is not known whether nivolumab is secreted in human breast milk. Because many drugs, including antibodies, can be secreted in human milk, a risk to newborns/infants cannot be excluded. Clinical judgement is required to determine whether to discontinue breast-feeding or to discontinue OPDIVO SC therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamic properties, OPDIVO SC is unlikely to affect this ability. Because of potential adverse reactions such as fatigue (see Section 4.8 Adverse effects), patients should be advised to use caution when driving or operating machinery until they are certain that OPDIVO SC does not adversely affect them.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

OPDIVO SC

The safety of OPDIVO SC was similar to the known safety profile of intravenous OPDIVO. An additional adverse reaction of injection site reaction related to OPDIVO SC is reported in study CA20967T (7% in the subcutaneous nivolumab arm (n = 247) vs 0% in the intravenous nivolumab arm (n = 245)). The term "injection site reaction" 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.

INTRAVENOUS OPDIVO

The following sections present adverse reactions from studies investigating the use of intravenous OPDIVO monotherapy or intravenous OPDIVO in combination with other therapeutic agents.

NIVOLUMAB MONOTHERAPY ACROSS TUMOUR TYPES

Nivolumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of nivolumab (see Section 4.8 Adverse effects - Selected immune-related adverse reactions).

The overall safety profile of nivolumab 3 mg/kg two weekly as monotherapy was assessed from a pooled dataset (n=4646) which excluded study CA209040. The most frequent adverse reactions in the pooled dataset (≥ 10%) were fatigue (29.0%), rash (18.8%), pruritus (15.2%), diarrhoea (14.8%) and nausea (10.5%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 4646) are presented in Table 5. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 5 Adverse reactions from a pooled dataset of nivolumab monotherapy clinical trials

Infections and infestations	
Uncommon	upper respiratory tract infection, pneumonia[a], bronchitis
Rare	meningitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Uncommon	eosinophilia
Immune system disorders	
Common	Infusion-related reaction (including cytokine release syndrome), hypersensitivity (including anaphylactic reaction)
Uncommon	sarcoidosis

Endocrine disorders	
Common	hypothyroidism, hyperthyroidism
Uncommon	adrenal insufficiency[h], hypopituitarism, thyroiditis, hypophysitis, diabetes mellitus,
Rare	diabetic ketoacidosis
Metabolism and nutrition disorders	
Common	decreased appetite
Uncommon	dehydration
Hepatobiliary disorders	
Uncommon	hepatitis
Rare	cholestasis
Nervous system disorders	
Common	peripheral neuropathy, headache, dizziness
Rare	polyneuropathy, autoimmune neuropathy (including g facial and abducens nerve paralysis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,i]
Eye disorders	
Common	dry eye
Uncommon	uveitis, blurred vision
Cardiac disorders	
Uncommon	tachycardia, pericardial disorders[f] , atrial fibrillation, myocarditis[a,b]
Rare	arrhythmia (including ventricular arrhythmia)
Vascular disorders	
Uncommon	hypertension
Rare	vasculitis
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis[a] , dyspnoea[a], cough
Uncommon	pleural effusion
Rare	lung infiltration
Gastrointestinal disorders	
Very common	diarrhoea, nausea
Common	colitis[a], stomatitis, vomiting, abdominal pain, constipation, dry mouth
Uncommon	pancreatitis, gastritis
Rare	duodenal ulcer, coeliac disease, pancreatic exocrine insufficiency
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus
Common	vitiligo, dry skin, erythema, alopecia
Uncommon	psoriasis, urticaria, erythema multiforme, rosacea
Rare	rosacea, toxic epidermal necrolysis[a,b] Stevens-Johnson syndrome[a,b]
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain[d], arthralgia, arthritis
Uncommon	myositis (including polymyositis)[a,b], polymyalgia rheumatica
Rare	Sjogren's syndrome, myopathy, rhabdomyolysis[a,b]
Renal and urinary disorders	
Uncommon	renal failure (including acute kidney injury)[a]
Rare	tubulointerstitial nephritis
General disorders and administration site conditions	
Very common	fatigue
Common	pyrexia, oedema (including peripheral oedema)
Uncommon	pain, chest pain
Investigations[e]	
Very common	increased AST, increased ALT, increased alkaline phosphatase, increased lipase,

	increased amylase, hypocalcaemia, increased creatinine, hyperglycaemia[b], lymphopaenia, leucopoenia, thrombocytopaenia, anaemia[g], hypercalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia, neutropaenia, hypoalbuminaemia
Common	increased total bilirubin, hypermagnesaemia, hypernatraemia, weight decreased, hypoglycaemia

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

[b] Including those reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

[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] 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.

[e] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See also "Laboratory abnormalities" below.

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

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

[h] Includes adrenal insufficiency, secondary adrenocortical insufficiency and adrenocortical insufficiency acute.

[i] Includes encephalitis and limbic encephalitis.

Hepatocellular carcinoma

The safety of nivolumab was evaluated in a 154-patient subgroup of patients with HCC and Child-Pugh A cirrhosis who progressed on or were intolerant to sorafenib enrolled in an open-label trial (CA209040). Patients were required to have an AST and ALT of no more than five times the upper limit of normal and total bilirubin of less than 3 mg/dL. The median duration of exposure to nivolumab was 6 months.

The toxicity profile observed in patients with advanced HCC was generally similar to that observed in patients with other cancers, with the exception of a higher incidence of elevations in transaminases and bilirubin levels. Treatment with nivolumab resulted in treatment-emergent Grade 3 or 4 AST in 27 (18%) patients, Grade 3 or 4 ALT in 16 (11%) patients, and Grade 3 or 4 bilirubin in 11 (7%) patients. Immune-mediated hepatitis requiring systemic corticosteroids occurred in 8 (5%) patients.

NIVOLUMAB IN COMBINATION WITH IPILIMUMAB ACROSS TUMOUR TYPES

The overall safety profile of nivolumab in combination with ipilimumab was assessed from a pooled dataset for 448 patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for melanoma (studies CA209067 [combination group], CA209069, and CA209004-cohort 8), 332 patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg for unresectable or advanced HCC (study CA2099DW), 547 patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for RCC (study CA209214) and a total of 622 patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for and OSCC (study CA209648) and MPM (study CA209743), and 200 patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg for MSI-H/dMMR CRC (study CA2098HW).

Adverse reactions reported in the pooled dataset for patients treated with nivolumab in combination with ipilimumab (n=1,949) are presented in Table 6. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Melanoma

In the pooled dataset of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (CA209067 [combination group], CA209069, and CA209004-cohort 8), the most frequent adverse reactions (≥ 10%) were rash (52%), fatigue (46%), diarrhoea (43%), pruritus (36%), nausea (26%), pyrexia (19%), decreased appetite (16%), hypothyroidism (16%), colitis (15%), vomiting (14%), abdominal pain (13%), arthralgia (13%), headache (11%) and dyspnoea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Among the 313 patients treated with nivolumab 1mg/kg in combination with ipilimumab 3mg/kg in CA209067, 154/313 (49%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 147 patients in this group who continued treatment in the single-agent phase, 47 (32%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase.

Unresectable or metastatic HCC

In the dataset of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC (CA2099DW), the most frequent adverse reactions (≥ 10%) were rash (31%), pruritis (28%), increased transaminases (24.7%), fatigue (18.4%), diarrhoea (14.2%), hypothyroidism (12.3%), increased lipase (11.1%), hyperthyroidism (10.2%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Fatal adverse reactions occurred in 12 (3.6%) patients who received OPDIVO in combination with ipilimumab; these included 4 (1.2%) subjects who died due to immune-mediated or autoimmune hepatitis.

RCC

In the CA209214 dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n=547), with a minimum follow-up of 17.5 months, the most frequent adverse reactions (≥ 10%) were fatigue (48%), rash (34%), pruritus (28%), diarrhoea (27%), nausea (20%), hypothyroidism (16%), musculoskeletal pain (15%), arthralgia (14%), decreased appetite (14%), pyrexia (14%), vomiting (11%), hyperthyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

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

The majority of drug-related adverse reactions observed in patients in CA209214 were generally lower in frequency and severity compared to the pooled nivolumab in combination with ipilimumab data from melanoma studies, which utilised a higher ipilimumab dose and regimen (nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W).

MSI-H/dMMR CRC

In the CA2098HW dataset of nivolumab 240 mg in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC (n=200), the most frequent adverse reactions (≥ 10%) were fatigue (26.5%), pruritus (22.5%), diarrhoea (21%), hypothyroidism (16%), rash (15%), adrenal insufficiency (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Table 6 Adverse reactions with nivolumab in combination with ipilimumab in clinical trials

	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n=448)[g]	**Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC (n=332)[g]**	**Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n=547)[g]**	**Nivolumab 240 mg Q3W in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC (n=200)[g]**
Infections and infestations				
Common	pneumonia, upper respiratory tract infection (including cytokine release syndrome)		pneumonia, upper respiratory tract infection (including cytokine release syndrome)	
Uncommon	bronchitis	meningitis aseptic, upper respiratory tract infection	bronchitis, aseptic meningitis	bronchitis
Blood and lymphatic system disorders				
Common	eosinophilia	eosinophilia		
Uncommon		autoimmune haemolytic	eosinophilia	eosinophilia

	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n=448)[g]	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC (n=332)[g]	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n=547)[g]	Nivolumab 240 mg Q3W in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC (n=200)[g]
		anaemia, leukopaenia		
Immune system disorders				
Common	infusion-related reaction (including cytokine release syndrome), hypersensitivity		infusion-related reaction (including cytokine release syndrome), hypersensitivity	infusion-related reaction (including cytokine release syndrome), hypersensitivity
Uncommon	sarcoidosis	hypersensitivity		
Endocrine disorders				
Very common	hypothyroidism	hypothyroidism, hyperthyroidism	hypothyroidism, hyperthyroidism	hypothyroidism, adrenal insufficiency
Common	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis	adrenal insufficiency, hypophysitis, thyroiditis	adrenal insufficiency, hypophysitis, thyroiditis, diabetes mellitus	hyperthyroidism, hypophysitis, thyroiditis, diabetes mellitus
Uncommon	diabetic ketoacidosis, diabetes mellitus	hypopituitarism	diabetic ketoacidosis, hypopituitarism	hypopituitarism
Metabolism and nutrition disorders				
Very common	decreased appetite		decreased appetite	
Common	dehydration	decreased appetite	dehydration	decreased appetite
Uncommon		diabetes mellitus	metabolic acidosis	
Hepatobiliary disorders				
Common	hepatitis	hepatitis, hepatic failure	hepatitis	hepatitis
Uncommon		liver injury		
Nervous system disorders				
Very common	headache	headache, dizziness		
Common	peripheral neuropathy, dizziness		headache, peripheral neuropathy, dizziness	headache, dizziness, peripheral neuropathy
Uncommon	Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis	myasthenia gravis, peripheral neuropathy	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis	polyneuropathy, encephalitis
Eye disorders				
Common	uveitis, blurred vision		blurred vision	
Uncommon		blurred vision	uveitis	
Cardiac disorders				
Common	tachycardia		tachycardia	
Uncommon	arrhythmia (including ventricular arrhythmia)[a], atrial	myocarditis	arrhythmia (including ventricular	myocarditis[a]

	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n=448)[g]	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC (n=332)[g]	Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n=547)[g]	Nivolumab 240 mg Q3W in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC (n=200)[g]
	fibrillation, myocarditis[a,c]		arrhythmia), myocarditis	
Vascular disorders				
Common	hypertension	hypertension	hypertension	
Uncommon		hypovolaemic shock		
Respiratory, thoracic and mediastinal disorders				
Very Common	dyspnoea			
Common	pneumonitis[a], pulmonary embolism[a], cough	dyspnoea, pneumonitis	pneumonitis, dyspnoea, pleural effusion, cough	pneumonitis[a], dyspnoea, cough
Uncommon	pleural effusion	cough		
Gastrointestinal disorders				
Very common	colitis[a], diarrhoea, vomiting, nausea, abdominal pain	diarrhoea	diarrhoea, vomiting, nausea	diarrhoea
Common	stomatitis, pancreatitis, constipation, dry mouth	abdominal pain, colitis, constipation, dry mouth, nausea, pancreatitis, stomatitis, vomiting	colitis, stomatitis, pancreatitis, abdominal pain, constipation, dry mouth	nausea, vomiting, abdominal pain, colitis, constipation, stomatitis, dry mouth
Uncommon	intestinal perforation[a], gastritis, duodenitis	gastritis	gastritis	duodenitis, gastritis
Rare	coeliac disease		coeliac disease	
Skin and subcutaneous tissue disorders				
Very common	rash[b], pruritus	rash[b], pruritis	rash[b], pruritus	rash[b], pruritus
Common	vitiligo, dry skin, erythema, alopecia, urticaria	dry skin, psoriasis	dry skin, erythema, urticaria	dry skin, alopecia, erythema
Uncommon	psoriasis	alopecia, erythema, Steven-Johnson syndrome, urticaria	Stevens-Johnson syndrome, vitiligo, erythema multiforme, alopecia, psoriasis	urticaria, psoriasis
Rare	toxic epidermal necrolysis[a, c], Stevens-Johnson syndrome[c]			
Musculoskeletal and connective tissue disorders				
Very common	arthralgia		musculoskeletal pain[d], arthralgia	
Common	musculoskeletal pain[d]	arthralgia, musculoskeletal pain[d]	arthritis, muscle spasm, muscular weakness	arthralgia, musculoskeletal pain[d], arthritis, myositis
Uncommon	spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis)[a, c], rhabdomyolysis[a,d]	arthritis, muscle spasm, myositis, polymyalgia rheumatica	polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis	muscle spasm
Renal and urinary disorders				

	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n=448)[g]	**Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC (n=332)[g]**	**Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n=547)[g]**	**Nivolumab 240 mg Q3W in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC (n=200)[g]**
Common	renal failure (including acute kidney injury)[a,]		renal failure (including acute kidney injury)	renal failure (including acute kidney injury)
Uncommon	tubulointerstitial nephritis	nephritis, renal failure	tubulointerstitial nephritis	nephritis
General disorders and administration site conditions				
Very common	fatigue, pyrexia	fatigue	fatigue, pyrexia	fatigue
Common	oedema (including peripheral oedema), pain	oedema, pyrexia	oedema (including peripheral oedema), pain, chest pain, chills	pyrexia, oedema (including peripheral oedema)
Uncommon	chest pain	chills, pain		pain, chest pain
Investigations[e]				
Very common	increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia, hypoglycaemia, lymphopaenia, leucopoenia, neutropaenia, thrombocytopaenia, anaemia[f], hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia	anaemia[f], thrombocytopaenia, leucopoenia, lymphopaenia, neutropaenia, increased alkaline phosphatase increased AST, increased ALT, increased total bilirubin. creatinine, hypoalbuminaemia, increased amylase, increased lipase, hyponatraemia, hyperkalaemia, hypokalaemia, hypocalcaemia, hypomagnesaemia, hyperglycaemia	increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia, hypoglycaemia, lymphopaenia, leucopoenia, neutropaenia, thrombocytopaenia, anaemia[f], hypercalcaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia	increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hypoglycaemia, lymphopaenia, anaemia[f], hypercalcaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hyponatraemia, neutropaenia, leucopoenia
Common	hypercalcaemia, hypermagnesaemia, hypernatraemia,weight decreased	hypernatraemia, hypercalcaemia, hypermagnesaemia, hypoglycaemia	hypercalcaemia, hypermagnesaemia, hypernatraemia, weight decreased	thrombocytopaenia, hypernatraemia

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

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

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

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

[e] 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.

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

[g] Please refer to Section 5.1 - Clinical Trials for dosing schedule of nivolumab in combination with ipilimumab across indications.

NIVOLUMAB IN COMBINATION WITH CABOZANTINIB

RCC

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

In the dataset of nivolumab 240 mg in combination with cabozantinib 40 mg in RCC (n =320), with a minimum follow-up of 10.6 months, the most frequent adverse reactions (≥ 10%) were diarrhoea (56.9%), fatigue (42.5%), palmar-plantar erythrodysaesthesia syndrome (38.1%), hypothyroidism (33.4%), rash (32.8%), stomatitis (32.8%), hypertension (31.3%), dysgeusia (21.6%), nausea (21.3%), decreased appetite (20.3%), pruritus (16.3%), abdominal pain (11.9%), dysphonia (11.6%), vomiting (11.3%) and dyspepsia (10.0%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Adverse reactions reported in the dataset for patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg (n=320) are presented in Table 7. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100).

Table 7 Adverse reactions with nivolumab in combination with cabozantinib

Infections and infestations	
Common	upper respiratory tract infection
Uncommon	pneumonia
Blood and lymphatic system disorders	
Uncommon	eosinophilia
Immune system disorders	
Common	hypersensitivity (including anaphylactic reaction)
Uncommon	infusion related hypersensitivity reaction
Endocrine disorders	
Very common	hypothyroidism
Common	hyperthyroidism, adrenal insufficiency
Uncommon	hypophysitis, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration
Nervous system disorders	
Very common	dysgeusia
Common	headache, dizziness, peripheral neuropathy
Uncommon	encephalitis autoimmune, Guillain- Barré syndrome, myasthenic syndrome
Ear and labyrinth disorders	
Uncommon	tinnitus
Eye disorders	
Common	dry eye
Uncommon	uveitis, blurred vision
Cardiac disorders	
Uncommon	atrial fibrillation, tachycardia, myocarditis
Vascular disorders	
Very common	hypertension
Common	thrombosis[a]
Respiratory, thoracic and mediastinal disorders	
Very common	dysphonia
Common	pneumonitis, dyspnoea, pulmonary embolism, cough, epistaxis

Uncommon	pleural effusion
Gastrointestinal disorders	
Very common	diarrhoea, nausea, stomatitis, vomiting, abdominal pain, dyspepsia
Common	dry mouth, constipation, gastritis, oral pain
Uncommon	colitis, pancreatitis, small intestine perforation[b], glossodynia, haemorrhoids
Not known	coeliac disease
Hepatobiliary disorders	
Common	hepatitis
Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus
Common	dry skin, alopecia, erythema, hair colour change
Uncommon	psoriasis, urticaria
Musculoskeletal and connective tissue disorders	
Common	arthralgia, muscle spasm, musculoskeletal pain[d], arthritis
Uncommon	myopathy, osteonecrosis of the jaw, fistula
Renal and urinary disorders	
Common	proteinuria, renal failure, acute kidney injury
Uncommon	nephritis
General disorders and administration site conditions	
Very common	fatigue
Common	oedema, pyrexia, pain
Uncommon	chest pain
Investigations[e]	
Very common	increased ALT, increased AST, increased alkaline phosphatase, increased total bilirubin, hypocalcaemia, increased creatinine, hypoglycaemia, hyperglycaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hypermagnesaemia, hyponatraemia, hypernatraemia, hypophosphataemia, lymphopaenia, leucopoenia, thrombocytopaenia, anaemia, neutropaenia
Common	hypercalcaemia, weight decreased

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

[b] Fatal cases have been reported

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

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

[e] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See also "Laboratory abnormalities" below.

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 (9.8%) and AST increased (7.9%) were observed. In patients with Grade ≥2 increased ALT or AST (n=83): median time to onset was 2.3 months (range: 2.0 to 88.3 weeks), 28% received corticosteroids for median duration of 1.7 weeks (range: 0.9 to 52.3 weeks), and resolution to Grades 0-1 occurred in 89% with median time to resolution of 2.1 weeks (range: 0.4 to 83.6^{+} weeks). Among the 44 patients who were rechallenged with either nivolumab (n=11) or cabozantinib (n=9) monotherapy or with both (n=24), Grade ≥2 increased ALT or AST was observed in 2 patients receiving OPDIVO, 2 patients receiving cabozantinib, and 7 patients receiving both intravenous OPDIVO and cabozantinib. There were no Grade 5 hepatic events.

NIVOLUMAB IN COMBINATION WITH CHEMOTHERAPY

Adverse reactions reported in the dataset for patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC (n=176), nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC followed by adjuvant nivolumab monotherapy 480 mg after surgery (n=228), nivolumab 360 mg every 3 weeks in combination with

cisplatin-based chemotherapy in unresectable or metastatic urothelial carcinoma (n=304), nivolumab 240 mg every 2 weeks in combination with chemotherapy in OSCC (n=310) and nivolumab in combination with FOLFOX or XELOX chemotherapy in gastric cancer, gastro-oesophageal junction cancer or oesophageal adenocarcinoma (n=782) are presented in Table 8 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).

Neoadjuvant NSCLC

In the dataset of neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy for 3 cycles in resectable NSCLC (n=176), the most frequent adverse reactions (≥10%) were nausea (33%), constipation (21%), fatigue (21.6%), rash (19.3%), decreased appetite (17%), malaise (14.2%) and peripheral neuropathy (12.5%).

Neoadjuvant and Adjuvant NSCLC

In the dataset of nivolumab 360 mg in combination with platinum-doublet chemotherapy for up to 4 cycles followed after surgery by nivolumab monotherapy 480 mg every 4 weeks for up to 13 cycles (1 year) in resectable NSCLC (n=228) the most frequent adverse reactions (≥10%) were fatigue (28.1%), nausea (23.2%), alopecia (22.8%), constipation (22.4%), peripheral neuropathy (21.9%), rash (15.8%), decreased appetite (13.6%), arthralgia (11.4%), and diarrhea (11.4%).

Unresectable or metastatic urothelial carcinoma

In the dataset of nivolumab 360 mg every 3 weeks in combination with cisplatin-based chemotherapy in unresectable or metastatic urothelial carcinoma (n=304), the most frequent adverse reactions (≥10%) were nausea (47%), fatigue (39%), decreased appetite (23%), rash (20%), vomiting (18%), pruritus (15%), constipation (15%), diarrhoea (13%), hypothyroidism (13%) and peripheral neuropathy (12%).

OSCC

In the dataset of nivolumab 240 mg every 2 weeks in combination with chemotherapy in OSCC (n = 310), with a minimum follow-up of 12.9 months, the most frequent adverse reactions (≥ 10%) were nausea (58.7%), decreased appetite (42.6%), constipation (19%), stomatitis (41.6%), fatigue (25.5%), diarrhoea (19.4%), vomiting (18.1%), peripheral neuropathy (16.5%), rash (10%) and alopecia (10%).

Gastric Cancer, Gastro-oesophageal junction cancer or Oesophageal Adenocarcinoma

In the dataset of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with FOLFOX or XELOX chemotherapy in gastric cancer, gastro-oesophageal junction cancer or oesophageal adenocarcinoma (n =782), with a minimum follow-up of 12.1 months, the most frequent adverse reactions were peripheral neuropathy (50%), neutropaenia (43%), nausea (41%), thrombocytopaenia (36%), fatigue (33%), diarrhoea (32%), anaemia (28%), vomiting (25%), decreased appetite (20%), transaminases increased (18%), rash (14%), palmar-plantar erythrodysaesthaesia syndrome (12%) and lipase increased (11%). Median duration of therapy was 6.8 months (95% CI 6.11, 7.36) for nivolumab in combination with chemotherapy and 4.9 months (95% CI 4.47, 5.29) for chemotherapy.

Table 8 Adverse reactions with nivolumab in combination with chemotherapy

	Neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC[f]	**Neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab monotherapy after surgery in resectable NSCLC[f]**	**Nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in metastatic or unresectable urothelial carcinoma[f]**	**Nivolumab 240mg in combination with fluorouracil and cisplatin combination chemotherapy in 1st line OSCC[f]**	**Nivolumab 240 mg Q2W or 360 mg Q3W in combination with FOLFOX or XELOX chemotherapy in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma[f]**
Infections and infestations					
Very common					upper respiratory tract infection
Common	pneumonia	pneumonia	pneumonia, upper respiratory tract infection	pneumonia[e]	pneumonia
Uncommon		upper respiratory tract infection		upper respiratory tract infection	
Blood and lymphatic system disorders					
Common	febrile neutropaenia	febrile neutropaenia	febrile neutropaenia	febrile neutropaenia	febrile neutropaenia
Uncommon			eosinophilia		eosinophilia
Immune system disorders					
Common	infusion-related reaction (including cytokine release syndrome), hypersensitivity	hypersensitivity, infusion-related reaction (including cytokine release syndrome)	infusion-related reaction (including cytokine release syndrome)	infusion-related reaction (including cytokine release syndrome)	Infusion-related reaction (including cytokine release syndrome), hypersensitivity
Uncommon			hypersensitivity	hypersensitivity	
Endocrine disorders					
Very common			hypothyroidism		
Common	hyperthyroidism, hypothyroidism, thyroiditis	hypothyroidism, hyperthyroidism, adrenal insufficiency	hyperthyroidism	hypothyroidism, hyperthyroidism, adrenal insufficiency	hypothyroidism, hyperthyroidism
Uncommon	diabetes mellitus	diabetes mellitus, hypopituitarism	thyroiditis, hypopituitarism, hypophysitis, adrenal insufficiency, diabetes mellitus	hypopituitarism, diabetes mellitus[e]	hypopituitarism, adrenal insufficiency, hypophysitis, diabetes mellitus
Metabolism and nutrition disorders					
Very common	decreased appetite	decreased appetite	decreased appetite	decreased appetite	decreased appetite
Common	hypoalbunaemia	hypoalbuminaemia	hypoalbuminaemia	hypoalbuminaemia, hypophosphataemia	
Uncommon	hypophosphatemia	hypophosphatemia			

	Neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC[f]	**Neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab monotherapy after surgery in resectable NSCLC[f]**	**Nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in metastatic or unresectable urothelial carcinoma[f]**	**Nivolumab 240mg in combination with fluorouracil and cisplatin combination chemotherapy in 1st line OSCC[f]**	**Nivolumab 240 mg Q2W or 360 mg Q3W in combination with FOLFOX or XELOX chemotherapy in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma[f]**
Nervous system disorders					
Very common	peripheral neuropathy	peripheral neuropathy	peripheral neuropathy	peripheral neuropathy	peripheral neuropathy
Common	dizziness	headache, dizziness, paraesthesia	paraesthesia, dizziness, headache	headache, dizziness	paraesthesia, headache, dizziness
Uncommon	headache	Guillain-Barré syndrome		paraesthesia	Guillain-Barré syndrome
Eye disorders					
Common				blurred vision, dry eye, uveitis	dry eye, blurred vision
Uncommon	dry eye	dry eye, blurred vision	dry eye, blurred vision		uveitis
Cardiac disorders					
Common	atrial fibrillation				
Uncommon		myocarditis	atrial fibrillation, myocarditis, tachycardia	tachycardia	tachycardia, myocarditis
Vascular disorders					
Common	vasculitis		hypertension, vasculitis	hypertension	thrombosis, hypertension
Uncommon	thrombosis	hypertension	thrombosis	thrombosis	
Respiratory, thoracic and mediastinal disorders					
Common	pneumonitis, dyspnoea	dyspnoea, pneumonitis[e]	dyspnoea, cough, pneumonitis	pneumonitis, cough	pneumonitis[e], dyspnoea, cough
Uncommon	cough, tachypnoea	cough		dyspnoea	
Gastrointestinal disorders					
Very common	nausea, constipation	constipation, nausea, diarrhoea	nausea, vomiting, constipation, diarrhoea	nausea, constipation, stomatitis, vomiting, diarrhoea	nausea, diarrhoea, vomiting, stomatitis
Common	vomiting, diarrhoea, abdominal pain, stomatitis, dry mouth	vomiting, stomatitis, colitis, abdominal pain	stomatitis, abdominal pain, dry mouth	colitis[e]	constipation, abdominal pain, colitis, dry mouth
Uncommon		dry mouth	pancreatitis, colitis		pancreatitis
Not known	coeliac disease	coeliac disease	coeliac disease	coeliac disease	coeliac disease
Hepatobiliary disorders					
Uncommon			hepatitis		hepatitis
Skin and subcutaneous tissue disorders					

	Neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC[f]	**Neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab monotherapy after surgery in resectable NSCLC[f]**	**Nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in metastatic or unresectable urothelial carcinoma[f]**	**Nivolumab 240mg in combination with fluorouracil and cisplatin combination chemotherapy in 1st line OSCC[f]**	**Nivolumab 240 mg Q2W or 360 mg Q3W in combination with FOLFOX or XELOX chemotherapy in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma[f]**
Very common	rash[a]	rash[a], alopecia	rash[a], pruritus	rash[a], alopecia	rash[a], palmar-plantar erythrodysaesthaesia syndrome
Common	alopecia, pruritis, erythema	pruritus, dry skin	dry skin, erythema, alopecia	pruritus, dry skin, erythema	pruritus, skin hyperpigmentation, alopecia, dry skin, erythema
Uncommon	dry skin		palmar-plantar erythrodysaesthesia syndrome	palmar-plantar erythrodysaesthesia syndrome, skin hyperpigmentation	
Musculoskeletal and connective tissue disorders					
Very Common		arthralgia			
Common	musculoskeletal pain[b], arthralgia, muscular weakness	musculoskeletal pain[b], muscular weakness	musculoskeletal pain[b], arthralgia		musculoskeletal pain[b], arthralgia, muscular weakness
Uncommon			muscular weakness	musculoskeletal pain[b], arthralgia, muscular weakness	
Renal and urinary disorders					
Common		renal failure	renal failure	renal failure[e]	
Uncommon	renal failure	nephritis	nephritis		renal failure, nephritis
General disorders and administration site conditions					
Very common	fatigue, malaise	fatigue	fatigue	fatigue	fatigue
Common	oedema, pyrexia	pyrexia, oedema	malaise, pyrexia oedema	pyrexia, oedema (including peripheral oedema)	pyrexia, oedema (including peripheral oedema)
Investigations[c]					

	Neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC[f]	**Neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab monotherapy after surgery in resectable NSCLC[f]**	**Nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in metastatic or unresectable urothelial carcinoma[f]**	**Nivolumab 240mg in combination with fluorouracil and cisplatin combination chemotherapy in 1st line OSCC[f]**	**Nivolumab 240 mg Q2W or 360 mg Q3W in combination with FOLFOX or XELOX chemotherapy in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma[f]**
Very common	neutropaenia, anaemia[d], thrombocytopaenia	anaemia[d], thrombocytopaenia, leucopoenia, lymphopaenia, neutropaenia, increased alkaline phosphatase, increased transaminases, increased creatinine, hyponatraemia, hyperkalaemia, hypokalaemia; hypercalcaemia, hypocalcaemia, hyperglycaemia,	anaemia[d], leucopoenia, neutropaenia, lymphopenia, thrombocytopaenia increased alkaline phosphatase, increased aspartate aminotransferase increased alanine, aminotransferase, increased creatinine, increased amylase, increased lipase hyponatraemia, hyperkalaemia, hypokalaemia, hypercalcaemia, hypocalcaemia, hypomagnesaemia, hyperglycaemia, hypoglycaemia	anaemia[d], neutropaenia, thrombocytopaenia, lymphopenia, leucopaenia, increased creatinine, increased transaminases, increased alkaline phosphatase, hyponatraemia, hypocalcemia, hyperkalemia, hypokalaemia; hypomagnesaemia, hyperglycaemia, hypercalcemia, hypoglycemia	anaemia[d], thrombocytopaenia, leucopenia, lymphopenia, neutropaenia, increased transaminases, increased total bilirubin, increased creatinine, hypernatraemia, hyponatraemia, hyperkalaemia, hypokalaemia, hypocalcaemia, hypoglycaemia, hyperglycaemia, increased lipase
Common	increased transaminases, leucopoenia, increased lipase, increased amylase, increased creatinine, hyponatraemia, hypomagnesaemia, hyperglycaemia, hypoalbuminaemia		increased total bilirubin, hypernatraemia, hypermagnesaemia	increased bilirubin, hypernatraemia, hypermagnesaemia	hypercalcaemia, increased alkaline phosphatase, increased amylase
Uncommon	lymphopaenia, increased alkaline phosphatase, hypokalaemia, hypocalcaemia				

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

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

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

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

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

[f] Please refer to Section 5.1 - Clinical Trials for dosing schedule of nivolumab in combination with other therapeutic agents across indications.

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, 0.9% 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 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.8% for anaemia (all Grade 3), 1.2% for thrombocytopaenia, 0.5% for leucopoenia, 6.7% for lymphopaenia, 0.7% for neutropaenia, 4.3% for increased alkaline phosphatase, 12.4% for increased AST, 15.3% for increased ALT, 1.2% for increased total bilirubin, 2.4% for increased creatinine, 5.3% for hyperglycaemia, 8.7% for increased amylase, 19.5% for increased lipase, 1.2% for hypocalcaemia, 0.2% each for hypernatraemia and hypercalcaemia, 0.5% for hyperkalemia, 0.3% for hypermagnesaemia, 4.8% for hypokalaemia, and 9.5% for hyponatraemia.

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 5.2% for anaemia (all Grade 3), 4% for thrombocytopaenia, 3.3% leucopoenia, 6.1% for lymphopaenia, 4% for neutropaenia, 1.2% for increased alkaline phosphatase, 28.5% for increased AST, 16.6% for increased ALT, 9.1% for increased total bilirubin, 2.4% for increased creatinine, 0.9% for hypoalbuminaemia, 5.8% for increased amylase, 16.1% for increased lipase, 5.5% for hyponatraemia, 2.7% for hyperkalaemia, 2.1% for hypokalaemia, 0.6% for hypercalaemia, 0.9% for hypocalcaemia, 2.1% for hypermagnesemia, 0.9% for hypomagnesemia, 14.9% for hyperglycaemia, and 0.6% for hypoglycaemia.

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

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.1% for anaemia, 0.5% for thrombocytopaenia, 3.6% for lymphopaenia, 1.0% for neutropaenia, 1.5% for increased alkaline phosphatase, 3.6% for increased AST, 4.1% for increased ALT, 2.1% for increased total bilirubin, 3.1% for increased creatinine, 4.0% for increased amylase, 9.7% for increased lipase, 3.6% for hyponatraemia, 1.0% for hyperkalaemia, 1.0% for hypokalaemia, and 0.5% for hypocalcaemia.

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.8% for anaemia (all Grade 3), 0.3% for thrombocytopaenia, 0.3% for leucopoenia, 6.6% for lymphopaenia, 3.2% for neutropaenia, 2.8% for increased alkaline phosphatase, 7.9% for increased AST, 9.8% for increased ALT, 0.9% for increased total bilirubin, 1.3% for increased creatinine, 3.5% for hyperglycaemia, 0.8% for hypoglycemia, 9.8% for amylase, 13.6% for lipase, 1.9% for hypocalcaemia, 0.3% for hypercalcaemia, 4.7% for hyperkalemia, 3.2% for hypermagnesaemia, 1.6% for hypomagnesaemia, 3.2% for hypokalaemia, and 11.7% for hyponatraemia.

In patients treated with neoadjuvant nivolumab 360 mg in combination with chemotherapy in resectable NSCLC, 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, 2.9% for thrombocytopaenia, 5.3% for leukopaenia, 4.7% for lymphopaenia, 21.8% for neutropaenia, 3.6% for increased amylase, 6.5% for increased lipase, 2.4% for hyponatraemia, 1.2% for hyperkalaemia, 0.6% for hypokalaemia, 0.6% for hypocalcaemia, 1.8% for hypomagnesaemia and 5.5% for hyperglycaemia.

In patients treated with neoadjuvant nivolumab 360 mg in combination with chemotherapy in resectable NSCLC followed by adjuvant nivolumab monotherapy after surgery, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 7.2% for anaemia, 1.3% for thrombocytopaenia, 8.5% for leukopaenia, 6.7% for lymphopaenia, 17.5% for neutropaenia, 2.7% for increased AST, 2.2% for increased ALT, 0.9% for increased bilirubin, 0.4% for increased creatinine, 3.1% for hyponatraemia, 1.3% for hyperkalaemia, 1.3% for hypokalaemia, 0.5% for hypercalcaemia, 1.4% for hypocalcaemia, 5.3% for hyperglycaemia and 0.4% for hypoglycaemia.

In patients treated with nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in unresectable or metastatic urothelial carcinoma, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 21.3% for anaemia, 13.0% for thrombocytopenia, 18.3% for leucopenia, 17.4% for lymphopenia, 35.3% for neutropenia, 2.4% for increased alkaline phosphatase, 2.4% for increased aspartate aminotransferase, 2.4% for increased alanine aminotransferase, 2.4% for increased total bilirubin, 2.4% for increased creatinine, 4.2% for increased amylase, 4.8% for increased lipase, 0.3% for hypernatremia, 13.2% for hyponatremia, 3.0% for hyperkalemia, 2.0% for hypokalemia, 0.3% for hypercalcemia, 2.1% for hypocalcemia, 2.8% for hypermagnesemia, 3.8% for hypomagnesemia, 3.9% for hyperglycemia and 1.3% for hypoglycemia.

In patients treated with nivolumab 240 mg in combination with chemotherapy in OSCC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 16.0% for anaemia, 5.8% for thrombocytopaenia, 11.5% leucopoenia, 15.4% for lymphopaenia, 26.0% neutropaenia, 3.0% for increased alkaline phosphatase, 4.2% for increased AST, 3.1% for increased ALT, 2.3% for increased bilirubin, 1.4% for increased creatinine, 0.6% for hypernatraemia, 8.7% for hyponatraemia, 1.7% for hyperkalaemia, 7.4% for hypokalaemia, 1.0% for hypercalcaemia, 2.0% for hypocalcaemia, 1.5% for hypomagnesaemia, 3.1% for hyperglycaemia, and 0.6% for hypoglycaemia.

In patients treated with nivolumab 240 mg and 360 mg in combination with chemotherapy (FOLFOX or XELOX) in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 13.9% for anaemia, 6.8% for thrombocytopaenia, 11.8% leukopaenia, 12.2% for lymphopaenia, 29.3% neutropaenia, 4.6% for increased AST, 3.4% for increased ALT, 3.0% for increased bilirubin, 1.0% for increased creatinine, 0.5% for hypernatraemia, 6.3% for hyponatraemia, 1.4% for hyperkalaemia, 6.5% for hypokalaemia, 0.3% for hypercalcaemia, 1.6% for hypocalcaemia, 4.2% for hyperglycaemia, and 0.7% for hypoglycaemia.

DESCRIPTION OF SELECTED IMMUNE-RELATED ADVERSE REACTIONS

Both nivolumab monotherapy and nivolumab in combination with other therapeutic agents are associated with immune-related adverse reactions. With appropriate medical therapy, these resolved in most cases.

The management guidelines for these adverse reactions are described in Section 4.2 Dose and method of administration and Section 4.4 Warnings and precautions for use.

Note: Time to resolution may include censored observations.

Immune-related pneumonitis

OPDIVO SC
In Study CA20967T, immune-mediated pneumonitis occurred in 2.8% (7/247) of patients receiving OPDIVO SC, including Grade 3 (0.8%) and Grade 2 (2.0%) adverse reactions. Pneumonitis led to

permanent discontinuation of OPDIVO SC in 1.6% and withholding of OPDIVO SC in 1.6% of patients. Systemic corticosteroids were required in 100% (7/7) of patients with pneumonitis. Pneumonitis resolved in 27% of the 7 patients. Of the 4 patients in whom OPDIVO SC was withheld for pneumonitis, 2 reinitiated OPDIVO SC after symptom improvement; of these, 1 (50%) had recurrence of pneumonitis.

Intravenous OPDIVO monotherapy
In the pooled analysis 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. Grade 5 cases were reported in <0.1% (2/4646). One patient with Grade 3 pulmonary embolism and Grade 3 pneumonitis died in the SCCHN clinical trial. Median time to onset was 15.1 weeks (range: 0.7-85.1). Sixty-six patients (1.4%) required permanent discontinuation of nivolumab. One-hundred (64.5%) patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). 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.

Intravenous OPDIVO in combination with ipilimumab
In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of pneumonitis including interstitial lung disease, was 7.8% (35/448). Grade 2, Grade 3, and Grade 4 cases were reported in 4.7% (21/448), 1.1% (5/448), and 0.2% (1/448) of patients, respectively. One of the Grade 3 pneumonitis cases worsened over 11 days with a fatal outcome. Median time to onset was 2.6 months (range: 0.7-12.6). Nine patients (2.0%) required permanent discontinuation of nivolumab in combination with ipilimumab. Twenty-one patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 29 patients (87.9%) with a median time to resolution of 6.1 weeks (range: 0.3-46.9).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC, the incidence of pneumonitis was 2.1% (7/332). Grade 2 and Grade 3 cases were reported in 1.2% (4/332) and 0.3% (1/332) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 9.14 weeks (range: 4.7-33.6). Two patients (0.6%) required permanent discontinuation of nivolumab in combination with ipilimumab. Four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 5 patients (71.4%) with a median time to resolution of 16.14 weeks (range: 3.9-100.1+).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of pneumonitis including interstitial lung disease was 6.2% (34/547). Grade 2 and Grade 3 cases were reported in 3.1% (17/547) and 1.1% (6/547) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 2.6 months (range: 0.25-20.6). Twelve patients (2.2%) required permanent discontinuation of nivolumab in combination with ipilimumab. Fifty-nine patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 31 patients (91.2%) with a median time to resolution of 6.1 weeks (range: 4.3-11.4).

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC, the incidence of pneumonitis was 2.5% (5/200). Grade 1, Grade 2 and Grade 3 cases were reported in 1.0% (2/200), 0.5% (1/200) and 1.0% (2/200) of patients, respectively. One of the Grade 3 pneumonitis cases worsened over 40 days with a fatal outcome. Median time to onset was 1.38 months (range: 1.2-2.8). Two patients (1.0%) required permanent discontinuation of nivolumab in combination with ipilimumab. Three patients received high dose corticosteroids (at least 40 mg prednisolone equivalents). Resolution occurred in 5 patients (100%) with a median time to resolution of 7.14 weeks (range: 4.0-20.1).

Intravenous OPDIVO in combination with cabozantinib
In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC the incidence of pneumonitis including interstitial lung disease was 5.3% (17/320). Grade 2 and Grade 3 cases were reported in 1.9% (6/320) and 1.6% (5/320) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 24 weeks (range: 12.3 - 74.3 weeks). Three patients (0.9%) required permanent discontinuation of nivolumab in combination with cabozantinib. Eight patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution

occurred in 12 patients (70.6%) with a median time to resolution of 6.36 weeks (range: 0.1^{+}- 36.9^{+} weeks).

Intravenous OPDIVO in combination with chemotherapy
In patients treated with neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of pneumonitis including interstitial lung disease was 1.1% (2/176). Both cases were Grade 2. Median time to onset was 10.4 weeks (range: 10.3-10.6). No patients required permanent discontinuation of nivolumab in combination with chemotherapy. One patient received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 2 patients (100%) with a median time to resolution of 16.1 weeks (range: 5.7-26.6).

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab 480 mg alone after surgery in resectable NSCLC, the incidence of pneumonitis including interstitial lung disease was 6.1% (14/228). Grade 2, Grade 3 and Grade 5 cases were reported in 3.5% (8/228), 1.3% (3/228), and 0.4% (1/228) respectively. Two deaths due to pneumonitis were reported which occurred after completion of the neoadjuvant treatment period. Nine patients required permanent discontinuation of nivolumab in combination with chemotherapy. Nine patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Median time to onset was 21.1 weeks (range: 0.6-63.4). Resolution occurred in 10 patients (71.4%) with a median time to resolution of 11.6 weeks (range: 0.4-136.9 +).

In patients treated with nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in unresectable or metastatic urothelial carcinoma, the incidence of pneumonitis including interstitial lung disease and immune-mediated lung disease was 2.0% (6/304). Grade 1, Grade 2 and Grade 3 were reported in 1% (3/304), 0.7% (2/304) and 0.3% (1/304) respectively. Median time to onset was 28.21 weeks (range: 24.3 - 46.1). Two patients (0.7%) required permanent discontinuation of nivolumab in combination with chemotherapy. Three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 6 patients (100%) with a median time to resolution of 11.64 weeks (range: 0.9-62.1).

In patients treated with nivolumab 240 mg in combination with chemotherapy in OSCC, the incidence of pneumonitis including interstitial lung disease was 5.8% (18/310). Grade 2 and 3 cases were reported in 3.2% (10/310) and 0.6% (2/310) of patients, respectively. Median time to onset was 31.2 weeks (range: 5.0-85.1). Eleven patients (3.5%) required permanent discontinuation of nivolumab in combination with chemotherapy. Five patients received high dose corticosteroids (at least 40 mg prednisolone equivalents). Resolution occurred in 12 patients (66.7%) with a median time to resolution of 12.1 weeks (range: 1.0-39.9+).

In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy (FOLFOX or XELOX) in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the incidence of pneumonitis including interstitial lung disease was 5.1% (40/782). Grade 2, Grade 3, and Grade 4 cases were reported in 2.3% (18/782), 1.4% (11/782), and 0.4% (3/782), of patients, respectively. Median time to onset was 23.9 weeks (range: 1.6-96.9). Fifteen patients (1.9%) required permanent discontinuation of nivolumab in combination with chemotherapy. Twenty-six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 28 patients (70%) with a median time to resolution of 10.1 weeks (range: 0.3+-121.3+).

Immune-related colitis

OPDIVO SC
In Study CA20967T, immune-mediated colitis occurred in 2.8% (7/247) of patients receiving OPDIVO SC, including Grade 3 (0.4%) and Grade 2 (2.4%) adverse reactions. Colitis led to withholding of OPDIVO SC in 2.0% of patients. Systemic corticosteroids were required in 100% (7/7) of patients with colitis. Colitis resolved in 71% of the 7 patients. Of the 5 patients in whom OPDIVO SC was withheld for colitis, 3 reinitiated OPDIVO SC after symptom improvement; of these, 2 (67%) had recurrence of colitis.

Intravenous OPDIVO monotherapy
In the pooled analysis 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 cases

were reported in 1.4% (67/4646) of patients. Grade 4 cases were reported in <0.1% (1/4646) of patients in these studies. No Grade 5 cases were reported. Median time to onset was 8.3 weeks (range: 0.1-115.6). Fifty-five patients (1.2%) required permanent discontinuation of nivolumab. One-hundred and one (14.1%) patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 639 patients (90.3%) with a median time to resolution of 2.9 weeks (range: 0.1-124.4+).

Intravenous OPDIVO in combination with ipilimumab

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of diarrhoea or colitis was 46.7% (209/448). Grade 2, Grade 3, and Grade 4 cases were reported in 13.6% (61/448), 15.8% (71/448), and 0.4% (2/448) of patients, respectively. No deaths due to diarrhoea or colitis were reported. Median time to onset was 1.2 months (range: 0.0-22.61). Seventy-one patients (15.8%) required permanent discontinuation of nivolumab in combination with ipilimumab. Ninety-six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 184 patients (90.6%) with a median time to resolution of 3.0 weeks (range: 0.1-78.7).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC, the incidence of diarrhoea, colitis, immune-mediated enterocolitis, enteritis or haemorrhagic enterocolitis was 16.9% (56/332). Grade 2 and Grade 3 cases were reported in 5.4% (18/332) and 5.1% (17/332) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 6.29 weeks (range: 0.3-93.6). Seven patients (2.1%) required permanent discontinuation of nivolumab in combination with ipilimumab. Twenty-six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 51 patients (91.1%) with a median time to resolution of 3.57 weeks (range: 0.3-170.0+).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of diarrhoea or colitis was 28.2% (154/547). Grade 2 and Grade 3 cases were reported in 10.4% (57/547) and 4.9% (27/547) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 1.2 months (range: 0.0-24.7). Twenty-two patients (4.0%) required permanent discontinuation of nivolumab in combination with ipilimumab. Twenty-six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 140 patients (91.5%) with a median time to resolution of 2.4 weeks (range: 01-103.1).

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC, the incidence of diarrhoea or colitis was 23.0% (46/200). Grade 1, Grade 2, Grade 3 and Grade 4 cases were reported in 13.5% (27/200), 5.0% (10/200), 4.0% (8/200) and 0.5% (1/200) of patients, respectively. Median time to onset was 2.84 months (range: 0.1-18.5). Six patients (3.0%) required permanent discontinuation of nivolumab in combination with ipilimumab. Nine patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 43 patients (93.5%) with a median time to resolution of 4.14 weeks (range: 0.1-93.0+).

Intravenous OPDIVO in combination with cabozantinib

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of diarrhoea, colitis, frequent bowel movements or enteritis was 57.5% (184/320). Grade 2 and Grade 3 cases were reported in 25% (80/320) and 5.3% (17/320) of patients, respectively. Grade 4 were reported in 0.6% (2/320). No Grade 5 cases were reported. Median time to onset was 12.36 weeks (range: 0.3 - 75.7 weeks). Three patients (0.9%) required permanent discontinuation of nivolumab in combination with cabozantinib. Fifteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 127 patients (69.4%) with a median time to resolution of 11.14 weeks (range: 0.1 - 109.1^{+} weeks).

Intravenous OPDIVO in combination with chemotherapy

In patients treated with neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of diarrhoea was 5.7% (10/176). Grade 2 and Grade 3 cases were reported in 0.6% (1/176) in each grade, respectively. No patients required permanent discontinuation of nivolumab in combination with chemotherapy. One patient received high-dose corticosteroids (at least 40 mg prednisone equivalents). Median time to onset was 1.0 week (range: 0.3-4.9). Resolution occurred in all patients (100%) with a median time to resolution of 0.7 week (range: 0.1-1.3).

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab 480 mg alone after surgery in resectable NSCLC, the incidence of diarrhea or colitis was 12.3% (28/228). Grade 2 and Grade 3 cases were reported in 6.6% (15/228) and 2.2% (5/228) respectively. Four patients required permanent discontinuation of nivolumab in combination with chemotherapy. Four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Median time to onset was 3.8 weeks (range: 0.3-67.3). Resolution occurred in 28 patients (100%) with a median time to resolution of 1.1 weeks (range: 0.3-28.1).

In patients treated with nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in unresectable or metastatic urothelial carcinoma, the incidence of diarrhoea or colitis was 13.8% (42/304). Grade 1, Grade 2 and Grade 3 were reported in 8.2% (25/304), 3.6% (11/304) and 2.0% (6/304) respectively. Median time to onset was 6.64 weeks (range: 0.1-48.3). Two patients (0.7%) required permanent discontinuation of nivolumab in combination with chemotherapy. Four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 36 patients (85.7%) with a median time to resolution of 2.64 weeks (range: 0.1 - 212.3+).

In patients treated with nivolumab 240 mg in combination with chemotherapy in OSCC, the incidence of diarrhoea or colitis was 20.6% (64/310). Grade 2, Grade 3, and 4 cases were reported in 7.4% (23/310), 1.9% (6/310), and 0.3% (1/310) of patients, respectively. Median time to onset was 5.1 weeks (range: 0.3-53.1). Six patients (1.9%) required permanent discontinuation of nivolumab in combination with chemotherapy. Five patients received high dose corticosteroids (at least 40 mg prednisolone equivalents). Resolution occurred in 58 patients (90.6%) with a median time to resolution of 1.5 weeks (range: 0.1-65.9+).

In patients treated with nivolumab 240 mg and 360 mg in combination with chemotherapy (FOLFOX or XELOX) in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the incidence of diarrhoea or colitis was 33.5% (262/782). Grade 2, Grade 3, and Grade 4 cases were reported in 10.2% (80/782), 4.9% (38/262), and 0.6% (5/782) of patients, respectively. Median time to onset was 4.3 weeks (range: 0.1-93.6). Twenty-two patients (2.8%) required permanent discontinuation of nivolumab in combination with chemotherapy. Twenty-one patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 228 patients (87.4%) with a median time to resolution of 1.6 weeks (range: 0.1-117.6+).

Immune-related hepatitis

OPDIVO SC
In Study CA20967T, immune-mediated hepatitis occurred in 2.4% (6/247) of patients receiving OPDIVO SC, including Grade 3 (1.6%), and Grade 2 (0.8%) adverse reactions. Hepatitis led to permanent discontinuation of OPDIVO SC in 0.8% and withholding of OPDIVO SC in 1.6% of patients. Systemic corticosteroids were required in 100% (6/6) of patients with hepatitis. Hepatitis resolved in 67% of the 6 patients. Of the 2 patients in whom OPDIVO SC was withheld for hepatitis, 2 reinitiated OPDIVO SC after symptom improvement; of these, 1 (50%) had recurrence of hepatitis.

Intravenous OPDIVO monotherapy
In the pooled analysis 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. No Grade 5 cases were reported. Median time to onset was 10.6 weeks (0.1 - 132.0). Fifty-two patients (1.1%) required permanent discontinuation of nivolumab. Seventy-eight (21.0%) patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 298 patients (81.4%) with a median time to resolution of 6.1weeks (range: 0.1-126.4+).

Safety data for the HCC indication are limited to a cohort of 154 patients with Child-Pugh A disease and WHO PS 0-1. Close monitoring is recommended in patients with cirrhosis, in case immune-related hepatitis might precipitate decompensation.

Intravenous OPDIVO in combination with ipilimumab
In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of liver function test abnormalities was 29.5% (132/448). Grade 2, Grade 3, and Grade 4 cases were reported in 6.7% (30/448), 15.4% (69/448), and 1.8% (8/448) of patients, respectively. No

deaths due to liver function abnormalities were reported. Median time to onset was 1.5 months (range: 0.0-30.1). Forty-one patients (9.2%) required permanent discontinuation of nivolumab in combination with ipilimumab. Fifty-eight patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 116 patients (92.8%) with a median time to resolution of 5.0 weeks (range: 0.1-53.1).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC, the incidence of liver function test abnormalities was 34.3% (114/332). Grade 2, Grade 3, and Grade 4 cases were reported in 8.4% (28/332), 14.2% (47/332), and 2.7% (9/332) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 4.71 weeks (range: 0.9-88.9). Twenty patients (6%) required permanent discontinuation of nivolumab in combination with ipilimumab. Fifty-four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 94 patients (82.5%) with a median time to resolution of 6.0 weeks (range: 0.4+-129.3+).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of liver function test abnormalities was 18.5% (101/547). Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (26/547), 6.6% (36/547), and 1.6% (9/547) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.0 months (range: 0.4-26.8). Twenty-four patients (4.4%) required permanent discontinuation of nivolumab in combination with ipilimumab. Thirty-five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 86 patients (85.1%) with a median time to resolution of 6.1 weeks (range: 0.1-82.9).

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC, the incidence of liver function test abnormalities was 19.5% (39/200). Grade 1, Grade 2, Grade 3, and Grade 4 cases were reported in 7.5% (15/200), 7.5% (15/200), 4.0% (8/200) and 0.5% (1/200) of patients, respectively. Median time to onset was 2.79 months (range: 0.4-15.8). Five patients (2.5%) required permanent discontinuation of nivolumab in combination with ipilimumab. Ten patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 36 patients (92.3%) with a median time to resolution of 7.14 weeks (range: 0.9-98.3+).

Intravenous OPDIVO in combination with cabozantinib

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of liver function test abnormalities was 40% (128/320). Grade 2, Grade 3, and Grade 4 cases were reported in 15% (48/320), 9.7% (31/320), and 0.6% (2/320) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 8.14 weeks (range: 0.1 - 88.3 weeks). Ten patients (3.1%) required permanent discontinuation of nivolumab in combination with cabozantinib. Thirty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 99 patients (77.3%) with a median time to resolution of 9.14 weeks (range: 0.1 - 65.7^{+} weeks).

Intravenous OPDIVO in combination with chemotherapy

In patients treated with neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of liver function test abnormalities was 8.0% (14/176). Thirteen cases were reported as Grade 1 and one case was reported as Grade 3. No patients required permanent discontinuation of nivolumab in combination with chemotherapy or received high-dose corticosteroids (at least 40 mg prednisone equivalents). Median time to onset was 1.3 weeks (range: 1.0-6.9). Resolution occurred in 13 patients (100%) with a median time to resolution of 2.4 weeks (range: 0.7-21.1).

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab 480 mg alone after surgery in resectable NSCLC, the incidence of liver function test abnormalities was 13.2% (30/228). Grade 2 and Grade 3 cases were reported in 1.8% (4/228) and 1.3% (3/228) of patients, respectively. No patients required permanent discontinuation of nivolumab in combination with chemotherapy or received high-dose corticosteroids (at least 40 mg prednisone equivalents). Median time to onset was 3.7 weeks (range: 0.6-55.9). Resolution occurred in 27 patients (90%) with a median time to resolution of 5.7 weeks (range: 0.6-123.3+).

In patients treated with nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in unresectable or metastatic urothelial carcinoma, the incidence of liver function test abnormalities was

13.2% (40/304). Grade 1, Grade 2 and Grade 3 were reported in 7.2% (22/304), 3.3% (10/304) and 2.6% (8/304) respectively. Median time to onset was 14.79 weeks (range: 0.4-99.0). No patient required permanent discontinuation of nivolumab in combination with chemotherapy. Three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 29 patients (72.5%) with a median time to resolution of 5.29 weeks (range: 0.6 - 240.0+).

In patients treated with nivolumab 240 mg in combination with chemotherapy in OSCC, the incidence of liver function test abnormalities was 10.3% (32/310). Grade 2, Grade 3 and 4 cases were reported in 1.9% (6/310), 1.9% (6/310) and 0.3% (1/310) of patients, respectively. Median time to onset was 7.9 weeks (range: 0.3-84.1). Three patients (1.0%) required permanent discontinuation of nivolumab in combination with chemotherapy. One patient received high dose corticosteroids (at least 40 mg prednisolone equivalents). Resolution occurred in 28 patients (90.3%) with a median time to resolution of 2.4 weeks (range: 0.4-24.0+).

In patients treated with nivolumab 240 mg and 360 mg in combination with chemotherapy (FOLFOX or XELOX) in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the incidence of liver function test abnormalities was 26% (203/782). Grade 2 and Grade 3 cases were reported in 9.0% (70/782) and 3.7% (29/782) of patients, respectively. Median time to onset was 7.9 weeks (range: 0.1-61.3 Nine patients (1.2%) required permanent discontinuation of nivolumab in combination with chemotherapy. Eighteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 156 patients (78%) with a median time to resolution of 10.1 weeks (range: 0.4-150.6+).

Immune-related nephritis and renal dysfunction

OPDIVO SC
In Study CA20967T, Grade 2 immune-mediated nephritis and renal dysfunction occurred in 1.2% (3/247) of patients receiving OPDIVO SC. Immune-mediated nephritis and renal dysfunction led to withholding of OPDIVO SC in 1.2% of patients. Systemic corticosteroids were required in 100% (3/3) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 100% of the 3 patients. Of the 3 patients in whom OPDIVO SC was withheld for nephritis or renal dysfunction, 1 reinitiated OPDIVO SC after symptom improvement without recurrence of nephritis or renal dysfunction.

Intravenous OPDIVO monotherapy
In the pooled analysis in patients treated with nivolumab monotherapy, the incidence of nephritis and renal dysfunction was 3.6% (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). Fifteen patients (0.3%) required permanent discontinuation of nivolumab. Twenty-seven (22.3%) patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 80 patients (69.0%) with a median time to resolution of 8.0 weeks (range: 0.3-79.1+).

Intravenous OPDIVO in combination with ipilimumab
In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of nephritis or renal dysfunction was 5.1% (23/448). Grade 2, Grade 3, and Grade 4 cases were reported in 1.6% (7/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No deaths due to nephritis or renal dysfunction were reported. Median time to onset was 2.6 months (range: 0.5-21.8). Four patients (0.9%) required permanent discontinuation of nivolumab in combination with ipilimumab. Four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 17 patients (89.5%) with a median time to resolution of 1.9 weeks (range: 0.4-42.6).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC, the incidence of nephritis or renal dysfunction was 1.8% (6/332). Grade 2 and Grade 3 cases were reported in 0.6% (2/332) and 0.3% (1/332) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 12.5 weeks (range: 1.9-58.1). One patient (0.3%) required permanent discontinuation of nivolumab in combination with ipilimumab. Two patients received high-dose

corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 6 patients (100%) with a median time to resolution of 3.64 weeks (range: 0.6-23.9).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of nephritis or renal dysfunction was 8.8% (48/547). Grade 2, Grade 3, and Grade 4 cases were reported in 4.4% (24/547), 0.7% (4/547), and 0.5% (3/547) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.1 months (range: 0.0-16.1). Seven patients (1.3%) required permanent discontinuation of nivolumab in combination with ipilimumab. Twenty-seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 37 patients (77.1%) with a median time to resolution of 13.2 weeks (range: 4.1-21.1).

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC, the incidence of renal dysfunction was 3.5% (7/200). Grade 1, Grade 2 and Grade 4 cases were reported in 2.5% (5/200), 0.5% (1/200) and 0.5% (1/200) of patients, respectively. Median time to onset was 4.57 months (range: 0.6-17.5). Two patients (1.0%) required permanent discontinuation of nivolumab in combination with ipilimumab. Two patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 7 patients (100%) with a median time to resolution of 1.14 weeks (range: 0.3-12.3).

Intravenous OPDIVO in combination with cabozantinib
In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of nephritis, immune mediated nephritis, renal failure, acute kidney injury, blood creatinine increased or blood urea increased was 9.7% (31/320). Grade 2, Grade 3, and Grade 4 cases were reported in 3.4% (11/320), and 1.3% (4/320), respectively. No Grade 4 or 5 cases were reported. Median time to onset was 14.14 weeks (range: 2.1 - 86 weeks.). One patient (0.3%) required permanent discontinuation of nivolumab in combination with cabozantinib. Three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 21 patients (70%) with a median time to resolution of 3.5 weeks (range: 0.6 - 83.9^{+} weeks).

Intravenous OPDIVO in combination with chemotherapy
In patients treated with neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of renal dysfunction including acute kidney injury was 7.4% (13/176). Grade 2 and Grade 3 cases were reported in 1.1% (2/176) and 0.6% (1/176) of patients, respectively. Two patients required permanent discontinuation of nivolumab in combination with chemotherapy. No patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Median time to onset was 1.3 weeks (range: 0.9-9.1). Resolution occurred in 10 patients (76.9%) with a median time to resolution of 2.9 weeks (range: 0.7-140.7+).

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab 480 mg alone after surgery in resectable NSCLC, the incidence of renal dysfunction including acute kidney injury was 11.4% (26/228). Grade 2, Grade 3 and Grade 4 cases were reported in 0.9% (2/228), 0.4 (1/228) and 0.4% (1/228) of patients, respectively. Three patients required permanent discontinuation of nivolumab in combination with chemotherapy. Five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Median time to onset was 5.9 weeks (range: 0.4-59.6). Resolution occurred in 22 patients (84.6%) with a median time to resolution of 4.7 weeks (range: 0.3-92.1+).

In patients treated with nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in unresectable or metastatic urothelial carcinoma, the incidence of renal dysfunction including acute kidney injury was 19.1% (58/304). Grade 1, Grade 2 and Grade 3 were reported in 8.2% (25/304), 7.2% (22/304) and 3.6% (11/304) respectively. Median time to onset was 4.14 weeks (range: 0.1 - 38.3). Fourteen patients (4.6%) required permanent discontinuation of nivolumab in combination with chemotherapy. Two patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 39 patients (67.2%) with a median time to resolution of 18.29 weeks (range: 0.6 - 226.0+).

In patients treated with nivolumab 240 mg in combination with chemotherapy in OSCC, the incidence of renal dysfunction was 23.9% (74/310). Grade 2, Grade 3, and 4 cases were reported in 10.6% (33/310), 1.9% (6/310), and 0.3% (1/310) of patients, respectively. Median time to onset was 10.1 weeks (range: 0.7-60.7). Twenty-seven patients (8.7%) required permanent discontinuation of

nivolumab in combination with chemotherapy. Four patients received high dose corticosteroids (at least 40 mg prednisolone equivalents). Resolution occurred in 42 patients (56.8%) with a median time to resolution of 17.1 weeks (range: 0.4-128.1+).

In patients treated with nivolumab 240 mg and 360 mg in combination with chemotherapy (FOLFOX or XELOX) in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the incidence of nephritis or renal dysfunction was 3.3% (26/782). Grade 2, Grade 3, and Grade 4 cases were reported in 1% (8/782), 0.6% (5/782), and 0.1% (1/782) of patients, respectively. Median time to onset was 12.4 weeks (range: 1.7-59.4). Nine patients (1.2%) required permanent discontinuation of nivolumab in combination with chemotherapy. Four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 19 patients (73.1%) with a median time to resolution of 3.1 weeks (range: 0.1-42.4+).

Immune-related endocrinopathies

OPDIVO SC
In Study CA20967T, adrenal insufficiency occurred in 2% (5/247) of patients receiving OPDIVO SC, including Grade 3 (0.8%) and Grade 2 (1.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO SC in 0.4% of patients and withholding of OPDIVO SC in 0.4% of patients. Systemic corticosteroids were required in 100% (5/5) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 20% of the 5 patients. Thyroiditis occurred in 0.4% (1/247) of patients receiving OPDIVO SC, including a Grade 1 (0.4%) adverse reaction. Systemic corticosteroids were not required in the patient with thyroiditis. Thyroiditis did not resolve in this patient. Hyperthyroidism occurred in 0.8% (2/247) of patients receiving OPDIVO SC, including Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were not required in patients with hyperthyroidism. Hyperthyroidism resolved in 50% of the 2 patients. Hypothyroidism occurred in 9% (23/247) of patients receiving OPDIVO SC, including Grade 2 (5.7%) adverse reactions. Hypothyroidism led to withholding of OPDIVO SC in 0.8% of patients. Systemic corticosteroids were not required in patients with hypothyroidism. Hypothyroidism resolved in 4.3% of the 23 patients. Of the 1 patient in whom OPDIVO SC was withheld for hypothyroidism, OPDIVO SC was not reinitiated after symptom improvement. Grade 3 diabetes occurred in 0.4% (1/247) of patients receiving OPDIVO SC. No patients with diabetes required systemic corticosteroids. Diabetes did not resolve in this patient.

Intravenous OPDIVO monotherapy
In the pooled analysis 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 disorders (including adrenal insufficiency, secondary adrenocortical insufficiency and adrenocortical insufficiency acute)) (2 Grade 1; 23 Grade 2; and 11 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus) (1 Grade 1, 3 Grade 2, 5 Grade 3 and 1 Grade 4), and diabetic ketoacidosis (2 Grade 3 and 1 Grade 4) were also reported. Median time to onset of these endocrinopathies was 11.1 weeks (range: 0.1-126.7). Twenty-four patients (0.5%) required permanent discontinuation of nivolumab. Thirty-six (5.4%) patients received high dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 323 patients (48.7%). Time to resolution ranged from 0.4 to 204.4+ weeks.

Intravenous OPDIVO in combination with ipilimumab
In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of thyroid disorders was 25.2% (113/448). Grade 2 and Grade 3 thyroid disorders were reported in 14.5% (65/448) and 1.3% (6/448) of patients, respectively. Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 5.8% (26/448) and 2.0% (9/448) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.4% (2/448) and 0.7% (3/448) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 1.6% (7/448), 1.3% (6/448) and 0.2% (1/448) of patients respectively. Grade 1, Grade 2, Grade 3 and Grade 4 diabetes mellitus and Grade 4 diabetic ketoacidosis were each reported in 0.2% (1/448) of patients. No deaths due to endocrinopathy were reported. Median time to onset of these endocrinopathies was 1.9 months (range: 0.0-28.1). Eleven patients (2.5%) required permanent discontinuation of nivolumab in combination with ipilimumab. Thirty-six patients

received high dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 59 patients (45.0%). Time to resolution ranged from 0.4 to 74.4 weeks.

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC, the incidence of thyroid disorders was 24.7% (82/332). Grade 2 and Grade 3 thyroid disorders cases were reported in 15.7% (52/332) and 0.9% (3/332) of patients, respectively. Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 1.2% (4/332) and 0.9% (3/332) of patents, respectively. Grade 3 hypopituitarism occurred in 0.3% (1/332) of patients. Grade 2 and Grade 3 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 3.0% (10/332) and 1.2% (4/332) of patients, respectively. Only Grade 3 diabetes mellitus was reported in 0.6% (2/332) of patients. No Grade 4 or 5 endocrinopathies were reported in this study. Median time to onset of these endocrinopathies was 8.71 weeks (range: 0.1-102.3). Six patients (1.8%) required permanent discontinuation of nivolumab in combination with ipilimumab. Ten patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 43 patients (45.7%). Time to resolution ranged from 0.6 to 191.1+ weeks.

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of thyroid disorders was 27.2% (149/547). Grade 2 and Grade 3 thyroid disorders were reported in 15.7% (86/547) and 1.3% (7/547) of patients, respectively. Hypophysitis occurred in 4.0% (22/547) of patients. Grade 2, Grade 3, and Grade 4 cases were reported in 0.5% (3/547), 2.4% (13/547), and 0.4% (2/547) of patients, respectively. Grade 2 hypopituitarism occurred in 0.4% (2/547) of patients. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 2.9% (16/547), 2.2% (12/547) and 0.4% (2/547) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus (3 Grade 2, 2 Grade 3, and 3 Grade 4), and diabetic ketoacidosis (1 Grade 4) were reported. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 1.9 months (range: 0.0-22.3). Three patients (2.9%) required permanent discontinuation of nivolumab in combination with ipilimumab. Twenty-five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 71 patients (42.7%) with a median time to resolution of 0.4 to 130.3 weeks.

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC, the incidence of thyroid disorders was 24.0% (48/200). Grade 1, Grade 2 and Grade 3 thyroid disorders were reported in 12.5% (25/200), 10.0% (20/200) and 1.5% (3/200) of patients, respectively. Hypophysitis occurred in 4.5% (9/200) of patients. Grade 1, Grade 2, and Grade 3 cases were reported in 1.0% (2/200), 1.5% (3/200), and 2.0% (4/200) of patients, respectively. Grade 3 hypopituitarism occurred in 0.5% (1/200) of patients. Grade 1, Grade 2 and Grade 3 adrenal insufficiency occurred in 1.5% (3/200), 5.5% (11/200) and 3.0% (6/200) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus (2 Grade 2) were reported. Median time to onset of these endocrinopathies was 2.86 months (range: 0.7-23.6). Six patient (3.0%) required permanent discontinuation of nivolumab in combination with ipilimumab. Eleven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 27 patients (40.3%). Time to resolution ranged from 0.9 to 201.6+ weeks.

Intravenous OPDIVO in combination with cabozantinib

In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of thyroid disorders was 42.2% (135/320). Grade 2 and Grade 3 thyroid disorders were reported in 21.9% (70/320) and 0.9% (3/320) of patients, respectively. Hypophysitis occurred in 0.6% (2/320) of patients. Grade 2, and Grade 3 cases were reported in 0.3% (1/320), and 0.3% (1/320) of patients, respectively. Grade 2, and Grade 3 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 1.6% (5/320) and 1.9% (6/320) of patients, respectively. No Grade 4 or Grade 5 endocrinopathies were reported. Median time to onset of these endocrinopathies was 12.4 weeks (range: 2.0-84.7 weeks). Five patients (1.6%) required permanent discontinuation of nivolumab in combination with cabozantinib. Six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 47 patients (34.3%). Time to resolution ranged from 0.9 to 101.4+ weeks.

Intravenous OPDIVO in combination with chemotherapy

In patients treated with neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of thyroid disorders was 5.1% (9/176). Grade 2 thyroid disorders were reported in 0.6% (1/176) of patients. Diabetes mellitus (Grade 1) was reported

in 0.6% (1/176) of patients. Median time to onset of these endocrinopathies was 6.1 weeks (range: 3.1-10.7). No patients required permanent discontinuation of nivolumab in combination with chemotherapy or received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 7 patients (70.0%). Time to resolution ranged from 0.9 to 169.1+ weeks.

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab 480 mg alone after surgery in resectable NSCLC, the incidence of thyroid disorders was 13.2% (30/228). Grade 2 and Grade 3 thyroid disorders were reported in 7.5% (17/228) and 0.4% (1/228) of patients, respectively. Grade 2 adrenal insufficiency cases were reported in 0.9% (2/228) of patients. Grade 2 diabetes mellitus and hypopituitarism was reported in 0.4% (1/228) of patients. Median time to onset of these endocrinopathies was 20.9 weeks (range: 5.7-62.7). One patient required permanent discontinuation of nivolumab in combination with chemotherapy. No patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 19 patients (57.6%). Time to resolution ranged from 0.3+ to 140.1+ weeks.

In patients treated with nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in unresectable or metastatic urothelial carcinoma, the incidence of thyroid disorders was 20.4% (62/304). Grade 1, Grade 2 and Grade 3 thyroid disorders were reported in 8.2% (25/304), 11.8% (36/304) and 0.3% (1/304) respectively. Grade 1 and Grade 3 hypopituitarism occurred in 0.3% (1/304) and 0.3% (1/304) of patients, respectively. Grade 3 hypophysitis occurred in 0.3% (1/304) of patients. Grade 2 and Grade 3 adrenal insufficiency occurred in 0.3% (1/304) and 0.3% (1/304) of patients respectively. Grade 2 diabetes mellitus was reported in 0.3% (1/304) of patients. Diabetic ketoacidosis was reported in 0.3% (1/304) of patients. Median time to onset of these endocrinopathies was 17.93 weeks (range: 1.1-62.7). Four patients required permanent discontinuation of nivolumab in combination with chemotherapy. Three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 18 patients (28.1%) with a range of 2.1 - 233.6+ weeks.

In patients treated with nivolumab 240 mg in combination with chemotherapy in OSCC, the incidence of thyroid disorders was 9.7% (30/310). Grade 2 thyroid disorders were reported in 4.2% (13/310) of patients. Grade 2 and 3 adrenal insufficiency cases were reported in 1.6% (5/310) and 0.3% (1/310) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus and fulminant Type 1 diabetes mellitus (1 Grade 3 and 1 Grade 4), and diabetic ketoacidosis (1 Grade 4) were reported. Median time to onset of these endocrinopathies was 13.0 weeks (range: 5.0-100.0). Two patients (0.6%) required permanent discontinuation of nivolumab in combination with chemotherapy. One patient received high dose corticosteroids (at least 40 mg prednisolone equivalents). Resolution occurred in 10 patients (28.6%). Time to resolution ranged from 4.1 to 125.6+ weeks.

In patients treated with nivolumab 240 mg and 360 mg in combination with chemotherapy (FOLFOX or XELOX) in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the incidence of thyroid disorders was 12.3% (96/782). Grade 2 thyroid disorder was reported in 6% (47/782) patients. Grade 3 hypophysitis occurred in 0.1% (1/782) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.3% (2/782) and 0.3% (2/782) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 0.4% (3/782) and 0.1% (1/782) of patients, respectively. Grade 2 and Grade 3 diabetes mellitus including Type 1 diabetes mellitus were reported in 0.3% (2/782) of patients. Median time to onset of these endocrinopathies was 15.0 weeks (range: 2.0-124.3). Three patients (0.4%) required permanent discontinuation of nivolumab in combination with chemotherapy. Six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 46 patients (43%). Time to resolution ranged from 0.4 to 139.1+ weeks.

Immune-related skin adverse reactions

OPDIVO SC

In Study CA20967T, immune-mediated rash occurred in 7% (17/247) of patients, including Grade 3 (0.8%) and Grade 2 (2.8%) adverse reactions. Immune-mediated rash led to withholding of OPDIVO SC in 1.2% of patients. Systemic corticosteroids were required in 47% (8/17) of patients with immune-mediated rash. Rash resolved in 77% of the 17 patients. Of the 3 patients in whom OPDIVO SC was withheld for immune-mediated rash, all reinitiated OPDIVO SC after symptom improvement; of these, all (100%) had recurrence of immune-mediated rash.

Intravenous OPDIVO monotherapy
In the pooled analysis 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). Thirty-five patients (0.8%) required permanent discontinuation of nivolumab. Forty-six (3.3%) patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 896 patients (64.6%) with a median time to resolution of 20.1 weeks (0.1-192.7+).

Intravenous OPDIVO in combination with ipilimumab
In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of rash was 65% (291/448). Grade 2 and Grade 3 cases were reported in 20.3% (91/448) and 7.6% (34/448) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 0.5 months (range: 0.0-19.4). Three patients (0.7%) required permanent discontinuation of nivolumab in combination with ipilimumab. Twenty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 192 patients (67.6%) with a median time to resolution of 10.4 weeks (range: 0.1-74.0).

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC, the incidence of rash was 51.8% (172/332). Grade 2, Grade 3, and Grade 4 cases were reported in 18.7% (62/332), 5.4% (18/332), and 0.3% (1/332) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 3.0 weeks (range: 0.1-104.1). Four patients (1.2%) required permanent discontinuation of nivolumab in combination with ipilimumab. Fourteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 119 patients (69.6%) with a median time to resolution of 15.71 weeks (range: 0.1-170.7+).

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of rash was 48.8% (267/547). Grade 2 and Grade 3 cases were reported in 13.7% (75/547) and 3.7% (20/547) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 0.9 months (range: 0.0-17.9). Eight patients (1.5%) required permanent discontinuation of nivolumab in combination with ipilimumab. Seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 192 patients (72.2%) with a median time to resolution of 11.6 weeks (range: 8.7-17.1).

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC, the incidence of rash was 34.5% (69/200). Grade 1, Grade 2 and Grade 3 cases were reported in 24.5% (49/200), 7.5% (15/200) and 2.5% (5/200) of patients, respectively. Median time to onset was 1.22 months (range: 0.0-14.7). Two patients (1.0%) required permanent discontinuation of nivolumab in combination with ipilimumab. Five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 52 patients (75.4%) with a median time to resolution of 11.86 weeks (range: 0.1-154.6+).

Intravenous OPDIVO in combination with chemotherapy
In patients treated with neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of rash was 22.2% (39/176). Grade 2 and Grade 3 cases were reported in 5.7% (10/176) and 2.3% (4/176) of patients, respectively. Two patients required permanent discontinuation of nivolumab in combination with chemotherapy. No patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Median time to onset was 1.3 weeks (range: 0.1-6.3). Resolution occurred in 36 patients (92.3%) with a median time to resolution of 3.0 weeks (range: 0.3-142.7+).

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab 480 mg alone after surgery in resectable NSCLC, the incidence of rash was 23.7% (54/228). Grade 2 and Grade 3 cases were reported in 6.1% (14/228) and 1.3% (3/228) of patients, respectively. Two patients required permanent discontinuation of nivolumab in combination with chemotherapy. Four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Median time to onset was 4.3 weeks (range: 0.1-61.0). Resolution occurred in 46 patients (85.2%) with a median time to resolution of 10.1 weeks (range: 0.1-117.4+).

In patients treated with nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in unresectable or metastatic urothelial carcinoma, the incidence of rash was 31.6% (96/304). Grade 1,

Grade 2 and Grade 3 were reported in 23.7% (72/304), 5.3% (16/304) and 2.6% (8/304) respectively. Median time to onset was 8.86 weeks (range: 0.1 - 77.7). One patient required permanent discontinuation of nivolumab in combination with chemotherapy. Six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 68 patients (71.6%) with a median time to resolution of 10.29 weeks (range: 0.3 - 258.7+).

In patients treated with nivolumab 240 mg in combination with chemotherapy in OSCC, the incidence of rash was 17.1% (53/310). Grade 2 and 3 cases were reported in 4.5% (14/310) and 0.3% (1/310) of patients, respectively. Median time to onset was 5.9 weeks (range: 0.1-61.1). No patients permanently discontinued nivolumab in combination with chemotherapy. One patient received high dose corticosteroids (at least 40 mg prednisolone equivalents). Resolution occurred in 40 patients (75.5%) with a median time to resolution of 8.1 weeks (range: 0.1-157.0+).

In patients treated with nivolumab 240 mg and 360 mg in combination with chemotherapy (FOLFOX or XELOX) in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the incidence of rash was 27.4% (214/782). Grade 2 and Grade 3 cases were reported in 7% (55/782), and 3.3% (26/782) of patients, respectively. Median time to onset was 9.6 weeks (range: 0.1-97.4). Eleven patients (1.4%) required permanent discontinuation of nivolumab in combination with chemotherapy. Fourteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 124 patients (57.9%) with a median time to resolution of 23.4 weeks (range: 0.1-153.6+).

Intravenous OPDIVO in combination with cabozantinib
In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of rash was 62.2% (199/320). Grade 2 and Grade 3 cases were reported in 22.5% (72/320) and 10.6% (34/320) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 6.14 weeks (range: 0.1 - 92.3 weeks). Four patients (1.3%) required permanent discontinuation of nivolumab in combination with cabozantinib. Fifteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 131 patients (65.8%) with a median time to resolution of 17.71 weeks (range: 0.1 - 106.6^{+} weeks).

Infusion reactions

Intravenous OPDIVO monotherapy
In the pooled analysis in patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions, including anaphylactic reaction, was 4.0% (188/4646), including 1.7% Grade 1, 2.1% Grade 2, 0.2% Grade 3 and <0.1% Grade 4 cases. No Grade 5 cases were reported.

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

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in HCC, the incidence of hypersensitivity/infusion reactions was 2.4% (8/332). Grade 1, Grade 2 and Grade 3 cases were reported in 0.6% (2/332), 1.5% (5/332) and 0.3% (1/332) of patients, respectively. No Grade 4 or 5 cases were reported.

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

In patients treated with nivolumab 240 mg in combination with ipilimumab 1 mg/kg in MSI-H/dMMR CRC, the incidence of hypersensitivity/infusion reactions was 4.0% (8/200); Grade 1 and Grade 2 cases were reported in 1.5% (3/200) and 2.5% (5/200) of patients, respectively. No Grade 3-5 cases were reported.

Intravenous OPDIVO in combination with cabozantinib
In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of hypersensitivity/infusion reactions was 2.5% (8/320); All 8 patients were Grade 1 or 2 in severity. Grade 2 cases were reported in 0.3% (1/320) of patients. No Grade 3-5 cases were reported.

Intravenous OPDIVO in combination with chemotherapy
In patients treated with neoadjuvant nivolumab 360 mg in combination with platinum-doublet chemotherapy in resectable NSCLC, the incidence of hypersensitivity/infusion reactions was 5.7% (10/176). Grade 2, Grade 3, and Grade 4 cases were reported in 1.1% (2/176), 1.7% (3/176), and 0.6% (1/176) of patients, respectively.

In patients treated with nivolumab 360 mg in combination with platinum-doublet chemotherapy followed by nivolumab 480 mg alone after surgery in resectable NSCLC, the incidence of hypersensitivity/infusion reactions was 6.1% (14/228). Grade 2 and Grade 3 cases were reported in 3.1% (7/228), and 0.9% (2/228) of patients, respectively.

In patients treated with nivolumab 360 mg every 3 weeks in combination with cisplatin and gemcitabine in unresectable or metastatic urothelial carcinoma, the incidence of hypersensitivity/infusion reactions was 3.3% (10/304). Grade 1 and Grade 2 were reported in 2.0% (6/304) and 1.3% (4/304) respectively.

In patients treated with nivolumab 240 mg in combination with chemotherapy in OSCC, the incidence of hypersensitivity/infusion reactions was 1.9% (6/310). All 6 patients were Grade 1 or 2 in severity 1.0% (3/310) and 1.0% (3/310), respectively.

In patients treated with nivolumab 240 mg and 360 mg in combination with chemotherapy in (FOLFOX or XELOX) gastric cancer, gastro-oesophageal junction cancer or oesophageal adenocarcinoma, the incidence of hypersensitivity/infusion reactions was 14.2% (111/782). Grade 2, Grade 3, and Grade 4 cases were reported in 8.8% (69/782), 1.9% (15/782) and 0.3% (2/782) of patients, respectively.

Immune-related neurological adverse reactions

The following adverse events observed across clinical trials of intravenous nivolumab or intravenous nivolumab in combination with ipilimumab were reported in less than 1% of patients: demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, and encephalitis. No immune-related neurological adverse reactions were reported for OPDIVO SC in Study CA20967T.

Other immune-related adverse reactions

Other clinically significant immune-related adverse reactions have been observed. Some of these have had fatal outcome. Across clinical trials of nivolumab or nivolumab in combination with ipilimumab investigating various doses and tumour types, the following immune-related adverse reactions were reported in less than 1% of patients: pancreatitis, uveitis, gastritis, sarcoidosis, duodenitis, aseptic meningitis, myositis, myocarditis, rhabdomyolysis and myocarditis-myositis-myasthenia gravis overlap syndrome.

POSTMARKETING EXPERIENCE

The following events have been identified during post approval use of intravenous nivolumab or intravenous nivolumab in combination with ipilimumab. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Eye disorders: Vogt-Koyanagi-Harada syndrome

Immune-system disorders: solid organ transplant rejection, treatment refractory, severe acute and chronic graft-versus-host-disease, haemophagocytic lymphohistiocytosis (including fatal cases), systemic inflammatory response syndrome

Endocrine-system disorders: hypoparathyroidism

Blood and lymphatic disorders: autoimmune anaemia and haemolytic anaemia (including fatal cases)

Nervous System Disorders: myelitis (including transverse myelitis), myocarditis-myositis-myasthenia gravis overlap syndrome

Hepatobiliary: cholangitis

Musculoskeletal and connective tissue disorders: arthritis (including immune-mediated arthritis), tenosynovitis.

Gastrointestinal disorders: enterocolitis

Metabolism and nutrition disorders: tumour lysis syndrome*

* Specific to nivolumab in combination with ipilimumab

REPORTING SUSPECTED ADVERSE EFFECTS

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdosage with OPDIVO SC.

In case of overdosage, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

MECHANISM OF ACTION

OPDIVO SC contains the active substance nivolumab, which provides the therapeutic effect of this medicinal product, and recombinant human hyaluronidase PH20 (vorhyaluronidase alfa; rHuPH20), an enzyme used to increase the dispersion and absorption of co-formulated substances when administered subcutaneously.

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb) which binds to programmed death-1 (PD-1) receptor and blocks its interaction with the ligands PD L1 and PD L2. The PD-1 receptor is a negative regulator of T-cell activity. Engagement of PD-1 with 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 PD1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Human hyaluronidase increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. In the doses administered, human hyaluronidase in OPDIVO SC acts locally.

The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

CLINICAL TRIALS

This section presents clinical experience from studies investigating the use of intravenous OPDIVO monotherapy or intravenous OPDIVO in combination with other therapeutic agents. With the exception of CA20967T, all of the studies were conducted using intravenous OPDIVO. The use of OPDIVO SC for the indications studied in intravenous OPDIVO is based on the pharmacokinetic non-inferiority of subcutaneous formulation of nivolumab to intravenous formulation of nivolumab, as demonstrated in CA20967T (see Section 5.2 Pharmacokinetic properties).

OPDIVO SC

Results from a simulation-based pharmacokinetic bridging analyses showed that across all solid tumour types evaluated, OPDIVO SC dosing regimens (600 mg every 2 weeks, 900 mg every 3 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, 360 mg every 3 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 and tolerable in clinical studies. The exposures achieved from the subcutaneous dosing regimen were shown to be within the safe, tolerable, and efficacious range.

The clinical safety profile of OPDIVO SC was comparable to intravenous nivolumab.

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

The safety and efficacy of nivolumab subcutaneous formulation was evaluated in a multicenter, randomized, 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 renal cell carcinoma with a clear cell component, including those with sarcomatoid features, and who received no more than 2 prior systemic treatment regimens were randomized to receive OPDIVO SC 1,200 mg every 4 weeks subcutaneously, or nivolumab 3 mg/kg every 2 weeks intravenously. Patients with untreated, symptomatic central nervous system (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 randomization were weight (<80 kg vs ≥80 kg) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification (favorable 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 OPDIVO SC to the intravenous administration of nivolumab. The key secondary objective of the study was to demonstrate noninferiority of the objective response rate (ORR) for the subcutaneous administration of OPDIVO SC to the intravenous administration of nivolumab, as assessed by blinded independent central review (BICR).

A total of 495 patients were randomized to receive either OPDIVO SC (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% favorable, 62% intermediate, and 17% poor.

CA20967T demonstrated noninferiority of OPDIVO SC 1,200 mg administered subcutaneously to nivolumab 3 mg/kg administered intravenously (see Section 5.2 Pharmacokinetic properties). Efficacy results are shown in Table 9.

Table 9 Efficacy Results – CA20967T

	OPDIVO SC	**Intravenous nivolumab**
ORR per BICR (n/N)	24% (60/248)	18% (45/247)
95% CI[a]	(19.0, 30.0)	(13.6, 23.6)
Complete response rate	2.0% (5/248)	1.6% (4/247)
Partial response rate	22% (55/248)	17% (41/247)
Estimate of objective response risk ratio (95% CI)[b, c, d]	1.33 (0.94, 1.87)	

[a] Confidence interval based on the Clopper and Pearson method.
[b] Stratified by weight (<80 kg vs ≥ 80 kg) and IMDC risk group (favourable vs intermediate vs poor).
[c] Strata adjusted risk ratio (subcutaneous nivolumab over intavenous nivolumab using Mantel-Haenszel method).
[d] To declare non-inferiority, the lower bound of the two-sided 95% CI of the objective response risk ratio has to be ≥0.60.

Intravenous OPDIVO

MELANOMA

Adjuvant melanoma – intravenous OPDIVO monotherapy
Randomised phase 3 study of nivolumab vs placebo (CA20976K)

CA20976K was a randomised, double-blind trial in 790 patients with completely resected Stage IIB/C melanoma. Patients were randomized (2:1) to receive intravenous OPDIVO 480 mg or placebo by intravenous infusion every 4 weeks for up to 1 year or until disease recurrence or unacceptable toxicity. Enrolment required complete resection of the primary melanoma with negative margins and a negative sentinel lymph node within 12 weeks prior to randomisation, and ECOG performance status of 0 or 1. The trial excluded patients with ocular/uveal or mucosal melanoma, 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. Randomisation was stratified by AJCC 8th edition (T3b vs. T4a vs. T4b). The primary efficacy outcome measure was recurrence-free survival (RFS) 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 occurs first and as assessed by the investigator. Tumour assessments were conducted every 26 weeks during years 1-3 and every 52 weeks from 36 months to 60 months.

The trial population characteristics were: median age was 62 years (range: 19 to 92), 61% were male, 98% were White, and 94% had an ECOG performance status of 0. Sixty one percent had stage IIB and 39% had stage IIC melanoma.

CA20976K demonstrated a statistically significant improvement in RFS for patients randomised to the intravenous OPDIVO arm compared with the placebo arm. Efficacy results are shown in Figure 1 and Table 10. The median follow-up for all randomised patients was 15.8 months for the nivolumab arm and 15.9 months for the placebo arm.

Figure 1 Recurrence-free Survival – CA209076K

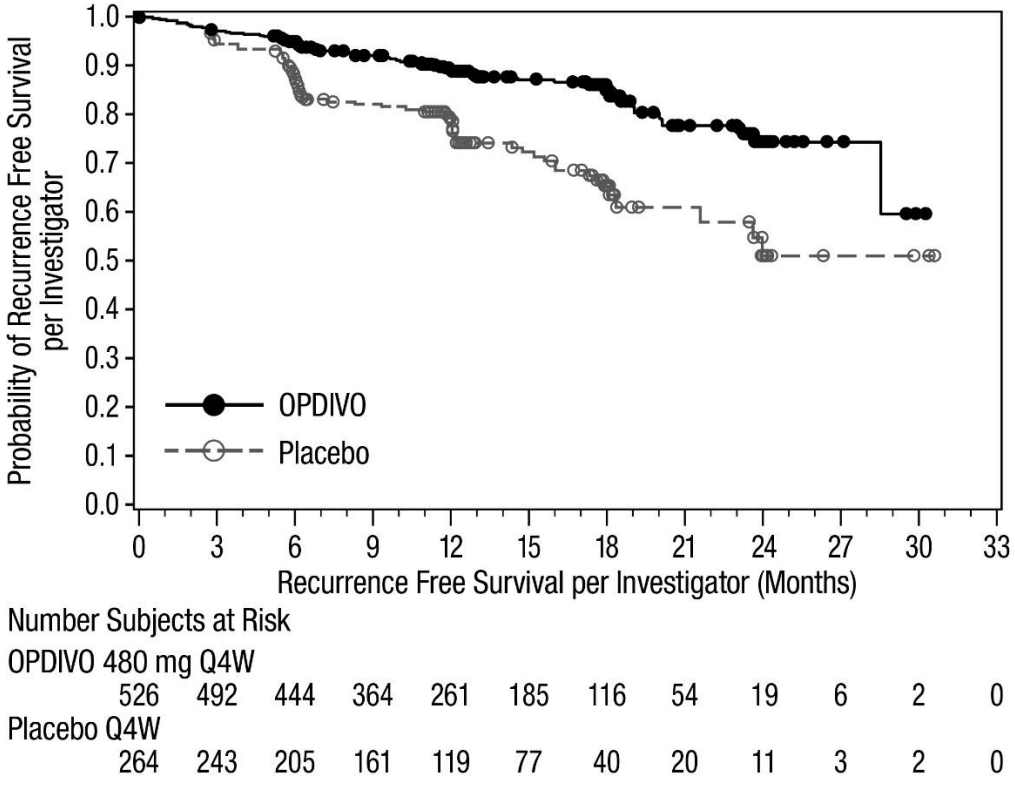


Table 10 Efficacy Results – CA20976K

	Intravenous OPDIVO N=526	Placebo N=264
Recurrence-free Survival		
Number of events, n (%)	66 (13%)	69 (26%)
Median (months) [b] (95% CI)	NR[a] (28.52, NR)	NR (21.62, NR)
Hazard ratio[c] (95% CI) p-value[d]	0.42 (0.30, 0.59) p<0.0001	

[a] Not reached.
[b] Based on a Kaplan-Meier Estimates.
[c] Hazard Ration is nivolumab over placebo from Cox proportional hazard model stratified by AJCC T Stage Entry (T3b vs T4a vs T4b) as entered into the IRT.
[d] 2-sided Log-rank test stratified by the same factor as used in the Cox proportional hazard model. Boundary for statistical significance: p-value <0.033.

An updated RFS analysis was performed with a median follow up duration of approximately 24 months. Overall, 19.4% of patients receiving intravenous nivolumab and 31.8% of patients receiving placebo experienced a recurrence event, HR (95%CI) 0.53 (0.40, 0.71).

Randomised phase 3 study of nivolumab vs ipilimumab 10 mg/kg (CA209238)
The safety and efficacy of nivolumab 3 mg/kg as a monotherapy for the treatment of patients with completely resected melanoma were evaluated in a phase 3, randomised, double-blind study (CA209238). The protocol allowed for the inclusion of patients (15 years or older), 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 (Stage III) or metastases (Stage IV). 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 surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomisation 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. Ipilimumab (10mg/kg) was chosen as the comparator as it has demonstrated a superior overall survival (OS) compared to standard of care after complete resection of high-risk stage III patients with melanoma (HR=0.72 95.1% CI: 0.58, 0.88; p=0.0013). 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). Key secondary endpoint were OS and QoL.

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. Forty-two percent of patients were BRAF V600 mutation positive, 45% were BRAF wild type; and for 13% BRAF status was unknown. Among patients with quantifiable tumour PD-L1 expression (>5%), the distribution of patients was balanced across the treatment groups. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Minimum follow-up was approximately 18 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 based on a pre-specified interim analysis. At the time the study reached its primary endpoint of RFS, the secondary endpoint of OS was not yet available and subjects continue to be monitored. RFS results are shown in Figure 2 and Table 11 (all randomised population).

Figure 2 Recurrence-free survival – CA209238

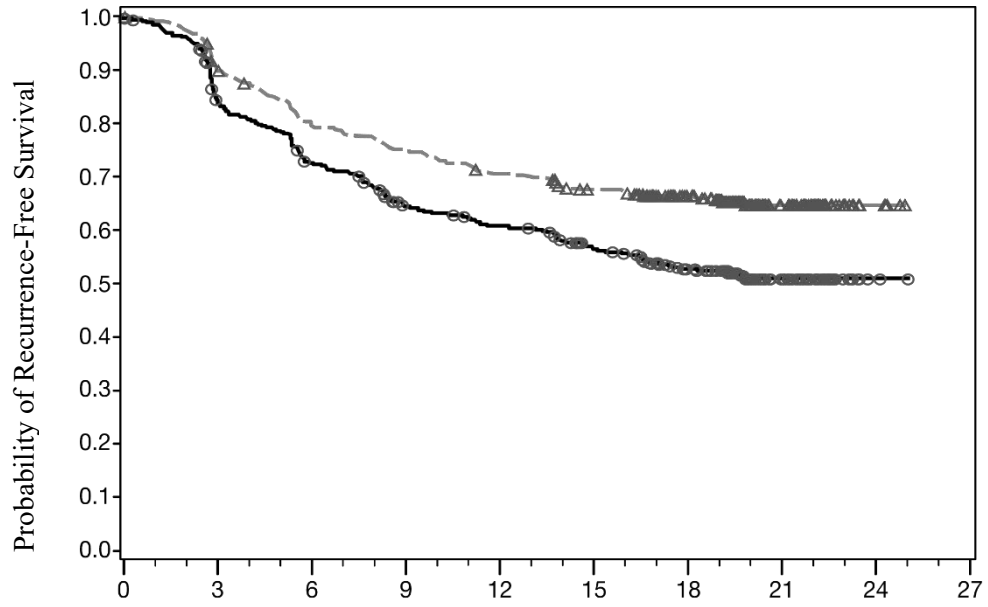


Table 11 Efficacy results – CA209238

	nivolumab (n = 453)		ipilimumab 10 mg/kg[c] (n = 453)
Recurrence-free Survival			
Events	154 (34.0%)		206 (45.5%)
Hazard ratio[a]		0.65	
97.56% CI		(0.51, 0.83)	
p-value[b]		p<0.0001	
Median (95% CI) months	Not Reached		Not Reached (16.56, NR)
Rate (95% CI) at 12 months	70.5 (66.1, 74.5)		60.8 (56.0, 65.2)
Rate (95% CI) at 18 months	66.4 (61.8, 70.6)		52.7 (47.8, 57.4)

[a] Derived from a stratified proportional hazards model.
[b] P-value is derived from a log-rank test stratified by tumour PD-L1 expression and stage of disease; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0244.
[c] Not registered in Australia

RFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF status, and stage of disease.

Quality of life (QoL) was assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the EQ-5D utility index and visual analog scale (VAS). QoL with nivolumab remained stable and close to baseline values during treatment.

Previously untreated unresectable or metastatic melanoma - Intravenous OPDIVO monotherapy

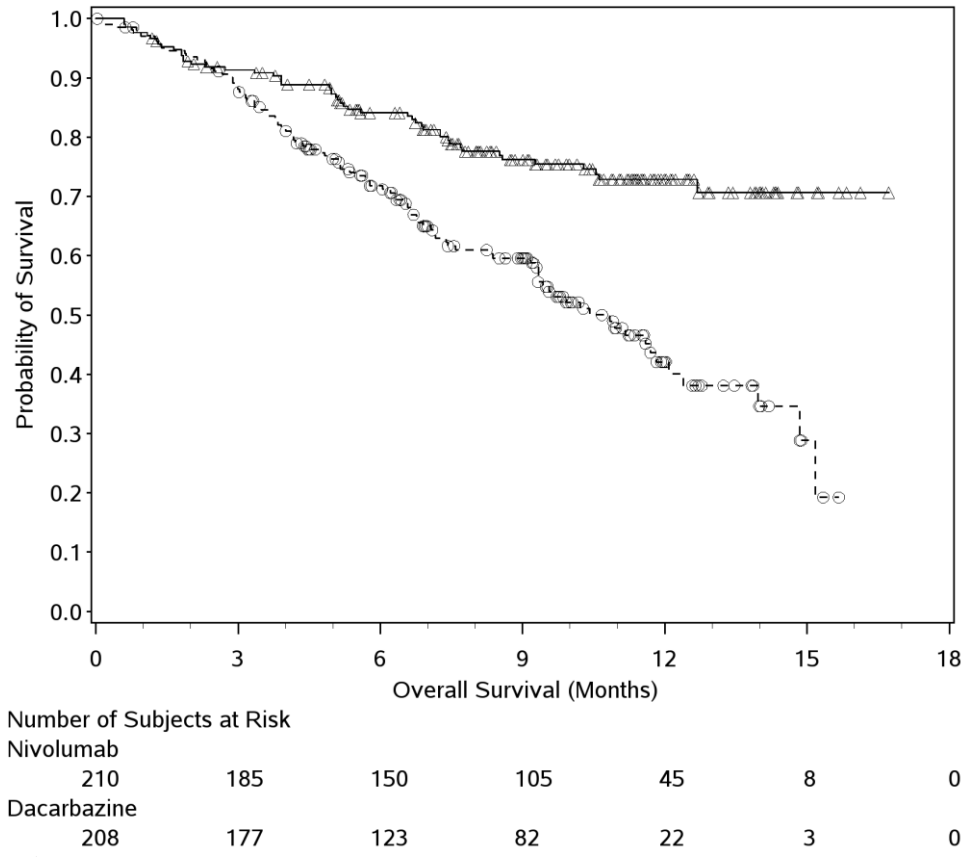
Randomised phase 3 study vs. dacarbazine (CA209066)
The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209066). The study included adult patients (18 years or older) 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 effects with the study drug, as determined by the investigator. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed progression free survival (PFS) and objective response rate (ORR).

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

The observed OS (Figure 3, Table 12) 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 PD-L1 expression was above or below a PD-L1 tumour membrane expression cut-off of 5% or 10%.

Figure 3 Overall survival – CA209066



—Δ— Nivolumab (events: 50/210), median and 95% CI: N.A.

- - -O- - - Dacarbazine (events: 96/208), median 10.84 months 95% CI: (9.33, 12.09)

Table 12 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)

Previously untreated unresectable or metastatic melanoma - Intravenous OPDIVO in combination with ipilimumab

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 in combination with ipilimumab and nivolumab monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209067). The study included adult patients (18 years or older) with confirmed unresectable Stage III or Stage IV melanoma, regardless of PD-L1 expression. 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 as monotherapy (n = 316), or ipilimumab as monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks. Patients in the nivolumab monotherapy arm received nivolumab 3 mg/kg every 2 weeks. Patients in the comparator arm received ipilimumab 3 mg/kg and nivolumab-matched placebo intravenously every 3 weeks for 4 doses followed by placebo every 2 weeks. Randomisation was stratified by PD-L1 expression (≥5% vs. <5% tumour cell membrane expression), BRAF status, and M stage per the American Joint Committee on Cancer (AJCC) staging system. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments were conducted 12 weeks after randomisation then every 6 weeks for the first year, and every 12 weeks thereafter. The co-primary outcome measures were PFS and OS. ORR and the duration of response were also assessed. This study evaluated whether PD-L1 expression was a predictive biomarker for the co-primary endpoints. The efficacy of nivolumab in combination with ipilimumab and nivolumab monotherapy was each compared with that of ipilimumab. In addition, the differences between the two intravenous OPDIVO containing groups were evaluated descriptively, but not included in formal hypothesis testing.

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. Baseline tumour tissue specimens were systematically collected prior to randomisation in order to conduct planned analyses of efficacy according to PD-L1 expression. Quantifiable tumour PD-L1 expression was measured in 89% (278/314) of patients randomised to nivolumab in combination with ipilimumab, 91% (288/316) of patients randomised to nivolumab monotherapy, and 88% (277/315) of patients randomised to ipilimumab alone. Among patients with quantifiable PD-L1 expression, the distribution of patients was

balanced across the three treatment groups at the predefined tumour PD-L1 expression level of ≥5% (24% in the nivolumab in combination with ipilimumab arm, 28% in the nivolumab monotherapy arm, and 27% in the ipilimumab arm). Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Both nivolumab-containing arms demonstrated a significant PFS and OS benefit and greater ORR compared with ipilimumab monotherapy.

Efficacy results for all randomised patients are shown in Table 13 and Figure 4 (PFS), and Figure 5 (OS).

Among 128 patients who discontinued nivolumab in combination with ipilimumab due to adverse reaction after 18 months of follow-up, median PFS was 16.7 months (95% CI: 10.2, NA). Among 131 patients who discontinued the combination due to adverse reaction after 28 months of follow-up, the ORR was 71% (93/131) with 20% (26/131) achieving a complete response and median OS was not reached.

Table 13 Efficacy results – CA209067

	nivolumab+ ipilimumab (n=314)	**nivolumab (n=316)**	**ipilimumab (n=315)**
Progression-free survival			
Events, n (%)	161 (51.3%)	183 (57.9%)	245 (77.8%)
Hazard ratio (vs. ipilimumab) (99.5% CI)	0.42 (0.32, 0.56)	0.55 (0.42, 0.73)	
p-value	p<0.0001	p<0.0001	
Hazard ratio (vs. nivolumab monotherapy) (95% CI) [c]	0.76 (0.62, 0.95)		
Median months (95% CI)	11.5 (8.9, 22.18)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
Rate % (95% CI)			
At 6 months	62 (56, 67)	52 (46, 57)	29 (24, 34)
At 9 months	49 (44, 56)	42 (36, 47)	18 (14, 23)
At 18 months	46 (41, 52)	39 (34, 45)	14 (10, 18)
Overall survival[b]			
Events (%)	128 (41%)	142 (45%)	197 (63%)
Hazard ratio (vs ipilimumab) (98% CI)	0.55 (0.42, 0.72)	0.63 (0.48, 0.81)	
p-value	p<0.0001	p<0.0001	
Hazard ratio (vs nivolumab monotherapy) (95% CI) [c]	0.88 (0.69, 1.12)		
Median months (95% CI)	Not reached	Not reached (29.1, NE)	20.0 (17.1, 24.6)
Rate (95% CI)			
At 12 months	73% (68, 78)	74% (69, 79)	67% (61, 72)
At 24 months	64% (59, 69)	59% (53, 64)	45% (39, 50)
Objective response rate	185 (59%)	141 (45%)	60 (19%)
(95% CI)	(53.3, 64.4)	(39.1, 50.3)	(14.9, 23.8)
Odds ratio (vs ipilimumab) (95% CI)	6.5 (3.81, 11.08)	3.54 (2.1, 5.95)	
Complete response (CR)	54 (17%)	47 (15%)	14 (4%)
Partial response (PR)	131 (42%)	94 (30%)	46 (15%)
Stable disease (SD)	36 (12%)	31 (10%)	67 (21%)
Duration of Response			
Median (range), months	Not reached (0^+-33.3^+)	31.1 (0^+-32.3^+)	18.2 (0^+-31.5^+)
Proportion ≥ 12 months in duration	64%	70%	53%

Proportion ≥ 24 months in duration	50%	49%	32%

[a] Minimum follow up of 18 months.
[b] Minimum follow up of 28 months.
[c] Unadjusted for multiplicity
NE=not estimable.
"+" denotes a censored observation.

Figure 4 Progression-free survival – CA209067

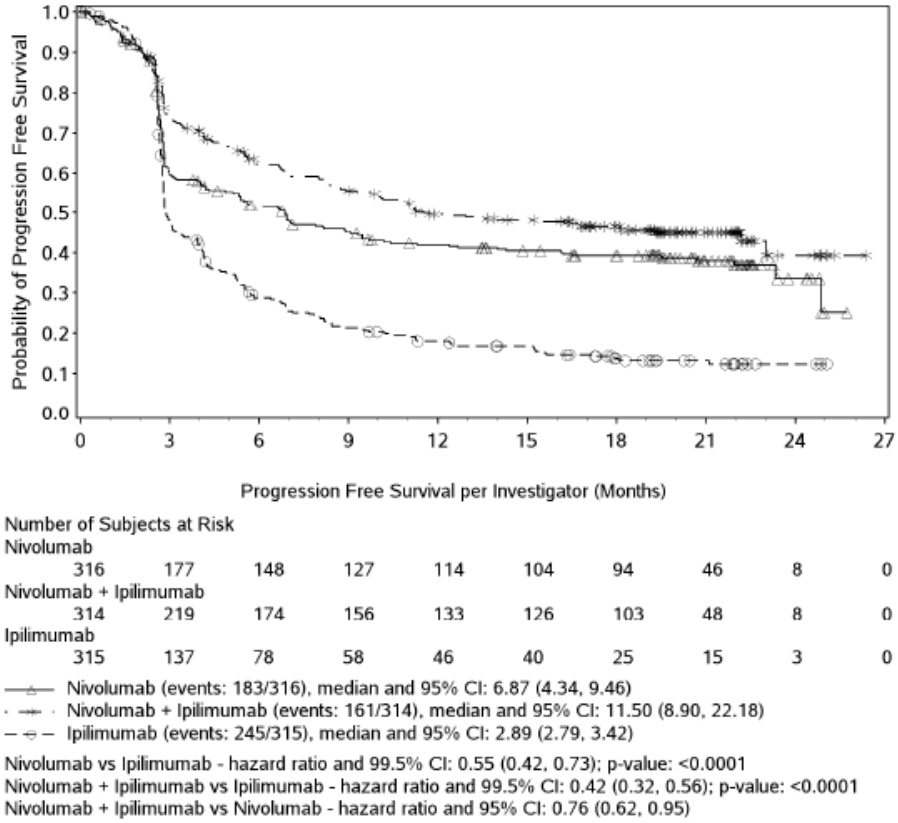
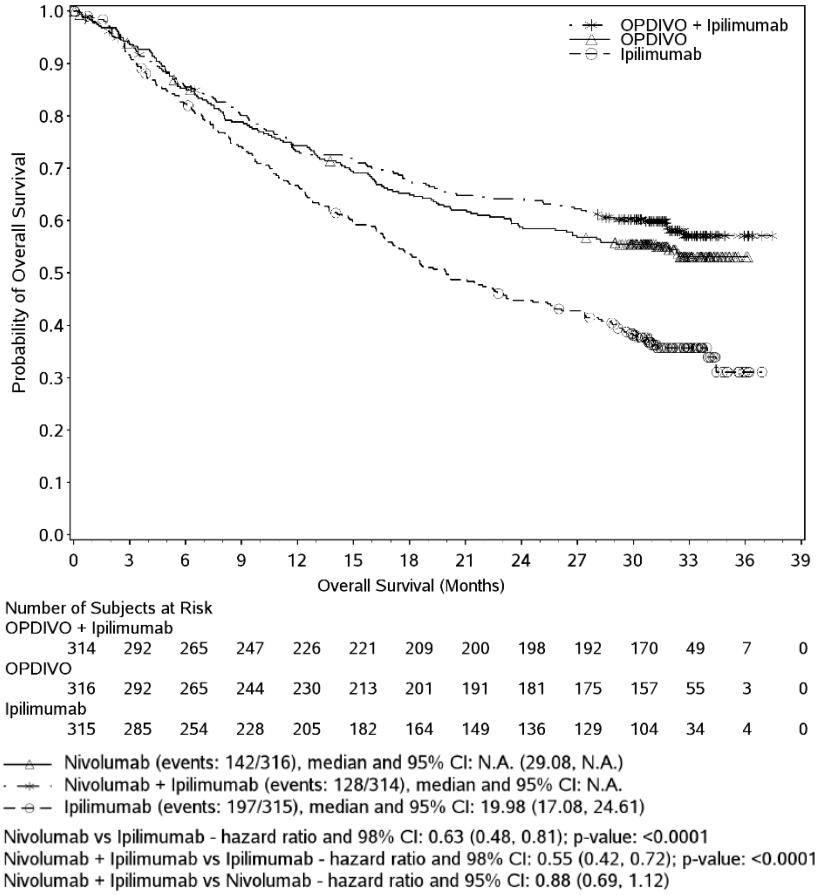


Figure 5 Overall survival – CA209067



The improvements in PFS, OS, ORR and DOR that were seen in both nivolumab-containing arms compared to ipilimumab monotherapy (Table 13) were consistent across patient subgroups including baseline ECOG performance status, BRAF status, M stage (7th Edition of AJCC melanoma of the skin staging classification system), age, history of brain metastases, baseline LDH level and tumour PD-L1 expression levels

Greater objective response rates were demonstrated for nivolumab in combination with ipilimumab relative to nivolumab monotherapy across tumour PD-L1 expression levels, with a best overall response of complete response correlating to an improved survival rate.

Analyses comparing nivolumab monotherapy to nivolumab in combination with ipilimumab were all descriptive. Kaplan-Meier plots of these exploratory subgroup analyses comparing PFS and OS in patients with tumour PD-L1 expression of <1% versus ≥1% are included below as Figure 6 and Figure 7.

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

Figure 6 **Progression-free survival by tumour PD-L1 expression level (CA209067) at 18 months of follow-up**

< 1% **≥ 1%**

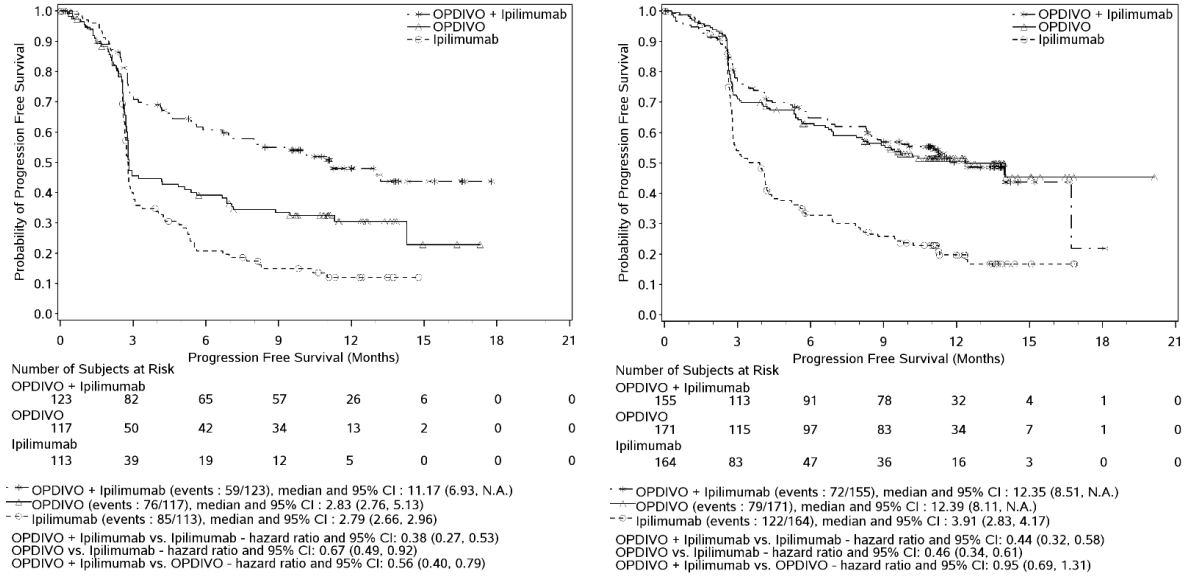
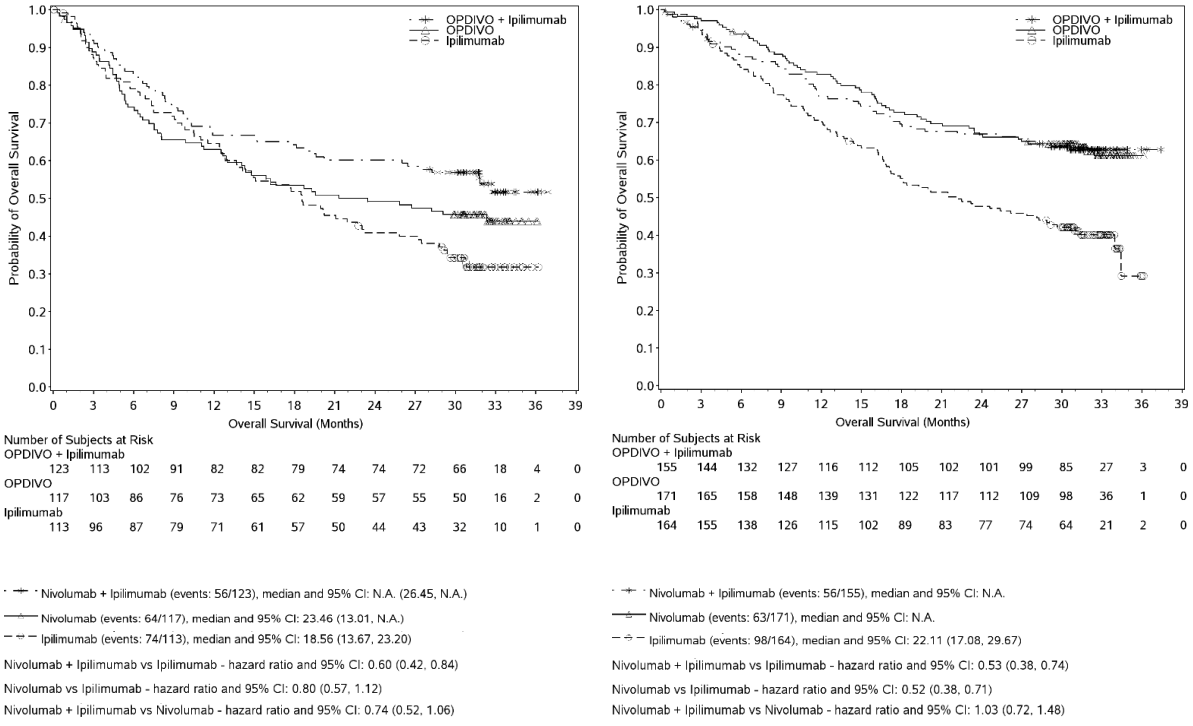


Figure 7 **Overall survival by tumour PD-L1 expression level (CA209067) at 2 years of follow-up**

< 1% **≥ 1%**



The safety of the combination of nivolumab and ipilimumab in patients across all pre-defined subgroups was consistent with that in all randomised patients.

Randomised phase 2 study of nivolumab in combination with ipilimumab vs 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 12 and 18 month OS rates were 79% (95% CI: 67, 87) and 73% (95% CI: 61, 82) respectively for the combination and 62% (95% CI: 44, 75) and 56% (95% CI: 39, 70) respectively for ipilimumab.

Previously treated unresectable or metastatic melanoma - intravenous OPDIVO monotherapy

Randomised phase 3 study vs. chemotherapy (CA209037)

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

A total of 405 patients were randomised to receive either nivolumab (n = 272) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or chemotherapy (n = 133) which consisted of the investigator's choice of either dacarbazine (1000 mg/m^2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks). Randomisation was stratified by BRAF and 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 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 14.

Table 14 Efficacy results – 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)

Objective responses to nivolumab (according to the definition of the co-primary endpoint) were observed in patients with or without BRAF mutation-positive melanoma. Of the patients who received

nivolumab, the ORR in the BRAF mutation-positive subgroup (n = 26) was 23% (95% CI: 9.0, 43.6), and 34% (95% CI: 24.6, 44.5) in patients whose tumours were BRAF wild-type (n = 94). Objective responses to nivolumab were 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%). However, the role of this biomarker (tumour PD-L1 expression) has not been fully elucidated.

The OS data were not mature at the time of the PFS analysis. There was no statistically significant difference between nivolumab and chemotherapy in the preliminary OS analysis that was not adjusted for the potentially confounding effects of subsequent therapy. It is of note that 42 (31.6%) patients in the chemotherapy arm subsequently received an anti-PD1 treatment.

PFS numerically favoured the nivolumab group vs. the chemotherapy group in all randomised patients, BRAF mutation positive patients, and BRAF wild-type patients (HRs 0.74 [95% CI: 0.57, 0.97], 0.98 [95% CI: 0.56, 1.70], and 0.63 [95% CI: 0.47, 0.85], respectively).

Phase 1 dose-escalation study (CA209003/MDX1106-03)
The safety and tolerability of intravenous OPDIVO were investigated in a phase 1, open-label dose-escalation study in various tumour types, including malignant melanoma. Of the 306 patients enrolled in the study, 107 had melanoma and received intravenous OPDIVO 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, 36.7), and the estimated OS rates were 63% (95% CI: 53, 71) at 1 year, 48% (95% CI: 38, 57) at 2 years, and 41% (95% CI: 31, 51) at 3 years.

Intravenous OPDIVO

NON-SMALL CELL LUNG CANCER (NSCLC)

Neoadjuvant treatment of resectable NSCLC - Intravenous OPDIVO in combination with chemotherapy

Randomised phase 3 study vs. platinum-doublet chemotherapy (CA209816)
CA209816 was a randomised, open label trial in patients with resectable NSCLC. The trial included patients with resectable, histologically confirmed Stage IB (≥4 cm), II, or IIIA NSCLC (per the 7th edition American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging criteria), ECOG performance status 0 or 1, and measurable disease (per RECIST version 1.1). Patients were enrolled regardless of their tumour PD-L1 status. Patients with unresectable or metastatic NSCLC, known EGFR mutations or ALK translocations, Grade 2 or greater peripheral neuropathy, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

Patients were randomised to receive either:

- Intravenous OPDIVO 360 mg administered intravenously over 30 minutes and platinum-doublet chemotherapy administered intravenously every 3 weeks for up to 3 cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for up to 3 cycles.

Platinum-doublet 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 (non-squamous histology); or gemcitabine 1000 mg/m^2 or 1250 mg/m^2 and cisplatin 75 mg/m^2 (squamous histology). In the platinum-doublet 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). Stratification factors for randomisation were tumour PD-L1 expression level (≥1% versus <1% or non-quantifiable), disease stage (IB/II versus IIIA), and sex (male versus female). 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 pathologic complete response (pCR) as evaluated by blinded independent pathology review (BIPR). Secondary efficacy outcome measures included OS.

A total of 358 patients were randomised to receive either intravenous OPDIVO in combination with platinum doublet chemotherapy (n=179) or platinum-doublet chemotherapy (n=179). The median age was 65 years (range: 34 to 84) with 51% of patients ≥65 years and 7% of patients ≥75 years, 50% were Asian, 47% were White, 2% were Black, and 71% were male. Baseline ECOG performance status was 0 (67%) or 1 (33%); 50% had tumours with PD-L1 expression ≥1% and 43% had tumours with PD-L1 expression that was <1%; 5% had stage IB, 17% had stage IIA, 13% had stage IIB, and 64% had stage IIIA disease; 51% had tumours with squamous histology and 49% had tumours with non-squamous histology; and 89% were former/current smokers.

Numerically more patients in the intravenous OPDIVO in combination with platinum-doublet chemotherapy arm (83%) had definitive surgery compared to patients in the platinum-doublet chemotherapy arm (75%).

The study demonstrated statistically significant improvement in EFS and pCR. Efficacy results are presented in Figure 8 and Table 15.

Figure 8 Event-Free Survival – CA209816

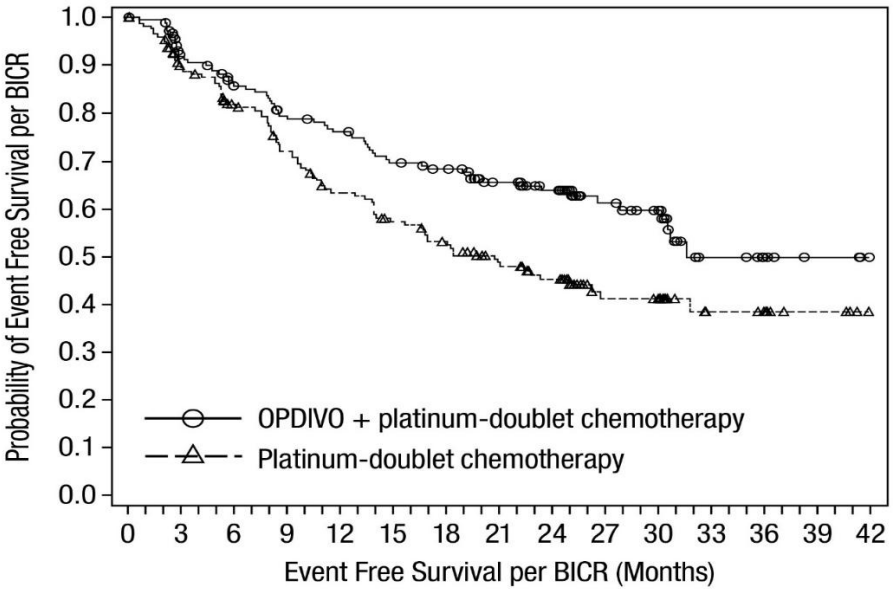


Table 15 Efficacy Results – CA209816

	Intravenous OPDIVO and Platinum-Doublet Chemotherapy (n=179)	**Platinum-Doublet Chemotherapy (n=179)**
Event-free Survival (EFS) per BICR		
Events (%)	64 (35.8)	87 (48.6)
Median (months)[a] (95% CI)	31.6 (30.2, NR)	20.8 (14.0, 26.7)
Hazard Ratio[b] (97.38% CI)	0.63 (0.43, 0.91)	

	Intravenous OPDIVO and Platinum-Doublet Chemotherapy (n=179)	Platinum-Doublet Chemotherapy (n=179)
Stratified log-rank p-value[c]	0.0052	
Rate (95% CI) at 12 months	76.1 (68.8, 81.9)	63.4 (55.3, 70.4)
Rate (95% CI) at 24 months	63.8 (55.7, 70.9)	45.3 (37.0, 53.2)
Pathologic Complete Response (pCR) per BIPR		
Responses (%)	43 (24.0)	4 (2.2)
95% CI[d]	18.0, 31.0	0.6, 5.6
Difference of pCR (99% CI)[e]	21.6 (13.0, 30.3)	
Odds ratio of pCR (99% CI)[f]	13.9 (3.49, 55.75)	
Stratified log-rank p-value[g]	<0.0001	

Minimum follow-up for EFS was 21 months.

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

[c] Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0262.

[d] Based on Clopper and Pearson method.

[e] Strata-adjusted difference based on Cochran-Mantel-Haenszel method of weighting.

[f] Strata-adjusted using Mantel-Haenszel method.

[g] From stratified CMH test.

An exploratory subgroup analysis of EFS stratified according to level of PD-L1 expression in the patient's tumour was performed with a minimum follow-up of 21 months. Greater EFS benefit was observed in patients treated with nivolumab in combination with chemotherapy who had PD-L1 expression ≥ 1% (HR [95% CI] 0.41 [0.24, 0.70]) than in patients with PD-L1 expression < 1% (HR [95% CI] 0.85 [0.54, 1.32].

Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

Randomised phase 3 study vs. platinum-doublet chemotherapy (CA20977T)
CA20977T was a randomised, double-blind trial in patients with resectable NSCLC. The trial included patients with resectable, suspected or histologically confirmed Stage IIA (>4 cm) to IIIB (T3-T4 N2) NSCLC (AJCC 8th edition) and ECOG performance status 0 or 1.

In the neoadjuvant phase, patients were randomised to receive either:

- intravenous OPDIVO 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.

In the adjuvant phase, within 90 days after the surgery patients received either:

- intravenous OPDIVO 480 mg administered intravenously over 30 minutes every 4 weeks, or
- placebo administered every 4 weeks,

until disease progression, recurrence, or unacceptable toxicity for up to 13 cycles (up to 1 year).

Platinum-doublet 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 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 is confirmed by BICR.

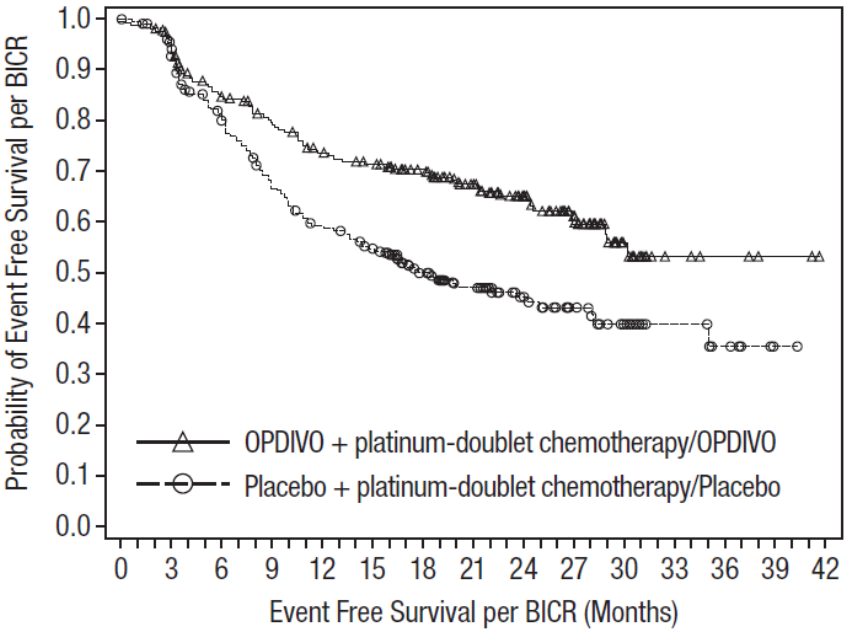
The major efficacy outcome measure was event-free survival (EFS) based on BICR assessment. Additional efficacy outcome measures included pathologic complete response (pCR) and major pathologic response as evaluated by blinded independent pathology review (BIPR).

A total of 461 patients were randomised to receive either neoadjuvant intravenous OPDIVO in combination with platinum-doublet chemotherapy followed by adjuvant intravenous OPDIVO (n=229) or neoadjuvant placebo and platinum-doublet chemotherapy followed by adjuvant placebo (n=232). The median age was 66 years (range: 35 to 86) with 56% of patients ≥65 years and 7% of patients ≥75 years, 72% were White, 25% were Asian, 1.7% were Black, and 71% were male. Baseline ECOG performance status was 0 (62%) or 1 (38%); 56% had tumours with PD-L1 expression ≥1% and 40% had tumours with PD-L1 expression <1%; 35% had stage II and 64% had stage III disease; 23% were N1 and 39% were N2; 24% were single-station and 15% were multistation; 51% had tumours with squamous histology and 49% had tumours with non-squamous histology; and 90% were former/current smokers.

Seventy-eight percent of patients in the neoadjuvant intravenous OPDIVO in combination with platinum-doublet chemotherapy followed by adjuvant intravenous OPDIVO arm had definitive surgery compared to 77% of patients in the neoadjuvant placebo and platinum-doublet chemotherapy followed by placebo arm.

The study demonstrated statistically significant and clinically meaningful improvement of EFS. Efficacy results are presented in Figure 9 and Table 16.

Figure 9 Event-Free Survival – CA20977T



Number of Subjects at Risk

OPDIVO + platinum-doublet chemotherapy/OPDIVO	229	208	173	157	141	134	115	89	69	46	20	7	4	2	0
Placebo + platinum-doublet chemotherapy/Placebo	232	204	165	138	118	106	78	59	44	29	19	10	6	1	0

Table 16 Efficacy Results – CA20977T

	Neoadjuvant intravenous OPDIVO and Platinum-Doublet Chemotherapy/Adjuvant intravenous OPDIVO (n=229)	Neoadjuvant Placebo and Platinum-Doublet Chemotherapy/Adjuvant Placebo (n=232)
Event-free Survival (EFS) per BICR		
Events (%)	76 (33%)	113 (49%)
Median (months)[a] (95% CI)	NR (28.94, NR)	18.43 (13.63, 28.06)
Hazard Ratio[b] (95% CI)	0.58 (0.43, 0.78)	
Stratified log-rank p-value[c]	0.00025	
Pathologic Complete Response (pCR) per BIPR		
Number of patients with pCR	58	11
pCR Rate (%), (95% CI)[d]	25.3 (19.8, 31.5)	4.7 (2.4, 8.3)
Estimated treatment difference (95% CI)[e]	20.5 (14.3, 26.6)	
Major Pathologic Response (MPR) per BIPR		
Number of patients with MPR	81	28
MPR Rate (%), (95% CI)	35.4 (29.2, 41.9)	12.1 (8.2, 17.0)
Estimated treatment difference (95% CI)[e]	23.2 (15.8, 30.6)	

Minimum follow-up for EFS was 15.7 months.

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

[c] Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0264.

[d] CI based on Clopper and Pearson method.

[e] Strata adjusted difference based on Cochran-Mantel-Haenszel method of weighting.

Previously treated advanced or metastatic squamous (SQ) NSCLC - Intravenous OPDIVO monotherapy

Randomised phase 3 study vs. docetaxel (CA209017)

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced or metastatic SQ 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. Patients were enrolled regardless of their PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (n = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m^2 every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to the 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 observed OS benefit (Figure 10, Table 17) was consistently demonstrated across subgroups of patients. At the pre-defined PD-L1 tumour membrane expression cutoff levels of 1%, 5%, and 10%, similar survival was observed regardless of PD-L1 expression status.

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.

Figure 10 Overall survival – CA209017

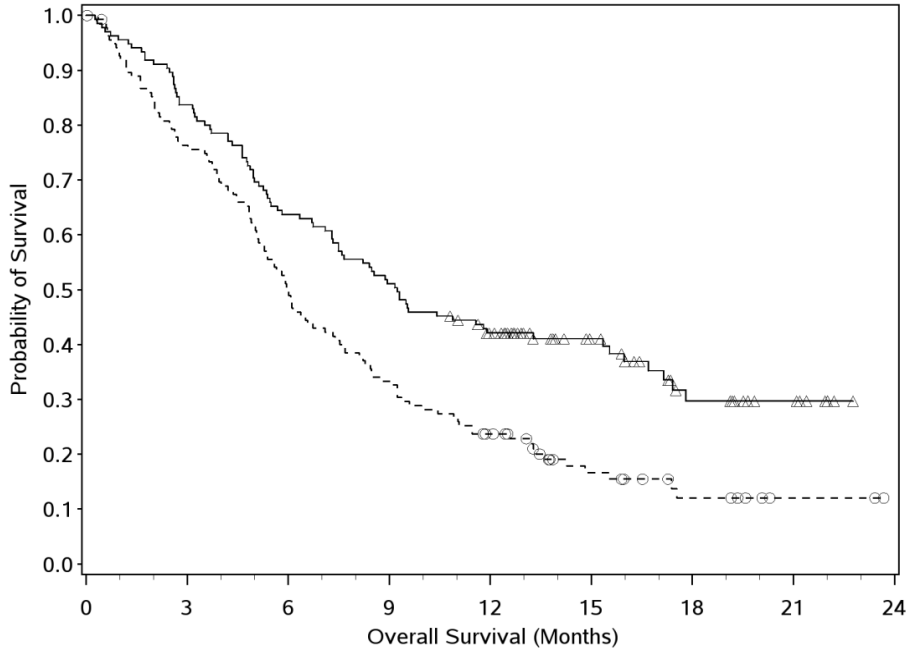


Table 17 Efficacy results – CA209017

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

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.

The OS rates at 24 months were 22.9% (95% CI: 16.2, 30.3) for nivolumab and 8.0% (95% CI: 4.3, 13.3) for docetaxel. The PFS rate at 24 months for nivolumab was 15.6% (95% CI: 9.7, 22.7) and for docetaxel there were no patients at risk at 24 months as all patients had either progressed, were censored, or lost to follow-up. With minimum 24 months follow-up, objective response rates remain 20.0% for nivolumab and 8.8% for docetaxel with median durations of response 25.2 months (range: 2.9, 30.4) and 8.4 months (range: 1.4+, 18.0+), respectively.

Single-arm phase 2 study (CA209063)

Study CA209063 was a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous NSCLC after two or more lines of therapy; otherwise similar inclusion criteria as study CA209017 were applied. Nivolumab 3 mg/kg showed an overall response rate of 14.5% (95% CI: 8.7, 22.2%), a median OS of 8.21 months (95% CI: 6.05, 10.9), 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%.

Previously treated advanced or metastatic non-squamous (NSQ) NSCLC - Intravenous OPDIVO monotherapy

Randomised phase 3 study vs. docetaxel (CA209057)

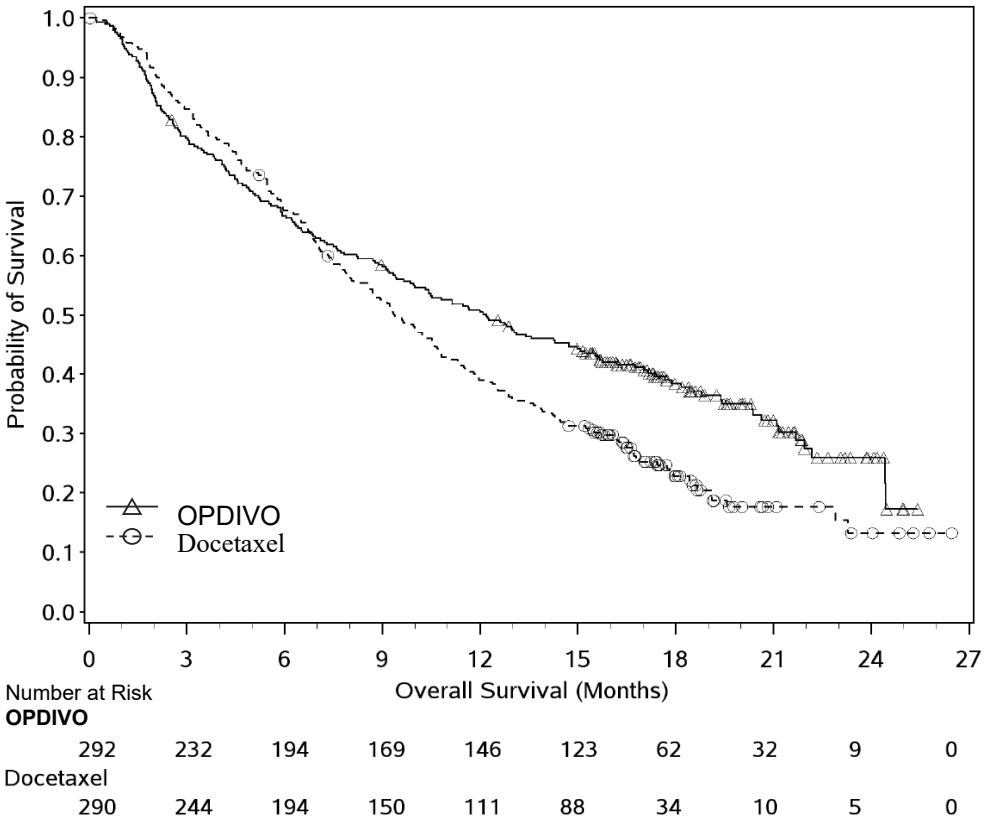
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic non-squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209057). The study included patients (18 years or older) who have experienced disease progression during or after 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 PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

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

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

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

Figure 11 Overall survival – CA209057



The trial demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 18. Within the first three months, a higher number of deaths was observed with nivolumab monotherapy compared to docetaxel, followed by a long-term survival benefit (see Figure 11). Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumour PD-L1 expression.

Table 18 Efficacy Results – CA209057

	nivolumab (n = 292)	**docetaxel (n = 290)**
Prespecified interim analysis		
Overall survival		
Events (%)	190 (65.1%)	223 (76.9%)
Hazard ratio[a]	0.73	
(95.92% CI)	(0.59, 0.89)	
p-value[b]	0.0015	
Median (95% CI) months	12.19 (9.66, 14.98)	9.36 (8.05, 10.68)
Rate % (95% CI) at 12 months	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)
Confirmed objective response	56 (19.2%)	36 (12.4%)
(95% CI)	(14.8, 24.2)	(8.8, 16.8)
Odds ratio (95% CI)	1.68 (1.07, 2.64)	
p-value	0.0246	
Complete response (CR)	4 (1.4%)	1 (0.3%)
Partial response (PR)	52 (17.8%)	35 (12.1%)
Stable disease (SD)	74 (25.3%)	122 (42.1%)
Median duration of response		
Months (range)	17.15 (1.8, 22.6+)	5.55 (1.2+, 15.2+)

Median time to response			
Months (range)	2.10 (1.2, 8.6)		2.61 (1.4, 6.3)
Progression-free survival			
Events	234 (80.1%)		245 (84.5%)
Hazard ratio		0.92	
95% CI		(0.77, 1.11)	
p-value		0.3932	
Median (95% CI) months	2.33 (2.17, 3.32)		4.21 (3.45, 4.86)
Rate % (95% CI) at 12 months	18.5 (14.1, 23.4)		8.1 (5.1, 12.0)

[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.

The rate of disease-related symptom improvement, as measured by LCSS, was similar between the nivolumab group (17.8%) and the docetaxel group (19.7%). The average EQ-VAS increased over time for both treatment groups, indicating better overall health status for patients remaining on treatment.

The OS rates at 24 months were 28.7% (95% CI: 23.6, 34.0) for nivolumab and 15.8% (95% CI: 11.9, 20.3) for docetaxel. The PFS rates at 24 months were 11.9% (95% CI: 8.3, 16.2) for nivolumab and 1.0% (95% CI: 0.2, 3.3) for docetaxel. With minimum 24 months follow-up, objective response rates remain 19.2% for nivolumab and 12.4% for docetaxel with median durations of response 17.2 months (range: 1.8, 33.7+) and 5.6 months (range: 1.2+, 16.8), respectively.

Intravenous OPDIVO

RENAL CELL CARCINOMA (RCC)

Previously untreated advanced or metastatic RCC - Intravenous OPDIVO in combination with ipilimumab

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 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 and Karnofsky performance status ≥ 70%. Prior adjuvant or neoadjuvant therapy was allowed if such therapy did not include an agent that targets vascular endothelial growth factor (VEGF) or VEGF receptors and recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy. The primary efficacy population includes 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 randomization, 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 any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were stratified by (IMDC) prognostic score and region.

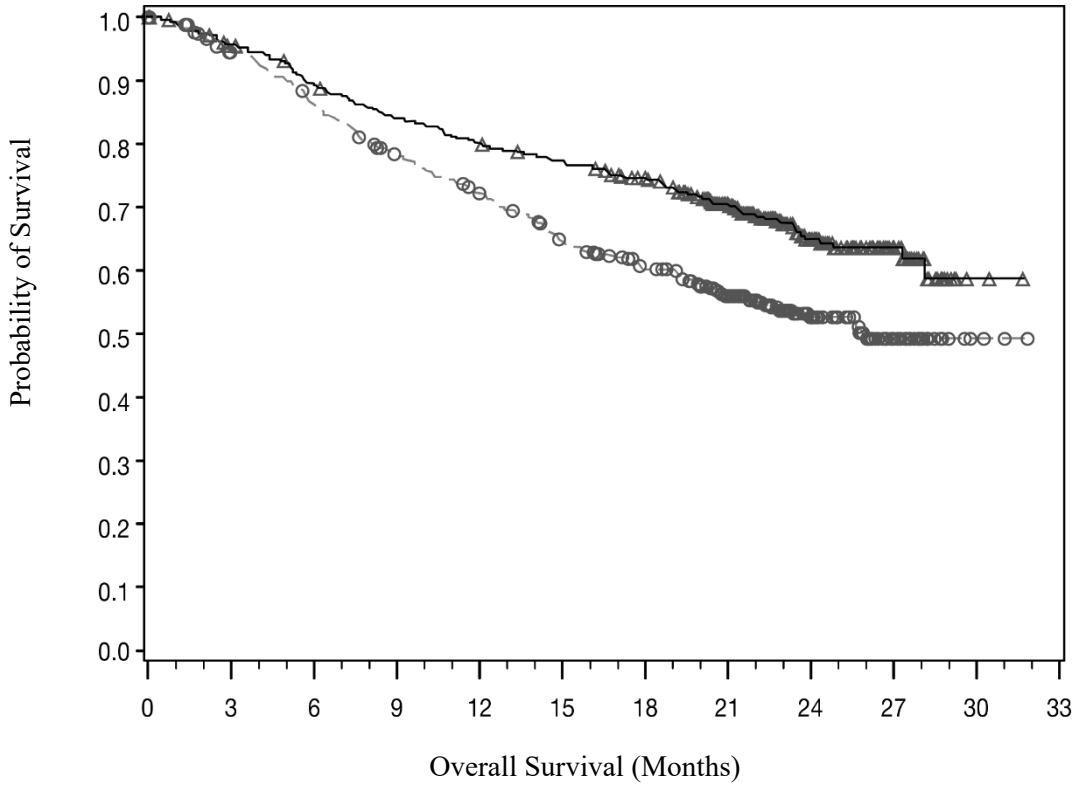
A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either nivolumab 3 mg/kg (n = 425) administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks for 4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

primary efficacy outcome measures were OS, ORR and PFS as determined by a Blinded Independent Central Review (BICR) in intermediate/poor risk patients.

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

The Kaplan-Meier curves for OS in intermediate/poor risk patients is shown in Figure 12.

Figure 12 Overall survival in intermediate/poor risk patients with RCC – CA209214



Number of Subjects at Risk

Nivolumab + Ipilimumab											
425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib											
422	387	352	315	288	253	225	179	89	34	3	0

Nivolumab + ipilimumab (events: 140/425), median and 95.0% CI: NE (28.2, NE)

Sunitinib (events: 188/422), median and 95.0% CI: 25.9 (22.1, NE)

The trial demonstrated superior OS and ORR and an improvement in PFS for intermediate/poor risk patients randomised to nivolumab plus ipilimumab as compared with sunitinib.. OS benefit was observed regardless of tumour PD-L1 expression level.

Efficacy results are shown in Table 19.

Table 19 Efficacy results for intermediate/poor risk patients with RCC – CA209214

	nivolumab + ipilimumab (n = 425)	**sunitinib (n = 422)**
Overall survival		
Events	140 (33%)	188 (45%)

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

[a] Based on a stratified proportional hazards model.
[b] Based on a stratified log-rank test.
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[d] Strata adjusted difference.
[e] Based on the stratified DerSimonian-Laird text.
[f] p-value is compared to nominal alpha 0.001 in order to achieve statistical significance.
[g] Computed using Kaplan-Meier method.
[h] p-value did not meet the threshold of statistical significance as compared to alpha 0.009
"+" denotes a censored observation.
NE = non-estimable

The median time to onset of objective response was 2.8 months (range: 0.9-11.3 months) after the start of nivolumab with ipilimumab treatment. One hundred seventy-seven (41.6%) responders had ongoing responses with a duration ranging from 1.4^{+}-25.5^{+} months.

Disease related symptoms, cancer symptoms and non-disease specific Quality of Life (QoL) were assessed as an exploratory endpoint using the FKSI-19, FACT-G, and EQ-5D scales. Fewer patients in the nivolumab in combination with ipilimumab arm reported symptom deterioration than in the sunitinib arm, and scores for QoL were greater for nivolumab in combination with ipilimumab patients vs. those in the sunitinib arm at each assessment during the first six months of the study, when completion rates exceeded 80%. As patients were not blinded to treatment, interpretation of these patient-reported outcomes is limited.

Previously untreated advanced or metastatic RCC - Intravenous OPDIVO in combination with cabozantinib

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. 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

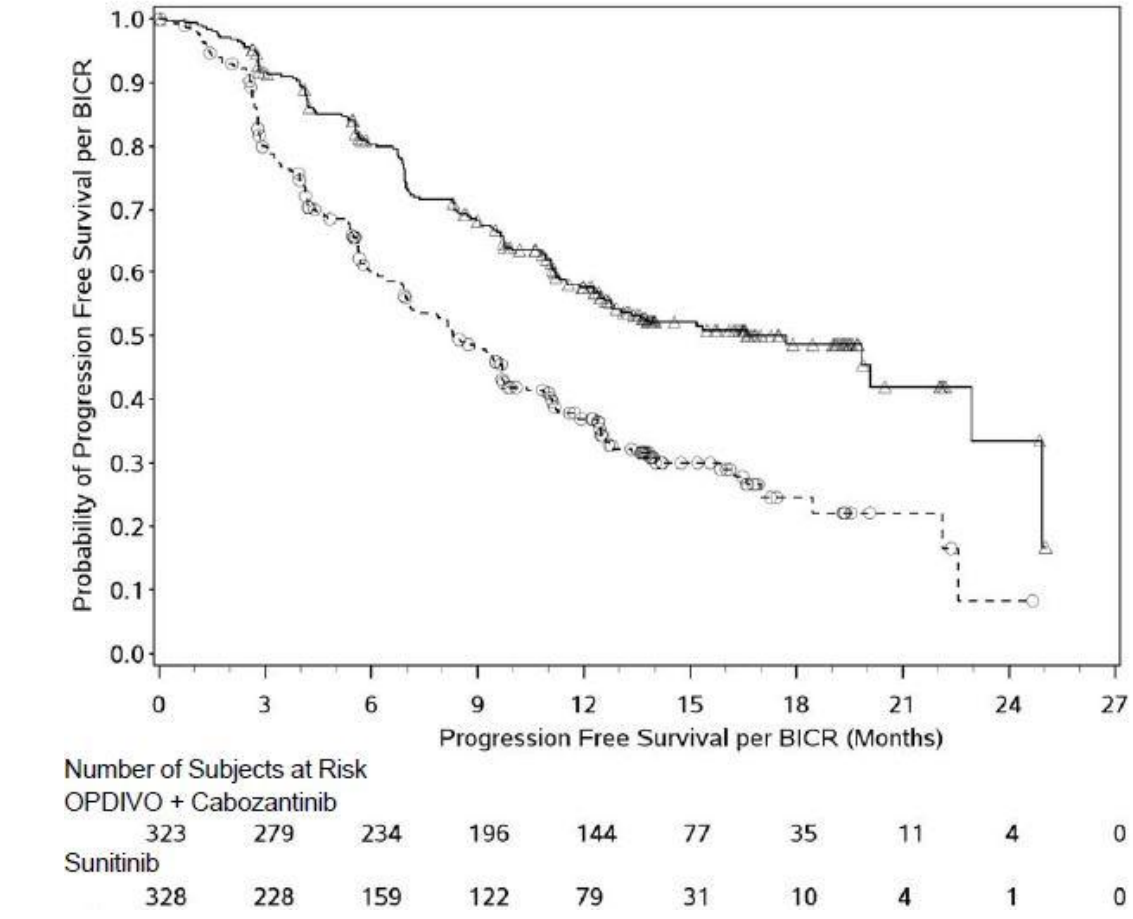
until disease progression or unacceptable toxcity with nivolumab administration for up to 24 months. Treatment beyond initial Investigator-assessed RECIST version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. 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.

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%), and 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. 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 primary efficacy outcome measure was PFS as determined by a BICR. Additional efficacy measures included OS and ORR as key secondary endpoints for hierarchical statistical testing. 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. Consistent results were observed across pre-specified subgroups, IMDC risk categories, and PD-L1 tumour expression status.

The Kaplan-Meier curves for PFS and OS (with a minimum follow-up of 10.6 months) in all risk patients are shown in Figure 13 and Figure 14.

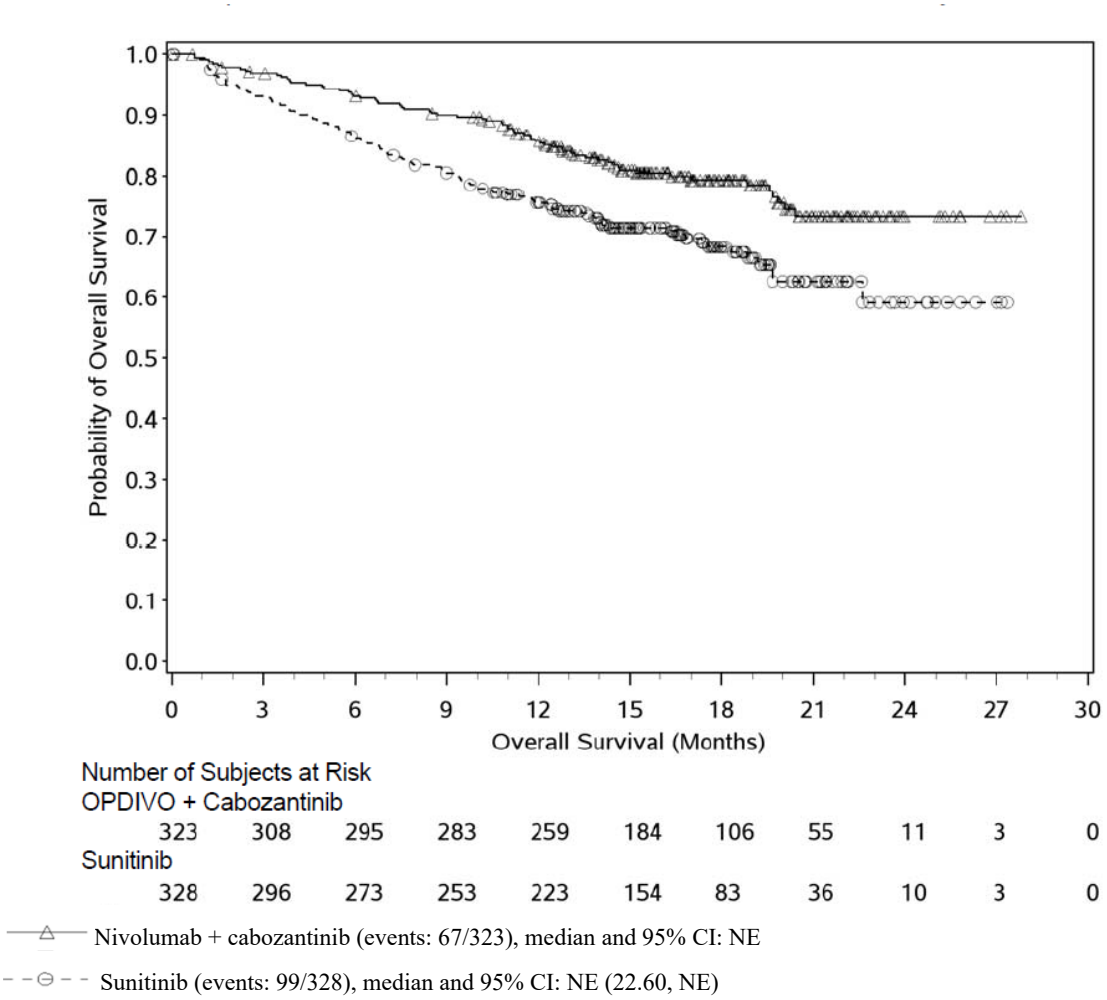
Figure 13 Kaplan-Meier curves of PFS – CA2099ER



Nivolumab + cabozantinib (events: 142/323), median and 95.0% CI: 16.59 (12.45, 24.94)

Sunitinib (events: 191/328), median and 95.0% CI:8.31 (6.97, 9.69)

Figure 14 Kaplan-Meier curves of OS – CA2099ER



Efficacy results from the primary analysis (minimum follow-up 10.6 months) are shown in Table 20.

Table 20 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]	16.6 (12.5, 24.9)	8.3 (7.0, 9.7)
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)
At 9 months	89.9 (86.0, 92.8)	80.5 (75.7, 84.4)
Confirmed objective response (BICR)[f]	180 (55.7%)	89 (27.1%)
(95% CI)	(50.1, 61.2)	(22.4, 32.3)
Difference in ORR (95% CI)[f]	28.6 (21.7, 35.6)	
p-value[g]	< 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] Based on Kaplan-Meier estimates.
[c] 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.
[d] 2-sided p-values from stratified regular log-rank test.
[e] Boundary for statistical significance p-value <0.0111.
[f] CI based on the Clopper and Pearson method.
[g] 2-sided p-value from CMH test.
NE = non-estimable

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 12.8 months in the sunitinib arm (HR = 0.60; 95% CI: 0.37, 0.98). Median PFS for the intermediate risk group was 17.7 months for nivolumab in combination with cabozantinib and was 8.4 months in the sunitinib arm (HR = 0.54; 95% CI: 0.41, 0.73). Median PFS for the poor risk group was 12.3 months for nivolumab in combination with cabozantinib and was 4.2 months in the sunitinib arm (HR = 0.36; 95% CI: 0.23, 0.58).

Previously treated advanced or metastatic RCC - Intravenous OPDIVO monotherapy

Randomised phase 3 study of nivolumab vs everolimus (CA209025)
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced RCC 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%. All patients had clear cell histology component. This study included patients regardless of their 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 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.

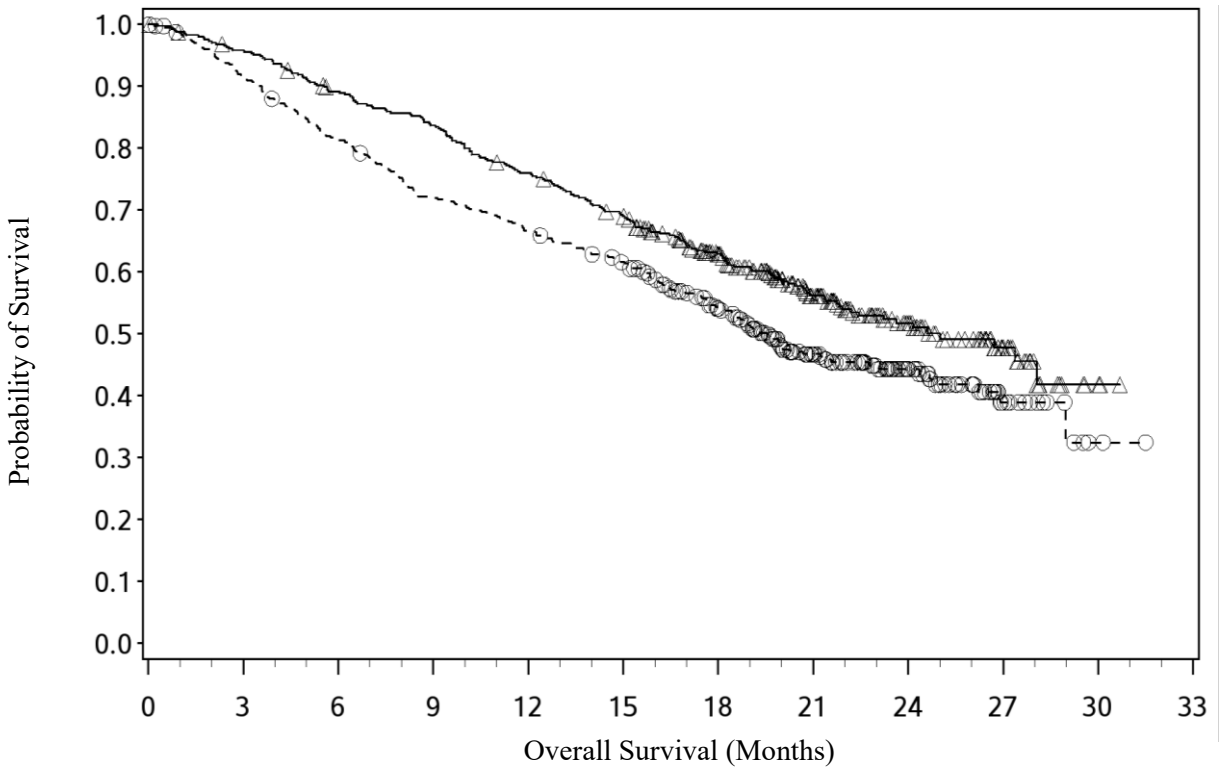
Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range: 18-88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and white (88%), all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups were represented, 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 15.

Figure 15 Overall survival – 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). OS benefit was observed regardless of PD-L1 expression level.

Efficacy results are shown in Table 21.

Table 21 Efficacy results – CA209025

	nivolumab (n = 410)		everolimus (n = 411)
Overall survival			
Events	183 (45)		215 (52)
Hazard ratio		0.73	
95% CI		(0.57, 0.93)	
p-value		< 0.0018	
Median (95% CI) months	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) months	4.6 (3.71, 5.39)		4.4 (3.71, 5.52)
Rate % (95% CI)			
At 6 months	39 (35, 44)		39 (33, 44)
At 12 months	23 (19, 27)		19 (15, 23)

"+" denotes a censored observation.

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.

Disease-related symptoms and non-disease specific quality of life (QoL) were assessed as a secondary endpoint using the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) and the EuroQoL EQ-5D scales. Patients in the nivolumab arm reported better symptom improvement and time to improvement than those in the everolimus arm. As patients were not blinded to treatment, interpretation of these patient-reported outcomes is limited.

Intravenous OPDIVO

SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)

Previously treated recurrent or metastatic SCCHN - Intravenous OPDIVO monotherapy

Randomised phase 3 study vs. chemotherapy (CA209141)

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) who have experienced disease progression during or within 6

months of receiving a prior platinum-based therapy regimen and had an Eastern Cooperative Oncology Group (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 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 histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or untreated brain metastasis were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

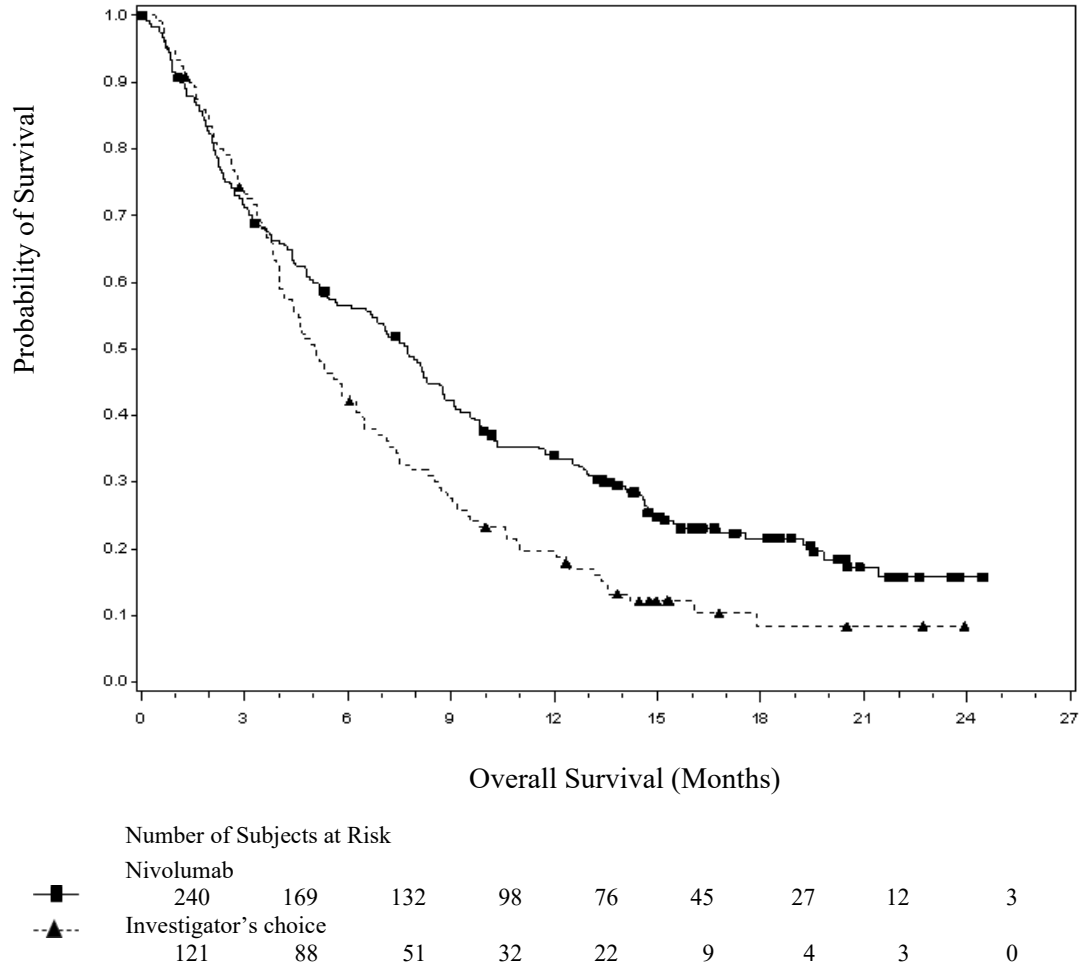
A total of 361 patients were randomised to receive either nivolumab 3 mg/kg (n=240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n=15), 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly or methotrexate (n=52) 40 to 60 mg/m^2 weekly, or docetaxel (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.

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.

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 16. Efficacy results are shown in Table 22.

Figure 16 Overall survival – CA209141



Nivolumab (events: 184/240), median 7.72 months and 95% CI: (5.68, 8.77)
Investigator's choice (events: 105/121), median 5.06 months and 95% CI: (4.04, 6.24).

Table 22 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	7.7 (5.7, 8.8)	5.1 (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 (1.9, 2.1)	2.3 (2.0 , 3.1)
Rate % (95% CI) at 6 months	21.0 (15.9, 26.6)	11.1 (5.9,18.3)

Rate % (95% CI) at 12 months	9.5 (6.0, 13.9)		2.5 (0.5,7.8)
Confirmed objective response	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 (95% CI)	9.7 (5.6, NR)		4.0 (2.9, NR)

[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.

Patients with investigator-assessed primary site of oropharyngeal cancer were tested for HPV by p16 immunohistochemistry. OS benefit was observed regardless of p16 status (p16-positive status: HR= 0.63; 95% CI: 0.38, 1.04 and p16-negative status: HR = 0.64, 95% CI: 0.40, 1.03, and p16-unknown* HR= 0.78, (95% CI: 0.55, 1.10). * Unknown includes patients with non-oropharyngeal cancer of the head and neck in whom HPV testing was not required.

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

Intravenous OPDIVO

UROTHELIAL CARCINOMA (UC)

Adjuvant muscle invasive urothelial carcinoma at high risk of recurrence - Intravenous OPDIVO monotherapy

Randomised phase 3 study of nivolumab vs placebo (CA209274)

The 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 neo-adjuvant cisplatin chemotherapy, and pT3-pT4a or pN+ for adult patients who did not receive neo-adjuvant 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 (2 for patients ineligible for neo-adjuvant cisplatin chemotherapy). Patients were within 120 days of radical resection (R0) of UC of the bladder or upper urinary tract (renal pelvis or ureter). 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. Randomisation was stratified by pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), tumour PD-L1 expression (≥ 1% vs.< 1%/indeterminate), and use of cisplatin neo-adjuvant 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 tumours expressing PD-L1 ≥ 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 include overall survival (OS), non-urothelial tract recurrence free survival (NUTRFS) and disease-specific survival (DSS).

Baseline characteristics were generally balanced between the two groups. The median age was 67 years (range: 30 to 92), 76% were male and 76% were white. Twenty one percent had upper tract urothelial carcinoma, 43% of patients received prior cisplatin in the neo-adjuvant setting, 47% of patients were N+ at radical resection, patients had ECOG performance status of 0 (63%), 1 (35%), or 2 (2%), and 7% of patients had a haemoglobin < 10 g/dL.

Of the 709 patients, 40% had tumour cell PD-L1 expression of ≥ 1%, 59% had tumour cell PD-L1 expression of < 1%, and 1% had tumour cell PD-L1 expression indeterminate, not evaluable or not reported. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

In all randomised patients and all randomised patients with tumour cell PD-L1 expression ≥ 1%, the median follow-up for the primary analysis was 22.4 and 25.5 months for the nivolumab arm, respectively. With a minimum follow-up of 11.0 months in the all randomised patients and a minimum follow-up of 11.4 months in randomised patients with tumours expressing PD-L1 ≥ 1%, the study demonstrated a statistically significant improvement in DFS for patients randomised to nivolumab as compared to placebo, as shown in Figure 17 and Table 23.

Figure 17 Disease-free Survival in All Randomised Patients – CA209274

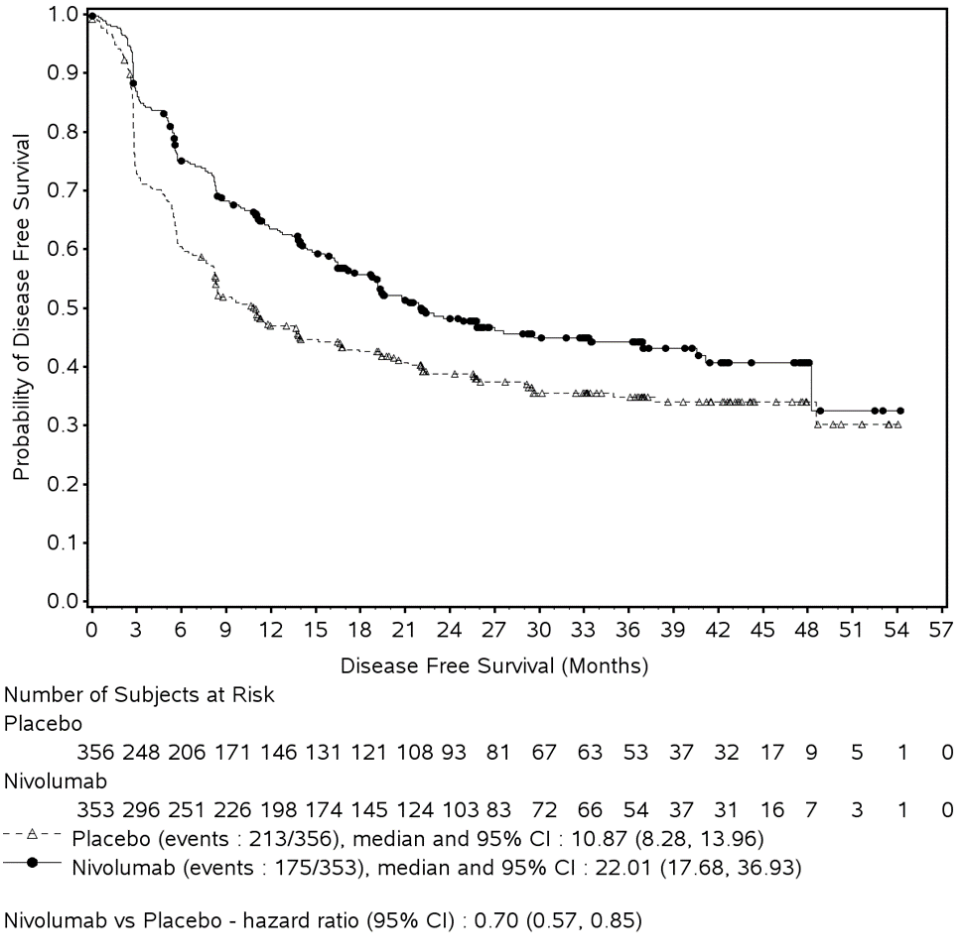


Table 23 Efficacy Results – CA209274

	All Randomised		PD-L1 ≥1%	
	Intravenous OPDIVO **(n=353)**	**Placebo (n=356)**	Intravenous OPDIVO **(n=140)**	**Placebo (n=142)**
Disease-free Survival, n (%)	175 (49.6%)	213 (59.8%)	56 (40.0%)	85 (59.9%)
Median DFS (months)[a]	22.01	10.87	N.R.	8.41
(95% CI)	(17.68, 36.93)	(8.28, 13.96)	(22.11, N.E.)	(5.59, 20.04)
Hazard ratio[b]	0.70		0.53	
(95 % CI)	(0.57, 0.85)		(0.38, 0.75)	

N.R. Not reached, N.E. Not estimable

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazard model. Hazard ratio is nivolumab over placebo.

OS data are immature with 33% of deaths in the overall randomised population.

In an exploratory subgroup analyses in patients with PD-L1 < 1% median DFS with nivolumab vs placebo treatment was 17.68 months (95% CI: 14.06, 22.37) and 11.07 months (95% CI: 8.31, 16.89) respectively (HR of 0.80 (95% CI: 0.62,1.03). In an exploratory subgroup analyses in patients with upper tract UC the unstratified DFS hazard ratio estimate for Renal Pelvis was 1.25 (95% CI: 0.70, 2.25) and for Ureter was 1.54 (95% CI: 0.69, 3.44).

Unresectable or metastatic urothelial cancer – Intravenous OPDIVO in combination with chemotherapy

Randomised phase 3 study of nivolumab in combination with chemotherapy vs chemotherapy (CA209901)

The safety and efficacy of nivolumab plus 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.

Patients were randomised 1:1 to receive either:

- Intravenous OPDIVO 360 mg and cisplatin 70 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle of a 21-day cycle for up to 6 cycles followed by single-agent intravenous OPDIVO 480 mg every 4 weeks until disease progression or unacceptable toxicity, intravenous OPDIVO was continued for up to 2 years from first dose.
- Cisplatin 70 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle for up to 6 cycles, until disease progression or unacceptable toxicity.

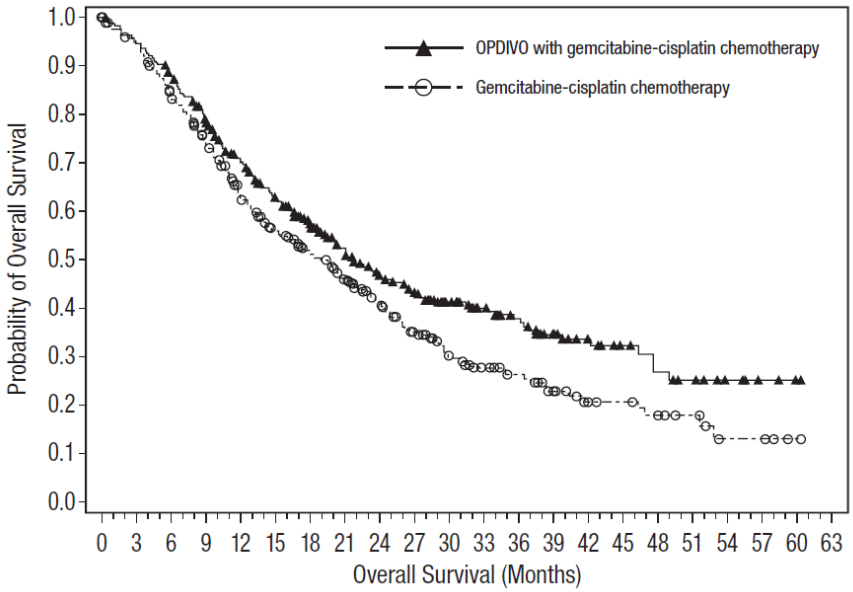
The study included male and female patients (≥18 years) with histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra, who were eligible for cisplatin-based chemotherapy as defined by protocol established criteria. Minor histologic variants (<50% overall) were acceptable (TCC must be the dominant histology). All patients were required to have measurable disease by CT or MRI per RECIST 1.1 criteria.

No prior systemic anti-cancer therapy for metastatic or surgically unresectable UC 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 also permitted if completed at least 4 weeks prior to the initiation of study treatment. Radiation therapy (with or without chemotherapy) for curative intent was permitted as well if the treatment was completed ≥12 months before enrollment in this study. In the case of palliative radiotherapy, it was permitted as long as it was completed at least 2 weeks prior to study drug administration.

A total of 608 patients were randomized to receive either nivolumab in combination with cisplatin and gemcitabine (n=304) or cisplatin and gemcitabine (n=304). The median age was 65 years of age (range: 32 to 86) with 49% of patients ≥65 years of age and 11% of patients ≥75 years of age, 23% were Asian, 72% were White, 0.3% were Black, 77% were male, and 23% were female. Baseline ECOG performance status was 0 (53%) or 1 (46%). At baseline, 87% of patients had metastatic UC, including 20% with liver metastases, 11% had locally advanced UC, and 51% had UC histologic variants. 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 primary efficacy outcome measures were OS and PFS in all randomised patients. Efficacy results are presented in Figure 18 and Table 24. The minimum follow-up was 7.4 months.

Figure 18 Overall Survival in All Randomised Patients – CA209901



Number of Subjects at Risk

OPDIVO with 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

Figure 19 Progression Free Survival in All Randomised Patients – CA209901

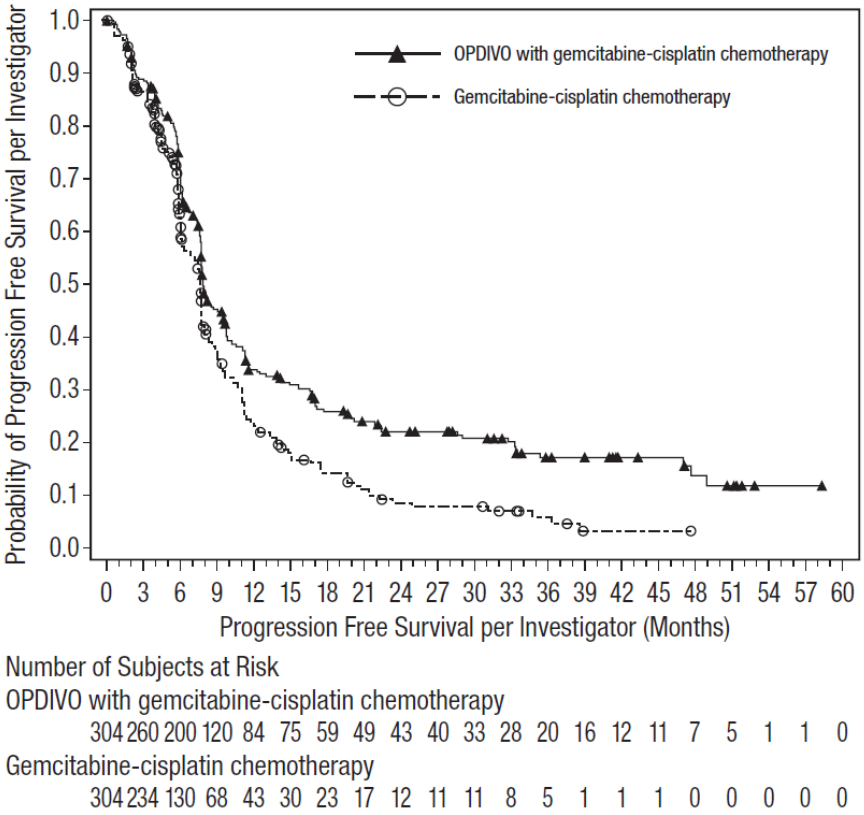


Table 24 Efficacy Results – CA209901

	Intravenous OPDIVO and gemcitabine-cisplatin chemotherapy (n=304)	**gemcitabine-cisplatin chemotherapy (n=304)**
Overall Survival[a] (OS)		
Events	172 (56.6)	193 (63.5)
Median (months) (95% CI)	21.7 (18.6, 26.4)	18.9 (14.7, 22.4)
Rate (95% CI) at 12 months	70.2 (64.6, 75.1)	62.7 (56.8, 68.1)
Rate (95% CI) at 24 months	46.9 (40.7, 52.8)	40.7 (34.6, 46.7)
Hazard ratio (95% CI)[b]	0.78 (0.63, 0.96)	
p-value[c]	0.0171	
Progression-free Survival[a] (PFS)		
Events	211 (69.4)	191 (62.8)
Median (months) (95% CI)	7.92 (7.62, 9.49)	7.56 (6.05, 7.75)
Rate (95% CI) at 12 months	34.2 (28.6, 40.0)	21.8 (16.1, 27.9)
Rate (95% CI) at 24 months	23.5 (18.3, 29.0)	9.6 (5.6, 15.0)
Hazard ratio (95% CI)[b]	0.72 (0.59, 0.88)	
Objective Response Rate (ORR)		
Events	175 (57.6)	131 (43.1)
(95% CI)	(51.8, 63.2)	(37.5, 48.9)
Duration of Response (DoR)		

	Intravenous OPDIVO and gemcitabine-cisplatin chemotherapy (n=304)	gemcitabine-cisplatin chemotherapy (n=304)
Median (months) (95% CI)	9.53 (7.59, 15.08)	7.26 (5.72, 8.90)
Duration of Complete Response		
Events	66 (21.7)	36 (11.8)
Median (months) (95% CI)[d]	37.06 (18.14, NA)	13.24 (7.33, 18.40)

[a] Based on Kaplan-Meier Estimates.

[b] Stratified Cox proportional hazard model.

[c] Log-rank test stratified by 2 sided p values from stratified weighted log-rank test.

[d] Median computed using Kaplan-Meier method.

Previously treated metastatic or unresectable UC – Intravenous OPDIVO monotherapy
Two open-label studies evaluated the safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of locally advanced or metastatic urothelial carcinoma.

Single-arm 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 received nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks. 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 Blinded Independent Central Review (BICR). Additional efficacy measures included duration of response, PFS and OS.

A total of 270 patients with a minimum follow-up of 21.3 months were evaluable for efficacy. 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%), as shown in Table 25.

Table 25 Efficacy results – CA209275

	nivolumab (n = 270)
Confirmed objective response	55 (20.4%)
(95% CI)	(15.7, 25.7)
Complete response (CR)	17 (6.3%)
Partial response (PR)	38 (14.1%)
Stable disease (SD)	57 (21.1%)
Median duration of response	
Months (range)	17.7 (11.5-22.0)

Median time to response	
Months (range)	1.9 (1.6 - 13.8)
Progression Free Survival	
Events (%)	216 (80%)
Median (95% CI) months	2.0 months (1.9, 2.6)
Rate (95% CI) at 12 months	17.5% (13.2, 22.4)
Rate (95% CI) at 24 months	7.9 (4.4, 12.8)
Overall survival	
Events (%)	154 (57%)
Median (95% CI) months	8.6 (6.1, 11.3)
Rate (95% CI) at 12 months	40.3 (34.4, 46.2)
Rate (95% CI) at 24 months	29.4 (23.9, 35.1)

Objective response per IRRC with nivolumab was observed regardless of baseline tumour PD-L1 expression status.

In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%).

Disease-related and non-disease specific quality of life (QoL) was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and the EuroQoL EQ-5D scales. Overall QoL scores remained stable while Global Health Status (GHS) based on the EORTC-QLQ-C30, continued to improve through week 49. EQ-5D VAS scores showed clinically relevant improvement in QoL by Week 9, with continued improvement through Week 49. While both scales showed no detriment, QoL data should be interpreted cautiously in the context of the single arm study design.

Single-arm phase 1/2 study (CA209032)
CA209032 was a Phase 1/2 open-label multi-cohort study which included a cohort of 78 patients 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.

Intravenous OPDIVO

HEPATOCELLULAR CARCINOMA (HCC)

Unresectable or metastatic HCC – Intravenous OPDIVO in combination with ipilimumab

Randomised, open label, phase 3 study of nivolumab in combination with ipilimumab vs lenvatinib or sorafenib (CA2099DW)
CA2099DW was a randomised (1:1), open-label trial in patients with unresectable or advanced HCC. The trial included adult patients (18 years of age 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 trial excluded patients with active autoimmune disease, brain or leptomeningeal metastases, a history of hepatic encephalopathy (within 12 months of randomisation), a platelet count <60,000, 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).

Patients were randomised to receive either:

- Intravenous OPDIVO 1 mg/kg administered intravenously over 30 minutes in combination with ipilimumab 3 mg/kg administered intravenously over 30 minutes every 3 weeks, for a maximum of 4 doses, followed by single agent intravenous OPDIVO at 480 mg administered intravenously over 30 minutes every 4 weeks, or
- Investigator's choice:

- 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

Randomisation was stratified by etiology (HBV vs. HCV vs. non-viral), macrovascular invasion and/or extrahepatic spread (present or absent), and alpha-fetoprotein levels (≥400 or <400 ng/mL). Study treatment for intravenous OPDIVO in combination with ipilimumab continued until disease progression, unacceptable toxicity, or up to 2 years. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue intravenous OPDIVO as a single agent. Treatment beyond RECIST 1.1 defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumour assessments were performed 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.

The primary efficacy outcome measure was OS in all randomised patients. Additional efficacy measures included BICR-assessed ORR and DOR based on RECIST 1.1 criteria, and time to symptom deterioration (TTSD) based on a validated quality of life scale.

A total of 668 patients were randomised to receive intravenous OPDIVO in combination with ipilimumab (n=335) or investigator's choice (n=333) of lenvatinib or sorafenib. In the investigator arm, 85% and 15% of treated patients received lenvatinib or sorafenib, respectively. The trial population characteristics were: 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.

Efficacy results are presented in Figure 20 and Table 26. The results for intravenous OPDIVO in combination with ipilimumab compared to investigator's choice of lenvatinib or sorafenib are based on a minimum follow-up of 26.8 months.

Figure 20 Kaplan-Meier curve of OS – CA2099DW

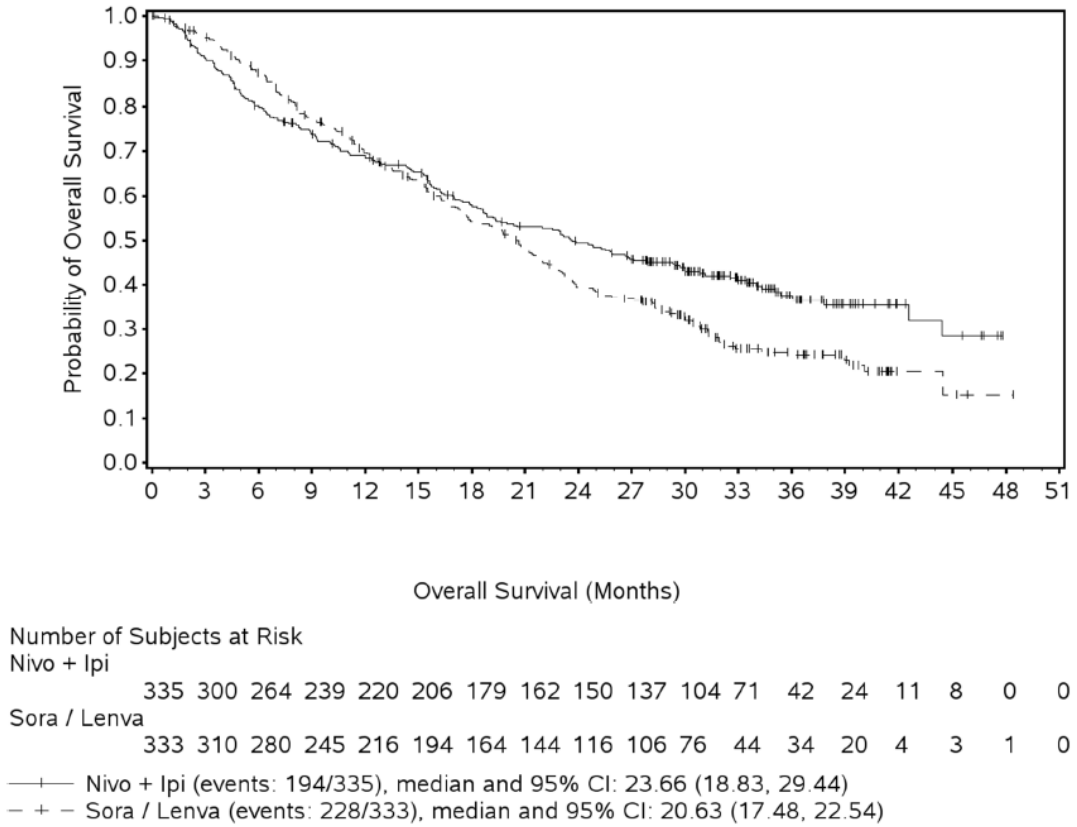


Table 26 Efficacy results – CA2099DW

	nivolumab + ipilimumab (n = 335)	lenvatinib or sorafenib (n = 333)
Overall survival		
Deaths (%)	194 (58%)	228 (68%)
Median (months) (95% CI)	23.7 (18.8, 29.4)	20.6 (17.5, 22.5)
Hazard ratio (95% CI) [a]	0.79 (0.65, 0.96)	
p-value [b]	0.0180	
Overall Response Rate, n (%)[c]	121 (36.1)	44 (13.2)
(95% CI)	(31.0, 41.5)	(9.8, 17.3)
p-value[d]	<0.0001	
Complete response (%)	23 (6.9)	6 (1.8)
Partial response (%)	98 (29.3)	38 (11.4)
Duration of Response (months)[c]		
Median (95% CI)	30.4 (21.2, N.A.)	12.9 (10.2, 31.2)
Range	1.5+, 36.9+	2.1+, 32.5+

[a] Based on stratified Cox proportional hazard model.
[b] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value ≤0.0257.
[c] Assessed by BICR using RECIST 1.1.
[d] Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: p-value ≤0.025.
\+ Censored observation.

Previously treated metastatic HCC – Intravenous OPDIVO monotherapy and in combination with ipilimumab

Single-arm phase 2 study of nivolumab (CA209040)
CA209040 was a multicenter, multiple cohort, open-label trial that evaluated the efficacy of intravenous OPDIVO as a single agent and in combination with ipilimumab in patients with HCC who progressed on or were intolerant to sorafenib.

Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, 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); however, patients with only active HBV or HCV were eligible.

Tumour assessments were conducted every 6 weeks for 48 weeks and every 12 weeks thereafter. The primary efficacy outcome measure was confirmed overall response rate (ORR), as determined by blinded independent central review (BICR) using RECIST version 1.1 and modified RECIST (mRECIST) for HCC. Duration of response (DOR) was also assessed.

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced HCC in patients previously treated with sorafenib (patients had either progressed on or were intolerant to sorafenib) were evaluated in a 154-patient subgroup of CA209040, Cohort 1.

A total of 154 patients received nivolumab 3 mg/kg monotherapy administered intravenously every 2 weeks until disease progression or unacceptable toxicity. This group consisted of 9 patients who were treated at a 3 mg/kg dose out of a dose-escalation cohort (n=37), plus all 145 patients who were treated at a 3 mg/kg dose in a dose-expansion cohort. All 154 patients had been previously treated with sorafenib, and either had progressed on or were intolerant to it. The median age was 63 years (range: 19 to 81), 77% were male, and 46% were white. Across the population, 31% had active HBV infection, 21% had active HCV infection, and 49% had no evidence of active HBV or HCV. The aetiology for HCC was alcoholic liver disease in 18% and non- alcoholic liver disease in 6.5% of patients. Baseline ECOG performance status was 0 (65%) or 1 (35%). Child-Pugh class and score was A5 for 68%, A6 for 31%, and B7 for 1% of patients. Seventy one percent (71%) of patients had extrahepatic spread, 29% had macrovascular invasion, and 37% had alpha-fetoprotein (AFP) levels ≥ 400 µg/L. Prior treatment history included surgical resection (66%), radiotherapy (24%), or locoregional treatment (58%). All patients had received prior sorafenib, of whom 36 (23%) were unable to tolerate sorafenib; h 19% of patients had received 2 or more prior systemic therapies.

The efficacy results after a minimum follow-up of 15 months are summarised in Table 27.

Table 27: Efficacy results – (CA209040, Cohort 1)

	nivolumab (n = 154)
BICR-Assessed Overall Response Rate[a], n(%), RECIST v1.1	22 (14.3%)
(95% CI)[b]	(9.2, 20.8)
Complete response	3 (1.9%)
Partial response	19 (12.3%)
BICR-Assessed Duration of Response, RECIST v1.1	(n=22)
Range (months)	(3.2, 38.2+)
% with duration ≥ 6 months	91%
% with duration ≥ 12 months	55%
BICR-Assessed Overall Response Rate[a], mRECIST	28 (18.2%)
(95% CI)[b]	(12.4, 25.2)
Complete response	5 (3.2%)
Partial response	23 (14.9%)

[a] Overall response rate confirmed by BICR

[b] Confidence interval is based on the Clopper and Pearson method

The efficacy of intravenous OPDIVO in combination with ipilimumab was evaluated in 49 patients in Study CA209040 (Cohort 4) who received intravenous OPDIVO 1 mg/kg and ipilimumab 3 mg/kg administered every 3 weeks for 4 doses, followed by single-agent intravenous OPDIVO at 240 mg every 2 weeks until disease progression or unacceptable toxicity. The median age was 60 years (range: 18 to 80), 88% were male, 74% were Asian, and 25% were White. Baseline ECOG performance status was 0 (61%) or 1 (39%). Fifty-seven (57%) percent of patients had active HBV infection, 8% had active HCV infection, and 35% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 16% and nonalcoholic fatty liver disease in 6% of patients. Child-Pugh class and score was A5 for 82% and A6 for 18%; 80% of patients had extrahepatic spread; 35% had vascular invasion; and 51% had AFP levels ≥400 µg/L. Prior cancer treatment history included surgery (74%), radiotherapy (29%), or local treatment (59%). All patients had received prior sorafenib, of whom 10% were unable to tolerate sorafenib; 29% of patients had received 2 or more prior systemic therapies.

Efficacy results are shown in Table 28. The results for intravenous OPDIVO in combination with ipilimumab in Cohort 4 are based on a minimum follow-up of 28 months.

Table 28: Efficacy Results (CA209040, Cohort 4)

	Intravenous OPDIVO and Ipilimumab (Cohort 4) (n=49)
Overall Response Rate per BICR,[a] n (%), RECIST v1.1	16 (33%)
(95% CI)[b]	(20, 48)
Complete response	4 (8%)
Partial response	12 (24%)
Duration of Response per BICR,[a] RECIST v1.1	n=16
Range (months)	4.6, 30.5+
Percent with duration ≥6 months	88%
Percent with duration ≥12 months	56%
Percent with duration ≥24 months	31%
Overall Response Rate per BICR,[a] n (%), mRECIST	17 (35%)
(95% CI)[b]	(22, 50)
Complete response	6 (12%)
Partial response	11 (22%)

[a] Confirmed by BICR
[b] Confidence interval is based on the Clopper and Pearson method

Intravenous OPDIVO

OESOPHAGEAL SQUAMOUS CELL CARCINOMA (OSCC)

Previously untreated unresectable advanced, recurrent or metastatic OSCC – Intravenous OPDIVO in combination with other agents.

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)
CA209648 was a randomised, active-controlled, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic OSCC. The trial enrolled patients with evaluable tumour cell PD-L1 status, and tumour specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay. Patients were required to have squamous cell carcinoma or adenosquamous cell carcinoma of the 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 enrolment. The trial excluded patients with brain metastasis 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.

Patients were randomised to receive one of the following treatments:

- Intravenous OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks.
- Intravenous OPDIVO 240 mg on days 1 and 15, 5-FU (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).
- 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 were treated with intravenous OPDIVO until disease progression, unacceptable toxicity, or up to 2 years.

Patients who discontinued intravenous OPDIVO in combination with ipilimumab because of an adverse reaction attributed to ipilimumab were permitted to continue intravenous OPDIVO as a single agent.

In patients who received intravenous OPDIVO in combination with chemotherapy and in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued.

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). The primary efficacy endpoints were OS and progression-free survival per blinded independent central review in subjects with tumour cell PD-L1 ≥ 1%.

Secondary efficacy outcome measures tested hierarchically included OS in all randomised patients, PFS assessed by BICR in all randomised patients, and ORR assessed by BICR in tumour cell PD-L1 ≥1% and 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.

The trial population characteristics were: median age 64 years (range: 26 to 81), 45.9% were ³65 years of age, 83.8% were male, 70.5% were Asian, 25.1% were White, and 1.5% were Black. Patients had histological confirmation of squamous cell carcinoma (98.6%) or adenosquamous cell carcinoma (1.4%) in the oesophagus. The baseline tumour cell PD-L1 status was positive for 48.5% patients, defined as ≥1% of tumour cells expressing PD-L1, negative for 50.7%, or indeterminate for 0.8% of patients. Baseline ECOG performance status was 0 (46.2%) or 1 (53.6%).

Nivolumab plus chemotherapy versus chemotherapy

CA209648 demonstrated a statistically significant improvement in OS and PFS for patients with tumour cell PD-L1 ≥1%. The minimum follow-up was 12.9 months. Efficacy results are shown in Figure 21 and Table 29.

Figure 21 **Overall Survival – Intravenous OPDIVO + chemotherapy PD-L1 ≥ 1% – CA209648**

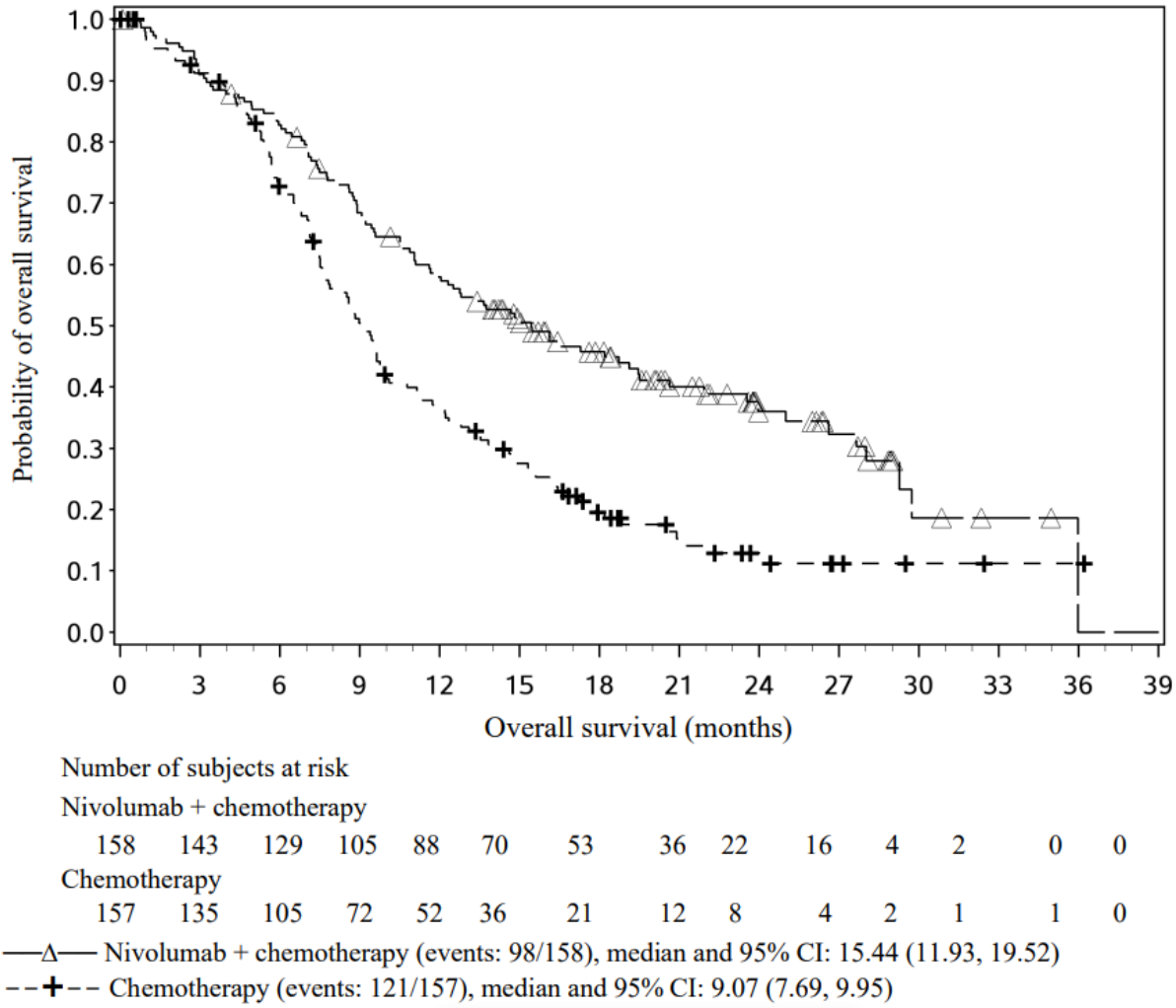


Table 29 **Efficacy Results - Intravenous OPDIVO + chemotherapy PD-L≥1% - CA209648**

	Intravenous OPDIVO with Cisplatin and Fluorouracil (n=321)	**Cisplatin and Fluorouracil (n=324)**
	Tumour cell PD-L1 ≥ 1%	
Overall Survival		
Deaths (%)	98 (62)	121 (77)
Median (months) (95% CI)	15.4 (11.9, 19.5)	9.1 (7.7, 10)
Hazard ratio (95% CI)[b]	0.54 (0.41, 0.71)	
p-value[c]	< 0.0001	
Progression-free Survival[a]		
Disease progression or death (%)	117 (74)	100 (64)
Median (months) (95% CI)	6.9 (5.7, 8.3)	4.4 (2.9, 5.8)
Hazard ratio (95% CI)[b]	0.65 (0.49, 0.86)	
p-value[c]	< 0.0001	
Overall Response Rate, n (%)[a]	84 (53.2)	31 (19.7)

	Intravenous OPDIVO with Cisplatin and Fluorouracil (n=321)	Cisplatin and Fluorouracil (n=324)
	Tumour cell PD-L1 ≥ 1%	
(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 (months) [a]		
Median (95% CI)	8.4 (6.9, 12.4)	5.7 (4.4, 8.7)

[a] Assessed by BICR.
[b] Based on stratified Cox proportional hazard model.
[c] Based on a stratified 2-sided log-rank test.

Previously treated OSCC – Intravenous OPDIVO monotherapy

Randomised, open-label, multicentre Phase 3 study (CA209473)
The safety and efficacy of nivolumab monotherapy for the treatment of OSCC was evaluated in a Phase 3, multicenter, randomised (1:1), active-controlled, open-label study in patients with unresectable advanced, recurrent, or metastatic OSCC, refractory or intolerant to at least one fluoropyrimidine and platinum based regimen who had previously received one treatment regimen (CA209473 also known as ONO-24 or ATTRACTION-3). The study included patients regardless of PD-L1 status. The study excluded patients with a baseline performance score ≥ 2, brain metastases that were symptomatic or required treatment, apparent tumour invasion on organs located adjacent to the oesophagus (e.g., the aorta or respiratory tract), active autoimmune disease, or use of systemic corticosteroids or immunosuppressants. Patients received nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=210) or investigator's choice taxane chemotherapy of 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.

Patients were treated until disease progression, assessed by the investigator per RECIST v1.1, or unacceptable toxicity. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab or chemotherapy if there was no worsening of symptoms due to progression, treatment could be safely administered and there was an expectation continued treatment would lead to clinical benefit, as determined by the investigator.

The tumour assessments were conducted every 6 weeks for 1 year and every 12 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures included ORR and PFS, as assessed by the investigator using RECIST v1.1, and DOR. The trial population characteristics were: median age 65 years (range: 33 to 87), 53% were ≥65 years of age, 87% were male, 96% were Asian, and 4% were White. Baseline ECOG performance status was 0 (50%) or 1 (50%).

The study demonstrated a statistically significant improvement in OS for patients randomised to nivolumab as compared with investigator's choice taxane chemotherapy. OS benefit was observed regardless of PD-L1 expression level. The minimum follow-up was 17.6 months.

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.

Efficacy results are shown in Figure 22 and Table 30.

Figure 22 Overall Survival – CA209473

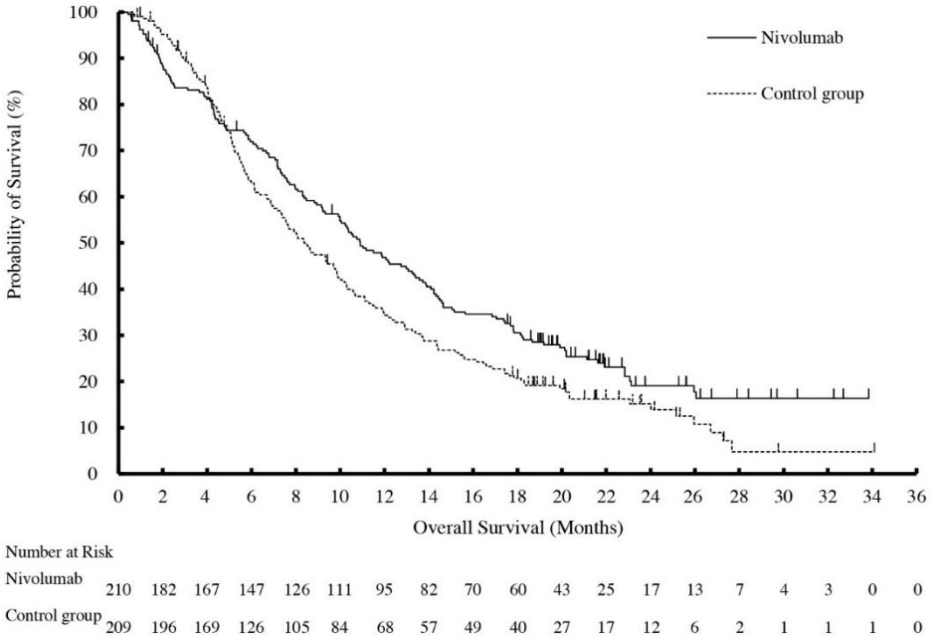


Table 30 Efficacy Results – CA209473

	Nivolumab (n=210)	**Chemotherapy (n=209)**
Overall Survival[a]		
Deaths (%)	160 (76%)	173 (83%)
Median (months) (95% CI)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)
Hazard ratio (95% CI)[b]	0.77 (0.62, 0.96)	
p-value[c]	0.0189	
Progression-free Survival[a]		
Disease progression or death (%)	187 (89)	176 (84)
Median (months) (95% CI)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
Hazard ratio (95% CI)b	1.1 (0.9, 1.3)	
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)
Median duration of response (months) (95% CI)	6.9 (5.4, 11.1)	3.9 (2.8, 4.2)

[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.

Intravenous OPDIVO

ADJUVANT OESOPHAGEAL OR GASTRO-OESOPHAGEAL CANCER

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer – Intravenous OPDIVO monotherapy

Randomised phase 3 study (CA209577)
CA209577 was a randomised, multicenter, double-blind trial in 794 patients with resected oesophageal or gastro-oesophageal junction cancer who had residual pathologic disease. Patients were randomised (2:1) to receive either nivolumab 240 mg or placebo by intravenous infusion over 30 minutes every 2 weeks for 16 weeks followed by 480 mg or placebo by intravenous infusion over 30 minutes every 4 weeks beginning at week 17. Treatment was until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration. Enrolment required complete resection with negative margins within 4 to 16 weeks prior to randomisation. 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). The major efficacy outcome measure was disease-free survival (DFS) 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 as assessed by the investigator prior to subsequent anti-cancer therapy. 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.

The trial population characteristics were: median age 62 years (range: 26 to 86), 36.1% were ≥65 years of age, 84.5% were male, 14.7% were Asian, and 81.6% were White. Disease characteristics were AJCC Stage II (35%) or Stage III (64.7%) at initial diagnosis carcinoma, oesophageal cancer (59.8%) or gastro-oesophageal junction cancer (40.2%) at initial diagnosis, with pathologic positive lymph node status (57.6%) at study entry and histological confirmation of predominant adenocarcinoma (70.9%) or squamous cell carcinoma (29%). The baseline tumour PD-L1 status was positive for 16.2% patients, defined as ≥1% of tumour cells expressing PD-L1, and negative for 71.8% of patients. Baseline ECOG performance status was 0 (58.4%) or 1 (41.6%).

CA209577 demonstrated a statistically significant improvement in DFS for patients randomised to the nivolumab arm as compared with the placebo arm. DFS benefit was observed regardless of tumour PD-L1 expression and histology.

Efficacy results are shown in Figure 23 and Table 31.

Figure 23 Disease-free Survival – CA209577

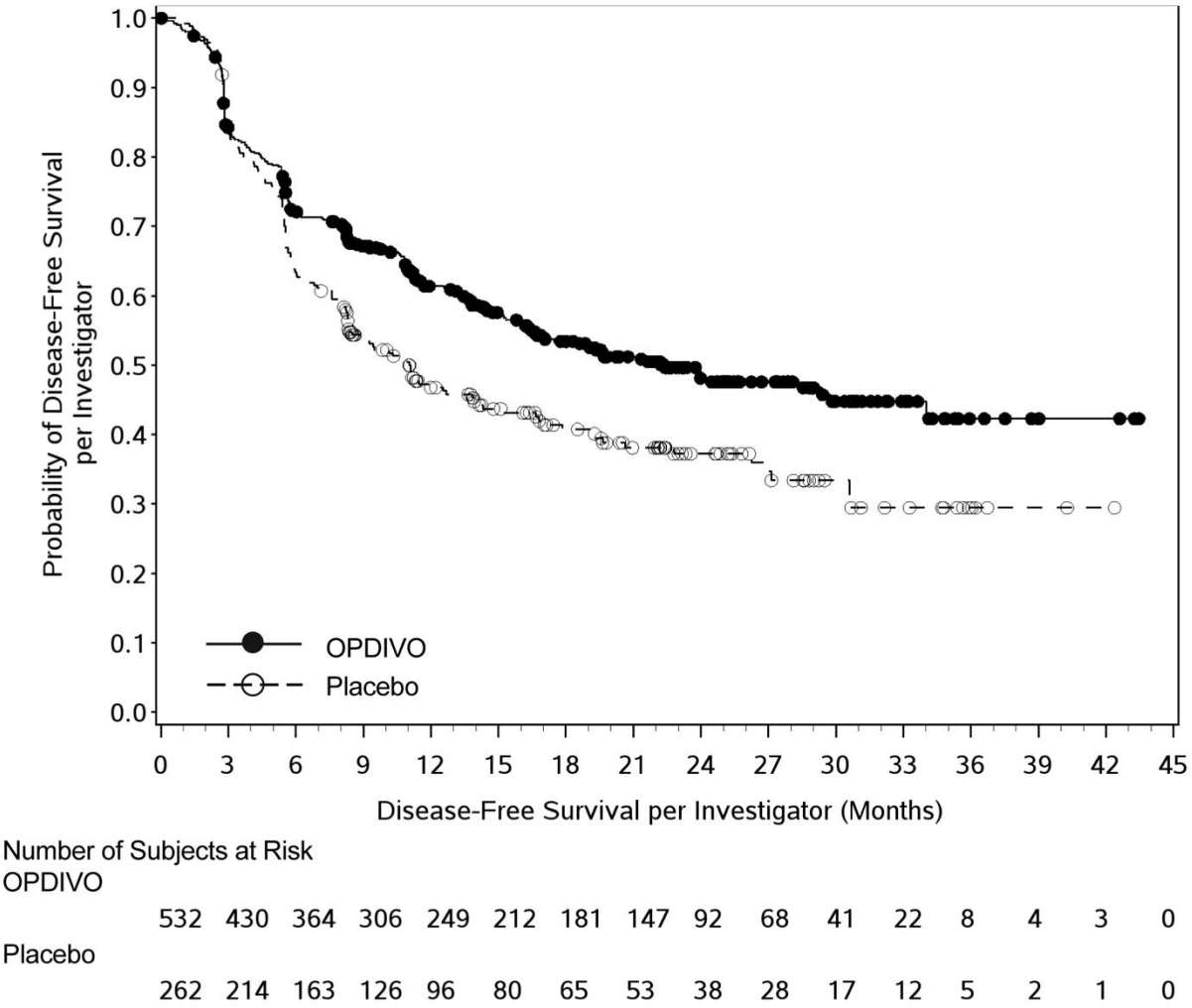


Table 31 Efficacy Results – CA209577

	Intravenous OPDIVO (n=532)	**Placebo (n=262)**
Disease-free Survival[a]		
Number of events, n (%)	241 (45.3%)	155 (59.2%)
Median (months) (95% CI)	22.41 (16.62, 34.00)	11.04 (8.34, 14.32)
Hazard ratio[b] (vs. placebo) (96.4% CI)	0.69 (0.56, 0.86)	
p-value[c]	0.0003	

[a] Based on all randomised patients.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.

In adenocarcinoma subgroup, the hazard ratio (HR) for DFS was 0.75 (95% CI: 0.59, 0.96) with median survivals of 19.35 and 11.10 months for the nivolumab and placebo arms, respectively. In the squamous cell carcinoma subgroup, the HR for DFS was 0.61 (95% CI: 0.42, 0.88) with median survivals of 29.73 and 11.04 months for the nivolumab and placebo arms, respectively.

Intravenous OPDIVO

GASTRIC CANCER (GC), GASTRO-OESOPHAGEAL JUNCTION CANCER (GOJC), OR OESOPHAGEAL ADENOCARCINOMA (OAC)

Previously untreated advanced gastric cancer, gastro-oesophageal junction cancer, or oesophageal adenocarcinoma – Intravenous OPDIVO in combination with chemotherapy

Randomised phase 3 study of nivolumab in combination with chemotherapy vs. chemotherapy (CA209649)

CA209649 was a randomised, multicentre, open-label trial in patients with previously untreated advanced or metastatic gastric cancer, gastro-oesophageal junction cancer, or oesophageal adenocarcinoma. The trial enrolled patients regardless of PD-L1 status, and tumour specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive or had untreated CNS metastases. Patients were randomised to receive intravenous OPDIVO in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

- Intravenous OPDIVO 240 mg in combination with FOLFOX (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or FOLFOX every 2 weeks.
- Intravenous OPDIVO 360 mg in combination with XELOX (capecitabine and oxaliplatin) every 3 weeks or XELOX every 3 weeks.

Patients were treated until disease progression, unacceptable toxicity, or up to 2 years. In patients who received intravenous OPDIVO in combination with chemotherapy and in whom chemotherapy was discontinued, intravenous OPDIVO 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 2 years after treatment initiation.

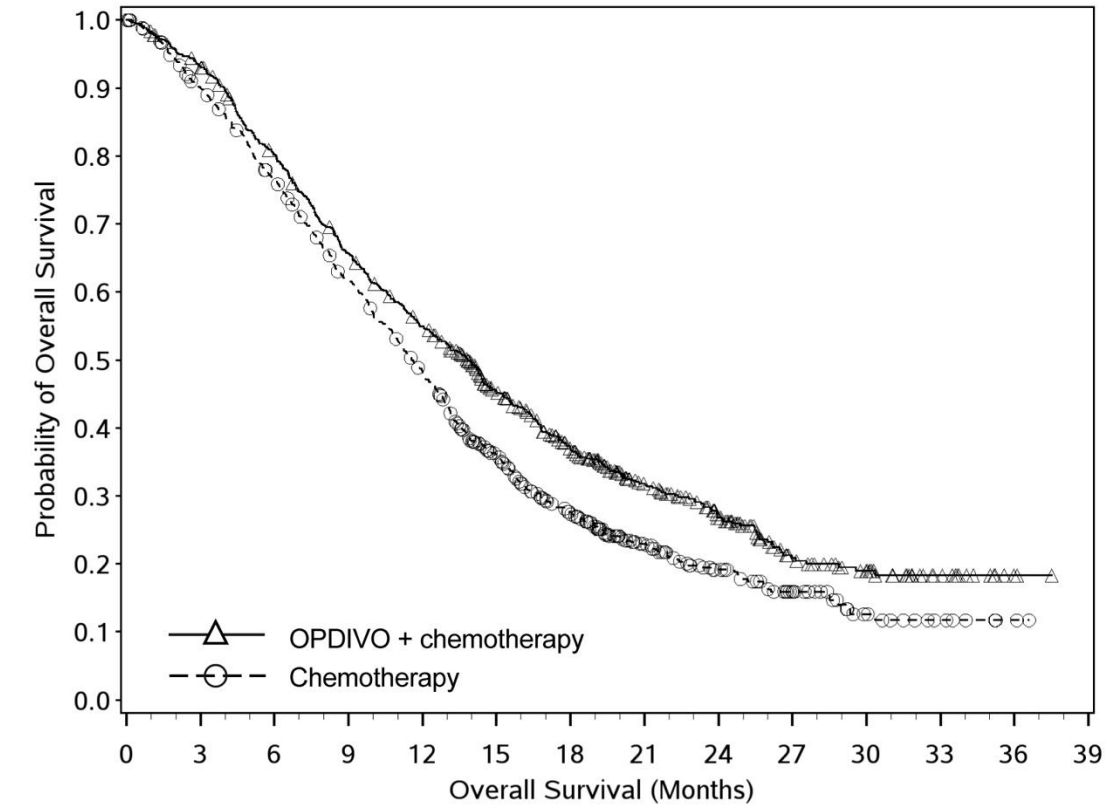
Randomisation was stratified by tumour cell PD-L1 status (≥1% vs. <1% or indeterminate), region (Asia vs. US vs. Rest of World), ECOG performance status (0 vs. 1), and chemotherapy regimen (FOLFOX vs. XELOX). The primary efficacy outcome measure, assessed in patients with PD-L1 CPS ≥5, were PFS assessed by BICR and OS. Secondary efficacy outcome measures tested hierarchically included OS in patients with PD-L1 CPS ≥ 1 and OS in all randomised patients. Other efficacy outcome measures included PFS in all randomised patients and ORR in PD-L1 CPS ≥5 and 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.

A total of 1581 patients were randomised; 789 to the intravenous OPDIVO in combination with chemotherapy arm and 792 to the chemotherapy arm. The trial population characteristics were: median age 61 years (range: 18 to 90), 39% were ≥65 years of age, 70% were male, 24% were Asian, and 69% were White. Baseline ECOG performance status was 0 (42%) or 1 (58%). Seventy percent of patients had adenocarcinoma tumours in the stomach, 16% in the gastro-oesophageal junction, and 13% in the oesophagus.

CA209649 demonstrated a statistically significant improvement in OS and PFS for patients with PD-L1 CPS ≥5. Statistically significant improvement in OS was also demonstrated for all randomized patients. The minimum follow-up was 12.1 months.

The Kaplan-Meier curves for OS are shown in Figure 24 and Figure 25.

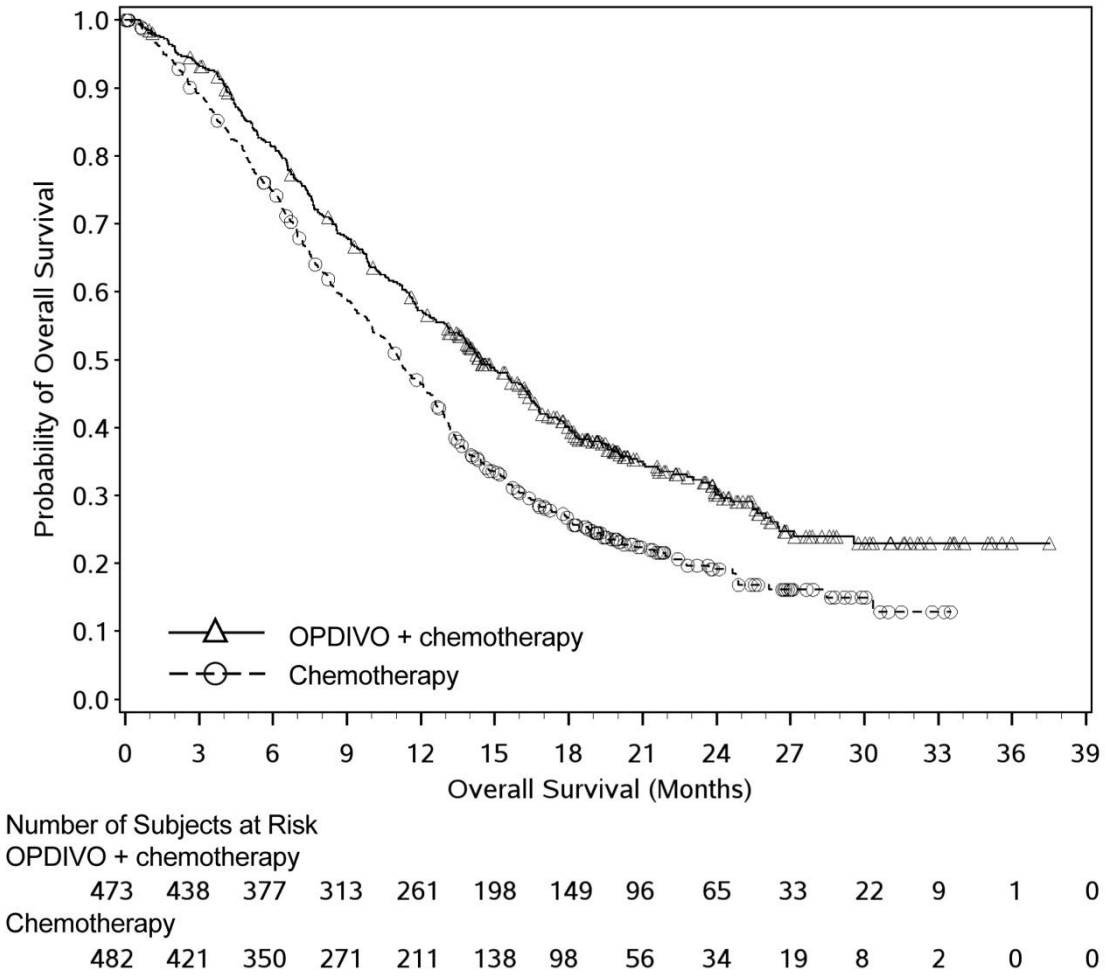
Figure 24 Kaplan-Meier curves of OS - All Patients – CA209649



Number of Subjects at Risk

OPDIVO + chemotherapy	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemotherapy	792	697	586	469	359	239	160	94	59	35	15	7	2	0

Figure 25 Kaplan-Meier curves of OS - PD-L1 CPS ≥5 – CA209649



Efficacy results are shown in Table 32.

Table 32 Efficacy Results – CA209649

	Intravenous OPDIVO and FOLFOX or XELOX (n=789)	FOLFOX or XELOX (n=792)	Intravenous OPDIVO and FOLFOX or XELOX (n=473)	FOLFOX or XELOX (n=482)
	All Patients		**PD-L1 CPS ≥5**	
Overall Survival				
Deaths (%)	544 (69)	591 (75)	309 (65)	362 (75)
Median (months)[a] (95% CI)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)
Hazard ratio (CI)[b]	0.80 (99.3% CI: 0.68, 0.94)		0.71 (98.4% CI: 0.59, 0.86)	
p-value[c]	0.0002		<0.0001	
Progression-free Survival[d]				
Disease progression or death (%)	559 (70.8)	557 (70.3)	328 (69.3)	350 (72.6)
Median (months)[a]	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)	7.69 (7.03, 9.17)	6.05 (5.55, 6.90)

	Intravenous OPDIVO and FOLFOX or XELOX (n=789)	FOLFOX or XELOX (n=792)	Intravenous OPDIVO and FOLFOX or XELOX (n=473)	FOLFOX or XELOX (n=482)
(95% CI)				
Hazard ratio (CI)[b]	0.77 (95% CI: 0.68, 0.87)		0.68 (98% CI: 0.56, 0.81)	
p-value[c]	Not tested		<0.0001	
Number of patients with measurable disease at baseline	**n=603**	**n=608**	**n=378**	**n=391**
Overall Response Rate [d,e], n (%)	350 (58)	280 (46)	226 (60)	177 (45)
(95% CI)	(54, 62)	(42, 50)	(55, 65)	(40, 50)
Complete response (%)	59 (10)	39 (6)	44 (12)	27 (7)
Partial response (%)	291 (48)	241 (40)	182 (48)	150 (38)
Duration of Response[d,e]				
Median (months)[a](95% CI) Range	8.51 (7.23, 9.92) 1.0+, 29.6+	6.93 (5.82, 7.16) 1.2+, 30.8+	9.49 (7.98, 11.37) 1.1+, 29.6+	6.97 (5.65, 7.85) 1.2+, 30.8+

[a] Kaplan-Meier estimate.
[b] Based on stratified log Cox proportional hazard model.
[c] Based on stratified log-rank test.
[d] Confirmed by BICR.
[e] Not evaluated for statistical significance.

Intravenous OPDIVO

MICROSATELLITE INSTABILITY HIGH (MSI-H) OR MISMATCH REPAIR DEFICIENT (DMMR) COLORECTAL CANCER (CRC)

Previously untreated unresectable or metastatic CRC that is MSI-H or dMMR – Intravenous OPDIVO in combination with ipilimumab

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

CA2098HW was a randomised, multi-arm, phase 3, open-label trial in patients with unresectable or metastatic CRC with known tumour MSI-H or dMMR (MSI-H/dMMR) status as 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 study population. The evaluation of efficacy relied on comparison between 2 treatment arms: intravenous OPDIVO in combination with ipilimumab, or investigator's choice of chemotherapy.

In the first-line setting, the trial enrolled unresectable or metastatic disease patients. The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors.

Patients were randomised to receive one of the following treatments:

- Intravenous OPDIVO 240 mg every 3 weeks and ipilimumab 1 mg/kg every 3 weeks for a maximum of 4 doses, then intravenous OPDIVO 480 mg every 4 weeks
- Investigator's choice chemotherapy
  - mFOLFOX6 (oxaliplatin, leucovorin, and FU) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus

followed by FU 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.

- FOLFIRI (irinotecan, leucovorin, and FU) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus and FU 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.

The evaluation of efficacy relied on the comparison of patients with centrally confirmed MSI-H/dMMR mCRC randomised to intravenous OPDIVO plus ipilimumab arm versus chemotherapy arm.

Randomisation was stratified by tumour location (right vs left). Patients randomised to the chemotherapy arm could receive intravenous OPDIVO plus ipilimumab combination upon progression assessed by BICR.

Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue intravenous OPDIVO as a single agent. Intravenous OPDIVO with or without ipilimumab could be administered beyond RECIST 1.1-assessed progressive disease if there was a clinical benefit as determined by investigator and therapy was tolerated. Tumour assessments per RECIST v1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter up until week 96, then every 16 weeks thereafter up until week 146, and then every 24 weeks.

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.

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.

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%).

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 Figure 26 and Table 33. At the time of this interim analysis, the other endpoints were not tested, due to testing hierarchy.

Figure 26 Kaplan Meier curve of PFS in first-line patients with MSI-H/dMMR CRC – CA2098HW

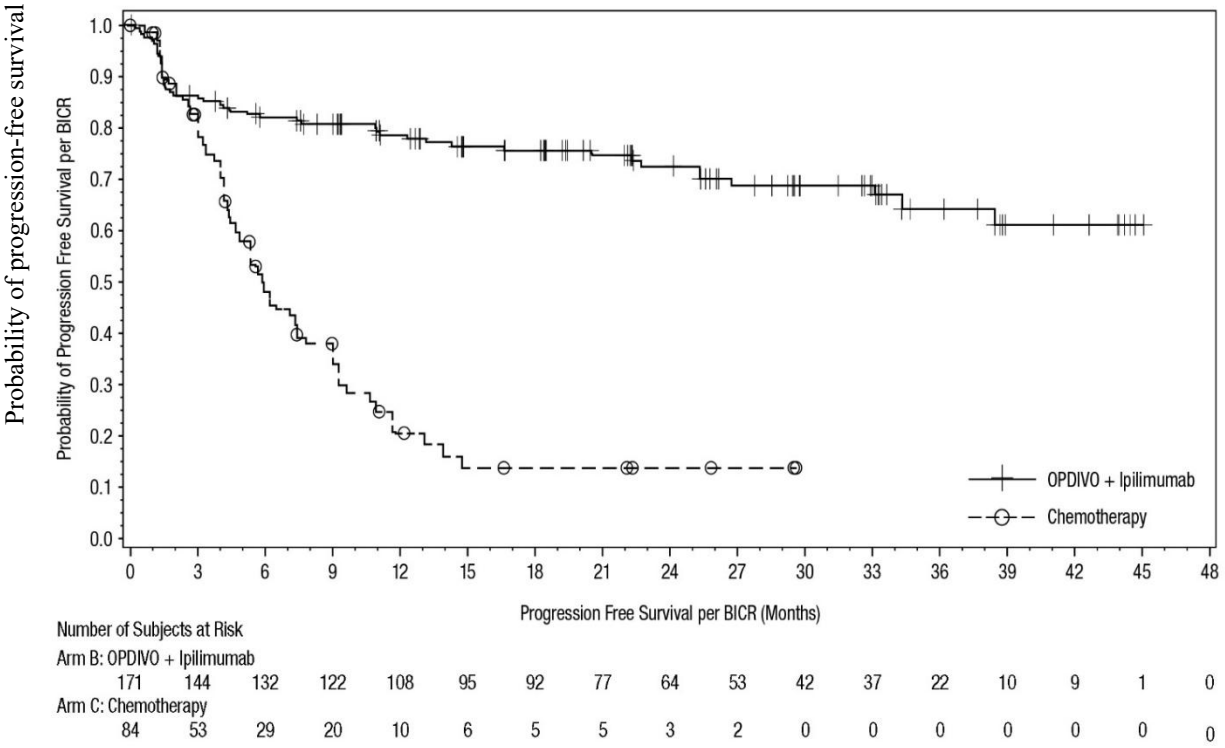


Table 33 Efficacy results in first-line MSI-H/dMMR CRC – CA2098HW[a]

	Intravenous OPDIVO and Ipilimumab (n=171)	**Chemotherapy (n=84)**
Progression-free Survival		
Disease progression or death n (%)	48 (28)	52 (62)
Median (months) (95% CI)	NR (38.4, NR)	5.9 (4.4, 7.8)
Hazard ratio (95% CI)	0.21 (0.14, 0.32)	
p-value[b]	<0.0001	

[a] Median follow-up was 31.5 months (range: 6.1 to 48.4 months).
[b] Based on log-rank test stratified by the same factors as used in the Cox proportional hazard model.

Previously treated unresectable or metastatic CRC that is MSI-H or dMMR – Intravenous OPDIVO in combination with ipilimumab

Open-label study of nivolumab in combination with ipilimumab versus chemotherapy in dMMR or MSI-H CRC 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, multicentre, 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 34.

Table 34 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

IMMUNOGENICITY

As with all therapeutic proteins, there is a potential for an immunogenic response to nivolumab.

OPDIVO SC

Of the 202 patients who were treated with OPDIVO SC as a single agent 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 corresponding incidence of anti-nivolumab antibodies was 7% (15/215) and neutralizing antibodies against nivolumab was 0% (0/15) for intravenous nivolumab in the same study. The incidence of treatment-emergent anti-recombinant human hyaluronidase PH20 antibodies was 8.8% (19/215); 5 (26%) of these 19 patients developed neutralizing antibodies against nivolumab.

Effects of Anti-Drug Antibodies

When OPDIVO SC was administered as a single agent, the clearance of nivolumab increased by approximately 26% in the presence of treatment-emergent anti-nivolumab antibodies. These anti-drug antibody-associated pharmacokinetic changes were not considered to be clinically significant. Of patients in CA20967T who were treated with OPDIVO SC and evaluable for anti-drug antibodies, local injection-site reaction adverse events were reported in a greater proportion of patients who developed anti-drug antibodies to nivolumab or recombinant human hyaluronidase PH20; however, all events were Grade 1 or 2 and resolved. Local injection-site reactions were reported in 15% (7/46) of patients who developed anti-drug antibodies to nivolumab and 7% (10/155) of patients who did not develop anti-drug antibodies to nivolumab. The effects of antidrug antibodies on effectiveness have not been fully characterised.

Intravenous Nivolumab

Nivolumab Monotherapy:

In a pooled analysis of 2022 patients who were treated with nivolumab 3 mg/kg every 2 weeks and were evaluable for the presence of anti-product-antibodies, 231 patients (11.4%) tested positive for treatment-emergent anti-product-antibodies by an electrochemiluminescent (ECL) assay. Two (0.1%) patients were persistently positive. Neutralising antibodies were detected in only 15 (0.7% of the total) of the positive anti-product-antibody patients. There was no evidence of altered pharmacokinetic profile, or toxicity profile associated with anti-product-antibody development. Neutralising antibodies were not associated with loss of efficacy.

Nivolumab in Combination with Ipilimumab:

Of the patients who were treated with nivolumab in combination with ipilimumab and were evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26.0% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks and 24.9% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks. Of the patients who were treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 33.8%. The incidence of neutralising antibodies against nivolumab was 0.5% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks, 1.5% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks and 2.6% with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy. Of the patients who were treated with nivolumab in combination with ipilimumab and 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%.There was no evidence of altered toxicity profile associated with anti-product antibody development. Neutralising antibodies were not associated with loss of efficacy.

Nivolumab in Combination with chemotherapy:

Co-administration with chemotherapy did not appear to affect nivolumab immunogenicity. Of the 276 patients who were treated with nivolumab 240 mg every 2 weeks in combination with chemotherapy

and evaluable for the presence of anti-product-antibodies in the CA209648 study, 12 patients (4.3%) tested positive for treatment-emergent anti-product-antibodies with 3 patients (1.1%) testing positive for neutralising antibodies.

Of the 198 patients who were treated with nivolumab 360 mg every 3 weeks in combination with platinum-doublet chemotherapy, followed by nivolumab 480 mg every 4 weeks along after surgery and evaluable for the presence of anti-product-antibodies in the CA20977T study, 24 patients (12.1%) tested positive for treatment-emergent anti-product-antibodies with 1 patient (0.5 %) testing positive for neutralising antibodies.

5.2 PHARMACOKINETIC PROPERTIES

Nivolumab pharmacokinetics (PK) were assessed using a population PK approach for single agent OPDIVO SC. The PK of nivolumab was studied at a dose of 1,200 mg co-formulated with 20,000 units of recombinant human hyaluronidase PH20 administered as multiple doses of OPDIVO SC as a solution for subcutaneous injection every 4 weeks.

Nivolumab time-averaged serum concentration over 28 days (Cavgd28) showed non-inferiority (geometric mean ratio >1) 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 (Cminss) 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 OPDIVO SC 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

OPDIVO SC 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 POPULATION

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

5.3 PRECLINICAL SAFETY DATA

GENOTOXICITY

Studies to evaluate the genotoxic potential of nivolumab have not been performed.

CARCINOGENICITY

Studies to evaluate the carcinogenic potential of nivolumab have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Vorhyaluronidase alfa
Histidine

Histidine hydrochloride monohydrate
Sucrose
Pentetic acid
Polysorbate 80
Methionine
Water for injections

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vial
Store OPDIVO SC vials in a refrigerator at 2°C to 8°C in the original carton to protect from light. Do not freeze or shake.

Storage in syringe
Once transferred from the vial to the syringe, OPDIVO SC should be used immediately since it does not contain any antimicrobial preservative or bacteriostatic agents. If not used immediately, OPDIVO SC 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. Do not freeze. Aseptic handling should be ensured during the preparation of the syringe for injection.

6.5 NATURE AND CONTENTS OF CONTAINER

Type I glass vial with a butyl rubber stopper and an aluminium seal with an orange plastic flip-off cap containing a nominal fill volume of 5 mL solution for injection.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

EACH VIAL OF OPDIVO® SC IS FOR SINGLE USE IN ONE PATIENT ONLY. DISCARD ANY RESIDUE.

In Australia, any unused medicinal product or waste material should be discarded in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS NUMBER

CAS: 946414-94-4.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave,
Victoria 3170, Australia.
Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9 DATE OF FIRST APPROVAL (ARTG ENTRY)

12 December 2025

10 DATE OF REVISION OF THE TEXT

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	New PI

OPDIVO® SC is a registered trademark of Bristol-Myers Squibb Company.