AUSTRALIAN PRODUCT INFORMATION
OPDIVO® (NIVOLUMAB)

WARNING: IMMUNE-RELATED ADVERSE REACTIONS WITH OPDIVO AND IPILIMUMAB COMBINATION THERAPY

Immune-related adverse reactions are seen more frequently, and are more severe, with OPDIVO and ipilimumab combination therapy than with OPDIVO or ipilimumab monotherapy.

Immune-related adverse reactions can involve any organ system. The majority of these initially manifest during treatment; however, a minority can occur weeks to months after discontinuation. Some immune-related adverse reactions can be permanent (such as thyroid dysfunction and diabetes mellitus). Life-threatening or fatal immune-related adverse reactions that have occurred include colitis, intestinal perforation, hepatitis, pneumonitis, hypophysitis, adrenal insufficiency, toxic epidermal necrolysis, myocarditis, encephalitis and myasthenia gravis (see Sections 4.4 Special warnings and precautions for use and 4.8 Adverse Effects).

Early diagnosis and appropriate management are essential to minimise life-threatening complications (see Section 4.2 Dose and method of administration). Monitoring at least prior to each dose is recommended. Advise patients of the importance of immediately reporting possible symptoms.

Physicians should consult the ipilimumab product information prior to initiation of OPDIVO in combination with ipilimumab. The combination of OPDIVO and ipilimumab should be administered and monitored under the supervision of physicians experienced with the use of immunotherapy in the treatment of cancer.

1. NAME OF THE MEDICINE

Nivolumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg/mL concentrate solution for infusion

Each 1 mL of concentrate contains 10 mg of nivolumab.

One 10 mL vial contains 40 mg of nivolumab in 4 mL.

One 10 mL vial contains 100 mg of nivolumab in 10 mL.

One 25 mL vial contains 240 mg of nivolumab in 24 mL.

OPDIVO (nivolumab (rch)) is a fully human anti-PD-1 monoclonal antibody (IgG4) produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology.

Excipient with known effect

Each 1 mL of concentrate contains 0.1 mmol (or 2.5 mg) sodium.

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

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

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

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Melanoma

OPDIVO, as monotherapy, is indicated for the adjuvant treatment of adults and adolescent patients 12 years and older with completely resected Stage IIB, IIC, III or IV melanoma.

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

OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma. 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, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of patients with resectable non-small cell lung cancer (NSCLC).

OPDIVO, 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 as a single agent in the adjuvant setting after surgical resection.

OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumour aberrations.

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

OPDIVO, as monotherapy, is indicated for the treatment of 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 should be used after progression on or after targeted therapy.

Malignant Pleural Mesothelioma (MPM)

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

Renal Cell Carcinoma (RCC)

OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with intermediate/poor-risk, previously untreated advanced renal cell carcinoma.

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

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

Classical Hodgkin Lymphoma (cHL)

OPDIVO, as monotherapy, is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant and treatment with brentuximab vedotin. The approval of this indication is based on objective response rate in a single arm study.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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

Urothelial Carcinoma (UC)

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

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

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

OPDIVO, as monotherapy, is indicated for the treatment of 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 in combination with ipilimumab is indicated for the first-line treatment of 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 in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of 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, as monotherapy, is indicated for the treatment of 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, as monotherapy, is indicated for the adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer in patients who have received neoadjuvant chemoradiotherapy.

Gastric Cancer (GC), Gastro-oesophageal Junction Cancer (GOJC), or Oesophageal Adenocarcinoma (OAC)

OPDIVO, in combination with fluoropyrimidine- and platinum-based combination chemotherapy, is indicated for the first-line treatment of 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 in combination with ipilimumab is indicated for the treatment of adult patients with unresectable or metastatic colorectal cancer (CRC) that is MSI-H or dMMR as determined by a validated test.

4.2. DOSE AND METHOD OF ADMINISTRATION

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

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

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

Dose escalation or reduction is not recommended. 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 as a single agent are presented in Table 1

Table 1 Recommended Doses for OPDIVO as Monotherapy

Indication^	Recommended OPDIVO Dosage	Duration of Therapy
Unresectable or metastatic melanoma	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated.
Locally advanced or metastatic squamous non-small cell lung cancer		
Locally advanced or metastatic non-squamous non-small cell lung cancer		
Advanced renal cell carcinoma		
Relapsed/refractory classical Hodgkin lymphoma		

Indication^	Recommended OPDIVO Dosage	Duration of Therapy
Recurrent or metastatic squamous cell carcinoma of the head and neck		
Unresectable or metastatic urothelial carcinoma		
Previously treated Hepatocellular carcinoma		
Oesophageal Squamous Cell Carcinoma	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated.
Adjuvant treatment of melanoma	Adults and adolescents (age 12 years and older and weighing 40 kg or more): 3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated to maximum duration of 12 months.
	Adults and adolescents (age 12 years and older and weighing less than 40 kg): 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks	
Adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	After completing 16 weeks of therapy, administer as 480 mg every 4 weeks until disease progression or unacceptable toxicity for a total treatment duration of 1 year
Adjuvant Treatment of Muscle Invasive Urothelial Carcinoma	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated to maximum duration of 12 months.

^ As per monotherapy indications in Section 4.1 Therapeutic Indications.

The recommended doses of OPDIVO 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 for the recommended dose information, as appropriate.

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

Indication^	Recommended OPDIVO Dosage	Duration of Therapy
Unresectable or metastatic melanoma	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg intravenously over 30 minutes	In combination with ipilimumab for 4 doses
	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks* (30-minute intravenous infusion) or 480 mg every 4 weeks* (30-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.
Neoadjuvant treatment of resectable non-small cell lung cancer	360 mg every 3 weeks (30-minute intravenous infusion) 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: 360 mg every 3 weeks (30-minute intravenous infusion) 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: 3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Adjuvant: following neoadjuvant therapy and surgery, administer as a single agent until disease progression, recurrence, or unacceptable toxicity, for up to 13 cycles (up to 1 year)
Metastatic or recurrent non-small cell lung cancer	360 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) and platinum chemotherapy every 3 weeks	After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg OPDIVO administered as an intravenous infusion every 3 weeks in combination with 1 mg/kg ipilimumab every 6 weeks until disease progression, is no longer tolerated, or up to 2 years in patients without disease progression.
Malignant pleural mesothelioma	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 360 mg every 3 weeks (30-minute intravenous infusion) Administer OPDIVO in combination with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion).	Treatment should be continued until disease progression, is no longer tolerated, or up to 2 years in patients without disease progression.

Indication^	Recommended OPDIVO Dosage	Duration of Therapy
Advanced renal cell carcinoma	3 mg/kg every 3 weeks (30-minute intravenous infusion) Administer OPDIVO in combination with ipilimumab 1 mg/kg (30-minute intravenous infusion)	In combination with ipilimumab for 4 doses
	3 mg/kg every 2 weeks* (30-minute intravenous infusion) or 240 mg every 2 weeks* (30-minute intravenous infusion) or 480 mg every 4 weeks* (30-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion) Administer OPDIVO 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: Treatment should be continued as long as clinical benefit is observed, until treatment is no longer tolerated by the patient, or up to 2years in patients without disease progression. Cabozantinib: Until disease progression or unacceptable toxicity
Unresectable or metastatic hepatocellular carcinoma	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg intravenously over 30 minutes	In combination with ipilimumab for a maximum 4 doses
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	After completing a maximum 4 doses of combination therapy, administer as single agent until disease progression, is no longer tolerated, or up to 2 years
Unresectable or metastatic urothelial carcinoma	360 mg every 3 weeks (30-minute intravenous infusion) Administer OPDIVO in combination with cisplatin-based chemotherapy on the same day every 3 weeks.	In combination with cisplatin-based chemotherapy for up to 6 cycles
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	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
Oesophageal squamous cell carcinoma	3 mg/kg every 2 weeks or 360 mg every 3 weeks (30-minute intravenous infusion) Administer OPDIVO in combination with ipilimumab 1 mg/kg every 6 weeks	In combination with ipilimumab until disease progression, or until treatment is no longer tolerated by the patient, or up to 2 years

Indication^	Recommended OPDIVO Dosage	Duration of Therapy
	(30-minute intravenous infusion)	
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion) Administer OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy	OPDIVO: 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	360 mg every 3 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks or 240 mg every 2 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks	Treatment should be continued until disease progression, is no longer tolerated or up to 2 years in patients without disease progression.
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) Colorectal Cancer	240 mg every 3 weeks (30-minute intravenous infusion) Administer OPDIVO in combination with ipilimumab 1 mg/kg (30-minute intravenous infusion)	In combination with ipilimumab for a maximum of 4 doses
	3 mg/kg every 2 weeks[#] (30-minute intravenous infusion) or 240 mg every 2 weeks[#] (30-minute intravenous infusion) or 480 mg every 4 weeks[#] (30-minute intravenous infusion)	After completing a maximum of 4 doses of combination therapy, administer as single agent until disease progression or is no longer tolerated, or up to 2 years.

*Following the last dose of the combination of nivolumab and ipilimumab, the first dose of nivolumab monotherapy should be administered after 3 weeks when using 3 mg/kg or 240 mg or 6 weeks when using 480 mg

[#] Following the last dose of the combination of nivolumab and ipilimumab, the first dose of nivolumab monotherapy should be administered after 3 weeks when using 3 mg/kg or 240 mg or 480 mg

^ As per combination indications in Section 4.1 Therapeutic Indications.

Recommended treatment modifications for OPDIVO as monotherapy and OPDIVO in combination with other therapeutic agents

Dose escalation or reduction is not recommended for OPDIVO as monotherapy or in combination with other therapeutic agents. Dosing delay or discontinuation may be required based on individual safety and tolerability. When nivolumab is administered in combination, refer to the Product Information of the other combination therapy agents regarding dosing.

When OPDIVO is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. 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 for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

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

Table 3 Recommended treatment modifications for OPDIVO as monotherapy or OPDIVO 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.
	AST/ALT >10 time ULN or Grade 3 or 4 elevation in total bilirubin.	Permanently discontinue treatment.

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

Immune-related adverse reaction	Severity of Adverse Reaction[a]	Treatment modification
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.

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

Immune-related adverse reaction	Severity of Adverse Reaction[a]	Treatment modification
	Recurrence of same Grade 3 adverse reaction	Permanently discontinue treatment.
	Grade 3 myotoxicity	Permanently discontinue treatment.
	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 in combination with cabozantinib in RCC

For RCC patients treated with OPDIVO 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 in combination with cabozantinib:

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

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

SPECIAL POPULATIONS

Paediatric patients

The safety and effectiveness of OPDIVO have been established in paediatric patients aged 12 years and older as a single agent for the adjuvant treatment of completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

Elderly patients

No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). No dose adjustment is required for elderly patients (≥ 65 years) (see Section 5.2 Pharmacokinetics).

Patients with renal impairment

Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see Section 5.2 Pharmacokinetics). OPDIVO has not been studied in patients with severe renal impairment.

Patients with hepatic impairment

Based on the population PK results, 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

Pharmacokinetics). OPDIVO has not been studied in patients with severe hepatic impairment or cirrhosis of Child-Pugh B or C severity and OPDIVO must be administered with caution in these patients (see Section 4.4 Special warnings and precautions for use).

METHOD OF ADMINISTRATION

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

Administer the OPDIVO infusion intravenously over a period of 30 minutes.

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

Administer OPDIVO or OPDIVO in combination with other therapeutic agents as follows:

- With ipilimumab: administer OPDIVO first followed by ipilimumab on the same day.
- With platinum-doublet chemotherapy: administer OPDIVO first followed by platinum-doublet chemotherapy on the same day.
- With ipilimumab and platinum-doublet chemotherapy: administer OPDIVO first followed by ipilimumab and then platinum-doublet chemotherapy on the same day.
- With fluoropyrimidine- and platinum-containing chemotherapy: administer OPDIVO first followed by fluoropyrimidine- and platinum-containing chemotherapy on the same day.

Use separate infusion bags and filters for each infusion. Administer OPDIVO first followed by ipilimumab, no earlier than 30 minutes after completion of the OPDIVO infusion.

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

OPDIVO infusion is compatible with:

- PVC or non-PVC containers
- Polyolefin containers
- Glass bottles
- PVC infusion sets
- In-line filters with polyethersulfone membranes with pore sizes of 0.2 μm to 1.2 μm.

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

Calculating the dose

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

When the prescribed dose for the patient is 240 mg, 360 mg or 480 mg, it is given regardless of body weight.

When the prescribed dose for the patient is 3 mg/kg or 1 mg/kg, calculate the total dose to be given.

- Each 4 mL vial of OPDIVO concentrate contains 40 mg of nivolumab; each 10 mL vial of OPDIVO contains 100 mg of nivolumab.
- The total nivolumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The volume of OPDIVO concentrate to prepare the dose (mL) = the total dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

Preparing the infusion

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

OPDIVO can be used for intravenous administration without dilution, after transfer to an infusion container using an appropriate sterile syringe.

OPDIVO can also be used for intravenous administration after diluting with either sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For 3 mg/kg or 1 mg/kg dose, the final infusion concentration should range between 1 and 10 mg/mL. For 240 mg, 360 mg or 480 mg, the concentrate may be diluted to not exceed a total infusion volume of 160 mL. For patients with body weight less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of body weight.

STEP 1

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

STEP 2

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

4.3. CONTRAINDICATIONS

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

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

When 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 with or without ipilimumab.

OPDIVO monotherapy is associated with immune-related adverse reactions. In clinical trials, almost all immune-related adverse reactions have occurred at higher frequencies when OPDIVO was administered in combination with ipilimumab compared with 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 monotherapy or OPDIVO in combination with ipilimumab 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 monotherapy or OPDIVO in combination with ipilimumab 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 monotherapy or OPDIVO in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy.

Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

OPDIVO monotherapy or OPDIVO in combination with ipilimumab must be permanently discontinued for any severe immune related adverse reaction that recurs and for any life threatening immune related adverse reaction (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 OPDIVO monotherapy, OPDIVO in combination with ipilimumab or OPDIVO 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 monotherapy or OPDIVO in combination with ipilimumab must be permanently discontinued and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

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

Immune-related colitis

Severe diarrhoea or colitis has been observed with OPDIVO monotherapy or OPDIVO 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 monotherapy or OPDIVO in combination with ipilimumab must be permanently discontinued and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 3 diarrhoea or colitis observed with OPDIVO in combination with ipilimumab, permanently discontinue both agents and follow the management guideline for Grade 4 diarrhoea or colitis above.

OPDIVO monotherapy should be withheld for Grade 3 diarrhoea or colitis and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, OPDIVO monotherapy may be resumed (after corticosteroid taper). If worsening or no improvement occurs despite initiation of corticosteroids, OPDIVO monotherapy must be permanently discontinued.

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

For Grade 2 transaminase or total bilirubin elevation, OPDIVO monotherapy or OPDIVO in combination with ipilimumab should be withheld. Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, OPDIVO monotherapy or OPDIVO in combination with ipilimumab may be resumed (after corticosteroid taper).

If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and OPDIVO monotherapy or OPDIVO in combination with ipilimumab 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 monotherapy or OPDIVO in combination with ipilimumab 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 OPDIVO monotherapy or OPDIVO 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 monotherapy or OPDIVO in combination with ipilimumab must be permanently discontinued and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

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

Immune-related endocrinopathies

Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), hypoparathyroidism, diabetes mellitus, and diabetic ketoacidosis have been observed with OPDIVO monotherapy or OPDIVO 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 monotherapy or OPDIVO in combination with ipilimumab should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, OPDIVO monotherapy or OPDIVO in combination with ipilimumab 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 monotherapy or OPDIVO in combination with ipilimumab may be resumed (after corticosteroid taper). Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. OPDIVO monotherapy or OPDIVO in combination with ipilimumab should be permanently discontinued for life-threatening (Grade 4) hypothyroidism or hyperthyroidism.

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

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

For symptomatic diabetes, OPDIVO monotherapy or OPDIVO in combination with ipilimumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. OPDIVO monotherapy or OPDIVO in combination with ipilimumab 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 OPDIVO in combination with ipilimumab and less commonly with OPDIVO monotherapy. OPDIVO monotherapy or OPDIVO in combination with ipilimumab 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 or OPDIVO in combination with ipilimumab should be withheld and the patient referred for specialist assessment and treatment. If the patient has confirmed SJS or TEN, permanent discontinuation of OPDIVO or OPDIVO in combination with ipilimumab is recommended.

Caution should be used when considering the use of OPDIVO 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 OPDIVO or OPDIVO in combination with ipilimumab: demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis and encephalitis.

Withhold OPDIVO 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 for immune-related encephalitis and myasthenic syndrome/myasthenia gravis.

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT) in classical Hodgkin Lymphoma

PD-1/PD-L1 inhibitors including nivolumab, when administered before allogeneic haematopoietic stem cell transplant (HSCT), may be associated with an increased risk of transplant-related complications, including GVHD. Fatal cases have been reported in clinical studies.

Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications should be made case by case (see Section 4.8 Adverse effects - Selected immune-related adverse reactions). Patients should be monitored closely for early evidence of transplant-related complications.

Other immune-related adverse reactions

Other clinically significant immune-related adverse reactions, including some with fatal outcome, have been observed across clinical trials of OPDIVO or OPDIVO in combination with ipilimumab investigating various doses across tumour types (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 monotherapy or OPDIVO in combination with ipilimumab should be withheld and corticosteroids administered. Upon improvement, OPDIVO monotherapy or OPDIVO in combination with ipilimumab may be resumed after corticosteroid taper. OPDIVO monotherapy or OPDIVO in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab.

If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued (see Section 4.2 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 OPDIVO or OPDIVO 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

Severe infusion reactions have been reported in clinical trials of OPDIVO monotherapy or 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 OPDIVO monotherapy or OPDIVO in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Opdivo in combination with ipilimumab

Review the Product Information for ipilimumab prior to initiation of the OPDIVO in combination with ipilimumab. Both agents are associated with immune-related adverse reactions and may require immunosuppression. In clinical trials, the immune-related adverse reactions that are described in the PRECAUTIONS section occurred at higher frequencies when OPDIVO was administered in combination with ipilimumab compared with OPDIVO as a monotherapy. Most immune-related adverse reactions (except for endocrinopathies) improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications.

Patients receiving OPDIVO in combination with ipilimumab should be monitored for immune-related adverse reactions clinically and with appropriate investigations prior to each dose during the combination phase.

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).

Opdivo and EGFR TKIs in NSCLC

OPDIVO 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 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.

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 Alert Card

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

Special populations

Populations excluded from registrational clinical trials

Populations excluded from clinical studies of OPDIVO or OPDIVO in combination with other therapeutic agents are listed in Table 4 according to studied indication. In the absence of data, OPDIVO 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* • 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.
MPM	• Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, or interstitial lung disease
cHL	• Patients with symptomatic interstitial lung disease
SCCHN	• Patients with carcinoma of the nasopharynx or salivary gland as the primary tumour site

HCC	*Unresectable or metatstatic 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 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 have not been studied in patients with severe hepatic impairment or with cirrhosis of Child-Pugh B or C severity. OPDIVO 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).

Patients on controlled sodium diet

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

Use in the elderly

See Section 4.2 Dose and method of administration.

Paediatric use

The safety and efficacy of OPDIVO for the adjuvant treatment of melanoma in paediatric patients who are at least 12 years old and weigh at least 40 kg have been established. This usage is supported by the same evidence that supports this use in adults (see 5.1 Pharmacodynamic properties - Clinical trials), plus additional data analyses that suggest that at the recommended OPDIVO dose, nivolumab exposures in paediatric patients 12 years of age who weigh at least 40 kg are expected to result in similar safety

and efficacy to that of adults. The pharmacokinetics of monoclonal antibodies and the nature of melanoma is sufficiently similar to allow extrapolation of data from adult patients to paediatric patients 12 years of age or older (who weigh at least 40 kg).

The safety and efficacy of OPDIVO in children below 12 years have not been established. No data are available.

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 metabolizing 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 OPDIVO on male and female fertility is unknown.

Use in pregnancy (Category D)

OPDIVO 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 for at least 5 months following the last dose of OPDIVO.

There are no data on the use of OPDIVO 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, nivolumab 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 at 10 and 50 mg/kg twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels 8 and 35 times, respectively, those observed at the clinical dose of 3 mg/kg nivolumab (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 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 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 does not adversely affect them.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 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

Classical Hodgkin Lymphoma

The safety of OPDIVO 3 mg/kg every 2 weeks as monotherapy was evaluated in 266 adult patients with cHL post high-dose chemotherapy and ASCT (243 patients in study CA209205 and 23 patients in CA209039). The median number of doses was higher in the cHL nivolumab monotherapy population compared with the pooled nivolumab monotherapy population across tumours (N=1991) (23 versus 10, respectively). The median duration of study therapy was longer in the cHL nivolumab monotherapy population compared with the pooled nivolumab monotherapy population across tumours (18.6 months versus 5.3 months, respectively). Some adverse reactions (all grades) were reported at a higher frequency in the cHL nivolumab monotherapy population compared with the pooled nivolumab monotherapy population across tumours: infusion related reaction (13.2%), lipase increased (7.1%), neutropenia (6.8%) and thrombocytopenia (6.4%). Grade 3 or 4 adverse reactions of lipase increased (3.8%) and neutropenia (3.8%) were also reported at a higher frequency in the cHL nivolumab monotherapy population. All other adverse reactions (all grades and Grade 3 or 4) were similar to the pooled nivolumab monotherapy population across tumours.

Hepatocellular Carcinoma

The safety of OPDIVO 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 OPDIVO 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 OPDIVO 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 metastatic 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).

1L OSCC and Malignant Pleural Mesothelioma

In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma (n=300), the most frequent adverse reactions (≥10%) were rash (25%), fatigue (22%), diarrhea (21%), pruritus (16%), hypothyroidism (11%), and nausea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Median duration of therapy was 5.55 months (range: 0-26.2 months) for nivolumab in combination with ipilimumab.

In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in 1L OSCC (n=322), the most frequent adverse reactions (≥10%) were rash (25.2%), pruritus (13.4%), hypothyroidism

(13.4%), and fatigue (11.2%). The most frequent all-causality serious adverse events reported in ≥2% were pneumonia (7.5%), pyrexia (2.7%), pneumonitis (3.7%), dysphagia (3.4%), aspiration pneumonia (3.1%), hepatic function abnormal (2.8%), decreased appetite (2.2%), adrenal insufficiency (2.2%) and dehydration (2.2%). Fatal treatment-related adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with ipilimumab; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome.

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 3 mg/kg in combination with ipilimumab 1 mg/kg in OSCC and MPM (n=622)** [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		pneumonia, upper respiratory tract infection		
Uncommon	bronchitis	meningitis aseptic, upper respiratory tract infection	bronchitis, aseptic meningitis	pneumonia, upper respiratory tract infection	bronchitis
Blood and lymphatic system disorders					
Common	eosinophilia	eosinophilia			
Uncommon			eosinophilia		eosinophilia
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	infusion-related reaction (including cytokine release syndrome), hypersensitivity
Uncommon	sarcoidosis	hypersensitivity			
Endocrine disorders					
Very common	hypothyroidism	hypothyroidism, hyperthyroidism	hypothyroidism, hyperthyroidism	hypothyroidism	hypothyroidism, adrenal insufficiency
Common	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis	adrenal insufficiency, hypophysitis, thyroiditis	adrenal insufficiency, hypophysitis, thyroiditis, diabetes mellitus	hyperthyroidism, adrenal insufficiency, hypophysitis, hypopituitarism, thyroiditis	hyperthyroidism, hypophysitis, thyroiditis, diabetes mellitus
Uncommon	diabetic ketoacidosis, diabetes mellitus	hypopituitarism	diabetic ketoacidosis, hypopituitarism	diabetes mellitus	hypopituitarism
Metabolism and nutrition disorders					
Very common	decreased appetite		decreased appetite		
Common	dehydration	decreased appetite	dehydration	decreased appetite	decreased appetite
Uncommon		diabetes mellitis	metabolic acidosis		
Hepatobiliary disorders					
Common	hepatitis	hepatitis, hepatic failure	hepatitis	hepatitis	hepatitis
Uncommon		liver injury			

Nervous system disorders					
Very common	headache	headache, dizziness			
Common	peripheral neuropathy, dizziness		headache, peripheral neuropathy, dizziness		headache, dizziness, neuropathy peripheral
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	encephalitis	polyneuropathy, encephalitis
Eye disorders					
Common	uveitis, blurred vision		blurred vision		
Uncommon		blurred vision	uveitis	uveitis	
Cardiac disorders					
Common	tachycardia		tachycardia		
Uncommon	arrhythmia (including ventricular arrhythmia)[a,] , atrial fibrillation, myocarditis[a,c]	myocarditis	arrhythmia (including ventricular arrhythmia), myocarditis	tachycardia, myocarditis	myocarditis[a]
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]	pneumonitis[a], dyspnoea, cough
Uncommon	pleural effusion	cough			
Gastrointestinal disorders					
Very common	colitis[a], diarrhoea, vomiting, nausea, abdominal pain	diarrhoea	diarrhoea, vomiting, nausea	diarrhoea	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, constipation, colitis, pancreatitis	nausea, vomiting, abdominal pain, colitis, constipation, stomatitis, dry mouth
Uncommon	intestinal perforation[a], gastritis, duodenitis	gastritis	gastritis		duodenitis, gastritis
Rare	coeliac disease		coeliac disease	coeliac disease	coeliac disease
Skin and subcutaneous tissue disorders					
Very common	rash[b], pruritus	rash[b], pruritis	rash[b], pruritus	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	erythema multiforme	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	musculoskeletal pain[d], arthritis	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	myositis	muscle spasm
Renal and urinary disorders					
Common	renal failure (including acute kidney injury)[a,]		renal failure (including acute kidney injury)	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	fatigue
Common	oedema (including peripheral oedema), pain	oedema, pyrexia	oedema (including peripheral oedema), pain, chest pain, chills	pyrexia	pyrexia, oedema (including peripheral oedema)
Uncommon	chest pain	chills, pain			pain, chest pain
Investigations[f]					
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 alkaline phosphatase, increased creatinine, hyperglycaemia, lymphopaenia, anaemia[f,] hypercalcaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypomagnesaemia, increased total bilirubin, hypoglycaemia, thrombocytopaenia	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	leucopaenia, neutropaenia, hypernatraemia, hypermagnesaemia, increased lipase, increased amylase	thrombocytopaenia, hypernatraemia
Uncommon				hypophosphataemia	

[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 ipilimumab and platinum-based chemotherapy

NSCLC

In the dataset of nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC (n = 358), the most frequent adverse reactions (≥ 10%) were fatigue (36%), nausea (26%), rash (25%), diarrhoea (20%), pruritus (18%), decreased appetite (16%), hypothyroidism (15%) and vomiting (13%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Median duration of therapy was 6.1 months (95% CI 4.93, 7.06) for nivolumab in combination with ipilimumab and 2.4 months (95% CI 2.30, 2.83) for platinum-based chemotherapy.

Adverse reactions reported in the dataset for patients treated with nivolumab in combination with ipilimumab and platinum-based chemotherapy (n = 358) are presented in Table 7 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 7 Adverse reactions with nivolumab in combination with ipilimumab and platinum based chemotherapy

	Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC
Infections and infestations	
Common	conjunctivitis, pneumonia, respiratory tract infection
Uncommon	bronchitis, sepsis
Blood and lymphatic system disorders	
Common	febrile neutropenia
Uncommon	eosinophilia
Immune system disorders	
Common	infusion-related reaction (including cytokine release syndrome), hypersensitivity
Endocrine disorders	
Very common	hypothyroidism
Common	hyperthyroidism, adrenal insufficiency, hypophysitis, thyroiditis
Uncommon	hypopituitarism, hypoparathyroidism
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration, hypoalbunaemia, hypophosphatemia
Nervous system disorders	
Common	peripheral neuropathy, dizziness, headache
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis
Eye disorders	
Common	dry eye
Uncommon	blurred vision, episcleritis
Cardiac disorders	
Uncommon	tachycardia, atrial fibrillation, bradycardia
Vascular disorders	
Uncommon	hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis, dyspnoea, cough
Uncommon	pleural effusion

Gastrointestinal disorders	
Very common	nausea, diarrhoea, vomiting
Common	constipation, stomatitis, abdominal pain, colitis, dry mouth, pancreatitis
Not known	coeliac disease
Hepatobiliary disorders	
Common	hepatitis[a]
Skin and subcutaneous tissue disorders	
Very common	rash[b], pruritus
Common	alopecia, dry skin, erythema, urticaria
Uncommon	psoriasis, Stevens-Johnson syndrome, vitiligo
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain[c], arthralgia, arthritis
Uncommon	muscular weakness, muscle spasms, polymyalgia rheumatica
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)
Uncommon	nephritis
General disorders and administration site conditions	
Very common	fatigue
Common	pyrexia, oedema (including peripheral oedema)
Uncommon	Chills, chest pain
Investigations[d]	
Very common	anaemia[e], thrombocytopaenia, leucopoenia, lymphopaenia, neutropaenia, increased alkaline phophatases, increased transaminases, increased creatinine, increased amylase, increased lipase, hypokalaemia, hypomagnesaemia, hyponatraemia
Common	increased total bilirubin, increased thyroid stimulating hormone
Uncommon	increased gamma-glutamyltransferase

[a] Hepatitis as a composite term which includes hepatitis and hepatotoxicity

[b] 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.

[c] 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.

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

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

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 8. These reactions are presented by system

organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100).

Table 8 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, dermaititis 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 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 480mg 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 9 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 9 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 neutropenia	febrile neutropenia	febrile neutropenia	febrile neutropenia	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	hypoalbuminemia	hypoalbuminaemia	hypoalbuminaemia, hypophosphataemia	
Uncommon	hypophosphatemia	hypophosphatemia			
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-Barre 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, pneumonitise	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					

Very common	rash[a]	rasha, 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 painb, 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]					
Very common	neutropaenia, anaemia[d], thrombocytopaenia	anaemiad, thrombocytopaenia , leucopoenia, lymphopaenia, neutropaenia, increased alkaline phosphatase, increased transaminases, increased creatinine, hyponatraemia, hyperkalaemia, hypokalemia; hypercalcemia, hypocalcaemia, hyperglycaemia,	anaemia[d], leucopenia, neutropenia, 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], neutropenia, thrombocytopaeniae, lymphopenia, leukopenia, increased creatinine, increased transaminases, increased alkaline phosphatase, hyponatraemia, hypocalcemia, hyperkalemia, hypokalemia; hypomagnesaemia, hyperglycemia, hypercalcemia, hypoglycemia	anaemia[d], thrombocytopaenia, leucopoenia, lymphopaenia, 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 3 mg/kg in combination with ipilimumab 1 mg/kg in OSCC and MPM, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.5% for anaemia, 1.0% for thrombocytopaenia, 1.2% for leucopoenia, 10.6% for lymphopaenia, 1.3% for neutropaenia, 3.2% for increased alkaline phosphatase, 6.3% for increased AST, 6.5% for increased ALT, 1.2% for increased total bilirubin, 0.5% for increased creatinine, 3.6% for hyperglycaemia, 0.9% for hypoglycaemia, 5.4% for increased amylase, 12.8% for

increased lipase, 0.7% for hypernatraemia, 10.0% for hyponatraemia, 2.8% for hyperkalaemia, 3.7% for hypokalaemia, 1.0% for hypercalcaemia, 0.2% for hypocalcaemia and 0.3% for hypomagnesaemia.

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

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 OPDIVO and OPDIVO 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 4.4 warnings and precautions for use.

Note: Time to resolution may include censored observations.

Immune-related pneumonitis

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.

OPDIVO in combination with ipilimumab
In patients treated with nivolumab 1mg/kg in combination with ipilimumab 3mg/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 3 mg/kg in combination with ipilimumab 1 mg/kg in OSCC and malignant pleural mesothelioma, the incidence of pneumonitis including interstitial lung disease was 7.4% (46/622). Grade 2, Grade 3 and Grade 4 cases were reported in 3.7% (23/622) , 1.1% (7/622) and 0.6% (4/622) of patients, respectively. Median time to onset was 2.7 months (range: 0.3-20.8). Eighteen patients (2.9%) required permanent discontinuation of nivolumab in combination with ipilimumab. Eighteen patients received high dose corticosteroids (at least 40 mg prednisolone equivalents). Resolution occurred in 33 patients (71.7%) with a median time to resolution of 7.1 weeks (range: 0.1+-119.3+).

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).

OPDIVO in combination with ipilimumab and platinum-based chemotherapy

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of pneumonitis including interstitial lung disease was 5.3% (19/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.1% (4/358), 0.6% (2/358) and of patients, respectively. No Grade 5 cases were reported. Median time to onset was 18.1 weeks (range: 0.6-52.4). Resolution occurred in 14 patients (74%) with a median time to resolution of 4.3 weeks (range: 0.7-27.9^{+}).

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).

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 occured 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 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+).

OPDIVO in combination with ipilimumab

In patients treated with nivolumab 1mg/kg in combination with ipilimumab 3mg/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 or colitis 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 3 mg/kg in combination with ipilimumab 1 mg/kg in OSCC and malignant pleural mesothelioma, the incidence of diarrhoea or colitis was 16.7% (104/622). Grade 2 and Grade 3 cases were reported in 5.5% (34/622) and 3.4% (21/622) of patients, respectively. Median time to onset was 3.3 months (range: 0.0-21.7). Nineteen patients (3.1%) 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 98 patients (94.2%) with a median time to resolution of 3.1 weeks (range: 0.1-100.0+).

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+).

OPDIVO in combination with ipilimumab and platinum-based chemotherapy

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

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).

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 diarrhea 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 occured 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 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.

OPDIVO in combination with ipilimumab

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3mg/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 3 mg/kg in combination with ipilimumab 1 mg/kg in OSCC and malignant pleural mesothelioma, the incidence of liver function test abnormalities was 12.5% (78/622). Grade 2, Grade 3, and Grade 4 cases were reported in 2.3% (14/622), 4.3% (27/622) and 0.5% (3/622) of patients, respectively. Median time to onset was 1.4 months (range: 0.2-20.3). Twenty patients (3.2%) required permanent discontinuation of nivolumab in combination with ipilimumab. Twenty-four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 68 patients (87.2%) with a median time to resolution of 4.1 weeks (range: 1.0-78.3+).

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+).

OPDIVO in combination with ipilimumab and platinum-based chemotherapy

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of liver function test abnormalities was 13.4% (48/358). Grade 2, Grade 3, and Grade 4 cases were reported in 3.1% (11/358), 3.4% (12/358), and 1.1% (4/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 10.6 weeks (range: 1.1-68.3). Resolution occurred in 37 patients (80.4%) with a median time to resolution of 5 weeks (range: 0.3^{+}-45.0^{+}).

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).

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 occured 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 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+).

OPDIVO in combination with ipilimumab
In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3mg/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 3 mg/kg in combination with ipilimumab 1 mg/kg in OSCC and malignant pleural mesothelioma, the incidence of renal dysfunction was 3.7% (23/622). Grade 2 and Grade 3 cases were reported in 1.4% (9/622) and 1.0% (6/622) of patients, respectively. Median time to onset was 2.6 months (range: 0.3-14.4). Six patients (1.0%) required permanent discontinuation of nivolumab in combination with ipilimumab. Nine patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 17 patients (73.9%) with a median time to resolution of 19.6 weeks (range: 0.7-142.3+).

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).

OPDIVO in combination with ipilimumab and platinum-based chemotherapy

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC, the incidence of nephritis or renal dysfunction was 7% (25/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.7% (6/358), and 0.6 (2/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 10.6 weeks (range: 0.1-51.3). Resolution occurred in 14 patients (56%) with a median time to resolution of 6.3 weeks (range: 0.1^{+}-82.9^{+}).

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 creatinin 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).

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 occured 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 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.

OPDIVO in combination with ipilimumab

In patients treated with nivolumab 1mg/kg in combination with ipilimumab 3mg/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 3 mg/kg in combination with ipilimumab 1 mg/kg in OSCC and malignant pleural mesothelioma, the incidence of thyroid disorders was 18.2% (113/622). Grade 2 and Grade 3 thyroid disorders were reported in 7.9% (49/622) and 0.5% (3/622) of patients, respectively. Hypophysitis occurred in 2.4% (15/622) of patients. Grade 2 cases were reported in 1.3% (8/622)of patients. Grade 2 and Grade 3 hypopituitarism occurred in 1.3% (8/622) and 1.3% (8/622) of patients, respectively. Grade 2, Grade 3 and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 2.3% (14/622), 1.3% (8/622) and 0.2% (1/622)of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus and fulminant Type 1 diabetes mellitus (3 Grade 2 and 2 Grade 3) were reported. Median time to onset of these endocrinopathies was 2.4 months (range: 0.4-20.8). Twelve patient (1.9%) 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 42 patients (30%). Time to resolution ranged from 0.3 to 154+ 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.

OPDIVO in combination with ipilimumab and platinum-based chemotherapy

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC , the incidence of thyroid disorders was 24% (86/358). Grade 2 and Grade 3 thyroid disorders were reported in 12.3% (44/358) and 0.3% (1/358) of patients, respectively. Hypophysitis occurred in 1.4% (5/358) of patients. Grade 2 and Grade 3 cases were reported in 0.6% (2/358) and 0.8% (3/358) of patients, respectively. Grade 2 hypopituitarism occurred in 0.3% (1/358) of patients. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (6/358) and 1.4% (5/358) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus was not reported. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 12.1 weeks (range:1.9-58.3). Resolution occurred in 30 patients (35.3%).Time to resolution ranged from 1.4 to 72.4+ weeks.

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.

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 patinets 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 occured 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 occured in 18 patients (28.1%) with a the 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 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+).

OPDIVO in combination with ipilimumab

In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3mg/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 3 mg/kg in combination with ipilimumab 1 mg/kg in OSCC and malignant pleural mesothelioma, the incidence of rash was 35% (218/622). Grade 2, Grade 3 and Grade 4 cases were reported in 11.3% (70/622), 3.4% (21/622) and 0.2% (1/622) of patients, respectively. Median time to onset was 1.6 months (range: 0.0-22.3). Five patients (0.8%) required permanent discontinuation of nivolumab in combination with ipilimumab. Seventeen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 148 patients (68.2%) with a median time to resolution of 11.9 weeks (range: 0.4-146.6+).

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+).

OPDIVO in combination with ipilimumab and platinum-based chemotherapy

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC , the incidence of rash was 37.7% (135/358). Grade 2, Grade 3, and Grade 4 cases were reported in 11.5% (41/358), 4.2% (14/358), and 0.3% (1/358) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 3.3 weeks (range: 0.1-83.1). Resolution occurred in 96 patients (71.6%) with a median time to resolution of 9.4 weeks (range: 0.1^{+}-84.1^{+}).

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 occured 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 discontined 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+).

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

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.

OPDIVO in combination with ipilimumab
In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3mg/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 3 mg/kg in combination with ipilimumab 1 mg/kg in OSCC and malignant pleural mesothelioma, the incidence of hypersensitivity/infusion reactions was 7.2% (45/622); Grade 1, Grade 2 and Grade 3 cases were reported in 3.4% (21/622), 3.2% (20/622) and 0.6% (4/622) of patients, respectively.

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.

OPDIVO in combination with ipilimumab and platinum-based chemotherapy
In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC , the incidence of hypersensitivity/infusion reactions was 4.7% (17/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively. No Grade 5 cases were reported.

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.

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 nivolumab or 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.

Complications of allogeneic HSCT in classical Hodgkin Lymphoma

In 49 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 13/49 patients (26.5%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in three patients (6%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (12%) within the first 6 weeks post-transplantation, with five patients responding to steroids. Hepatic veno-occlusive disease occurred in one patient, who died of GVHD and multi-organ failure. Nine of 49 patients (18.4%) died from complications of allogeneic HSCT after nivolumab. The 49 patients had a median follow-up from subsequent allogeneic HSCT of 5.6 months (range: 0-19 months).

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 nivolumab or 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, graft-versus-host-disease, haemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome

Endocrine-system disorders: hypoparathyroidism

Blood and lymphatic disorders: autoimmune anaemia, haemolytic anaemia

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 reactions

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.

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

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.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.

Clinical trials

MELANOMA

Adjuvant melanoma - 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 OPDIVO 480 mg or placebo by intravenous infusion every 4 weeks for up to 1 year or until disease recurrence or unacceptable toxicity. Enrollment 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. Tumor 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 OPDIVO arm compared with the placebo arm. Efficacy results are shown in Table 10 and Figure 1.

Figure 1. The median follow-up for all randomised patients was 15.8 months for the nivolumab arm and 15.9 months for the placebo arm.

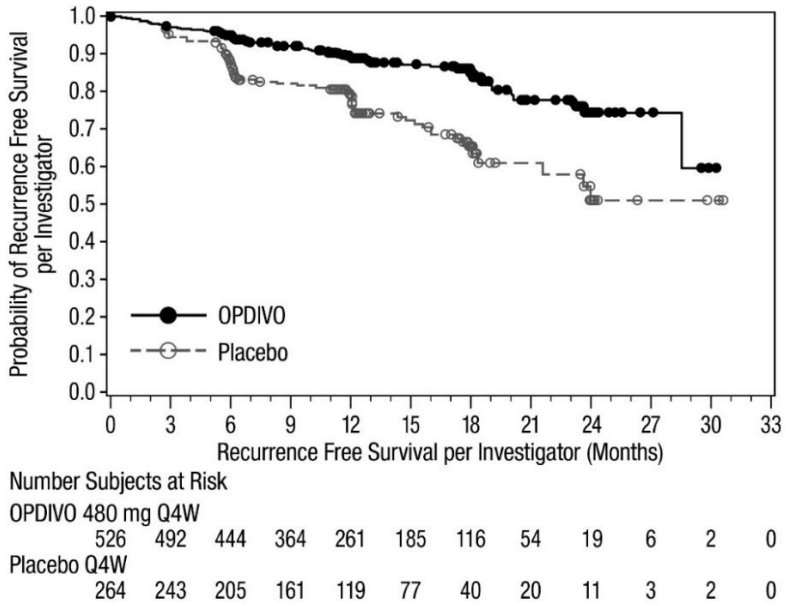
Table 10 Efficacy Results - CA20976K

	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.

Figure 1: Recurrence-free Survival -CA209076K



An updated RFS analysis was performed with a median follow up duration of approximately 24 months. Overall, 19.4% of patients receiving 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)

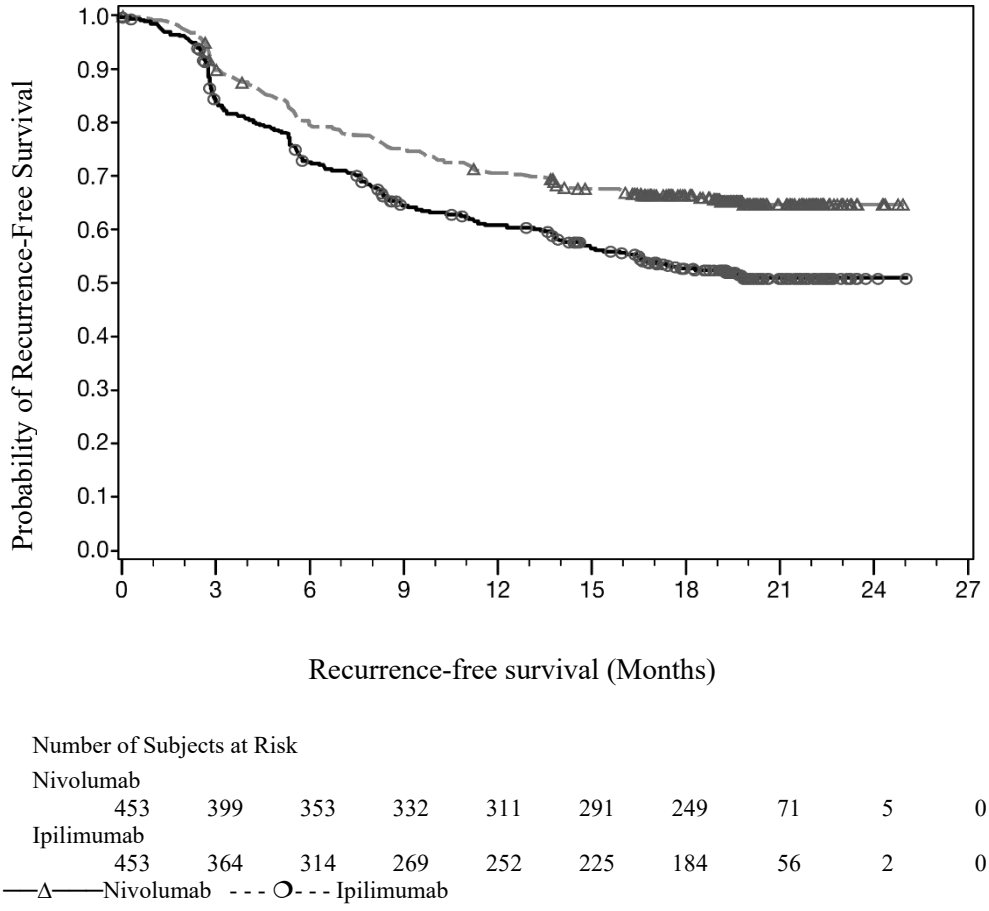


Table 11 Efficacy results (CA209238)

	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 - OPDIVO monotherapy

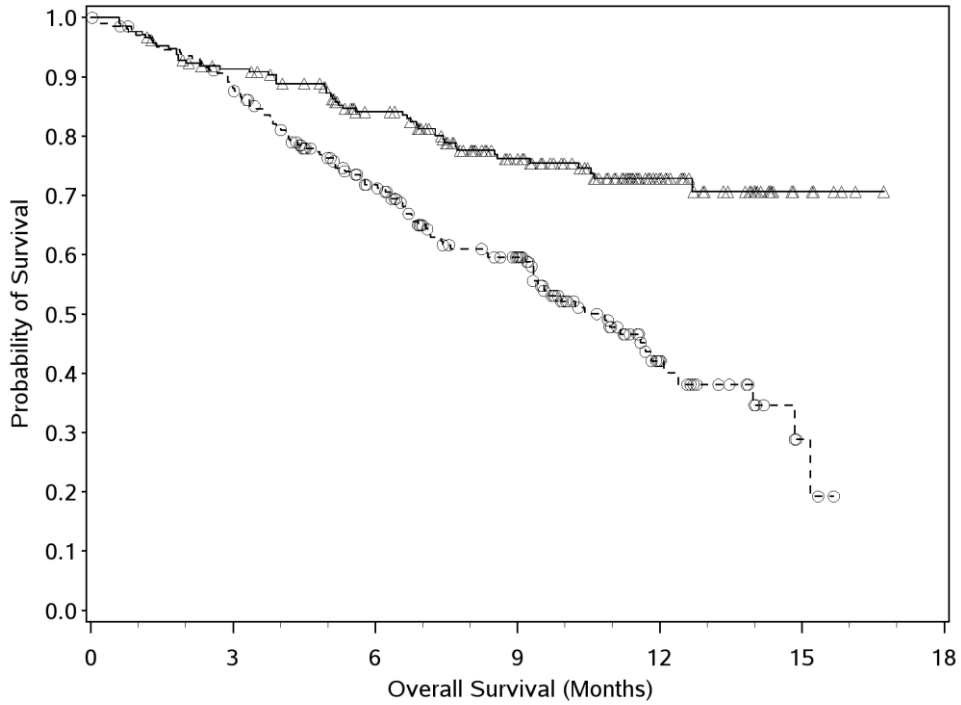
Randomised phase 3 study vs. dacarbazine (CA209066)
The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209066). The study included adult patients (18 years or older) 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 (≥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)



Number of Subjects at Risk

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

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

- - -Ɔ- - - 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 - 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 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 .

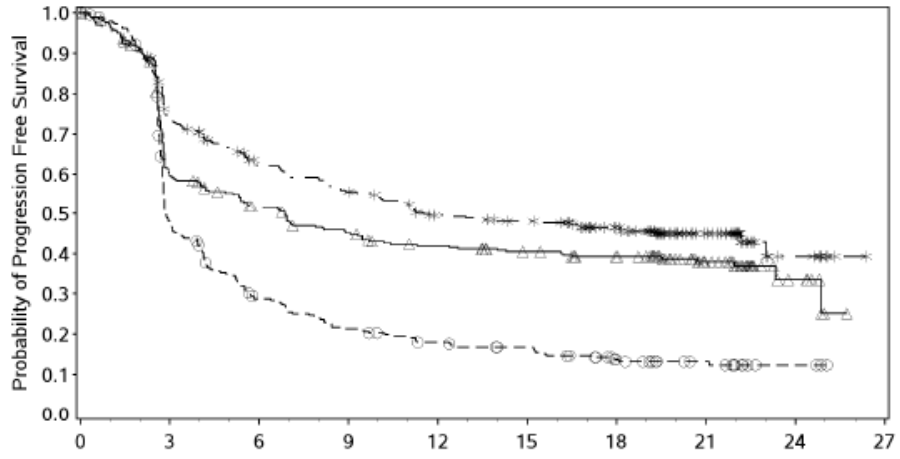
b Minimum follow up of 28 months.

c Unadjusted for multiplicity

NE=not estimable.

"+" denotes a censored observation.

Figure 4 Progression-free survival (CA209067)



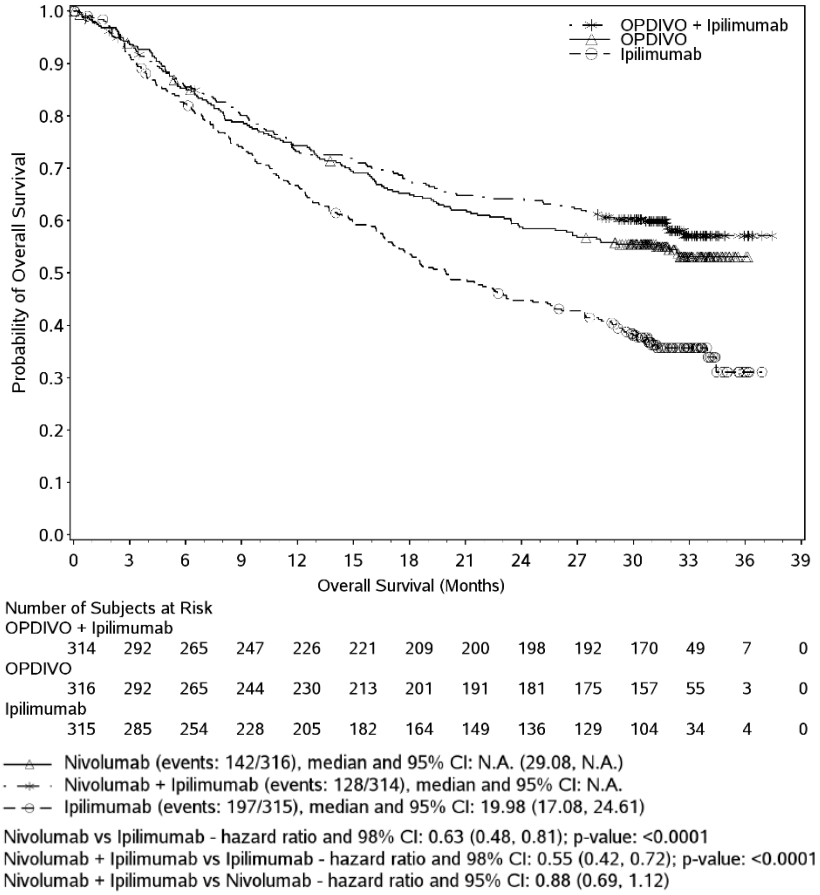
Number of Subjects at Risk

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

Nivolumab (events: 183/316), median and 95% CI: 6.87 (4.34, 9.46)
Nivolumab + Ipilimumab (events: 161/314), median and 95% CI: 11.50 (8.90, 22.18)
Ipilimumab (events: 245/315), median and 95% CI: 2.89 (2.79, 3.42)

Nivolumab vs Ipilimumab - hazard ratio and 99.5% CI: 0.55 (0.42, 0.73); p-value: <0.0001
Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 99.5% CI: 0.42 (0.32, 0.56); p-value: <0.0001
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.76 (0.62, 0.95)

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%**

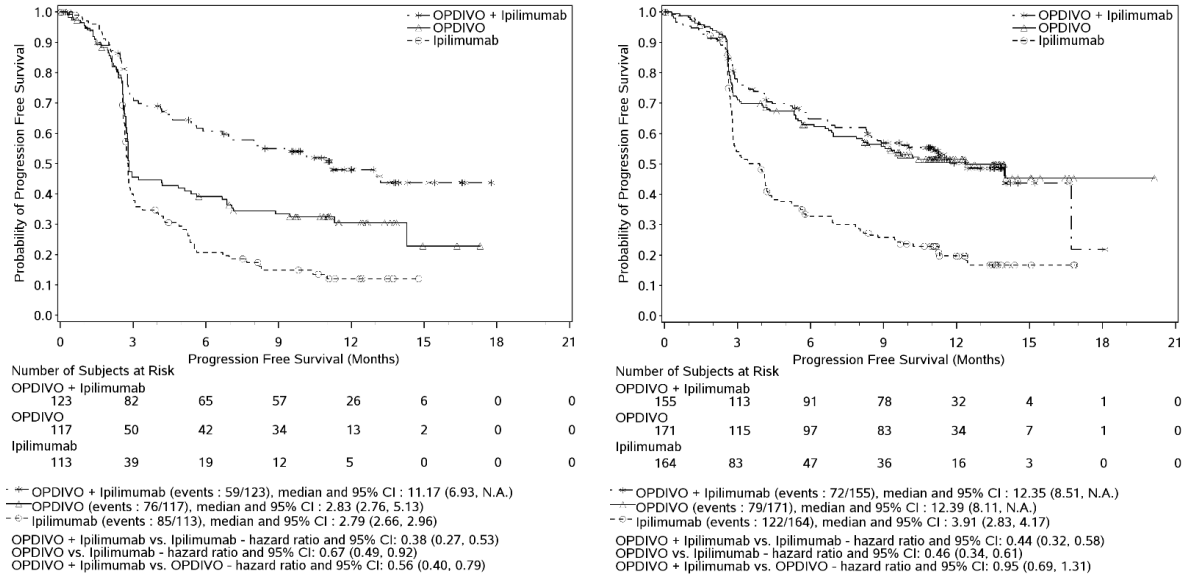
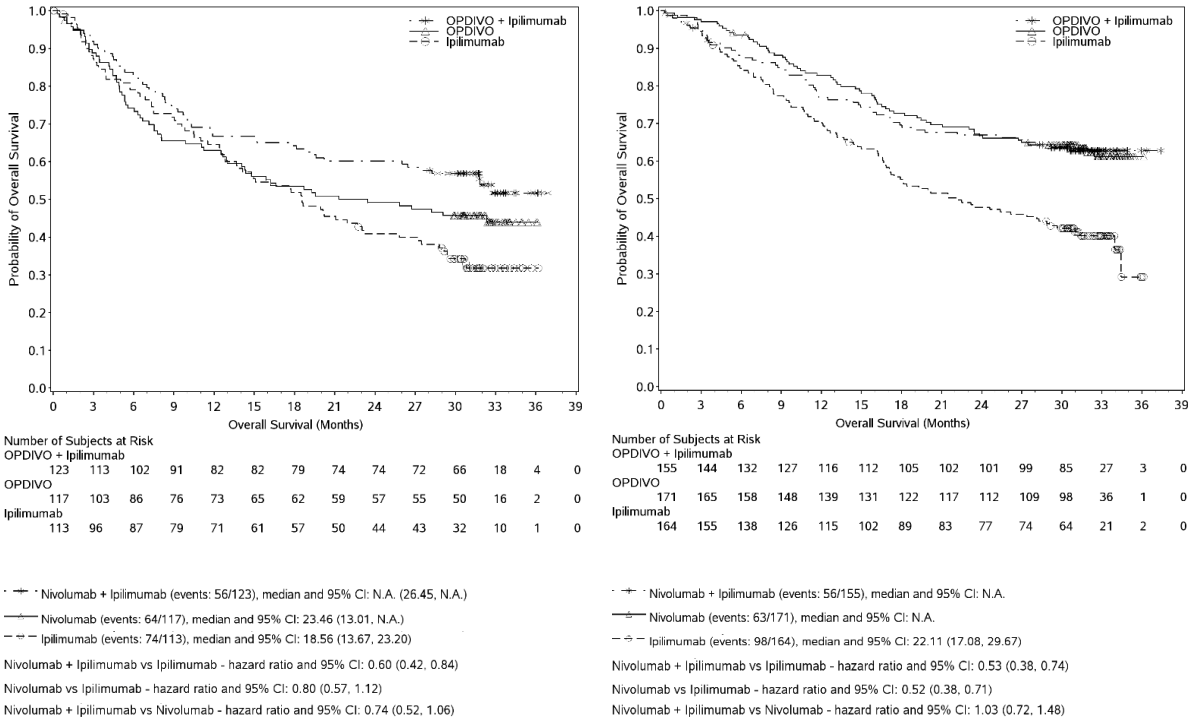


Figure 7 Overall survival by tumour PD-L1 expression level (CA209067) at 2 years of follow-up

< 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 - OPDIVO monotherapy

Randomised phase 3 study vs. chemotherapy (CA209037)
The safety and efficacy of 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 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 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.

NON-SMALL CELL LUNG CANCER (NSCLC)

Neoadjuvant treatment of resectable NSCLC - 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:

- 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 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 tumors 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 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 Table 15 and Figure 8.

Figure 8: Event-Free Survival - CA209816

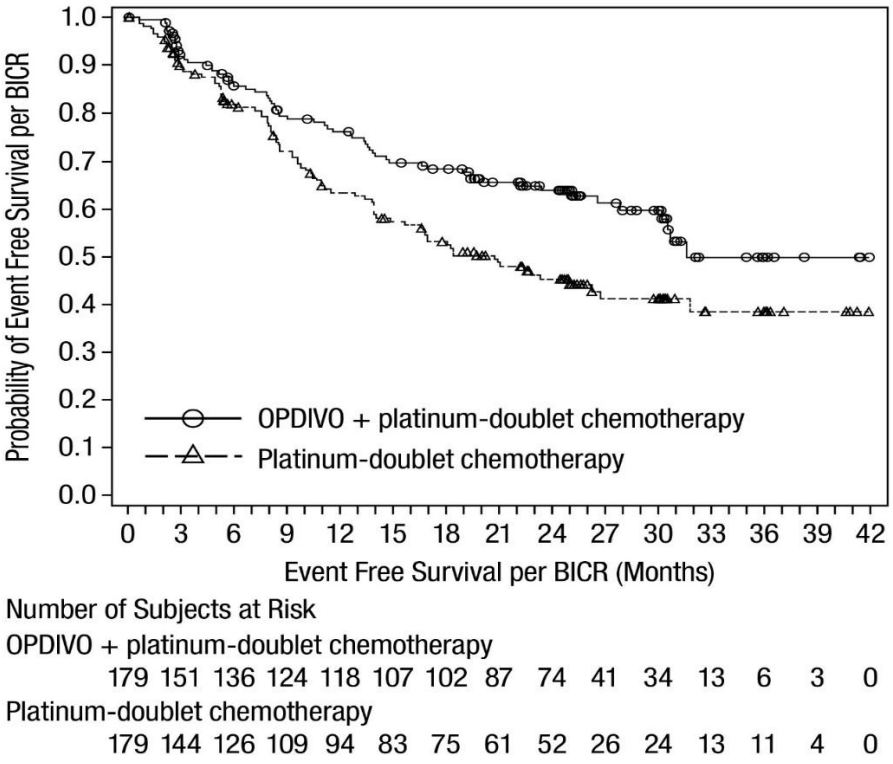


Table 15: Efficacy Results - CA209816

	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)	
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:

- 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:

- 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 tumor PD-L1 expression level (≥1% versus <1% versus indeterminate/not evaluable), disease stage (Stage II versus Stage III), and tumor histology (squamous versus nonsquamous). Tumor 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.

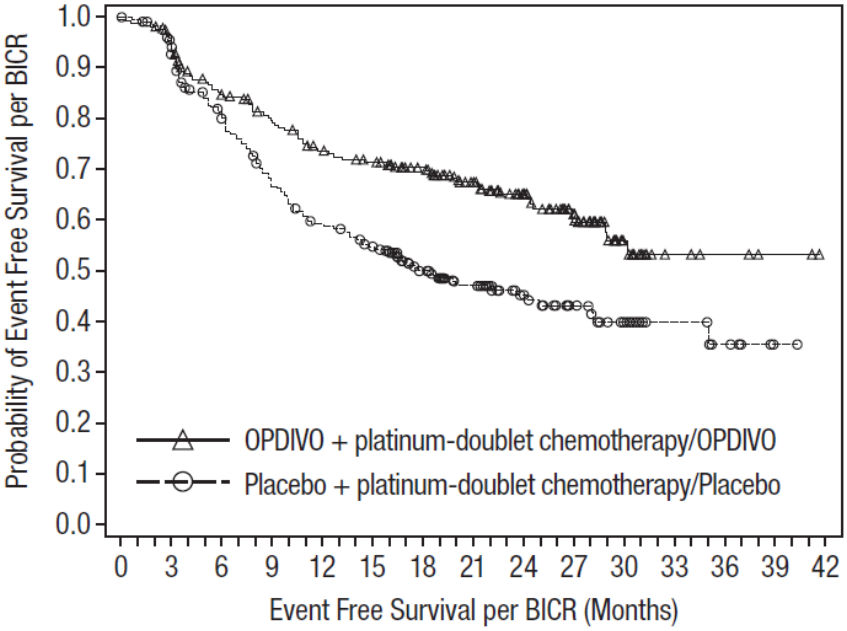
The major efficacy outcome measure was event-free survival (EFS) based on BICR assessment. Additional efficacy outcome measures included pathologic complete response (pCR) and major pathologic response as evaluated by blinded independent pathology review (BIPR).

A total of 461 patients were randomised to receive either neoadjuvant OPDIVO in combination with platinum-doublet chemotherapy followed by adjuvant 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 tumors with PD-L1 expression ≥1% and 40% had tumors 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 tumors with squamous histology and 49% had tumors with non-squamous histology; and 90% were former/current smokers.

Seventy-eight percent of patients in the neoadjuvant OPDIVO in combination with platinum-doublet chemotherapy followed by adjuvant 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 – CA209-77T



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 OPDIVO and Platinum-Doublet Chemotherapy/Adjuvant 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		

	Neoadjuvant OPDIVO and Platinum-Doublet Chemotherapy/Adjuvant OPDIVO (n=229)	Neoadjuvant Placebo and Platinum-Doublet Chemotherapy/Adjuvant Placebo (n=232)
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 untreated advanced or metastatic NSCLC - OPDIVO in combination with ipilimumab and chemotherapy

Randomised phase 3 study vs. platinum-doublet chemotherapy (CA2099LA)

CA2099LA was a randomised, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior systemic anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

Patients were randomized 1:1 to receive either nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy. Stratification factors for randomisation were tumour PD-L1 expression level (≥1% versus <1% or non-quantifiable), histology (squamous versus non-squamous), and gender (male versus female). Platinum-doublet-chemotherapy consisted of either:

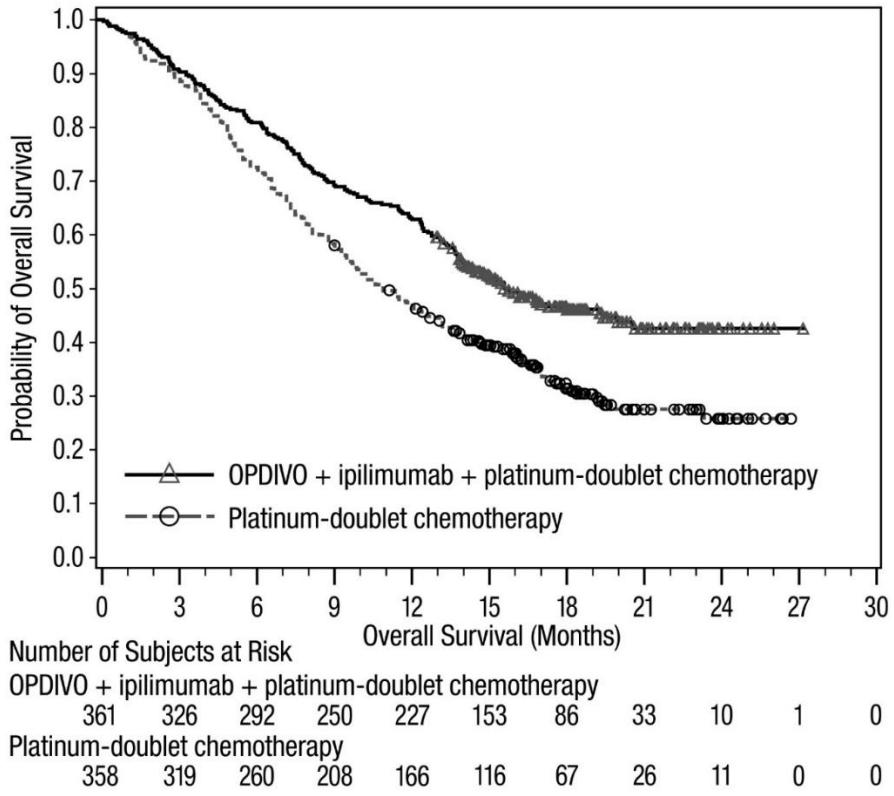
- carboplatin (AUC 5 or 6) and pemetrexed 500 mg/mg^2; or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC, or
- carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC.

Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Treatment continued beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to ipilimumab were permitted to continue nivolumab as a single agent. Tumour assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

A total of 719 patients were randomized to receive either nivolumab in combination with ipilimumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients ≥65 years and 10% of patients ≥75 years. The majority of patients were white (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% of patients had tumours with PD-L1expression ≥1% and 37% had tumours with PD-L1 expression <1%, 31% had tumours with squamous histology and 69% had tumours with non-squamous histology, 17% had brain metastases and 86% were former or current smokers.

Efficacy results from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) demonstrated a statistically significant benefit in OS, PFS, and ORR, and a clinically meaningful benefit in duration of response (Table 17). With an additional 4.6 months of follow-up, the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving nivolumab and ipilimumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 10).

Figure 10: Overall Survival - updated analysis (CA2099LA)



nivolumab in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy v/s platinum-doublet chemotherapy

HR 0.66 (95% CI: 0.55, 0.80)

Table 17 Efficacy Results (CA2099LA)

	Nivolumab and Ipilimumab and Chemotherapy (n=361)	Chemotherapy (n=358)
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Rate (95% CI) at 6 months	80.9 (76.4, 84.6)	72.3 (67.4, 76.7)
Progression-free Survival per BICR		
Events (%)	232 (64.3)	249 (69.6)
Hazard ratio (97.48% CI)[a]	0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]	0.0001	
Median (months)[d] (95% CI)	6.8 (5.6, 7.7)	5.0 (4.3, 5.6)
Rate (95% CI) at 6 months	51.7 (46.2, 56.8)	35.9 (30.5, 41.3)
Overall Response Rate per BICR (%)[e]	38	25
(95% CI)	(33, 43)	(21, 30)
Stratified CMH test p-value[f]	0.0003	
Duration of Response per BICR		
Median (months) (95% CI)[d]	10.0 (8.2, 13.0)	5.1 (4.3, 7.0)

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

[b] p-value is compared with the allocated alpha of 0.

9 for this interim analysis.

[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.

[d] Kaplan-Meier estimate.

[e] Proportion with complete or partial response; confidence interval based on the Clopper and Pearson Method.

[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.

Previously treated advanced or metastatic squamous (SQ) NSCLC - 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 11, Table 18) 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 11 Overall survival (CA209017)

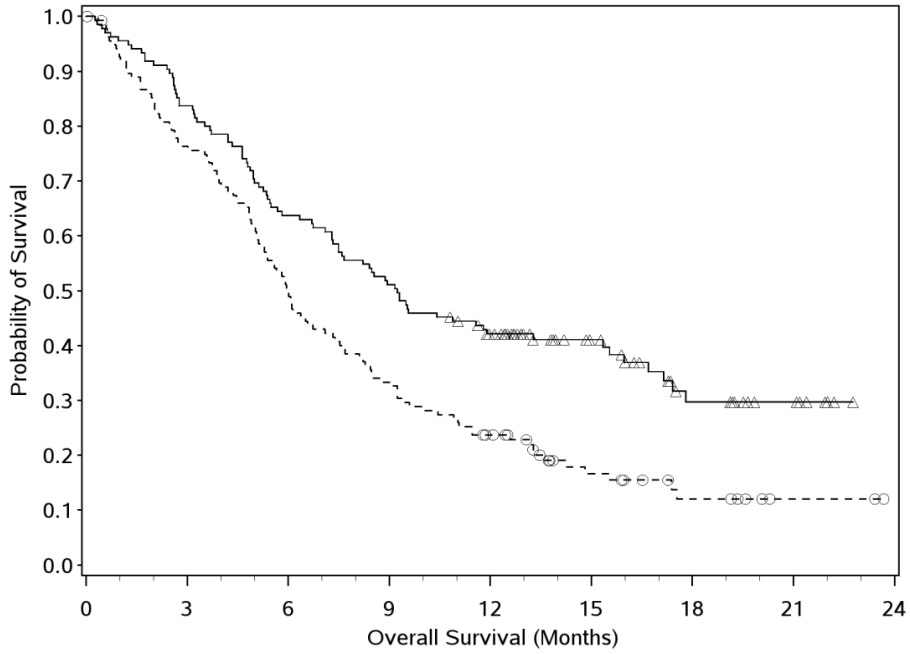


Table 18 Efficacy results (CA209017)

	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 - OPDIVO monotherapy

Randomised phase 3 study vs. docetaxel (CA209057)

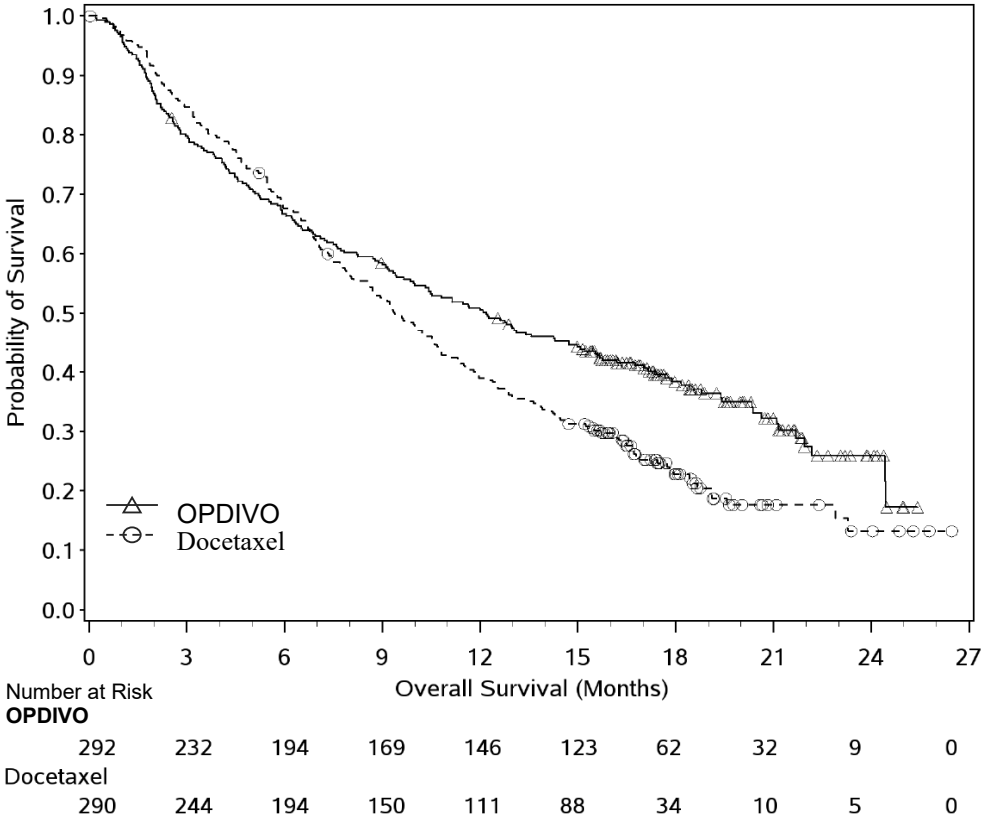
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic non-squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209057). The study included patients (18 years or older) who have experienced disease progression during or after 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 12.

Figure 12 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 19. 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 10). Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumour PD-L1 expression.

Table 19 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.

MALIGNANT PLEURAL MESOTHELIOMA (MPM)

Previously untreated unresectable malignant pleural mesothelioma - OPDIVO in combination with ipilimumab

Randomised phase 3 study vs. chemotherapy (CA209743)

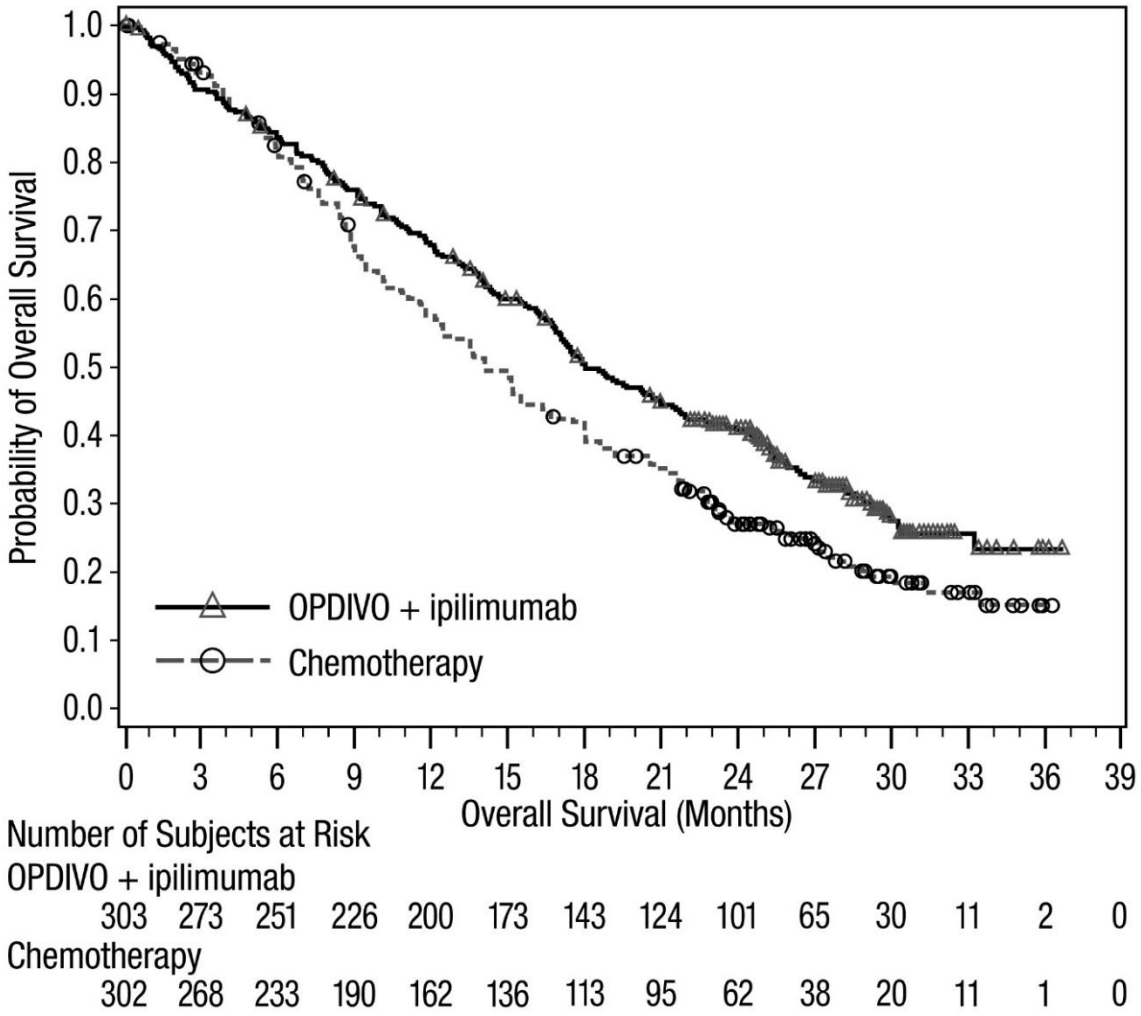
CA209743 was a randomised, open-label trial in patients with unresectable malignant pleural mesothelioma. The trial included patients (18 years of age and older) with histologically confirmed and previously untreated malignant pleural mesothelioma of epithelioid or non-epithelioid histology, ECOG performance status 0 or 1, and no palliative radiotherapy within 14 days of first trial therapy. Patients

with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the trial) were excluded from the trial. Patients received nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks and ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years, or chemotherapy consisting of cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 or carboplatin 5 AUC and pemetrexed 500 mg/m^2 for up to 6 cycles (each cycle was 21 days). Stratification factors for randomisation were tumor histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and gender (male vs. female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent as part of the study. Treatment continued beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Tumour assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, duration of response, and disease control rate (DCR) as assessed by BICR utilizing modified RECIST criteria.

A total of 605 patients were randomised to receive either nivolumab in combination with ipilimumab (n=303) or chemotherapy (n=302). The median age was 69 years (range: 25 to 89) with 72% ≥65 and 26% ≥75 years, 85% White, and 77% male. Baseline ECOG performance status was 0 (40%) or 1 (60%), and 75% had epithelioid and 25% had non-epithelioid histology.

The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab in combination with ipilimumab compared to chemotherapy with a minimum follow-up of 22 months. Efficacy results from the prespecified interim analysis when at least 403 events were observed (85% of the planned number of events for final analysis) are presented in Table 20 and Figure 13.

Figure 13: Overall Survival (CA209743)



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

In a prespecified exploratory analysis based on histology, in the subgroup of patients with epithelioid histology, the hazard ratio (HR) for OS was 0.85 (95% CI: 0.68, 1.06), with median OS of 18.7 months in the OPDIVO and ipilimumab arm and 16.2 months in the chemotherapy arm. In the subgroup of patients with non-epithelioid histology, the HR for OS was 0.46 (95% CI: 0.31, 0.70), with median OS of 16.9 months in the OPDIVO and ipilimumab arm and 8.8 months in the chemotherapy arm.

Table 20 Efficacy Results (CA209743)

	Nivolumab and Ipilimumab (n=303)	**Chemotherapy (n=302)**
Overall Survival		
Events (%)	200 (66)	219 (73)
Median (months)[a] (95% CI)	18.1 (16.8, 21.5)	14.1 (12.5, 16.2)
Hazard ratio (96.6% CI)[b]	0.74 (0.60, 0.91)	
Stratified log-rank p-value[c]	0.002	
Rate (95% CI) at 24 months[a]	41% (35.1, 46.5)	27% (21.9, 32.4)

Table 20 Efficacy Results (CA209743)

	Nivolumab and Ipilimumab (n=303)	Chemotherapy (n=302)
Progression-free Survival		
Events (%)	218 (72)	209 (69)
Hazard ratio (95% CI)[b]	1.0 (0.82, 1.21)	
Median (months)[a] (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)
Overall Response Rate	40%	43%
(95% CI)	(34.1, 45.4)	(37.1, 48.5)
Complete response	1.7%	0
Partial response	38%	43%
Duration of Response		
Median (months)[a] (95% CI)	11.0 (8.1, 16.5)	6.7 (5.3, 7.1)
% with duration ≥6 months	69%	53%
Disease Control Rate (95% CI)	77% (71.4, 81.2)	85% (80.6, 88.9)

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

RENAL CELL CARCINOMA (RCC)

Previously untreated advanced or metastatic RCC - 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.

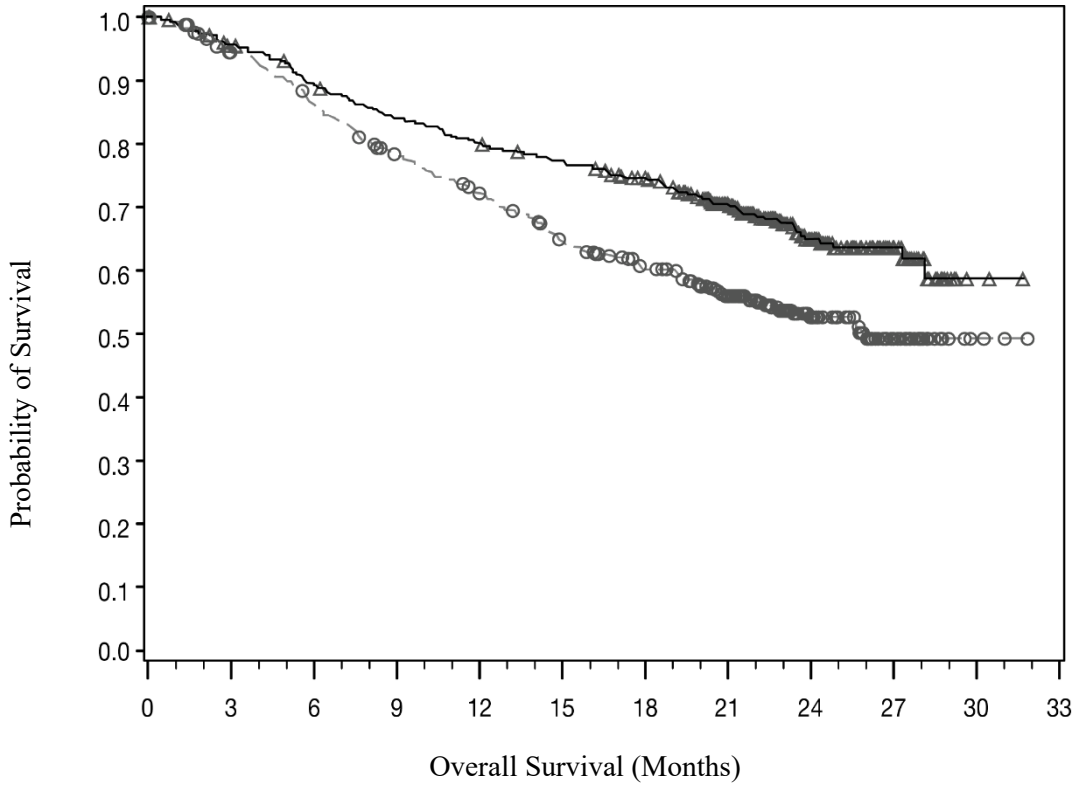
A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either nivolumab 3 mg/kg (n = 425) administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks for 4 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 14.

Figure 14 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 21.

Table 21 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 ~~is~~ 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.

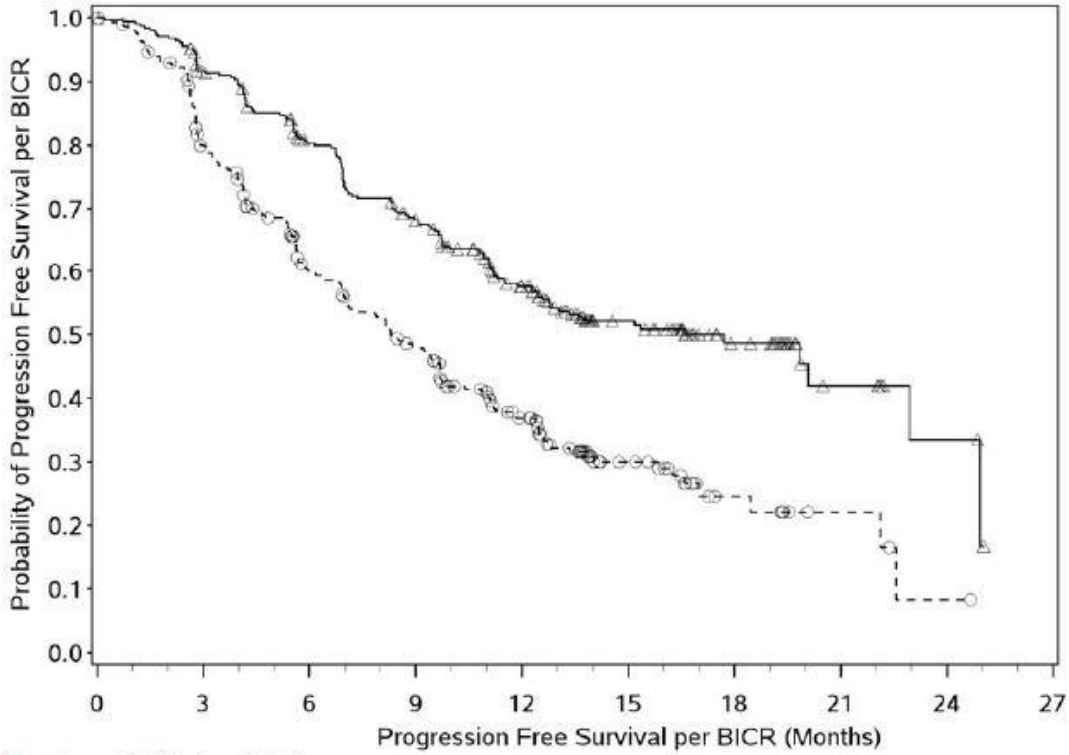
Previously untreated advanced or metastatic RCC - OPDIVO in combination with cabozantinib

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 15 and Figure 16.

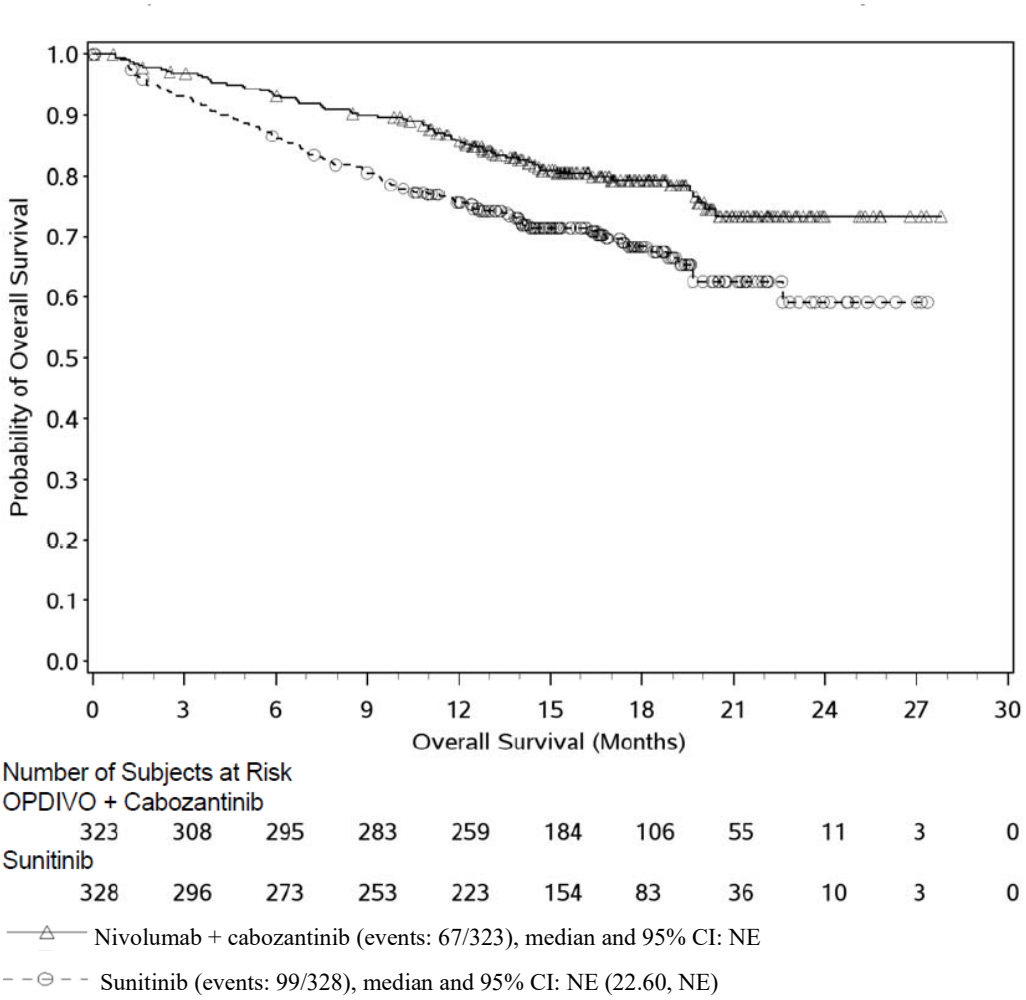
Figure 15 Kaplan-Meier curves of PFS (CA2099ER)



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 16 Kaplan-Meier curves of OS (CA2099ER)



Efficacy results from the primary analysis (minimum follow-up 10.6 months) are shown in Table 22.

Table 22 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 - 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.

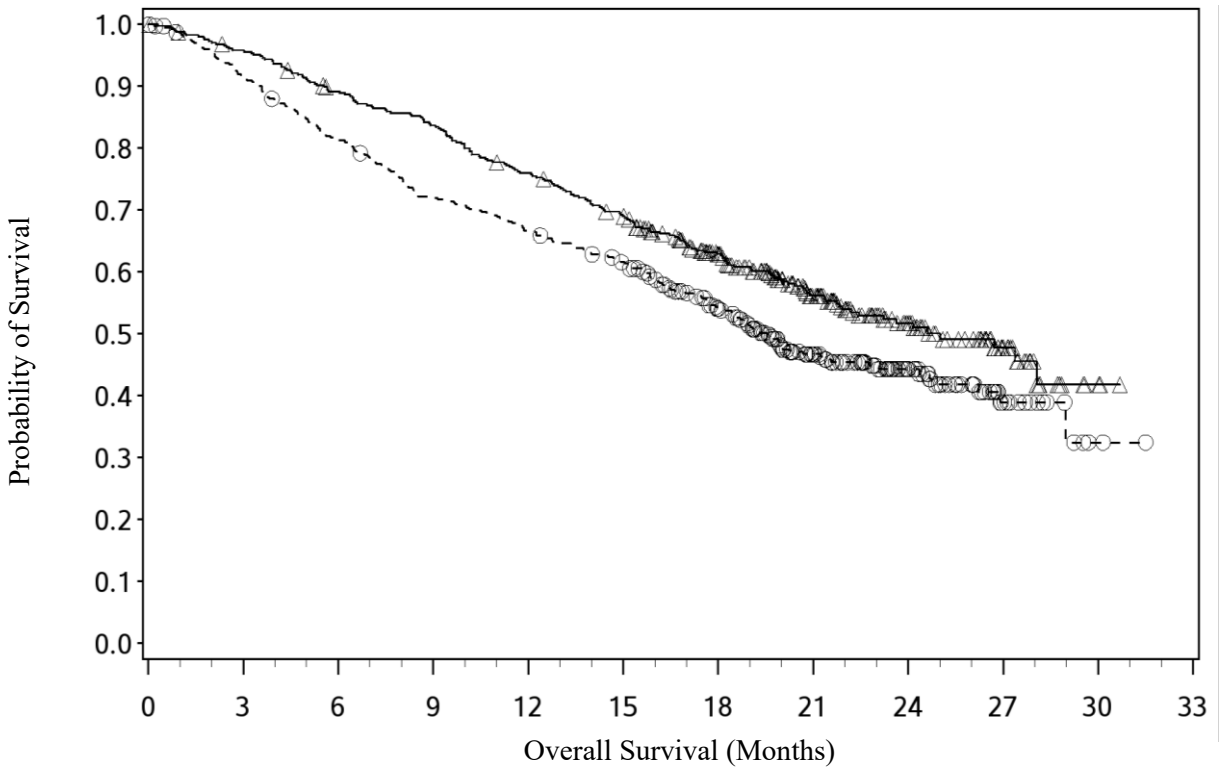
A total of 821 patients were randomised to receive either nivolumab 3 mg/kg (n = 410) administered intravenously over 60 minutes every 2 weeks or everolimus (n = 411) 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. 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 17.

Figure 17 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 23.

Table 23 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.

CLASSICAL HODGKIN LYMPHOMA (cHL)

Previously treated relapsed or refractory cHL - OPDIVO monotherapy

Single-arm phase 2 study (CA209205) and phase 1 dose escalation study (CA209039)
Two open-label studies evaluated the safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of relapsed or refractory cHL following autologous stem cell transplantation (ASCT).

Study CA209205 is an ongoing Phase 2, open-label, multi-cohort, single-arm study of nivolumab in cHL. It includes 243 patients who had ASCT; Cohort A included 63 (26%) patients who were brentuximab vedotin naïve; Cohort B included 80 (33%) patients who had received brentuximab vedotin after ASCT failure; and Cohort C included 100 (41%) patients who had received brentuximab vedotin before and/or after ASCT out of which 33 (14%) patients received brentuximab vedotin only prior to ASCT. Study CA209039 was an open-label, multicentre, dose escalation Phase 1 study that included 23 patients with cHL, 15 of whom received nivolumab following ASCT and brentuximab vedotin treatment and 5 of whom were ASCT naive.

Both studies included patients regardless of their tumour PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, hepatic transaminases more than 3 times ULN, creatinine clearance less than 40 mL/min, prior allogeneic haematopoietic stem cell transplant (HSCT), chest irradiation within 24 weeks or symptomatic interstitial lung disease.

In both studies, patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes every 2 weeks until disease progression or unacceptable toxicity (or maximal clinical benefit in CA209039). Dose reduction was not permitted. Tumour assessments were conducted 4 weeks (CA209039) or 9 weeks (CA209205) after the start of treatment and continued thereafter until disease progression or treatment discontinuation.

The primary efficacy outcome measure was Objective Response Rate (ORR). Additional efficacy measures included duration of response, PFS and OS. Data from post-ASCT patients in study CA209205 were pooled (Cohort A+B+C referred to as Combined Cohorts). The baseline and disease characteristics of the patients in each study were similar. In CA209205, the median age was 34 years with 7 subjects aged 65 years or older; 87% were white, 58% were male; 57.2% had Stage IV disease at study entry; the median number of prior systemic regimens was 4 (range 2 to 15); 84% had had a best response of CR or PR to regimen prior to ASCT. In CA209039, the median age was 35 years (range 20-54), 87% were white, the median number of prior systemic regimens was 5 (range 2 to 15).

Efficacy from both studies was evaluated by the same IRRC using the 2007 revised International Working Group criteria. Median duration of follow-up 22.7 months (range 1.9 to 27.2 months) in Cohort B in Study CA209205, 17.8 months (range 1.0 to 27.2 months) in the Combined Cohorts in Study CA209205 and 21.9 months (range 11.2 to 27.6 months) in Study CA209039. Follow-up was ongoing at the time of data submission. Results are shown in Table 24.

Table 24 Efficacy results (CA209205, CA209039)

Efficacy Parameter	CA209205 Cohort B[a] (n = 80)	CA209039 ASCT-Bren failed group (n = 15)	CA209205 Combined Cohorts (n=243) [b]
Objective Response Rate; (95% CI)	54 (68%); (56, 78)	9 (60%); (32, 84)	168 (69%); (63, 75)
Complete Remission Rate; (95% CI)	10 (13%); (6, 22)	0 (0%); (0, 22)	40 (17%); (12, 22)
Partial Remission Rate; (95% CI)	44 (55%); (44, 66)	9 (60%); (32, 84)	128 (53%); (46, 59)
Stable disease, n (%)	17 (21)	5 (33)	47 (19)
Median Duration of Response (months)	15.9	12.0	16.6
(95% CI)	(7.8, 20.3)	(1.8, N.A.)	(13.2, 20.3)
Min, Max	0.0+, 21.0+	1.8, 23.1+	0.0+, 21.0+
Median Time to Response (months)	2.2	0.8	2.1
Min, Max	1.6, 9.1	0.7, 4.1	0.8, 9.1

[a] Follow-up was ongoing at the time of data submission
[b] Patients in Cohort C (n = 33) who have received brentuximab vedotin only prior to ASCT had ORR of 70% (95% CI: 51, 84), CR of 15% (95% CI: 5, 32), PR of 55% (95% CI: 36, 72). Median duration of response was 13.2 months (95% CI: 8.2, NE)
N.A. = not available

PFS and OS were exploratory endpoints in these studies. The median PFS was 14.7 months (95% CI: 10.5, 19.6), 12.7 months (95% CI: 5.91, NA) and 14.7 months (11.3, 18.5) in CA209205 Cohort B, CA209039 and CA209205 combined Cohorts, respectively. The PFS rate at 12 months was 51% (95% CI 38, 62), 69% (95% CI 37, 88) and 51% (95% CI 44, 58) in CA209205 Cohort B, CA209039 and CA209205 combined Cohorts, respectively. At the time of database lock, OS data were immature and the median had not been reached in CA209205 and CA209039. The OS rate at 12 months was 95% (95% CI 87, 98), 93% (95% CI 61, 99) and 92% (CI 88, 95) in CA209205 Cohort B, CA209039 and CA209205 combined Cohorts, respectively.

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

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

Health related Quality of Life (QoL) was assessed in CA209205 using the patient reported EQ 5D VAS and EORTC-QLQ-C30 (overall health status). There was a high rate of completion up to Week 33 of treatment. During this time, mean EQ-5D VAS scores increased from baseline and EORTC QLQ-C30 scores remained stable.

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

SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)

Previously treated recurrent or metastatic SCCHN - 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 (eg, 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.

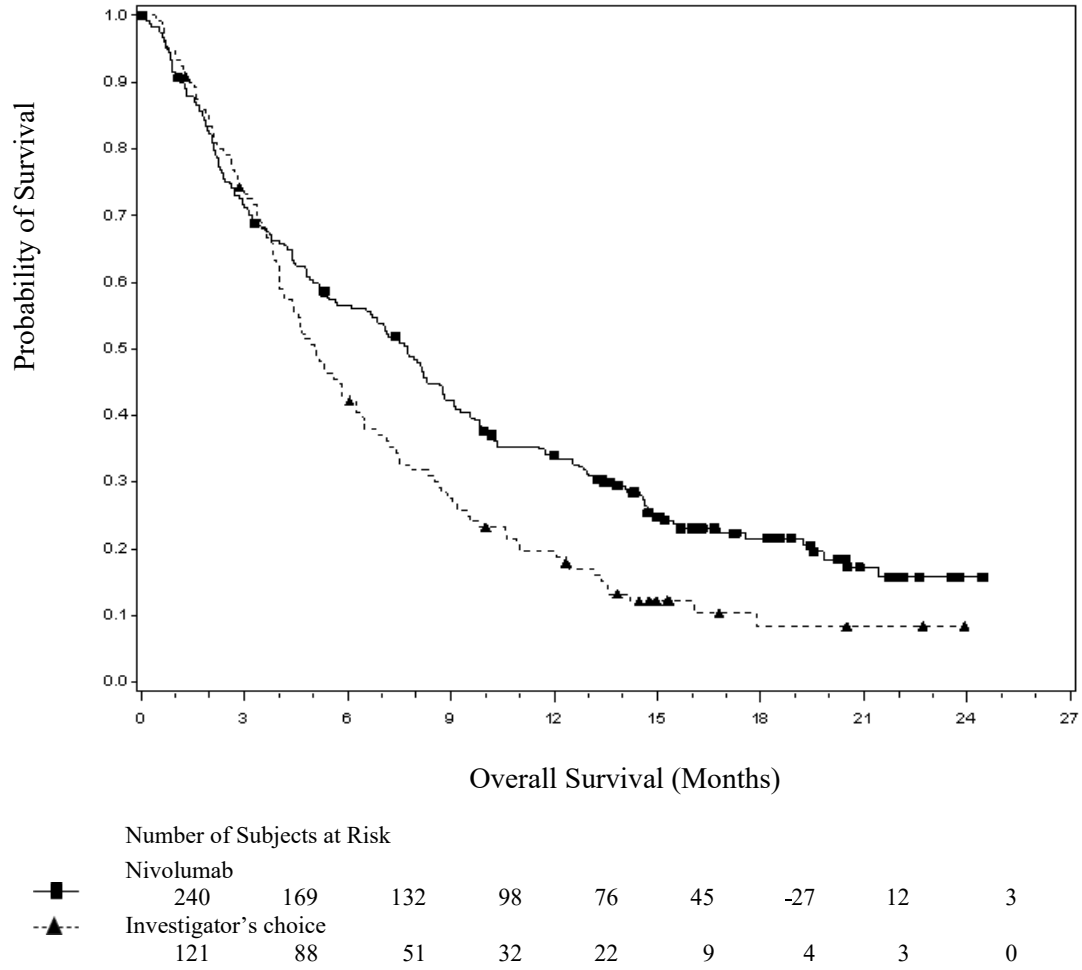
A total of 361 patients were randomised to receive either nivolumab 3 mg/kg (n=240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n=15), 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly or methotrexate (n=52) 40 to 60 mg/m^2 weekly, or docetaxel (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 18. Efficacy results are shown in Table 25.

Figure 18 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 25 Efficacy results (CA209141)

	nivolumab (n = 240)	investigator's choice (n = 121)
Overall survival		
Events	184 (76.7%)	105 (86.8%)
Hazard ratio[a]	0.71	
(95% CI)	(0.55,0.90)	
p-value[b]	0.0048	
Median (95% CI) months	7.7 (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.

UROTHELIAL CARCINOMA (UC)

Adjuvant muscle invasive urothelial carcinoma at high risk of recurrence - 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.

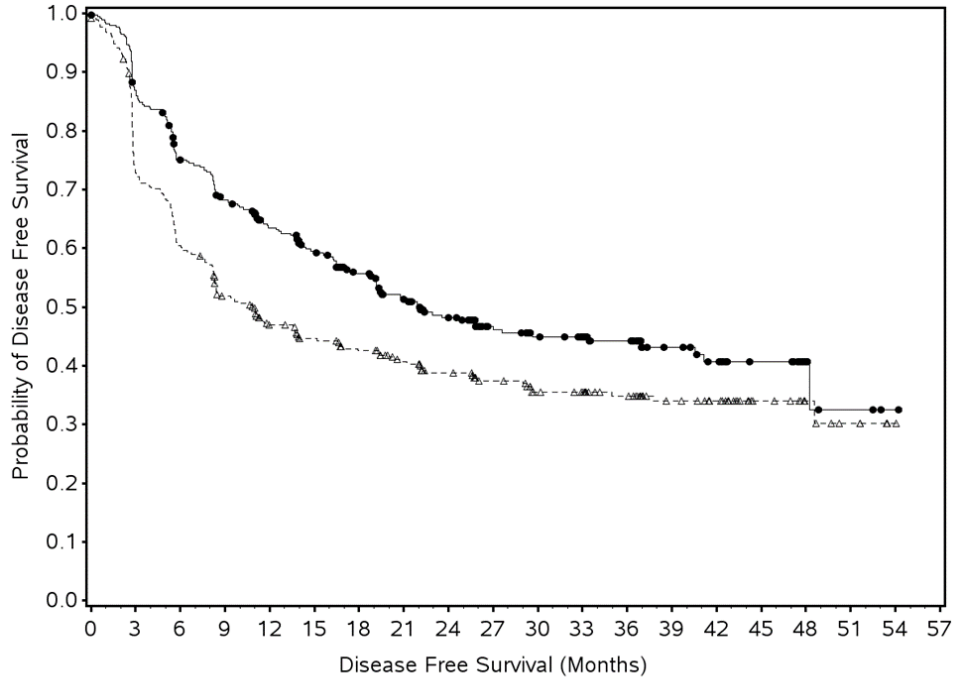
A total of 709 patients were randomised to receive either nivolumab 240 mg (n = 353) every 2 weeks or placebo (n = 356) every 2 weeks until recurrence or unacceptable toxicity for a maximum treatment duration of 1 year. Randomisation was stratified by pathologic nodal status (N+ vs. N0/x with < 10 nodes 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 Table 26 and Figure 19.

Figure 19 Disease-free Survival in All Randomised Patients (CA209274).



Number of Subjects at Risk

Placebo

356 248 206 171 146 131 121 108 93 81 67 63 53 37 32 17 9 5 1 0

Nivolumab

353 296 251 226 198 174 145 124 103 83 72 66 54 37 31 16 7 3 1 0

Placebo (events : 213/356), median and 95% CI : 10.87 (8.28, 13.96)

Nivolumab (events : 175/353), median and 95% CI : 22.01 (17.68, 36.93)

Nivolumab vs Placebo - hazard ratio (95% CI) : 0.70 (0.57, 0.85)

Table 26 Efficacy Results (CA209274)

	All Randomised		**PD-L1 ≥1%**	
	OPDIVO (n=353)	**Placebo (n=356)**	**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 metatstatic urothelial cancer – 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:

- 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 OPDIVO 480 mg every 4 weeks until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, 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 randomised 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 Table 27, Figure 20 and Figure 21. The minimum follow-up was 7.4 months.

Table 27: Efficacy Results (CA209901)

	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)		
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)

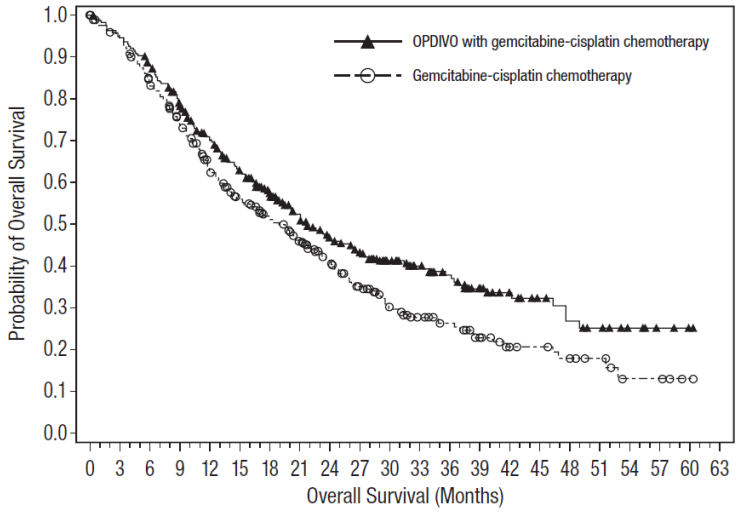
[a] Based on Kaplan-Meier Estimates

[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.

Figure 20: Overall Survival in All Randomised Patients (CA209901)



Number of Subjects at Risk

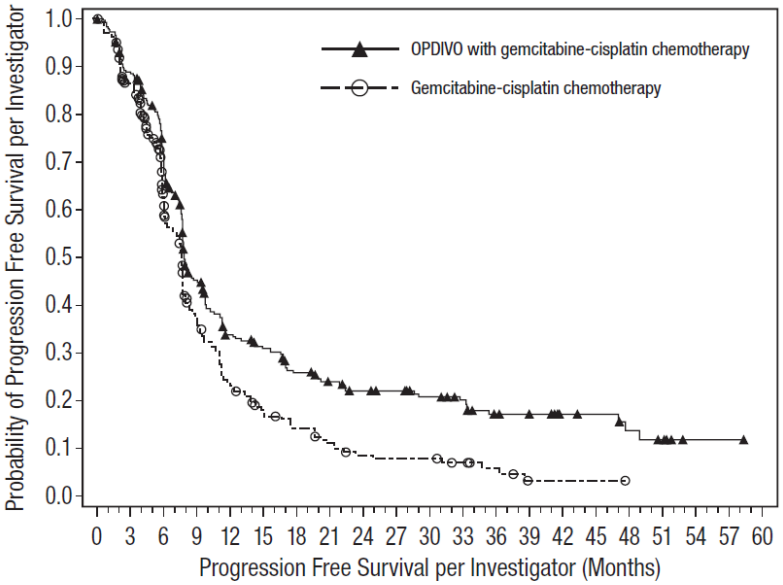
OPDIVO with gemcitabine-cisplatin chemotherapy

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 21: Progression Free Survival in All Randomised Patients (CA209901)



Number of Subjects at Risk

OPDIVO with gemcitabine-cisplatin chemotherapy

304 260 200 120 84 75 59 49 43 40 33 28 20 16 12 11 7 5 1 1 0

Gemcitabine-cisplatin chemotherapy

304 234 130 68 43 30 23 17 12 11 11 8 5 1 1 1 0 0 0 0 0

Previously treated metastatic or unresectable UC - 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%).

Table 28 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.

HEPATOCELLULAR CARCINOMA (HCC)

Unresectable or metastatic HCC - 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:

- 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 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 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 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 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.

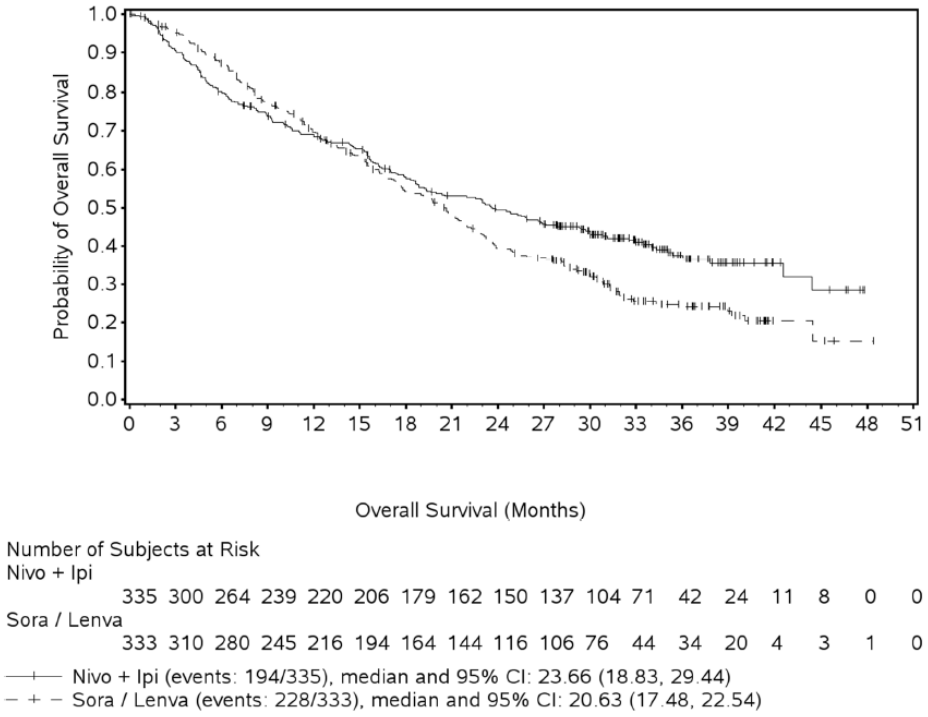
Efficacy results are presented in Table 29 and Figure 22. The results for OPDIVO in combination with ipilimumab compared to investigator's choice of lenvatinib or sorafenib are based on a minimum follow-up of 26.8 months.

Table 29 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~~19.2~~, 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.

Figure 22 Kaplan-Meier curve of OS - (CA2099DW)



Previously treated metastatic HCC - 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 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 30.

Table 30 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 OPDIVO in combination with ipilimumab was evaluated in 49 patients in Study CA209040 (Cohort 4) who received OPDIVO 1 mg/kg and ipilimumab 3 mg/kg administered every 3 weeks for 4 doses, followed by single-agent 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 non-alcoholic 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 31. The results for OPDIVO in combination with ipilimumab in Cohort 4 are based on a minimum follow-up of 28 months.

Table 31: Efficacy Results (CA209040, Cohort 4)

	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

Table 31: Efficacy Results (CA209040, Cohort 4)

	OPDIVO and Ipilimumab (Cohort 4) (n=49)
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

OESOPHAGEAL SQUAMOUS CELL CARCINOMA (OSCC)

Previously untreated unresectable advanced, recurrent or metastatic OSCC- 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:

- OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks.
- 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 OPDIVO until disease progression, unacceptable toxicity, or up to 2 years.

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

In patients who received 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 ≥65 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 ipilimumab versus chemotherapy

CA209648 demonstrated a statistically significant improvement in OS for patients with tumour cell PD-L1 ≥1%. The minimum follow-up was 13.1 months. Efficacy results are shown in Table 32and Figure 23.

Figure 23 Overall Survival - PD-L1 ≥ 1% (CA209648)

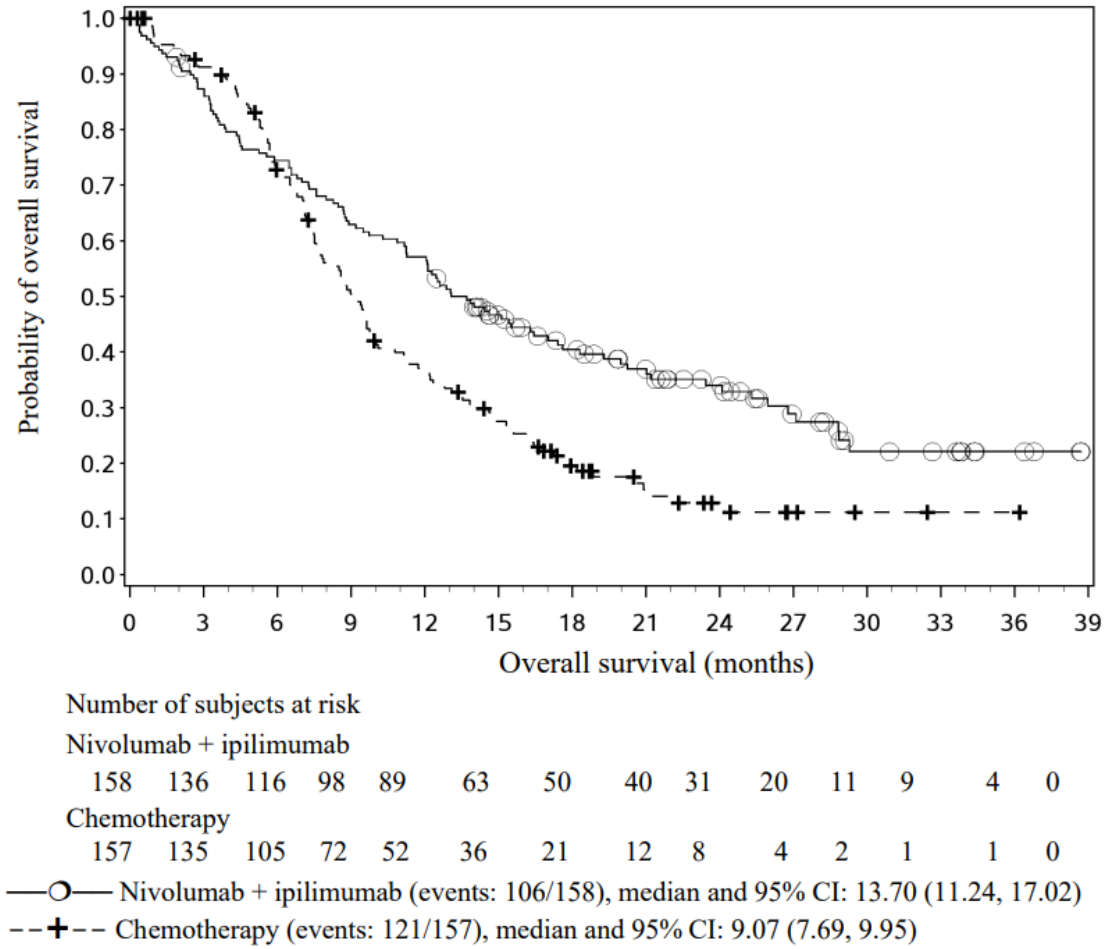


Table 32 Efficacy Results - Opdivo + Ipilimumab - CA209648

	OPDIVO and Ipilimumab (n=325)	Cisplatin and Fluorouracil (n=324)
	Tumour cell PD-L1 ≥ 1%	
Overall Survival		
Deaths (%)	106 (67)	121 (77)
Median (months) (95% CI)	13.7 (11.2, 17.0)	9.1 (7.7, 10)
Hazard ratio (95% CI)[b]	0.64 (0.49, 0.84)	
p-value[c]	0.0010	
Progression-free Survival[a]		
Disease progression or death (%)	123 (78)	100 (64)
Median (months) (95% CI)	4.0 (2.4, 4.9)	4.4 (2.9, 5.8)
Hazard ratio (CI)[b]	1.02 (0.78, 1.34)	
p-value[c]	0.8958	
Overall Response Rate, n (%)[a]	56 (35.4)	31 (19.7)
(95% CI)	(28.0, 43.4)	(13.8, 26.8)
Complete response (%)	28 (17.7)	8 (5.1)
Partial response (%)	28 (17.7)	23 (14.6)
Duration of Response (months) [a]		
Median (95% CI)	11.8 (7.1, 27.4)	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.

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 Table 33 and Figure 24.

Figure 24 Overall Survival - PD-L1 ≥ 1% (CA209648)

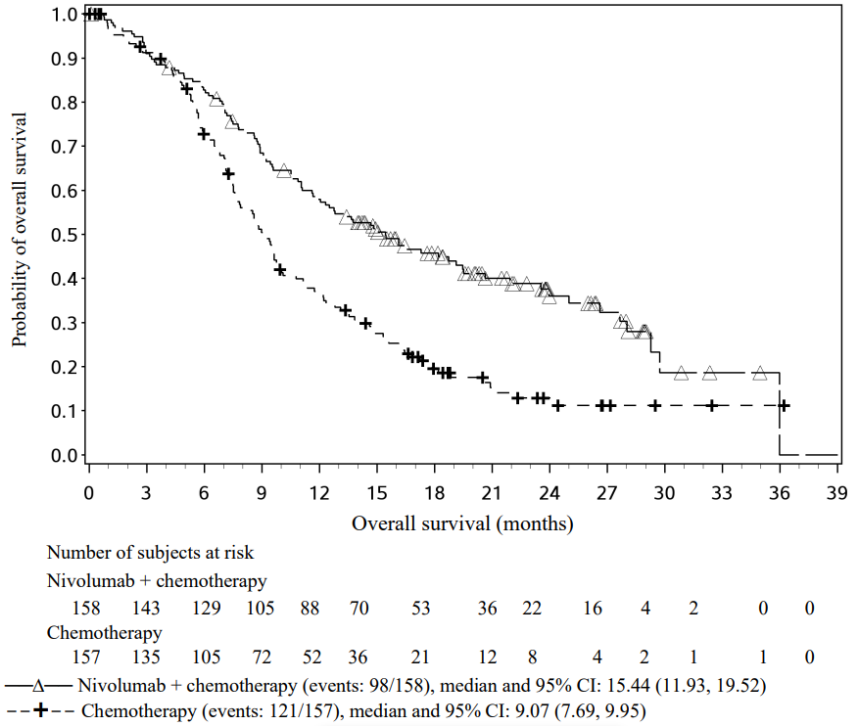


Table 33: Efficacy Results - Opdivo + chemotherapy - CA209648

	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)
(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 - 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 (eg, 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 Table 34 and Figure 25

Figure 25 Overall Survival - CA209473

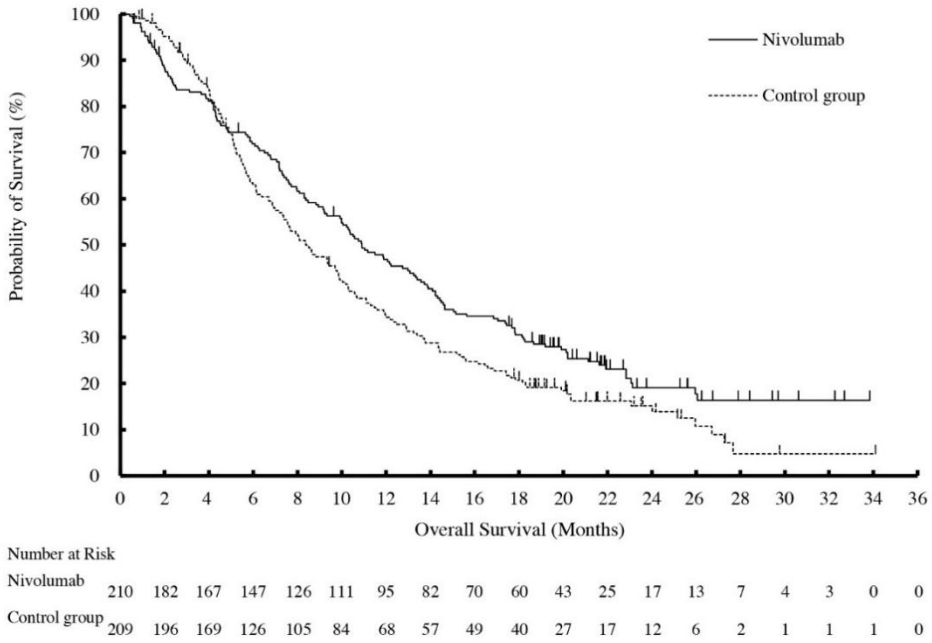


Table 34 Efficacy Results - CA209473

	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.

ADJUVANT OESOPHAGEAL OR GASTRO-OESOPHAGEAL CANCER

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer - 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. Enrollment 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 tumor PD-L1 expression and histology.

Efficacy results are shown in Table 35 and Figure 26.

Figure 26 Disease-free Survival - CA209577

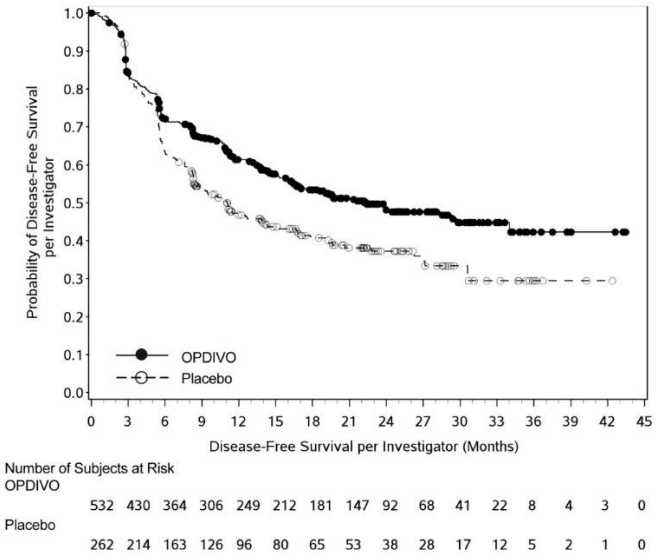


Table 35 Efficacy Results - CA209577

	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.

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

Previously untreated advanced gastric cancer, gastro-oesophageal junction cancer, or oesophageal adenocarcinoma - 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 OPDIVO in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

- OPDIVO 240 mg in combination with FOLFOX (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or FOLFOX every 2 weeks.
- 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 OPDIVO in combination with chemotherapy and in whom chemotherapy was discontinued, 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 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 randomised patients. The minimum follow-up was 12.1 months.

The Kaplan-Meier curves for OS are shown in Figure 27 and Figure 28.

Figure 27 Kaplan-Meier curves of OS - All Patients (CA209649)

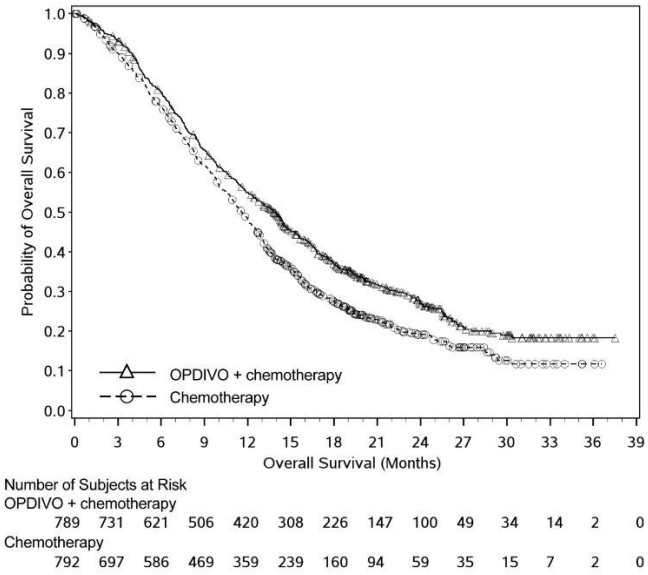
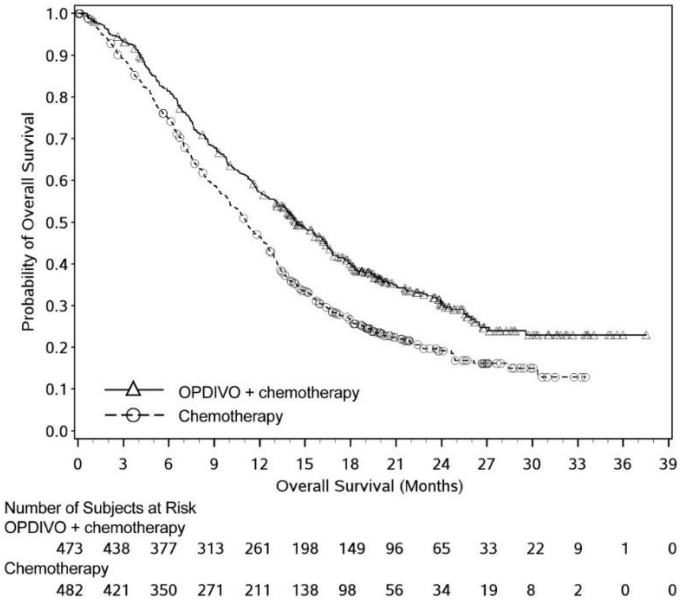


Figure 28 Kaplan-Meier curves of OS - PD-L1 CPS ≥5 (CA209649)



Efficacy results are shown in Table 36.

Table 36 Efficacy Results (CA209649)

	OPDIVO and FOLFOX or XELOX (n=789)	FOLFOX or XELOX (n=792)	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] (95% CI)	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)	7.69 (7.03, 9.17)	6.05 (5.55, 6.90)
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.

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 - 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: 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:

- OPDIVO 240 mg every 3 weeks and ipilimumab 1 mg/kg every 3 weeks for a maximum of 4 doses, then 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 OPDIVO plus ipilimumab arm versus chemotherapy arm.

Randomisation was stratified by tumour location (right vs left). Patients randomised to the chemotherapy arm could receive 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 OPDIVO as a single agent. 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 Table 37 and Figure 29. At the time of this interim analysis, the other endpoints were not tested, due to testing hierarchy.

Figure 29 Kaplan-Meier curve of PFS in first-line patients with MSI-H/dMMR CRC (CA2098HW)

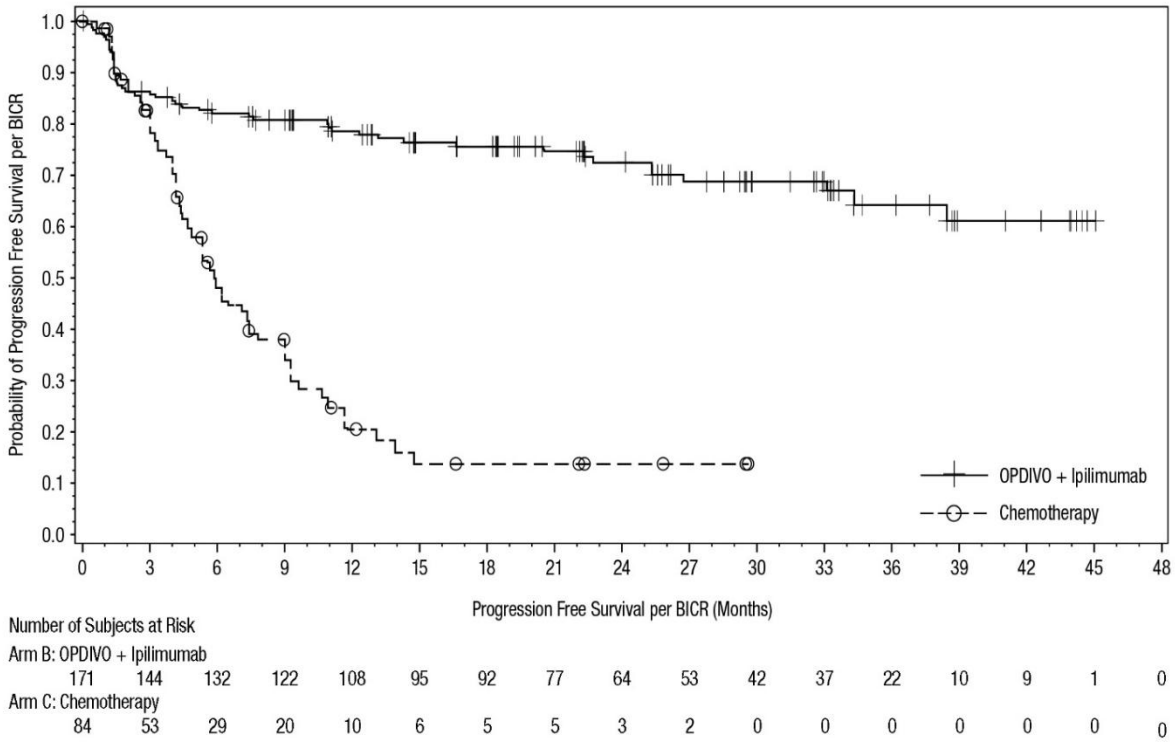


Table 37 Efficacy results in first-line MSI-H/dMMR CRC (CA2098HW)

	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 - 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 MSIH 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 38.

Table 38 Efficacy results (CA209142)*

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

* per investigator assessment
"+" denotes a censored observation.
NR = not reached

Immunogenicity

As with all therapeutic proteins, there is a potential for an immunogenic response to 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) was assessed using a population PK approach for both single-agent nivolumab and nivolumab in combination with ipilimumab.

Nivolumab monotherapy

The pharmacokinetics (PK) of nivolumab is linear in the dose range of 0.1 to 10 mg/kg. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 26% (32.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 7.91 mL/h (46%) in patients with metastatic tumours; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.6 L (24.4%) and geometric mean elimination half-life ($t_{1/2}$) is 25 days (55.4%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold.

Nivolumab CL increased with increasing body weight. Body weight normalised dosing produced approximately uniform steady-state trough concentration over a wide range of body weights (34-162 kg).

The metabolic pathway of nivolumab has not been characterised. As a fully human IgG4 monoclonal antibody, nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

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

In patients with cHL, nivolumab CL was lower resulting in a 15 day increase in the half-life and a 43% increase in exposure (as measured by median Cavgss). The lower nivolumab CL was not considered clinically meaningful; there was a flat predicted exposure-response relationship.

Paediatric Patients
For nivolumab monotherapy, the exposures of nivolumab in adolescent patients 12 years of age or older weighing 40 kg or greater are expected to be comparable to that in adult patients at the recommended dosage. The recommended dose regimens for patients with body weight <40 kg are based on pharmacokinetic modelling.

Nivolumab in combination with ipilimumab

When nivolumab 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 29% and the CL of ipilimumab was increased by 9%, which was not considered clinically relevant. When nivolumab 3 mg/kg every 2 weeks was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab was increased by 17% and the CL of ipilimumab was increased by 18%, which were not considered clinically relevant.

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

When nivolumab 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy, the CL of nivolumab decreased approximately 10% compared to nivolumab administered alone and the CL of ipilimumab increased approximately 22% compared to ipilimumab administered alone.

Special populations

Population PK analysis suggested no difference in CL of nivolumab based on age, gender, race, solid tumour type, tumour size, and hepatic impairment. The majority of patients in this analysis were diagnosed with NSCLC. Although ECOG status, baseline glomerular filtration rate (GFR) and body weight had an effect on nivolumab CL, the effect was not clinically meaningful.

Patients with lower baseline serum albumin tended to have lower exposure to nivolumab. However, because of the flat exposure-response relationship between nivolumab exposure and overall survival, this effect is unlikely to be clinically meaningful and no dose adjustment is recommended for patients with lower serum albumin.

Renal impairment

The effect of renal impairment on the CL of nivolumab was evaluated in patients with mild* (n = 1399), moderate* (n = 651), or severe* (n = 6) renal impairment compared to patients with normal* renal function (n = 1354) in population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. There were insufficient data to determine the effect of severe renal impairment on the CL of nivolumab (see Section 4.2. Dose and method of administration and 4.4. Special warnings and precautions for use).

**Per National Kidney Foundation criteria of renal impairment: Normal: GFR ≥ 90 mL/min/1.73 m^2; Mild: GFR < 90 and ≥ 60 mL/min/1.73 m^2; Moderate: GFR < 60 and ≥ 30 mL/min/1.73 m^2; Severe: GFR < 30 and ≥15 mL/min/1.73 m^2*

Hepatic impairment

The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with mild* hepatic impairment (n=351) and in patients with moderate* hepatic impairment (n=10) compared to patients with normal* hepatic function (n = 3096) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild/moderate hepatic impairment and patients with normal hepatic function, although the number of patients with moderate hepatic impairment was limited. Nivolumab has not been studied in patients with severe* hepatic impairment (see Section 4.2. Dose and method of administration and 4.4. Special warnings and precautions for use).

**Per National Cancer Institute criteria of hepatic dysfunction: Normal: total bilirubin and AST ≤ ULN; Mild: total bilirubin > 1.0 to 1.5 times ULN or AST > ULN; Moderate: total bilirubin > 1.5 to 3 times ULN and any AST; Severe: total bilirubin > 3 times ULN and any AST*

Cardiac electrophysiology

The potential effect of nivolumab on QTc interval was evaluated in 146 patients at doses up to 10 mg/kg every three weeks. No changes in mean QT interval were detected in nivolumab-treated patients based on Fredericia correction method.

Ipilimumab did not have a clinically meaningful effect on the QTc interval at doses up to 10mg/kg. Thus, QT interval prolongation is not expected with the nivolumab and ipilimumab combination.

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

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

This medicinal product does not contain any preservatives.

6.2. INCOMPATIBILITIES

OPDIVO should not be infused concomitantly in the same intravenous line with other medicinal products.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

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

After opening:

- To reduce microbiological hazard, once opened, the medicinal product should be infused immediately.
- After preparation of infusion: The administration of the OPDIVO infusion must be completed within 7 days of preparation. If not used immediately, the solution may be stored under refrigeration conditions: 2°-8°C and protected from light for up to 7 days (a maximum of 8 hours of the total 7 days can be at room temperature 20°-25°C and room light – the maximum 8 hour period under room temperature and room light conditions should be inclusive of the product administration period).

This medicinal product does not contain any preservatives.

6.5. NATURE AND CONTENTS OF CONTAINER

40 mg of nivolumab in 4 mL of concentrate solution for infusion is supplied in a 10 mL vial (Type I glass) with a stopper (coated butyl rubber) and an aluminium dark blue “flip off” seal. Pack of 1 vial containing 4 mL.

100 mg of nivolumab in 10 mL of concentrate solution for infusion is supplied in a 10mL vial (Type I glass) with a stopper (coated butyl rubber) and an aluminium grey “flip off” seal. Pack of 1 vial containing 10 mL.

240 mg of nivolumab in 10 mL of concentrate solution for infusion is supplied in a 25 mL vial (Type I glass) with a stopper (coated butyl rubber) and an aluminium red “flip off” seal. Pack of 1 vial containing 24 mL.

Not all presentations may be available.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

EACH VIAL OF OPDIVO® 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

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9. DATE OF FIRST APPROVAL (ARTG ENTRY)

11 January 2016

10. DATE OF REVISION OF THE TEXT

11 December 2025

10.1 SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Update to Other immune-related adverse reactions section to include Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome

4.8	Update to the Postmarketing experience section to include Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome

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