AUSTRALIAN PRODUCT INFORMATION
OPDIVO® (NIVOLUMAB)

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

Immune-related adverse reactions are seen more frequently, and are more severe, with OPDIVO and YERVOY combination therapy than with OPDIVO or YERVOY 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 YERVOY product information prior to initiation of OPDIVO in combination with YERVOY. The combination of OPDIVO and YERVOY 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

OPDIVO ® (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.

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.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to opalescent, colorless 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 patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

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

OPDIVO, in combination with YERVOY (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, 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.

Renal Cell Carcinoma (RCC)

OPDIVO, in combination with YERVOY (ipilimumab), is indicated for the treatment of patients with intermediate/poor-risk, previously untreated 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

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

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.

4.2. DOSE AND METHOD OF ADMINISTRATION

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

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 1. Detailed guidelines for the management of immune-related adverse reactions are described in Section 4.4 Special warnings and precautions for use.

OPDIVO MONOTHERAPY

Unresectable or metastatic melanoma, Squamous NSCLC, non-squamous NSCLC, renal cell carcinoma, relapsed/refractory classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, urothelial carcinoma, melanoma with involvement of lymph nodes or metastatic disease after complete resection and hepatocellular carcinoma.

The recommended dose of OPDIVO as a monotherapy is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

The maximum treatment duration with OPDIVO as monotherapy for adjuvant melanoma is 12 months.

OPDIVO IN COMBINATION WITH YERVOY (ipilimumab)

OPDIVO and YERVOY should be administered and monitored under the supervision of physicians experienced with the use of immunotherapy.

Please review the full prescribing information for YERVOY (ipilimumab) prior to initiation of OPDIVO in combination with ipilimumab.

In the initial combination phase, administer OPDIVO and YERVOY (ipilimumab) on the same day. Use separate infusion bags and filters for each infusion. Administer OPDIVO first followed by YERVOY (ipilimumab), after completion of the OPDIVO infusion.

Unresectable or metastatic melanoma

Combination Phase:
The recommended dose of OPDIVO in the combination phase is 1mg/kg administered intravenously over 60 minutes every 3 weeks for the first 4 doses in combination with YERVOY (ipilimumab) 3mg/kg administered intravenously over 90 minutes. This should be followed by OPDIVO monotherapy therapy in the single-agent phase (see below).

Single-agent Phase:
The recommended dose of OPDIVO in the single-agent phase is 3mg/kg as a monotherapy administered intravenously over 60 minutes every 2 weeks.

Treatment with OPDIVO in the single-agent phase should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

RCC

Combination Phase:
The recommended dose is 3 mg/kg nivolumab administered as an intravenous infusion over 60 minutes every 3 weeks for the first 4 doses in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes.

Single-agent Phase:
This is then followed by a second phase in which 3 mg/kg nivolumab is administered as an intravenous infusion over 60 minutes every 2 weeks. The first dose of nivolumab monotherapy should be administered 3 weeks following the last dose of the combination of nivolumab and ipilimumab.

Treatment with OPDIVO in the single-agent phase should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Recommended treatment modifications for OPDIVO as monotherapy and OPDIVO in combination with YERVOY (ipilimumab).

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

When OPDIVO is administered in combination with YERVOY (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.

Table 1: Recommended treatment modifications for OPDIVO as monotherapy or OPDIVO in combination with YERVOY (ipilimumab)

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	Withhold dose(s) until laboratory values return to baseline and

Table 1: Recommended treatment modifications for OPDIVO as monotherapy or OPDIVO in combination with YERVOY (ipilimumab)

Immune-related adverse reaction	Severity of Adverse Reaction[a]	Treatment modification
	aminotransferase (ALT), or total bilirubin	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.
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	Permanently discontinue treatment.

Table 1: Recommended treatment modifications for OPDIVO as monotherapy or OPDIVO in combination with YERVOY (ipilimumab)

Immune-related adverse reaction	Severity of Adverse Reaction[a]	Treatment modification
	Confirmed SJS/TEN	
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.
Other immune-related adverse reactions	Other Grade 3 adverse reaction First occurrence	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete.
	Recurrence of same Grade 3 adverse reaction	Permanently discontinue treatment.
	Grade 3 myotoxicity	Permanently discontinue treatment.
	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.

SPECIAL POPULATIONS

Paediatric patients

The safety and efficacy of OPDIVO in children below 18 years of age have not been established. No data are available. OPDIVO should not be used in children below 18 years of age.

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 60 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.

When OPDIVO is administered in combination with YERVOY (ipilimumab), administer both therapeutics on the same day. Use separate infusion bags and filters for each infusion. Administer OPDIVO first followed by YERVOY (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

The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given. More than one vial of OPDIVO concentrate may be needed to give the total dose for the patient.

- 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 either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting to concentrations as low as 1 mg/mL. The final infusion concentration should range between 1 and 10 mg/mL. OPDIVO concentrate may be diluted with either sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

STEP 1

- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake. OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid that may contain a few light 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

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 or OPDIVO in combination with ipilimumab.

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

For Grade 3 or 4 pneumonitis, 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.

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.

Based on limited data from clinical trials on the management of corticosteroid-refractory diarrhoea or colitis, administration of other systemic immunosuppressants (e.g., anti-TNF-α agents) can be considered.

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 DOSAGE AND ADMINISTRATION)

In patients with HCC, nivolumab monotherapy 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, nivolumab 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, nivolumab should be withheld
- Regardless of baseline transaminase levels, nivolumab 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), 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.

Rare cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis) 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.

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.

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 Yervoy (ipilimumab)

Review the full prescribing information for YERVOY (ipilimumab) prior to initiation of the OPDIVO in combination with YERVOY (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 YERVOY (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 YERVOY should be monitored for immune-related adverse reactions clinically and with appropriate investigations prior to each dose during the combination phase.

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.

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 Management Guide. 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 ipilimumab are listed in Table 2 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 2: 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
cHL	• Patients with symptomatic interstitial lung disease
SCCHN	• Patients with carcinoma of the nasopharynx or salivary gland as the primary tumour site
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.

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

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacokinetic interaction studies have not been conducted. Nivolumab is a human monoclonal antibody. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolizing 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 OPDIVO 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 OPDIVO is an IgG4; therefore OPDIVO has the potential to be transmitted from the mother to the developing fetus. It is not known whether nivolumab can cause foetal harm when administered to a pregnant woman (See 5.3 Preclinical safety data).

Use in lactation

It is not known whether OPDIVO 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=2578) across tumour types (melanoma: CA209066, CA209037, CA209067 [monotherapy group only], SQ NSCLC: CA209017, CA209063, NSQ NSCLC: CA209057, RCC: CA209025, cHL: CA209205 and CA209039, SCCHN: CA209141 and UC: CA209275 and CA209032). The most frequent adverse reactions in the pooled dataset (≥ 10%) were fatigue (30%), rash (17%), pruritus (13%), diarrhoea (13%) and nausea (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 2578) are presented in Table 3. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

A summary of laboratory abnormalities that worsened from baseline in the pooled dataset for patients treated with nivolumab monotherapy is presented in Table 4.

Table 3: Adverse reactions from a pooled dataset of nivolumab monotherapy clinical trials

Infections and infestations	
Common	upper respiratory tract infection
Uncommon	pneumonia[a], bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Very Common	neutropenia[a,f]
Uncommon	eosinophilia
Immune system disorders	
Common	infusion related reaction[b], hypersensitivity[b]
Rare	anaphylactic reaction[b]
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism
Uncommon	adrenal insufficiency, hypopituitarism, hypophysitis, diabetes mellitus, thyroiditis
Rare	diabetic ketoacidosis
Metabolism and nutrition disorders	
Common	decreased appetite
Uncommon	dehydration, metabolic acidosis
Hepatobiliary disorders	
Uncommon	hepatitis[b]
Rare	cholestasis
Nervous system disorders	

Table 3: Adverse reactions from a pooled dataset of nivolumab monotherapy clinical trials

Common	peripheral neuropathy, headache, dizziness
Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis [a,b]
Eye disorders	
Uncommon	uveitis, blurred vision, dry eye
Cardiac disorders	
Uncommon	tachycardia
Rare	arrhythmia (including ventricular arrhythmia), myocarditis [a,d], atrial fibrillation
Vascular disorders	
Common	hypertension
Rare	vasculitis
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis[a,b], 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	gastritis, duodenal ulcer
Skin and subcutaneous tissue disorders	
Very common	rash[d], pruritus
Common	vitiligo, dry skin, erythema, alopecia
Uncommon	erythema multiforme, psoriasis, rosacea, urticaria
Rare	toxic epidermal necrolysis[a,c] Stevens-Johnson syndrome[a,c]
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain[e], arthralgia
Uncommon	polymyalgia rheumatica, arthritis
Rare	myopathy, myositis (including polymyositis)[a,c], rhabdomyolysis[a,c] , Sjogren's syndrome
Renal and urinary disorders	
Uncommon	tubulointerstitial nephritis, renal failure (including acute kidney injury)[a,b]
General disorders and administration site conditions	
Very common	fatigue
Common	pyrexia, oedema (including peripheral oedema)
Uncommon	pain, chest pain
Investigations[b]	
Common	weight decreased

[a] Fatal cases have been reported in completed or ongoing clinical studies
[b] Life-threatening cases have been reported in completed or ongoing clinical studies.
[c] Including those reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure.
[d] 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.
[e] 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.

[f] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Table 3: laboratory abnormalities" below.

Table 4: Laboratory abnormalities from a pooled data of nivolumab monotherapy clinical trials

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**
Anaemia[b]	2515	933 (37.1)	130 (5.2)
Thrombocytopenia	2513	364 (14.5)	24 (1.0)
Leukopenia	2519	390 (15.5)	25 (1.0)
Lymphopenia	2499	1063 (42.5)	249 (10.0)
Neutropenia	2501	312 (12.5)	27 (1.1)
Increased alkaline phosphatase	2491	648 (26.0)	53 (2.1)
Increased AST	2495	693 (27.8)	67 (2.7)
Increased ALT	2503	551 (22.0)	56 (2.2)
Increased total bilirubin	2500	223 (8.9)	30 (1.2)
Increased creatinine	2510	58.4 (25.3)	22 (0.9)
Increased total amylase	1057	174 (16.5)	37 (3.5)
Increased total lipase	1171	258 (22.0)	93 (7.9)
Hypercalcaemia	2416	256 (10.6)	28 (1.2)
Hypocalcaemia	2416	467 (19.3)	16 (0.7)
Hyperkalaemia	2454	490 (20.0)	45 (1.8)
Hypokalaemia	2454	274 (11.2)	37 (1.5)
Hypermagnesaemia	2215	111 (5.0)	15 (0.7)
Hypomagnesaemia	2215	353 (15.9)	10 (0.5)
Hypernatraemia	2456	134 (5.5)	3 (0.1)
Hyponatraemia	2456	731 (29.8)	157 (8.6)
Hyperglycemia[c]	312	129 (41.3)	12 (3.8)
Hypoglycemia	309	25 (8.1)	3 (1.0)

Toxicity scale: CTC Version 4.0.
Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.
[a] The total number of patients who had both baseline and on-study laboratory measurements available.
[b] Per anaemia criteria in CTC version 4.0, there is no Grade 4 for haemoglobin.
[c] Life-threatening hyperglycemia has been reported in completed or ongoing clinical studies.

Adjuvant melanoma

In the dataset of nivolumab 3 mg/kg as monotherapy for the adjuvant treatment of melanoma (n = 452), the most frequent adverse reactions (≥ 10%) were fatigue (46%), rash (29%), diarrhoea

(24%), pruritus (23%), nausea (15%), arthralgia (13%), musculoskeletal pain (11%), and hypothyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

The overall safety profile of OPDIVO 3 mg/kg for the treatment of adjuvant melanoma was consistent with that established across tumour types for nivolumab monotherapy.

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) and 547 patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for RCC (study CA209214).

Adverse reactions reported in the pooled dataset for patients treated with nivolumab in combination with ipilimumab (n=995) 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).

A summary of laboratory abnormalities that worsened from baseline in the pooled dataset for patients treated with nivolumab in combination with ipilimumab is presented in Table 6.

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.

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).

Table 5: 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)	**Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n=547)**
Infections and infestations		
Common	pneumonia, upper respiratory tract infection	pneumonia, upper respiratory tract infection
Uncommon	bronchitis	bronchitis, aseptic meningitis
Blood and lymphatic system disorders		
Common	eosinophilia	
Uncommon		eosinophilia
Immune system disorders		
Common	infusion related reaction, hypersensitivity	infusion-related reaction, hypersensitivity
Uncommon	sarcoidosis	
Endocrine disorders		
Very common	hypothyroidism	hypothyroidism, hyperthyroidism
Common	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis	adrenal insufficiency[b], hypophysitis[b], thyroiditis, diabetes mellitus[b]
Uncommon	diabetic ketoacidosis[b], diabetes mellitus[b]	diabetic ketoacidosis[b], hypopituitarism
Metabolism and nutrition disorders		
Very common	decreased appetite	decreased appetite
Common	dehydration	dehydration
Uncommon		metabolic acidosis
Hepatobiliary disorders		
Common	hepatitis[b]	hepatitis[b]
Nervous system disorders		
Very common	headache	
Common	peripheral neuropathy, dizziness	headache, peripheral neuropathy, dizziness
Uncommon	Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis[b]	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis[b]
Eye disorders		
Common	uveitis, blurred vision	blurred vision
Uncommon		uveitis
Cardiac disorders		
Common	tachycardia	tachycardia
Uncommon	arrhythmia (including ventricular arrhythmia)[a,c], atrial fibrillation, myocarditis[a,e]	arrhythmia (including ventricular arrhythmia), myocarditis[b]
Vascular disorders		
Common	hypertension	hypertension
Respiratory, thoracic and mediastinal disorders		
Very Common	dyspnoea	
Common	pneumonitis[a,b], cough	pneumonitis, dyspnoea, pleural effusion, cough
Uncommon	pleural effusion	
Gastrointestinal disorders		

Very common	colitis[a], diarrhoea, vomiting, nausea, abdominal pain	diarrhoea, vomiting, nausea
Common	stomatitis, pancreatitis, constipation, dry mouth	colitis, stomatitis, pancreatitis, abdominal pain, constipation, dry mouth
Uncommon	intestinal perforation[a], gastritis, duodenitis	gastritis
Skin and subcutaneous tissue disorders		
Very common	rash[d], pruritus	rash[d], pruritus
Common	vitiligo, dry skin, erythema, alopecia, urticaria	dry skin, erythema, urticaria
Uncommon	psoriasis	Stevens-Johnson syndrome, vitiligo, erythema multiforme, alopecia, psoriasis
Rare	toxic epidermal necrolysis[a,e], Stevens-Johnson syndrome[e]	
Musculoskeletal and connective tissue disorders		
Very common	arthralgia	musculoskeletal pain[f], arthralgia
Common	musculoskeletal pain[f]	arthritis
Uncommon	spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis)[a,e], rhabdomyolysis[a,e]	polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis
Renal and urinary disorders		
Common	renal failure (including acute kidney injury)[a,b]	renal failure (including acute kidney injury)[b]
Uncommon	tubulointerstitial nephritis	tubulointerstitial nephritis
General disorders and administration site conditions		
Very common	fatigue, pyrexia	fatigue, pyrexia
Common	oedema (including peripheral oedema), pain	oedema (including peripheral oedema), pain, chest pain
Uncommon	chest pain	
Investigations[b]		
Common	weight decreased	

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

[b] Life-threatening cases have been reported in completed or ongoing clinical studies.

[c] The frequency of adverse events in the cardiac disorders system organ class regardless of causality was higher in the nivolumab group than in the chemotherapy group in post-CTLA4/BRAF inhibitor metastatic melanoma population. Incidence rates per 100 person-years of exposure were 9.3 vs. 0; serious cardiac events were reported by 4.9% patients in the nivolumab group vs. 0 in the investigator´s choice group. The frequency of cardiac adverse events was lower in the nivolumab group than in the dacarbazine group in the metastatic melanoma without prior treatment population. All were considered not related to nivolumab by investigators except arrhythmia (atrial fibrillation, tachycardia and ventricular arrhythmia).

[d] 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.

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

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

Table 6: Laboratory abnormalities with nivolumab in combination with ipilimumab in clinical trials

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n=448)			Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n=547)		
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**	**N[a]**	**Grades 1-4**	**Grades 3-4**
Anaemia[b]	424	215 (50.7)	12 (2.8)	537	230 (42.8)	16 (3.0)
Thrombocytopenia	422	51 (12.1)	5 (1.2)	537	83 (15.5)	4 (0.7)
Leukopenia	426	60 (14.1)	2 (0.5)	537	79 (14.7)	3 (0.6)
Lymphopenia	421	173 (41.1)	28 (6.7)	534	191 (35.8)	27 (5.1)
Neutropenia	423	64 (15.1)	3 (0.7)	535	65 (12.1)	6 (1.1)
Increased alkaline phosphatase	418	160 (38.3)	18 (4.3)	538	154 (28.6)	11 (2.0)
Increased AST	420	207 (49.3)	52 (12.4)	537	215 (40.0)	26 (4.8)
Increased ALT	425	225 (52.9)	65 (15.3)	538	223 (41.4)	35 (6.5)
Increased total bilirubin	422	54 (12.8)	5 (1.2)	535	66 (12.3)	6 (1.1)
Increased creatinine	424	107 (25.2)	10 (2.4)	536	229 (42.7)	11 (2.1)
Increased total amylase	366	96 (26.2)	32 (8.7)	490	190 (38.8)	60 (12.2)
Increased total lipase	401	164 (40.9)	78 (19.5)	517	246 (47.6)	104 (20.1)
Hypercalcaemia	406	29 (7.1)	1 (0.2)	529	72 (13.6)	7 (1.3)
Hypocalcaemia	406	133 (32.8)	5 (1.2)	529	115 (21.7)	2 (0.4)
Hyperkalaemia	421	73 (17.3)	2 (0.5)	534	155 (29.0)	13 (2.4)
Hypokalaemia	421	84 (20.0)	20 (4.8)	534	57 (10.7)	10 (1.9)
Hyperglycemia[c]	75	39 (52.0)	4 (5.3)	222	103 (46.4)	16 (7.2)
Hypoglycaemia	71	8(11.3)	0	223	34 (15.2)	4 (1.8)
Hypermagnesaemia	370	11 (3.0)	1 (0.3)	528	35 (6.6)	6 (1.1)
Hypomagnesaemia	370	58 (15.7)	0	528	100 (18.9)	2 (0.4)
Hypernatraemia	442	20 (4.7)	1 (0.2)	535	48 (9.0)	0
Hyponatraemia	442	185 (43.8)	40 (9.5)	535	211 (39.4)	53 (9.9)

Toxicity scale: CTC Version 4.0.
Includes laboratory results reported after the first dose and within 30 days of the last dose of study therapy. The frequencies are regardless of causality.
[a] The total number of patients who had both baseline and on-study laboratory measurements available.
[b] Per anemia criteria in CTC version 4.0, there is no Grade 4 for haemoglobin.
[c] Life-threatening hyperglycemia has been reported in completed or ongoing clinical studies.

Description of selected immune-related adverse reactions

Both OPDIVO and OPDIVO in combination with ipilimumab 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 3.4% (87/2578). The majority of cases were Grade 1 or 2 in severity reported in 0.8% (21/2578) and 1.7% (44/2578) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (19/2578) and <0.1 (1/2578) of patients respectively. Two Grade 5 cases (<0.1%) were reported in these studies. One patient with Grade 3 pulmonary embolism and Grade 3 pneumonitis died in the SCCHN clinical trial. Median time to onset was 3.6 months (range: 0.2-19.6). Thirty-one patients (1.2%), required permanent discontinuation of nivolumab. Sixty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 63 patients (72%) with a median time to resolution of 6.1 weeks (range: 0.1-96.7).

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 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).

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 13.1% (339/2578). The majority of cases were Grade 1 or 2 in severity reported in 8.5% (220/2578) and 3.0% (78/2578) of patients respectively. Grade 3 cases were reported in 1.6% (41/2578) of patients. No Grade 4 or 5 cases were reported. Median time to onset was 1.8 months (range: 1 day-26.6 months). Twenty patients (0.8%) required permanent discontinuation of nivolumab. Forty-nine patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 296 patients (88%) with a median time to resolution of 2.1 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 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).

Immune-related hepatitis

OPDIVO monotherapy

In the pooled analysis in patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 6.7% (173/2578). The majority of cases were Grade 1 or 2 in severity reported in 3.5% (91/2578) and 1.2% (32/2578) of patients respectively. Grade 3 and 4 cases were reported in 1.6% (41/2578) and 0.3% (9/2578) of patients, respectively. No deaths due to liver function abnormalities were reported. Median time to onset was 2.1 months (range: 1 day - 27.6 months). Twenty-seven (1.0%) required permanent discontinuation of nivolumab. Thirty-six patients (1.4%) received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 132 patients (77%) with a median time to resolution of 9 weeks (range: 0.1-82.6).

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 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).

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 2.8% (71/2578). The majority of cases were Grade 1 or 2 in severity reported in 1.6% (41/2578) and 0.7% (18/2578) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (11/2578) and <0.1% (1/2578) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported in these studies. Median time to onset was 2.3 months (range: 1 day - 18.2 months). Seven patients (0.3%), required permanent discontinuation of nivolumab. Nineteen patients

received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 42 patients (62%) with a median time to resolution of 12.1 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 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).

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 9.6% (248/2578). The majority of cases were Grade 1 or 2 in severity reported in 4.2% (107/2578) and 5.4% (139/2578) of patients respectively. Grade 3 thyroid disorders were reported in <0.1% (2/2578) of patients. Hypophysitis (1 Grade 1; 2 Grade 2, 5 Grade 3 and 1 Grade 4), hypopituitarism (4 Grade 2 and 1 Grade 3), adrenal insufficiency (1 Grade 1; 9 Grade 2; and 5 Grade 3), diabetes mellitus (3 Grade 2 and 1 Grade 3), and diabetic ketoacidosis (2 Grade 3) were also reported. No Grade 5 endocrinopathies were reported. Median time to onset of these endocrinopathies was 2.8 months (range: 0.3-29.1). Three patients (0.1%) required permanent discontinuation of nivolumab. Eighteen patients received high dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 117 patients (43%). Time to resolution ranged from 0.4 to 144 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 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.

Immune-related skin adverse reactions

OPDIVO monotherapy

In the pooled analysis in patients treated with nivolumab monotherapy, the incidence of rash was 26.4% (680/2578). The majority of cases were Grade 1 in severity reported in 20.1% (518/2578) of patients. Grade 2 and Grade 3 cases were reported in 5.1% (131/2578) and 1.2% (31/2578) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 1.4 months (range: 1 day - 27.9 months). Eight patients (0.3%) required permanent discontinuation of nivolumab. Twenty-eight patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 428 patients (64%) with a median time to resolution of 17.1 weeks (0.1-150.0).

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 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).

Infusion reactions

OPDIVO monotherapy

In the pooled analysis in patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions, including anaphylactic reaction, was 4.7% (121/2578), including 6 Grade 3 (0.2%) and 2 Grade 4 (<0.1%) cases. No deaths due to infusion reactions 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 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.

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 40 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 7/40 patients (17.5%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in two patients (5%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (15%) 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. Six of 40 patients (15%) died from complications of allogeneic HSCT after nivolumab. The 40 patients had a median follow-up from subsequent allogeneic HSCT of 2.9 months (range: 0-22 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, and rhabdomyolysis.

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

Reporting of 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. Inadvertent rapid administration (over 30 minutes instead of 60 minutes) without adverse consequences has been reported in a small number of patients in the clinical studies.

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 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.

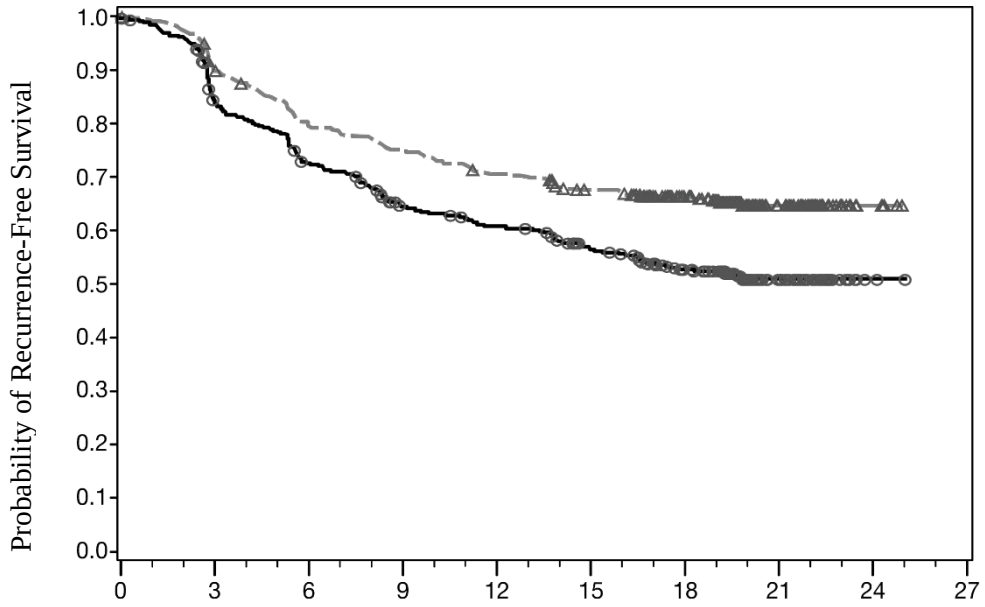
RFS, assessed by investigator, was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death due to any cause, whichever occurred first.

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 1 and Table 7 (all randomised population).

Figure 1: Recurrence-free survival (CA209238)



Number of Subjects at Risk

Nivolumab									
453	399	353	332	311	291	249	71	5	0
Ipilimumab									
453	364	314	269	252	225	184	56	2	0

—Δ—Nivolumab - - - ❍- - - Ipilimumab

Table 7: 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

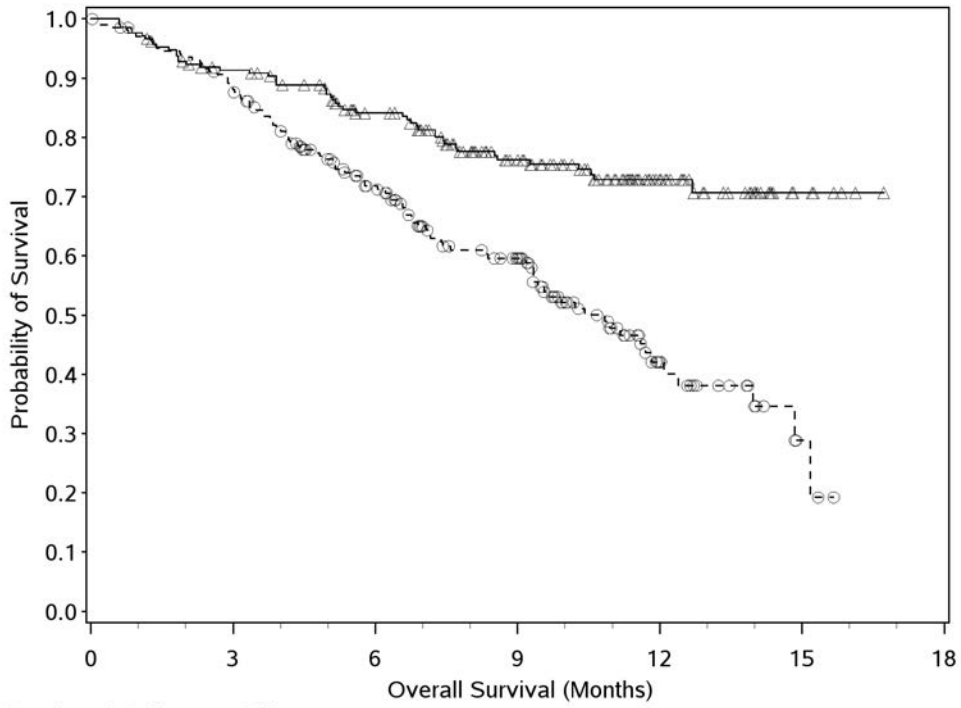
Randomised phase 3 study vs. dacarbazine (CA209066)
The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209066). The study included adult patients (18 years or older) 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 2, Table 8) 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 2: 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.

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

Table 8: 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 10 and Figure 3 (PFS), and Figure 4 (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 10: Efficacy results (CA209067)

	OPDIVO + Ipilimumab (n=314)	OPDIVO (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 (95% CI)	185 (59%) (53.3, 64.4)	141 (45%) (39.1, 50.3)	60 (19%) (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 .

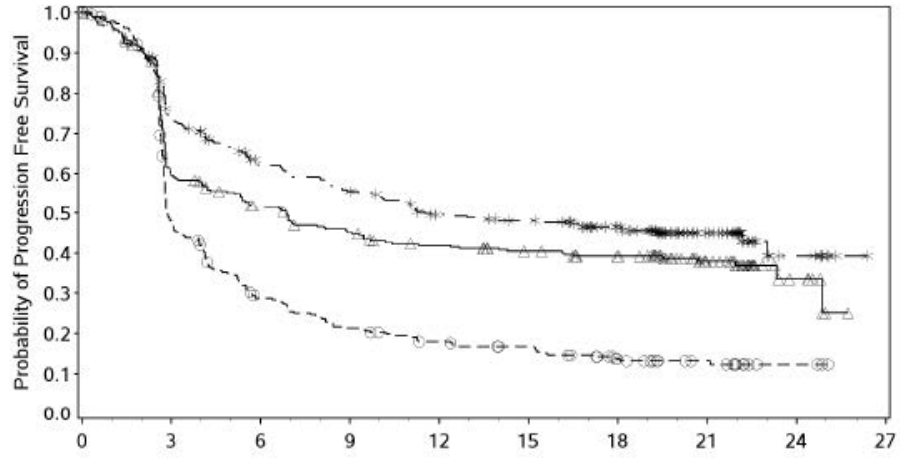
b Minimum follow up of 28 months.

c Unadjusted for multiplicity

NE=not estimable.

"+" denotes a censored observation.

Figure 3 Progression-free survival (CA209067)



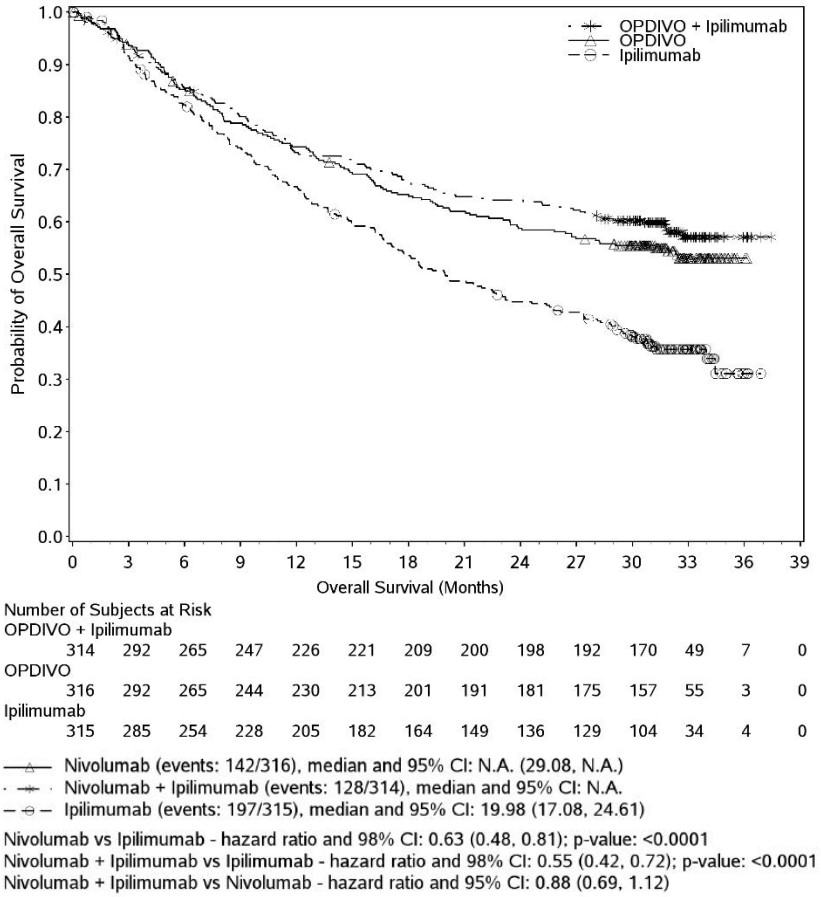
Number of Subjects at Risk

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 4: Overall survival(CA209067)



The improvements in PFS, OS, ORR and DOR that were seen in both nivolumab-containing arms compared to ipilimumab monotherapy (Table 10) 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 Figures 5 and 6.

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

Figure 5 Progression-free survival by tumour PD-L1 expression level (CA209067) at 18 months of follow-up

< 1% **≥ 1%**

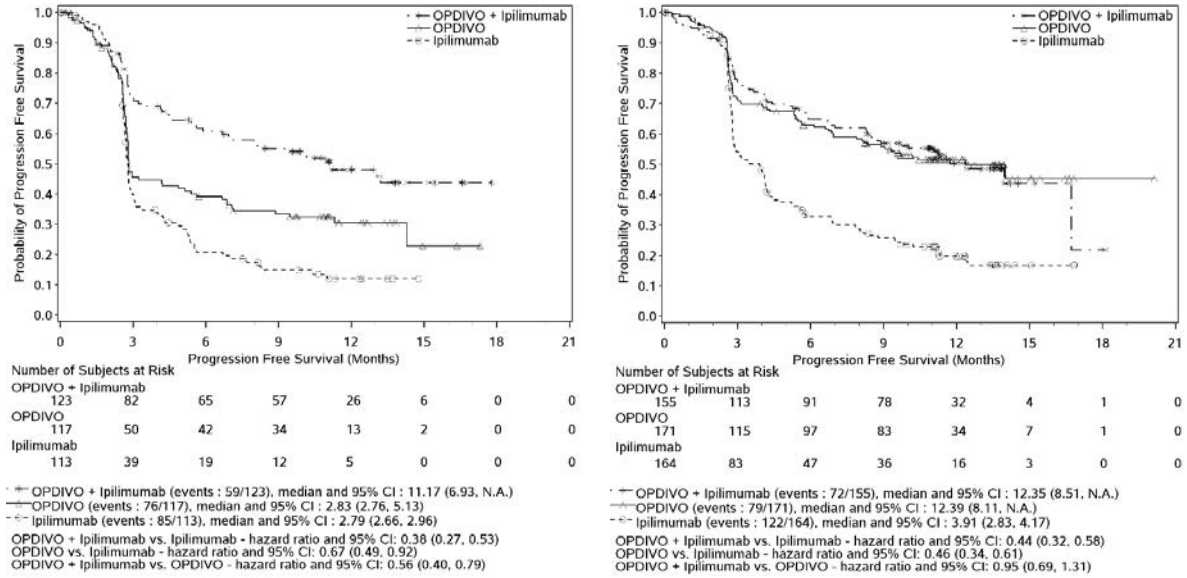
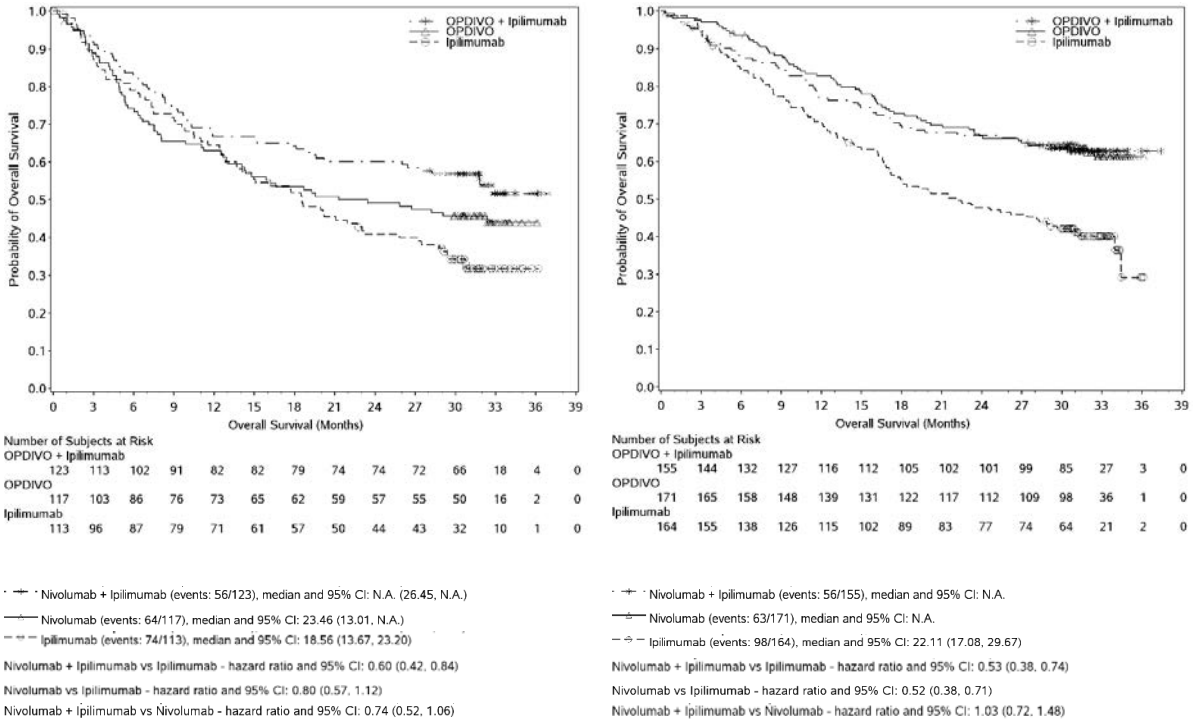


Figure 6 Overall survival by tumour PD-L1 expression level (CA209067) at 2 years of follow-up

< 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 9.

Table 9: 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)

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 7, Table 11) 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 7: Overall survival (CA209017)

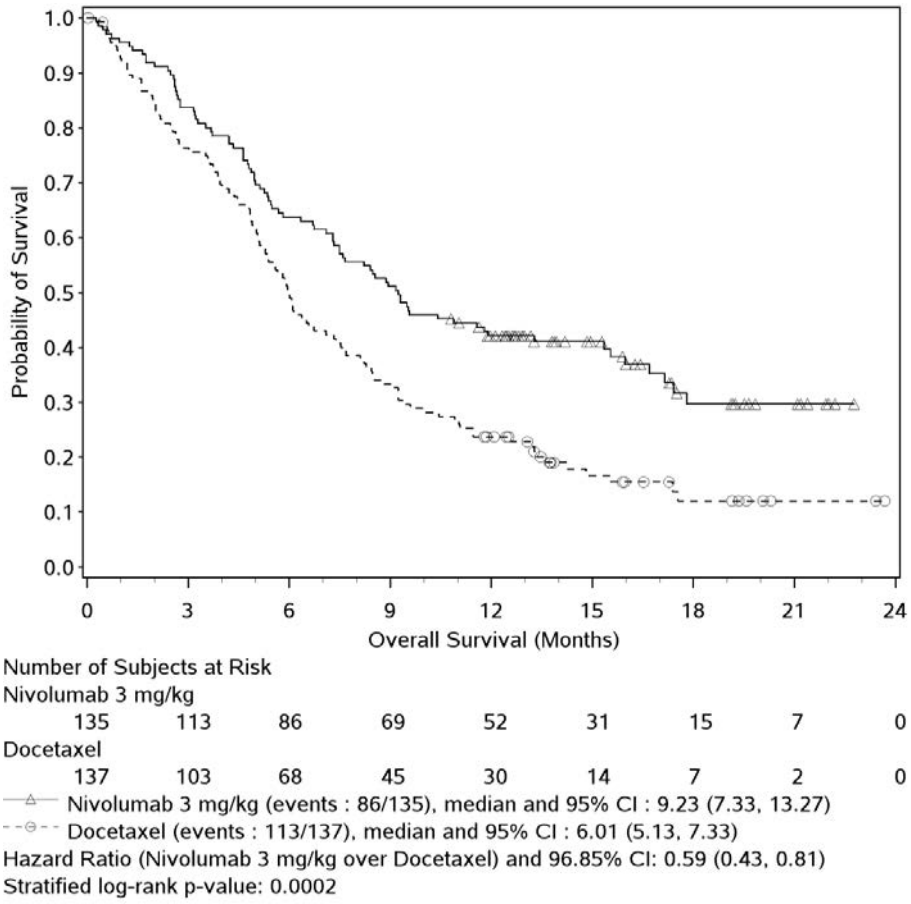


Table 11: Efficacy results (CA209017)

	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)

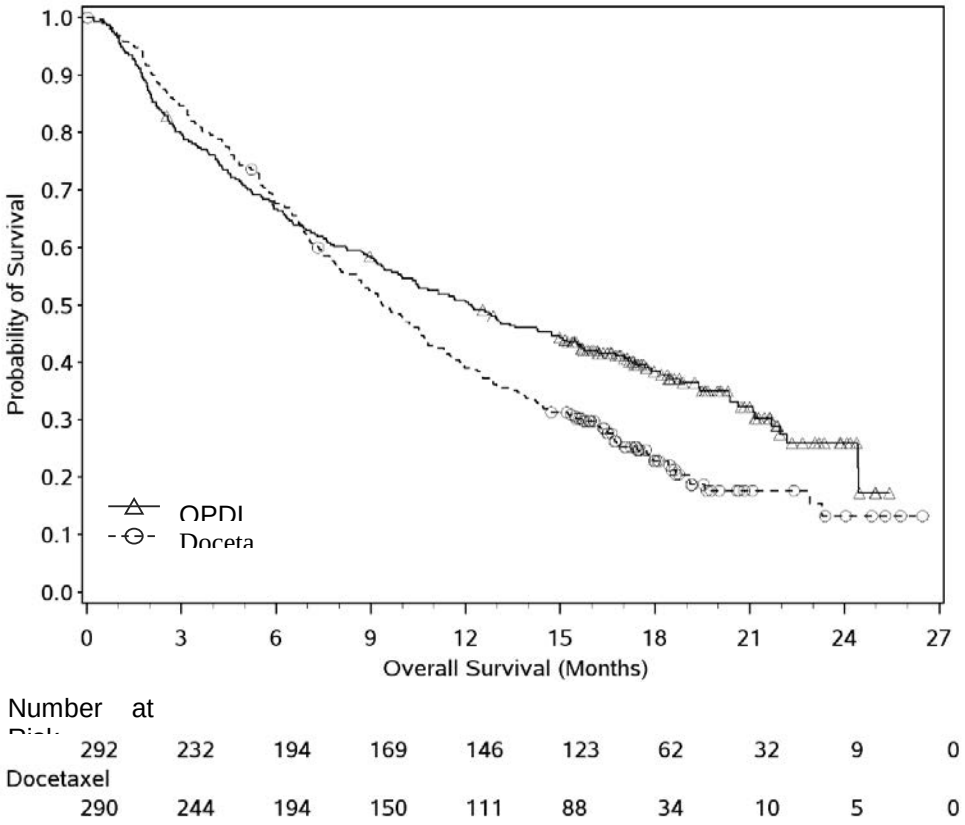
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic non-squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209057). The study included patients (18 years or older) who have experienced disease progression during or after 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 8.

Figure 8: 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 12.

Table 12: 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.

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

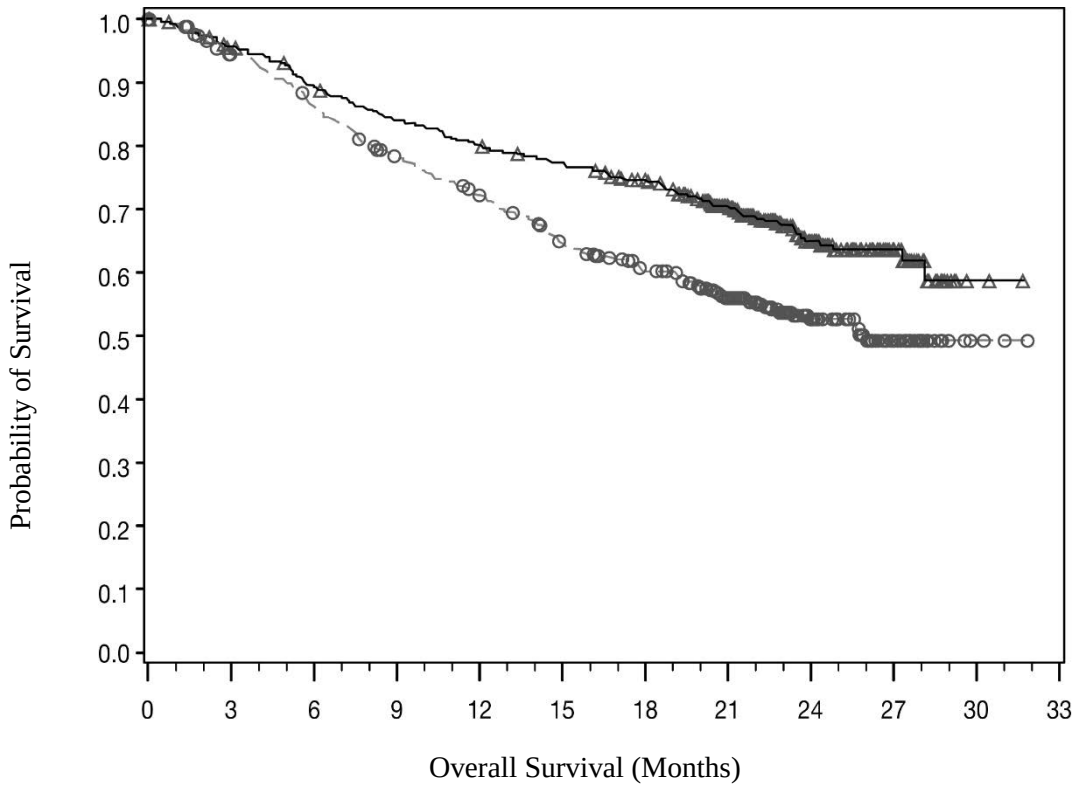
renal cell carcinoma and Karnofsky performance status ≥ 70%. Prior adjuvant or neoadjuvant therapy was allowed if such therapy did not include an agent that targets vascular endothelial growth factor (VEGF) or VEGF receptors and recurrence occurred at least 6 months after the last dose of adjuvant or 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 9.

Figure 9: 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. (Table 13 and Figure 9). OS benefit was observed regardless of tumour PD-L1 expression level.

Efficacy results are shown in Table 13.

Table 13: **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 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.

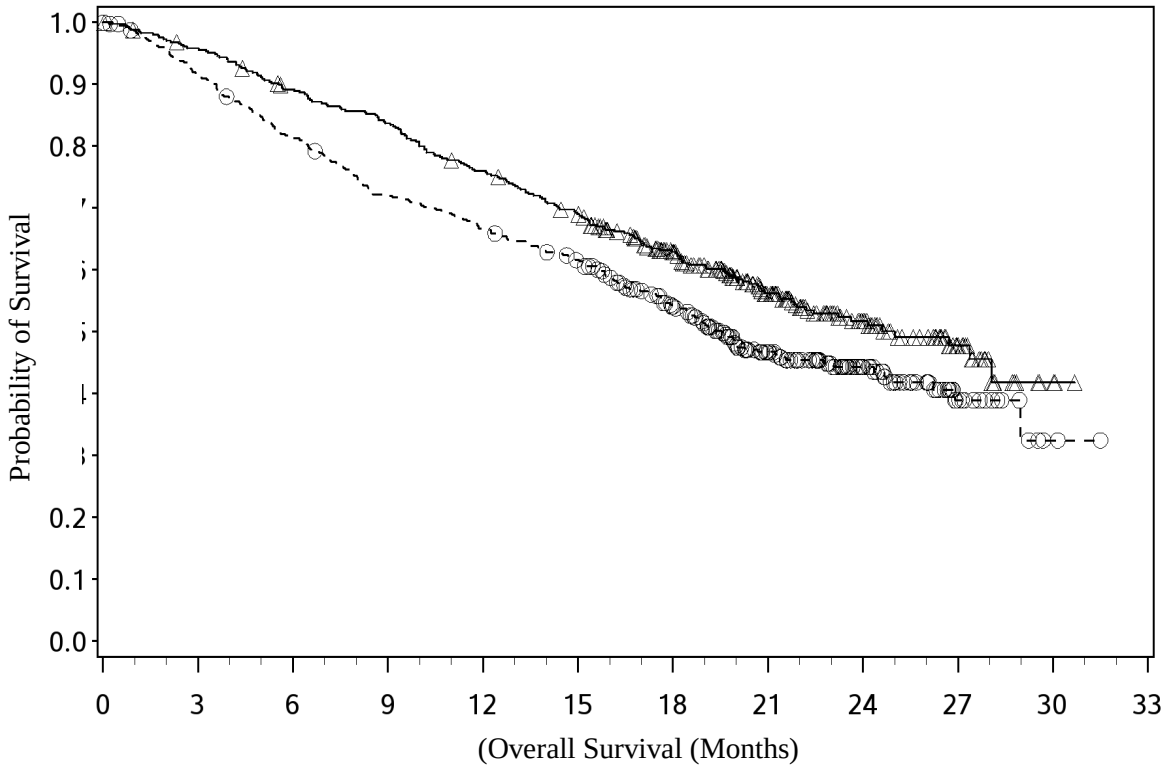
A total of 821 patients were randomised to receive either nivolumab 3 mg/kg (n = 410) administered intravenously over 60 minutes every 2 weeks or everolimus (n = 411) 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated.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

Figure 10: 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) (Table 14 and Figure 8). OS benefit was observed regardless of PD-L1 expression level.

Efficacy results are shown in Table 14.

Table 14: 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) and treatment with brentuximab vedotin.

Study CA209205 is an ongoing Phase 2, open-label, multi-cohort, single-arm study of nivolumab in cHL - Cohort B of this study included 80 patients who received nivolumab following ASCT and brentuximab vedotin treatment. Study CA209039 was an open-label, multicenter, 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. The baseline and disease characteristics of the patients in each study were similar. In CA209205, the median age was 37 years with 3 subjects aged 65 years or older; 89% were white, 64% were male; 67.5% had Stage IV disease at study entry; the median number of prior systemic regimens was 4 (range 3 to 15); 89% 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 15.4 months (range 1.9 to 18.5 months) 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 15.

Table 15: Efficacy results (CA209205, CA209039)

Efficacy Parameter	CA209205 Cohort B[a] (n = 80)	CA209039 ASCT-Bren failed group (n = 15)
Objective Response Rate; (95% CI)	54 (68%); (56, 78)	9 (60%); (32, 84)
Complete Remission Rate; (95% CI)	6 (8%); (3, 16)	0 (0%); (0, 22)
Partial Remission Rate; (95% CI)	48 (60%); (48, 71)	9 (60%); (32, 84)
Stable disease, n (%)	17 (21)	5 (33)
Median Duration of Response (months)[b]	13.1	12.0
(95% CI)	(8.7, N.A.)	(1.8, N.A.)
Min, Max	0.0+, 14.2+	1.8, 23.1+
Median Time to Response (months)	2.1	0.8
Min, Max	1.6, 11.1	0.7, 4.1

[a] Follow-up was ongoing at the time of data submission
[b] Data unstable due to the limited DOR for Cohort B resulting from censoring.
N.A. = not available

PFS and OS were exploratory endpoints in these studies. The median PFS was 14.8 months (95% CI: 11.3, NA) and 12.7 months (95% CI: 5.91, NA) in CA209205 Cohort B and CA209039, respectively. The PFS rate at 12 months was 55% (95% CI 41, 66) and 69% (95% CI 37, 88) in CA209205 Cohort B and CA209039, respectively. At the time of database lock, OS data were immature and the median had not been reached in CA209205 Cohort B and CA209039. The OS rate at 12 months was 95% (95% CI 87, 98) and 93% (95% CI 61, 99) in CA209205 Cohort B and CA209039, respectively.

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

B -symptoms were present in 25% (18/80) of the patients in CA209205 Cohort B at baseline. Nivolumab treatment resulted in rapid resolution of B-symptoms in 88.9% (16/18) 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.

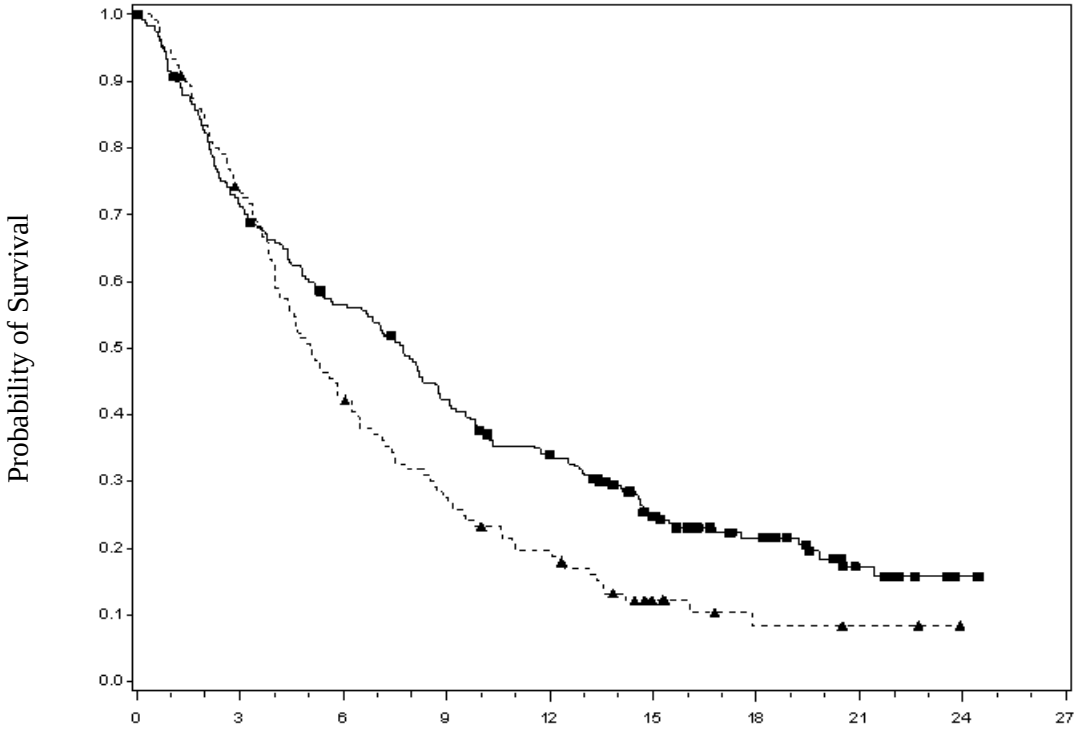
A total of 361 patients were randomised to receive either nivolumab 3 mg/kg (n=240) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n=15), 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly or methotrexate (n=52) 40 to 60 mg/m^2 weekly, or docetaxel (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 11. Efficacy results are shown in Table 16.

Figure 11: Overall survival (CA209141)



Overall Survival (Months)

Number of Subjects at Risk

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

Nivolumab (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 16: **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)

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 17: 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 improvementin 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)

Previously treated advanced HCC - OPDIVO monotherapy

Single-arm phase 2 study of nivolumab(CA209040)

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 a phase 2, open-label, multi-cohort study (CA209040) conducted in patients with advanced HCC.

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.

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 alfa-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 20.

Table 20: Efficacy results in patients with HCC treated with OPDIVO 3 mg/kg after prior sorafenib therapy in CA209040

	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] Confidene interval is based on the Clopper and Pearson method

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. The incidence of neutralising antibodies against nivolumab was 0.5% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of 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 8.4% and neutralising antibodies against ipilimumab ranged from 0 to 0.3%.There was no evidence of altered toxicity profile associated with anti-product antibody development. Neutralising antibodies were not associated with loss of efficacy.

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.

Based on a population PK analysis, using data predominantly from patients with melanoma, NSCLC and RCC, the geometric mean clearance (CL), terminal half-life, and average exposure at steady state at 3 mg/kg every 2 weeks of nivolumab were 7.9 mL/h, 25.0 days, and 86.6 µg/mL, respectively.

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.

Nivolumab in combination with ipilimumab

In the nivolumab and ipilimumab combination, nivolumab 1mg/kg had no effect on the CL of ipilimumab, and ipilimumab 3mg/kg had a 24% increase in CL of nivolumab based on a population PK analysis.

In the nivolumab and ipilimumab combination, the CL of nivolumab increased by 42% in the presence of anti-nivolumab antibody based on a population PK analysis. There was no effect of anti-ipilimumab antibodies on the clearance of ipilimumab based on a population PK analysis.

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 = 379), moderate* (n = 179), or severe* (n = 2) renal impairment compared to patients with normal* renal function (n = 342) in population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. 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

The effects of OPDIVO on prenatal and postnatal development were evaluated in monkeys that received OPDIVO 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 of OPDIVO (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 OPDIVO-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.

Genotoxicity

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

Carcinogenicity

Studies to evaluate the carcinogenic potential of OPDIVO 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 24 hours of preparation. If not used immediately, the solution may be stored under refrigeration conditions: 2°-8°C and protected from light for up to 24 hours (a maximum of 8 hours of the total 24 hours 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.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

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

Any unused medicinal product or waste material should be discarded in accordance with local requirements.
In Australia, unwanted medicines can be returned to local pharmacies involved in the Return Unwanted Medicines (RUM) Project.

6.7. PHYSICOCHEMICAL PROPERTIES

CAS number

CAS: 946414-94-4.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4. Prescription Only Medicine

8. SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
Level 2, 4 Nexus Court
MULGRAVE VIC 3170.
Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9. DATE OF FIRST APPROVAL (ARTG ENTRY)

11 January 2016

10. DATE OF REVISION OF THE TEXT

18 September 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	Addition of new indication for use as monotherapy in patients with hepatocellular carcinoma after prior sorafenib therapy.

4.2	Addition of treatment modifications for patients with hepatocellular carcinoma with immune-related hepatitis. Updated dosing recommendations for patients with hepatic impairment.
4.4	Addition of management guidelines for elevated transaminases in patients with hepatocellular carcinoma. Update to Populations excluded from registrational clinical trials to describe patient populations excluded from hepatocellular carcinoma clinical trials. Updated precautions for patients with hepatic impairment.
4.8	Addition of a description of the safety profile in patients with hepatocellular carcinoma with prior sorafenib treatment. Relocation of text on immunogenicity to Section 5.1
5.1	Clinical Trials: Addition of clinical data to support the use of nivolumab as monotherapy in patients with hepatocellular carcinoma after prior sorafenib therapy (study CA209040) Relocation of text on immunogenicity from Section 4.8
5.2	Update to text on hepatic impairment.