DATA SHEET

1. PRODUCT NAME

WINGLORE ® (ipilimumab) 5mg per 1mL concentrate solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of concentrate contains 5 mg ipilimumab.

One 10 mL vial contains 50 mg of ipilimumab.

One 40 mL vial contains 200 mg of ipilimumab.

CAS: 477202-00-9. WINGLORE (ipilimumab (rch)) is a recombinant, fully human monoclonal antibody that binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

Excipient with known effect

Each ml of concentrate contains 0.1 mmol sodium, which is 2.30 mg sodium.

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

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

WINGLORE is a sterile, preservative free liquid for intravenous (IV) administration, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates.

WINGLORE has a pH of 7.0 and an osmolarity of 260-300mOsm/kg. It is supplied at a nominal concentration of 5 mg/mL ipilimumab in 50-mg and 200-mg single-use vials.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Melanoma

WINGLORE, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma in adults, 18 years of age or older.

WINGLORE, in combination with nivolumab, 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.

Renal Cell Carcinoma (RCC)

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

Non-Small Cell Lung Cancer (NSCLC)

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

Malignant Pleural Mesothelioma (MPM)

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

4.2. DOSE AND METHOD OF ADMINISTRATION

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

Liver function tests (LFTs) and thyroid function tests should be evaluated at baseline and before each dose of WINGLORE. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, should be assessed during treatment with WINGLORE (see Tables 1, 2 and 4.4 Special warnings and precautions for use).

WINGLORE MONOTHERAPY

Unresectable or metastatic melanoma

The recommended dose of WINGLORE is 3mg/kg administered intravenously over 30 minutes every 3 weeks for a total of 4 doses. Where there is any withholding of a dose, WINGLORE should be resumed at a dose of 3mg/kg every 3 weeks until administration of all 4 planned doses or 16 weeks from the first administration, whichever occurs earlier.

Assessments of tumour response to WINGLORE should be conducted only after completion of induction therapy. The planned induction course should not be discontinued because of the appearance of new lesions or growth of existing lesions.

Additional treatment with WINGLORE (re-induction with 4 doses) may be considered for patients who develop PD after prior CR or PR or after SD lasting longer than 3 months from the first tumour assessment. The recommended re-induction regimen of WINGLORE is 3 mg/kg administered IV over a 30-minute period every 3 weeks for a total of 4 doses as tolerated, regardless of the appearance of new lesions or growth of existing lesions.

WINGLORE IN COMBINATION WITH NIVOLUMAB

WINGLORE and nivolumab should be administered and monitored under the supervision of physicians experienced with the use of immunotherapy.

Please review the full prescribing information for nivolumab prior to initiation of WINGLORE in combination with nivolumab.

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

Unresectable or metastatic melanoma

Combination Phase:

The recommended dose of nivolumab in the combination phase is 1mg/kg administered intravenously over 30 minutes every 3 weeks for the first 4 doses in combination with WINGLORE 3mg/kg administered intravenously over 30 minutes. This should be followed by nivolumab monotherapy therapy in the single-agent phase (see below).

Single-agent Phase:

The recommended dose of nivolumab in the single-agent phase is administered intravenously over 30 minutes is 3 mg/kg every every 2 weeks or 240 mg every 2 weeks or 480 mg every 4 weeks. Following

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

Treatment with nivolumab 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 over30 minutes every 3 weeks for the first 4 doses in combination with 1 mg/kg WINGLORE administered intravenously over 30 minutes.

Single-agent Phase:
The recommended dose of nivolumab in the single agent phase administered intravenously over30 minutes is 3 mg/kg every 2 weeks or 240 mg every 2 weeks or 480 mg every 4 weeks. Following the last dose of the combination of nivolumab and ipilimumab, the first dose of nivolumab monotherapy should be administered after 3 weeks when using 3 mg/kg or 240 mg or 6 weeks when using 480 mg.

Treatment with nivolumab 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.

NSCLC

The recommended dose is 360 mg nivolumab administered as an intravenous infusion over 30 minutes every 3 weeks in combination with 1 mg/kg WINGLORE administered as an intravenous infusion over 30 minutes every 6 weeks, and platinum chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab administered as an intravenous infusion every 3 weeks in combination with 1 mg/kg WINGLORE every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

MPM

The recommended dose of nivolumab administered as an intravenous infusion over 30 minutes is 3 mg/kg every 2 weeks or 360 mg every 3 weeks in combination with 1 mg/kg WINGLORE administered as an intravenous infusion over 30 minutes every 6 weeks. Treatment should be continued until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.

Recommended treatment modifications

Ipilimumab monotherapy

Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of WINGLORE therapy and institution of systemic high-dose corticosteroid. In some cases, addition of other immunosuppressive therapy may be considered (see 4.4 Special warnings and precautions for use). Dose reduction is not recommended.

WINGLORE should be permanently discontinued in patients who:

- experience severe or life-threatening adverse reactions (see Table 1).
- experience adverse events (Grade 2 protracted, Grade 3 or Grade 4) that are not responsive to corticosteroids and/or require additional immunosuppressive therapy such as TNF-alpha inhibitors.

WINGLORE should be discontinued in patients who are unable to complete a full course of WINGLORE (4 doses) within 16 weeks from administration of first dose. Any future re-induction in such patients should not be undertaken if they experienced an adverse event fulfilling the criteria for permanent discontinuation described above.

Guidelines for permanent discontinuation or withholding of WINGLORE as monotherapy doses are described in Table 1 and Table 2. Detailed guidelines for the management of immune related adverse reactions are described in 4.4 Special warnings and precautions for use. Not adhering to the dose withholding and discontinuation guidelines may increase the risk of severe adverse events.

Permanent discontinuation of WINGLORE as monotherapy

Table 1: When to Permanently Discontinue WINGLORE as monotherapy

Permanently discontinue WINGLORE in patients with the following adverse reactions. Management of these adverse reactions may also require systemic high-dose corticosteroid therapy if demonstrated or suspected to be immune-related. See 4.4 Special warnings and precautions for use for detailed management guidelines.	
Severe or Life-Threatening Adverse Reactions	**NCI-CTCAE v4 Grade[a]**
Gastrointestinal:	
Severe symptoms (colitis with abdominal pain, fever, ileus, or peritoneal signs, increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal haemorrhage, gastrointestinal perforation	Grade 3 or 4 diarrhoea or colitis
Hepatic:	
Severe elevations in AST, ALT, or total bilirubin or symptoms of hepatotoxicity	Grade 3 or 4 elevation in AST, ALT or total bilirubin
Skin:	
Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis), rash complicated by full thickness dermal ulceration, or severe widespread pruritus interfering with activities of daily living or requiring medical intervention, or necrotic, bullous, or haemorrhagic manifestations.	Grade 4 rash or Grade 3 pruritus
Neurologic:	
New onset or worsening severe motor or sensory neuropathy, Guillain-Barré syndrome, myasthenia gravis	Grade 3 or 4 motor or sensory neuropathy
Other organ systems[b]:	
Severe immune-related reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis).	≥ Grade 3 immune-related reactions[c]
Immune-related ocular disease that is unresponsive to topical immunosuppressive therapy	≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy
Adverse reactions that are not responsive to corticosteroids and/or require additional immunosuppressive therapy such as TNF-alpha inhibitors.	Grade 2 protracted, Grade 3 or Grade 4 adverse reactions of any kind

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

[b] Any other organ system adverse reactions that are demonstrated or suspected to be immune-related should be graded according to CTCAE. Decision whether to discontinue WINGLORE should be based on severity.

[c] Patients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy may remain on therapy.

Withholding WINGLORE monotherapy dose

Withhold WINGLORE monotherapy dose in patients with the following immune-related adverse reactions described in Table 2.

WINGLORE monotherapy should be administered 3-weekly either for all 4 doses OR be completed within 16 weeks from the first dose, whichever occurs earlier. Detailed guidelines for the management of immune related adverse reactions are described in 4.4 Special warnings and precautions for use. Not adhering to the dose withholding guidelines may increase the risk of severe adverse events.

Table 2: When to Withhold Dose of WINGLORE as monotherapy

Withhold WINGLORE dose[a] in patients with the following immune-related adverse reactions. See 4.4 Special warnings and precautions for use for detailed management guidelines.	
Mild to Moderate Adverse Reactions	**Action**
Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs **Hepatic:** Grade 2[b] elevation in AST, ALT, or total bilirubin **Skin:** Moderate to severe (Grade 3)[b] skin rash or widespread/intense pruritus regardless of etiology **Endocrine:** Severe adverse reactions in the endocrine glands, such as hypophysitis and thyroiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy **Neurological:** Moderate (Grade 2) [b] unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days) **Other moderate adverse reactions**[c]	1. Withhold WINGLORE dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline) and management with corticosteroids is complete. 2. If resolution occurs , resume therapy[d] . 3. If resolution has not occurred , continue to withhold doses until resolution then resume treatment[d]. 4. Discontinue WINGLORE if resolution to Grade 1 or Grade 0 (or baseline) does not occur.

[a] No dose reduction of WINGLORE is recommended.

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

[c] Any other organ system adverse reactions that are considered immune-related should be graded according to CTCAE. The decision whether to withhold a dose of WINGLORE should be based on severity.

[d] Until administration of all 4 doses or 16 weeks from first dose, whichever occurs earlier.

Ipilimumab in combination with nivolumab

When WINGLORE is administered in combination with nivolumab, if either agent is withheld, the other agent should also be withheld. See Table 3. Detailed guidelines for the management of immune related adverse reactions are described in Section 4.4 Special warnings and precautions for use.

Table 3: Recommended treatment modifications for WINGLORE in combination with nivolumab

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

Immune-related adverse reaction	Severity of Adverse Reaction[a]	Treatment modification
	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. Nivolumab should be continued in the presence of hormone replacement therapy[b] as long as no symptoms are present.
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment.
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete.
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s).
	Grade 4 rash Confirmed SJS/TEN	Permanently discontinue treatment.
Immune-related neurological adverse reactions	New onset moderate or severe neurologic signs or symptoms	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete.
	Immune-related encephalitis Immune-related myasthenic syndrome/myasthenia gravis	Permanently discontinue treatment.
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 WINGLORE in children below 18 years have not been established. No data are available. The use of WINGLORE in children or adolescents is not recommended until further data become available.

Elderly patients

No overall differences in safety or efficacy were reported between the elderly (≥ 65 years) and younger patients (< 65 years). No specific dose adjustment is necessary in this population.

Renal impairment

The safety and efficacy of WINGLORE have not been studied in patients with renal impairment. Based on population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild to moderate renal dysfunction (see 5.2 Pharmacokinetic properties).

Hepatic impairment

The safety and efficacy of WINGLORE have not been studied in patients with hepatic impairment. Based on the population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild hepatic impairment (see Pharmacokinetics). WINGLORE must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline (see 5.1 Pharmacodynamic properties, clinical trials)

METHOD OF ADMINISTRATION

WINGLORE (ipilimumab) solutions must not be administered as an IV push or bolus injection. A separate infusion line must be used for the infusion, and the line must be flushed with sterile sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose injection at the end of infusion.

WINGLORE should not be infused concomitantly in the same IV line with other medicinal products.

WINGLORE may be used for IV administration without dilution after transferring to an infusion container using an appropriate sterile syringe, or after diluting with sterile sodium chloride 9 mg/ml (0.9% solution) or 5% glucose injection solution to a concentration ranging from 4 mg/ml to 1 mg/ml. An in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm or 1.2 µm) must be used for IV administration. Care must be taken to ensure aseptic handling when preparing the infusion.

When WINGLORE is administered in combination with nivolumab, or with nivolumab and chemotherapy, nivolumab should be given first followed by WINGLORE and then chemotherapy on the same day Use separate infusion bags and filters for each infusion. Administer nivolumab first followed by WINGLORE, no earlier than 30 minutes after completion of the nivolumab infusion.

Determine the number of vials of WINGLORE needed.

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 WINGLORE concentrate may be needed to give the total dose for the patient. Each 10 ml vial of WINGLORE concentrate provides 50 mg of ipilimumab; each 40 ml vial provides 200 mg of ipilimumab.

The total ipilimumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg. The volume of WINGLORE concentrate to prepare the dose (ml) = the total dose in mg, divided by 5 (the WINGLORE concentrate strength is 5 mg/ml).

Allow the vials to stand at room temperature for approximately 5 minutes. Withdraw the required volume of ipilimumab solution (5 mg/ml) using an appropriate sterile syringe and transfer into a sterile, evacuated glass bottle or IV bag (PVC or non-PVC).

Ipilimumab solution is compatible with:

- Glass, polyvinyl chloride (PVC) and non-PVC bags.
- PVC IV extension/administration sets.
- Polyethersulfone (0.2 µm and 1.2 µm) and nylon (0.2 µm) in-line filters.

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

Prior to administration, the ipilimumab should be inspected visually for particulate matter and discolouration. The vial should be discarded if solution is cloudy, there is pronounced discolouration (solution may have pale yellow colour), or there is foreign particulate matter.

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

Immune-related adverse reactions

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

Early diagnosis and appropriate management are essential to minimise life-threatening complications. Patients should be monitored continuously, as an immune-related adverse reaction with WINGLORE monotherapy or WINGLORE in combination with nivolumab 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. Patients should be monitored for signs and symptoms suggestive of immune-mediated adverse reactions; appropriate investigations (e.g electrolytes, creatinine, liver and thyroid functions) should be evaluated at baseline and before each dose.

Clinicians should consider immune-related adverse reactions for all unexplained illnesses. Adequate evaluation should be performed to confirm aetiology or exclude other causes. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, liver function test (LFT) elevations, rash, and endocrinopathy must be considered inflammatory and WINGLORE-related.

Based on the severity of the adverse reaction, interruption or permanent discontinuation of WINGLORE monotherapy or WINGLORE in combination with nivolumab and use of systemic corticosteroids (with or without additional immunosuppressive therapy) may be required (see Section 4.2 Dose and method of administration).

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.

WINGLORE monotherapy or WINGLORE in combination with nivolumab 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.

Immune-related gastrointestinal reactions/colitis

Ipilimumab monotherapy
WINGLORE is associated with serious immune-related gastrointestinal reactions. Fatalities due to gastrointestinal perforation have been reported in clinical trials (see 4.8 Undesirable effects).

In patients who received WINGLORE 3 mg/kg monotherapy in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20, see 5.1 Pharmacodynamic properties, Clinical Trials), the median time to onset of severe or fatal (Grade 3-5) immune-related gastrointestinal reactions was 8 weeks (range 5 to 13 weeks) from the start of treatment. With protocol-specified management guidelines, resolution (defined as improvement to mild [Grade 1] or less or to the severity at baseline) occurred in most cases (90%), with a median time from onset to resolution of 4 weeks (range 0.6 to 22 weeks).

Patients must be carefully monitored for gastrointestinal signs and symptoms that may be indicative of immune-related colitis or gastrointestinal perforation. Clinical presentation may include diarrhoea, increased frequency of bowel movements, abdominal pain, or haematochezia, with or without fever. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic and neutrophilic infiltration. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Stool infections workup (including CMV, other viral aetiology, culture, Clostridium difficile, ova, and parasite) should be performed upon presentation of diarrhoea or colitis to exclude infectious or other alternate aetiologies.

Management recommendations for diarrhoea or colitis are based on severity of symptoms (per National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v4] severity grading classification). Patients with mild to moderate (Grade 1 or 2) diarrhoea (an increase of up to 6 stools per day) or suspected mild to moderate colitis (eg abdominal pain or blood in stools) may remain on WINGLORE therapy. Symptomatic treatment (eg loperamide, fluid replacement) and close monitoring are advised. If mild to moderate symptoms recur or persist for 5-7 days, the scheduled dose of WINGLORE should be withheld, and corticosteroid therapy (eg prednisone 1 mg/kg orally once daily or equivalent) should be initiated. If resolution to Grades 0-1 or return to baseline occurs, WINGLORE may be resumed (see 4.2 Dose and method of administration).

WINGLORE must be permanently discontinued in patients with severe (Grade 3 or 4) diarrhoea or colitis (see 4.2 Dose and method of administration), and high-dose IV corticosteroid therapy should be initiated immediately (in clinical trials, methylprednisolone 2 mg/kg/day has been used). Once diarrhoea and other symptoms are controlled, corticosteroid taper should occur over a period of at least 1 month. In clinical trials, rapid tapering (over periods < 1 month) resulted in recurrence of diarrhoea or colitis in some patients. Patients must be evaluated for evidence of gastrointestinal perforation or peritonitis.

The experience from clinical trials on the management of corticosteroid-refractory diarrhoea or colitis is limited. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded (including CMV infection/reactivation evaluated with viral PCR on biopsy, and other viral, bacterial, and parasitic aetiology). In clinical trials, a single dose of infliximab 5 mg/kg was added unless contraindicated. Infliximab must not be used if gastrointestinal perforation or sepsis is suspected. Refer to the Product Information for infliximab.

Ipilimumab in combination with nivolumab
Severe diarrhoea or colitis has been observed with WINGLORE in combination with nivolumab. 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, WINGLORE in combination with nivolumab, 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 WINGLORE in combination with nivolumab, permanently discontinue both agents and follow the management guideline for Grade 4 diarrhoea or colitis above.

For Grade 2 diarrhoea or colitis, WINGLORE in combination with nivolumab, 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, WINGLORE in combination with nivolumab, 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 WINGLORE in combination with nivolumab, 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 pneumonitis

Ipilimumab in combination with nivolumab
Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with WINGLORE in combination with nivolumab.

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, WINGLORE in combination with nivolumab, 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, WINGLORE in combination with nivolumab, should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, WINGLORE in combination with nivolumab, 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 WINGLORE in combination with nivolumab, must be permanently discontinued.

Immune-related hepatitis

Ipilimumab monotherapy
WINGLORE is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in clinical trials of WINGLORE (see 4.8 Undesirable effects).

In patients who received WINGLORE 3 mg/kg monotherapy in MDX010-20, time to onset of moderate to severe or fatal (Grade 2-5) immune-related hepatotoxicity ranged from 3 to 9 weeks from the start of treatment. With protocol-specified management guidelines, time to resolution ranged from 0.7 to 2 weeks.

Hepatic transaminase and bilirubin must be evaluated before each dose of WINGLORE as early laboratory changes may be indicative of emerging immune-related hepatitis (see 4.2 Dose and method of administration). Elevations in LFTs may develop in the absence of clinical symptoms. Increases in AST and ALT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, tumour progression, or concomitant medications and monitored until resolution. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

For patients with Grade 2 transaminase or total bilirubin, the scheduled dose of WINGLORE should be withheld, and LFTs must be monitored until resolution. Upon improvement, WINGLORE therapy may be resumed (see 4.2 Dose and method of administration).

For patients with Grade 3 or 4 transaminase or bilirubin elevation treatment must be permanently discontinued (see 4.2 Dose and method of administration), and systemic high-dose IV corticosteroid therapy (eg, methylprednisolone 2 mg/kg daily or equivalent) should be initiated immediately. In such patients, LFTs must be monitored until normalization. Once symptoms have resolved and LFTs show sustained improvement or return to baseline, corticosteroid taper should occur over a period of at least 1 month. Elevations in LFTs during taper may be managed with an increase in the dose of corticosteroid and a slower taper.

For patients with significant LFT elevations that are refractory to corticosteroid therapy, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered. In clinical trials, mycophenolate mofetil was used in patients without response to corticosteroid therapy, or who had an LFT elevation during corticosteroid tapering that was not responsive to an increase in the dose of corticosteroids. Refer to the Product Information for mycophenolate mofetil.

Ipilimumab in combination with nivolumab
Severe hepatitis has been observed with WINGLORE in combination with nivolumab. 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, WINGLORE in combination with nivolumab, 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, WINGLORE in combination with nivolumab 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 WINGLORE in combination with nivolumab, 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 WINGLORE in combination with nivolumab must be permanently discontinued.

Immune-related skin adverse reactions

Caution should be used when considering the use of WINGLORE monotherapy or WINGLORE in combination with nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune stimulatory therapy.

Ipilimumab monotherapy
WINGLORE is associated with serious skin adverse reactions that may be immune-related. Steven Johnson Syndrome (SJS) or fatal toxic epidermal necrolysis (TENS) have been reported in clinical trials (see 4.8 Undesirable effects).

WINGLORE-induced rash and pruritus were predominantly mild or moderate (Grade 1 or 2) and responsive to symptomatic therapy. In patients who received WINGLORE 3 mg/kg monotherapy in MDX010-20, the median time to onset of moderate to severe or fatal (Grade 2-5) skin adverse reactions was 3 weeks (range 0.9-16 weeks) from start of treatment. With protocol-specified management guidelines, resolution occurred in most cases (87%), with a median time from onset to resolution of 5 weeks (range 0.6 to 29 weeks).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been very rarely reported with WINGLORE in post-marketing use.

WINGLORE-induced rash and pruritus should be managed based on severity. Patients with a mild to moderate (Grade 1 or 2) skin adverse reaction may remain on WINGLORE therapy with symptomatic treatment (eg antihistamines). For mild to moderate rash or pruritus that persists for 1 to 2 weeks and does not improve with topical corticosteroids, oral corticosteroid therapy should be initiated (eg prednisone 1 mg/kg once daily or equivalent).

For patients with a severe (Grade 3) skin adverse reaction, the scheduled dose of WINGLORE should be withheld. If initial symptoms improve to mild (Grade 1) or resolve, WINGLORE therapy may be resumed (see 4.2 Dose and method of administration).

WINGLORE must be permanently discontinued in patients with a very severe (Grade 4) rash (including SJS and TENS) or severe (Grade 3) pruritus (see 4.2 Dose and method of administration), and systemic high-dose IV corticosteroid therapy (eg methylprednisolone 2 mg/kg/day) should be initiated immediately. Once rash or pruritus is controlled, corticosteroid taper should occur over a period of at least 1 month.

Ipilimumab in combination with nivolumab
Patients should be monitored for rash. Severe rash has been observed WINGLORE in combination with nivolumab and less commonly with nivolumab monotherapy. WINGLORE in combination with nivolumab 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, WINGLORE in combination with nivolumab should be withheld and the patient referred for specialist assessment and treatment. If the patient has confirmed SJS or TEN, permanent discontinuation of WINGLORE in combination with nivolumab is recommended.

Immune-related neurological adverse reactions

Ipilimumab monotherapy
WINGLORE is associated with serious immune-related neurological adverse reactions. In clinical trials, fatal Guillain-Barré syndrome has been reported. Myasthenia gravis-like symptoms have also been reported (see 4.8 Undesirable effects). Patients may present with muscle weakness. Sensory neuropathy may also occur.

Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting > 4 days must be evaluated, and non-inflammatory causes such as disease progression, infections, metabolic syndromes and concomitant medications should be excluded. For patients with moderate (Grade 2) neuropathy (motor with or without sensory) likely related to WINGLORE, the scheduled dose should be withheld. If neurologic symptoms resolve to baseline, WINGLORE may be resumed (see 4.2 Dose and method of administration).

WINGLORE must be permanently discontinued in patients with severe (Grade 3 or 4) sensory neuropathy suspected to be related to WINGLORE (see 4.2 Dose and method of administration).

Patients must be treated according to institutional guidelines for management of sensory neuropathy, and intravenous corticosteroids (eg methylprednisolone 2 mg/kg/day) should be initiated immediately.

Progressive signs of motor neuropathy must be considered immune-related and managed accordingly. WINGLORE must be permanently discontinued in patients with severe (Grade 3 or 4) motor neuropathy regardless of causality (see 4.2 Dose and method of administration).

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

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.

Immune-related nephritis and renal dysfunction

Ipilimumab in combination with nivolumab
Severe nephritis and renal dysfunction have been observed with WINGLORE in combination with nivolumab. 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, WINGLORE in combination with nivolumab 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, WINGLORE in combination with nivolumab, should be withheld and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, WINGLORE in combination with nivolumab, 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 WINGLORE in combination with nivolumab, must be permanently discontinued.

Immune-related endocrinopathy

Ipilimumab monotherapy
WINGLORE can cause inflammation of the endocrine system organs which may be irreversible and require long-term hormone replacement therapy. These events may manifest as hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism (see 4.8 Undesirable effects) and patients may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioral changes, electrolyte disturbances, and hypotension. Adrenal crisis as a cause of the patient's symptoms must be excluded. Clinical experience with WINGLORE-associated endocrinopathy is limited.

In patients who received WINGLORE 3 mg/kg monotherapy in MDX010-20, time to onset of moderate to very severe (Grade 2-4) immune-related endocrinopathy ranged from 7 to nearly 20 weeks from the start of treatment. Immune-related endocrinopathy observed in clinical trials was generally controlled with immunosuppressive therapy and hormone replacement therapy.

If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, immediate administration of IV corticosteroids with mineralocorticoid activity is recommended, and the patient must be evaluated for presence of sepsis or infections.

If there are signs of adrenal insufficiency but the patient is not in adrenal crisis, further investigations should be considered including laboratory and imaging assessment. Evaluation of laboratory results to assess endocrine function may be performed before corticosteroid therapy is initiated. If pituitary imaging or laboratory tests of endocrine function are abnormal, a short course of high-dose corticosteroid therapy (eg dexamethasone 4 mg every 6 hrs or equivalent) is recommended to treat the inflammation of the affected gland, and the scheduled dose of WINGLORE should be withheld (see DOSAGE AND ADMINISTRATION). It is currently unknown if the corticosteroid treatment reverses the gland dysfunction. Appropriate hormone replacement should also be initiated. Long-term hormone replacement therapy may be necessary.

Once symptoms or laboratory abnormalities are controlled and overall patient improvement is evident, treatment with WINGLORE may be resumed, and corticosteroid taper should occur over a period of at least 1 month.

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

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, WINGLORE in combination with nivolumab, should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, WINGLORE in combination with nivolumab, 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, WINGLORE in combination with nivolumab, may be resumed (after corticosteroid taper). Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised WINGLORE in combination with nivolumab should be permanently discontinued for life-threatening (Grade 4) hypothyroidism or hyperthyroidism.

For symptomatic Grade 2 adrenal insufficiency, WINGLORE in combination with nivolumab, should be withheld, and physiologic corticosteroid replacement should be initiated as needed. WINGLORE in combination with nivolumab 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, WINGLORE in combination with nivolumab 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, WINGLORE in combination with nivolumab may be resumed (after corticosteroid taper). WINGLORE in combination with nivolumab 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, WINGLORE in combination with nivolumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure

appropriate insulin replacement is utilised. WINGLORE in combination with nivolumab should be permanently discontinued for life-threatening (Grade 4) diabetes.

Other immune-related adverse reactions

Ipilimumab monotherapy
The following additional adverse reactions suspected to be immune-related have been reported in patients treated with WINGLORE 3 mg/kg monotherapy in MDX010-20: uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, hemolytic anaemia, amylase elevations, multi-organ failure, and pneumonitis have been reported in patients treated with WINGLORE 3 mg/kg + gp100 peptide vaccine in MDX010-20. Cases of Vogt-Koyanagi-Harada syndrome and serous retinal detachment have been reported post-marketing (see 4.8 Undesirable effects).

For WINGLORE-related uveitis, iritis, serous retinal detachment or episcleritis, topical corticosteroid eye drops should be considered as medically indicated. Transient vision loss has been reported in patients with ipilimumab-related ocular inflammations.

Fatal or serious graft versus- host disease (GVHD) can occur in patients who receive a CTLA-4 receptor blocking antibody either before or after allogeneic haematopoietic stem cell transplantation (HSCT). Follow patients closely for evidence of GVHD and intervene promptly. Consider the benefit versus risks of treatment with a CTLA-4 receptor blocking antibody after allogeneic HSCT.

If severe (Grade 3 or 4), these reactions may require immediate high-dose corticosteroid therapy and discontinuation of WINGLORE (see 4.2 Dose and method of administration). For WINGLORE-related uveitis, iritis, or episcleritis, topical corticosteroid eye drops should be considered as medically indicated.

Solid organ transplant rejection has been reported in the post-marketing setting in patients who receive treatment with a CTLA-4 receptor blocking antibody. Treatment with ipilimumab may increase the risk of rejection in solid organ transplant recipients (see Section 4.8 Adverse effects – Postmarketing experience).

Histiocytosis haematophagic has been reported in relation to ipilimumab therapy. The adverse reaction mostly responded well to treatment with corticosteroids. In most reported cases prior or concurrent therapy with a PD-1 or PD-L1 inhibitor has occurred (see Section 4.8 Undesirable effects – Postmarketing experience).

Ipilimumab in combination with nivolumab
Other clinically significant immune-related adverse reactions, including some with fatal outcome, have been observed across clinical trials of WINGLORE in combination with nivolumab investigating various doses across tumour types (see Section 4.8 Adverse effects). These include rare cases of myotoxicity. Cases of Vogt-Koyanagi-Harada syndrome and serous retinal detachment have been reported post-marketing (see Section 4.8 Undesirable effects). Transient vision loss has been reported in patients with ipilimumab-related ocular inflammations. Refer to the Product Information for nivolumab.

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, WINGLORE in combination with nivolumab, should be withheld and corticosteroids administered. Upon improvement, WINGLORE in combination with nivolumab, maybe resumed after corticosteroid taper. WINGLORE in combination with nivolumab, 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 WINGLORE in combination with nivolumab. 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, WINGLORE in combination with

nivolumab should be withheld or discontinued (see Section 4.2 Dose and method of administration), and appropriate treatment instituted.

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

Infusion reaction

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

WINGLORE in combination with nivolumab

Review the full prescribing information for nivolumab prior to initiation of WINGLORE in combination with nivolumab. Both agents are associated with immune-related adverse reactions and may require immunosuppression. In clinical trials, immune-related adverse reactions described in Section 4.4, Special warnings and precautions, have occurred at higher frequencies when nivolumab was administered in combination with WINGLORE compared with nivolumabas 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 WINGLORE in combination with nivolumab should be monitored for immune-related adverse reactions clinically and with appropriate investigations prior to each dose during the combination phase.

Populations excluded from registrational clinical trials

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

Table 4: Populations excluded from registrational clinical trials

Indication	Excluded populations
Melanoma	• Patients with ocular melanoma • Patients with primary CNS melanoma • Patients with active brain metastases
RCC	• Patients with any history of or concurrent brain metastases • Patients with active autoimmune disease or medical conditions requiring systemic immunosuppression
Previously untreated NSCLC	• Patients with sensitising EGFR mutations or ALK translocations
MPM	• Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, or interstitial lung disease

Patients with autoimmune disease

Patients with a history of autoimmune disease (other than vitiligo and adequately controlled endocrine deficiencies such as hypothyroidism), including those who require systemic immunosuppressive therapy for pre-existing active autoimmune disease or for organ transplantation graft maintenance, were not evaluated in clinical studies. Ipilimumab is a T-cell potentiator that enables the immune response (see 5.1 Pharmacodynamic properties) and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection.

WINGLORE should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening. In other patients with a history of autoimmune disease, WINGLORE should be administered with caution after careful consideration of the potential risk-benefit on an individual basis.

Concurrent administration with vemurafenib

A Phase 1 study was conducted to investigate the safety of the concurrent administration of vemurafenib and WINGLORE in patients with BRAFV600-mutated metastatic melanoma not previously treated with CTLA-4 blocking antibodies or with BRAF or MEK inhibitors. Following a 1 month lead-in with monotherapy vemurafenib (960 mg or 720 mg twice daily), patients received combination therapy with WINGLORE (3 mg/kg IV every 3 weeks) and vemurafenib administered concurrently. Asymptomatic Grade 3 LFT elevations (ALT/AST with or without total bilirubin) were reported in 6 of 10 patients treated with the combination regimen. All were reversible with either interruption or permanent discontinuation of the drugs, and/or treatment with corticosteroids. Based on these data, the concurrent administration of WINGLORE and vemurafenib is not recommended outside of a clinical trial. These results do not impact the currently approved use of WINGLORE as monotherapy.

Patient counselling information

Patients should be advised to report immediately any signs or symptoms suggestive of immune-related events as described in Section 4.4 Special warnings and precautions. 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.

Hepatic impairment

The safety and efficacy of WINGLORE have not been studied in patients with hepatic impairment. In the population pharmacokinetic analysis of data from clinical studies in patients with metastatic melanoma, pre-existing mild hepatic impairment did not influence the clearance of ipilimumab. No specific dose adjustment is necessary in patients with mild hepatic impairment (see 5.2 Pharmacokinetic properties). WINGLORE must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline (see 5.1 Pharmacodynamic properties, Clinical Trials).

Renal impairment

The safety and efficacy of WINGLORE have not been studied in patients with renal impairment. Based on population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild to moderate renal dysfunction (see 5.2 Pharmacokinetic properties).

Paediatric use

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

Patients on controlled sodium diet

Each mL of this medicinal product contains 0.1 mmol (or 2.3 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Ipilimumab is a human monoclonal antibody that is not metabolized by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes. In a drug-interaction study, ipilimumab did not have a significant effect on the pharmacokinetics of substrates of CYP1A2, CYP2E1, CYP2C8, and CYP3A4 when coadministered with substrates of these CYP isozymes (dacarbazine or paclitaxel/carboplatin).

Other forms of interaction

Corticosteroids

The use of systemic corticosteroids at baseline, before starting WINGLORE, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of WINGLORE. However, systemic corticosteroids or other immunosuppressants can be used after starting WINGLORE to treat immune-related adverse reactions. The use of systemic corticosteroids after starting WINGLORE treatment does not appear to impair the efficacy of WINGLORE.

Anticoagulants

The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with WINGLORE, patients who require concomitant therapy should be monitored closely.

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy

WINGLORE is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk.

There are no data on the use of ipilimumab in pregnant women. It is not known whether ipilimumab can cause foetal harm when administered to a pregnant woman.

The effects of ipilimumab on prenatal and postnatal development were investigated in a study in cynomolgus monkeys. Pregnant monkeys received ipilimumab every 3 weeks from the onset of

organogenesis in the first trimester through delivery, at exposure (AUC) levels either 3 or 7 times higher than those associated with the clinical dose of 3mg/kg of ipilimumab. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, both ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and infant mortality relative to control animals; these findings were dose-dependent. Additionally, visceral abnormalities were identified in the urogenital system of 2 infants of the 30 mg/kg group. One female infant had unilateral renal agenesis of the left kidney and ureter, and one male infant had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal oedema. A no adverse effect level was not identified. Due to the low incidences, the relationship of these malformations to treatment is unclear.

Ipilimumab was detected in the serum of monkey infants at similar levels to their mothers post-partum, likely through in utero exposure. Very low levels of ipilimumab were detected in milk. Human IgG1 is known to cross the placental barrier; therefore, ipilimumab has the potential to be transmitted from the mother to the developing foetus.

Breast-feeding

Ipilimumab has been shown to be present at very low levels in milk from cynomolgus monkeys treated during pregnancy. It is not known whether ipilimumab is secreted in breast milk; however, because human IgG1 is known to be secreted in human breast milk, there is potential for infant exposure to ipilimumab via nursing. A risk to the newborns/infants cannot be excluded. Women who are taking WINGLORE should not breast-feed.

Fertility

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

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Because of potential adverse reactions such as fatigue (see 4.8 Undesirable effects), patients should be advised to use caution when driving or operating machinery until they are reasonably certain that WINGLORE does not adversely affect them.

4.8. UNDESIRABLE EFFECTS

Ipilimumab monotherapy

WINGLORE has been administered to approximately 10,000 patients in a clinical program evaluating its use with various doses and tumor types. Unless otherwise specified, the data described below reflect exposure to WINGLORE monotherapy at 3 mg/kg (n= 131) in previously treated patients with advanced melanoma from a Phase 3 study (MDX010-20. See 5.1 Pharmacodynamic properties, Clinical Trials). Patients received a median of 4 doses (range 1-4).

WINGLORE is most commonly associated with adverse reactions resulting from increased or excessive immune activity (see 4.4 Special warnings and precautions for use for the management of immune-related adverse reactions). Most of these adverse reactions, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of WINGLORE.

The safety profile of WINGLORE 3mg/kg in chemotherapy-naïve patients pooled across Phase 2 and 3 clinical trials (N=75; treated) and in treatment-naïve patients in two retrospective observational studies (N= 273 and N= 157) was similar to that in previously-treated advanced melanoma.

Adverse Events reported in study MDX010-20

In patients who received 3 mg/kg WINGLORE monotherapy in MDX010-20, the most frequently reported adverse events (≥ 10% of patients) were fatigue, diarrhoea, pruritus, rash, decreased, appetite,

nausea, vomiting, abdominal pain, cough, headache, pyrexia, and insomnia (Table 5). The majority of adverse events were mild to moderate (Grade 1 or 2). WINGLORE therapy was discontinued for adverse reactions in 10% of patients.

Adverse events, regardless of causality, reported in ≥1% of patients treated with either WINGLORE-containing regimen in MDX010-20 are presented in Table 6. This table includes adverse events that occurred at a greater incidence in a WINGLORE group than in the gp100 group (before rounding).

These adverse events are presented by system organ class and by frequency.

Table 5: Adverse Events Reported in ≥1% of patients treated with WINGLORE monotherapy

	Percentage (%) of Patients[a]		
System Organ Class/Preferred Term	WINGLORE3 mg/kg n=131	WINGLORE3mg/kg +gp100[b] n=380	gp100[b] n=132
Gastrointestinal Disorders			
Diarrhea	33	38	20
Vomiting	24	20	22
Abdominal pain	23	23	23
Colitis	8	6	2
Gastrointestinal haemorrhage	4	6	2
Stomatitis	2	0	1
Dysphagia	2	1	2
Retching	2	1	0
General Disorders and Administration Site Conditions			
Fatigue	42	37	31
Pyrexia	13	21	18
Chills	7	6	5
Injection site reaction	4	50	38
Chest pain	1	2	2
Vaccination site reaction	1	4	4
Skin and Subcutaneous Tissue Disorders			
Pruritus	33	23	11
Rash	30	25	8
Erythema	8	7	5
Vitiligo	3	4	2
Alopecia	2	3	2
Dry skin	2	3	2
Night Sweats	2	4	3
Dermatitis	2	2	1
Urticaria	1	3	1
Eczema	1	2	0
Skin hypopigmentation	0	1	0
Metabolism and Nutrition Disorders			
Decreased appetite	27	23	22
Hypokalaemia	6	3	2
Hyperglycaemia	4	2	0
Hypoalbuminaemia	3	1	3
Hyponatraemia	2	2	2

System Organ Class/Preferred Term	Percentage (%) of Patients[a]		
	WINGLORE3 mg/kg n=131	WINGLORE3mg/kg +gp100[b] n=380	gp100[b] n=132
Musculoskeletal and Connective Tissue Disorders			
Myalgia	6	7	3
Muscle spasms	2	3	3
Infections and Infestations			
Upper respiratory tract infection	8	5	5
Urinary tract infection	7	3	5
Sepsis	3	1	0
Lower respiratory tract infection	2	3	1
Gastroenteritis	1	2	0
Infectious hepatitis	2	0	0
Oral candidiasis	1	2	2
Cellulitis	0	2	2
Respiratory, Thoracic and Mediastinal Disorders			
Cough	17	16	14
Oropharyngeal pain	2	2	2
Wheezing	2	1	0
Nasal disorder	1	3	1
Sinus congestion	0	1	0
Nervous System Disorders			
Headache	15	18	14
Lethargy	4	3	2
Tremor	2	1	0
Brain oedema	1	2	1
Cranial neuropathy	1	1	0
Peripheral neuropathy	1	1	1
Aphasia	0	1	1
Vascular Disorders			
Hypotension	8	3	5
Flushing	5	3	1
Hypertension	3	1	0
Haematoma	2	1	2
Venous thrombosis	2	2	1
Thrombosis	1	1	0
Haemorrhage	0	6	1
Lymphoedema	0	3	2
Psychiatric Disorders			
Insomnia	12	9	11
Depression	5	5	5
Anxiety	4	8	8
Decreased libido	2	<1	0
Blood and Lymphatic System Disorders			
Lymphadenopathy	2	1	2
Eosinophilia	2	<1	0
Neutropenia	2	1	2
Thrombocytopenia	1	2	2

System Organ Class/Preferred Term	Percentage (%) of Patients[a]		
	WINGLORE3 mg/kg n=131	WINGLORE3mg/kg +gp100[b] n=380	gp100[b] n=132
Investigations			
Increased blood creatinine	4	1	2
Increased blood bilirubin	2	<1	2
Decreased blood corticotrophin	2	0	0
Increased lipase	1	2	0
Eye Disorders			
Blurred vision	4	4	4
Conjunctivitis	2	2	2
Uveitis	2	<1	1
Eye pain	1	1	1
Dry eye	0	1	1
Hepatobiliary Disorders			
Abnormal hepatic function	5	3	5
Hepatic failure	2	1	0
Hepatomegaly	2	1	0
Jaundice	0	1	0
Endocrine Disorders			
Hypopituitarism (including hypophysitis)	4	1	0
Hypothyroidism	4	2	2
Adrenal insufficiency	2	1	0
Hyperthyroidism	2	1	0
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)			
Tumour pain	5	4	4
Cancer pain	2	1	1
Cardiac Disorders			
Arrhythmia	3	5	5
Atrial fibrillation	2	1	2
Cardiac failure	2	1	0
Injury, Poisoning and Procedural Complications			
Contusion	2	1	2
Excoriation	2	1	2
Renal and Urinary Disorders			
Renal failure	3	1	2
Haematuria	2	1	2
Immune System Disorders			
Contrast media allergy	2	0	0
Seasonal allergy	2	<1	0

a Incidences presented in this table are based on reports of adverse events regardless of causality.

b Combination of WINGLORE + gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control (see Section 4.2 Dose and method of administration for the recommended dosage).

Immune-Related Adverse Reactions in MDX010-20 (Table 6).

Table 6: Immune-Related Adverse Reactions in MDX010-20 (Induction Phase)

	Percentage (%) of Patients		
	WINGLORE3 mg/kg n= 131	WINGLORE3 mg/kg +gp100[a] n= 380	Gp100 n=132
Any immune-related adverse reactions[b]			
Any Grade	**60**	57	32
Grade 3/4	**13**	10	3
Gastrointestinal			
Any Grade	**28**	31	14
Grade 3/4	**8**	5	1
Colitis	**5**	3	0
Diarrhoea	**5**	3	1
Gastrointestinal haemorrhage	**0**	< 1	0
Intestinal perforation	**0**	< 1	0
Large intestine perforation	**0**	1	0
Hepatic			
Any Grade	**3**	2	4
Grade 3/4	**0**	1	2
Abnormal hepatic function	**0**	0	2
Increased ALT	**0**	1	0
Increased AST	**0**	< 1	0
Abnormal liver function test	**0**	< 1	0
Hepatitis	**0**	< 1	0
Skin			
Any Grade	**42**	39	17
Grade 3/4	**1**	2	0
Rash	**1**	2	0
Dermatitis	**0**	< 1	0
Erythema	**0**	< 1	0
Leukocytoclastic vasculitis	**0**	< 1	0
Pruritus	**0**	< 1	0
Toxic epidermal necrolysis	**0**	< 1	0
Neurological			
Any Grade	**0**	1	0
Grade 3/4	**0**	< 1	0
Meningitis (aseptic)	**0**	< 1	0
Endocrine			
Any Grade	**8**	3	2
Grade 3/4	**4**	1	0
Hypopituitarism	**3**	1	0
Adrenal insufficiency	**0**	1	0
Hypogonadism	**0**	< 1	0
Hypothyroidism	**0**	< 1	0

	Percentage (%) of Patients		
	WINGLORE3 mg/kg n= 131	WINGLORE3 mg/kg +gp100[a] n= 380	Gp100 n=132
Decreased blood corticotrophin	**1**	0	0
Other organ systems			
Any Grade	**4**	3	2
Grade 3/4	**2**	1	1
Glomerulonephritis	**1**	0	0
Pneumonitis	**0**	< 1	0
Eosinophilia	**0**	< 1	0
Hemolytic anaemia	**0**	< 1	0
Increased lipase	**1**	1	0
Increased amylase	**0**	1	1

[a] Combination of WINGLORE + gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control (see Section 4.2 Dose and method of administration for the recommended dosage).

[b] Includes the following immune-related adverse reactions with fatal outcomes occurring in either WINGLORE-containing regimen at a frequency of <1%: gastrointestinal perforation, colitis, hepatic failure, toxic epidermal necrolysis (patient developed Stevens-Johnson syndrome which evolved into toxic epidermal necrolysis), Guillain-Barré syndrome, and multi-organ failure

Adverse reactions observed in Phase 2 studies in patients receiving 3 mg/kg of WINGLORE (n=111) were consistent with those in MDX010-20. Rates of immune-related adverse reactions in HLA-A2*0201 positive patients who received WINGLORE in MDX010-20 were similar to those observed in the overall clinical program.

Other Adverse Reactions reported in Ipilimumab Monotherapy Clinical Trials

In addition, the following adverse reactions were reported in other clinical studies. These additional adverse reactions occurred at a frequency of <1% unless otherwise noted: large intestinal ulcer, oesophagitis, ileus, Myasthenia gravis-like syndrome, erythema multiforme, blepharitis, psoriasis, paraneoplastic syndrome, lymphopenia (1%), leucopenia, thyroiditis, hypoparathyroidism, peripheral sensory neuropathy (2%), dizziness (2%), syncope, myoclonus, vitreous haemorrhage, reduced visual acuity, foreign body sensation in eyes, hot flush (1%), orthostatic hypotension, pulmonary oedema, allergic rhinitis, constipation (4%), gastroesophageal reflux disease (1%), gastrointestinal perforation, diverticulitis, gastric ulcer, proctitis, skin exfoliation, palmer-plantar erythrodysesthesia syndrome, amenorrhoea, asthenia (3%), pain (3%), weight decrease (4%), increased blood thyroid stimulating hormone, decreased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood testosterone, decreased blood gonadotophin and decreased thyroxine, cytokine release syndrome and hair colour changes.

Serious Adverse Reactions Reported in Other Ipilimumab Monotherapy Clinical Trials

The following serious adverse reactions were also reported in patients with advanced melanoma treated with WINGLORE in clinical studies (regardless of dose or regimen; N= 1498). Adverse reactions presented elsewhere in section 4.8 Undesirable effects are excluded.

Infections and infestations
Uncommon: septic shock
Rare: respiratory tract infection

Blood and lymphatic system disorders
Uncommon: anaemia
Rare: polycythemia

Immune System Disorders
Uncommon: infusion related reaction
Rare: hypersensitivity,sarcoidosis[a]
Very rare: anaphylactic reaction (shock)

Endocrine disorders
Rare: secondary adrenocortical insufficiency, hyperpituitarism, autoimmune thyroiditis

Metabolism and nutrition disorders
Common: dehydration
Uncommon: hypophosphatemia,
Rare: alkalosis, tumour lysis syndrome

Psychiatric disorders
Rare: confusional state, mental status change

Nervous system disorders
Uncommon: ataxia, dysarthria.
Rare: Guillain-Barré syndrome, meningism, autoimmune central neuropathy (encephalitis)[a]

Eye disorders
Rare: episcleritis, scleritis, iritis, eye oedema, ocular myositis[a]
Vary Rare: Vogt-Koyanagi-Harada syndrome

Ear and labyrinth disorders
Rare: neurosensory hypoacusis[a]

Cardiac disorders
Rare: myocarditis, cardiomyopathy, pericardial effusion (pericarditis)

Vascular disorders
Rare: angiopathy, peripheral ischemia, vasculitis, temporal arteritis, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders
Uncommon: lung infiltration,
Rare: dyspnoea, acute respiratory distress syndrome, respiratory failure

Gastrointestinal disorders
Uncommon: enterocolitis, nausea, pancreatitis (autoimmune), peritonitis (infectious), mucosal inflammation, stomatitis.

Hepatobiliary disorders
Uncommon: autoimmune hepatitis

Skin and subcutaneous tissue disorders
Uncommon: toxic epidermal necrolysis (including Stevens Johnson syndrome) [a,b,c]

Musculoskeletal and connective tissue disorders
Uncommon: arthralgia, musculoskeletal pain[d], arthritis
Rare: polymyalgia rheumatica, myositis[a], polymyositis[a]

Renal and urinary disorders
Uncommon: haematuria
Rare: autoimmune nephritis, proteinuria, renal tubular acidosis

General disorders and administration site conditions
Common: influenza-like illness (symptoms)
Uncommon: multi-organ failure, oedema
Rare: systemic inflammatory response syndrome

Investigations
Common: increased blood alkaline phosphatase
Uncommon: increased gamma-glutamyltransferase
Rare: abnormal blood prolactin

[a] Including fatal outcome
[b]. Additional information about these potentially inflammatory adverse reactions is provided in section 4.8 Undesirable effects. Data presented in those sections primarily reflect experience from a Phase 3 study, MDX010-20.
[c] Patient developed Stevens-Johnson syndrome which evolved into toxic epidermal necrolysis
[d] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain

Ipilimumab in combination with nivolumab

Melanoma

In the pooled dataset of ipilimumab 3mg/kg in combination with nivolumab 1mg/kg in melanoma (n=448, 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 ipilimumab 3mg/kg in combination with nivolumab 1mg/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 ipilimumab 1 mg/kg in combination with nivolumab 3 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 ipilimumab 1 mg/kg in combination with nivolumab 3 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 IV + ipilimumab 3 mg/kg IV Q3W).

Malignant Pleural Mesothelioma

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

Tabulated summary of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with ipilimumab 3mg/kg in combination with nivolumab 1mg/kg (n = 448) in melanoma, with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg (n = 547) in RCC and with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg (n = 300) in MPM are presented in Table 7. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). A summary of laboratory abnormalities that worsened from baseline is presented in Table 8.

Table 7: Adverse reactions with ipilimumab in combination with nivolumab in clinical trials

	Ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg in melanoma (n=448)	**Ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in RCC (n=547)**	**Ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in MPM (n=300)**
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	infusion-related reaction, hypersensitivity
Uncommon	Sarcoidosis		
Endocrine disorders			
Very common	Hypothyroidism	hypothyroidism, hyperthyroidism	hypothyroidism
Common	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis	adrenal insufficiency[b], hypophysitis[b], thyroiditis, diabetes mellitus[b]	hyperthyroidism, adrenal insufficiency, hypophysitis, hypopituitarism
Uncommon	diabetic ketoacidosis[b], diabetes mellitus[b]	diabetic ketoacidosis[b], hypopituitarism	thyroiditis
Metabolism and nutrition disorders			
Very common	decreased appetite	decreased appetite	
Common	Dehydration	Dehydration	decreased appetite
Uncommon		metabolic acidosis	
Hepatobiliary disorders			
Common	hepatitis[b]	hepatitis[b]	hepatitis
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]	encephalitis
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]	myocarditis
Vascular disorders			
Common	hypertension	Hypertension	
Respiratory, thoracic and mediastinal disorders			
Very Common	Dyspnoea		

Common	pneumonitis[a,b], pulmonary embolism[a],cough	pneumonitis, dyspnoea, pleural effusion, cough	pneumonitis
Uncommon	pleural effusion		
Gastrointestinal disorders			
Very common	colitis[a], diarrhoea, vomiting, nausea, abdominal pain	diarrhoea, vomiting, nausea	diarrhoea, nausea
Common	stomatitis, pancreatitis, constipation, dry mouth	colitis, stomatitis, pancreatitis, abdominal pain, constipation, dry mouth	constipation, colitis, pancreatitis
Uncommon	intestinal perforation[a], gastritis, duodenitis	Gastritis	
Skin and subcutaneous tissue disorders			
Very common	rash[d], pruritus	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, muscle spasm, muscular weakness	musculoskeletal pain, arthritis
Uncommon	spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis)[a,e], rhabdomyolysis[a,e]	polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis	myositis
Renal and urinary disorders			
Common	renal failure (including acute kidney injury)[a,b]	renal failure (including acute kidney injury)[b]	acute kidney injury
Uncommon	tubulointerstitial nephritis	tubulointerstitial nephritis	renal failure
General disorders and administration site conditions			
Very common	fatigue, pyrexia	fatigue, pyrexia	fatigue
Common	oedema (including peripheral oedema), pain	oedema (including peripheral oedema), pain, chest pain, chills	
Uncommon	chest pain		
Investigations[b]			
Common	weight decreased	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 8: Laboratory abnormalities with ipilimumab in combination with nivolumab in clinical trials

	Number (%) of Patients with Worsening Laboratory Test from Baseline								
	Ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg in melanoma (n=448)			Ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in RCC (n=547)			Ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in MPM (n=300)		
Test	**N[a]**	**Grades 1-4**	**Grades 3-4**	**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)	297	127 (42.8)	7 (2.4)
Thrombocytopenia	422	51 (12.1)	5 (1.2)	537	83 (15.5)	4 (0.7)	296	26 (8.8)	3 (1.0)
Leukopenia	426	60 (14.1)	2 (0.5)	537	79 (14.7)	3 (0.6)	297	24 (8.1)	3 (1.0)
Lymphopenia	421	173 (41.1)	28 (6.7)	534	191 (35.8)	27 (5.1)	296	128 (43.2)	25 (8.4)
Neutropenia	423	64 (15.1)	3 (0.7)	535	65 (12.1)	6 (1.1)	297	16 (5.4)	4 (1.3)
Increased alkaline phosphatase	418	160 (38.3)	18 (4.3)	538	154 (28.6)	11 (2.0)	295	91 (30.8)	9 (3.1)
Increased AST	420	207 (49.3)	52 12.4)	537	215 (40.0)	26 (4.8)	294	111 (37.8)	21 (7.1)
Increased ALT	425	225 (52.9)	65 (15.3)	538	223 (41.4)	35 (6.5)	295	108 (36.6)	21 (7.1)
Increased total bilirubin	422	54 (12.8)	5 (1.2)	535	66 (12.3)	6 (1.1)	295	29 (9.8)	5 (1.7)
Increased creatinine	424	107 (25.2)	10 (2.4)	536	229 (42.7)	11 (2.1)	294	60 (20.4)	1 (0.3)
Increased total amylase	366	96 (26.2)	32 (8.7)	490	190 (38.8)	60 (12.2)	259	68 (26.3)	14 (5.4)
Increased total lipase	401	164 (40.9)	78 (19.5)	517	246 (47.6)	104 (20.1)	281	96 (34.2)	36 (12.8)
Hypercalcaemia	406	29 (7.1)	1 (0.2)	529	72 (13.6)	7 (1.3)	290	31 (10.7)	0
Hypocalcaemia	406	133 (32.8)	5 (1.2)	529	115 (21.7)	2 (0.4)	290	83 (28.6)	1 (0.3)
Hyperkalaemia	421	73 (17.3)	2 (0.5)	534	155 (29.0)	13 (2.4)	296	88 (29.7)	12 (4.1)
Hypokalaemia	421	84 (20.0)	20 (4.8)	534	57 (10.7)	10 (1.9)	296	30 (10.1)	6 (2.0)
Hyperglycemia[c]	75	39 (52.0)	4 (5.3)	222	103 (46.4)	16 (7.2)	109	57 (52.3)	3 (2.8)
Hypoglycaemia	71	8(11.3)	0	223	34 (15.2)	4 (1.8)	109	10 (9.2)	0
Hypermagnesaemia	370	11 (3.0)	1 (0.3)	528	35 (6.6)	6 (1.1)	287	14 (4.9)	0

Hypomagnesaemia	370	58 (15.7)	0	528	100 (18.9)	2 (0.4)	287	52 (18.1)	0
Hypernatraemia	442	20 (4.7)	1 (0.2)	535	48 (9.0)	0	296	23 (7.8)	2 (0.7)
Hyponatraemia	442	185 (43.8)	40 (9.5)	535	211 (39.4)	53 (9.9)	296	94 (31.8)	24 (8.1)

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.

Ipilimumab in combination with nivolumab and platinum-based chemotherapy

NSCLC

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

Adverse reactions reported in the dataset for patients treated with nivolumab in combination with ipilimumab and platinum-doublet chemotherapy (n = 358) are presented in Table 9 by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

A summary of laboratory abnormalities that worsened from baseline in the dataset for patients treated with nivolumab in combination with ipilimumab and platinum-doublet chemotherapy is presented in Table 10 very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 9: Adverse reactions with nivolumab in combination with ipilimumab and platinum-doublet chemotherapy

Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC	
Infections and infestations	
Common	Conjunctivitis, pneumonia, respiratory tract infection
Uncommon	Bronchitis, sepsis
Blood and lymphatic system disorders	
Common	Febrile neutropenia
Uncommon	Eosinophilia
Immune system disorders	
Common	Infusion-related reaction, hypersensitivity
Endocrine disorders	
Very common	Hypothyroidism
Common	Hyperthyroidism, adrenal insufficiency, hypophysitis, thyroiditis
Uncommon	Hypopituitarism, hypoparathyroidism
Metabolism and nutrition disorders	
Very common	Decreased appetite
Common	Dehydration, hypoalbunaemia, hypophosphatemia
Nervous system disorders	
Common	Peripheral neuropathy, dizziness, headache
Uncommon	Polyneuropathy,autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis
Eye disorders	
Common	Dry eye
Uncommon	Blurred vision, episcleritis
Cardiac disorders	
Uncommon	tachycardia, atrial fibrillation, bradycardia
Vascular disorders	
Uncommon	Hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	
Common	Pneumonitis, dyspnoea, cough
Uncommon	Pleural effusion
Gastrointestinal disorders	
Very common	Nausea, diarrhoea, vomiting
Common	Constipation, stomatitis, abdominal pain, colitis, dry mouth, pancreatitis
Hepatobiliary disorders	
Common	Hepatitis[a]
Skin and subcutaneous tissue disorders	
Very common	Rash[b], pruritus
Common	Alopecia, dry skin, erythema, urticaria
Uncommon	Psoriasis, Stevens-Johnson syndrome, vitligo
Musculoskeletal and connective tissue disorders	
Common	Musculoskeletal pain[c], arthralgia, arthritis
Uncommon	Muscular weakness, muscle spasms, polymyalgia rheumatica
Renal and urinary disorders	
Common	Renal failure (including acute kidney injury)

Uncommon	Nephritis
General disorders and administration site conditions	
Very common	Fatigue
Common	Pyrexia, oedema (including peripheral oedema)
Uncommon	Chills, chest pain

a Hepatitis is a composite term which includes hepatitis and hepatotoxicity

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

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

Table 10: Laboratory abnormalities with nivolumab in combination with ipilimumab and platinum-doublet chemotherapy in clinical trials (NSCLC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
	Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC		
Test	N[a]	**Grades 1-4**	**Grades 3-4**
Anemia[b]	347	243 (70.0)	32 (9.2)
Thrombocytopenia	347	80 (23.1)	15 (4.3)
Leukopenia	347	126 (36.3)	34 (9.8)
Lymphopenia	257	105 (40.9)	15 (5.8)
Neutropenia	346	140 (40.5)	51 (14.7)
Increased alkaline phosphatase	342	106 (31.0)	4 (1.2)
Increased AST	345	102 (29.6)	12 (3.5)
Increased ALT	345	118 (34.2)	15 (4.3)
Increased total bilirubin	344	26 (7.6)	0
Increased creatinine	346	91 (26.3)	4 (1.2)
Increased total amylase	312	95 (30.4)	21 (6.7)
Increased total lipase	337	105 (31.2)	40 (11.9)
Hypercalcemia	345	39 (11.3)	4 (1.2)
Hypocalcemia	345	95 (27.5)	5 (1.4)
Hyperkalemia	345	77 (22.3)	6 (1.7)
Hypokalemia	345	53 (15.4)	12 (3.5)
Hypermagnesemia	334	35 (10.5)	1 (0.3)

Table 10: Laboratory abnormalities with nivolumab in combination with ipilimumab and platinum-doublet chemotherapy in clinical trials (NSCLC)

	Number (%) of Patients with Worsening Laboratory Test from Baseline		
Hypomagnesemia	334	107 (32.0)	4 (1.2)
Hypernatremia	345	15 (4.3)	0
Hyponatremia	345	128 (37.1)	37 (10.7)
Hyperglycemia	197	89 (45.2)	14 (7.1)
Hypoglycemia	273	35 (12.8)	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 anemia criteria in CTC version 4.0, there is no Grade 4 for haemoglobin.

Description of selected immune-related adverse reactions

Both WINGLORE and WINGLORE in combination with nivolumab is 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.

Note: Time to resolution may include censored observations.

Immune-related pneumonitis

In patients treated with ipilimumab 3mg/kg in combination with nivolumab 1mg/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 ipilimumab in combination with nivolumab. 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 ipilimumab 1 mg/kg in combination with nivolumab 3 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 ipilimumab in combination with nivolumab. Fifty-nine patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 31 patients (91.2%) with a median time to resolution of 6.1 weeks (range: 4.3-11.4).

In patients treated with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in malignant pleural mesothelioma, the incidence of pneumonitis including interstitial lung disease was 6.7% (20/300). Grade 2 and Grade 3 cases were reported in 5.3% (16/300) and 0.7% (2/300) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 1.8 months (range: 0.3-20.8). Seven patients (2.3%) required permanent discontinuation of nivolumab in combination with ipilimumab. Fourteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 16 patients (80%) with a median time to resolution of 6.1 weeks (range: 1.1-113.1+).

In patients treated with ipilimumab 1 mg/kg in combination with nivolumab 360 mg and chemotherapy in NSCLC, the incidence of pneumonitis including interstitial lung disease was 5.3% (19/358). Grade 2,

Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.1% (4/358), 0.6% (2/358) and of patients, respectively. No Grade 5 cases were reported. Median time to onset was 18.1 weeks (range: 0.6-52.4). Resolution occurred in 14 patients (74%) with a median time to resolution of 4.3 weeks (range: 0.7-27.9^{+}).

Immune-related colitis

In patients treated with ipilimumab 3mg/kg in combination with nivolumab 1mg/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 ipilimumab in combination with nivolumab. 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 ipilimumab 1 mg/kg in combination with nivolumab 3 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 ipilimumab in combination with nivolumab. Twenty-six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 140 patients (91.5%) with a median time to resolution of 2.4 weeks (range: 01-103.1).

In patients treated with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in malignant pleural mesothelioma, the incidence of diarrhoea or colitis was 22.0% (66/300). Grade 2 and Grade 3 cases were reported in 7.3% (22/300) and 5.3% (16/300) of patients, respectively. Median time to onset was 3.9 months (range: 0.0-21.7). Fifteen patients (5.0%) required permanent discontinuation of nivolumab in combination with ipilimumab. Twenty-two patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 62 patients (93.9%) with a median time to resolution of 3.1 weeks (range: 0.1-100.0+).

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

Immune-related hepatitis

In patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1mg/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 ipilimumab in combination with nivolumab. 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 ipilimumab 1 mg/kg in combination with nivolumab 3 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 ipilimumab in combination with nivolumab. Thirty-five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 86 patients (85.1%) with a median time to resolution of 6.1 weeks (range: 0.1-82.9).

In patients treated with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in malignant pleural mesothelioma, the incidence of liver function test abnormalities was 12.0% (36/300). Grade 2,

Grade 3, and Grade 4 cases were reported in 1.7% (5/300), 4.3% (13/300), and 1.0% (3/300) of patients, respectively. Median time to onset was 1.8 months (range: 0.5-20.3). Eleven patients (3.7%) required permanent discontinuation of nivolumab in combination with ipilimumab. Fifteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 31 patients (86.1%) with a median time to resolution of 4.1 weeks (range: 1.0-78.3+).

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

Immune-related nephritis and renal dysfunction

In patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1mg/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 ipilimumab in combination with nivolumab. 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 ipilimumab 1 mg/kg in combination with nivolumab 3 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 ipilimumab in combination with nivolumab. Twenty-seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 37 patients (77.1%) with a median time to resolution of 13.2 weeks (range: 4.1-21.1).

In patients treated with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in malignant pleural mesothelioma, the incidence of renal dysfunction was 5.0% (15/300). Grade 2 and Grade 3 cases were reported in 2.0% (6/300) and 1.3% (4/300) of patients, respectively. Median time to onset was 3.6 months (range: 0.5-14.4). Four patients (1.3%) required permanent discontinuation of nivolumab in combination with ipilimumab. Six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 12 patients (80.0%) with a median time to resolution of 6.1 weeks (range: 0.9-126.4+).

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

Immune-related endocrinopathies

In patients treated with ipilimumab 3mg/kg in combination with nivolumab 1mg/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 ipilimumab in combination with nivolumab. 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 ipilimumab 1 mg/kg in combination with nivolumab 3 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 ipilimumab in combination with nivolumab. Twenty-five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 71 patients (42.7%) with a median time to resolution of 0.4 to 130.3 weeks.

In patients treated with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in malignant pleural mesothelioma, the incidence of thyroid disorders was 14% (43/300). Grade 2 and Grade 3 thyroid disorders were reported in 9.3% (28/300) and 1.3% (4/300) of patients, respectively. Hypophysitis occurred in 2% (6/300) of patients. Grade 2 cases were reported in 1.3% (4/300) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 1.0% (3/300) and 1.0% (3/300) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (5/300) and 0.3% (1/300) of patients, respectively. No cases of immune-related diabetes mellitus were reported. Median time to onset of these endocrinopathies was 2.8 months (range: 0.5-20.8). One patient (0.3%) required permanent discontinuation of nivolumab in combination with ipilimumab. Five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 17 patients (32.7%). Time to resolution ranged from 0.3 to 144.1+ weeks.

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

Immune-related skin adverse reactions

In patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1mg/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 ipilimumab in combination with nivolumab. 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 ipilimumab 1 mg/kg in combination with nivolumab 3 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 ipilimumab in combination with nivolumab. Seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 192 patients (72.2%) with a median time to resolution of 11.6 weeks (range: 8.7-17.1).

In patients treated with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in malignant pleural mesothelioma, the incidence of rash was 36.0% (108/300). Grade 2 and Grade 3 cases were reported in 10.3% (31/300) and 3.0% (9/300) of patients, respectively. Median time to onset was 1.6 months (range: 0.0-22.3). Two patients (0.7%) required permanent discontinuation of nivolumab in combination with ipilimumab. Nine patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Resolution occurred in 71 patients (66.4%) with a median time to resolution of 12.1 weeks (range: 0.4-146.4+).

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

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

In patients treated with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in malignant pleural mesothelioma, the incidence of hypersensitivity/infusion reactions was 12% (36/300); Grade 2 and Grade 3 cases were reported in 5.0% (15/300) and 1.3% (4/300) of patients, respectively.

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

Immune-related neurological adverse reactions
The following adverse events observed across clinical trials of ipilimumab in combination with nivolumab 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.

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 ipilimumab in combination with nivolumab investigating various doses and tumour types, the following immune-related adverse reactions were reported in less than 1% of patients: pancreatitis, uveitis, gastritis, sarcoidosis, duodenitis, aseptic meningitis, myositis, myocarditis, rhabdomyolysis and Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome.

Postmarketing experience

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

Blood and lymphatic system disorders: histiocytosis haematophagic

Immune system disorders: graft-versus-host disease, solid organ transplant rejection

Eye disorders: Serous retinal detachment

Nervous system disorders: myelitis (including transverse myelitis), Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome*

Metabolism and nutrition disorders: tumour lysis syndrome*

* Specific to nivolumab in combination with ipilimumab

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9. OVERDOSE

The maximum tolerated dose of WINGLORE has not been determined. In clinical trials, patients received up to 20 mg/kg without apparent toxic effects.

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

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC11.

Mechanism of action

CTLA-4 is a key regulator of T cell activity. Ipilimumab is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of tumor reactive T effector cells which mobilize to mount a direct T-cell immune attack against tumor cells. CTLA-4 blockade can also reduce T regulatory cell function, which may lead to an increase in anti-tumor immune response.

Pharmacodynamic effects

In patients with melanoma who received WINGLORE, the mean peripheral blood absolute lymphocyte counts (ALC) increased throughout the induction dosing period. In Phase 2 studies, this increase occurred in a dose-dependent fashion. In MDX010-20 (see 5.1 Pharmacodynamic properties, Clinical Trials), WINGLORE given at 3 mg/kg with or without gp100 increased ALC throughout the induction dosing period, but no meaningful change in ALC was observed in the control group of patients who received an investigational gp100 peptide vaccine alone.

In peripheral blood of patients with melanoma, a mean increase in the percent of activated HLA-DR+ CD4+ and CD8+ T cells and a mean decrease in the percent of naive (CCR7+ CD45RA+) CD4+ and CD8+ T cells were observed after treatment with WINGLORE, consistent with its mechanism of action. A mean increase in the percent of central memory (CCR7+ CD45RA-) CD4+ and CD8+ T cells and a smaller, but significant, mean increase in the percent of effector memory (CCR7- CD45RA-) CD8+ T cells also was observed after treatment with WINGLORE.

Clinical trials

WINGLORE MONOTHERAPY

First line treatment of advanced (unresectable or metastatic melanoma).
Clinical data to support the use of ipilimumab 3mg/kg monotherapy in a first line clinical setting in patients with unresectable or metastatic melanoma is derived from observational clinical data and

pooled data sourced from multiple studies. A prospective, randomised, Phase 3 study of ipilimumab 3mg/kg monotherapy has not been performed in this setting.

OS of WINGLORE 3mg/kg monotherapy in chemotherapy-naïve patients pooled across Phase 2 and 3 clinical trials (N=78; randomised) and in treatment-naïve patients in two retrospective observational studies (N= 273 and N= 157) were generally consistent. In the two observational studies, 12.1% and 33.1% of the patients had brain metastases at the time of diagnosis. In these studies the estimated 1-year survival rates were 59.2% (95% CI: 53.0 – 64.8) and 46.7% (95% CI: 38.1-54.9). The estimated 1-year, 2-year and 3-year survival rates for pooled chemotherapy-naïve patients were 54.1% (95% CI: 42.5 – 65.6), 31.6% (95% CI: 20.7 – 42.9) and 23.7% (95% CI: 14.3-34.4), respectively.

Previously treated advanced (unresectable or metastatic melanoma).
Overall survival advantage (OS) of WINGLORE at the recommended dose of 3 mg/kg in patients with previously-treated advanced (unrescetable or metastatic) melanoma was demonstrated in a Phase 3 study (MDX010-20). WINGLORE has not been investigated in patients with active or a history of serious chronic viral infections, including hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). Clinical studies excluded patients without liver metastasis who had a baseline AST > 2.5 x ULN or patients with liver metastasis who had a baseline AST greater than > 5 x ULN. Patients with a baseline total bilirubin ≥ 3 x ULN were also excluded.

Study MDX010-20

A Phase 3, double-blind study enrolled patients with unresectable or metastatic melanoma who had previously been treated with regimens containing one or more of the following: IL-2, dacarbazine, temozolomide, fotemustine, or carboplatin. Patients were randomized in a 3:1:1 ratio to receive WINGLORE 3 mg/kg in combination with an investigational gp100 peptide vaccine (gp100), WINGLORE 3 mg/kg monotherapy, or gp100 alone. All patients in this study were HLA-A2*0201 type; this HLA type supports the immune presentation of gp100. BRAF status was not collected at entry. Patients received WINGLORE every 3 weeks for 4 doses as tolerated (induction therapy). Patients with apparent tumour burden increase before completion of the induction period were continued on induction therapy as tolerated if they had adequate performance status. Assessment of tumor response to WINGLORE was conducted at approximately Week 12 after completion of induction therapy.

Additional treatment with WINGLORE (re-induction therapy) was offered to patients who developed progressive disease (PD) after initial clinical response (partial response [PR] or complete response [CR]) or after stable disease (SD, per the modified WHO criteria) lasting longer than 3 months from the first tumour assessment. The primary endpoint was overall survival (OS) in the WINGLORE+ gp100 group vs. the gp100 group. Key secondary endpoints were OS in the WINGLORE+ gp100 group vs. the WINGLORE monotherapy group and in the WINGLORE monotherapy group vs. the gp100 group. Other secondary endpoints included best overall response rate (BORR) up to Week 24 and duration of response.

A total of 676 patients were randomized: 137 to the WINGLORE monotherapy group, 403 to the WINGLORE + gp100 group, and 136 to the gp100 alone group. The majority of patients had received all 4 doses during induction. Thirty-two evaluable patients received a re-induction dose: 8 in the WINGLORE monotherapy group, 23 in the WINGLORE + gp100 group, and 1 in the gp100 group. Duration of follow-up ranged up to 55 months. Baseline characteristics were well balanced across treatment groups. The median age was 57 years. The majority (71-73%) of patients had M1c stage disease and 37-40% of patients had an elevated LDH at baseline. A total of 77 patients had a history of previously treated brain metastases.

The WINGLORE-containing regimens demonstrated a statistically significant advantage over the gp100 group in OS. The hazard ratio (HR) for comparison of OS between the WINGLORE monotherapy and gp100 groups was 0.66 (95% CI: 0.51, 0.87; p = 0.0026). This result was consistent

with the HR for comparison between the WINGLORE + gp100 group and the gp100 group (HR 0.68 [95% CI: 0.55, 0.85]; p = 0.0004).

The observed OS benefit was consistently demonstrated across subgroups of patients (M [metastases]-stage, prior interleukin-2, baseline LDH, age, gender, and the type and number of prior therapies).

Overall survival results are shown in Figure 1. Median and estimated rates of OS at 1 year and 2 years are presented in Table 11.

Figure 1: Overall Survival in Study MDX010-20

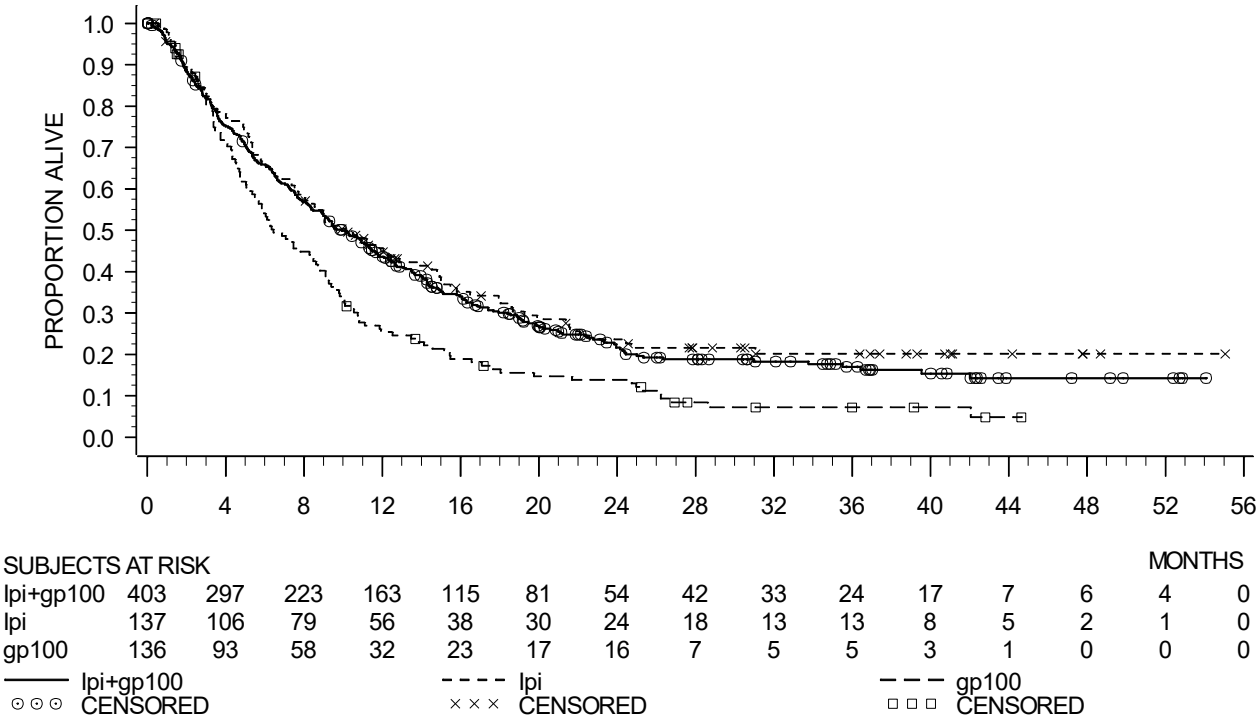


Table 11: Overall Survival in MDX010-20

	WINGLORE 3mg/kg n= 137	WINGLORE 3mg/kg + gp100[a] n= 403	gp100[a] n= 136
Median Months (95% CI)	**10 months (8.0, 13.8)**	10 months (8.5, 11.5)	6 months (5.5, 8.7)
OS at 1 year % (95% CI)	**46% (37.0, 54.1)**	44% (38.6, 48.5)	25% (18.1, 32.9)
OS at 2 years % (95% CI)	**24% (16.0, 31.5)**	22% (17.2, 26.1)	14% (8.0, 20.0)

[a] Combination of WINGLORE + gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control. See 4.2 Dosage and method of administration for the recommended dosage.

In the WINGLORE 3 mg/kg monotherapy group, median OS was 22 months and 8 months for patients with SD and those with PD, respectively. At the time of this analysis, medians were not reached for patients with CR or PR.

Efficacy was demonstrated across the primary and secondary endpoints. Additional efficacy results are presented in Table 12.

Table 12: Efficacy of WINGLORE in MDX010-20

		WINGLORE 3mg/kg n= 137	WINGLORE 3mg/kg + gp100[a] n= 403	gp100[a] n= 136
BORR (up to Week 24)% (95% CI)		**10.9% (6.3, 17.4)**	5.7% (3.7, 8.4)	1.5% (0.2, 5.2)
WINGLORE vs gp100		**p= 0.0012**		
WINGLORE + gp100 vs gp100			p= 0.0433	
CR	(%)	**1.5%**	0.2%	0
PR	(%)	**9.5%**	5.5%	1.5%
SD	(%)	**17.5%**	14.4%	9.6%
Median Duration of Response (range)		**Not Reached (2.8-44.2+)**	11.5 months (1.9-44.4+)	Not Reached (2.0-5.6+)

[a] Combination of WINGLORE + gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control. See 4.2 Dosage and method of administration for the recommended dosage.

Tumour responses were observed as late as 5.5 months from the start of WINGLORE therapy.

For patients who required re-induction therapy, the BORR was 38% (3/8 patients) in the WINGLORE monotherapy group, 13% (3/23 patients) in the WINGLORE + gp100 group, and 0% in the gp100 group. The disease control rate (DCR, defined as CR+PR+SD) was 75% (6/8 patients), 65% (15/23 patients), and 0%, respectively.

The development or maintenance of clinical activity following WINGLORE treatment was similar with or without the use of systemic corticosteroids.

Study CA184022

The activity of three doses of WINGLORE was investigated in a blinded, randomized Phase 2 study in patients with advanced melanoma. Patients who progressed after or were intolerant to prior therapy were enrolled in the study. A total of 217 patients were randomized to three groups: 0.3 mg/kg (n= 73), 3 mg/kg (n= 72), and 10 mg/kg (n= 72). In this study, some objective responses were observed after initial evidence of tumour burden increase, including new lesions. Clinical response, disease control, and survival were similar regardless of the HLA subtype.

WINGLORE IN COMBINATION WITH NIVOLUMAB

Unresectable or metastatic melanoma
Study CA209067 Randomised phase 3 study of nivolumab in combination with ipilimumab or nivolumab as monotherapy versus ipilimumab

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 nivolumab-containing groups were evaluated descriptively, but not included in formal hypothesis testing.

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

Baseline tumour tissue specimens were systematically collected prior to randomisation in order to conduct planned analyses of efficacy according to PD-L1 expression. Quantifiable tumour PD-L1 expression was measured in 89% (278/314) of patients randomised to nivolumab in combination with ipilimumab, 91% (288/316) of patients randomised to nivolumab monotherapy, and 88% (277/315) of patients randomised to ipilimumab alone. Among patients with quantifiable PD-L1 expression, the distribution of patients was balanced across the three treatment groups at the predefined tumour PD-L1 expression level of ≥5% (24% in the nivolumab in combination with ipilimumab arm, 28% in the nivolumab monotherapy arm, and 27% in the ipilimumab arm). Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Both nivolumab-containing arms demonstrated a significant PFS and OS benefit and greater ORR compared with ipilimumab monotherapy. Efficacy results for all randomised patients are shown in Table 13, Figure 2 (PFS), and Figure 3 (OS).

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

Table 13: Efficacy results (CA209067)

	Nivolumab+ Ipilimumab (n=314)	Nivolumab (n=316)	Ipilimumab (n=315)
Progression-free survival[a]			
Events, n (%)	161 (51.3)	183 (57.9%)	245 (77.8%)
Hazard ratio (vs. ipilimumab)	0.42	0.55	
(99.5% CI)	(0.32,0.56)	(0.42, 0.73)	
p-value	p<0.0001	p<0.0001	
Hazard ratio (vs. nivolumab monotherapy)	0.76		
(95% CI)[c]	(0.62, 0.95)		
Median months	11.5	6.9	2.9
(95% CI)	(8.9, 22.18)	(4.3, 9.5)	(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)	0.55	0.63	
(98% CI)	(0.42, 0.72)	(0.48, 0.81)	
p-value	p<0.0001	p<0.0001	
Hazard ratio (vs nivolumab monotherapy)	0.88		
(95% CI) [c]	(0.69, 1.12)		
Median months	Not reached	Not reached	20.0
(95% CI)		(29.1, NE)	(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 n(%)	185 (59%)	141 (45%)	60 (19%)
(95% CI)	(53.3, 64.4)	(39.1, 50.3)	(14.9, 23.8)
Odds ratio (vs ipilimumab)	6.5	3.54	
(95% CI)	(3.81,11.08)	(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.

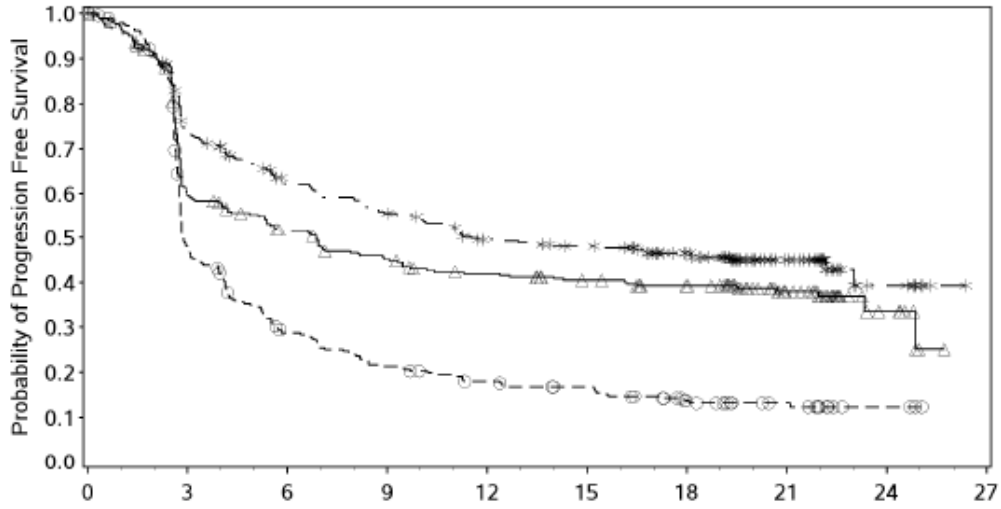
b Minimum follow up of 28 months.

c Unadjusted for multiplicity

NE=not estimable.

"+" denotes a censored observation.

Figure 2: Progression-free Survival: Unresectable or Metastatic Melanoma (Study CA209067)



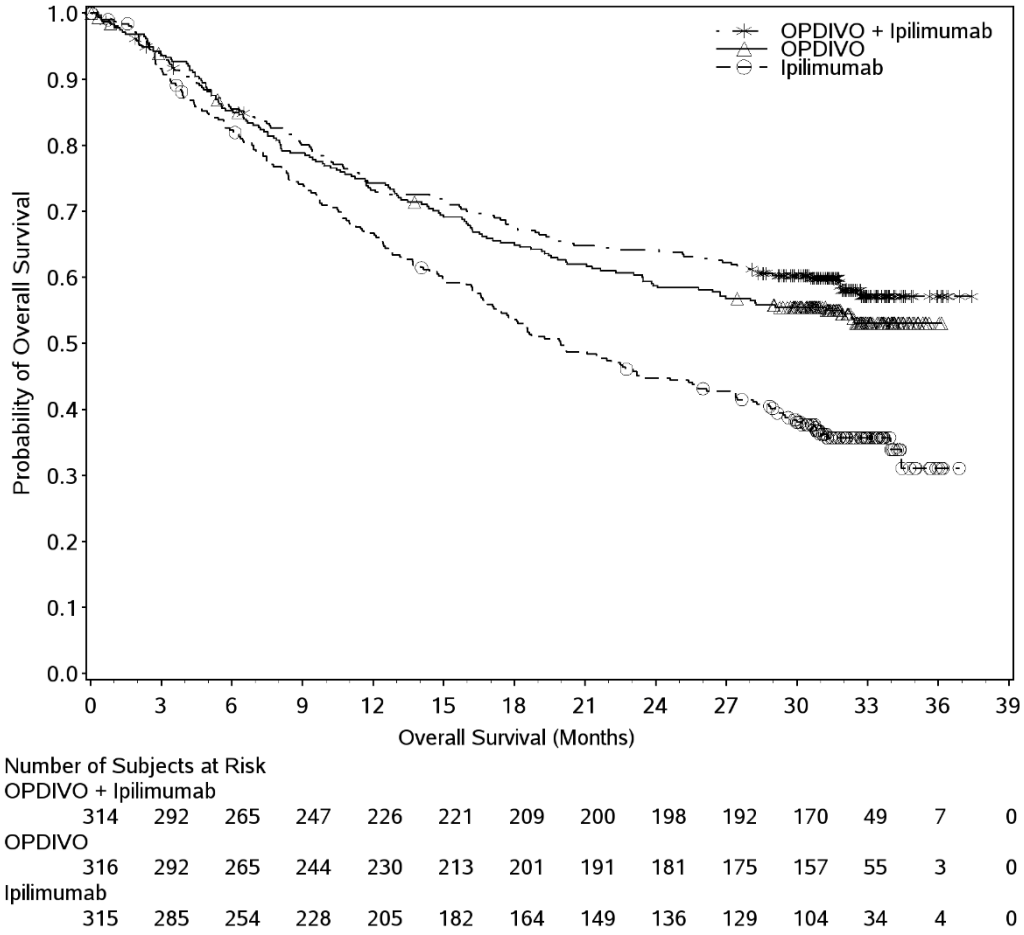
Number of Subjects at Risk

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 3: Overall Survival: Unresectable or Metastatic Melanoma (Study 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.

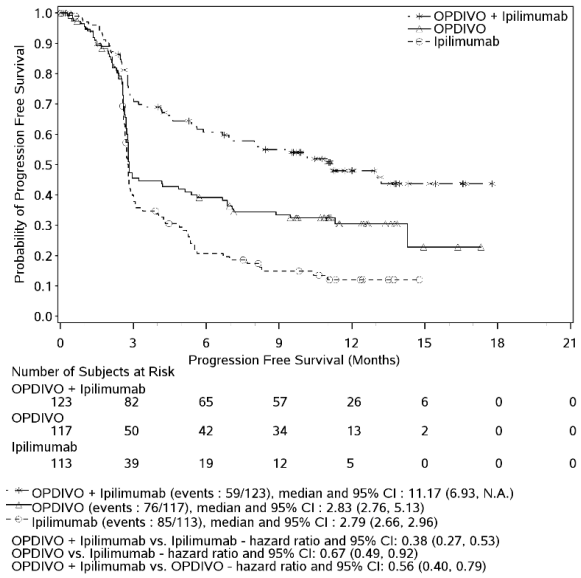
Greater objective response rates were demonstrated for nivolumab in combination with ipilimumab relative to nivolumab monotherapy across tumour PD-L1 expression levels, with a best overall response of complete response correlating to an improved survival rate.

Analyses comparing nivolumab monotherapy to nivolumab in combination with ipilimumab were all descriptive. Kaplan-Meier plots for exploratory subgroup analyses comparing PFS and OS in patients with tumour PD-L1 expression of <1% versus ≥1% are included below as Figure 4 and Figure 5.

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

Figure 4: Progression-free survival by tumour PD-L1 expression level (CA209067) at 18 months of follow-up

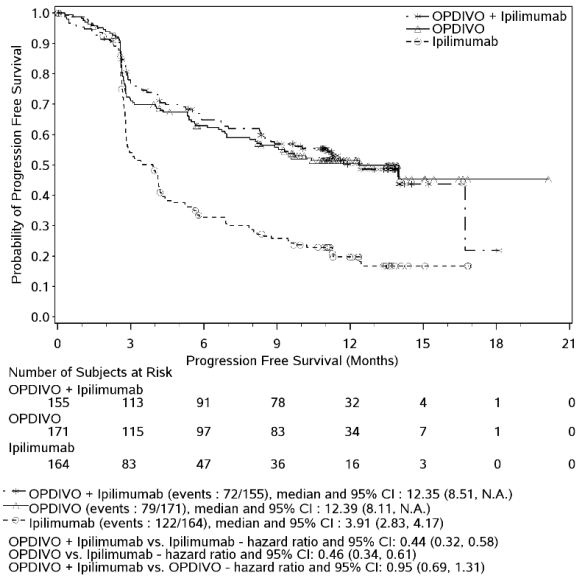
< 1%



OPDIVO + Ipilimumab (events : 59/123), median and 95% CI : 11.17 (6.93, N.A.)
OPDIVO (events : 76/117), median and 95% CI : 2.83 (2.76, 5.13)
Ipilimumab (events : 85/113), median and 95% CI : 2.79 (2.66, 2.96)

OPDIVO + Ipilimumab vs. Ipilimumab - hazard ratio and 95% CI: 0.38 (0.27, 0.53)
OPDIVO vs. Ipilimumab - hazard ratio and 95% CI: 0.67 (0.49, 0.92)
OPDIVO + Ipilimumab vs. OPDIVO - hazard ratio and 95% CI: 0.56 (0.40, 0.79)

≥ 1%

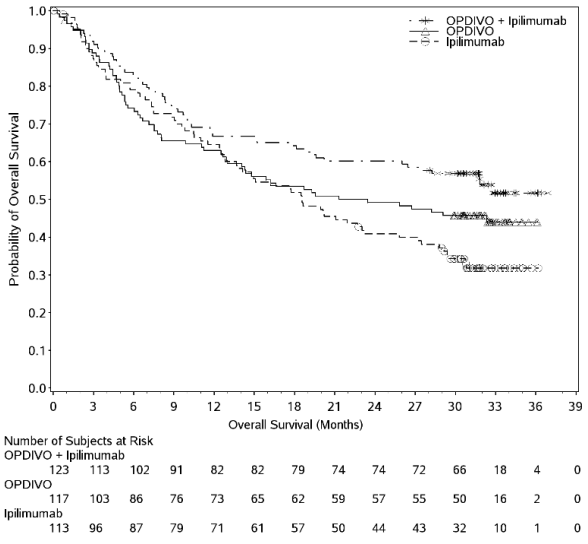


OPDIVO + Ipilimumab (events : 72/155), median and 95% CI : 12.35 (8.51, N.A.)
OPDIVO (events : 79/171), median and 95% CI : 12.39 (8.11, N.A.)
Ipilimumab (events : 122/164), median and 95% CI : 3.91 (2.83, 4.17)

OPDIVO + Ipilimumab vs. Ipilimumab - hazard ratio and 95% CI: 0.44 (0.32, 0.58)
OPDIVO vs. Ipilimumab - hazard ratio and 95% CI: 0.46 (0.34, 0.61)
OPDIVO + Ipilimumab vs. OPDIVO - hazard ratio and 95% CI: 0.95 (0.69, 1.31)

Figure 5: Overall survival by tumour PD-L1 expression level (CA209067) at 2 years of follow-up

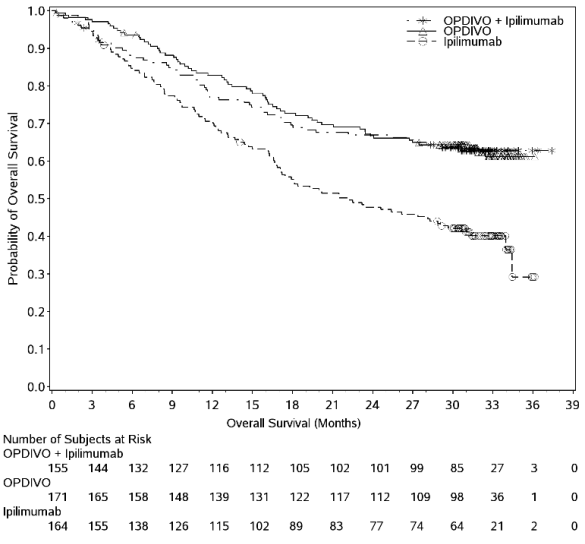
< 1%



Nivolumab + Ipilimumab (events: 56/123), median and 95% CI: N.A. (26.45, N.A.)
Nivolumab (events: 64/117), median and 95% CI: 23.46 (13.01, N.A.)
Ipilimumab (events: 74/113), median and 95% CI: 18.56 (13.67, 23.20)

Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 95% CI: 0.60 (0.42, 0.84)
Nivolumab vs Ipilimumab - hazard ratio and 95% CI: 0.80 (0.57, 1.12)
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.74 (0.52, 1.06)

≥ 1%



Nivolumab + Ipilimumab (events: 56/155), median and 95% CI: N.A.
Nivolumab (events: 63/171), median and 95% CI: N.A.
Ipilimumab (events: 98/164), median and 95% CI: 22.11 (17.08, 29.67)

Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 95% CI: 0.53 (0.38, 0.74)
Nivolumab vs Ipilimumab - hazard ratio and 95% CI: 0.52 (0.38, 0.71)
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 1.03 (0.72, 1.48)

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

Study CA209069. A randomised, phase 2 study of nivolumab in combination with ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma

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 Untreated Renal Cell Carcinoma(RCC)
Study CA209214: A Randomised, Open-label, phase 3 study of nivolumab in combination with Ipilimumab versus Sunitinib in Subjects with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma.

The safety and efficacy of ipilimumab 1 mg/kg in combination with nivolumab 3 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 randomisation, Karnofsky performance status <80%, haemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal). This study included patients regardless of their tumour PD-L1 status. Patients with 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.

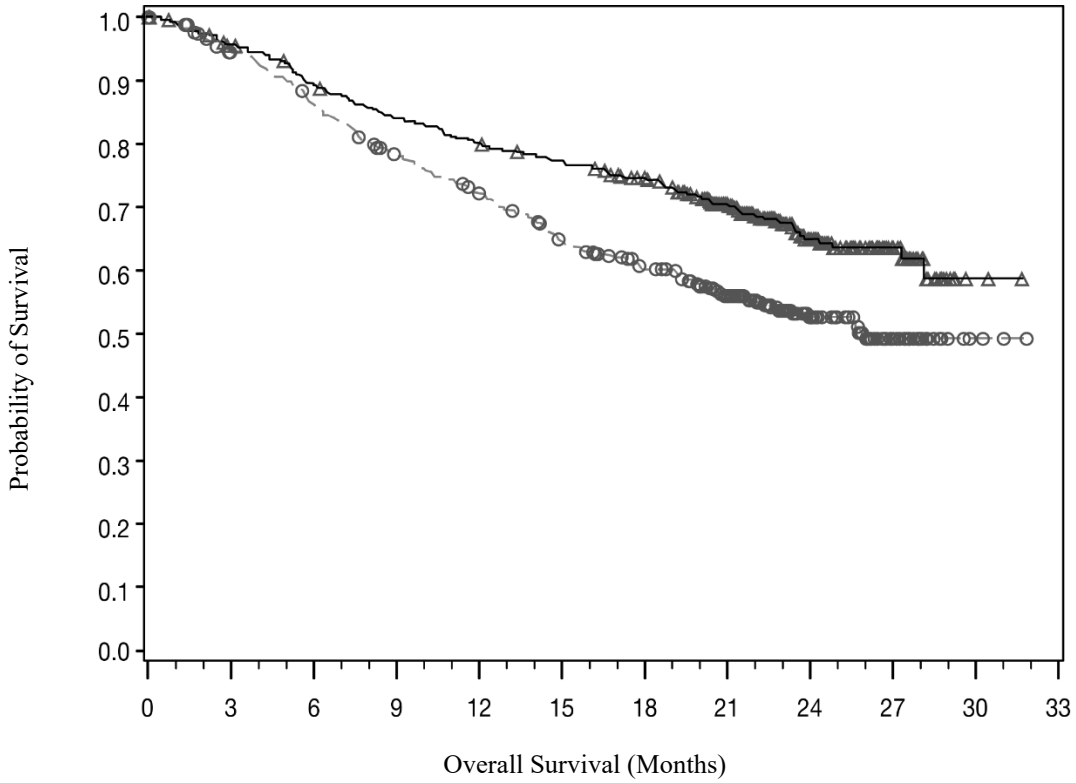
A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either ipilimumab 1 mg/kg (n = 425) administered intravenously over 30 minutes in combination with nivolumab 3 mg/kg administered intravenously over 60 minutes every 3 weeks for 4 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 ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg and sunitinib groups. The median duration of treatment was 7.9 months (range: 1 day- 21.4^{+} months) in ipilimumab with

nivolumab- treated patients and was 7.8 months (range: 1 days- 20.2+ months) in sunitinib-treated patients. Ipilimumab with nivolumab was continued beyond progression in 29% of patients.

The Kaplan-Meier curves for OS in intermediate/poor risk patients is shown in Figure 6.

Figure 6: Overall Survival in intermediate/poor risk patients with RCC (CA209214)



Number of Subjects at Risk

Ipilimumab + Nivolumab											
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

Ipilimumab + Nivolumab (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 ipilimumab plus nivolumab as compared with sunitinib.. OS benefit was observed regardless of tumour PD-L1 expression level.

Efficacy results are shown in Table 14.

Table 14: 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 statistical significance as compared to alpha 0.009.
"+" denotes a censored observation.
NE = non-estimable

The median time to onset of objective response was 2.8 months (range: 0.9-11.3 months) after the start of ipilimumab with nivolumab 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.

NON-SMALL CELL LUNG CANCER (NSCLC)

Previously untreated advanced or metastatic NSCLC - WINGLORE in combination with nivolumab and chemotherapy

Randomised phase 3 study vs. platinum-doublet chemotherapy (CA2099LA)
CA2099LA was a randomised, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior systemic anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumour PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

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

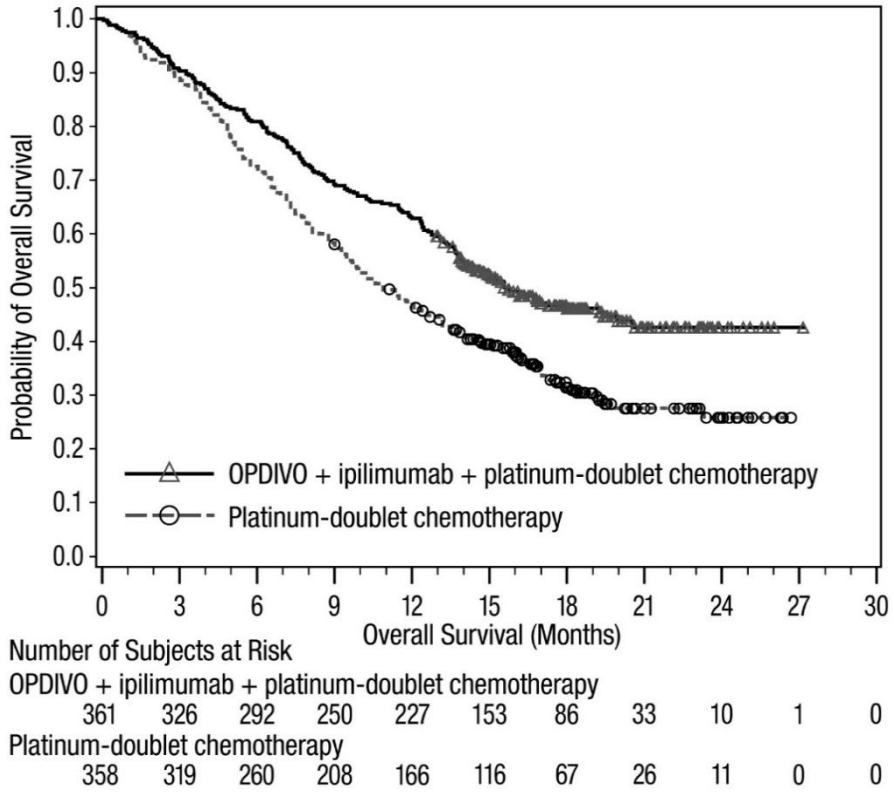
- carboplatin (AUC 5 or 6) and pemetrexed 500 mg/mg^2; or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC, or
- carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC.

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

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

Efficacy results from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) demonstrated a statistically significant benefit in OS, PFS, and ORR, and a clinically meaningful benefit in duration of response (Table 15). With an additional 4.6 months of follow-up, the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving nivolumab and ipilimumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 7).

Figure 7: Overall Survival - updated analysis (CA2099LA)



nivolumab in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy v/s platinum-doublet chemotherapy
HR 0.66 (95% CI: 0.55, 0.80)

Table 15: Efficacy Results (CA2099LA)

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

Table 15: Efficacy Results (CA2099LA)

	nivolumab and ipilimumab and Chemotherapy (n=361)	Chemotherapy (n=358)
(95% CI)	(33, 43)	(21, 30)
Stratified CMH test p-value[f]	0.0003	
Complete response (%)	7 (1.9)	3 (0.8)
Partial response (%)	129 (35.7)	87 (24.3)
Duration of Response per BICR		
Median (months) (95% CI)[d]	10.0 (8.2, 13.0)	5.1 (4.3, 7.0)

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

MALIGNANT PLEURAL MESOTHELIOMA (MPM)

Previously untreated unresectable malignant pleural mesothelioma - WINGLORE in combination with nivolumab

Randomised phase 3 study vs. chemotherapy (CA209743)
CA209743 was a randomised, open-label trial in patients with unresectable malignant pleural mesothelioma. The trial included patients (18 years of age and older) with histologically confirmed and previously untreated malignant pleural mesothelioma of epithelioid or non-epithelioid histology, ECOG performance status 0 or 1, and no palliative radiotherapy within 14 days of first trial therapy. Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the trial) were excluded from the trial. Patients received nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks and ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years, or chemotherapy consisting of cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 or carboplatin 5 AUC and pemetrexed 500 mg/m^2 for up to 6 cycles (each cycle was 21 days). Stratification factors for randomization were tumor histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and gender (male vs. female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent as part of the study. Treatment continued beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Tumour assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, duration of response, and disease control rate (DCR) as assessed by BICR utilizing modified RECIST criteria.

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

The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab in combination with ipilimumab compared to chemotherapy with a minimum follow-up of

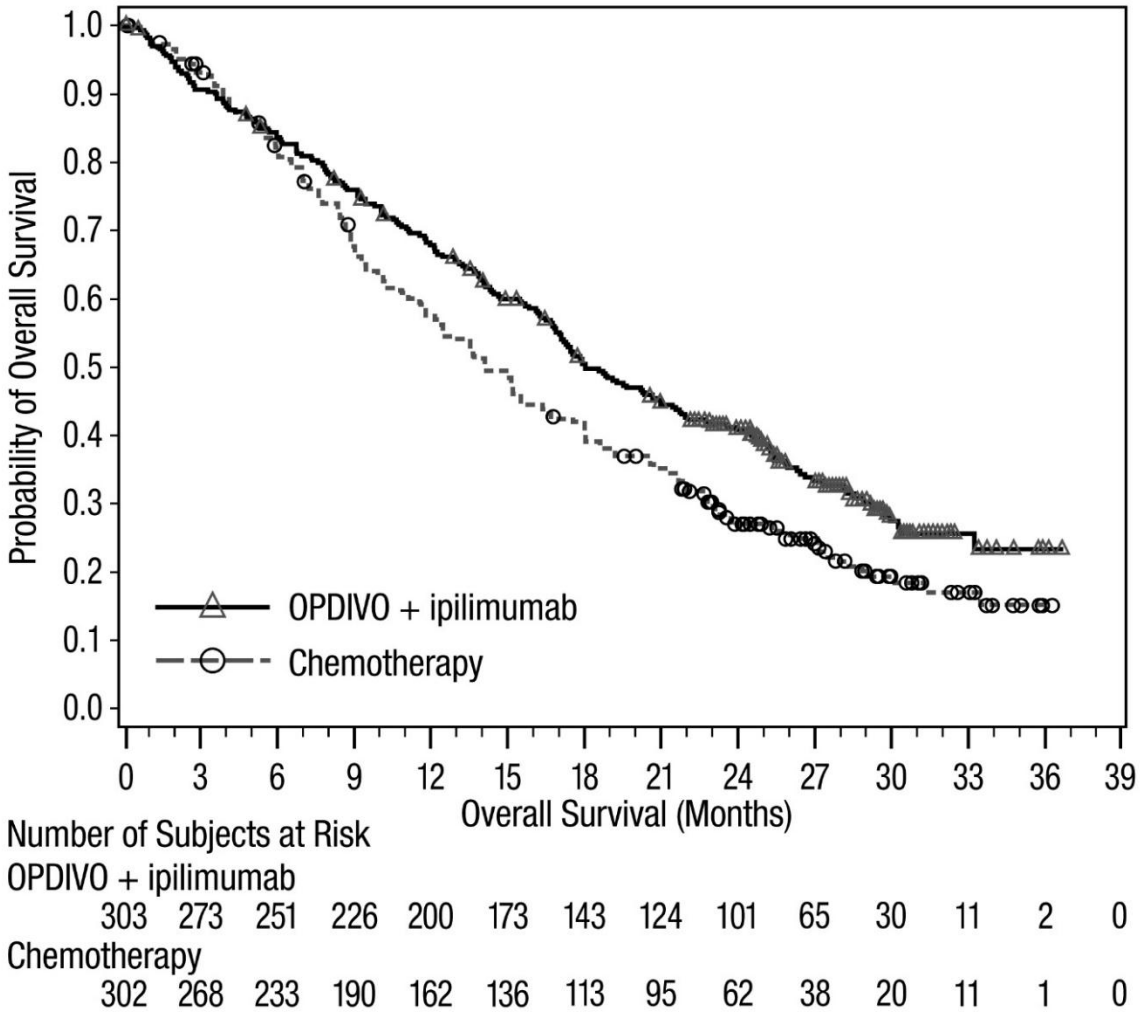
22 months. Efficacy results from the prespecified interim analysis when at least 403 events were observed (85% of the planned number of events for final analysis) are presented in Table 16 and Figure 8.

Table 16: Efficacy Results (CA209743)

	Nivolumab and Ipilimumab (n=303)	**Chemotherapy (n=302)**
Overall Survival		
Events (%)	200 (66)	219 (73)
Median (months)[a] (95% CI)	18.1 (16.8, 21.5)	14.1 (12.5, 16.2)
Hazard ratio (96.6% CI)[b]	0.74 (0.60, 0.91)	
Stratified log-rank p-value[c]	0.002	
Rate (95% CI) at 24 months[a]	41% (35.1, 46.5)	27% (21.9, 32.4)
Progression-free Survival		
Events (%)	218 (72)	209 (69)
Hazard ratio (95% CI)[b]	1.0 (0.82, 1.21)	
Median (months)[a] (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)
Overall Response Rate	40%	43%
(95% CI)	(34.1, 45.4)	(37.1, 48.5)
Complete response	1.7%	0
Partial response	38%	43%
Duration of Response		
Median (months)[a] (95% CI)	11.0 (8.1, 16.5)	6.7 (5.3, 7.1)
% with duration ≥6 months	69%	53%
Disease Control Rate (95% CI)	77% (71.4, 81.2)	85% (80.6, 88.9)

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

Figure 8: Overall Survival (CA209743)



--○-- Nivolumab + ipilimumab (events: 200/303), median and 95% CI: 18.07 (16.82, 21.45)
--+-- Chemotherapy (events: 219/302), median and 95% CI: 14.09 (12.45, 16.23)
In a prespecified exploratory analysis based on histology, in the subgroup of patients with epithelioid histology, the hazard ratio (HR) for OS was 0.85 (95% CI: 0.68, 1.06), with median OS of 18.7 months in the WINGLORE and nivolumab arm and 16.2 months in the chemotherapy arm. In the subgroup of patients with non-epithelioid histology, the HR for OS was 0.46 (95% CI: 0.31, 0.70), with median OS of 16.9 months in the WINGLORE and nivolumab arm and 8.8 months in the chemotherapy arm.

Immunogenicity

Ipilimumab monotherapy
Less than 2% of patients with advanced melanoma who received WINGLORE in Phase 2 and 3 clinical studies developed antibodies against ipilimumab. None had any infusion-related or peri-infusional hypersensitivity or anaphylactic reactions. Neutralizing antibodies against ipilimumab were not detected. Overall, no apparent association was observed between antibody development and adverse events, or clearance of ipilimumab (see 5.2 Pharmacokinetic properties).

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

nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 25.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of the patients who were treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 33.8%. The incidence of neutralising antibodies against nivolumab was 0.5% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 0.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks and 2.6% with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy. Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged for 6.3 to 13.7% and neutralising antibodies against ipilimumab ranged from 0 to 0.4%. There was no evidence of altered toxicity profile associated with anti-product antibody development. Neutralising antibodies were not associated with loss of efficacy.

5.2. PHARMACOKINETIC PROPERTIES

Ipilimumab pharmacokinetics (PK) was assessed using a population PK approach for WINGLORE monotherapy and WINGLORE in combination with nivolumab.

WINGLORE monotherapy

The exposure of ipilimumab increased in a dose proportional manner over the dose range of 0.3 to 10 mg/kg when administered as a 90 minute infusion to advanced melanoma patients every 3 weeks for 4 doses.

Ipilimumab clearance (CL) decreases over time by approximately 5% to a geometric mean value (% coefficient of variation [CV%]) of 12.1 mL/h (42%) in patients with advanced melanoma. This decrease in CL is not considered clinically relevant. The geometric mean (CV%) volume of distribution at steady state (Vss) is 7.2 L (17.3%), and terminal half-life (t½) is ~20 days. The systemic accumulation achieved after the 4th dose of ipilimumab 3mg/kg Q3W was approximately 1.7 fold.

Ipilimumab clearance and volume of distribution were found to increase with increasing body weight and dosing is therefore administered on a mg/kg basis. Ipilimumab clearance was not affected by age (range 23-88 years), gender, concomitant use of budesonide, performance status, HLA-A2*0201 status, tumour type, mild hepatic impairment, mild to moderate renal impairment, immunogenicity, and previous systemic anticancer therapy. The effect of race was not examined as there was insufficient data in non-Caucasian ethnic groups.

The CL of ipilimumab increased by 5.7% in the presence of anti-ipilimumab antibodies and was not considered clinically relevant.

No controlled studies have been conducted to evaluate the pharmacokinetics of ipilimumab in the paediatric population or in patients with hepatic or renal impairment.

Based on an exposure-response analysis in 497 patients with advanced melanoma, overall survival (OS) was independent of prior anti-cancer therapy.

WINGLORE in combination with nivolumab

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

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

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

The decrease in ipilimumab CL over time when administered in combination with nivolumab was 22%. These differences in CL relative to monotherapy are not considered clinically relevant when ipilimumab is only administered for four doses.

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

Renal impairment

The effect of renal impairment on the clearance of ipilimumab was evaluated in patients with mild (GFR <90 and ≥60 mL/min/1.73m^2; n=349), moderate (GFR <60 and ≥30mL/min/1.73m^2; n=82), or severe (GFR < 30 and ≥15mL/min/1.73 m^2; n=4) renal impairment compared to patients with normal renal function (GFR ≥90 mL/min/1.73 m^2; n=350) in population pharmacokinetic analyses. No clinically important differences in the clearance of ipilimumab were found between patients with mild to moderate renal impairment and patients with normal renal function (see 4.4 Special warnings and precautions for use: Renal Impairment).

Hepatic impairment

No clinically important differences in the clearance of ipilimumab were found between patients with mild hepatic impairment (Total Bilirubin 1.0-1.5xULN or AST>ULN as defined using the National Cancer Institute criteria for hepatic dysfunction; n=76) and normal hepatic function (n=708). Ipilimumab has not been studied in patients with moderate (Total Bilirubin > 1.5- 3 xULN and any AST) or severe hepatic impairment (Total Bilirubin > 3x ULN and any AST) (see 4.4 Special warnings and precautions for use: Hepatic impairment).

5.3. PRECLINICAL SAFETY DATA

Studies to evaluate the genotoxic and carcinogenic potential of ipilimumab have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Tris hydrochloride (2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride)

Sodium chloride

Mannitol (E421)

Pentetic acid (diethylenetriaminepentaacetic acid)

Polysorbate 80

Sodium hydroxide (for pH-adjustment)

Hydrochloric acid (for pH-adjustment)

Water for injections

6.2. INCOMPATIBILITIES

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

6.3. SHELF LIFE

Unopen vial: 36 months

Solution for infusion: The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 mg/mL and 4 mg/mL) has been demonstrated for 24 hours at 25°C and 2°C to 8°C. However, to reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours.

This medicinal product does not contain any preservatives.

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.

For storage conditions after first opening or dilution of the medicinal product, see section 6.3.

6.5. NATURE AND CONTENTS OF CONTAINER

50 mg of ipilimumab in 10 mL of concentrate solution for infusion is supplied in a vial (Type I glass) with a stopper (coated butyl rubber) and an aluminium light blue “flip off” seal

200 mg of ipilimumab in 40 mL of concentrate solution for infusion is supplied in a vial (Type I glass) with a stopper (coated butyl rubber) and an aluminium purple “flip off” seal

Pack of 1 vial containing 10 mL.
Pack of 1 vial containing 40 mL.
Not all pack sizes may be marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

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

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

Bristol-Myers Squibb (NZ) Limited
Private Bag 92518
Auckland 1141

Tel: Toll free 0800 167 567

9. DATE OF FIRST APPROVAL

22 March 2012

10. DATE OF REVISION OF THE TEXT

27 November 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Update to Other immune-related adverse reactions section to include Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome associated with the use of ipilimumab in combination with nivolumab.
4.8	Update to the Postmarketing experience section to include Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome associated with the use of ipilimumab in combination with nivolumab.

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