

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

YERVOY 5 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 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.

Ipilimumab is a fully human anti-CTLA-4 monoclonal antibody (IgG1 κ) produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipients 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.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates and has a pH of 7.0 and an osmolarity of 260-300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

YERVOY as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older (see section 4.4).

YERVOY in combination with nivolumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

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

Renal Cell Carcinoma (RCC)

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

4.2 Posology and method of administration

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

Posology

YERVOY as monotherapy

Melanoma

Adults and adolescents 12 years of age and older

The recommended induction regimen of YERVOY is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of 4 doses. Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response should be conducted only after completion of induction therapy.

YERVOY in combination with nivolumab

Melanoma

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

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

Table 1: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab

	Combination phase, every 3 weeks for 4 dosing cycles	Monotherapy phase
Nivolumab	1 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Ipilimumab	3 mg/kg over 90 minutes	-

Renal Cell Carcinoma

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

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

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

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

Treatment with YERVOY in combination with nivolumab, should be continued for the four doses of combination therapy as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with YERVOY in combination with nivolumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Liver function tests (LFTs) and thyroid function tests should be evaluated at baseline and before each dose of YERVOY. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with YERVOY (see Tables 3A, 3B, and section 4.4).

Children younger than 12 years of age

The safety and efficacy of ipilimumab in children younger than 12 years of age has not been established.

Permanent discontinuation of treatment or withholding of doses

Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of YERVOY therapy and institution of systemic high-dose corticosteroid. In some cases, addition of other immunosuppressive therapy may be considered (see section 4.4).

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

Guidelines for permanent discontinuation or withholding of doses are described in Tables 3A and 3B for YERVOY as monotherapy, and in Table 3C for YERVOY in combination with nivolumab or administration of the second phase of treatment (nivolumab monotherapy) following combination treatment. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 3A When to permanently discontinue YERVOY as monotherapy	
Permanently discontinue YERVOY 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 section 4.4 for detailed management guidelines).	
<u>Severe or life-threatening adverse reactions</u>	NCI-CTCAE v4 Grade^a
Gastrointestinal: Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation)	<ul style="list-style-type: none"> ▪ Grade 3 or 4 diarrhoea or colitis
Hepatic: Severe elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or symptoms of hepatotoxicity	<ul style="list-style-type: none"> ▪ Grade 3 or 4 elevation in AST, ALT, or total bilirubin
Skin: Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or severe widespread pruritus interfering with activities of daily living or requiring medical intervention	<ul style="list-style-type: none"> ▪ Grade 4 rash or Grade 3 pruritus
Neurologic: New onset or worsening severe motor or sensory neuropathy	<ul style="list-style-type: none"> ▪ Grade 3 or 4 motor or sensory neuropathy
Other organ systems^b: (e.g. nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)	<ul style="list-style-type: none"> ▪ ≥ Grade 3 immune-related reactions^c ▪ ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy

^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 adverse reactions that are demonstrated or suspected to be immune-related should be graded according to CTCAE. Decision whether to discontinue YERVOY should be based on severity.

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

Table 3B When to withhold dose of YERVOY as monotherapy	
Withhold YERVOY dose^a in patients with the following immune-related adverse reactions. See section 4.4 for detailed management guidelines.	
<u>Mild to moderate Immune-related adverse reactions</u>	Action
Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs	<ol style="list-style-type: none"> 1. Withhold dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). 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 YERVOY if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
Hepatic: Grade 2 elevation in AST, ALT, or total bilirubin	
Skin: Moderate to severe (Grade 3) ^b skin rash or (Grade 2) 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	

^a No dose reduction of YERVOY 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. Decision whether to withhold a dose should be based on severity.

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

Table 3C: Recommended treatment modifications for YERVOY in combination with nivolumab or administration of the second phase of treatment (nivolumab monotherapy) following combination treatment

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 or 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency, Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy ^a as long as no symptoms are present
	Grade 4 hypothyroidism	Permanently discontinue treatment
	Grade 4 hyperthyroidism	
	Grade 4 hypophysitis	
	Grade 3 or 4 adrenal insufficiency	
	Grade 4 diabetes	
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 3 myocarditis	Permanently discontinue treatment
	Grade 4 or recurrent Grade 3 ; persistent Grade 2 or 3 despite treatment modification ; inability to	Permanently discontinue treatment

Table 3C: Recommended treatment modifications for YERVOY in combination with nivolumab or administration of the second phase of treatment (nivolumab monotherapy) following combination treatment

reduce corticosteroid dose to 10 mg
prednisone or equivalent per day

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

^a Recommendation for the use of hormone replacement therapy is provided in section 4.4.

YERVOY in combination with nivolumab should be permanently discontinued for:

- Grade 4 or recurrent Grade 3 adverse reactions;
- Persistent Grade 2 or 3 adverse reactions despite management.

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

Special populations

Paediatric population

The safety and efficacy of YERVOY in children younger than 12 years of age have not been established. Very limited data are available. YERVOY should not be used in children younger than 12 years of age.

Elderly

No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from first-line RCC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). No specific dose adjustment is necessary in this population (see section 5.1).

Renal impairment

The safety and efficacy of YERVOY 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 section 5.2).

Hepatic impairment

The safety and efficacy of YERVOY 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 section 5.2). YERVOY must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline (see section 5.1).

Method of administration

YERVOY is for intravenous use. The recommended infusion period is 30 or 90 minutes, depending on the dose.

YERVOY can be used for intravenous administration without dilution or may be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection to concentrations between 1 and 4 mg/ml.

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

When administered in combination with nivolumab, nivolumab should be given first followed by YERVOY on the same day. Use separate infusion bags and filters for each infusion.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Ipilimumab in combination with nivolumab

When ipilimumab is administered in combination with nivolumab, refer to the Summary of Product Characteristics for nivolumab prior to initiation of treatment. For additional information on warnings and precautions associated with nivolumab treatment, please refer to the nivolumab SmPC. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see section 4.2). Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy.

Cardiac and pulmonary adverse events including pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. Ipilimumab in combination with nivolumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions (see section 4.2).

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with ipilimumab in combination with nivolumab may occur at any time during or after discontinuation of therapy.

Immune-related reactions

Ipilimumab is associated with inflammatory adverse reactions resulting from increased or excessive immune activity (immune-related adverse reactions), likely to be related to its mechanism of action. Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. While most immune-related adverse reactions occurred during the induction period, onset months after the last dose of ipilimumab has also been reported. Unless an alternate etiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and ipilimumab-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Ipilimumab specific management guidelines for immune-related adverse reactions are described below for use as monotherapy and in combination with 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, ipilimumab in combination with nivolumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction that occurs as a consequence of combination therapy, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

Ipilimumab 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.

Ipilimumab 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.

Immune-related gastrointestinal reactions

Ipilimumab as monotherapy

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

In patients who received ipilimumab 3 mg/kg monotherapy in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20, see section 5.1), 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 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. Post-marketing cases of cytomegalovirus (CMV) infection/reactivation have been reported in patients with corticosteroid-refractory immune-related colitis. Stool infections work-up should be performed upon presentation of diarrhoea or colitis to exclude infectious or other alternate etiologies.

Management recommendations for diarrhoea or colitis are based on severity of symptoms (per 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 (e.g. abdominal pain or blood in stools) may remain on ipilimumab. Symptomatic treatment (e.g. loperamide, fluid replacement) and close monitoring are advised. If mild to moderate symptoms recur or persist for 5-7 days, the scheduled dose of ipilimumab should be withheld and corticosteroid therapy (e.g. prednisone 1 mg/kg orally once daily or equivalent) should be initiated. If resolution to Grades 0-1 or return to baseline occurs, ipilimumab may be resumed (see section 4.2).

Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) diarrhoea or colitis (see section 4.2), and systemic high-dose intravenous corticosteroid therapy should be initiated immediately. (In clinical trials, methylprednisolone 2 mg/kg/day has been used). Once diarrhoea and other symptoms are controlled, the initiation of corticosteroid taper should be based on clinical judgment. 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 regimen should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded (including Cytomegalovirus (CMV) infection/reactivation evaluated with viral PCR on biopsy, and other viral, bacterial and parasitic etiology). 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 (see the Summary of Product Characteristics for infliximab).

Immune-related colitis

Ipilimumab in combination with nivolumab

Severe diarrhoea or colitis has been observed with ipilimumab in combination with nivolumab (see section 4.8). Patients should be monitored for diarrhoea and additional symptoms of colitis, such as

abdominal pain and mucus or blood in stool. Infectious and disease-related aetiologies should be ruled out.

For Grade 4 diarrhoea or colitis, ipilimumab 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.

Grade 3 diarrhoea or colitis observed with ipilimumab in combination with nivolumab requires permanent discontinuation of treatment and initiation of corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

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

Immune-related pneumonitis

Ipilimumab in combination with nivolumab

Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with ipilimumab in combination with nivolumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy infiltrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 pneumonitis, ipilimumab 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, ipilimumab in combination with nivolumab should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, ipilimumab 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 ipilimumab in combination with nivolumab must be permanently discontinued.

Immune-related hepatotoxicity

Ipilimumab as monotherapy

Ipilimumab is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in clinical trials (see section 4.8).

In patients who received ipilimumab 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 ipilimumab, as early laboratory changes may be indicative of emerging immune-related hepatitis (see section 4.2). 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 medication 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 elevation, the scheduled dose of ipilimumab should be withheld, and LFTs must be monitored until resolution. Upon improvement, ipilimumab may be resumed (see section 4.2).

For patients with Grade 3 or 4 transaminase or total bilirubin elevation, treatment must be permanently discontinued (see section 4.2), and systemic high-dose intravenous corticosteroid therapy (e.g. 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, the initiation of corticosteroid taper should be based on clinical judgment. Tapering 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 (see the Summary of Product Characteristics for mycophenolate mofetil).

Ipilimumab in combination with nivolumab

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

For Grade 3 or 4 transaminase or total bilirubin elevation, ipilimumab 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, ipilimumab 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, ipilimumab in combination with nivolumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and ipilimumab in combination with nivolumab must be permanently discontinued.

Immune-related skin adverse reactions

Caution should be used when considering the use of ipilimumab or ipilimumab 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 as monotherapy

Ipilimumab is associated with serious skin adverse reactions that may be immune-related. Rare cases of toxic epidermal necrolysis (TEN) (including Steven Johnson Syndrome) have been observed, some with fatal outcome. Rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported in clinical trials and during post-marketing use (see section 4.8).

DRESS presents as a rash with eosinophilia associated with one or more of the following features: fever, lymphadenopathy, facial oedema, and internal organ involvement (hepatic, renal, pulmonary). DRESS may be characterized by a long latency (two to eight weeks) between medicinal product exposure and disease onset.

Ipilimumab-induced rash and pruritus were predominantly mild or moderate (Grade 1 or 2) and responsive to symptomatic therapy. In patients who received ipilimumab 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).

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

For patients with a severe (Grade 3) rash, the scheduled dose of ipilimumab should be withheld. If initial symptoms improve to mild (Grade 1) or resolve, ipilimumab therapy may be resumed (see section 4.2).

Ipilimumab must be permanently discontinued in patients with a very severe (Grade 4) rash or severe (Grade 3) pruritus (see section 4.2), and systemic high-dose intravenous corticosteroid therapy (e.g. methylprednisolone 2 mg/kg/day) should be initiated immediately. Once rash or pruritus is controlled, initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month.

Ipilimumab in combination with nivolumab

Severe rash has been observed with ipilimumab in combination with nivolumab (see section 4.8).

Ipilimumab in combination with nivolumab should be withheld for Grade 3 rash and discontinued for Grade 4 rash. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

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

Immune-related neurological reactions

Ipilimumab as monotherapy

Ipilimumab is associated with serious immune-related neurological adverse reactions. Fatal Guillain-Barré syndrome has been reported in clinical trials. Myasthenia gravis-like symptoms have also been reported (see section 4.8). 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 medication should be excluded. For patients with moderate (Grade 2) neuropathy (motor with or without sensory) likely related to ipilimumab, the scheduled dose should be withheld. If neurologic symptoms resolve to baseline, the patient may resume ipilimumab (see section 4.2).

Ipilimumab must be permanently discontinued in patients with severe (Grade 3 or 4) sensory neuropathy suspected to be related to ipilimumab (see section 4.2). Patients must be treated according to institutional guidelines for management of sensory neuropathy, and intravenous corticosteroids (e.g. methylprednisolone 2 mg/kg/day) should be initiated immediately.

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

Immune-related nephritis and renal dysfunction

Ipilimumab in combination with nivolumab

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

For Grade 4 serum creatinine elevation, ipilimumab 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, ipilimumab 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, ipilimumab 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 ipilimumab in combination with nivolumab must be permanently discontinued.

Immune-related endocrinopathy

Ipilimumab as monotherapy

Ipilimumab can cause inflammation of the endocrine system organs, manifesting as hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism (see section 4.8), 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, behavioural changes, electrolyte disturbances, and hypotension. Adrenal crisis as a cause of the patient's symptoms must be excluded. Clinical experience with ipilimumab-associated endocrinopathy is limited.

For patients who received ipilimumab 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 intravenous 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 (e.g. dexamethasone 4 mg every 6 hrs or equivalent) is recommended to treat the inflammation of the affected gland, and the scheduled dose of ipilimumab should be withheld (see section 4.2). 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 ipilimumab may be resumed and initiation of corticosteroid taper should be based on clinical judgment. Tapering 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 with ipilimumab in combination with nivolumab (see section 4.8).

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

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

For symptomatic Grade 2 adrenal insufficiency, ipilimumab in combination with nivolumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed. ipilimumab 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, ipilimumab 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, ipilimumab in combination with nivolumab may be resumed after corticosteroid taper, if needed. Ipilimumab 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, ipilimumab 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. Ipilimumab in combination with nivolumab must be permanently discontinued for life-threatening diabetes.

Infusion reaction

Ipilimumab as monotherapy or in combination with nivolumab

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

Other immune-related adverse reactions

Ipilimumab as monotherapy

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

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

Ipilimumab as monotherapy or in combination with a PD-1 or PD-L1 inhibitor

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. Caution should be taken when ipilimumab is given following or in combination with a PD-1 or PD-L1 inhibitor.

Ipilimumab in combination with nivolumab

The following immune-related adverse reactions were reported in less than 1% of patients treated with ipilimumab in combination with nivolumab in clinical trials across doses and tumour types: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenia gravis, myasthenic syndrome, aseptic meningitis, encephalitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, and rhabdomyolysis. Cases of Vogt-Koyanagi-Harada syndrome have been reported post-marketing (see section 4.8).

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, ipilimumab in combination with nivolumab should be withheld and corticosteroids administered. Upon improvement, ipilimumab in combination with nivolumab may be resumed after corticosteroid taper. Ipilimumab 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), some with fatal outcome, have been reported with ipilimumab 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, ipilimumab in combination with nivolumab should be withheld or discontinued (see section 4.2), and appropriate treatment instituted.

Disease specific precautions

Melanoma

Patients with ocular melanoma, primary CNS melanoma and active brain metastases were not included in the MDX010-20 trial (see section 5.1).

Patients with ocular melanoma were not included in the CA184-169 clinical trial. However, patients with brain metastases were included in this study, if they were free of neurologic symptoms related to metastatic brain lesions and if they did not require or receive systemic corticosteroid therapy in the 10 days prior to beginning ipilimumab therapy (see section 5.1).

Patients with ocular melanoma, active brain metastases and prior therapy with ipilimumab were not included in the paediatric trial CA184070 (see section 5.1).

Patients with ocular melanoma, active brain metastases and prior therapy with CTLA-4, PD-1, PD-L1, or CD137 targeted agents were not included in the paediatric trial CA184178 (see section 5.1).

Patients with a baseline performance score ≥ 2 , active brain metastases or autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the clinical trials of ipilimumab in combination with nivolumab. Patients with ocular/uveal melanoma were excluded from clinical trials of melanoma. In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

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

Use of ipilimumab in combination with nivolumab in melanoma patients with rapidly progressing disease.

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

Renal Cell Carcinoma

Patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of ipilimumab in combination with nivolumab (see sections 4.5 and 5.1). In the absence of data, ipilimumab in combination with nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

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 trials. Ipilimumab is a T-cell potentiator that enables the immune response (see section 5.1) and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection. Ipilimumab 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, ipilimumab should be used with caution after careful consideration of the potential risk-benefit on an individual basis.

Patients on controlled sodium diet

Each ml of this medicinal product contains 0.1 mmol (or 2.30 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

Concurrent administration with vemurafenib

In a Phase 1 trial, asymptomatic grade 3 increases in transaminases (ALT/AST $> 5 \times$ ULN) and bilirubin (total bilirubin $> 3 \times$ ULN) were reported with concurrent administration of ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID). Based on these preliminary data, the concurrent administration of ipilimumab and vemurafenib is not recommended.

Sequential administration with vemurafenib

In a Phase 2 trial, the sequential treatment with vemurafenib followed by 10 mg/kg ipilimumab in patients with BRAF-mutated metastatic melanoma showed a higher incidence of Grade 3+ skin adverse reactions than with ipilimumab alone. Caution should be used when ipilimumab is administered following prior vemurafenib.

Paediatric population

Limited, but no long-term, safety data is available on the use of ipilimumab in adolescents 12 years of age and older.

Only very limited data are available in children younger than 12 years of age. Therefore, ipilimumab should not be used in children younger than 12 years of age.

Before initiating treatment with ipilimumab monotherapy in adolescents of 12 years and older, physicians are advised to carefully evaluate the individual patient, taking into consideration the limited available data, the observed benefits and the toxicity of ipilimumab monotherapy in the paediatric population (see sections 4.8 and 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Ipilimumab is a human monoclonal antibody that is not metabolized by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes.

A drug-interaction study in adults of ipilimumab administered alone and in combination with chemotherapy (dacarbazine or paclitaxel/carboplatin) was conducted evaluating interaction with CYP isozymes (particularly CYP1A2, CYP2E1, CYP2C8, and CYP3A4) in patients with treatment-naïve advanced melanoma. No clinically relevant pharmacokinetic drug-drug interaction was observed between ipilimumab and paclitaxel/carboplatin, dacarbazine or its metabolite, 5-aminoimidazole-4-carboxamide (AIC).

Other forms of interaction

Corticosteroids

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

Anticoagulants

The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with ipilimumab (see section 4.8), patients who require concomitant anticoagulant therapy should be monitored closely.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of ipilimumab in pregnant women. Animal reproduction studies have shown reproductive toxicity (see section 5.3). Human IgG1 crosses the placental barrier. The potential risk of treatment to the developing foetus is unknown. YERVOY is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk.

Breast-feeding

Ipilimumab has been shown to be present at very low levels in milk from cynomolgus monkeys treated during pregnancy. It is unknown whether ipilimumab is secreted in human milk. Secretion of IgGs in human milk is generally limited and IgGs have a low oral bioavailability. Significant systemic exposure of the infant is not expected and no effects on the breast-fed newborn/infant are anticipated. However, because of the potential for adverse reactions in nursing infants, a decision must be made whether to discontinue breast-feeding or to discontinue from YERVOY therapy taking into account the benefit of breast-feeding for the child and the benefit of YERVOY therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

YERVOY has minor influence on the ability to drive and use machines.

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

4.8 Undesirable effects

Ipilimumab as monotherapy (see section 4.2)

a. Summary of safety profile

Ipilimumab has been administered to approximately 10,000 patients in a clinical program evaluating its use with various doses and tumour types. Unless otherwise specified, the data below reflect exposure to ipilimumab at 3 mg/kg in clinical trials of melanoma. In the Phase 3 study MDX010-20, (see section 5.1), patients received a median of 4 doses (range 1-4).

Ipilimumab is most commonly associated with adverse reactions resulting from increased or excessive immune activity. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of ipilimumab (see section 4.4 for management of immune-related adverse reactions).

In patients who received 3 mg/kg ipilimumab monotherapy in MDX010-20, the most frequently reported adverse reactions ($\geq 10\%$ of patients) were diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, and abdominal pain. The majority were mild to moderate (Grade 1 or 2). *Ipilimumab* therapy was discontinued for adverse reactions in 10% of patients.

b. Tabulated list of adverse reactions

Adverse reactions reported in patients with advanced melanoma who were treated with ipilimumab 3 mg/kg in clinical trials (n= 767) are presented in Table 4.

These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Rates of immune-related adverse reactions in HLA-A2*0201 positive patients who received ipilimumab in MDX010-20 were similar to those observed in the overall clinical program.

The safety profile of ipilimumab 3 mg/kg in chemotherapy-naive patients pooled across Phase 2 and 3 clinical trials (N= 75; treated), in treatment-naive patients in two retrospective observational studies (N= 273 and N= 157), and in CA184-169 (N=362) was similar to that in previously-treated advanced melanoma.

Table 4: Adverse reactions in patients with advanced melanoma treated with ipilimumab 3 mg/kg (n= 767)^a	
Infections and infestations	
Uncommon	sepsis ^b , septic shock ^b , urinary tract infection, respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common	tumour pain
Uncommon	paraneoplastic syndrome
Blood and lymphatic system disorders	
Common	anaemia, lymphopenia
Uncommon	haemolytic anaemia ^b , thrombocytopenia, eosinophilia, neutropenia
Not known	histiocytosis haematophagic ^c
Immune system disorders	
Uncommon	hypersensitivity
Very rare	anaphylactic reaction
Endocrine disorders	
Common	hypopituitarism (including hypophysitis) ^c , hypothyroidism ^c
Uncommon	adrenal insufficiency ^c , secondary adrenocortical insufficiency ^d , hyperthyroidism ^c , hypogonadism
Rare	autoimmune thyroiditis ^d , thyroiditis ^d
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration, hypokalemia
Uncommon	hyponatremia, alkalosis, hypophosphatemia, tumour lysis syndrome, hypocalcaemia ^d
Psychiatric disorders	
Common	confusional state
Uncommon	mental status changes, depression, decreased libido
Nervous system disorders	
Common	peripheral sensory neuropathy, dizziness, headache, lethargy
Uncommon	Guillain-Barré syndrome ^{b,c} , meningitis (aseptic), autoimmune central neuropathy (encephalitis) ^d , syncope, cranial neuropathy, brain oedema, peripheral neuropathy, ataxia, tremor, myoclonus, dysarthria
Rare	myasthenia gravis ^d
Eye disorders	
Common	blurred vision, eye pain
Uncommon	uveitis ^c , vitreous haemorrhage, iritis ^c , eye oedema ^d , blepharitis ^d , reduced visual acuity, foreign body sensation in eyes, conjunctivitis
Rare	Vogt-Koyanagi-Harada syndrome ^c
Cardiac disorders	
Uncommon	arrhythmia, atrial fibrillation
Vascular disorders	
Common	hypotension, flushing, hot flush
Uncommon	vasculitis, angiopathy ^b , peripheral ischaemia, orthostatic hypotension
Rare	temporal arteritis ^d
Respiratory, thoracic and mediastinal disorders	
Common	dyspnea, cough
Uncommon	respiratory failure, acute respiratory distress syndrome ^b , lung infiltration, pulmonary oedema, pneumonitis, allergic rhinitis
Gastrointestinal disorders	
Very common	diarrhoea ^c , vomiting, nausea
Common	gastrointestinal haemorrhage, colitis ^{b,c} , constipation, gastroesophageal reflux disease, abdominal pain, mucosal inflammation ^d
Uncommon	gastrointestinal perforation ^{b,c} , large intestine perforation ^{b,c} , intestinal perforation ^{b,c} ,

	peritonitis ^b , gastroenteritis, diverticulitis, pancreatitis, enterocolitis, gastric ulcer, large intestinal ulcer, oesophagitis, ileus ^d
Rare	proctitis ^d
Hepatobiliary disorders	
Common	abnormal hepatic function
Uncommon	hepatic failure ^{b,c} , hepatitis, hepatomegaly, jaundice
Skin and subcutaneous tissue disorders	
Very common	rash ^c , pruritus ^c
Common	dermatitis, erythema, vitiligo, urticaria, eczema ^d , alopecia, night sweats, dry skin
Uncommon	toxic epidermal necrolysis ^{b,c} , leukocytoclastic vasculitis, skin exfoliation, hair colour changes ^d
Rare	erythema multiforme ^d , psoriasis ^d , Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) ^d
Not known	pemphigoid
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, musculoskeletal pain, muscle spasms
Uncommon	polymyalgia rheumatica, myositis ^d , arthritis, muscular weakness ^d
Rare	polymyositis ^d
Renal and urinary disorders	
Uncommon	renal failure ^b , glomerulonephritis ^c , autoimmune nephritis ^d , renal tubular acidosis, haematuria ^d
Rare	proteinuria ^d
Reproductive system and breast disorders	
Uncommon	amenorrhea
General disorders and administration site conditions	
Very common	fatigue, injection site reaction, pyrexia
Common	chills, asthenia, oedema, pain, influenza-like illness ^d
Uncommon	multi-organ failure ^{b,c} , systemic inflammatory response syndrome ^d , infusion related reaction
Investigations	
Common	increased alanine aminotransferase ^c , increased aspartate aminotransferase ^c , increased blood alkaline phosphatase ^d , increased blood bilirubin, weight decreased
Uncommon	increased gamma-glutamyltransferase ^d , increased blood creatinine, increased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood corticotrophin, increased lipase ^c , increased blood amylase ^c , positive antinuclear antibody ^d , decreased blood testosterone
Rare	decreased blood thyroid stimulating hormone ^d , decreased thyroxine ^d , abnormal blood prolactin ^d

^a Frequencies are based on pooled data from 9 clinical trials investigating the ipilimumab 3 mg/kg dose in melanoma.

^b Including fatal outcome.

^c Additional information about these potentially inflammatory adverse reactions is provided in “Description of selected adverse reactions” and section 4.4. Data presented in those sections primarily reflect experience from a Phase 3 study, MDX010-20.

^d Data outside the 9 completed clinical trials in melanoma were included in frequency determinations.

^e Post-marketing event (also see section 4.4).

Additional adverse reactions not listed in Table 4 have been reported in patients who received other doses (either < or > 3 mg/kg) of ipilimumab in clinical trials of melanoma. These additional reactions occurred at a frequency of < 1% unless otherwise noted: meningism, myocarditis, pericardial effusion, cardiomyopathy, autoimmune hepatitis, erythema nodosum, autoimmune pancreatitis, hyperpituitarism, hypoparathyroidism, infectious peritonitis, episcleritis, scleritis, Raynaud’s phenomenon, palmar-plantar erythrodysesthesia syndrome, cytokine release syndrome, sarcoidosis, decreased blood gonadotrophin, leukopenia, polycythaemia, lymphocytosis, ocular myositis, and neurosensory hypoaacusis.

The overall safety profile of ipilimumab 3 mg/kg in clinical trial CA184-169 (N=362) was consistent with that established for ipilimumab in patients treated for advanced melanoma.

Ipilimumab in combination with nivolumab (see section 4.2)

a. Summary of the safety profile

When ipilimumab is administered in combination with nivolumab, refer to the Summary of Product Characteristics for nivolumab prior to initiation of treatment. For additional information on warnings and precautions associated with nivolumab treatment, please refer to the nivolumab SmPC.

Melanoma

In the pooled dataset of ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg in melanoma (n = 448) with minimum follow-up ranging from 6 to 28 months, the most frequent adverse reactions ($\geq 10\%$) were rash (52%), fatigue (46%), diarrhoea (43%), pruritus (36%), nausea (26%), pyrexia (19%), decreased appetite (16%), hypothyroidism (16%), colitis (15%), vomiting (14%), arthralgia (13%), abdominal pain (13%), headache (11%), and dyspnoea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Among the patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/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 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 ($\geq 10\%$) 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.

b. Tabulated summary of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg (n = 448) are presented in Table 5. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 5: Adverse reactions with ipilimumab in combination with nivolumab

	Ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg*	Ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg**
Infections and infestations		
Common	pneumonia, upper respiratory tract infection	pneumonia, upper respiratory tract infection, conjunctivitis
Uncommon	bronchitis	bronchitis, aseptic meningitis
Blood and lymphatic system disorders		
Common	eosinophilia	
Uncommon		eosinophilia
Immune system disorders		
Common	infusion related reaction, hypersensitivity	infusion-related reaction, hypersensitivity
Uncommon	sarcoidosis	
Not known	solid organ transplant rejection ^h	
Endocrine disorders		
Very common	hypothyroidism	hypothyroidism, hyperthyroidism
Common	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis	adrenal insufficiency ^c , hypophysitis ^c , thyroiditis, diabetes mellitus ^c
Uncommon	diabetic ketoacidosis ^c , diabetes mellitus ^c	diabetic ketoacidosis ^c , hypopituitarism
Metabolism and nutrition disorders		
Very common	decreased appetite	decreased appetite
Common	dehydration	dehydration
Uncommon		metabolic acidosis
Not known	tumour lysis syndrome ⁱ	
Hepatobiliary disorders		
Common	hepatitis ^c	hepatitis ^c
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 ^c	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis ^c
Eye disorders		
Common	uveitis, blurred vision	blurred vision
Uncommon		uveitis
Not known	Vogt-Koyanagi-Harada syndrome ^h	
Cardiac disorders		
Common	tachycardia	tachycardia
Uncommon	arrhythmia (including ventricular arrhythmia) ^{a,d} , atrial fibrillation, myocarditis ^{a,f}	arrhythmia (including ventricular arrhythmia), myocarditis ^c
Not known	pericardial disorders ^l	
Vascular disorders		
Common	hypertension	hypertension
Respiratory, thoracic and mediastinal disorders		
Very common	dyspnoea	

Common	pneumonitis ^{a,c} , pulmonary embolism ^a , cough	pneumonitis, dyspnoea, pleural effusion, cough
Uncommon	pleural effusion	
Gastrointestinal disorders		
Very common	colitis ^a , diarrhoea, vomiting, nausea, abdominal pain	diarrhoea, vomiting, nausea
Common	stomatitis, pancreatitis, constipation, dry mouth	colitis, stomatitis, pancreatitis, abdominal pain, constipation, dry mouth
Uncommon	intestinal perforation ^a , gastritis, duodenitis	gastritis
Skin and subcutaneous tissue disorders		
Very common	rash ^c , pruritus	rash ^c , 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,f} , Stevens-Johnson syndrome ^f	
Musculoskeletal and connective tissue disorders		
Very common	arthralgia	musculoskeletal pain ^g , arthralgia
Common	musculoskeletal pain ^g	arthritis, muscle spasms, muscular weakness
Uncommon	spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis) ^{a,c} , rhabdomyolysis ^{a,f}	polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis
Renal and urinary disorders		
Common	renal failure (including acute kidney injury) ^{a,c}	renal failure (including acute kidney injury) ^c
Uncommon	tubulointerstitial nephritis	tubulointerstitial nephritis
General disorders and administration site conditions		
Very common	fatigue, pyrexia	fatigue, pyrexia
Common	oedema (including peripheral oedema), pain	oedema (including peripheral oedema), pain, chest pain, chills
Uncommon	chest pain	
Investigations^b		
Very common	increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia ^c , hypoglycaemia, lymphopaenia, leucopenia, neutropaenia, thrombocytopaenia, anaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia	increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia ^c , hypoglycaemia, lymphopaenia, leucopenia, neutropaenia ^c , thrombocytopaenia, anaemia, hypercalcaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia
Common	hypercalcaemia, hypermagnesaemia, hypernatraemia, weight decreased	hypermagnesaemia, hypernatraemia, weight decreased

* ipilimumab in combination with nivolumab for the first 4 doses then followed by nivolumab monotherapy in melanoma.

** ipilimumab in combination with nivolumab for the first 4 doses then followed by nivolumab monotherapy in RCC.

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

- b Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See “Description of selected adverse reactions; laboratory abnormalities” below.
- c Life-threatening cases have been reported in completed or ongoing clinical studies.
- d 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).
- e 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.
- f Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.
- g 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.
- h Post-marketing event (also see section 4.4)
- i Reported in clinical studies and in the post-marketing setting.
- j Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler’s syndrome.

c. Description of selected adverse reactions

Except where noted, data relating to ipilimumab monotherapy are based on patients who received either ipilimumab 3 mg/kg monotherapy (n= 131) or ipilimumab 3 mg/kg in combination with gp100 (n= 380) in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20, see section 5.1).

Ipilimumab in combination with nivolumab is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment was required in a greater proportion of patients receiving ipilimumab in combination with nivolumab than in those receiving nivolumab monotherapy. Table 6 presents the percentage of patients with immune-related adverse reactions who were permanently discontinued from treatment with ipilimumab in combination with nivolumab. Additionally, for patients who experienced an event, Table 6 presents the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents). The management guidelines for these adverse reactions are described in section 4.4.

Table 6: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen

	Ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg %	Ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg %
Immune-related adverse reaction leading to permanent discontinuation		
Pneumonitis	2.0	2.2
Colitis	16	4.0
Hepatitis	9	4.4
Nephritis and Renal Dysfunction	1.1	1.3
Endocrinopathies	2.7	2.9
Skin	0.9	1.5
Hypersensitivity/Infusion Reaction	0	0
Immune-related adverse reaction requiring high-dose corticosteroids^{a,b}		

Pneumonitis	63	59
Colitis	46	26
Hepatitis	46	35
Nephritis and Renal Dysfunction	17	27
Endocrinopathies	27	25
Skin	7	7
Hypersensitivity/Infusion Reaction	6	9

^a at least 40 mg daily prednisone equivalents

^b frequency is based on the number of patients who experienced the immune-related adverse reaction

Immune-related gastrointestinal reactions

Ipilimumab is associated with serious immune-related gastrointestinal reactions. Fatalities due to gastrointestinal perforation have been reported in < 1% of patients who received ipilimumab 3 mg/kg in combination with gp100.

In the ipilimumab 3 mg/kg monotherapy group, diarrhoea and colitis of any severity were reported in 27% and 8%, respectively. The frequency of severe (Grade 3 or 4) diarrhoea and severe (Grade 3 or 4) colitis was 5% each. The median time to onset of severe or fatal (Grade 3 to 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). In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic and neutrophilic infiltration.

Immune-related colitis

In patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg in melanoma, the incidence of diarrhoea or colitis was 46.7% (209/448). Grade 2, Grade 3, and Grade 4 cases were reported in 13.6% (61/448), 15.8% (71/448), and 0.4% (2/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.2 months (range: 0.0-22.6). Resolution occurred in 186 patients (89.4%) with a median time to resolution of 3.0 weeks (range: 0.1-159.4⁺).

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). Resolution occurred in 140 patients (91.5%) with a median time to resolution of 2.4 weeks (range: 0.1-103.1⁺).

Immune-related pneumonitis

In patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg in melanoma, the incidence of pneumonitis including interstitial lung disease, was 7.8% (35/448). Grade 2, Grade 3, and Grade 4 cases were reported in 4.7% (21/448), 1.1% (5/448), and 0.2% (1/448) of patients, respectively. One of the Grade 3 pneumonitis cases worsened over 11 days with a fatal outcome. Median time to onset was 2.6 months (range: 0.7-12.6). Resolution occurred in 33 patients (94.3%) with a median time to resolution of 6.1 weeks (range: 0.3-35.1).

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). Resolution occurred in 31 patients (91.2%) with a median time to resolution of 6.1 weeks (range: 0.7-85.9⁺).

Immune-related hepatotoxicity

Ipilimumab is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in < 1% of patients who received ipilimumab 3 mg/kg monotherapy.

Increases in AST and ALT of any severity were reported in 1% and 2% of patients, respectively. There were no reports of severe (Grade 3 or 4) AST or ALT elevation. Time to onset of moderate to severe or fatal (Grade 2 to 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. In clinical trials, liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

In patients receiving ipilimumab at a higher than recommended dose in combination with dacarbazine, immune-related hepatotoxicity occurred more frequently than in patients receiving ipilimumab 3 mg/kg monotherapy.

In patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg, 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 Grade 5 cases were reported. Median time to onset was 1.5 months (range: 0.0-30.1). Resolution occurred in 124 patients (93.9%) with a median time to resolution of 5.1 weeks (range: 0.1-106.9).

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). Resolution occurred in 86 patients (85.1%) with a median time to resolution of 6.1 weeks (range: 0.1⁺-82.9⁺).

Immune-related skin adverse reactions

Ipilimumab is associated with serious skin adverse reactions that may be immune-related. Fatal toxic epidermal necrolysis (including SJS) has been reported in < 1% of patients who received ipilimumab in combination with gp100 (see section 5.1). Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been rarely reported with Ipilimumab in clinical studies and during post-marketing use. Incidental cases of pemphigoid have been reported during post-marketing use.

In the ipilimumab 3 mg/kg monotherapy group, rash and pruritus of any severity were each reported in 26% of patients. Ipilimumab-induced rash and pruritus were predominantly mild (Grade 1) or moderate (Grade 2) and responsive to symptomatic therapy. The median time to onset of moderate to severe or fatal (Grade 2 to 5) skin adverse reactions was 3 weeks from start of treatment (range 0.9 to 16 weeks). 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).

In patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg in melanoma, the incidence of rash was 65.0% (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). Resolution occurred in 191 patients (65.9%) with a median time to resolution of 11.4 weeks (range: 0.1-150.1⁺). Rare cases of SJS and TEN some of them with fatal outcome have been observed (see sections 4.2 and 4.4).

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). Resolution occurred in 192 patients (72.2%) with a median time to resolution of 11.6 weeks (range: 0.1-126.7⁺).

Immune-related neurological reactions

Ipilimumab is associated with serious immune-related neurological reactions. Fatal Guillain-Barré syndrome has been reported in < 1% of patients who received ipilimumab 3 mg/kg in combination with gp100. Myasthenia gravis-like symptoms have also been reported in < 1% of patients who received higher doses of ipilimumab in clinical trials.

Immune-related nephritis and renal dysfunction

In patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg in melanoma, the incidence of nephritis or renal dysfunction was 5.1% (23/448). Grade 2, Grade 3, and Grade 4 cases were reported in 1.6% (7/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.6 months (range: 0.5-21.8). Resolution occurred in 21 patients (91.3%) with a median time to resolution of 2.1 weeks (range: 0.1- 125.1⁺).

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). Resolution occurred in 37 patients (77.1%) with a median time to resolution of 13.2 weeks (range: 0.1⁺-106.0⁺).

Immune-related endocrinopathy

In the ipilimumab 3 mg/kg monotherapy group, hypopituitarism of any severity was reported in 4% of patients. Adrenal insufficiency, hyperthyroidism, and hypothyroidism of any severity were each reported in 2% of patients. The frequency of severe (Grade 3 or 4) hypopituitarism was reported in 3% of patients. There were no reports of severe or very severe (Grade 3 or 4) adrenal insufficiency, hyperthyroidism, or hypothyroidism. Time to onset of moderate to very severe (Grade 2 to 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 hormone replacement therapy.

In patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg in melanoma, the incidence of thyroid disorders was 25.2% (113/448). Grade 2 and Grade 3 thyroid disorders were reported in 14.5% (65/448) and 1.3% (6/448) of patients, respectively.

Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 5.8% (26/448) and 2.0% (9/448) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.4% (2/448) and 0.7% (3/448) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 1.6% (7/448), 1.3% (6/448) and 0.2% (1/448) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus and Grade 4 diabetic ketoacidosis were each reported in 0.2% (1/448) of patients. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 1.9 months (range: 0.0-28.1). Resolution occurred in 64 patients (45.4%). Time to resolution ranged from 0.4 to 155.4⁺ 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). Resolution occurred in 76 patients (42.7%). Time to resolution ranged from 0.4 to 130.3⁺ weeks.

Infusion reactions

In patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg, 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, 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.

Immunogenicity

Less than 2% of patients with advanced melanoma who received ipilimumab in Phase 2 and 3 clinical trials developed antibodies against ipilimumab. None had any infusion-related or peri-infusional hypersensitivity or anaphylactic reactions. Neutralising antibodies against ipilimumab were not detected. Overall, no apparent association was observed between antibody development and adverse reactions.

Of the patients who were treated with ipilimumab in combination with nivolumab and evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 8.4%. Neutralising antibodies against ipilimumab ranged from 0 to 0.3%. Of patients evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralising antibodies against nivolumab was 0.5% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks.

When administered in combination with nivolumab, the CL of ipilimumab was unchanged in the presence of anti-ipilimumab antibodies and there was no evidence of altered toxicity profile.

Laboratory abnormalities with ipilimumab in combination with nivolumab

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

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

d. Paediatric population

No new adverse drug reactions were reported in adolescents 12 years of age and older.

In study CA184070, no immune-related adverse reactions (irAR) \geq Grade 3 were reported for the single patient 12 years of age and older who was treated with ipilimumab 3 mg/kg. Two (25.0%) of 8 patients treated with 5 mg/kg and 1 (11.1%) of 9 patients treated with 10 mg/kg reported Grade 3–4 events. None of the events were fatal. The types of irARs were consistent with the adult experience, with the most commonly reported irARs across all groups in the categories of gastrointestinal (0 [3 mg/kg], 62.5% [5 mg/kg], and 44.4% [10 mg/kg]), hepatic function (0 [3 mg/kg], 75.0% [5 mg/kg], 33.3% [10 mg/kg]), and skin (0 [3 mg/kg], 25.0% [5 mg/kg], 33.3% [10 mg/kg]) events. No new or unexpected irARs were observed in this study. No differences in the spectrum of irARs reported in adults and the paediatric population were evident.

In study CA184178, no new or unexpected irARs were observed, and the observed irARs were similar in frequency, intensity and organ site to what has been reported in adult studies. Two patients in the 10

mg/kg group experienced a Grade 1 and Grade 3 on-study endocrine irAR of hyperglycemia. No other endocrine abnormalities were reported.

A summary of adverse events in adolescents 12 years of age and older, as well as adults, is presented in Table 7.

Table 7: Summary of Adverse Events after up to Four Doses of 3, 5 and 10 mg/kg, All Treated Patients

	Number of Patients (%)						
	Age ≥ 12 to 21 years			Age 12 to < 18 years		Adults	
	Advanced Melanoma and Non-Melanoma Solid Tumors			Advanced Melanoma		Advanced Melanoma	
	CA184070			CA184178		CA184004/ 022Pooled	CA184004/007/ 008/022 Pooled
	3 mg/kg n = 1	5 mg/kg n = 8	10 mg/kg n = 9	3 mg/kg n = 4	10 mg/kg n = 8	3 mg/kg n = 111	10 mg/kg n = 325
All Deaths, n (%)	1 (100.0)	4 (50.0)	2 (22.2)	2 (50.0)	3 (37.5)	26 (23.4)	71 (21.8)
Treatment-Related Deaths, n (%)	0	0	0	0	0	2 (1.8)	6 (1.8)
SAEs, n (%)	1 (100.0)	7 (87.5)	4 (44.4)	1 (25.0)	6 (75.0)	50 (45.0)	168 (51.7)
SAEs, drug-related, n (%)	1 (100.0)	5 (62.5)	4 (44.4)	1 (25.0)	5 (62.5)	19 (17.1)	95 (29.2)
AEs leading to study drug discontinuation, n (%)	0	3 (37.5)	2 (22.2)	1 (25.0)	5 (62.5)	12 (10.8)	88 (27.1)
Drug-related AEs leading to study drug discontinuation, n (%)	0	3 (37.5)	2 (22.2)	1 (25.0)	5 (62.5)	9 (8.1)	61 (18.8)
irAEs, n (%)	1 (100.0)	7 (87.5)	7 (77.8)	2 (50.0)	4 (50.0)	68 (61.3)	234 (72.0)
AE, n (%)	1 (100.0)	8 (100.0)	9 (100.0)	4 (100.0)	8 (100.0)	108 (97.3)	315 (96.9)
Drug-related AEs, n (%)	1 (100.0)	7 (87.5)	9 (100.0)	2 (50.0)	7 (87.5)	88 (79.3)	274 (84.3)

MedDRA v.17.0 for CA184070, v.19.0 for CA184178, and V.12.1 for Adult Safety Pool. NA = not assessed
For adults, deaths reported in this table are within 70 days of the last dose, regardless of relationship. Deaths for pediatric patients are those with on-study events within 30 days of the last dose, except for “All Deaths,” which were >30 days after the last dose. In CA184178, deaths were reported at least 90 days of the last dose.

Attribution to ipilimumab reported as Possible, Probable, Definite, or Missing for CA184178 and Adult Safety Pool, and Related or Missing for CA184070.

Abbreviations: SAEs = serious adverse events; AEs = adverse events; irAEs = immune-related adverse events

Reporting of suspected adverse reactions

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

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Cytotoxic T-lymphocyte antigen-4 (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 reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intratumoral T-effector/ T-regulatory cell ratio which drives tumour cell death.

Pharmacodynamic effects

In patients with melanoma who received ipilimumab, the mean peripheral blood absolute lymphocyte counts (ALC) increased throughout the induction dosing period. In Phase 2 studies, this increase was dose-dependent. In MDX010-20 (see section 5.1), ipilimumab 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 was observed after treatment with ipilimumab, 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 ipilimumab.

Clinical efficacy and safety

Ipilimumab in combination with nivolumab

For additional information on clinical efficacy and safety associated with the dosing recommendations of nivolumab when administered as monotherapy following combination therapy with ipilimumab, please refer to the nivolumab SmPC.

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

Clinical trials

Melanoma

Overall survival (OS) advantage of ipilimumab at the recommended dose of 3 mg/kg in patients with previously-treated advanced (unresectable or metastatic) melanoma was demonstrated in a Phase 3 study (MDX010-20). Patients with ocular melanoma, primary CNS melanoma, active brain metastases, human immunodeficiency virus (HIV), hepatitis B, and hepatitis C were not included in the MDX010-20 clinical trial. Clinical trials excluded patients with ECOG performance status > 1 and mucosal melanoma. Patients without liver metastasis who had a baseline AST > 2.5 x ULN, patients with liver metastasis who had a baseline AST > 5 x ULN, and patients with a baseline total bilirubin \geq 3 x ULN were also excluded.

For patients with a history of autoimmune disease, see also section 4.4.

MDX010-20

A Phase 3, double-blind study enrolled patients with advanced (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 ipilimumab 3 mg/kg + an investigational gp100 peptide vaccine (gp100), ipilimumab 3 mg/kg monotherapy, or gp100 alone. All patients were HLA-A2*0201 type; this HLA type supports the immune presentation of gp100. Patients were enrolled regardless of their baseline BRAF mutation status. Patients received ipilimumab 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 tumour response to ipilimumab was conducted at approximately Week 12, after completion of induction therapy.

Additional treatment with ipilimumab (re-treatment) was offered to those who developed PD after initial clinical response (PR or CR) or after SD (per the modified WHO criteria) > 3 months from the first tumour assessment. The primary endpoint was OS in the ipilimumab+ gp100 group vs. the gp100 group. Key secondary endpoints were OS in the ipilimumab+ gp100 group vs. the ipilimumab monotherapy group and in the ipilimumab monotherapy group vs. the gp100 group.

A total of 676 patients were randomized: 137 to the ipilimumab monotherapy group, 403 to the ipilimumab + gp100 group, and 136 to the gp100 alone group. The majority had received all 4 doses during induction. Thirty-two patients received re-treatment: 8 in the ipilimumab monotherapy group, 23 in the ipilimumab + gp100 group, and 1 in the gp100 group. Duration of follow-up ranged up to 55 months. Baseline characteristics were well balanced across 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 lactate dehydrogenase (LDH) at baseline. A total of 77 patients had a history of previously treated brain metastases.

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

By subgroup analysis, the observed OS benefit was consistent within most of the subgroups of patients (M [metastases]-stage, prior interleukin-2, baseline LDH, age, sex, and the type and number of prior therapy). However, for women above 50 years of age, the data supporting an OS benefit of ipilimumab treatment were limited. As the subgroups analysis includes only small numbers of patients, no definitive conclusions can be drawn from these data.

Median and estimated rates of OS at 1 year and 2 years are presented in Table 8.

Table 8:	Overall survival in MDX010-20	
	Ipilimumab 3 mg/kg n= 137	gp100 ^a n= 136
Median Months (95% CI)	10 months (8.0, 13.8)	6 months (5.5, 8.7)
OS at 1 year % (95% CI)	46% (37.0, 54.1)	25% (18.1, 32.9)
OS at 2 years % (95% CI)	24% (16.0, 31.5)	14% (8.0, 20.0)

^a gp100 peptide vaccine is an experimental control.

In the ipilimumab 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.

For patients who required re-treatment, the BORR was 38% (3/8 patients) in the ipilimumab monotherapy group, and 0% in the gp100 group. The disease control rate (DCR) (defined as CR+PR+SD) was 75% (6/8 patients) and 0%, respectively. Because of the limited number of patients

in these analyses, no definitive conclusion regarding the efficacy of ipilimumab re-treatment can be drawn.

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

CA184-169

A Phase 3, double-blind study enrolled patients with previously treated or untreated unresectable Stage III or Stage IV melanoma. A total of 727 patients were randomized, 362 to receive ipilimumab 3 mg/kg and 365 to receive ipilimumab 10 mg/kg every 3 weeks for 4 doses. In the ipilimumab 10 mg/kg group, the median OS (95% CI) was 16 months (11.63, 17.84) and in the ipilimumab 3 mg/kg group the median OS (95% CI) was 12 months (9.86, 13.27). Overall survival compared between Ipilimumab 10 mg/kg and 3 mg/kg groups showed HR = 0.84 (95% CI: 0.70, 0.99; P-value = 0.04). No statistically significant difference in progression free survival (PFS) was observed between the 10 mg/kg and the 3 mg/kg groups. (HR 0.89 with a 95% CI of 0.76, 1.04 and log-rank test P-value = 0.1548). BORR was similar in the 10 mg/kg and 3 mg/kg groups. BORR in the 10 mg/kg group was 15.3% (95% CI: 11.8, 19.5) and in the 3 mg/kg group was 12.2% (95% CI: 9.0, 16.0). Ipilimumab 10 mg/kg was associated with higher rates of adverse events compared with the 3 mg/kg dose. The frequencies of serious adverse reactions in the 10 mg/kg and 3 mg/kg groups were 37% and 18%, with the 3 most common serious adverse reactions being diarrhea (10.7% vs 5.5%), colitis (8.0% vs 3.0%), and hypophysitis (4.4% vs 1.9%). Adverse events leading to discontinuation in the 10 mg/kg and 3 mg/kg groups occurred in 31% and 19% of patients, with AEs leading to death in 4 and 2 patients, respectively.

At the recommended dose of 3 mg/kg median OS was similar in the subgroup of females \geq 50 years of age compared to the overall population: (11.40 vs 11.53 months). Median OS in the subgroup with brain metastases at baseline was 5.67 months at the recommended dose of 3 mg/kg.

Other studies

OS of ipilimumab 3 mg/kg monotherapy in chemotherapy-naive patients pooled across Phase 2 and 3 clinical trials (N= 78; randomised) and in treatment-naive 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 advanced melanoma diagnosis. Median OS and estimated 1-year, 2-year, 3-year and 4-year survival rates are presented in Table 9. The estimated 1-year, 2-year and 3-year survival rates for chemotherapy-naive patients (N= 78) pooled across Phase 2 and 3 clinical trials 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.

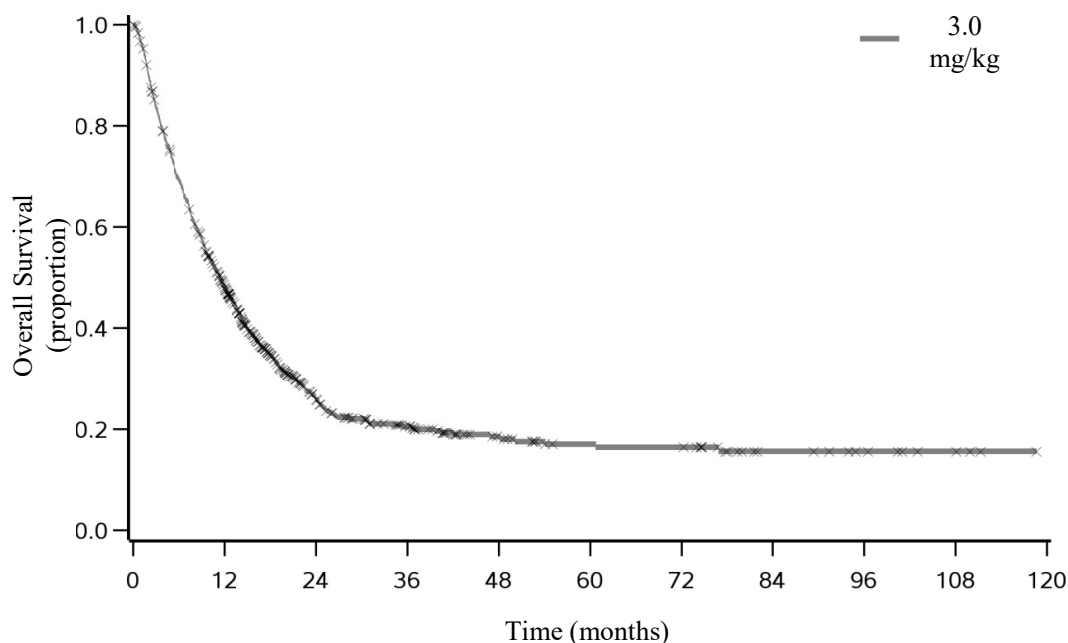
	CA184338 n= 273	CA184332 n= 157
Median OS (95% CI)	14 months (12.8-18.7)	10 months (7.0-12.8)
OS at 1 year % (95% CI)	59% (52.5-64.3)	44% (35.5, 51.4)
OS at 2 years % (95% CI)	39% (33.1-44.8)	26% (18.9-33.3)
OS at 3 years % (95% CI)	31% (25.5-36.7)	22% (15.5-29.2)
OS at 4 years % (95% CI)	26% (20.4-31.3)	22% (15.5-29.2)

Patients with brain metastases in study CA184332 had a median OS of 7 months (95% CI: 5.06 - 12.81) and patients without brain metastases had a median OS of 14.1 months (95% CI: 9.96-Not estimated).

Patients with brain metastases in study CA184338 had a median OS of 6.3 months (95% CI: 3.2 - 12.0) and patients without brain metastases had a median OS of 17.7 months (95% CI: 13.6 – 12.1).

Long term survival benefit of treatment with ipilimumab (at 3mg/kg) is demonstrated through a pooled analysis of OS data from clinical trials in patients with previously treated and treatment naive advanced melanoma (N = 965). The Kaplan-Meier OS curve revealed a plateau beginning around year 3 (OS rate = 21% [95% CI: 17-24]) that extended up to 10 years in some patients (see Figure 1).

Figure 1: Overall Survival with ipilimumab 3 mg/kg in pooled analysis



No. at Risk											
3.0 mg/kg	965	429	127	73	41	29	28	12	8	4	0

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

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

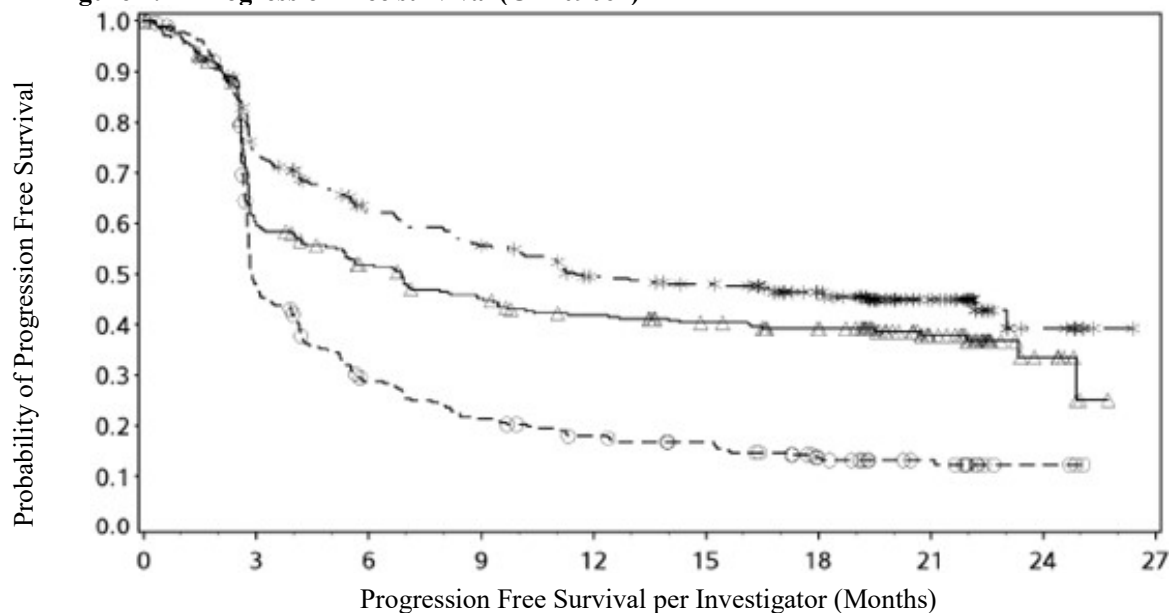
A total of 945 patients were randomised to receive ipilimumab in combination with nivolumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks. Patients in the nivolumab monotherapy arm received nivolumab 3 mg/kg every 2 weeks. Patients in the comparator arm received ipilimumab 3 mg/kg and nivolumab-matched placebo intravenously every 3 weeks for 4 doses followed by placebo every 2 weeks. Randomisation was stratified by PD-L1 expression ($\geq 5\%$ 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 progression-free survival and OS. ORR and the duration of response were also assessed.

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

PFS results (with minimum follow up of 18 months) are shown in Figure 2 (all randomised population), Figure 3 (at the tumour PD-L1 5% cut off), and Figure 4 (at the tumour PD-L1 1% cut off).

Figure 2: Progression-free survival (CA209067)



Number of Subjects at Risk

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

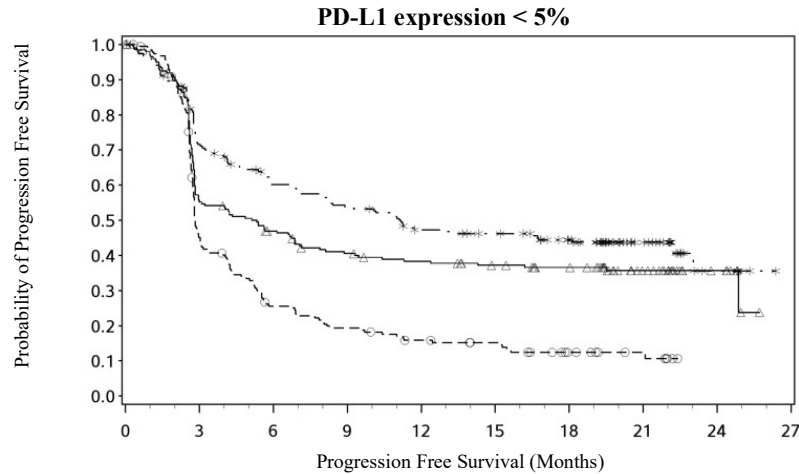
- *--- Nivolumab+ipilimumab (events: 161/314), median and 95% CI: 11.50 (8.90, 22.18).
PFS rate at 12 months and 95% CI: 49% (44, 55)
- △— Nivolumab (events: 183/316), median and 95% CI: 6.87 (4.34, 9.46).
PFS rate at 12 months and 95% CI: 42% (36, 47)
- Ipilimumab (events: 245/315), median and 95% CI: 2.89 (2.79, 3.42).
PFS rate at 12 months and 95% CI: 18% (14, 23)

Nivolumab+ipilimumab vs. ipilimumab (primary analysis) - HR (99.5% CI): 0.42 (0.32, 0.56); p-value: < 0.0001

Nivolumab vs. ipilimumab (primary analysis) - HR (99.5% CI): 0.55 (0.42, 0.73); p-value: < 0.0001

Nivolumab+ipilimumab vs. nivolumab (descriptive analysis) - HR (95% CI): 0.76 (0.62, 0.95)

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



Number of Subjects at Risk

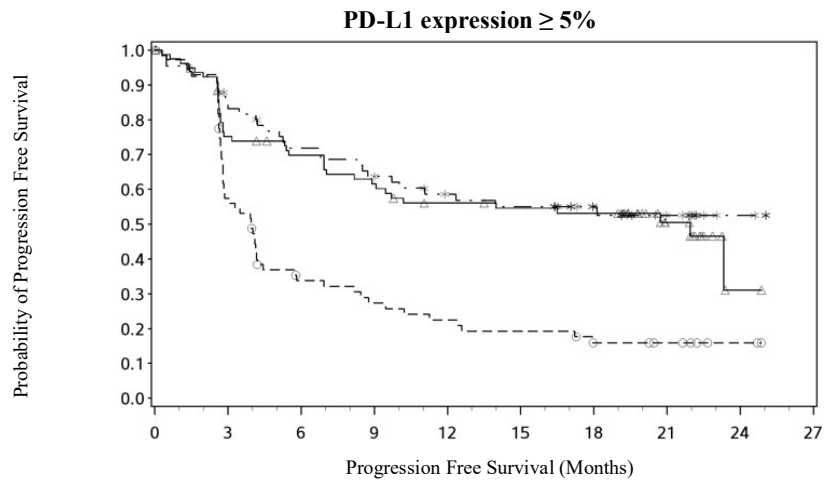
	0	3	6	9	12	15	18	21	24	27
Nivolumab + Ipilimumab	210	142	113	101	86	81	69	31	5	0
Nivolumab	208	108	89	75	69	62	55	29	7	0
Ipilimumab	202	82	45	34	26	22	12	7	0	0

- *--- Nivolumab+Ipilimumab (events: 111/210), median and 95% CI: 11.10 (7.98, 22.18)
- △— Nivolumab (events: 125/208), median and 95% CI: 5.32 (2.83, 7.06)
- Ipilimumab (events: 159/202), median and 95% CI: 2.83 (2.76, 3.09)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.42 (0.33, 0.54)

Nivolumab vs. Ipilimumab - hazard ratio: 0.57 (0.45, 0.72)

Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.74 (0.58, 0.96)



Number of Subjects at Risk

	0	3	6	9	12	15	18	21	24	27
Nivolumab + Ipilimumab	68	53	44	39	33	31	22	13	3	0
Nivolumab	80	57	51	45	39	37	36	16	1	0
Ipilimumab	75	40	21	17	14	12	8	6	2	0

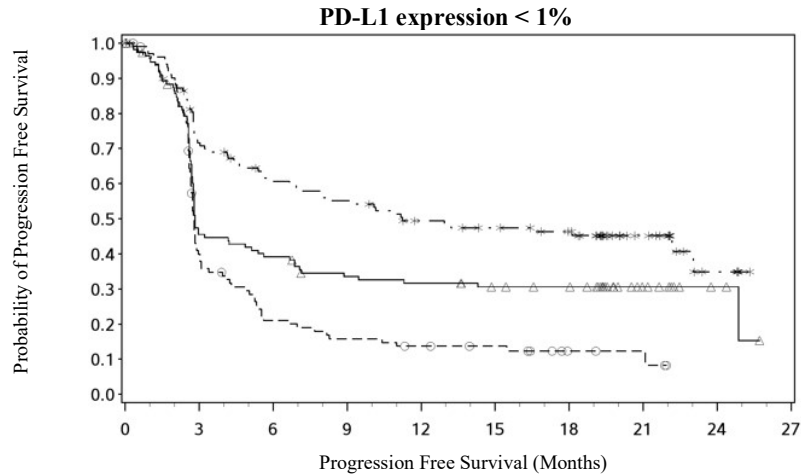
- *--- Nivolumab+Ipilimumab (events: 29/68), median and 95% CI: N.A. (9.72, N.A.)
- △— Nivolumab (events: 38/80), median and 95% CI: 21.95 (8.90, N.A.)
- Ipilimumab (events: 57/75), median and 95% CI: 3.94 (2.79, 4.21)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.35 (0.22, 0.55)

Nivolumab vs. Ipilimumab - hazard ratio: 0.41 (0.27, 0.62)

Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.87 (0.54, 1.41)

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



Number of Subjects at Risk

Nivolumab + Ipilimumab									
123	82	65	59	50	46	41	18	4	0
Nivolumab									
117	50	43	35	33	29	27	11	3	0
Ipilimumab									
113	39	20	15	12	10	4	3	0	0

---*--- Nivolumab+Ipilimumab (events: 63/123), median and 95% CI: 11.24 (6.93, 23.03)

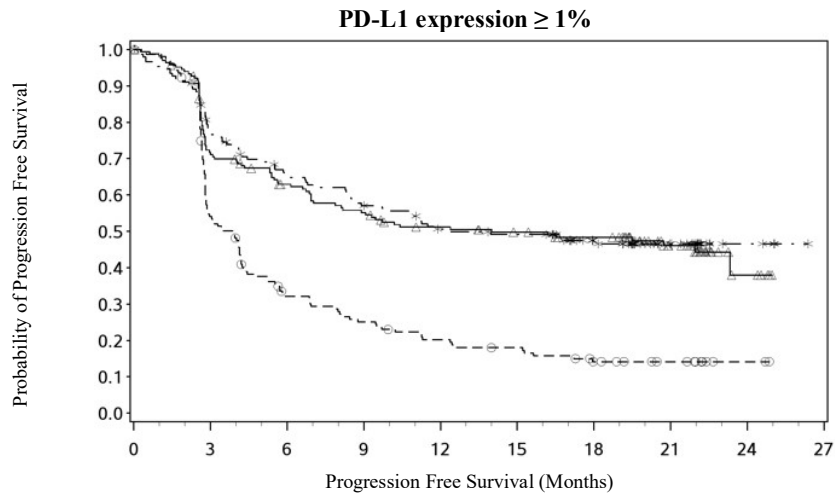
—△— Nivolumab (events: 77/117), median and 95% CI: 2.83 (2.76, 5.13)

---○--- Ipilimumab (events: 87/113), median and 95% CI: 2.79 (2.66, 2.96)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.39 (0.28, 0.54)

Nivolumab vs. Ipilimumab - hazard ratio: 0.65 (0.48, 0.88)

Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.60 (0.43, 0.84)



Number of Subjects at Risk

Nivolumab + Ipilimumab									
155	113	92	81	69	66	50	26	4	0
Nivolumab									
171	115	97	85	75	70	64	34	5	0
Ipilimumab									
164	83	46	36	28	24	16	10	2	0

---*--- Nivolumab+Ipilimumab (events: 77/155), median and 95% CI: 12.35 (8.74, N.A.)

—△— Nivolumab (events: 86/171), median and 95% CI: 14.00 (7.03, N.A.)

---○--- Ipilimumab (events: 129/164), median and 95% CI: 3.91 (2.83, 4.17)

Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.42 (0.31, 0.55)

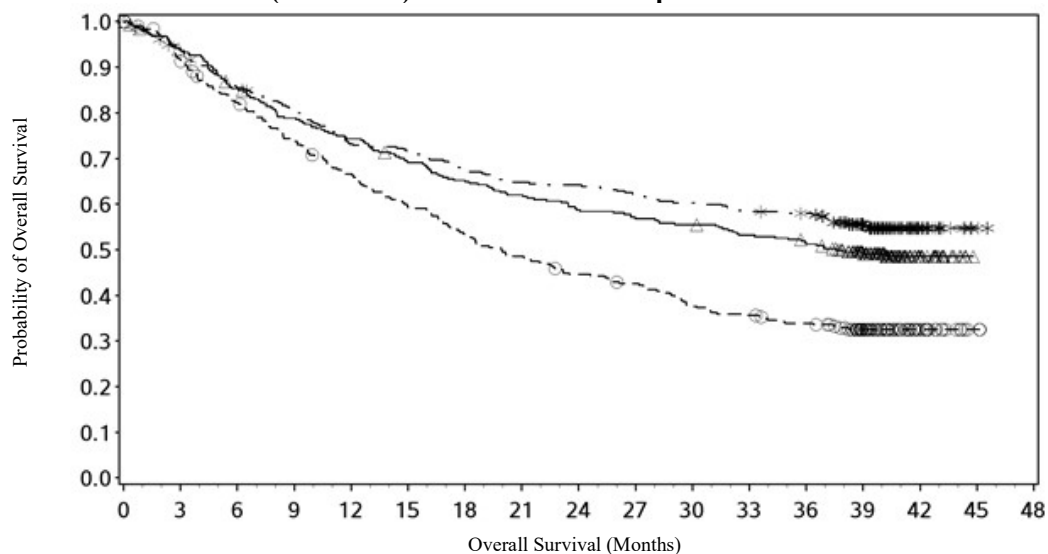
Nivolumab vs. Ipilimumab - hazard ratio: 0.44 (0.34, 0.58)

Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.94 (0.69, 1.28)

The final OS analysis occurred when all patients had a minimum follow-up of 28 months. OS results at an additional analysis undertaken at a minimum follow-up of 36 months show outcomes consistent with the original analysis. OS results from this follow-up analysis are shown in Figure 5 (all randomised), Figure 6 (at the tumour PD-L1 1% cut off), and Table 10 (at the tumour PD-L1 5% cut off).

The OS analysis was not adjusted to account for subsequent therapies received. Subsequent systemic therapy was received by 31.8%, 44.3%, and 62.2% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively. Subsequent immunotherapy (including anti-PD1 therapy, anti-CTLA-4 antibody, or other immunotherapy) was received by 14.6%, 29.1%, and 44.1% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively.

Figure 5 Overall survival (CA209067) - Minimum follow-up of 36 months



Number of Subjects at Risk

Nivolumab + Ipilimumab

314 292 265 247 226 221 209 200 198 192 186 180 177 131 27 3 0

Nivolumab

316 292 265 244 230 213 201 191 181 175 171 163 156 120 28 0 0

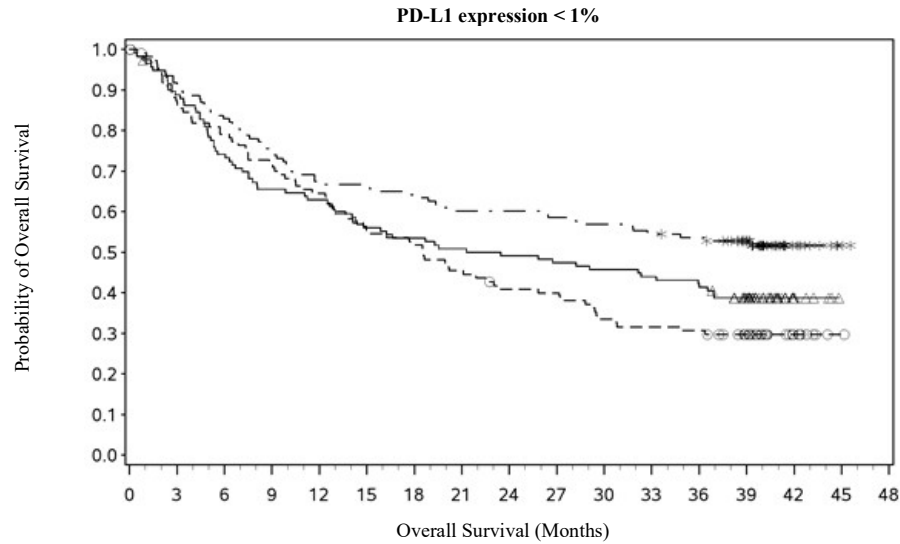
Ipilimumab

315 285 253 227 203 181 163 148 135 128 113 107 100 68 20 2 0

- *-- Nivolumab+ipilimumab (events: 139/314), median and 95% CI: N.A. (38.18, N.A.)
OS rate and 95% CI at 12 months: 73% (68, 78), 24 months: 64% (59, 69), and 36 months: 58% (52, 63)
- △— Nivolumab (events: 158/316), median and 95% CI: 37.59 months (29.08, N.A.)
OS rate and 95% CI at 12 months: 74% (69, 79), 24 months: 59% (53, 64), and 36 months: 52% (46, 57)
- Ipilimumab (events: 206/315), median and 95% CI: 19.94 months (16.85, 24.61)
OS rate and 95% CI at 12 months: 67% (61, 72), 24 months: 45% (39, 50), and 36 months: 34% (29, 39)

Nivolumab+ipilimumab vs ipilimumab (primary analysis) - HR (95% CI): 0.55 (0.45, 0.69); p-value: <0.0001
 Nivolumab vs ipilimumab (primary analysis) - HR (95% CI): 0.65 (0.53, 0.80); p-value: <0.0001
 Nivolumab+ipilimumab vs nivolumab (descriptive analysis) - HR (95% CI): 0.85 (0.68, 1.07)

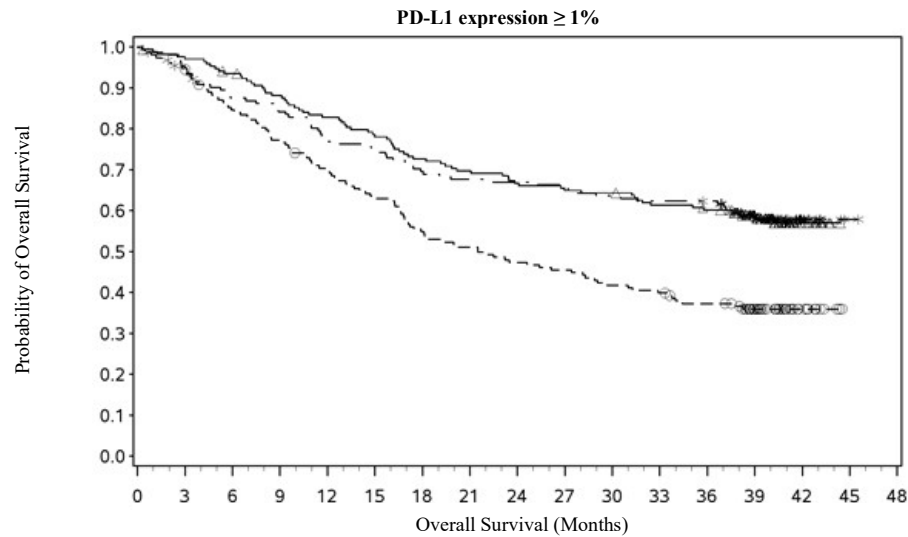
Figure 6: Overall survival by PD-L1 expression: 1% cut off (CA209067) - Minimum follow-up of 36 months



Number of Subjects at Risk

Nivolumab + Ipilimumab																
123	113	102	91	82	82	79	74	74	72	70	67	65	50	11	2	0
Nivolumab																
117	103	86	76	73	65	62	59	57	55	53	51	49	37	7	0	0
Ipilimumab																
113	96	87	79	71	61	57	50	44	43	36	34	33	24	8	1	0

---*--- Nivolumab+Ipilimumab (events: 59/123), median and 95% CI: N.A. (26.45, N.A.)
 —△— Nivolumab (events: 71/117), median and 95% CI: 23.46 months (13.01, 36.53)
 ---○--- Ipilimumab (events: 77/113), median and 95% CI: 18.56 months (13.67, 23.20)
 Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.59 (0.42, 0.82)
 Nivolumab vs. Ipilimumab - hazard ratio: 0.84 (0.61, 1.16)
 Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 0.70 (0.49, 0.99)



Number of Subjects at Risk

Nivolumab + Ipilimumab																
155	144	132	127	116	112	105	102	101	99	96	94	93	66	14	1	0
Nivolumab																
171	165	158	148	139	131	122	117	112	109	108	102	99	76	18	0	0
Ipilimumab																
164	155	137	125	113	101	88	82	76	73	67	64	58	38	10	0	0

---*--- Nivolumab+Ipilimumab (events: 63/155), median and 95% CI: N.A. (39.06, N.A.)
 —△— Nivolumab (events: 71/171), median and 95% CI: N.A. (40.21, N.A.)
 ---○--- Ipilimumab (events: 103/164), median and 95% CI: 21.49 months (16.85, 29.08)
 Nivolumab+Ipilimumab vs. Ipilimumab - hazard ratio: 0.55 (0.40, 0.75)
 Nivolumab vs. Ipilimumab - hazard ratio: 0.54 (0.40, 0.73)
 Nivolumab+Ipilimumab vs. Nivolumab - hazard ratio: 1.02 (0.73, 1.43)

Table 10: Summary of overall survival by PD-L1 expression: 5% cut off - CA209067 - Minimum follow-up of 36 months

Tumour PD-L1 expression	n	nivolumab + ipilimumab Median OS (95% CI)	n	ipilimumab Median OS (95% CI)	Hazard Ratio (95% CI)
<5%	210	NR (32.72, NR)	202	18.40 (13.70, 22.51)	0.56 (0.43, 0.72)
≥5%	68	NR (39.06, NR)	75	28.88 (18.10, NR)	0.59 (0.36, 0.97)
		nivolumab Median OS (95% CI)	ipilimumab Median OS (95% CI)		Hazard Ratio (95% CI)
<5%	208	35.94 (23.06, NR)	202	18.40 (13.70, 22.51)	0.68 (0.53, 0.87)
≥5%	80	NR (35.75, NR)	75	28.88 (18.10, NR)	0.60 (0.38, 0.95)
		nivolumab + ipilimumab Median OS (95% CI)	nivolumab Median OS (95% CI)		Hazard Ratio (95% CI)
<5%	210	NR (32.72, NR)	208	35.94 (23.06, NR)	0.82 (0.62, 1.08)
≥5%	68	NR (39.06, NR)	80	NR (35.75, NR)	0.99 (0.59, 1.67)

NR = not reached

Minimum follow-up for the analysis of ORR was 28 months. Responses are summarised in Table 11.

Table 11: Objective response (CA209067)

	nivolumab + ipilimumab (n=314)	nivolumab (n=316)	ipilimumab (n=315)
Objective response	185 (59%)	141 (45%)	60 (19%)
(95% CI)	(53.3, 64.4)	(39.1, 50.3)	(14.9, 23.8)
Odds ratio (vs. ipilimumab)	6.50	3.54	
(99.5% CI)	(3.81, 11.08.)	(2.10, 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%
ORR (95% CI) by tumour PD-L1 expression			
<5%	56% (49.2, 63.0) n=210	42% (35.5, 49.3) n=208	18% (12.8, 23.8) n=202
≥5%	74% (61.4, 83.5) n=68	59% (47.2, 69.6) n=80	21% (12.7, 32.3) n=75
<1%	55% (45.2, 63.5) n=123	35% (26.5, 44.4) n=117	19% (11.9, 27.0) n=113
≥1%	65% (57.1, 72.6) n=155	55% (47.2, 62.6) n=171	19% (13.2, 25.7) n=164

“+” denotes a censored observation.

Both nivolumab-containing arms demonstrated a significant PFS and OS benefit and greater ORR compared with ipilimumab alone. The observed PFS results at 18 months of follow-up and ORR and OS results at 28 months of follow-up were consistently demonstrated across subgroups of patients

including baseline ECOG performance status, BRAF status, M stage, age, history of brain metastases, and baseline LDH level. This observation was maintained with the OS results with a minimum follow-up of 36 months.

Among 128 patients who discontinued ipilimumab in combination with nivolumab 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.

Both nivolumab-containing arms demonstrated greater objective response rates than ipilimumab regardless of PD-L1 expression levels. ORRs were higher for the combination of nivolumab and ipilimumab relative to nivolumab monotherapy across tumour PD-L1 expression levels (Table 11) after 28 months of follow-up, with a best overall response of complete response correlating to an improved survival rate.

After 28 months of follow-up, median durations of response for patients with tumour PD-L1 expression level $\geq 5\%$ were not reached (range: $0^+ - 31.6^+$) in the combination arm, not reached (range: $2.8 - 30.6^+$) in the nivolumab monotherapy arm and not reached (range: $1.4 - 30.6^+$) in the ipilimumab arm. At tumour PD-L1 expression $< 5\%$, median durations of response were not reached (range: $0^+ - 33.3^+$) in the combination arm, not reached (range: $0^+ - 32.3^+$) in the nivolumab monotherapy arm and 18.2 months (range: $0.0^+ - 31.5^+$) in the ipilimumab monotherapy arm.

No clear cut off for PD-L1 expression can reliably be established when considering the relevant endpoints of tumour response and PFS and OS. Results from exploratory multivariate analyses identified patient and tumour characteristics (ECOG performance status, M stage, baseline LDH, BRAF mutation status, PD-L1 status, and gender) which might contribute to the survival outcome.

Efficacy by BRAF status: After 18 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab in combination with nivolumab had a median PFS of 15.5 months (95% CI: 8.0, NA) and 11.3 months (95% CI: 8.3, 22.2), while those in the nivolumab monotherapy arm had a median PFS of 5.6 months (95% CI: 2.8, 9.3) and 7.1 months (95% CI: 4.9, 14.3), respectively. After 28 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab in combination with nivolumab had an ORR of 67.6% (95% CI: 57.7, 76.6; n = 102) and 54.7% (95% CI: 47.8, 61.5; n = 212), while those in the nivolumab monotherapy arm had an ORR of 36.7% (95% CI: 27.2, 47.1; n = 98) and 48.2% (95% CI: 41.4, 55.0; n = 218), respectively. After 28 months of follow-up, median OS was not reached in either of the nivolumab containing arms regardless of BRAF status. The OS HRs for ipilimumab in combination with nivolumab vs. nivolumab monotherapy were 0.71 (95% CI: 0.45, 1.13) for BRAF[V600] mutation-positive patients and 0.97 (95% CI: 0.74, 1.28) for BRAF wild-type patients.

Randomised phase 2 study of ipilimumab in combination with nivolumab and ipilimumab (CA209069)

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

Renal Cell Carcinoma (RCC)

Randomised phase 3 study of ipilimumab in combination with nivolumab vs. sunitinib (CA209214)

The safety and efficacy of ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg for the treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA209214). The study included patients (18 years or older) with previously untreated, advanced or

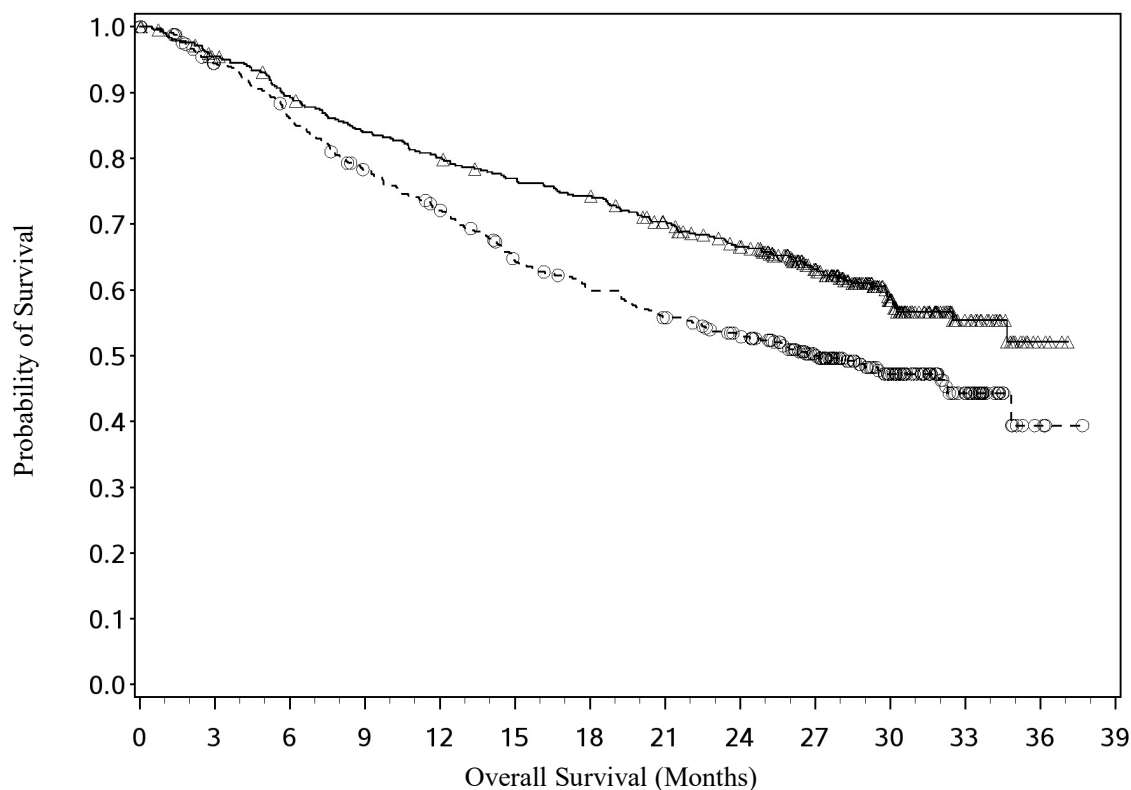
metastatic renal cell carcinoma with a clear-cell component. The primary efficacy population included those intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the International Metastatic RCC Database Consortium (IMDC) criteria (less than one year from time of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

A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either ipilimumab 1 mg/kg (n = 425) administered intravenously over 30 minutes in combination with nivolumab 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% \geq 65 years of age and 8% \geq 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 (with a minimum follow-up of 24 months) in intermediate/poor risk patients are shown in Figure 7.

Figure 7: Kaplan-Meier curves of OS in intermediate/poor risk patients (CA209214)



Number of Subjects at Risk

Nivolumab + Ipilimumab

425 399 372 348 332 317 306 282 257 201 102 33 4 0

Sunitinib

422 387 352 316 288 253 233 216 196 147 87 36 3 0

—△— Nivolumab + ipilimumab (events: 166/425), median and 95.0% CI: NA (32.49, NA)

--○-- Sunitinib (events: 209/422), median and 95.0% CI: 26.97 (22.08, 34.83)

In intermediate/poor-risk patients, OS benefit was observed in the ipilimumab in combination with nivolumab arm vs. sunitinib regardless of tumour PD-L1 expression. Median OS for tumour PD-L1 expression $\geq 1\%$ was not reached for ipilimumab in combination with nivolumab, and was 19.61 months in the sunitinib arm (HR = 0.52; 95% CI: 0.34, 0.78). For tumour PD-L1 expression $< 1\%$, the median OS was 34.7 months for the ipilimumab in combination with nivolumab and was 32.2 months in the sunitinib arm (HR = 0.70; 95% CI: 0.54, 0.92).

CA209214 also randomised 249 favourable risk patients as per IMDC criteria to nivolumab plus ipilimumab (n = 125) or to sunitinib (n = 124). These patients were not evaluated as part of the primary efficacy population. OS in favourable risk patients receiving nivolumab plus ipilimumab compared to sunitinib had a hazard ratio of 1.13 (95% CI: 0.64, 1.99; p = 0.6710).

There are no data on the use of ipilimumab in combination with nivolumab in patients with only a non clear-cell histology in first line RCC.

Efficacy results for the intermediate/poor risk patients are shown in Table 12.

Table 12: Efficacy results in intermediate/poor risk patients (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 (1.3 ⁺ -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 test.

^f p-value is compared to alpha 0.001 in order to achieve statistical significance.

^g Computed using Kaplan-Meier method.

^h p-value is compared to alpha 0.009 in order to achieve statistical significance.

“+” denotes a censored observation.

NE = non-estimable

An updated OS analysis was performed when all patients had a minimum follow-up of 24 months (see figure 7). At the time of this analysis, the hazard ratio was 0.66; (99.8% CI 0.48-0.91) with 166/425 events in the combination arm and 209/422 events in the sunitinib arm. At 18 months, the OS rate was 74.3 (95% CI 69.8-78.2) for ipilimumab in combination with nivolumab and 59.9 (95% CI 54.9-64.5) for sunitinib. At 24 months, the OS rate was 66.5 (95% CI 61.8-70.9) for ipilimumab in combination with nivolumab and 52.9 (95% CI 47.9- 57.7) for sunitinib.

Patients ≥ 75 years of age represented 8% of all intermediate/poor risk patients in CA209214, and the combination of ipilimumab with nivolumab showed numerically less effect on OS (HR 0.97, 95% CI: 0.48, 1.95) in this subgroup versus the overall population. Because of the small size of this subgroup, no definitive conclusions can be drawn from these data.

Paediatric population

Study CA184070 was a multi-center, Phase 1, open-label, dose-escalation study of ipilimumab in paediatric patients ≥ 1 year to ≤ 21 years of age with measurable/evaluable, untreatable, relapsed or refractory solid malignant tumors without a curative option with standard therapy. The study enrolled 13 patients < 12 of age and 20 patients ≥ 12 years of age. Ipilimumab was administered every 3 weeks for 4 doses and then every 12 weeks thereafter in the absence of dose limiting toxicity (DLT) and disease progression. The primary endpoints were safety and pharmacokinetics (PK). Of patients 12 years of age and older with advanced melanoma, ipilimumab 5 mg/kg was administered to three patients and ipilimumab 10 mg/kg was administered to two patients. Stable disease was achieved in two patients at the ipilimumab 5mg/kg dose, one with a duration of > 22 months.

Study CA184178 was a non-randomized, multicenter, open-label Phase 2 study, in adolescent patients 12 to < 18 years of age with previously treated or untreated, unresectable Stage III or Stage IV malignant melanoma. Ipilimumab was administered every 3 weeks for 4 doses. The primary efficacy endpoint was 1-year survival rate. Secondary efficacy endpoints of best overall response rate (BORR), stable disease (SD), disease control rate (DCR), and progression free survival (PFS) were based on mWHO criteria and determined by the investigator's assessment. Overall survival (OS) was also evaluated. Tumor assessment was performed at Week 12. All patients were followed for at least 1 year. Ipilimumab 3 mg/kg was administered to four patients and ipilimumab 10 mg/kg was administered to eight patients. Most patients were male (58%) and white (92%). Median age was 15 years. Stable disease was achieved for 260 days in one patient on ipilimumab 3 mg/kg and approximately 14 months in one patient on ipilimumab 10 mg/kg. Two patients treated with ipilimumab 10 mg/kg experienced a partial response, one of which was a durable response for more than 1 year. Additional efficacy results are presented in Table 13.

Table 13: Efficacy Results in CA184178		
	Ipilimumab 3 mg/kg N= 4	Ipilimumab 10 mg/kg N= 8
1-year OS (%) (95% CI)	75% (12.8, 96.1)	62.5% (22.9, 86.1)
BORR (%) (95% CI)	0% (0, 60.2)	25% (3.2, 65.1)
SD (n/N) ^a	1/4	1/8
DCR (%) (95% CI)	25% (0.6, 80.6)	37.5% (8.5, 75.5)
Median PFS (months) (95% CI)	2.6 (2.3, 8.5)	2.9 (0.7, NE ^a)
Median OS (months) (95% CI)	18.2 (8.9, 18.2)	Not reached (5.2, NE)

^a NE= not estimable

5.2 Pharmacokinetic properties

The pharmacokinetics of ipilimumab was studied in 785 patients with advanced melanoma who received induction doses ranging from 0.3 to 10 mg/kg administered once every 3 weeks for 4 doses. C_{max} , C_{min} and AUC of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of ipilimumab administered every 3 weeks, CL was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index 1.5 fold or less. Ipilimumab steady-state was reached by the third dose. Based on population pharmacokinetic analysis, the following mean (percent coefficient of variation) parameters of ipilimumab were obtained: terminal half-life of 15.4 days (34.4%); systemic CL of 16.8 ml/h (38.1%); and volume of distribution at steady-state of 7.47 l (10.1%). The mean (percent coefficient of variation) ipilimumab C_{min} achieved at steady-state with a 3 mg/kg induction regimen was 19.4 $\mu\text{g/ml}$ (74.6%).

Ipilimumab CL increased with increasing body weight and with increasing LDH at baseline; however, no dose adjustment is required for elevated LDH or body weight after administration on a mg/kg basis. CL was not affected by age (range 23-88 years), gender, concomitant use of budesonide or dacarbazine, performance status, HLA-A2*0201 status, mild hepatic impairment, renal impairment,

immunogenicity, and previous anticancer therapy. The effect of race was not examined as there was insufficient data in non-Caucasian ethnic groups. 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, OS was independent of prior systemic anti-cancer therapy and increased with higher ipilimumab C_{min} plasma concentrations.

Yervoy in combination with nivolumab: When ipilimumab 3 mg/kg was administered in combination with nivolumab 1 mg/kg, there was no effect of nivolumab on the CL of ipilimumab.

When administered in combination, there was no effect of anti-ipilimumab antibodies on the CL of ipilimumab.

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

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 anti-nivolumab antibodies. These changes were not considered clinically relevant.

Renal impairment

In the population pharmacokinetic analysis of data from clinical studies in patients with metastatic melanoma, pre-existing mild and moderate renal impairment did not influence the CL of ipilimumab. Clinical and pharmacokinetic data with pre-existing severe renal impairment are limited; the potential need for dose adjustment cannot be determined.

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 CL of ipilimumab. Clinical and pharmacokinetic data with pre-existing moderate hepatic impairment are limited; the potential need for dose adjustment cannot be determined. No patients with pre-existing severe hepatic impairment were identified in clinical studies.

Paediatric Population

Based on a population PK analysis using available pooled data from 565 patients from 4 phase 2 adult studies (N=521) and 2 paediatric studies (N=44), CL of ipilimumab increased with increasing baseline body weight. Age (2-87 years) had no clinically important effect on the CL of ipilimumab. The estimated geometric mean CL is 8.72 mL/h in adolescent patients aged ≥ 12 to < 18 years. Exposures in adolescents are comparable with those in adults receiving the same mg/kg dose. Based on the simulation in adults and paediatrics, comparable exposure is achieved in adults and paediatrics at the recommended dose of 3 mg/kg every 3 weeks.

5.3 Preclinical safety data

In intravenous repeat-dose toxicology studies in monkeys, ipilimumab was generally well tolerated. Immune-mediated adverse reactions were observed infrequently (~3%) and included colitis (which resulted in a single fatality), dermatitis, and infusion reaction (possibly due to acute cytokine release resulting from a rapid injection rate). A decrease in the weight of the thyroid and testes was seen in

one study without accompanying histopathologic findings; the clinical relevance of this finding is unknown.

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 similar to or higher than those associated with the clinical dose of 3 mg/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, developmental external or visceral abnormalities were identified in the urogenital system of 2 infants exposed *in utero* to ipilimumab. 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 edema. The relationship of these malformations to treatment is unclear.

Studies to evaluate the mutagenic and carcinogenic potential of ipilimumab have not been performed. Fertility studies 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.

6.3 Shelf life

Unopened vial

3 years

After opening

From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately. The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 and 4 mg/ml) has been demonstrated for 24 hrs at 25°C and 2°C to 8°C. If not used immediately, the infusion solution (undiluted or diluted) may be stored for up to 24 hours in a refrigerator (2°C to 8°C) or at room temperature (20°C to 25°C).

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

Store in the original package in order to protect from light.

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

6.5 Nature and contents of container

10 ml of concentrate in a vial (Type I glass) with a stopper (coated butyl rubber) and a flip-off seal (aluminium). Pack size of 1.

40 ml of concentrate in a vial (Type I glass) with a stopper (coated butyl rubber) and a flip-off seal (aluminium). Pack size of 1.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Calculating the dose:

Ipilimumab monotherapy or ipilimumab in combination with nivolumab:

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 YERVOY concentrate may be needed to give the total dose for the patient.

- Each 10 ml vial of YERVOY 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 YERVOY concentrate to prepare the dose (ml) = the total dose in mg, divided by 5 (the YERVOY concentrate strength is 5 mg/ml).

Preparing the infusion:

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

YERVOY can be used for intravenous administration either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe;
- or
- after diluting to up to 5 times the original volume of concentrate (up to 4 parts of diluent to 1 part of concentrate). The final concentration should range from 1 to 4 mg/ml. To dilute the YERVOY concentrate, you can use either:
 - sodium chloride 9 mg/ml (0.9%) solution for injection; or
 - 50 mg/ml (5%) glucose solution for injection

STEP 1

- Allow the appropriate number of vials of YERVOY to stand at room temperature for approximately 5 minutes.
- Inspect the YERVOY concentrate for particulate matter or discoloration. YERVOY concentrate is a clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates. Do not use if unusual amount of particles and signs of discoloration are present.
- Withdraw the required volume of YERVOY concentrate using an appropriate sterile syringe.

STEP 2

- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous bag (PVC or non-PVC).
- If applicable, dilute with the required volume of sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. Gently mix the infusion by manual rotation.

Administration:

The YERVOY infusion must not be administered as an intravenous push or bolus injection. Administer the YERVOY infusion intravenously over a period of 30 or 90 minutes, depending on the dose.

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

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

The YERVOY infusion is compatible with:

- PVC infusion sets
- Polyethersulfone (0.2 µm to 1.2 µm) and nylon (0.2 µm) in-line filters

Flush the line with sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection at the end of the infusion.

Any unused medicinal product or waste material should be discarded in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/698/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2011

Date of latest renewal: 21 April 2016

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S)
AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

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

Name and address of the manufacturer(s) of the biological active substance(s)

Bristol-Myers Squibb Company
6000 Thompson Road
East Syracuse, New York 13057
United States

Samsung Biologics Co. Ltd
300, Songdo Bio Way (Daero)
Yeonsu-gu, Incheon 21987
Korea

Name and address of the manufacturer(s) responsible for batch release

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
IT-03012 Anagni (FR)
Italy

Swords Laboratories T/A Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe YERVOY are provided with the following:

- Healthcare Professional FAQ Brochure
- Patient Information Brochures including Alert Cards

Key elements of the Healthcare Professional Brochure:

- Brief introduction to ipilimumab (indication and the purpose of this tool).
- List of important immune-related adverse reactions (irARs) and their symptoms, as outlined in section 4.4 of the Summary of Product Characteristics (SmPC):
 - Inflammation of the gastrointestinal tract, such as colitis, which can lead to bowel perforation
 - Inflammation of the liver, such as hepatitis, which can lead to liver failure
 - Inflammation of the skin that can lead to severe skin reaction (toxic epidermal necrolysis)
 - Inflammation of the nerves that can lead to neuropathy
 - Inflammation of the endocrine system. including the adrenal, pituitary, or thyroid glands
 - Inflammation of the eyes
 - Other related irARs (e.g. pneumonitis, glomerulonephritis, multi-organ failure...)
 - Severe infusion reaction
- Information that ipilimumab can cause serious side effects in many parts of the body that can lead to death and require early intervention, as outlined in the guidelines for the management of immune-related adverse reactions in section 4.4 of the SmPC.
- Importance of evaluating liver function tests (LFTs), TSH and signs/symptoms of irARs before each treatment.
- Follow-up of patients due to late onset (months after treatment) of irARs
- Reminder to distribute the Patient Information Brochure, and to educate patients/caregivers about symptoms of irARs and of the need to report them immediately to the physician.

Key elements for the Patient Information Brochure and Alert Card:

- Brief introduction to ipilimumab indication and the purpose of this tool.
- Information that ipilimumab can cause serious side effects in many parts of the body that can lead to death and need to be addressed immediately
- Request to inform the physician of all medical conditions before treatment.
- Description of the main symptoms of irARs and the importance of notifying their treating physician immediately if symptoms occur, persist or worsen.
 - Gastrointestinal: diarrhea, bloody stool, abdominal pain, nausea, or vomiting
 - Liver: yellowing of your skin or whites of your eyes
 - Skin: rash, blisters and/or peeling, mouth sores
 - Eye: blurred vision, vision changes, eye pain,
 - General: fever, headache, feeling tired, dizziness or fainting, dark urine, bleeding, weakness, numbness of legs, arms, or faces, changes in behavior, such as less sex drive, being irritable or forgetful
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional first.
- Placeholder including the weblink of the Package Leaflet on the EMA website
- The importance of carrying the detachable wallet-sized Patient Alert Card at all times to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency

healthcare professionals). The Card reminds patients about key symptoms that need to be reported immediately to the physician/nurse. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is treated with ipilimumab.

The Marketing Authorisation Holder shall agree the format and content of the above material with the National Competent Authority prior to launch in the Member State.

- **Obligation to conduct post-authorisation measure**

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

Description	Due date
Post authorisation efficacy study (PAES): In order to further elucidate the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab and ipilimumab, the MAH should conduct and submit the results of a randomised, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels. This study should be conducted according to an agreed protocol.	30 th September 2021

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

YERVOY 5 mg/ml concentrate for solution for infusion
Ipilimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of concentrate contains 5 mg ipilimumab.
Each vial contains 50 mg ipilimumab.
Each vial contains 200 mg ipilimumab.

3. LIST OF EXCIPIENTS

Excipients: Tris hydrochloride, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

50 mg/10 ml
200 mg/40 ml

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/698/001
EU/1/11/698/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
<NN:>

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

YERVOY 5 mg/ml sterile concentrate
Ipilimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of concentrate contains 5 mg ipilimumab.
Each vial contains 50 mg ipilimumab.
Each vial contains 200 mg ipilimumab.

3. LIST OF EXCIPIENTS

Excipients: Tris hydrochloride, sodium chloride, mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Sterile concentrate

50 mg/10 ml
200 mg/40 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/698/001
EU/1/11/698/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

YERVOY 5 mg/ml concentrate for solution for infusion ipilimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What YERVOY is and what it is used for
2. What you need to know before you use YERVOY
3. How to use YERVOY
4. Possible side effects
5. How to store YERVOY
6. Contents of the pack and other information

1. What YERVOY is and what it is used for

YERVOY contains the active substance ipilimumab, a protein which helps your immune system to attack and destroy cancer cells by your immune cells.

Ipilimumab alone is used to treat advanced melanoma (a type of skin cancer) in adults and adolescents 12 years of age and older.

Ipilimumab in combination with nivolumab is used to treat

- advanced melanoma (a type of skin cancer) in adults
- advanced renal cell carcinoma (advanced kidney cancer) in adults

As YERVOY may be given in combination with nivolumab, it is important that you also read the package leaflet for this medicine. If you have any questions about nivolumab, please ask your doctor.

2. What you need to know before you use YERVOY

You should not be given YERVOY

- if you are **allergic** to ipilimumab or any of the other ingredients of this medicine (listed in Section 6 "Contents of the pack and other information"). **Talk to your doctor** if you are not sure.

Warnings and precautions

Talk to your doctor before using YERVOY as it may cause:

- **problems with your heart** such as a change in the rhythm or rate of the heartbeat or an abnormal heart rhythm.
- **inflammation of the intestines (colitis)** which can worsen to bleedings or bowel perforation. Signs and symptoms of colitis may include diarrhoea (watery, loose or soft stools), an increased number of bowel movements than usual, blood in your stools or darker-coloured stools, pain or tenderness in your stomach area.
- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).

- **inflammation of the liver (hepatitis)** that can lead to liver failure. Signs and symptoms of hepatitis may include eye or skin yellowing (jaundice), pain on the right side of your stomach area, tiredness.
- **inflammation of the skin** that can lead to severe skin reaction (known as toxic epidermal necrolysis, Stevens-Johnson syndrome and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)). Signs and symptoms of severe skin reaction may include such as skin rash with or without itching, peeling of the skin, dry skin, fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells) and effects on liver, kidneys or lungs. Please note that the reaction called DRESS may develop weeks or months after your last dose.
- **inflammation of the nerves** that can lead to paralysis. Symptoms of nerve problems may include muscle weakness, numbness or tingling in your hands or feet, loss of consciousness or difficulty waking up.
- **Inflammation or problems with your kidneys.** Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.
- **inflammation of hormone producing glands** (especially the pituitary, adrenal and thyroid glands) that may affect how these glands work. Signs and symptoms that your glands are not working properly may include headaches, blurry or double vision, tiredness, decreased sexual drive, behavioral changes.
- **Diabetes** (symptoms include excessive thirst, the passing of a greatly increased amount of urine, increase in appetite with a loss of weight, feeling tired, drowsy, weak, depressed, irritable and generally unwell) or **diabetic ketoacidosis** (acid in the blood produced from diabetes).
- **Inflammation of the muscles** such as myocarditis (inflammation of the heart muscle), myositis (inflammation of the muscles) and rhabdomyolysis (stiffness in muscles and joints, muscle spasm). Signs and symptoms may include muscle pain, stiffness, weakness, chest pain, or severe fatigue.
- **inflammation of the eyes.** Signs and symptoms may include redness in the eye, pain in the eye, vision problems or blurry vision.
- **histiocytosis haematophagic.** A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

Tell your doctor immediately if you have any of these signs or symptoms or they get worse. **Do not try to treat your symptoms with other medicines.** Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms, withhold the next dose of YERVOY, or stop your treatment with YERVOY altogether.

Please note that these signs and symptoms are **sometimes delayed**, and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have **blood tests** during treatment.

Check with your doctor or nurse before you are given YERVOY

- if you have an **autoimmune disease** (a condition where the body attacks its own cells);
- if you have, or have ever had, **chronic viral infection of the liver**, including hepatitis B (HBV) or hepatitis C (HCV);
- if you have **human immunodeficiency virus (HIV)** infection or acquired immune deficiency syndrome (AIDS).

- if you have previously experienced a severe skin adverse reaction on a prior cancer therapy.
- if you have any history of inflammation of the lungs

Children and adolescents

YERVOY should not be used in children below 12 years of age.

Other medicines and YERVOY

Before you are given YERVOY, tell your doctor

- if you are taking any medicines that suppress your immune system, such as corticosteroids. These medicines may interfere with the effect of YERVOY. However, once you are treated with YERVOY, your doctor may give you corticosteroids to reduce the side-effects that you may have with YERVOY.
- if you are taking any medicines that stop your blood from clotting (anticoagulants). These medicines may increase the likelihood of bleeding in the stomach or intestine, which is a side-effect of YERVOY.
- if you have recently been prescribed Zelboraf (vemurafenib, another medicine for the treatment of skin cancer). When YERVOY is given following prior vemurafenib there may be an increased risk of skin side-effects.

Also tell your doctor if you are taking or have recently taken any other medicines.

Do not take any other medicines during your treatment without talking to your doctor first. Based on early data, the combination of YERVOY (ipilimumab) and vemurafenib is not recommended due to increased toxicity to the liver.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, if you are planning to become pregnant, or if you are breast-feeding.

You must not use YERVOY if you are pregnant unless your doctor specifically recommends it. The effects of YERVOY in pregnant women are not known, but it is possible that the active substance, ipilimumab, could harm an unborn baby.

- You must use **effective contraception** while you are being treated with YERVOY if you are a woman who could become pregnant.
- If you become pregnant while using YERVOY **tell your doctor**.

It is not known whether ipilimumab gets into breast milk. However, significant exposure of ipilimumab to the infant through breast milk is not expected and no effects on the breast-fed infant are anticipated. Ask your doctor if you can breast-feed during or after treatment with YERVOY.

Driving and using machines

Do not drive, cycle or use machines after you have been given YERVOY unless you are sure you are feeling well. Feeling tired or weak is a very common side effect of YERVOY. This can affect your ability to drive, cycle or to use machines.

YERVOY contains sodium

Tell your doctor if you are on a low-sodium (low-salt) diet before you are given YERVOY. It contains 2.3 mg sodium per ml of concentrate.

3. How to use YERVOY

How YERVOY is given

YERVOY will be given to you in a hospital or clinic under the supervision of an experienced doctor.

For the treatment of skin cancer, YERVOY will be given to you as an infusion (a drip) into a vein (intravenously) over a period of 90 minutes.

When YERVOY is given in combination with nivolumab for the treatment of skin cancer, you will be given an infusion over a period of 90 minutes every 3 weeks for the first 4 doses (combination phase). Thereafter, nivolumab will be given as an infusion over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When YERVOY is given in combination with nivolumab the treatment of advanced kidney cancer. You will be given an infusion over a period of 30 minutes every 3 weeks for the first 4 doses (combination phase). Thereafter, nivolumab will be given as an infusion over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

How much YERVOY is given

The recommended dose is 3 mg of ipilimumab per kilogram of your body weight.

The amount of YERVOY you will be given will be calculated based on your body weight. Depending on your dose, some or all of the content of the YERVOY vial may be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection before use. More than one vial may be necessary to obtain the required dose.

You will be treated with YERVOY once every 3 weeks, for a total of 4 doses. You may notice the appearance of new lesions or growth of existing lesions on your skin, which can be expected when you are being treated with YERVOY. Your doctor will continue giving you YERVOY for a total of 4 doses, depending on your tolerance to the treatment.

When YERVOY is given in combination with nivolumab for the treatment of skin cancer, the recommended dose of YERVOY is 3 mg of ipilimumab per kilogram of your body weight every 3 weeks for the first 4 doses (combination phase). Thereafter the recommended dose of nivolumab is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When YERVOY is given in combination with nivolumab for the treatment of advanced kidney cancer, the recommended dose of YERVOY is 1 mg of ipilimumab per kilogram of your body weight every 3 weeks for the first 4 doses (combination phase). Thereafter, the recommended dose of nivolumab is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

If you miss a dose of YERVOY

It is very important for you to keep all your appointments to receive YERVOY. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop using YERVOY

Stopping your treatment may stop the effect of the medicine. Do not stop treatment with YERVOY unless you have discussed this with your doctor.

If you have any further questions about your treatment or the use of this medicine, ask your doctor.

When YERVOY is given in combination with nivolumab, you will first be given nivolumab followed by YERVOY.

Please refer to the package leaflet of nivolumab in order to understand the use of this medicine. If you have questions about this medicine, please ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

Be aware of important symptoms of inflammation

YERVOY acts on your immune system and may cause **inflammation** in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening.

The following side effects have been reported in patients receiving 3 mg/kg ipilimumab alone:

Very common (may affect more than 1 in 10 people)

- loss of appetite
- diarrhoea (watery, loose or soft stools), vomiting or feeling sick (nausea)
- skin rash, itching
- feeling tired or weak, reaction at site of injection, fever

→ **Tell your doctor immediately** if you get any of these side effects.

Do not try to treat your symptoms with other medicines.

Common (may affect up to 1 in 10 people)

- tumour pain
- underactive function of the thyroid gland which can cause tiredness or weight gain, underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain
- dehydration
- confusion
- damage to the nerves (causing pain, weakness and cramps), dizziness, headache,
- blurred vision, pain in the eye
- low blood pressure, temporary redness of the face and neck, feeling of intense heat with sweating and rapid heart beat
- shortness of breath (dyspnoea), cough
- bleeding in the stomach or intestine, inflammation of the intestines (colitis), constipation, heartburn, stomach pain
- abnormal function of the liver
- inflammation of the inner surface lining of a particular organ
- inflammation and redness of the skin, skin colour change in patches (vitiligo), hives (itchy, bumpy rash), hair loss or thinning, excessive sweating at night, dry skin
- pain in muscles and joints (arthralgia), muscle spasms
- shivering, lack of energy, oedema (swelling), pain
- flu-like illness
- weight loss

→ **Tell your doctor immediately** if you get any of these side effects.

Do not try to treat your symptoms with other medicines.

Uncommon (may affect up to 1 in 100 people)

- serious bacterial infection of the blood (sepsis, septic shock), inflammation around the brain or spinal cord, inflammation of the stomach and intestines, inflammation of bowel wall (causing fever, vomiting and stomach pain), urinary tract infection, infection of the respiratory tract
- a group of symptoms due to cancer in the body such as high blood levels of calcium and cholesterol, and low blood levels of sugar (paraneoplastic syndrome)
- allergic reaction
- decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), overactive function of the thyroid gland, which can cause rapid heart rate, sweating and weight loss, defect of the glands producing sex hormones

- decreased function of the adrenal glands caused by an underactive hypothalamus (part of the brain)
- a group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome).
- changes in mental health, depression, lowered sex drive
- severe and possibly fatal inflammation of the nerves causing pain, weakness or paralysis in the extremities (Guillain-Barré syndrome), fainting, inflammation of the nerves within the brain, excessive accumulation of fluid in the brain, difficulty in coordinating movements (ataxia), shaking, brief involuntary muscle contraction, difficulty in speaking
- inflammation of the eye (conjunctivitis), bleeding in the eye, inflammation of the coloured part of the eye, reduced vision, a foreign body sensation in the eyes, swollen runny eyes, swelling of the eyelids
- irregular or abnormal heart beat
- inflammation of the blood vessels, disease of the blood vessels, restriction in the blood supply to the extremities, low blood pressure when standing up
- extreme difficulty in breathing, fluid accumulation in the lungs, inflammation of the lungs, hay fever
- bowel perforation, inflammation of the membrane of the stomach wall, inflammation of the small intestine, inflammation of the bowel or the pancreas (pancreatitis), peptic ulcer, inflammation of the food pipe, blockage of the intestines
- liver failure, inflammation of the liver, enlarged liver, yellowing of the skin or eyes (jaundice)
- severe and possibly fatal peeling of the skin (toxic epidermal necrolysis)
- inflammation of the muscles causing pain or stiffness in the hip and shoulder, painful joints (arthralgia)
- swelling of the thyroid gland, inflammation of the kidney, or the central nervous system
- multi organ inflammation
- inflammation of skeletal muscles
- muscle weakness
- kidney function failure, kidney disease
- absence of menstrual periods
- multi organ dysfunction, reaction related to infusion of the medicine
- change in hair colour

→ **Tell your doctor immediately** if you get any of these side effects.

Do not try to treat your symptoms with other medicines.

Rare (may affect up to 1 in 1,000 people)

- inflammatory disease of blood vessels (most commonly head arteries)
- inflammation of the anus and the rectal wall (marked by bloody stools and a frequent urge to defecate)
- skin disease characterized by dry red patches covered with scales (psoriasis)
- inflammation and redness of the skin (erythema multiforme)
- a type of severe skin reaction characterized by rash accompanied by one or more of the following features: fever, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidneys or lungs (a reaction called DRESS).

→ **Tell your doctor immediately** if you get any of these side effects.

Do not try to treat your symptoms with other medicines.

Very rare (may affect up to 1 in 10,000 people)

- Serious, potential life-threatening allergic reaction

→ **Tell your doctor immediately** if you get any of these side effects.

Do not try to treat your symptoms with other medicines.

In addition, the following uncommon (may affect up to 1 in 100 people) side effects have been reported in patients who received doses other than 3mg/kg of YERVOY in clinical trials:

- triad of symptoms (meningism): neck stiffness, intolerance of bright light and headache, flu-like discomfort
- inflammation of the heart muscle, weakness of the heart muscle, fluid around the heart
- inflammation of the liver or the pancreas, nodules of inflammatory cells in various organs of your body
- infection within the abdomen
- painful skin lesions of the arms and legs and face (erythema nodosum)
- overactive pituitary gland
- decreased function of the parathyroid gland
- inflammation of the eye, eye muscle inflammation
- decreased hearing
- poor blood circulation which makes toes and fingers numb or pale
- damage to the tissues of the hands and feet resulting in redness, swelling and blisters

→ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Other side effects that have been reported (frequency not known) include:

- a type of skin blistering disease (called pemphigoid)
- a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called histiocytosis haematophagic)

→ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Changes in test results

YERVOY may cause changes in the results of tests carried out by your doctor. These include:

- a variation in the number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- an abnormal variation of hormones and liver enzyme levels in the blood
- abnormal liver function test
- abnormal levels of calcium, sodium, phosphate or potassium in the blood
- presence of blood or proteins in the urine
- an abnormally high alkalinity of the blood and other body tissues
- kidneys unable to remove acids from blood normally
- presence of antibodies in the blood against some of your own cells

The following side effects have been reported **with ipilimumab in combination with nivolumab:**

Very common (may affect more than 1 in 10 people)

- underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- loss of appetite
- headache
- shortness of breath (dyspnoea)
- inflammation of the intestines (colitis), diarrhoea (watery, loose or soft stools), vomiting or feeling sick (nausea), stomach pain
- skin rash sometimes with blisters, itching
- pain in the muscles and bones (musculoskeletal pain), painful joints (arthralgia)
- feeling tired or weak, fever

→ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Common (may affect up to 1 in 10 people)

- serious lung infection (pneumonia), infections of the upper respiratory tract, inflammation of the eye (conjunctivitis)
- increase of eosinophils (type of white blood cells)
- allergic reaction, reactions related to the infusion of the medicine
- decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- dehydration
- inflammation of the liver
- inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness
- inflammation of the eye which causes redness or pain, blurred vision
- rapid heart beat
- high blood pressure (hypertension)
- inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), blood clots, fluid around the lungs, cough
- mouth ulcers and cold sores (stomatitis), inflammation of the pancreas (pancreatitis), constipation, dry mouth
- skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning, hives (itchy, bumpy rash)
- Inflammation of the joints (arthritis), muscle spasm, muscle weakness
- kidney failure (including abrupt loss of kidney function)
- oedema (swelling), pain, chest pain, chills

→ **Tell your doctor immediately** if you get any of these side effects.

Do not try to treat your symptoms with other medicines.

Uncommon (may affect up to 1 in 100 people)

- bronchitis
- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- acid in the blood produced from diabetes (diabetic ketoacidosis)
- Increased acid levels in the blood
- a temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome); damage to nerves causing numbness and weakness (polyneuropathy); inflammation of the nerves; foot drop (peroneal nerve palsy); inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy); muscle weakness and tiredness without atrophy (myasthenia gravis)
- inflammation of the brain
- changes in the rhythm or rate of the heartbeat, irregular or abnormal heart beat, inflammation of the heart muscle
- bowel perforation, inflammation of the stomach (gastritis), inflammation of the duodenum
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme)
- Severe and possibly fatal peeling of the skin (Stevens-Johnson syndrome)
- chronic disease of joints (spondyloarthropathy), disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), aching muscles, muscle tenderness of weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis), inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)
- inflammation of the kidney

→ **Tell your doctor immediately** if you get any of these side effects.

Do not try to treat your symptoms with other medicines.

Rare (may affect up to 1 in 1000 people)

- severe and possibly fatal peeling of the skin (toxic epidermal necrolysis)

→ **Tell your doctor immediately** if you get any of these side effects.

Do not try to treat your symptoms with other medicines.

Other side effects that have been reported (frequency not known) with ipilimumab in combination with nivolumab include:

- Solid organ transplant rejection
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)

Changes in test results

YERVOY in combination with nivolumab may cause changes in the results of tests carried out by your doctor. These include:

- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- Increased or decreased amount of calcium or potassium
- Increased or decreased blood levels of magnesium or sodium
- Decrease in body weight

Reporting of side effects

If you get any side effects, **talk to your doctor**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system listed in Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store YERVOY

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package in order to protect from light.

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

6. Contents of the pack and other information

What YERVOY contains

- The active substance is ipilimumab.
Each ml of concentrate contains 5 mg of ipilimumab.
Each 10 ml vial contains 50 mg of ipilimumab.
Each 40 ml vial contains 200 mg of ipilimumab.
- The other ingredients are Tris-hydrochloride, sodium chloride (see section 2 "YERVOY contains sodium"), mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid and water for injections.

What YERVOY looks like and contents of the pack

YERVOY concentrate for solution for infusion is clear to slightly opalescent, colourless to pale yellow and may contain light (few) particulates.

It is available in packs containing either 1 glass vial of 10 ml or 1 glass vial of 40 ml.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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Italy

Swords Laboratories T/A Bristol-Myers Squibb Cruiserath Biologics
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

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

Calculating the dose:

Ipilimumab monotherapy or ipilimumab in combination with nivolumab:

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 YERVOY concentrate may be needed to give the total dose for the patient.

- Each 10 ml vial of YERVOY 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 YERVOY concentrate** to prepare the dose (ml) = the total dose in mg, divided by 5 (the YERVOY concentrate strength is 5 mg/ml).

Preparing the infusion:

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

YERVOY can be used for intravenous administration either:

- **without dilution**, after transfer to an infusion container using an appropriate sterile syringe; or
- **after diluting** to up to 5 times the original volume of concentrate (up to 4 parts of diluent to 1 part of concentrate). The final concentration should range from 1 to 4 mg/ml. To dilute the YERVOY concentrate, you can use either:
 - sodium chloride 9 mg/ml (0.9%) solution for injection; or
 - 50 mg/ml (5%) glucose solution for injection

STEP 1

- Allow the appropriate number of vials of YERVOY to stand at room temperature for approximately 5 minutes.
- Inspect the YERVOY concentrate for particulate matter or discoloration. YERVOY concentrate is a clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates. Do not use if unusual amount of particles and signs of discoloration are present.
- Withdraw the required volume of YERVOY concentrate using an appropriate sterile syringe.

STEP 2

- Transfer the concentrate into a sterile, evacuated glass bottle or IV bag (PVC or non-PVC).
- If applicable, dilute with the required volume of sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. Gently mix the infusion by manual rotation.

Administration:

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

Administer the YERVOY infusion intravenously **over a period of 30 or 90 minutes, depending on the dose.**

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

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

The YERVOY infusion is compatible with:

- PVC infusion sets
- Polyethersulfone (0.2 µm to 1.2 µm) and nylon (0.2 µm) in-line filters

Flush the line with sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection at the end of the infusion.

Storage conditions and shelf life:

Unopened vial

YERVOY must be **stored in a refrigerator** (2°C to 8°C). The vials must be kept in the original package in order to protect from light. YERVOY should not be frozen.

Do not use YERVOY after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

YERVOY infusion

From a microbiological point of view, once opened, the medicine **should be infused or diluted and infused immediately**. The chemical and physical in-use stability of the undiluted or diluted infusion solution (between 1 and 4 mg/ml) has been demonstrated for 24 hours at room temperature (20°C to 25°C) or when refrigerated (2°C to 8°C). If not used immediately, the infusion solution (undiluted or diluted) must be used within 24 hours when stored either under refrigeration (2°C to 8°C) or at room temperature (20°C to 25°C). Other in-use storage time and conditions are the responsibility of the user.

Disposal:

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