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 (IgG1κ) 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 or in combination with nivolumab 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).

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).

Non-small cell lung cancer (NSCLC)

YERVOY in combination with nivolumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

Malignant pleural mesothelioma (MPM)

YERVOY in combination with nivolumab is indicated for the first line treatment of adult patients with unresectable malignant pleural mesothelioma.

Mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) colorectal cancer (CRC)

YERVOY in combination with nivolumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability high colorectal cancer in the following settings:
- first-line treatment of unresectable or metastatic colorectal cancer;
- treatment of metastatic colorectal cancer after prior fluoropyrimidine based combination chemotherapy (see section 5.1).

Oesophageal squamous cell carcinoma (OSCC)

YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

Hepatocellular carcinoma (HCC)

YERVOY in combination with nivolumab is indicated for the first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma.

4.2 Posology and method of administration

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

PD-L1 testing
If specified in the indication, patient selection for treatment with YERVOY based on the tumour expression of PD-L1 should be confirmed by a validated test (see sections 4.1, 4.4, and 5.1).

MSI/MMR testing
If specified in the indication, patient selection for treatment with YERVOY based on MSI-H/dMMR tumour status should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, 4.4, and 5.1).

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 30-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
In adults and adolescents 12 years of age and older and weighing at least 50 kg, 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 (see sections 5.1 and 5.2), 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.

In adolescents 12 years of age and older and weighing less than 50 kg, 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 3 mg/kg every 2 weeks **or** 6 mg/kg every 4 weeks (see sections 5.1 and 5.2), 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 3 mg/kg every 2 weeks; **or**
- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 6 mg/kg 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	Adults and adolescents 12 years of age and older: 1 mg/kg over 30 minutes	Adults and adolescents (12 years of age and older weighing at least 50 kg): 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes Adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30 minutes **or** 6 mg/kg every 4 weeks over 60 minutes
Ipilimumab	Adults and adolescents 12 years of age and older: 3 mg/kg over 30 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 for RCC

	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	-

dMMR or MSI H colorectal cancer
The recommended dose for first-line treatment of dMMR or MSI-H CRC is 1 mg/kg ipilimumab in combination with 240 mg of nivolumab administered intravenously every 3 weeks for a maximum of 4 doses, followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks, as presented in Table 3. 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. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

The recommended dose in patients who received prior fluoropyrimidine-based combination chemotherapy for dMMR or MSI-H CRC is 1 mg/kg ipilimumab in combination with 3 mg/kg nivolumab administered intravenously every 3 weeks for the first 4 doses, followed by nivolumab monotherapy administered intravenously 240 mg every 2 weeks, as presented in Table 3. 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.

Table 3: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab for dMMR or MSI-H CRC

		Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	First-line	240 mg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes
	After prior fluoropyrimidine-based combination chemotherapy	3 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes
Ipilimumab		1 mg/kg over 30 minutes	-

Malignant pleural mesothelioma
The recommended dose is 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks in combination with 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks. Treatment is continued for up to 24 months in patients without disease progression.

Oesophageal squamous cell carcinoma
The recommended dose is 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks in combination with either 3 mg/kg nivolumab every 2 weeks or 360 mg nivolumab every 3 weeks administered intravenously over 30 minutes. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Hepatocellular carcinoma
The recommended dose is 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab administered intravenously every 3 weeks for up to 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 (see sections 5.1 and 5.2), as presented in Table 4. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months. 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 480 mg every 4 weeks.

Table 4: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab for HCC

	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 30 minutes
Ipilimumab	3 mg/kg over 30 minutes	-

YERVOY in combination with nivolumab and chemotherapy

Non-small cell lung cancer
The recommended dose is 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks in combination with 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 1 mg/kg ipilimumab every 6 weeks in combination with 360 mg nivolumab administered intravenously every 3 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Duration of treatment
Treatment with YERVOY in combination with nivolumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (and up to maximum duration of therapy if specified for an indication).

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 5A, 5B, 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 5A and 5B for YERVOY as monotherapy, and in Table 5C 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 5A	**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).	
Adverse reactions	**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)	▪ Grade 3 or 4 diarrhoea or colitis
Hepatic: Severe elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or symptoms of hepatotoxicity	▪ Grade 3 or 4 elevation in AST, ALT, or total bilirubin
Skin: Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or severe widespread pruritus interfering with activities of daily living or requiring medical intervention	▪ Grade 4 rash or Grade 3 pruritus
Neurologic: New onset or worsening severe motor or sensory neuropathy	▪ Grade 3 or 4 motor or sensory neuropathy
Other organ systems[b]: (e.g. nephritis, pneumonitis, pancreatitis, non-infectious myocarditis, diabetes)	▪ ≥ Grade 3 immune-related reactions[c] ▪ ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy ▪ Grade 4 diabetes

[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 5B	**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.	
Adverse reactions	**Action**
Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs	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 Grade 3 diabetes	
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 5C:	**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 without HCC	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 hepatitis with HCC	If AST/ALT is within normal limits at baseline and increases to > 3 and ≤ 10 times ULN or Baseline AST/ALT is > 1 and ≤ 3 times ULN and increases to > 5 and ≤ 10 times ULN or Baseline AST/ALT is > 3 and ≤ 5 times ULN and increases to > 8 and ≤ 10 times ULN	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	AST/ALT increases to > 10 times ULN or Total bilirubin increases to > 3 times ULN	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	Symptomatic Grade 2 or 3	Withhold dose(s) until symptoms

Table 5C:	**Recommended treatment modifications for YERVOY in combination with nivolumab or administration of the second phase of treatment (nivolumab monotherapy) following combination treatment**	
endocrinopathies	hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes	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 Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[b]
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3 ; persistent Grade 2 or 3 despite treatment modification ; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment
Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome[c]	Grade 2 Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 3 or 4 Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome	Permanently discontinue treatment

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.

[b] The safety of re-initiating ipilimumab in combination with nivolumab therapy in patients previously experiencing immune-related myocarditis is not known.

[c] Presenting as an overlap of either two or all three conditions. The most severe CTCAE grade from the individual events should be considered to assess the recommended treatment modification.

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 as monotherapy 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.

The safety and efficacy of YERVOY in combination with nivolumab in children younger than 18 years of age have not been established, except in adolescents 12 years of age and older with melanoma. Currently available data are described in sections 4.2, 4.8, 5.1 and 5.2.

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 minutes.

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 or in combination with nivolumab and chemotherapy, nivolumab should be given first followed by YERVOY and then by chemotherapy (if applicable) 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

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded

Assessment of PD-L1 status
When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is used.

Assessment of MSI/MMR status
When assessing the MSI-H and dMMR status of the tumour, it is important that a well-validated and robust methodology is used.

Ipilimumab in combination with nivolumab
When ipilimumab is administered in combination, refer to the Summary of Product Characteristics of the other combination therapy components 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, or 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 filtrates), 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 characterised 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, hypothyroidism, Type 1 diabetes mellitus and diabetic ketoacidosis (see sections 4.2 and 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.

For symptomatic diabetes, ipilimumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. Ipilimumab must be permanently discontinued for life-threatening diabetes.

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, serous retinal detachment, and cystitis noninfective have been reported post-marketing (see sections 4.2 and 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, serous retinal detachment or episcleritis, topical corticosteroid eye drops should be considered as medically indicated. Transient vision loss has been reported in patients with ipilimumab-related ocular inflammations.

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with ipilimumab. Treatment with ipilimumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with ipilimumab versus the risk of possible organ rejection should be considered in these patients.

Ipilimumab as monotherapy or in combination with a PD-1 or PD-L1 inhibitor
Haemophagocytic lymphohistiocytosis (HLH) has been observed with ipilimumab as monotherapy and ipilimumab in combination with a PD-1 or PD-L1 inhibitor (including with nivolumab). Caution should be taken when ipilimumab is administered as monotherapy or in combination with a PD-1 or PD-L1 inhibitor. If HLH is confirmed, administration of ipilimumab or ipilimumab in combination with a PD-1 or PD-L1 inhibitor should be discontinued and treatment for HLH initiated.

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, Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome, myasthenic syndrome, aseptic meningitis, encephalitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, rhabdomyolysis and myelitis. Cases of Vogt-Koyanagi-Harada syndrome, serous retinal detachment, and cystitis noninfective have been reported post-marketing (see sections 4.2 and 4.8). Transient vision loss has been reported in patients with ipilimumab-related ocular inflammations.

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.

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.

The diagnosis of myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, ipilimumab in combination with nivolumab should be withheld or permanently discontinued (see section 4.2).

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

For Grade 3 or 4 Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome, ipilimumab in combination with nivolumab must be permanently discontinued (see section 4.2). Corticosteroids should be initiated as clinically indicated.

For Grade 2 Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome, ipilimumab in combination with nivolumab should be withheld and corticosteroids initiated as clinically indicated (see section 4.2). Upon improvement, resumption of ipilimumab in combination with nivolumab may be considered after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be adjusted as clinically indicated, and ipilimumab in combination with nivolumab must be permanently discontinued.

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 ≥ 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 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.

Non-small cell lung cancer
Patients with active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, active (untreated) brain metastasis, who received prior systemic treatment for advanced disease, or who had sensitising EGFR mutations or ALK translocations were excluded from the pivotal trial in first-line treatment of NSCLC (see sections 4.5 and 5.1). Limited data are available in elderly patients (≥ 75 years) (see section 5.1). In these patients, ipilimumab in combination with nivolumab and chemotherapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

Malignant pleural mesothelioma
Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the pivotal trial in first-line treatment of MPM (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.

dMMR or MSI-H colorectal cancer
Patients with a baseline performance score ≥ 2, active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trial in dMMR or MSI-H metastatic CRC (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.

Oesophageal squamous cell carcinoma
Patients with a baseline performance score ≥ 2, any history of concurrent brain metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the clinical trial in OSCC (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.

In the first-line OSCC trial, a higher number of deaths within 4 months was observed with ipilimumab in combination with nivolumab compared to chemotherapy. Physicians should consider the delayed onset of effect of ipilimumab in combination with nivolumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease (see section 5.1).

Hepatocellular carcinoma
Patients who had baseline ECOG performance score ≥ 2, prior liver transplant, Child-Pugh C liver disease, a history of concurrent brain metastases, a history of hepatic encephalopathy (within 12 months of randomization), clinically significant ascites, infection with HIV, or active co infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in HCC (see sections 4.5 and 5.1). Limited data are available in HCC patients with Child-Pugh B. In the absence of data, ipilimumab in combination with nivolumab followed by nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

In HCC, a higher number of deaths within 6 months was observed with ipilimumab in combination with nivolumab compared to lenvatinib or sorafenib. A higher risk of death may be associated with poor prognostic features. Physicians should consider this risk before initiating treatment with ipilimumab in combination with nivolumab in patients with poor prognostic features.

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

This medicinal product contains 23 mg sodium per 10 ml vial and 92 mg sodium per 40 ml vial, respectively equivalent to 1.15% and 4.60% of the WHO recommended maximum daily intake of 2 g sodium for an adult. 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 × ULN) and bilirubin (total bilirubin > 3 × 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 metabolised 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-naive 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 programme 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 (≥ 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) and from post-marketing surveillance are presented in Table 6.

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

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.

The safety data for patients with unresectable or metastatic melanoma, treated with ipilimumab (3 mg/kg, with a minimum of 3 year follow-up) and enrolled in multi-national, prospective, observational study CA184143 (N= 1151) were similar to what has been reported in ipilimumab clinical trials for advanced melanoma.

Table 6: Adverse reactions in patients with advanced melanoma treated with ipilimumab 3 mg/kg[a]

Infections and infestations	
Common	sepsis[b], urinary tract infection, respiratory tract infection
Uncommon	septic shock[b], pneumonia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common	tumour pain
Uncommon	paraneoplastic syndrome
Blood and lymphatic system disorders	
Common	anaemia, lymphopaenia, thrombocytopaenia, neutropaenia
Uncommon	haemolytic anaemia[b], eosinophilia
Not known	haemophagocytic lymphohistiocytosis[e]
Immune system disorders	
Uncommon	hypersensitivity
Very rare	anaphylactic reaction
Not known	solid organ transplant rejection[e]
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, hypokalaemia, weight decreased, hyponatremia
Uncommon	alkalosis, hypophosphatemia, tumour lysis syndrome, hypocalcaemia[d]
Rare	type 1 diabetes mellitus (including diabetic ketoacidosis)[h]
Psychiatric disorders	
Common	confusional state, depression
Uncommon	mental status changes, decreased libido
Nervous system disorders	
Common	peripheral sensory neuropathy, dizziness, headache, lethargy, cranial neuropathy, brain oedema, peripheral neuropathy
Uncommon	Guillain-Barré syndrome[b,c], meningitis (aseptic), autoimmune central neuropathy (encephalitis)[d], syncope, ataxia, tremor, myoclonus, dysarthria
Rare	myasthenia gravis[d]
Not known	myelitis
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[e], serous retinal detachment
Cardiac disorders	
Common	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	dyspnoea, cough, allergic rhinitis
Uncommon	respiratory failure, acute respiratory distress syndrome[b], lung infiltration, pulmonary oedema, pneumonitis

Gastrointestinal disorders	
Very common	diarrhoea[c], vomiting, nausea, constipation, abdominal pain
Common	gastrointestinal haemorrhage, colitis[b,c], gastroesophageal reflux disease, mucosal inflammation[d], gastroenteritis, stomatitis
Uncommon	gastrointestinal perforation[b,c], large intestine perforation[b,c], intestinal perforation[b,c], peritonitis[b], diverticulitis, pancreatitis, enterocolitis, gastric ulcer, large intestinal ulcer, oesophagitis, ileus[d], proctitis[d]
Rare	pancreatic exocrine insufficiency; coeliac disease
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	
Very common	musculoskeletal pain[f]
Common	arthralgia, myalgia, muscle spasms, arthritis
Uncommon	polymyalgia rheumatica, myositis[d], muscular weakness[d]
Rare	polymyositis[d]
Renal and urinary disorders	
Common	renal failure[b]
Uncommon	glomerulonephritis[c], autoimmune nephritis[d], renal tubular acidosis, haematuria[d], cystitis noninfective[g], proteinuria[d]
Reproductive system and breast disorders	
Uncommon	amenorrhea
General disorders and administration site conditions	
Very common	fatigue, injection site reaction, pyrexia, oedema, pain
Common	chills, asthenia, 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, increased lipase[c]
Uncommon	increased gamma-glutamyltransferase[d], increased blood creatinine, increased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood corticotrophin, 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]

Adverse reaction frequencies presented in Table 6 may not be fully attributable to ipilimumab, but may contain contributions from the underlying disease.

[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).
[f] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.
[g] Reported in clinical studies and in the post-marketing setting.
[h] Type 1 diabetes mellitus that may be associated with diabetic ketoacidosis

Additional adverse reactions not listed in Table 6 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 erythrodysaesthesia syndrome, cytokine release syndrome, sarcoidosis, decreased blood gonadotrophin, leukopenia, polycythaemia, lymphocytosis, ocular myositis, and neurosensory hypoacusis.

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 (with or without chemotherapy) (see section 4.2)

a. Summary of the safety profile

When ipilimumab is administered in combination, refer to the SmPC for the other therapeutic agent(s) prior to initiation of treatment. For additional information on the safety profile of the other therapeutic agents used in combination with ipilimumab, please refer to the respective SmPC.

In the pooled dataset of ipilimumab administered in combination with nivolumab (with or without chemotherapy) across tumour types (n = 2626) with minimum follow-up ranging from 6 to 47 months, the most frequent adverse reactions (≥ 10%) were fatigue (47%), diarrhoea (35%), rash (37%), nausea (27%), pruritus (29%), musculoskeletal pain (26%), pyrexia (23%), decreased appetite (22%), cough (21%), abdominal pain (18%), vomiting (18%), constipation (18%), arthralgia (18%), dyspnoea (17%), hypothyroidism (16%), headache (15%), upper respiratory tract infection (13%), oedema (13%) and dizziness (10%). The incidence of Grade 3-5 adverse reactions was 66% for ipilimumab in combination with nivolumab (with or without chemotherapy), with 1.0% fatal adverse reactions attributed to study drug. Among patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg for melanoma, fatigue (62%), rash (57%), diarrhoea (52%), nausea (42%), pruritus (40%), pyrexia (36%), and headache (26%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of ipilimumab in combination with nivolumab (with or without chemotherapy) incidence rate. Among patients treated with ipilimumab 1 mg/kg in combination with nivolumab 360 mg and chemotherapy for NSCLC, anaemia (32%) and neutropaenia (15%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of ipilimumab in combination with nivolumab (with or without chemotherapy) incidence rate.

b. Tabulated summary of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with ipilimumab in combination with nivolumab (with or without chemotherapy) (n= 2626) and from post-marketing are presented in Table 7. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); 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 7: Adverse reactions with ipilimumab in combination with other therapeutic agents

	Combination with nivolumab (with or without chemotherapy)
Infections and infestations	
Very common	upper respiratory tract infection
Common	pneumonia, bronchitis, conjunctivitis
Rare	aseptic meningitis
Blood and lymphatic system disorders	
Very common	anaemia[b,i], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]
Common	eosinophilia
Uncommon	febrile neutropaenia
Not known	haemophagocytic lymphohistiocytosis
Immune system disorders	
Common	infusion-related reaction (including cytokine release syndrome), hypersensitivity
Rare	sarcoidosis
Not known	solid organ transplant rejection[f]
Endocrine disorders	
Very common	hypothyroidism
Common	hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, hypopituitarism, diabetes mellitus
Uncommon	diabetic ketoacidosis
Rare	hypoparathyroidism

Metabolism and nutrition disorders	
Very common	decreased appetite, hyperglycaemia[b], hypoglycaemia[b]
Common	dehydration, hypoalbuminaemia, hypophosphataemia, weight decreased
Uncommon	metabolic acidosis
Not known	tumour lysis syndrome[g]
Nervous system disorders	
Very common	headache
Common	dizziness, peripheral neuropathy
Uncommon	polyneuropathy, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis, myasthenia gravis, Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome[k]
Rare	Guillain-Barré syndrome, neuritis, myelitis (including transverse myelitis)
Eye disorders	
Common	blurred vision, dry eye
Uncommon	uveitis, episcleritis
Rare	Vogt-Koyanagi-Harada syndrome, serous retinal detachment
Cardiac disorders	
Common	tachycardia, atrial fibrillation
Uncommon	myocarditis[a], arrhythmia (including ventricular arrhythmia)[a], bradycardia
Not known	pericardial disorders[h]
Vascular disorders	
Common	hypertension
Respiratory, thoracic and mediastinal disorders	
Very common	cough, dyspnoea
Common	pneumonitis[a], pulmonary embolism[a], pleural effusion
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation
Common	colitis[a], pancreatitis, stomatitis, gastritis, dry mouth
Uncommon	duodenitis
Rare	Intestinal perforation[a], pancreatic exocrine insufficiency, coeliac disease
Hepatobiliary disorders	
Common	hepatitis
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus
Common	alopecia, vitiligo, urticaria, dry skin, erythema
Uncommon	Stevens-Johnson syndrome, erythema multiforme, psoriasis, other lichen disorders[j]
Rare	toxic epidermal necrolysis[a,d], lichen sclerosus
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[e], arthralgia
Common	muscle spasms, muscular weakness, arthritis
Uncommon	polymyalgia rheumatica, myopathy, myositis (including polymyositis)[a]
Rare	spondyloarthropathy, Sjogren's syndrome, rhabdomyolysis[a]
Renal and urinary disorders	
Common	renal failure (including acute kidney injury)[a]
Uncommon	tubulointerstitial nephritis, nephritis
Rare	cystitis noninfective
General disorders and administration site conditions	
Very common	fatigue, pyrexia, oedema (including peripheral oedema)
Common	chest pain, pain, chills

Investigations	
Very common	increased alkaline phosphatase[b], increased AST[b], increased ALT[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hyponatraemia[b], hyperkalaemia[b], hypokalaemia[b], hypercalcaemia[b], hypocalcaemia[b]
Common	hypernatraemia[b], hypermagnesaemia[b], increased thyroid stimulating hormone, increased gamma-glutamyltransferase

Adverse reaction frequencies presented in Table 7 may not be fully attributable to ipilimumab alone or in combination with other therapeutic agents, but may contain contributions from the underlying disease or from medicinal product used in combination.

[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] 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, nodular rash, and pemphigoid.
[d] Reported also in studies outside the pooled dataset. The frequency is based on the programme-wide exposure.
[e] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, myalgia intercostal, neck pain, pain in extremity, and spinal pain.
[f] Post-marketing event (also see section 4.4).
[g] Reported in clinical studies and in the post-marketing setting.
[h] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.
[i] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia, haemoglobin decreased, iron deficiency anaemia, and red blood cell count decreased.
[j] Lichen disorders is a composite term which includes lichen keratosis and lichen planus.
[k] Cases of Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome (presenting as an overlap of either two or all three conditions), some with fatal outcome, have been reported (see section 4.4).

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 is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment generally was required in a greater proportion of patients receiving ipilimumab in combination with nivolumab than in those receiving nivolumab monotherapy. Table 8 presents the percentage of patients with immune-related adverse reactions who were permanently discontinued from treatment. Additionally, for patients who experienced an event, Table 8 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 8: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids

	Ipilimumab in combination with nivolumab (with or without chemotherapy) %
Immune-related adverse reaction leading to permanent discontinuation	
Pneumonitis	2.1
Colitis	6
Hepatitis	5
Nephritis and renal dysfunction	1.1
Endocrinopathies	2.2
Skin	1.0
Hypersensitivity/Infusion reaction	0.3

Immune-related adverse reaction requiring high-dose corticosteroids[a,b]	
Pneumonitis	59
Colitis	32
Hepatitis	39
Nephritis and renal dysfunction	27
Endocrinopathies	18
Skin	8
Hypersensitivity/Infusion reaction	18

[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 in combination with nivolumab (with or without chemotherapy), the incidence of diarrhoea or colitis was 26.0% (682/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 8.1% (212/2626), 6.4% (167/2626), and 0.2% (4/2626), of patients, respectively. Two patients (< 0.1%) had a fatal outcome. Median time to onset was 1.4 months (range: 0.0-48.9). Resolution occurred in 618 patients (91%) with a median time to resolution of 2.9 weeks (range: 0.1-170.0^{+}). Among patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg for melanoma, the incidence of diarrhoea or colitis was 46.7%, including Grade 2 (13.6%), Grade 3 (15.8%), and Grade 4 (0.4%).

Immune-related pneumonitis

In patients treated with ipilimumab in combination with nivolumab (with or without chemotherapy), the incidence of pneumonitis including interstitial lung disease, was 6.0% (157/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 3.0% (78/2626), 1.0% (27/2626), and 0.3% (8/2626) of patients, respectively. Four patients (0.2%) had a fatal outcome. Median time to onset was 2.7 months (range: 0.1-56.8). Resolution occurred in 129 patients (82.2%) with a median time to resolution of 6.1 weeks (range: 0.1^{+}-149.3^{+}).

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 in combination with nivolumab (with or without chemotherapy), the incidence of liver function test abnormalities was 21.2% (556/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 5.0% (132/2626), 8.3% (218/2626), and 1.3% (34/2626) of patients, respectively. Seven patients (0.3%) had a fatal outcome. Median time to onset was 1.5 months (range: 0.0-36.6). Resolution occurred in 482 patients (87.0%) with a median time to resolution of 5.9 weeks (range: 0.1-175.9^{+}). Among patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg for melanoma, the incidence of liver function test abnormalities was 30.1%, including Grade 2 (6.9%), Grade 3 (15.8%), and Grade 4 (1.8%). Among patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg for HCC, the incidence of liver function test abnormalities was 34.3% including Grade 2 (8.4%), Grade 3 (14.2%), and Grade 4 (2.7%).

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 in combination with nivolumab (with or without chemotherapy), the incidence of rash was 46.1% (1210/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 14.3% (375/2626), 4.6% (120/2626), and 0.1% (3/2626) of patients, respectively. Median time to onset was 0.7 months (range: 0.0-33.8). Resolution occurred in 843 patients (70%) with a median time to resolution of 12.1 weeks (range: 0.1-268.7^{+}). Among patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg for melanoma, the incidence of rash was 65.2%, including Grade 2 (20.3%) and Grade 3 (7.8%).

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 in combination with nivolumab (with or without chemotherapy), the incidence of nephritis or renal dysfunction was 5.4% (141/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 2.0% (52/2626), 0.8% (21/2626), and 0.4% (11/2626) of patients, respectively. Two patients (< 0.1%) had a fatal outcome. Median time to onset was 2.6 months (range: 0.0-34.8). Resolution occurred in 110 patients (78.0%) with a median time to resolution of 5.9 weeks (range: 0.1-172.1^{+}).

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. 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 in combination with nivolumab (with or without chemotherapy), the incidence of thyroid disorders was 23.2% (608/2626). Grade 2 and Grade 3 thyroid disorders were reported in 12.7% (333/2626) and 1.0% (27/2626) of patients, respectively.
Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 1.9% (49/2626) and 1.5% (40/2626) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.6% (16/2626) and 0.5% (13/2626) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute, blood corticotrophin decreased and immune-mediated adrenal insufficiency) occurred in 2.7% (72/2626), 1.6% (43/2626) and 0.2% (4/2626) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) occurred in < 0.1% (1/2626), 0.3% (8/2626), 0.3% (7/2626), and 0.2% (6/2626) of patients, respectively. Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-28.1). Resolution occurred in 297 patients (40.0%). Time to resolution ranged from 0.3 to 257.1^{+} weeks.

Infusion reactions
In patients treated with ipilimumab in combination with nivolumab (with or without chemotherapy), the incidence of hypersensitivity/infusion reactions was 4.5% (118/2626). Grade 1, Grade 2, Grade 3, and Grade 4 cases were reported in 1.9% (49/2626), 2.4% (62/2626), 0.2% (6/2626), and < 0.1% (1/2626) of patients, respectively. Among patients with MPM treated with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg, the incidence of hypersensitivity/infusion reactions was 12%.

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 13.7%. Neutralising antibodies against ipilimumab ranged from 0 to 0.4%. Of the patients who were treated with ipilimumab in combination with nivolumab and chemotherapy and evaluable for the presence of anti-ipilimumab antibodies or neutralising antibodies against ipilimumab, the incidence of anti-ipilimumab antibodies was 7.5% and neutralising antibodies against ipilimumab was 1.6%. 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, 24.9% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks, and 33.8% with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy. The incidence of neutralising antibodies against nivolumab was 0.8% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 1.5% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks and 2.6% with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy.

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
In patients treated with ipilimumab in combination with nivolumab (with or without chemotherapy), the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.8% for anaemia, 1.8% for thrombocytopaenia, 2.2% for leucopoenia, 6.9% for lymphopaenia, 3.3% for neutropaenia, 2.7% for increased alkaline phosphatase, 9.8% for increased AST, 9.3% for increased ALT, 2.3% for increased total bilirubin, 1.8% for increased creatinine, 1.4% for hypoalbuminaemia, 7.1% for hyperglycaemia, 0.7% for hypoglycaemia, 7.8% for increased amylase, 16.3% for increased lipase, 0.8% for hypocalcaemia, 0.2% for hypernatraemia, 0.8% for hypercalcaemia, 2.0% for hyperkalaemia, 0.8% for hypermagnesaemia, 0.4% for hypomagnesaemia, 3.0% for hypokalaemia, and 8.7% for hyponatraemia. Among patients treated with ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg for melanoma, a higher proportion of patients experienced a worsening from baseline to a Grade 3 or 4 increased ALT (15.3%).

Paediatric population

Ipilimumab as monotherapy

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

In study CA184070, no immune-related adverse reactions (irAR) ≥ 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 9.

Table 9: 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 tumours			Advanced melanoma		Advanced melanoma	
	CA184070			CA184178		CA184004/ 022 pooled	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 paediatric 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

Ipilimumab in combination with nivolumab

The safety of ipilimumab (1 mg/kg every 3 weeks) in combination with nivolumab (1 mg/kg or 3 mg/kg for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks) was evaluated in 33 paediatric patients aged ≥ 1 year to < 18 years (including 20 patients 12 to < 18 years) with recurrent or refractory solid or haematological tumours, including advanced melanoma, in clinical study CA209070. The safety profile in paediatric patients was generally similar to that seen in adults treated with ipilimumab in combination with nivolumab. No new safety signals were observed.
The most common adverse reactions (reported in at least 20% of paediatric patients) for ipilimumab in combination with nivolumab were fatigue (33.3%) and rash maculo-papular (21.2%). The majority of adverse reactions reported for ipilimumab in combination with nivolumab were of Grades 1 or 2 in severity. Ten patients (30%) had one or more Grades 3 to 4 adverse reactions.

No new safety signals were observed in clinical study CA209908 of 74 paediatric patients with high-grade primary central nervous system (CNS) malignancies (see section 5.1) relative to data available in adult studies across indications.

Elderly
In MPM patients, there was a higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older (68% and 35%, respectively) relative to all patients who received ipilimumab in combination with nivolumab (54% and 28%, respectively). Data from dMMR or MSI-H CRC patients 75 years of age or older are limited (see section 5.1). In HCC patients, there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (67% and 35%, respectively) relative to all patients who received ipilimumab with nivolumab (53% and 27%, respectively).

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:

Yellow Card Scheme
Website: at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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 and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX04.

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 intratumoural 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 advanced melanoma and RCC.

Clinical trials with ipilimumab monotherapy

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 ≥ 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 randomised 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 randomised: 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 10.

Table 10: 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 randomised, 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 diarrhoea (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 ≥ 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 with ipilimumab monotherapy

Melanoma

CA184332 and CA184338
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 11. 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.

Table 11: Overall survival in observational studies

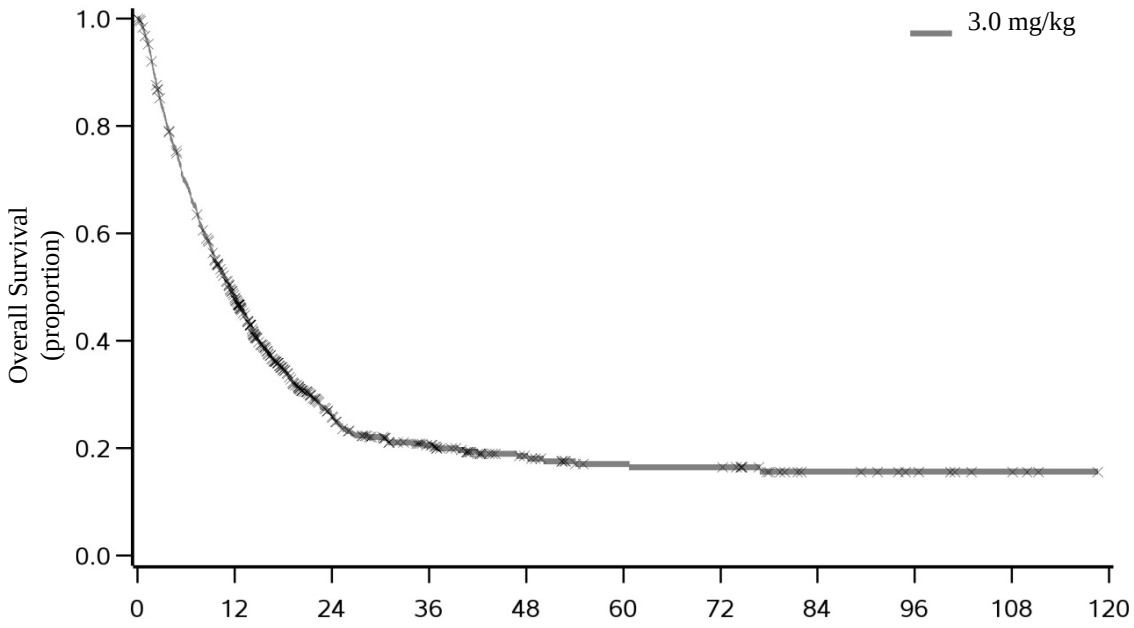
	CA184338 n= 273	CA184332 n= 157
Median OS (95% CI)	14 months (12.8-18.7)	10 months (7.0-12.8)
OS at 1 year % (95% CI)	59% (52.5-64.3)	44% (35.5, 51.4)
OS at 2 years % (95% CI)	39% (33.1-44.8)	26% (18.9-33.3)
OS at 3 years % (95% CI)	31% (25.5-36.7)	22% (15.5-29.2)
OS at 4 years % (95% CI)	26% (20.4-31.3)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

Clinical trials with ipilimumab in combination with nivolumab

Melanoma

Randomised phase 3 study of 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.

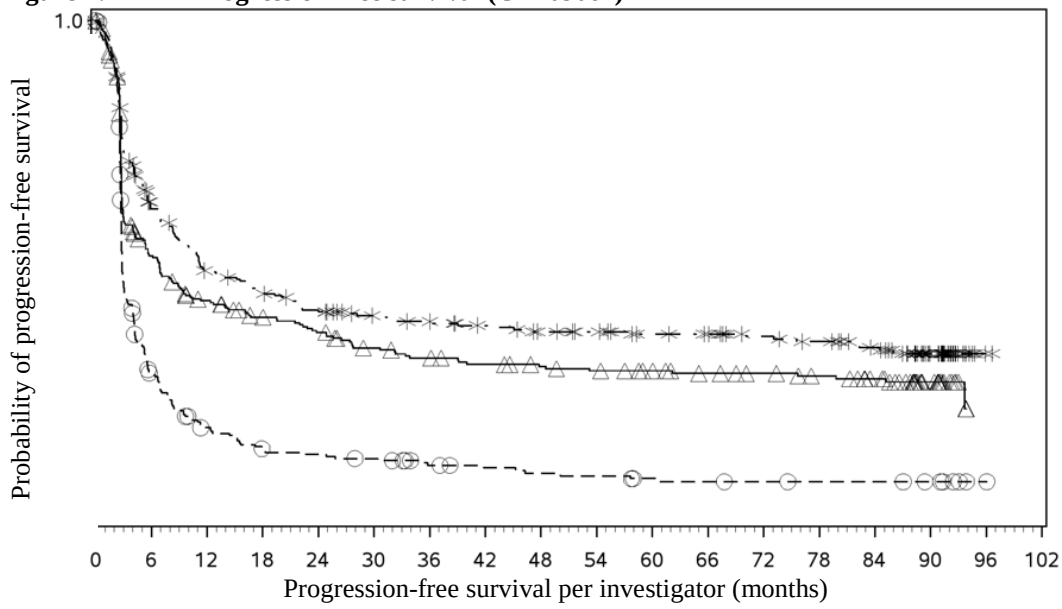
A total of 945 patients were randomised to receive ipilimumab in combination with nivolumab (n = 314), nivolumab monotherapy (n = 316), or ipilimumab monotherapy (n = 315). Patients in the combination arm received nivolumab 1 mg/kg over 60 minutes and ipilimumab 3 mg/kg over 90 minutes administered intravenously 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 (≥ 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 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 ≥ 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.

At primary analysis (minimum follow-up 9 months) the median PFS was 6.9 months in the nivolumab group as compared with 2.9 months in the ipilimumab group (HR = 0.57, 99.5% CI: 0.43, 0.76; p < 0.0001). The median PFS was 11.5 months in the ipilimumab in combination with nivolumab group, as compared with 2.9 months in the ipilimumab group (HR = 0.42, 99.5% CI: 0.31, 0.57; p < 0.0001).

PFS results from descriptive analysis (with minimum follow up of 90 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	175	138	126	112	103	99	93	87	84	78	76	70	66	57	33	1	-
Nivolumab	316	151	120	106	97	84	78	73	69	66	62	57	54	50	44	21	0	-
Ipilimumab	315	78	46	34	31	28	21	18	16	15	12	11	10	9	9	7	1	-

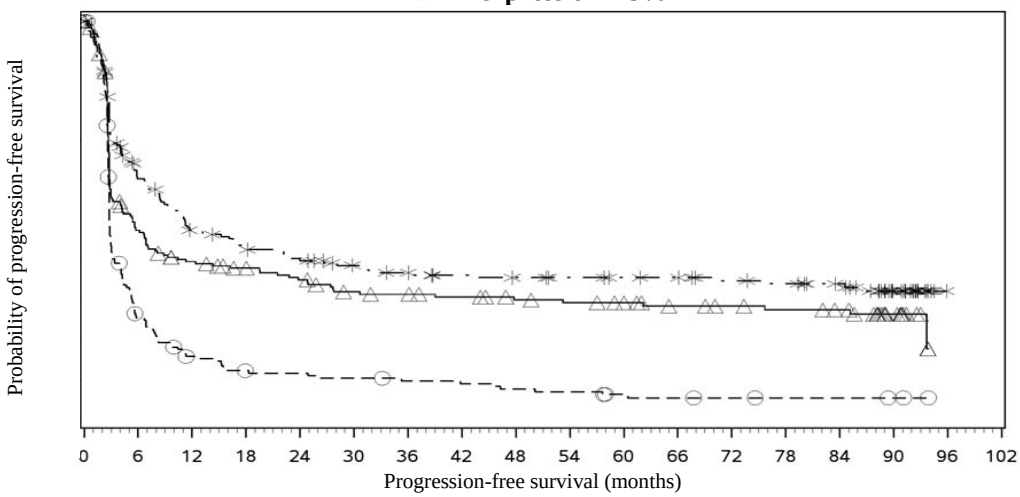
- - -*- - - - Nivolumab+ipilimumab (events: 189/314), median and 95% CI: 11.50 (8.90, 20.04). PFS rate at 12 months and 95% CI: 49% (44, 55), PFS rate at 60 months and 95% CI: 36% (32, 42), PFS rate at 90 months and 95% CI: 33% (27, 39)

——Δ—— Nivolumab (events: 208/316), median and 95% CI: 6.93 (5.13, 10.18). PFS rate at 12 months and 95% CI: 42% (36, 47), PFS rate at 60 months and 95% CI: 29% (24, 35), PFS rate at 90 months and 95% CI: 27% (22, 33)

- - -❍- - - Ipilimumab (events: 261/315), median and 95% CI: 2.86 (2.79, 3.09). PFS rate at 12 months and 95% CI: 18% (14, 23), PFS rate at 60 months and 95% CI: 8% (5, 12), PFS rate at 90 months and 95% CI: 7% (4, 11)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.35, 0.51);
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.53 (0.44, 0.64);
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.79 (0.65, 0.97)

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



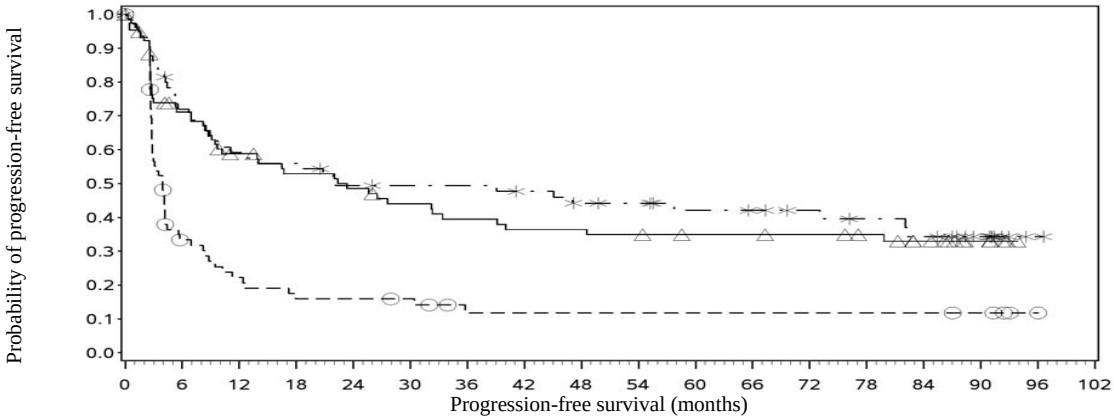
Number of subjects at risk

Nivolumab + ipilimumab	210	113	87	78	71	64	60	56	54	52	50	49	45	43	39	22	0	-
Nivolumab	208	91	73	66	60	51	49	46	42	40	38	33	31	29	27	12	0	-
Ipilimumab	202	45	26	19	18	16	14	13	11	10	7	6	5	4	4	3	0	-

- - -*- - - Nivolumab+ipilimumab (events: 127/210), median and 95% CI: 11.17 (7.98, 17.51)
—Δ— Nivolumab (events: 139/208), median and 95% CI: 5.39 (2.96, 7.13)
- - -O- - - Ipilimumab (events: 171/202), median and 95% CI: 2.79 (2.76, 3.02)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.33, 0.53)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.54 (0.43, 0.68)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.77 (0.61, 0.98)

PD-L1 expression ≥ 5%



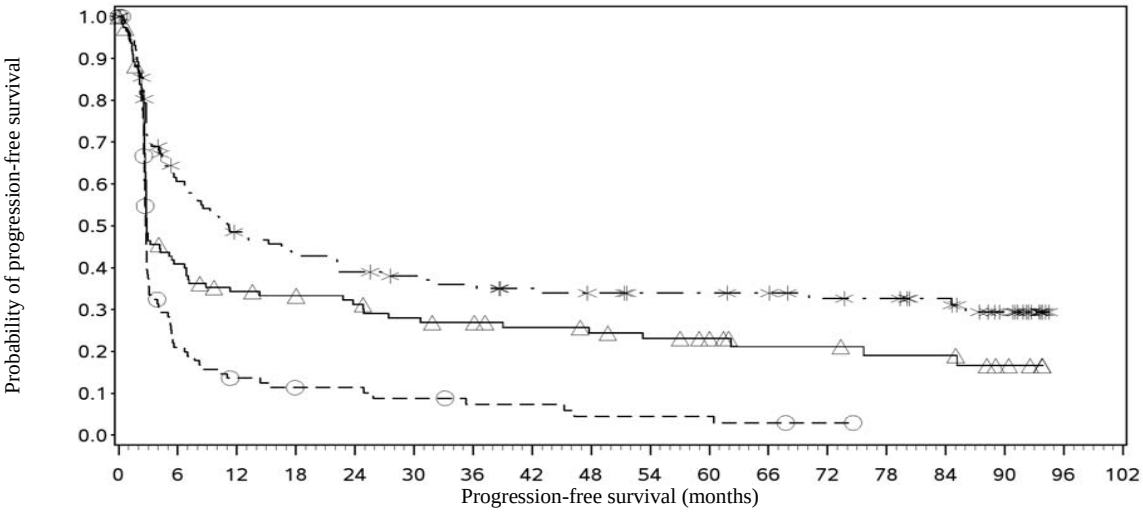
Number of subjects at risk

Nivolumab + ipilimumab																	
68	45	37	35	30	29	29	27	24	23	20	19	17	15	13	8	1	-
Nivolumab																	
80	52	41	36	33	29	26	24	24	23	21	21	20	18	14	7	0	-
Ipilimumab																	
75	21	14	10	10	9	5	5	5	5	5	5	5	5	5	4	1	-

- - -*- - - - Nivolumab+ipilimumab (events: 36/68), median and 95% CI: 22.11 (9.72, 82.07)
——Δ—— Nivolumab (events: 48/80), median and 95% CI: 22.34 (9.46, 39.13)
- - -❍- - - Ipilimumab (events: 60/75), median and 95% CI: 3.94 (2.79, 4.21)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.38 (0.25, 0.58)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.43 (0.29, 0.64)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.89 (0.58, 1.35)

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



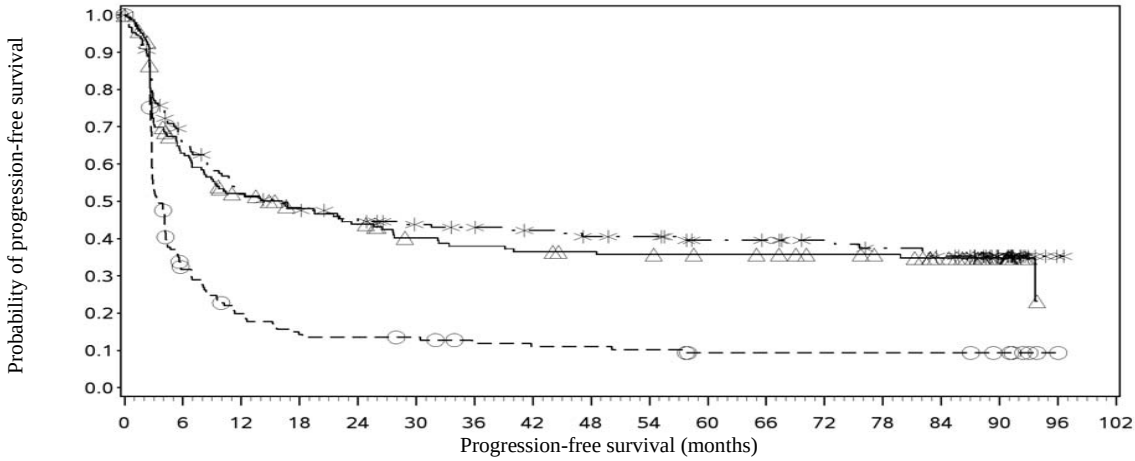
Number of subjects at risk

Nivolumab + ipilimumab	123	65	51	46	41	38	36	33	31	29	29	28	25	24	21	13	0	-
Nivolumab	117	44	35	33	30	26	24	21	19	17	15	11	11	9	9	5	0	-
Ipilimumab	113	20	12	9	9	7	5	5	3	3	3	2	1	0	0	0	0	-

- - -*- - - Nivolumab+ipilimumab (events: 76/123), median and 95% CI: 11.17 (6.93, 22.18)
——Δ—— Nivolumab (events: 85/117), median and 95% CI: 2.83 (2.76, 5.62)
- - -❍- - - Ipilimumab (events: 94/113), median and 95% CI: 2.73 (2.66, 2.83)

Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.39 (0.28, 0.53)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.59 (0.44, 0.79)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.66 (0.48, 0.90)

PD-L1 expression ≥ 1%



Number of subjects at risk

Nivolumab + ipilimumab	155	93	73	67	60	55	53	50	47	46	41	40	37	34	31	17	1	-
Nivolumab	171	99	79	69	63	54	51	49	47	46	44	43	40	38	32	14	0	-
Ipilimumab	164	46	28	20	19	18	14	13	13	12	9	9	9	9	9	7	1	-

- - -*- - - Nivolumab+ipilimumab (events: 90/155), median and 95% CI: 16.13 (8.90, 45.08)
—Δ—— Nivolumab (events: 102/171), median and 95% CI: 16.20 (8.11, 27.60)
- - -❍- - - Ipilimumab (events: 137/164), median and 95% CI: 3.48 (2.83, 4.17)

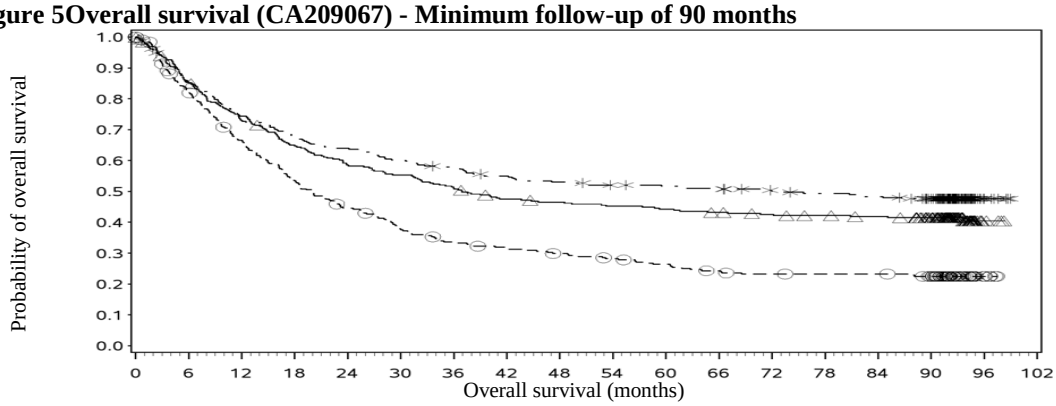
Nivolumab+ipilimumab vs. ipilimumab - hazard ratio and 95% CI: 0.42 (0.32, 0.55)
Nivolumab vs. ipilimumab - hazard ratio and 95% CI: 0.45 (0.35, 0.59)
Nivolumab+ipilimumab vs. nivolumab - hazard ratio and 95% CI: 0.92 (0.69, 1.22)

The final (primary) OS analysis occurred when all patients had a minimum follow-up of 28 months. At 28 months, median OS was not reached in the nivolumab group as compared with 19.98 months in the ipilimumab group (HR = 0.63, 98% CI: 0.48, 0.81; p-value: < 0.0001). Median OS was not reached in the ipilimumab in combination with nivolumab group as compared with the ipilimumab group (HR = 0.55, 98% CI: 0.42, 0.72; p-value: < 0.0001).

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 90 months show outcomes consistent with the original primary analysis. OS results from this follow-up analysis are shown in Figure 5 (all randomised), Figure 6 and 7 (at the tumour PD-L1 5% and 1% cut off).

The OS analysis was not adjusted to account for subsequent therapies received. Subsequent systemic therapy was received by 36.0%, 49.1%, and 66.3% 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 19.1%, 34.2%, and 48.3% of patients in the combination, nivolumab monotherapy, and ipilimumab arms, respectively.

Figure 5Overall survival (CA209067) - Minimum follow-up of 90 months



Number of subjects at risk

Nivolumab+ipilimumab																	
314	265	227	210	199	187	179	169	163	158	156	153	147	144	141	129	7	-
Nivolumab																	
316	266	231	201	181	171	158	145	141	137	134	130	126	123	120	107	4	-
Ipilimumab																	
315	253	203	163	135	113	100	94	87	81	75	68	64	63	63	57	5	-

- - -*- - - - Nivolumab+ipilimumab (events: 162/314), median and 95% CI: 72.08 (38.18, N.A.)
OS rate and 95% CI at 12 months: 73% (68, 78), 24 months: 64% (59, 69), 36 months: 58% (52, 63), 60 months: 52% (46, 57) and 90 months: 48% (42, 53)

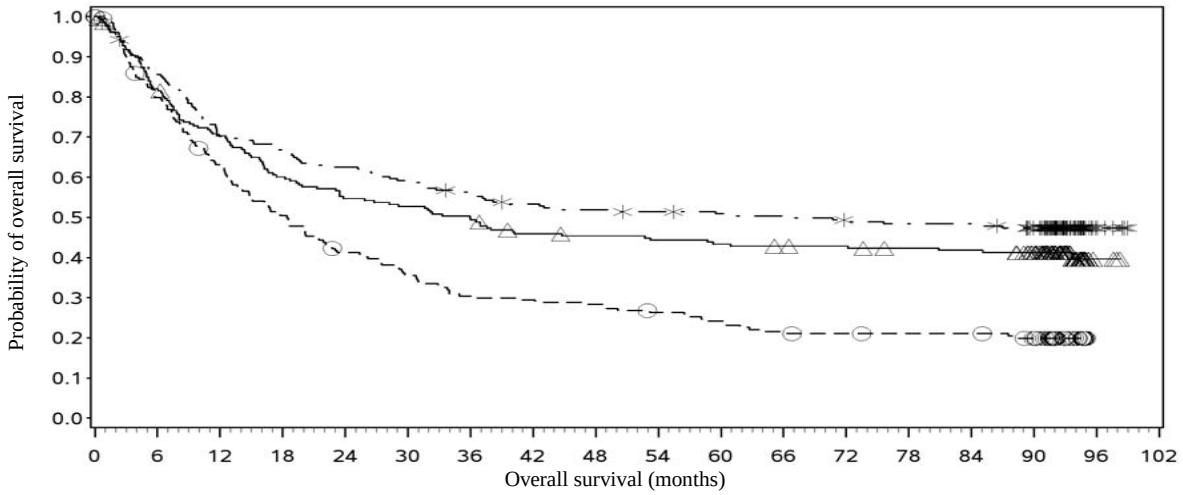
—Δ— Nivolumab (events: 182/316), median and 95% CI: 36.93 months (28.25, 58.71)
OS rate and 95% CI at 12 months: 74% (69, 79), 24 months: 59% (53, 64), 36 months: 52% (46, 57), 60 months: 44% (39, 50), and 90 months: 42% (36, 47)

- - -❍- - - Ipilimumab (events: 235/315), 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), 36 months: 34% (29, 39), 60 months: 26% (22, 31), and 90 months: 22% (18, 27)

Nivolumab+ipilimumab vs ipilimumab - HR (95% CI): 0.53 (0.44, 0.65);
Nivolumab vs ipilimumab - HR (95% CI): 0.63 (0.52, 0.77);
Nivolumab+ipilimumab vs nivolumab - HR (95% CI): 0.84 (0.68, 1.04)

Figure 6: Overall survival by PD-L1 expression: 5% cut off (CA209067) - Minimum follow-up of 90 months

PD-L1 expression < 5%



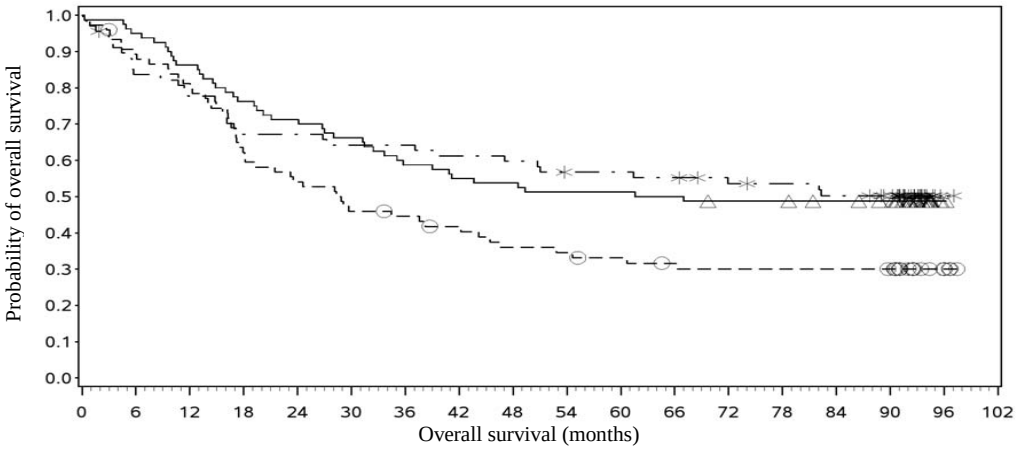
Number of subjects at risk

Nivolumab+ipilimumab	210	178	146	139	130	123	116	109	106	104	102	100	98	96	96	88	6	-
Nivolumab	208	169	144	123	112	108	102	92	90	88	86	84	83	80	79	70	3	-
Ipilimumab	202	158	124	99	80	69	59	57	55	50	46	41	39	38	38	33	0	-

- - -*- - - - Nivolumab+ipilimumab (events: 109/210), median and 95% CI: 65.94 (32.72, N.A.)
—Δ—— Nivolumab (events: 121/208), median and 95% CI: 35.94 months (23.06, 60.91)
- - -O- - - Ipilimumab (events: 157/202), median and 95% CI: 18.40 months (13.70, 22.51)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.51 (0.40, 0.66)
Nivolumab vs. ipilimumab - HR (95% CI): 0.62 (0.49, 0.79)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.83 (0.64, 1.07)

PD-L1 expression ≥ 5%



Number of subjects at risk

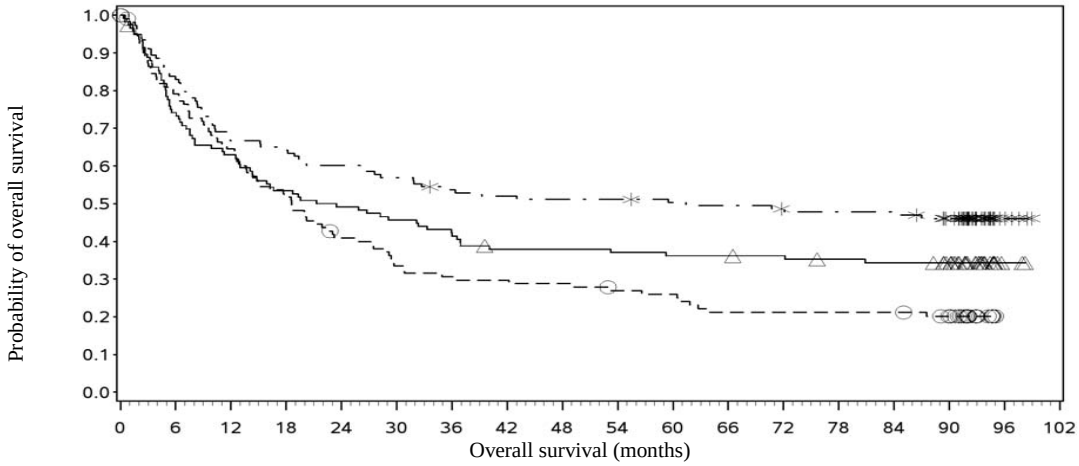
Nivolumab+ipilimumab	68	56	52	45	45	43	43	41	40	37	37	36	33	32	30	27	1	-
Nivolumab	80	76	69	61	57	53	47	44	43	41	41	40	38	38	36	33	1	-
Ipilimumab	75	66	60	46	40	34	32	29	25	24	22	20	19	19	19	18	4	-

- - -*- - - - Nivolumab+ipilimumab (events: 33/68), median and 95% CI: N.A. (39.06, N.A.)
—Δ—— Nivolumab (events: 41/80), median and 95% CI: 64.28 months (33.64, N.A.)
- - -O- - - Ipilimumab (events: 51/75), median and 95% CI: 28.88 months (18.10, 44.16)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.61 (0.39, 0.94)
Nivolumab vs. ipilimumab - HR (95% CI): 0.61 (0.41, 0.93)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.99 (0.63, 1.57)

Figure 7: Overall survival by PD-L1 expression: 1% cut off (CA209067) - Minimum follow-up of 90 months

PD-L1 expression < 1%



Number of subjects at risk

Nivolumab+ipilimumab	123	102	82	79	74	70	65	63	62	62	62	60	59	57	56	50	5	-
Nivolumab	117	86	73	62	57	53	49	43	43	42	41	41	40	38	37	33	2	-
Ipilimumab	113	87	71	57	44	36	33	32	31	28	27	22	22	22	22	18	0	-

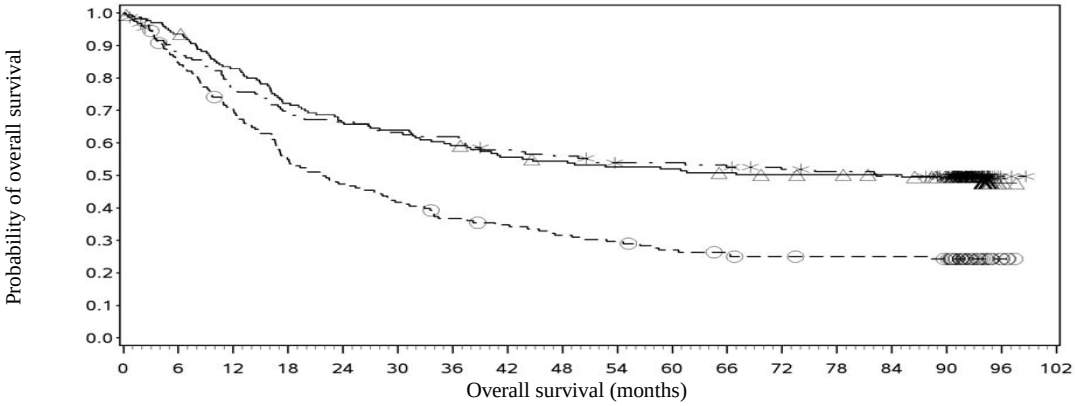
- - -*- - - - Nivolumab+ipilimumab (events: 66/123), median and 95% CI: 61.44 (26.45, N.A.)

—Δ— Nivolumab (events: 76/117), median and 95% CI: 23.46 months (13.01, 36.53)

- - -O- - - Ipilimumab (events: 87/113), median and 95% CI: 18.56 months (13.67, 23.20)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.55 (0.40, 0.76)
Nivolumab vs. ipilimumab - HR (95% CI): 0.77 (0.57, 1.05)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 0.71 (0.51, 0.99)

PD-L1 expression ≥ 1%



Number of subjects at risk

Nivolumab+ipilimumab	155	132	116	105	101	96	94	87	84	79	79	77	74	72	70	65	2	-
Nivolumab	171	159	140	122	112	108	100	93	90	87	86	83	81	80	78	70	2	-
Ipilimumab	164	137	113	88	76	67	58	54	49	46	41	39	36	35	35	33	4	-

- - -*- - - - Nivolumab+ipilimumab (events: 76/155), median and 95% CI: 82.30 (39.06, N.A.)
——Δ—— Nivolumab (events: 86/171), median and 95% CI: 85.09 months (39.00, N.A.)
- - -O- - - Ipilimumab (events: 121/164), median and 95% CI: 21.49 months (16.85, 29.08)

Nivolumab+ipilimumab vs. ipilimumab - HR (95% CI): 0.52 (0.39, 0.70)
Nivolumab vs. ipilimumab - HR (95% CI): 0.52 (0.39, 0.69)
Nivolumab+ipilimumab vs. nivolumab - HR (95% CI): 1.01 (0.74, 1.37)

Minimum follow-up for the analysis of ORR was 90 months. Responses are summarised in Table 12.

Table 12: Objective response (CA209067)

	nivolumab + ipilimumab (n = 314)	nivolumab (n = 316)	ipilimumab (n = 315)
Objective response	183 (58%)	142 (45%)	60 (19%)
(95% CI)	(52.6, 63.8)	(39.4, 50.6)	(14.9, 23.8)
Odds ratio (vs. ipilimumab)	6.35	3.5	
(95% CI)	(4.38, 9.22)	(2.49, 5.16)	
Complete response (CR)	71 (23%)	59 (19%)	19 (6%)
Partial response (PR)	112 (36%)	83 (26%)	41 (13%)
Stable disease (SD)	38 (12%)	29 (9%)	69 (22%)
Duration of response			
Median (range), months	N.A. (69.1-N.A.)	90.8 (45.7-N.A.)	19.3 (8.8-47.4)
Proportion ≥12 months in duration	68%	73%	44%
Proportion ≥24 months in duration	58%	63%	30%
ORR (95% CI) by tumour PD-L1 expression			
<5%	56% (48.7, 62.5) n = 210	43% (36, 49.8) n = 208	18% (12.8, 23.8) n = 202
≥5%	72% (59.9, 82.3) n = 68	59% (47.2, 69.6) n = 80	21% (12.7, 32.3) n = 75
<1%	54% (44.4, 62.7) n = 123	36% (27.2, 45.3) n = 117	18% (11.2, 26.0) n = 113
≥1%	65% (56.4, 72) n = 155	55% (47.2, 62.6) n = 171	20% (13.7, 26.4) n = 164

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 90 months.

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 12) after 90 months of follow-up, with a best overall response of complete response correlating to an improved survival rate.

After 90 months of follow-up, median durations of response for patients with tumour PD-L1 expression level ≥5% were 78.19 months (range: 18.07-N.A.) in the combination arm, 77.21 months (range: 26.25-N.A.) in the nivolumab monotherapy arm and 31.28 months (range: 6.08-N.A.) in the ipilimumab arm. At tumour PD-L1 expression <5%, median

durations of response were not reached (range: 61.93-N.A.) in the combination arm, were 90.84 months (range: 50.43-N.A.) in the nivolumab monotherapy arm and 19.25 months (range: 5.32-47.44) 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 90 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 16.76 months (95% CI: 8.28, 32.0) and 11.17 months (95% CI: 7.0, 19.32), while those in the nivolumab monotherapy arm had a median PFS of 5.62 months (95% CI: 2.79, 9.46) and 8.18 months (95% CI: 5.13, 19.55), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had a median PFS of 3.09 months (95% CI: 2.79, 5.19) and 2.83 months (95% CI: 2.76, 3.06), respectively.
After 90 months of follow-up, BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab in combination with nivolumab had an ORR of 67.0% (95% CI: 57.0, 75.9; n = 103) and 54.0% (95% CI: 47.1, 60.9; n = 211), while those in the nivolumab monotherapy arm had an ORR of 37.87% (95% CI: 28.2, 48.1; n = 98) and 48.2% (95% CI: 41.4, 55.0; n = 218), respectively. BRAF[V600] mutation-positive and BRAF wild-type patients randomised to ipilimumab monotherapy had an ORR of 23.0% (95% CI: 15.2, 32.5; n = 100) and 17.2% (95% CI: 12.4, 22.9; n = 215).
After 90 months of follow-up, in BRAF [V600] mutation-positive patients median OS was not reached in the combination arm and 45.5 months in the nivolumab monotherapy arm. Median OS for BRAF [V600] mutation-positive patients in the ipilimumab monotherapy arm was 24.6 months. In BRAF wild-type patients median OS was 39.06 months in the combination arm, 34.37 months in the nivolumab monotherapy arm, and 18.5 months in the ipilimumab monotherapy arm. The OS HRs for ipilimumab in combination with nivolumab vs. nivolumab monotherapy were 0.66 (95% CI: 0.44, 0.98) for BRAF[V600] mutation-positive patients and 0.95 (95% CI: 0.74, 1.22) 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

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

Efficacy results for the intermediate/poor risk patients are shown in Table 13 (primary analysis with a minimum follow-up of 17.5 months and with a minimum follow-up of 60 months) and in Figure 8 (minimum follow-up of 60 months).

OS results at an additional descriptive analysis undertaken at a minimum follow-up of 60 months show outcomes consistent with the original primary analysis.

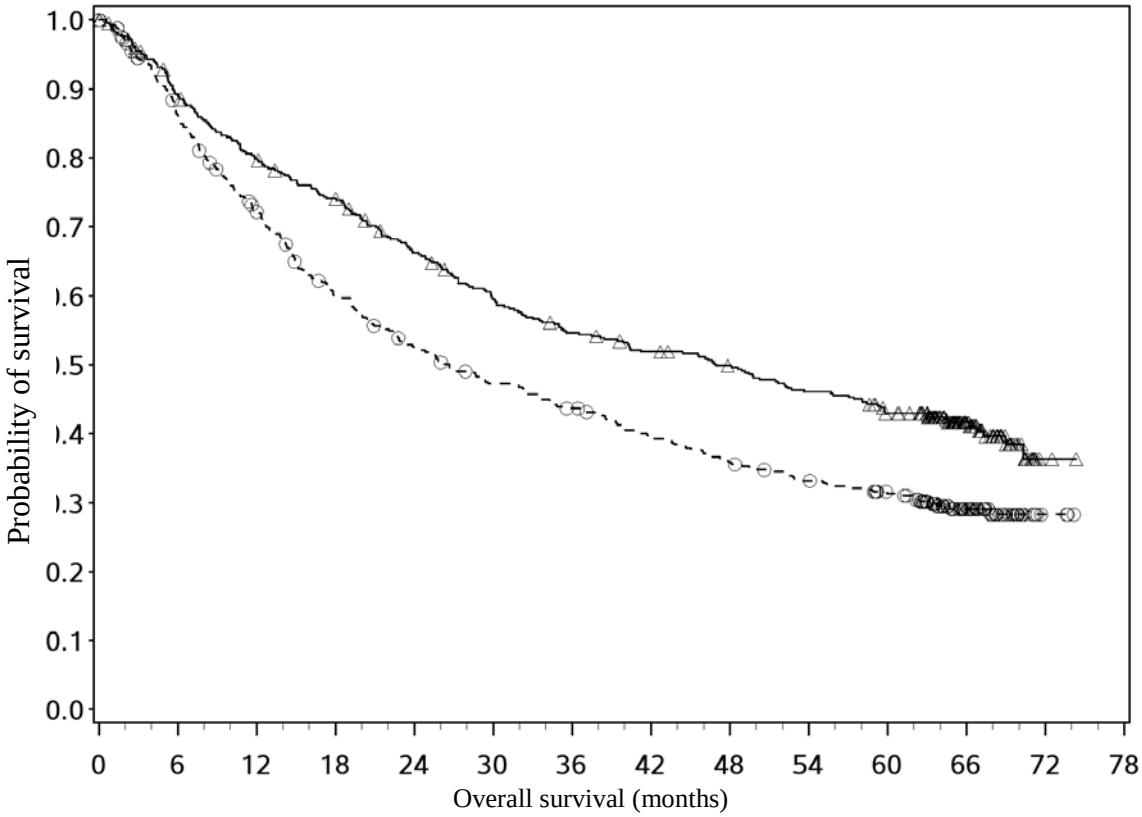
Table 13: **Efficacy results in intermediate/poor risk patients (CA209214)**

	nivolumab + ipilimumab (n = 425)		**sunitinib (n = 422)**
	Primary analysis minimum follow-up: 17.5 months		
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)
	Updated analysis* minimum follow-up: 60 months		
Overall survival			
Events	242 (57%)		282 (67%)
Hazard ratio[a]		0.68	
95% CI		(0.58, 0.81)	
Median (95% CI)	46.95 (35.35, 57.43)		26.64 (22.08, 33.54)
Rate (95% CI)			
At 24 months	66.3 (61.5, 70.6)		52.4 (47.4, 57.1)
At 36 months	54.6 (49.7, 59.3)		43.7 (38.7, 48.5)
At 48 months	49.9 (44.9, 54.6)		35.8 (31.1, 40.5)
At 60 months	43.0 (38.1, 47.7)		31.3 (26.8, 35.9)

Progression-free survival			
Events	245 (57.6%)		253 (60.0%)
Hazard ratio[a]		0.73	
95% CI		(0.61, 0.87)	
Median (95% CI)	11.6 (8.44, 16.63)		8.3 (7.03, 10.41)
Confirmed objective response (BICR)	179 (42.1%)		113 (26.8%)
(95% CI)	(37.4, 47.0)		(22.6, 31.3)
Difference in ORR (95% CI)[d,e]		16.2 (10.0, 22.5)	
Complete response (CR)	48 (11.3%)		9 (2.1%)
Partial response (PR)	131 (30.8%)		104 (24.6%)
Stable disease (SD)	131 (30.8%)		187 (44.3%)
Median duration of response[g]			
Months (range)	NE (50.89-NE)		19.38 (15.38-25.10)
Median time to response			
Months (range)	2.8 (0.9-35.0)		3.1 (0.6-23.6)

[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
* Descriptive analysis based on data cut-off: 26-Feb-2021.

Figure 8: Kaplan-Meier curves of OS in intermediate/poor risk patients (CA209214) Minimum follow-up of 60 months



Number of subjects at risk

Nivolumab + ipilimumab													
425	372	332	306	270	241	220	207	196	181	163	79	2	0
Sunitinib													
422	353	291	237	206	184	169	151	137	125	112	58	3	0

Nivolumab + ipilimumab (events: 242/425), median and 95.0% CI: 46.95 (35.35, 57.43)

Sunitinib (events: 282/422), median and 95.0% CI: 26.64 (22.08, 33.54)

An updated descriptive OS analysis was performed when all patients had a minimum follow-up of 24 months. 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. 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 ≥ 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 ipilimumab plus nivolumab (n = 125) or to sunitinib (n = 124). These patients were not evaluated as part of the primary efficacy population. At a minimum of 24 months follow-up, OS in favourable risk patients receiving ipilimumab plus nivolumab compared to sunitinib had a hazard ratio of 1.13 (95% CI: 0.64, 1.99; p = 0.6710). With 60 months minimum follow-up, the HR for OS was 0.94 (95% CI: 0.65, 1.37).

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.

Patients ≥ 75 years of age represented 8% of all intermediate/poor risk patients in CA209214, and the combination of ipilimumab and nivolumab showed numerically less effect on OS (HR 0.97, 95% CI: 0.48, 1.95) in this subgroup versus the overall population at a minimum follow-up of 17.5 months. Because of the small size of this subgroup, no definitive conclusions can be drawn from these data.

First-line treatment of non-small cell lung cancer

Randomised phase 3 study of ipilimumab in combination with nivolumab and 2 cycles of platinum-based chemotherapy vs. 4 cycles of platinum-based chemotherapy (CA2099LA)

The safety and efficacy of ipilimumab 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and 2 cycles of platinum-based chemotherapy were evaluated in a phase 3, randomised, open-label study (CA2099LA). The study included patients (18 years or older) with histologically confirmed non-squamous or squamous Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors). Patients were enrolled regardless of their tumour PD-L1 status.

Patients with sensitising EGFR mutations or ALK translocations, active (untreated) brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents. Randomisation was stratified by histology (squamous vs non-squamous), tumour PD-L1 expression level (≥ 1% vs < 1%), and gender (male vs female).

A total of 719 patients were randomised to receive either ipilimumab in combination with nivolumab and platinum-based chemotherapy (n = 361) or platinum-based chemotherapy (n = 358). Patients in the ipilimumab in combination with nivolumab and platinum-based chemotherapy arm received ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks in combination with nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks and platinum-based chemotherapy administered every 3 weeks for 2 cycles. Patients in the chemotherapy arm received platinum-based chemotherapy administered every 3 weeks for 4 cycles; non-squamous patients could receive optional pemetrexed maintenance therapy. Platinum-based chemotherapy consisted of carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m^2; or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC.

Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to ipilimumab were permitted to continue nivolumab monotherapy. Tumour assessments were performed every 6 weeks after first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued.

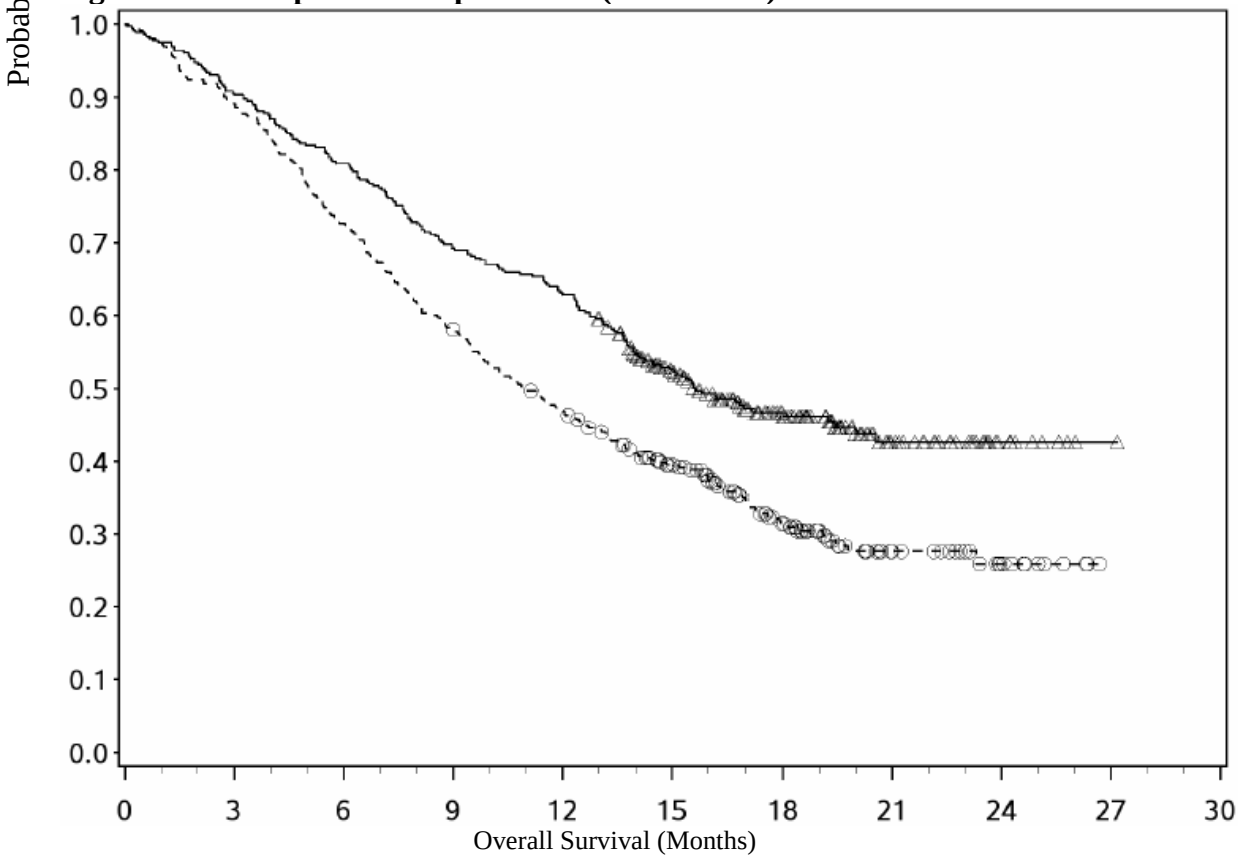
CA2099LA baseline characteristics were generally balanced across all treatment groups. The median age was 65 years (range: 26-86) with 51% ≥ 65 years of age and 10% ≥ 75 years of age. The majority of patients were white (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% of patients with PD-L1 ≥ 1% and 37% with PD-L1 < 1%, 31% had squamous and 69% had non-squamous histology, 17% had brain metastases, and 86% were former/current smokers. No patients received prior immunotherapy.

CA2099LA primary efficacy outcome measure was OS. Additional efficacy endpoints were PFS, ORR, and duration of response as assessed by BICR.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR for patients randomised to ipilimumab in combination with nivolumab and platinum-based chemotherapy as compared to platinum-based chemotherapy alone at the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis). Minimum follow-up for OS was 8.1 months.

Efficacy results are shown in Figure 9 (updated OS analysis with a minimum follow-up of 12.7 months) and Table 14 (primary analysis with a minimum follow-up of 8.1 months).
An updated efficacy analysis was performed when all patients had a minimum follow-up of 12.7 months (see Figure 9). At the time of this analysis, the hazard ratio for OS was 0.66 (95% CI: 0.55, 0.80) and the hazard ratio for PFS was 0.68 (95% CI: 0.57, 0.82).

Figure 9: Kaplan-Meier plot of OS (CA2099LA)



Number of subjects at risk

Nivolumab + ipilimumab + chemotherapy										
361	326	292	250	227	153	86	33	10	1	0
Chemotherapy										
358	319	260	208	166	116	67	26	11	0	0

Nivolumab + ipilimumab + chemotherapy (events: 190/361), median and 95% CI: 15.64 (13.93, 19.98)

Chemotherapy (events: 242/358), median and 95% CI: 10.91 (9.46, 12.55)

Table 14: Efficacy results (CA2099LA)

	ipilimumab + nivolumab + chemotherapy (n = 361)	**chemotherapy (n = 358)**

Table 14: Efficacy results (CA2099LA)

	ipilimumab + nivolumab + chemotherapy (n = 361)		chemotherapy (n = 358)
Overall Survival			
Events	156 (43.2%)		195 (54.5%)
Hazard ratio (96.71% CI)[a]		0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]		0.0006	
Median (months) (95% CI)	14.1 (13.24, 16.16)		10.7 (9.46, 12.45)
Rate (95% CI) at 6 months	80.9 (76.4,84.6)		72.3 (67.4,76.7)
Progression-free Survival			
Events	232 (64.3%)		249 (69.6%)
Hazard ratio (97.48% CI)[a]		0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]		0.0001	
Median (months)[d] (95% CI)	6.83 (5.55, 7.66)		4.96 (4.27, 5.55)
Rate (95% CI) at 6 months	51.7 (46.2, 56.8)		35.9 (30.5, 41.3)
Overall Response Rate[e] (95% CI)	136 (37.7%) (32.7, 42.9)		90 (25.1%) (20.7, 30.0)
Stratified CMH test p-value[f]		0.0003	
Complete response (CR)	7 (1.9%)		3 (0.8%)
Partial response (PR)	129 (35.7%)		87 (24.3%)
Duration of Response			
Median (months) (95% CI)[d]	10.02 (8.21, 13.01)		5.09 (4.34, 7.00)
% with duration ≥ 6 months[g]	74		41

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

Subsequent systemic therapy was received by 28.8% and 41.1% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA4) was received by 3.9% and 27.9% of patients in the combination and chemotherapy arms, respectively.

In study CA2099LA, subgroup descriptive analysis relative to chemotherapy, OS benefit was shown in patients treated with ipilimumab in combination with nivolumab and chemotherapy with squamous histology (HR [95% CI] 0.65 [0.46, 0.93], n = 227) and in patients with non-squamous histology (HR [95% CI] 0.72 [0.55, 0.93], n = 492).

Table 15 summarises efficacy results of OS, PFS, and ORR by tumour PD-L1 expression in pre-specified subgroup analyses.

Table 15: Efficacy results by tumour PD-L1 expression (CA2099LA)

	ipilimumab + nivolumab + chemotherapy	chemo-therapy	ipilimumab + nivolumab + chemotherapy	chemo-therapy	ipilimumab + nivolumab + chemotherapy	chemo-therapy	ipilimumab + nivolumab + chemotherapy	chemo-therapy
	PD-L1 < 1% (n = 264)		**PD-L1 ≥ 1% (n = 406)**		**PD-L1 ≥ 1% to 49% (n = 233)**		**PD-L1 ≥ 50% (n = 173)**	
OS Hazard Ratio (95% CI)[a]	0.65 (0.46, 0.92)		0.67 (0.51, 0.89)		0.69 (0.48, 0.98)		0.64 (0.41, 1.02)	
PFS Hazard Ratio (95% CI)[a]	0.77 (0.57, 1.03)		0.67 (0.53, 0.85)		0.71 (0.52, 0.97)		0.59 (0.40, 0.86)	
ORR %	31.1	20.9	41.9	27.6	37.8	24.5	48.7	30.9

[a] Hazard ratio based on unstratified Cox proportional hazards model.

A total of 70 NSCLC patients aged ≥ 75 years were enrolled in study CA2099LA (37 patients in the ipilimumab in combination with nivolumab and chemotherapy arm and 33 patients in the chemotherapy arm). A HR of 1.36 (95% CI: 0.74, 2.52) in OS and a HR of 1.12 (95% CI: 0.64, 1.96) in PFS was observed for ipilimumab in combination with nivolumab and chemotherapy vs. chemotherapy within this study subgroup. ORR was 27.0% in the ipilimumab in combination with nivolumab and chemotherapy arm and 15.2% in the chemotherapy arm. Forty-three percent of patients aged ≥ 75 years discontinued treatment with ipilimumab in combination with nivolumab and chemotherapy. Efficacy and safety data of ipilimumab in combination with nivolumab and chemotherapy are limited in this patient population.

In a subgroup analysis, a reduced survival benefit for ipilimumab in combination with nivolumab and chemotherapy compared to chemotherapy was observed in patients who were never smokers. However, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

Malignant pleural mesothelioma

Randomised phase 3 study of ipilimumab in combination with nivolumab vs. chemotherapy (CA209743)

The safety and efficacy of ipilimumab 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks were evaluated in a phase 3, randomised, open-label study (CA209743). The study included patients (18 years or older) with histologically confirmed and previously untreated malignant pleural mesothelioma of epithelioid or non-epithelioid histology, ECOG performance status 0 or 1, and no palliative radiotherapy within 14 days of first study therapy. Patients were enrolled regardless of their tumour PD-L1 status.

Patients with primitive peritoneal, pericardial, testis, or tunica vaginalis mesothelioma, interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, and brain metastasis (unless surgically resected or treated with stereotaxic radiotherapy and no evolution within 3 months prior to inclusion in the study) were excluded from the trial. Randomisation was stratified by histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and gender (male vs. female).

A total of 605 patients were randomised to receive either ipilimumab in combination with nivolumab (n = 303) or chemotherapy (n = 302). Patients in the ipilimumab in combination with nivolumab arm received ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks in combination with nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks for up to 2 years. Patients in the chemotherapy arm received chemotherapy for up to 6 cycles (each cycle was 21 days). Chemotherapy consisted of

cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 or carboplatin 5 AUC and pemetrexed 500 mg/m^2.

Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab monotherapy. Tumour assessments were performed every 6 weeks after first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued.

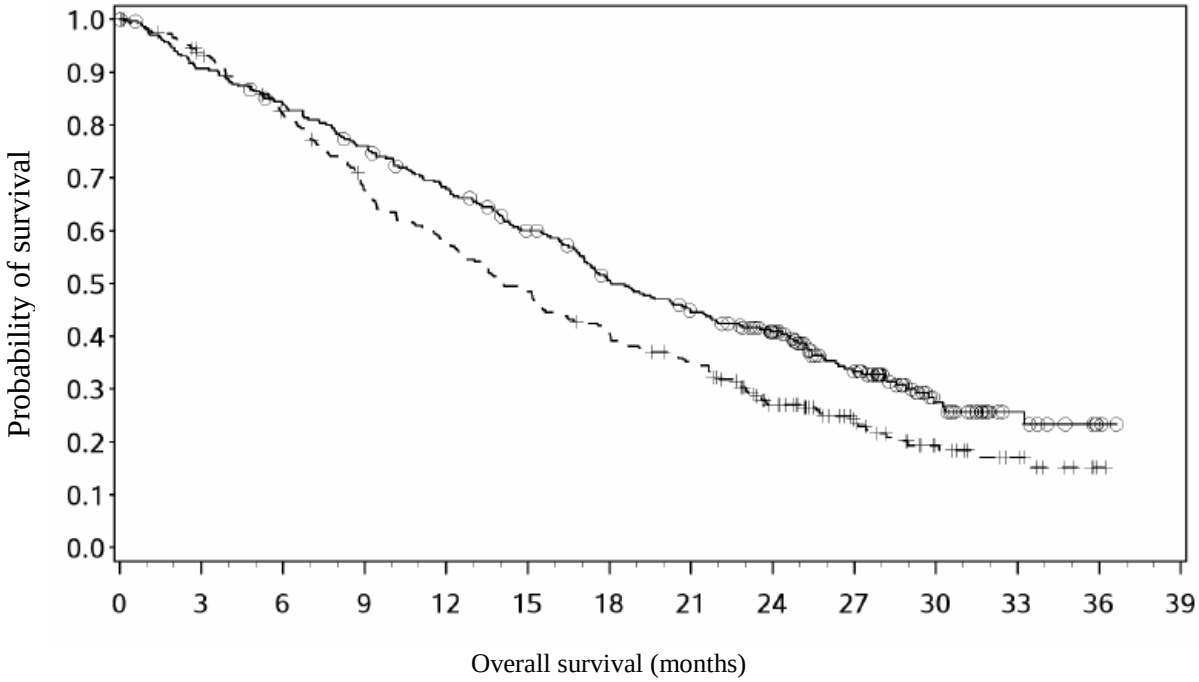
CA209743 baseline characteristics were generally balanced across all treatment groups. The median age was 69 years (range: 25-89) with 72% ≥ 65 years of age and 26% ≥ 75 years of age. The majority of patients were white (85%) and male (77%). Baseline ECOG performance status was 0 (40%) or 1 (60%), 80% of patients with PD-L1 ≥ 1% and 20% with PD-L1 < 1%, 75% had epithelioid and 25% had non-epithelioid histology.

CA209743 primary efficacy outcome measure was OS. Key secondary efficacy endpoints were PFS, ORR, and duration of response as assessed by BICR utilising modified RECIST criteria for pleural mesothelioma. Descriptive analyses for these secondary endpoints are presented in Table 16.

The study demonstrated a statistically significant improvement in OS for patients randomised to ipilimumab in combination with nivolumab as compared to chemotherapy at the prespecified interim analysis when 419 events were observed (89% of the planned number of events for final analysis). Minimum follow-up for OS was 22 months.

Efficacy results are shown in Figure 10 and Table 16.

Figure 10: Kaplan-Meier curves of OS (CA209743)



Number of subjects at risk

Nivolumab + ipilimumab	303	273	251	226	200	173	143	124	101	65	30	11	2	0
Chemotherapy	302	268	233	190	162	136	113	95	62	38	20	11	1	0

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

Table 16: Efficacy results (CA209743)

	ipilimumab + nivolumab (n = 303)		chemotherapy (n = 302)
Overall survival			
Events	200 (66%)		219 (73%)
Hazard ratio (96.6% CI)[a]		0.74 (0.60, 0.91)	
Stratified log-rank p-value[b]		0.002	
Median (months)[c]	18.1		14.1
(95% CI)	(16.8, 21.5)		(12.5, 16.2)
Rate (95% CI) at 24 months[c]	41% (35.1, 46.5)		27% (21.9, 32.4)
Progression-free survival			
Events	218 (72%)		209 (69%)
Hazard ratio (95% CI)[a]		1.0 (0.82, 1.21)	
Median (months)[c]	6.8		7.2
(95% CI)	(5.6, 7.4)		(6.9, 8.1)
Overall response rate	40%		43%
(95% CI)	(34.1, 45.4)		(37.1, 48.5)
Complete response (CR)	1.7%		0
Partial response (PR)	38%		43%
Duration of response			
Median (months)[c]	11.0		6.7
(95% CI)	(8.1, 16.5)		(5.3, 7.1)

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

Subsequent systemic therapy was received by 44.2% and 40.7% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA-4) was received by 3.3% and 20.2% of patients in the combination and chemotherapy arms, respectively.

Table 17 summarises efficacy results of OS, PFS, and ORR by histology in prespecified subgroup analyses.

Table 17: Efficacy results by histology (CA209743)

	Epithelioid (n = 471)		Non-epithelioid (n = 134)	
	ipilimumab + nivolumab (n = 236)	chemotherapy (n = 235)	ipilimumab + nivolumab (n = 67)	chemotherapy (n = 67)
Overall survival				
Events	157	164	43	55
Hazard ratio (95% CI)[a]	0.85 (0.68, 1.06)		0.46 (0.31, 0.70)	
Median (months)	18.73	16.23	16.89	8.80
(95% CI)	(17.05, 21.72)	(14.09, 19.15)	(11.83, 25.20)	(7.62, 11.76)
Rate (95% CI) at 24 months	41.2 (34.7, 47.6)	31.8 (25.7, 38.1)	39.5 (27.5, 51.2)	9.7 (3.8, 18.9)

Progression-free survival				
Hazard ratio	1.14		0.58	
(95% CI)[a]	(0.92, 1.41)		(0.38, 0.90)	
Median (months)	6.18	7.66	8.31	5.59
(95% CI)	(5.49, 7.03)	(7.03, 8.31)	(3.84, 11.01)	(5.13, 7.16)
Overall response rate	38.6%	47.2%	43.3%	26.9%
(95% CI)[b]	(32.3, 45.1)	(40.7, 53.8)	(31.2, 56.0)	(16.8, 39.1)
Duration of response	8.44	6.83	24.02	4.21
Median (months) (95% CI)[c]	(7.16, 14.59)	(5.59, 7.13)	(8.31, N.A.)	(2.79, 7.03)

[a] Hazard ratio based on unstratified Cox proportional hazards model.
[b] Confidence interval based on the Clopper and Pearson method
[c] Median computed using Kaplan-Meier method

Table 18 summarises efficacy results of OS, PFS, and ORR by baseline tumour PD-L1 expression in prespecified subgroup analyses.

Table 18: Efficacy results by tumour PD-L1 expression (CA209743)

	PD-L1 < 1% (n = 135)		**PD-L1 ≥ 1% (n = 451)**	
	ipilimumab + nivolumab (n = 57)	**chemotherapy (n = 78)**	**ipilimumab + nivolumab (n = 232)**	**chemotherapy (n = 219)**
Overall survival				
Events	40	58	150	157
Hazard ratio	0.94		0.69	
(95% CI)[a]	(0.62, 1.40)		(0.55, 0.87)	
Median (months)	17.3	16.5	18.0	13.3
(95% CI)[b]	(10.1, 24.3)	(13.4, 20.5)	(16.8, 21.5)	(11.6, 15.4)
Rate (95% CI) at 24 months	38.7 (25.9, 51.3)	24.6 (15.5, 35.0)	40.8 (34.3, 47.2)	28.3 (22.1, 34.7)
Progression-free survival				
Hazard ratio	1.79		0.81	
(95% CI)[a]	(1.21, 2.64)		(0.64, 1.01)	
Median (months)	4.1	8.3	7.0	7.1
(95% CI)[b]	(2.7, 5.6)	(7.0, 11.1)	(5.8, 8.5)	(6.2, 7.6)
Overall response rate	21.1%	38.5%	43.5%	44.3%
(95% CI)[c]	(11.4, 33.9)	(27.7, 50.2)	(37.1, 50.2)	(37.6, 51.1)

[a] Hazard ratio based on unstratified Cox proportional hazards model.
[b] Median computed using Kaplan-Meier method.
[c] Confidence interval based on the Clopper and Pearson method.

A total of 157 MPM patients aged ≥ 75 years were enrolled in study CA209743 (78 in the ipilimumab in combination with nivolumab arm and 79 in the chemotherapy arm). A HR of 1.02 (95% CI: 0.70, 1.48) in OS was observed for ipilimumab in combination with nivolumab vs. chemotherapy within this study subgroup. A higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older relative to all patients who received ipilimumab in combination with nivolumab was shown

(see section 4.8). However, due to the exploratory nature of this subgroup analysis, no definitive conclusions can be drawn.

dMMR or MSI-H colorectal cancer

Open-label study of nivolumab in combination with ipilimumab versus chemotherapy in dMMR or MSI-H CRC patients naive to treatment in the metastatic setting

The safety and efficacy of ipilimumab 1 mg/kg in combination with nivolumab 240 mg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks in the first-line treatment of unresectable or metastatic CRC with known tumour MSI-H or dMMR status was evaluated in a randomized, multi-arm, phase 3, open-label study (CA2098HW). Study treatment arms included nivolumab monotherapy, nivolumab in combination with ipilimumab, or investigator's choice of chemotherapy. MSI-H or dMMR tumour status was determined in accordance with local standard of practice using PCR, NGS or IHC, assays. Central assessment of MSI-H status using PCR (Idylla MSI) test and dMMR status using IHC (Omnis MMR) test was conducted retrospectively on patient tumour specimens used for local MSI-H/dMMR status determination. Patients with confirmed MSI-H/dMMR status by either central test comprised the primary efficacy population. Patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors were excluded from the study. Randomization was stratified by tumour location (right vs left). Patients randomized to the chemotherapy arm could receive ipilimumab plus nivolumab combination upon progression assessed by BICR.

A total of 303 previously untreated patients, in the metastatic setting, were randomised to study, including 202 patients to nivolumab in combination with ipilimumab and 101 patients to chemotherapy. Among them 255 had centrally confirmed MSI-H/dMMR status, 171 in the ipilimumab in combination with nivolumab arm and 84 in the chemotherapy arm. Patients in the ipilimumab plus nivolumab arm received ipilimumab 1 mg/kg every 3 weeks in combination with nivolumab 240 mg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks. Patients in the chemotherapy arm received: mFOLFOX6 (oxaliplatin, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m2, leucovorin 400 mg/m2, and fluorouracil 400 mg/m2 bolus followed by fluorouracil 2400 mg/m2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m2 administered prior to mFOLFOX6 every 2 weeks; or FOLFIRI (irinotecan, leucovorin, and fluorouracil) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m2, leucovorin 400 mg/m2, and fluorouracil 400 mg/m2 bolus and fluorouracil 2400 mg/m2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m2 administered prior to FOLFIRI every 2 weeks. Treatment continued until disease progression, unacceptable toxicity, or for ipilimumab in combination with nivolumab up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Tumour assessments per RECIST v1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter until week 96, then every 16 weeks thereafter until week 146, and then every 24 weeks.

The baseline characteristics of all randomised previously untreated for metastatic disease patients were: the median age was 63 years (range: 21 to 87), with 46% ≥ 65 years of age and 18% ≥ 75 years of age; 46% were male and 86% were White. Baseline ECOG performance status was 0 (54%) and ≥ 1 (46%); tumour location was right-sided or left-sided for 68% and 32% of patients, respectively; and 39 patients had confirmed Lynch syndrome among the 223 patients with a known status. The baseline characteristics of previously untreated for metastatic disease patients with centrally confirmed MSI-H/dMMR were consistent with all randomised previously untreated patients. Among the 101 patients randomised to receive chemotherapy, 88

received chemotherapy per the protocol, including oxaliplatin-containing regimens (58%) and irinotecan-containing regimens (42%). Additionally, 66 patients received a targeted agent, either bevacizumab (64%) or cetuximab (11%).

A primary efficacy outcome measure of the study was BICR-assessed PFS per RECIST 1.1. Additional efficacy measures included ORR assessed by BICR, OS, and duration of response.

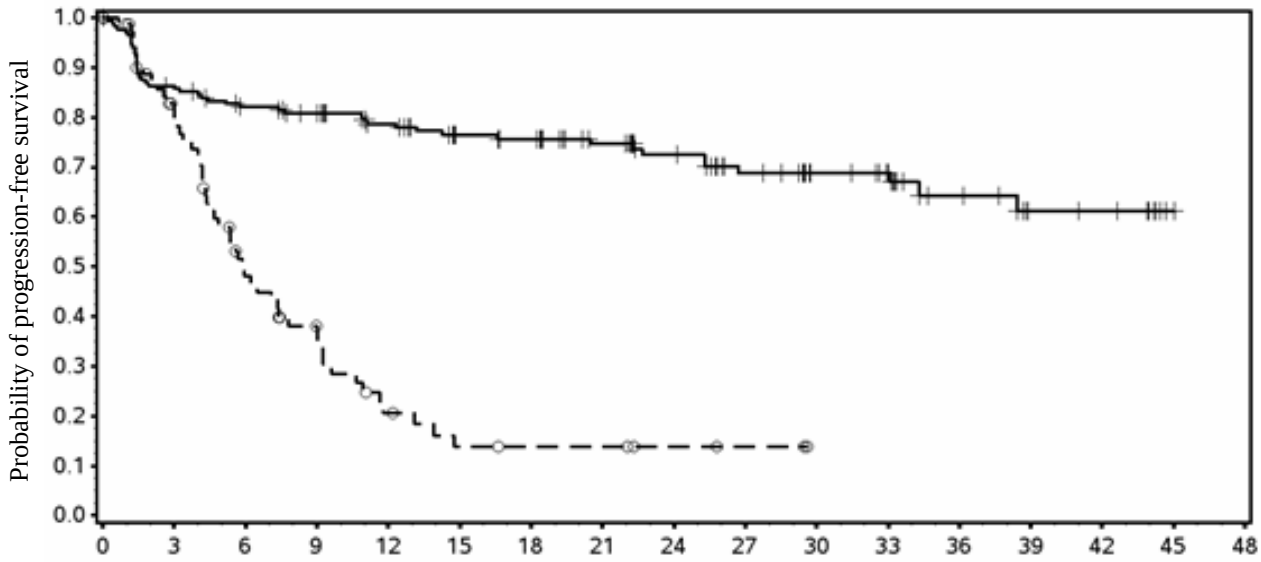
The study met the primary endpoint, at the planned interim analysis, demonstrating a statistically significant improvement in BICR assessed-PFS for patients with centrally confirmed MSI-H/dMMR randomized to the ipilimumab and nivolumab arm compared with chemotherapy. The BICR-assessed PFS results are presented in Table 19 and Figure 11. At the time of this interim analysis, the other endpoints, including the data from nivolumab monotherapy arm, were not tested, due to testing hierarchy.

Table 19: Efficacy results first-line MSI-H/dMMR centrally confirmed CRC (CA2098HW)[a]

	ipilimumab + nivolumab (n = 171)		**chemotherapy (n = 84)**
Progression-free survival			
Events	48 (28%)		52 (62%)
Hazard ratio		0.21	
95% CI		(0.14, 0.32)	
p-value [,b]		< 0.0001	
Median (95% CI) (months)	NR (38.4, NR)		5.9 (4.4, 7.8)

[a] Median follow-up of 31.5 months (range: 6.1 to 48.4 months).
[b] Based on stratified 2-sided log-rank test

Figure 11: Kaplan-Meier curve of PFS in first-line patients with MSI-H/dMMR centrally confirmed CRC (CA2098HW)



Progression free survival (months)

Number of subjects at risk																
Nivolumab + ipilimumab																
171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemotherapy																
84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

¾Æ¾¾ Nivolumab + ipilimumab (events: 48/171), median and 95% CI: N.A. (38.44, N.A.)
- - -¦- - - Chemotherapy (events: 52/84), median and 95% CI: 5.85 (4.37, 7.79)

Open-label study of nivolumab in combination with ipilimumab in dMMR or MSI-H CRC in patients who received prior fluoropyrimidine-based combination chemotherapy

The safety and efficacy of ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg for the treatment of dMMR or MSI-H metastatic CRC was evaluated in a Phase 2, multi-centre, open-label, single-arm study (CA209142).
The study included patients (18 years or older) with locally determined dMMR or MSI-H status, who had disease progression during, after, or were intolerant to, prior therapy with fluoropyrimidine and oxaliplatin or irinotecan. Patients who had their most recent prior treatment in the adjuvant setting should have progressed on or within 6 months of completion of adjuvant chemotherapy. Patients had an ECOG performance status score of 0 or 1 and were enrolled regardless of their tumour PD-L1 status. Patients with active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 119 patients were treated with ipilimumab 1 mg/kg administered intravenously over 90 minutes in combination with nivolumab 3 mg/kg administered intravenously over 60 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments according to RECIST version 1.1 were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The primary outcome measure was investigator-assessed ORR. Secondary outcome measures were BICR-assessed ORR and disease control rate. Analysis of ORR included duration of and time to response. Exploratory outcome measures included PFS and OS.

The median age was 58 years (range: 21-88) with 32% ≥ 65 years of age and 9% ≥ 75 years of age, 59% were male and 92% were white. Baseline ECOG performance status was 0 (45%) or 1 (55%), 25% of patients had BRAF mutations, 37% had KRAS mutations, and 12% were unknown. Of the 119 treated patients, 109 had received prior fluoropyrimidine based chemotherapy in the metastatic setting and 9 in the adjuvant setting. Before study enrolment, of the 119 treated patients, 118 (99%) had received fluorouracil, 111 (93%) had received oxaliplatin, 87 (73%) had received irinotecan as part of prior therapies; 82 (69%) had received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Twenty three percent, 36%, 24%, and 16% received 1, 2, 3, or 4 or more prior therapies respectively, and 29% of patients had received an EGFR inhibitor.

Efficacy results (minimum follow-up 46.9 months; median follow-up 51.1 months) are shown in Table 20.

Table 20: Efficacy results (CA209142) in dMMR or MSI-H CRC patients*

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

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

The BICR-assessed ORR was 61.3% (95% CI: 52.0, 70.1), including CR rate of 20.2% (95% CI: 13.4, 28.5), PR rate of 41.2% (95% CI: 32.2, 50.6) and stable disease reported in 22.7%. BICR assessments were generally consistent with the investigator assessment. Confirmed responses were observed regardless of BRAF or KRAS mutation status, and tumour PD-L1 expression levels.

Of 119 patients 11 (9.2%) patients were ≥ 75 years. The investigator assessed ORR in patients ≥ 75 years was 45.5% (95% CI: 16.7, 76.6).

Oesophageal squamous cell carcinoma

Randomised phase 3 study of ipilimumab in combination with nivolumab vs. chemotherapy as first-line treatment (CA209648)

The safety and efficacy of ipilimumab in combination with nivolumab were evaluated in a randomised, active-controlled, open-label phase 3 study (CA209648). The study included adult patients (18 years or older) with previously untreated, unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC). Patients were enrolled regardless of their tumour PD-L1 status, and tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. Patients were required to have squamous cell carcinoma or adenosquamous cell carcinoma of oesophagus, not amenable to chemoradiation and/or surgery. Prior adjuvant, neoadjuvant, or definitive, chemotherapy, radiotherapy or chemoradiotherapy was permitted if given as part of curative intent regimen prior to trial enrolment. Patients who had a baseline performance score ≥ 2, had brain metastases that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the study. Randomisation was stratified by tumour cell PD-L1 status (≥ 1% vs. < 1% or indeterminate), region (East Asia vs. rest of Asia vs. rest of world), ECOG performance status (0 vs. 1), and number of organs with metastases (≤1 vs. ≥2).

A total of 649 patients were randomised to receive either ipilimumab in combination with nivolumab (n=325), or chemotherapy (n=324), respectively. Of these, 315 patients had tumour cell PD-L1 expression ≥ 1%,158 in the ipilimumab plus nivolumab arm and 157 in the chemotherapy arm. Patients in the ipilimumab plus nivolumab arm received ipilimumab 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks. Patients in the chemotherapy arm received fluorouracil 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle). Treatment continued until disease progression, unacceptable toxicity, or up to 24 months. Patients who

discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent.

Baseline characteristics were generally balanced across treatment groups. In patients with tumour cell PD-L1 expression ≥ 1%, the median age was 63 years (range: 26-85), 8.2% were ≥ 75 years of age, 81.8% were male, 73.1% were Asian, and 23.3% were white. Patients had histological confirmation of squamous cell carcinoma (98.9%) or adenosquamous cell carcinoma (1.1%) in the oesophagus. Baseline ECOG performance status was 0 (45.2%) or 1 (54.8%).

The primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with tumour cell PD-L1expression ≥ 1%. Secondary endpoints per the pre-specified hierarchical testing included OS, PFS (by BICR), and ORR (by BICR) in all randomised patients. The tumour assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

At the primary pre-specified analysis, with a minimum follow-up of 13.1 months, the study demonstrated a statistically significant improvement in OS in patients with tumour cell PD-L1 expression ≥ 1%. Efficacy results are shown in Table 21.

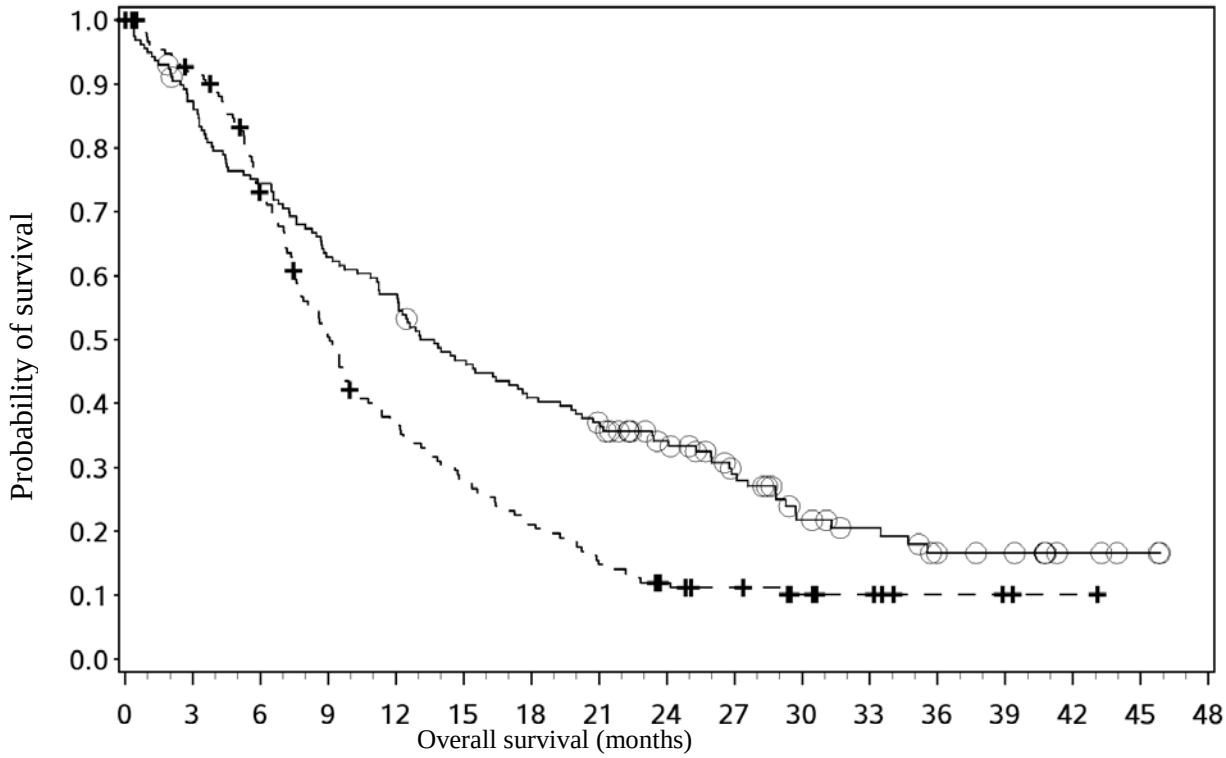
Table 21: Efficacy results in patients with tumour cell PD-L1 ≥ 1% (CA209648)

	ipilimumab + nivolumab (n = 158)	**chemotherapy[a] (n = 157)**
Overall survival		
Events	106 (67.1%)	121 (77.1%)
Hazard ratio (98.6% CI)[b]	0.64 (0.46, 0.90)	
p-value[c]	0.0010	
Median (95% CI) (months)[d]	13.70 (11.24, 17.02)	9.07 (7.69, 9.95)
Rate (95% CI) at 12 months[d]	57.1 (49.0, 64.4)	37.1 (29.2, 44.9)
Progression-free survival[e]		
Events	123 (77.8%)	100 (63.7%)
Hazard ratio (98.5% CI)[b]	1.02 (0.73, 1.43)	
p-value[c]	0.8958	
Median (95% CI) (months)[d]	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)
Rate (95% CI) at 12 months[d]	26.4 (19.5, 33.9)	10.5 (4.7, 18.8)
Overall response rate, n (%)[e]	56 (35.4)	31 (19.7)
(95% CI)	(28.0, 43.4)	(13.8, 26.8)
Complete response	28 (17.7)	8 (5.1)
Partial response	28 (17.7)	23 (14.6)
Duration of response[e]		
Median (95% CI) (months)[d]	11.83 (7.10, 27.43)	5.68 (4.40, 8.67)
Range	1.4^{+}, 34.5^{+}	1.4^{+}, 31.8^{+}

[a] Fluorouracil and cisplatin.
[b] Based on stratified Cox proportional hazard model.
[c] Based on stratified 2-sided log-rank test.
[d] Based on Kaplan-Meier estimates.
[e] Assessed by BICR.

At an updated descriptive analysis with a minimum follow-up of 20 months, OS improvements were consistent with the primary analysis. Median OS was 13.70 months (95% CI: 11.24, 17.41) for ipilimumab plus nivolumab vs. 9.07 months (95% CI: 7.69, 10.02) for chemotherapy (HR = 0.63; 95% CI: 0.49, 0.82). Median PFS was 4.04 months (95% CI: 2.40, 4.93) for ipilimumab plus nivolumab vs. 4.44 months (95% CI: 2.89, 5.82) for chemotherapy (HR = 1.02; 95% CI: 0.77, 1.34). The ORR was 35.4% (95% CI: 28.0, 43.4) for ipilimumab plus nivolumab vs. 19.7% (95% CI: 13.8, 26.8) for chemotherapy.
The Kaplan-Meier curves for OS with a minimum follow-up of 20 months are shown in Figure 12.

Figure 12: Kaplan-Meier curves of OS in patients with tumour cell PD-L1 ≥ 1% (CA209648)



Number of subjects at risk

Nivolumab + ipilimumab	158	136	116	98	89	72	63	55	43	31	20	16	10	9	4	2	0
Chemotherapy	157	137	107	73	53	40	30	21	15	12	8	6	3	2	1	0	0

—❍— Nivolumab + ipilimumab (events: 119/158), median and 95% CI: 13.70 (11.24, 17.41)
−−+−− Chemotherapy (events: 130/157), median and 95% CI: 9.07 (7.69, 10.02)
Based on data cut-off: 23-Aug-2021, minimum follow-up of 20 months

Hepatocellular carcinoma

The safety and efficacy of ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg every 3 weeks, for a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks in the first-line treatment of unresectable or advanced hepatocellular carcinoma (HCC) were evaluated in a phase 3, randomised, active-controlled, open-label study (CA2099DW). The study included adult patients (18 years or older) with histologically confirmed HCC, Child Pugh Class A, ECOG performance status 0 or 1, and no prior systemic therapy for advanced disease. Esophagogastroduodenoscopy was not mandated prior to enrolment. The study

enrolled adults whose disease was not amenable to or progressed after surgical and/or locoregional therapies. Prior neo-adjuvant or adjuvant systemic therapy was permitted. Patients with active autoimmune disease, brain or leptomeningeal metastases, prior liver transplant, a history of hepatic encephalopathy (within 12 months of randomisation), clinically significant ascites, medical conditions requiring systemic immunosuppression, infection with HIV, or active co infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV) were excluded from the study. Randomisation was stratified by aetiology (HBV vs. HCV vs. non-viral), macrovascular invasion and/or extrahepatic spread (present or absent), and alpha-fetoprotein levels (≥ 400 or < 400 ng/ml).

A total of 668 patients were randomised to receive ipilimumab in combination with nivolumab (n = 335) or investigator's choice (n = 333) of lenvatinib or sorafenib. In the investigator arm, 85% and 15% of treated patients received lenvatinib or sorafenib, respectively. Patients in the ipilimumab plus nivolumab arm received ipilimumab 3 mg/kg every 3 weeks in combination with nivolumab 1 mg/kg every 3 weeks, for up to a maximum of 4 doses, followed by nivolumab monotherapy 480 mg every 4 weeks. Patients in the investigators' choice arm received either lenvatinib 8 mg orally daily (if body weight < 60 kg) or 12 mg orally daily (if body weight ≥ 60 kg), or sorafenib 400 mg orally twice daily. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent. Tumour assessments were conducted at baseline, after randomisation at week 9 and week 16, then every 8 weeks up to 48 weeks, and then every 12 weeks thereafter until disease progression, treatment discontinuation, or initiation of subsequent therapy.

Baseline characteristics were generally balanced across treatment groups. The median age was 66 years (range: 20 to 89), with 53% ≥ 65 years and 16% ≥ 75 years, 53% were White, 44% were Asian, 2.2% were Black, and 82% were male. Baseline ECOG performance status was 0 (71%) or 1 (29%). Thirty-four percent (34%) of patients had HBV infection, 28% had HCV infection, and 36% had no evidence of HBV or HCV infection. Nineteen percent (19%) of patients had alcoholic liver disease and 11% had non-alcoholic fatty liver disease. The majority of patients had BCLC stage C (73%) disease at baseline, 19% had stage B, and 6% had stage A. Patients with Child-Pugh scores of 5, 6, and ≥ 7 were 77%, 20%, and 3%, respectively. A total of 54% of patients had extrahepatic spread; 25% had macrovascular invasion; and 33% had AFP levels ≥ 400 µg/l.

The study demonstrated a statistically significant benefit in OS and ORR for patients randomised to ipilimumab in combination with nivolumab compared to investigator's choice of lenvatinib or sorafenib. Efficacy results are presented in Table 22 and Figure 13.

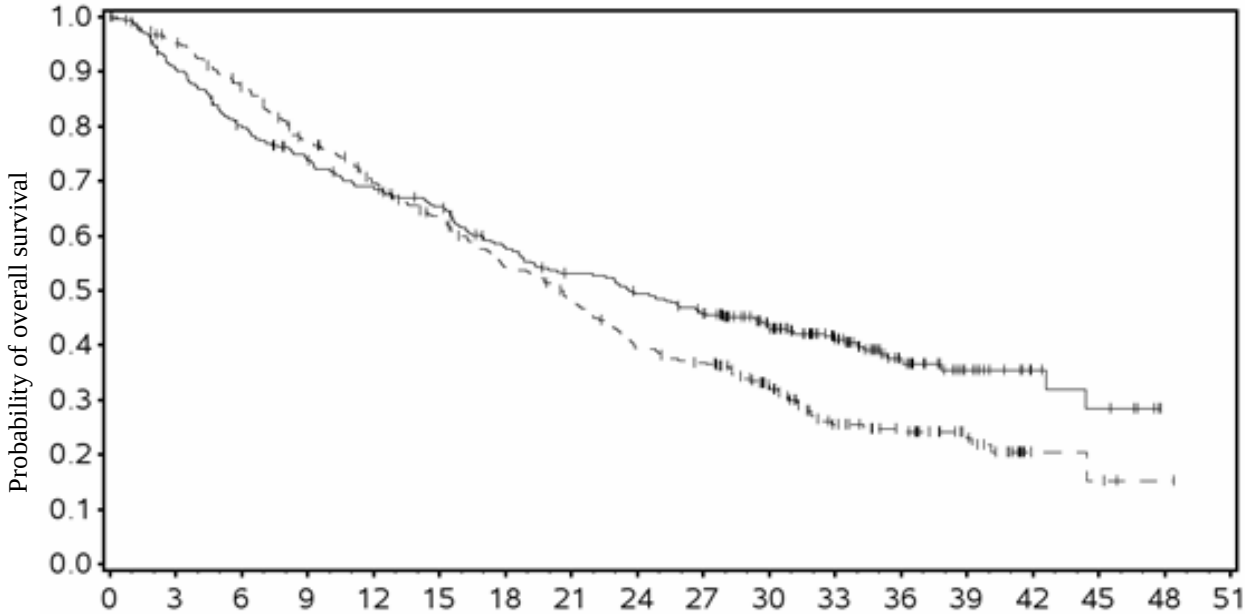
Table 22: Efficacy results in first-line HCC (CA2099DW)[a]

	ipilimumab + nivolumab (n = 335)	**lenvatinib or sorafenib (n = 333)**
Overall survival		
Events	194 (58%)	228 (68%)
Median (months) (95% CI)	23.7 (18.8, 29.4)	20.6 (17.5, 22.5)
Hazard ratio (95% CI)[b]	0.79 (0.65, 0.96)	
p-value[c]	0.0180	

	ipilimumab + nivolumab (n = 335)		lenvatinib or sorafenib (n = 333)
Overall Response Rate, n (%)[d]	121 (36.1)		44 (13.2)
(95% CI)	(31.0, 41.5)		(9.8, 17.3)
p-value[e]		<0.0001	
Complete response (%)	23 (6.9)		6 (1.8)
Partial response (%)	98 (29.3)		38 (11.4)
Duration of Response (months)[d]			
Median	30.4		12.9
(95% CI)	(21.2, N.A.)		(10.2, 31.2)

[a] Minimum follow-up of 26.8 months. Median follow up of 35.2 months.
[b] Based on stratified Cox proportional hazard model.
[c] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value ≤ 0.0257.
[d] Assessed by BICR using RECIST 1.1.
[e] Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: p-value ≤ 0.025.

Figure 13: Kaplan-Meier curve of OS in first-line patients with HCC (CA2099DW)



Overall survival (months)

Number of subjects at risk

Nivolumab + ipilimumab																	
335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
Investigator's choice																	
333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

—+—— Nivolumab + ipilimumab (events: 194/335), median and 95% CI: 23.66 (18.33, 29.44)
- - -+- - - Lenvatinib or sorafenib (events: 228/333), median and 95% CI: 20.63 (17.48, 22.54)

Paediatric population

Ipilimumab as monotherapy
Study CA184070 was a multi-centre, Phase 1, open-label, dose-escalation study of ipilimumab in paediatric patients ³ 1 year to £ 21 years of age with measurable/evaluable, untreatable, relapsed or refractory solid malignant tumours without a curative option with standard

therapy. The study enrolled 13 patients < 12 of age and 20 patients ³ 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 5 mg/kg dose, one with a duration of > 22 months.

Study CA184178 was a non-randomised, 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. Tumour 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 23.

Table 23: 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

Ipilimumab in combination with nivolumab

Study CA209070 was an open-label, single-arm, dose-confirmation and dose-expansion, phase 1/2 study of nivolumab as a single agent and in combination with ipilimumab in paediatric and young adult patients with recurrent or refractory solid or haematological tumours, including neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, advanced melanoma, cHL and non-Hodgkin lymphoma (NHL). Among the 126 treated patients, 97 were paediatric patients from 12 months to < 18 years of age. Of the 97 paediatric patients, 64 were treated with nivolumab monotherapy (3 mg/kg administered intravenously over 60 minutes every 2 weeks) and 33 were treated with ipilimumab in combination with nivolumab (nivolumab 1 mg/kg or 3 mg/kg administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 90 minutes every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks). Patients received either nivolumab as monotherapy for a median of 2 doses (range: 1, 89) or ipilimumab in combination with nivolumab for a median of 2 doses (range: 1, 24). The main primary outcome measures were safety, tolerability and antitumour activity as evaluated by descriptive ORR and OS.

Among the 64 paediatric patients treated with nivolumab monotherapy, 60 were response-evaluable patients (melanoma n = 1, solid tumours n = 47 and

haematological tumours n = 12). In the 48 response-evaluable paediatric patients with melanoma or solid tumours, no objective responses were observed. In the 12 response-evaluable paediatric patients with haematological tumours, ORR was 25.0% (95% CI: 5.5, 57.2), including 1 complete response in cHL and 2 partial responses, one in cHL and another one in NHL. In the descriptive analyses for the 64 paediatric patients treated with nivolumab monotherapy, the median OS was 6.67 months (95% CI: 5.98, NA); 6.14 months (95% CI: 5.39, 24.67) for patients with melanoma or solid tumours, and not reached for patients with haematological tumours.

Among the 30 response-evaluable paediatric patients treated with ipilimumab in combination with nivolumab (solid tumours other than melanoma only), no objective responses were observed. For the 33 paediatric patients treated with ipilimumab in combination with nivolumab, the median OS was 8.25 months (95% CI: 5.45, 16.95) in a descriptive analyses.

Study CA209908 was an open-label, sequential-arm, phase 1b/2 clinical study of nivolumab monotherapy and ipilimumab in combination with nivolumab in paediatric and young adult patients with high-grade primary CNS malignancies, including diffuse intrinsic pontine glioma (DIPG), high-grade glioma, medulloblastoma, ependymoma and other recurrent subtypes of high-grade CNS malignancy (e.g., pineoblastoma, atypical teratoid/rhabdoid tumour, and embryonal CNS tumours). Of the 151 paediatric patients (from ≥ 6 months to < 18 years old) enrolled in the study, 77 were treated with nivolumab monotherapy (3 mg/kg every 2 weeks) and 74 were treated with ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg, every 3 weeks for 4 doses, followed by nivolumab monotherapy 3 mg/kg every 2 weeks. The primary efficacy outcome measures were OS in the DIPG cohort and investigator-assessed PFS, based on RANO criteria, for all other tumour types. The median OS in the DIPG cohort was 10.97 months (80% CI: 9.92, 12.16) in patients treated with nivolumab monotherapy and 10.50 months (80% CI: 9.10, 12.32) in patients treated with ipilimumab in combination with nivolumab. For all other studied CNS paediatric tumour types, the median PFS ranged from 1.23 to 2.35 months in patients treated with nivolumab monotherapy and from 1.45 to 3.09 months in patients treated with ipilimumab in combination with nivolumab. There were no objective responses observed in the study with the exception of one ependymoma patient treated with nivolumab monotherapy who had a partial response. Results for OS, PFS, and ORR observed in study CA209908 do not suggest clinically meaningful improvement over what is expected in these patient populations.

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 µg/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 Cminss plasma concentrations.

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

YERVOY in combination with nivolumab and chemotherapy: When ipilimumab 1 mg/kg every 6 weeks was administered in combination with nivolumab 360 mg every 3 weeks and with 2 cycles of chemotherapy, the CL of ipilimumab increased approximately 22% and the CL of nivolumab decreased approximately 10%, which was 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

For ipilimumab monotherapy, 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.

For ipilimumab in combination with nivolumab, the exposures of ipilimumab and nivolumab in paediatric patients 12 years of age and older are expected to be comparable to that in adult patients at the recommended dose.

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 oedema. 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 minutes.

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

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