ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 10 mg of nivolumab.
One vial of 4 mL contains 40 mg of nivolumab.
One vial of 10 mL contains 100 mg of nivolumab.

Nivolumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipient with known effect
Each mL of concentrate contains 0.1 mmol (or 2.5 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OPDIVO as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

4.2 Posology and method of administration

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

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

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 Table 1. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 1: Recommended treatment modifications for OPDIVO

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold OPDIVO until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue OPDIVO
Immune- related colitis	Grade 2 or 3 diarrhoea or colitis	Withhold OPDIVO until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue OPDIVO
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold OPDIVO 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 OPDIVO
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold OPDIVO until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue OPDIVO
Immune-related endocrinopathies	Symptomatic endocrinopathies (including hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency and diabetes)	Withhold OPDIVO until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. OPDIVO should be continued in the presence of hormone replacement therapy[a] as long as no symptoms are present
Immune-related rash	Grade 3 rash	Withhold dose until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue OPDIVO

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.

OPDIVO should also be permanently discontinued for Grade 2 or 3 immune-related adverse reactions that persist despite treatment modifications (see section 4.4) or for inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day.

Special populations

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

Elderly
No dose adjustment is required for elderly patients (≥ 65 years) (see sections 5.1 and 5.2).

Renal impairment
Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Hepatic impairment
Based on the population PK results, no dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. OPDIVO must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment.

Method of administration

OPDIVO is for intraveous use only. It is to be administered as an intravenous infusion over a period of 60 minutes. The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 μm.

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

The total dose of OPDIVO required can be infused directly as a 10 mg/mL solution or can be diluted to as low as 1 mg/mL with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection.

For instructions on the 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

Nivolumab is associated with immune-related adverse reactions. Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab may occur at any time during or after discontinuation of nivolumab therapy.

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, nivolumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

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.

Nivolumab must be permanently discontinued for any severe immune related adverse reaction that recurs and for any life threatening immune related adverse reaction.

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

Immune-related pneumonitis
Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with nivolumab treatment (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, 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, nivolumab should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, 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 nivolumab must be permanently discontinued.

Immune-related colitis
Severe diarrhoea or colitis has been observed with nivolumab treatment (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, nivolumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

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

For Grade 2 diarrhoea or colitis, 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, 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 nivolumab must be permanently discontinued.

Immune-related hepatitis
Severe hepatitis has been observed with nivolumab treatment (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, 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, 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, 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 nivolumab must be permanently discontinued.

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

For Grade 4 serum creatinine elevation, 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, nivolumab should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, 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 nivolumab must be permanently discontinued.

Immue-related endocrinopathies
Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetes ketoacidosis have been observed with nivolumab treatment (see section 4.8).

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

For symptomatic hypothyroidism, nivolumab should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, nivolumab should be withheld and methimazole 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, nivolumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised.

For symptomatic adrenal insufficiency, nivolumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised.

For symptomatic hypophysitis, 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, nivolumab may be resumed after corticosteroid taper, if needed. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.

For symptomatic diabetes, 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.

Immune-related rash
Severe rash has been observed with nivolumab treatment that may be immune-related (see section 4.8). 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 prednisone equivalents.

Caution should be used when considering the use of nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Other immune-related adverse reactions
The following immune-related adverse reactions were reported in less than 1% of patients treated with nivolumab in clinical trials across doses and tumour types: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, hypopituitarism, and myasthenic syndrome.

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, nivolumab should be withheld and corticosteroids administered. Upon improvement, nivolumab may be resumed after corticosteroid taper. Nivolumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Infusion reactions
Severe infusion reactions have been reported in clinical trials (see section 4.8). In case of a severe infusion reaction, nivolumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab with close monitoring.

Special populations
Patients with a baseline performance score ≥ 2, active brain metastases, ocular melanoma, autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials. In addition, CA209037 excluded patients who have had a Grade 4 adverse reaction that was related to anti-CTLA-4 therapy (see section 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential risk-benefit on an individual basis.

Experience with nivolumab in previously untreated BRAF mutation-positive melanoma is limited.

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

4.5 Interaction with other medicinal products and other forms of interaction

Nivolumab is a human monoclonal antibody, as such pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab.

Other forms of interaction

Systemic immunosuppression
The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions. The preliminary results show that systemic immunosuppression after starting nivolumab treatment does not appear to preclude the response on nivolumab.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the use of nivolumab in pregnant women. Studies in animals have shown embryofetal toxicity (see section 5.3). Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore nivolumab has the potential to be transmitted from the mother to the developing foetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of OPDIVO.

Breast-feeding
It is unknown whether nivolumab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from nivolumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, nivolumab is unlikely to affect 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 nivolumab does not adversely affect them.

4.8 Undesirable effects

Summary of the safety profile
Nivolumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of nivolumab (see "Description of selected adverse reactions" below).

In the pooled dataset of two phase 3 studies in melanoma (CA209066 and CA209037), the most frequent adverse reactions (≥ 10%) were fatigue (33%), rash (20%), pruritus (18%), diarrhoea (16%), and nausea (14%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Tabulated summary of adverse reactions
Adverse reactions reported in the pooled dataset (n = 474) of CA209037 and CA209066 are presented in Table 2. 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in patients with advanced melanoma treated with nivolumab 3 mg/kg (CA209066 and CA209037)

Infections and infestations	
Common	upper respiratory tract infection
Immune system disorders	
Common	infusion related reaction
Uncommon	anaphylactic reaction[a], hypersensitivity[a]
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism, hyperglycaemia
Uncommon	adrenal insufficiency, hypopituitarism, hypophysitis, thyroiditis, diabetic ketoacidosis, diabetes mellitus
Metabolism and nutrition disorders	
Common	hyponatraemia, decreased appetite
Nervous system disorders	
Common	peripheral neuropathy, headache, dizziness
Uncommon	Guillain-Barré syndrome, demyelination, myasthenic syndrome[a], autoimmune neuropathy (including facial and abducens nerve paresis)
Eye disorders	
Uncommon	uveitis
Cardiac disorders	
Uncommon	arrhythmia (including ventricular arrhythmia)[b]
Vascular disorders	
Common	hypertension
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis, dyspnoea, cough
Gastrointestinal disorders	
Very common	diarrhoea, nausea
Common	colitis, stomatitis, vomiting, abdominal pain, constipation
Uncommon	pancreatitis
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus
Common	vitiligo, dry skin, erythema, alopecia
Uncommon	erythema multiforme, psoriasis, rosacea
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain[d], arthralgia
Renal and urinary disorders	
Uncommon	tubulointerstitial nephritis, renal failure
General disorders and administration site conditions	
Very common	fatigue
Common	pyrexia, oedema (including peripheral oedema)
Investigations	
Very common	increased AST[e], increased ALT[e], increased total bilirubin[e], increased alkaline phosphatase[e], increased creatinine[e], lymphopenia[e], thrombocytopenia[e], anaemia[e]
Common	increased lipase, increased amylase, neutropenia[c]

[a] Reported in studies outside the completed phase 3 clinical trials in melanoma (CA209066 and CA209037)

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

[c] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis allergic, and dermatitis exfoliative.

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

[e] Frequencies reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.

Description of selected adverse reactions

Data for the following immune-related adverse reactions are based on patients who received nivolumab 3 mg/kg in two phase 3 studies (CA209066 and CA209037, see section 5.1). The management guidelines for these adverse reactions are described in section 4.4.

Immune-related pneumonitis

In CA209066 and CA209037, the incidence of pneumonitis, including interstitial lung disease, was 2.3% (11/474). All of these cases were Grade 1 or 2 in severity. Grade 2 cases were reported in 1.7% (8/474) of patients.

Median time to onset was 2.1 months (range: 0.8-5.1). Eight patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.5 mg/kg (range: 0.7-4.8) for a median duration of 0.6 month (range: 0.1-1.0). Resolution occurred in 8 patients (73%) with a median time to resolution of 1.4 months (range: 0.2-2.8).

Immune-related colitis

In CA209066 and CA209037, the incidence of diarrhoea or colitis was 16.5% (78/474). Grade 2 and Grade 3 cases were reported in 3.2% (15/474) and 1.3% (6/474) of patients, respectively. No Grade 4 or 5 cases were reported in these studies.

Median time to onset was 1.9 months (range: 0.0-13.3). Seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.0 mg/kg (range: 0.6-4.7) for a median duration of 1.1 months (range: 0.1-2.4). Two patients (0.4%) with Grade 3 colitis required permanent discontinuation of nivolumab. Resolution occurred in 68 patients (88%) with a median time to resolution of 0.3 month (range: 0.0-12.5+); + denotes a censored observation.

Immune-related hepatitis

In CA209066 and CA209037, the incidence of liver function test abnormalities was 6.8% (32/474). Grade 2, Grade 3, and Grade 4 cases were reported in 0.8% (4/474), 1.5% (7/474), and 0.4% (2/474) of patients, respectively. No Grade 5 cases were reported in these studies.

Median time to onset was 2.8 months (range: 0.5 14.0). Four patients received high dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.6 mg/kg (range: 0.4-4.7) for a median duration of 1.2 months (range: 0.9-1.7). Six patients (1.3%), 4 with Grade 3 and 2 with Grade 4 liver function test abnormalities, required permanent discontinuation of nivolumab. Resolution occurred in 26 patients (81%) with a median time to resolution of 0.7 month (range: 0.2 9.6+).

Immune-related nephritis and renal dysfunction

In CA209066 and CA209037, the incidence of nephritis or renal dysfunction was 1.9% (9/474). Grade 2 and Grade 3 cases were reported in 0.2% (1/474) and 0.6% (3/474) of patients, respectively. No Grade 4 or 5 nephritis or renal dysfunction was reported in these studies.

Median time to onset was 3.5 months (range: 0.9 6.4). Four patients received high dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.3 mg/kg (range: 0.7-2.1) for a median duration of 0.5 month (range: 0.2-1.0). Resolution occurred in 7 patients (78%) with a median time to resolution of 1.25 months (range: 0.5- 4.7+).

Immune-related endocrinopathies
In CA209066 and CA209037, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 7.6% (36/474). Grade 2 and Grade 3 thyroid disorders were reported in 4.2% (20/474) and 0.2% (1/474) of patients. Hypophysitis (Grade 3), adrenal insufficiency (Grade 2), diabetes mellitus (Grade 2), and diabetic ketoacidosis (Grade 3) were each reported in 1 patient (0.2% each).

Median time to onset of these endocrinopathies was 2.4 months (range: 0.8 10.8). Two patients received high dose corticosteroids (at least 40 mg prednisone equivalents) at an initial dose of 0.7 mg/kg and 1.3 mg/kg for 0.4 month and 0.7 month, respectively. Resolution occurred in 18 patients (45%) with a median time to resolution of 6.4 months (0.2-15.4+).

Immune-related rash
In CA209066 and CA209037, the incidence of rash was 36.1% (171/474). Grade 2 and Grade 3 cases were reported in 6.1% (29/474) and 0.8% (4/474) of patients. No Grade 4 or 5 cases were reported in these studies.

Median time to onset was 1.4 months (range: 0.0-13.1). Two patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at an initial dose of 0.7 mg/kg and 0.9 mg/kg for 0.5 month and 0.1 month, respectively. Resolution occurred in 87 patients (51%) with a median time to resolution of 4.6 months (0.0-19.1^{+}).

Infusion reactions
In CA209066 and CA209037, the incidence of hypersensitivity/infusion reactions was 5.3% (25/474), including a Grade 3 case in 1 patient (0.2%).

Laboratory abnormalities
In CA209066 and CA209037, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.6% for anaemia (all Grade 3), 0.2% for thrombocytopenia, 7% for lymphopenia, 0.9% for neutropenia, 2.4% for increased alkaline phosphatase, 3.3% for increased AST, 2.4% for increased ALT, 1.5% for increased total bilirubin, and 0.9% for increased creatinine.

Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response to nivolumab. Of the 388 patients who were treated with nivolumab 3 mg/kg every 2 weeks and evaluable for the presence of anti-product-antibodies, 30 patients (7.7%) tested positive for treatment-emergent anti-product-antibodies by an electrochemiluminescent (ECL) assay. Only 2 patients (0.5%) were considered persistent positive. Neutralising antibodies were detected in only 2 (0.5%) of the positive anti-product-antibody samples. There was no evidence of altered pharmacokinetic profile, or toxicity profile associated with anti-product-antibody development.

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

4.9 Overdose

No cases of overdose have been reported in clinical trials. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC17.

Mechanism of action
Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

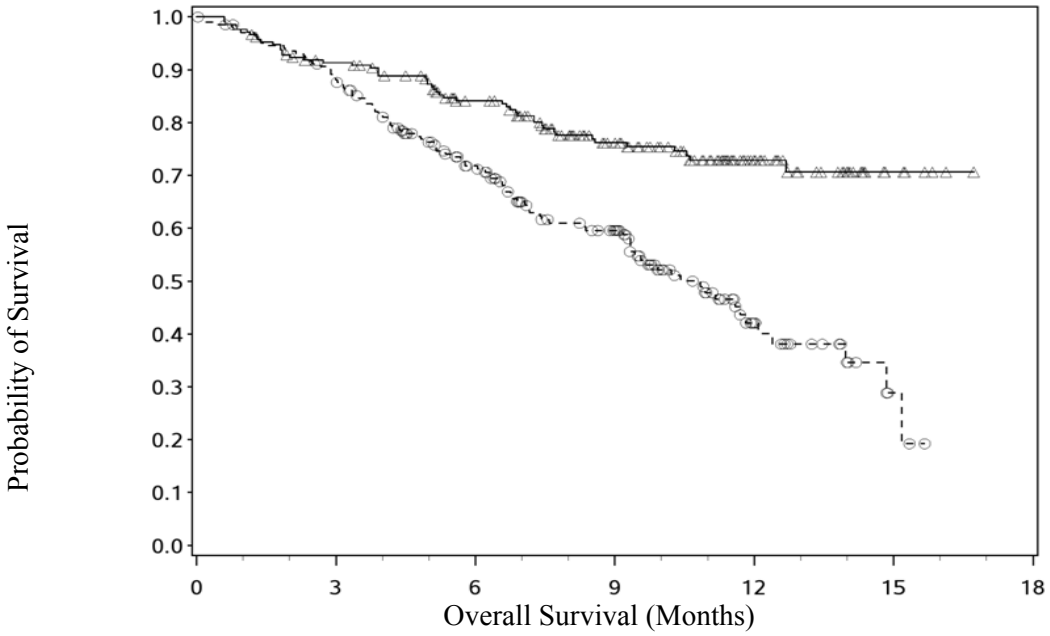
Clinical efficacy and safety

Randomised phase 3 study vs. dacarbazine (CA209066)
The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, double-blind study (CA209066). The study included adult patients (18 years or older) with confirmed, treatment-naive, Stage III or IV BRAF wild-type melanoma and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

A total of 418 patients were randomised to receive either nivolumab (n = 210) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine (n = 208) at 1000 mg/m^2 every 3 weeks. Randomisation was stratified by PD-L1 status and M stage (M0/M1a/M1b versus M1c). Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse effects with the study drug, as determined by the investigator. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks for the first year and then every 12 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed progression-free survival (PFS) and objective response rate (ORR).
Baseline characteristics were balanced between the two groups. The median age was 65 years (range: 18-87), 59% were men, and 99.5% were white. Most patients had ECOG performance score of 0 (64%) or 1 (34%). Sixty-one percent of patients had M1c stage disease at study entry. Seventy-four percent of patients had cutaneous melanoma, and 11% had mucosal melanoma; 35% of patients had PD-L1 positive melanoma ($\geq$5% tumour cell membrane expression). Sixteen percent of patients had received prior adjuvant therapy; the most common adjuvant treatment was interferon (9%). Four percent of patients had a history of brain metastasis, and 37% of patients had a baseline LDH level greater than ULN at study entry.

The Kaplan-Meier curves for OS are shown in Figure 1.

Figure 1: **Kaplan-Meier curves of OS (CA209066)**



Number of Subjects at Risk

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

—Δ— Nivolumab (events: 50/210), median and 95% CI: N.A.
- - -❍- - - Dacarbazine (events: 96/208), median and 95% CI: 10.84 (9.33, 12.09)

The observed OS benefit was consistently demonstrated across subgroups of patients including baseline ECOG performance status, M stage, history of brain metastases, and baseline LDH level. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 5% or 10%).
Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Response rates, time to response, and duration of response are shown in Table 3.

Table 3: **Efficacy Results (CA209066)**

	nivolumab (n = 210)		**dacarbazine (n = 208)**
Overall survival			
Events	50 (23.8)		96 (46.2)
Hazard ratio		0.42	
99.79% CI		(0.25, 0.73)	
95% CI		(0.30, 0.60)	
p-value		< 0.0001	
Median (95% CI)	Not reached		10.8 (9.33, 12.09)
Rate (95% CI)			
At 6 months	84.1 (78.3, 88.5)		71.8 (64.9, 77.6)
At 12 months	72.9 (65.5, 78.9)		42.1 (33.0, 50.9)
Progression-free survival			
Events	108 (51.4)		163 (78.4)
Hazard ratio		0.43	
95% CI		(0.34, 0.56)	
p-value		< 0.0001	
Median (95% CI)	5.1 (3.48, 10.81)		2.2 (2.10, 2.40)
Rate (95% CI)			
At 6 months	48.0 (40.8, 54.9)		18.5 (13.1, 24.6)
At 12 months	41.8 (34.0, 49.3)		NA
Confirmed objective response	84 (40.0%)		29 (13.9%)
(95% CI)	(33.3, 47.0)		(9.5, 19.4)
Odds ratio (95% CI)		4.06 (2.52, 6.54)	
p-value		< 0.0001	
Complete response (CR)	16 (7.6%)		2 (1.0%)
Partial response (PR)	68 (32.4%)		27 (13.0%)
Stable disease (SD)	35 (16.7%)		46 (22.1%)
Median duration of response			
Months (range)	Not reached (0^+ - 12.5^+)		6.0 (1.1 - 10.0^+)
Median time to response			
Months (range)	2.1 (1.2 - 7.6)		2.1 (1.8 - 3.6)

"+" denotes a censored observation.

Randomised phase 3 study vs. chemotherapy (CA209037)

The safety and efficacy of nivolumab 3 mg/kg for the treatment of advanced (unresectable or metastatic) melanoma were evaluated in a phase 3, randomised, open-label study (CA209037). The study included adult patients who had progressed on or after ipilimumab and if BRAF V600 mutation positive had also progressed on or after BRAF kinase inhibitor therapy. Patients with active autoimmune disease, ocular melanoma or a known history of prior ipilimumab-related high-grade (Grade 4 per CTCAE v4.0) adverse reactions, except for resolved nausea, fatigue, infusion reactions, or endocrinopathies, were excluded from the study.

A total of 405 patients were randomised to receive either nivolumab (n = 272) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or chemotherapy (n = 133) which consisted of the investigator's choice of either dacarbazine (1000 mg/m^2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks). Randomisation was stratified by BRAF and PD-L1 status and best response to prior ipilimumab.

The co-primary efficacy outcome measures were confirmed ORR in the first 120 subjects treated with nivolumab, as measured by independent radiology review committee (IRRC) using RECIST 1.1, and comparison of OS of nivolumab to chemotherapy. Additional outcome measures included duration and timing of response.

The median age was 60 years (range: 23-88). Sixty-four percent of patients were men and 98% were white. ECOG performance scores were 0 for 61% of patients and 1 for 39% of patients. The majority (75%) of patients had M1c stage disease at study entry. Seventy-three percent of patients had cutaneous melanoma and 10% had mucosal melanoma. The number of prior systemic regimen received was 1 for 27% of patients, 2 for 51% of patients, and > 2 for 21% of patients. Twenty-two percent of patients had tumours that tested BRAF mutation positive and 50% of patients had tumours that were considered PD-L1 positive. Sixty-four percent of patients had no prior clinical benefit (CR/PR or SD) on ipilimumab. Baseline characteristics were balanced between groups except for the proportions of patients who had a history of brain metastasis (19% and 13% in the nivolumab group and chemotherapy group, respectively) and patients with LDH greater than ULN at baseline (51% and 35%, respectively).

At the time of this final ORR analysis, results from 120 nivolumab-treated patients and 47 chemotherapy-treated patients who had a minimum of 6 months of follow-up were analyzed. Efficacy results are presented in Table 4.

Table 4: **Best overall response, time and duration of response (CA209037)**

	nivolumab (n = 120)	**chemotherapy (n = 47)**
Confirmed Objective Response (IRRC)	38 (31.7%)	5 (10.6%)
(95% CI)	(23.5, 40.8)	(3.5, 23.1)
Complete Response (CR)	4 (3.3%)	0
Partial Response (PR)	34 (28.3%)	5 (10.6%)
Stable Disease (SD)	28 (23.3%)	16 (34.0%)
Median Duration of Response		
Months (range)	Not Reached	3.6 (Not available)
Median Time to Response		
Months (range)	2.1 (1.6-7.4)	3.5 (2.1-6.1)

Objective responses to nivolumab (according to the definition of the co-primary endpoint) were observed in patients with or without BRAF mutation-positive melanoma. Of the patients who received nivolumab, the ORR in the BRAF mutation-positive subgroup (n=26) was 23% (95% CI: 9.0, 43.6), and 34% (95% CI: 24.6, 44.5) in patients whose tumours were BRAF wild-type (n=94). Objective responses to nivolumab were observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 5% or 10%). However the role of this biomarker (PD-L1 expression) has not been fully elucidated.

The OS data were not mature at the time of the PFS analysis. There was no statistically significant difference between nivolumab and chemotherapy in the preliminary OS analysis that was not adjusted for the potentially confounding effects of subsequent therapy. It is of note that 42 (31.6%) patients in the chemotherapy arm subsequently received an anti-PD1 treatment.
Data available indicate that the onset of nivolumab effect is delayed such that benefit of nivolumab above chemotherapy may take 2-3 months.

Investigator assessed, confirmed ORRs in all treated patients were 25.7% [95% CI: 20.6, 31.4] in the nivolumab group (n=268) vs. 10.8% [95% CI: 5.5, 18.5]) in the chemotherapy group, (n=102), with an ORR difference of 15.0% (95% CI: 6.0, 22.2). Investigator assessed, confirmed ORRs in BRAF mutation-positive patients (n=79) were 19.3% [95% CI: 10.0, 31.9] vs. 13.6% [95% CI: 2.9, 34.9]), respectively, and in BRAF wild-type patients (n=291) were 27.5% [95% CI: 21.6, 34.0] vs. 10.0% [95% CI: 4.4, 18.8]), respectively.

PFS numerically favoured the nivolumab group vs the chemotherapy group in all randomised patients, BRAF mutation positive patients, and BRAF wild-type patients (HRs 0.74 [95% CI: 0.57, 0.97], 0.98 [95% CI: 0.56, 1.70], and 0.63 [95% CI: 0.47, 0.85], respectively).

Safety and efficacy in elderly patients
No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years).

Open-label phase 1 dose-escalation study (MDX1106-03)
The safety and tolerability of nivolumab were investigated in a phase 1, open-label dose-escalation study in various tumour types, including malignant melanoma. Of the 306 previously treated patients enrolled in the study, 107 had melanoma and received nivolumab at a dose of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg for a maximum of 2 years. In this patient population, objective response was reported in 33 patients (31%) with a median duration of response of 22.9 months (95% CI: 17.0, NR). The median PFS was 3.7 months (95% CI: 1.9, 9.3). The median OS was 17.3 months (95% CI: 12.5, 36.7), and the estimated OS rates were 63% (95% CI: 53, 71) at 1 year, 48% (95% CI: 38, 57) at 2 years, and 41% (95% CI: 31, 51) at 3 years.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with nivolumab in all subsets of the paediatric population in the treatment of malignant solid tumours (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of nivolumab is linear in the dose range of 0.1 to 10 mg/kg. The geometric mean clearance (CL), terminal half-life, and average exposure at steady state at 3 mg/kg every 2 weeks of nivolumab were 9.5 mL/h, 26.7 days, and 75.3 μg/mL, respectively, based on a population PK analysis.

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

The metabolic pathway of nivolumab has not been characterised. Nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Special populations

A population PK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumour type, tumour size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful.

Renal impairment
The effect of renal impairment on the CL of nivolumab was evaluated in patients with mild (GFR < 90 and ≥ 60 mL/min/1.73 m^2; n = 379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 m^2; n = 179), or severe (GFR < 30 and ≥ 15 mL/min/1.73 m^2; n = 2) renal impairment compared to patients with normal renal function (GFR ≥ 90 mL/min/1.73 m^2; n = 342) in population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 4.2).

Hepatic impairment
The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 92) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 804) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild hepatic impairment and

normal hepatic function. Nivolumab has not been studied in patients with moderate (total bilirubin > 1.5 × to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST) (see section 4.2).

5.3 Preclinical safety data

Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to increase foetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels either 8 or 35 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). There was a dose-dependent increase in foetal losses and increased neonatal mortality beginning in the third trimester.

The remaining offspring of nivolumab-treated females survived to scheduled termination, with no treatment-related clinical signs, alterations to normal development, organ-weight effects, or gross and microscopic pathology changes. Results for growth indices, as well as teratogenic, neurobehavioral, immunological, and clinical pathology parameters throughout the 6-month postnatal period were comparable to the control group. However, based on its mechanism of action, foetal exposure to nivolumab may increase the risk of developing immune-related disorders or altering the normal immune response and immune-related disorders have been reported in PD-1 knockout mice.

Fertility studies have not been performed with nivolumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
2 years.

After opening
From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately.

After preparation of infusion
From a microbiological point of view, the product should be used immediately.

If not used immediately, chemical and physical in-use stability of OPDIVO has been demonstrated for 24 hours at 2ºC to 8ºC protected from light and a maximum of 4 hours at 20°C-25°C and room light (this 4-hour period of the total 24 hours should be inclusive of the product administration period).

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 preparation of the infusion, see section 6.3.

6.5 Nature and contents of container

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

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.

Preparation and administration

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

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

Preparing the infusion
Take care to ensure aseptic handling when you prepare the infusion. The infusion should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents.

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

STEP 1
- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake the vial. OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.
- Withdraw the required volume of OPDIVO concentrate using an appropriate sterile syringe.

STEP 2

- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. Gently mix the infusion by manual rotation. Do not shake.

Administration
OPDIVO infusion must not be administered as an intravenous push or bolus injection.
Administer the OPDIVO infusion intravenously over a period of 60 minutes.
OPDIVO infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

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

OPDIVO infusion is compatible with PVC and polyolefin containers, glass bottles, PVC infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

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

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

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer of the biological active substance

Lonza Biologics, Inc.
101 International Drive
Portsmouth, New Hampshire
03801
USA

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of OPDIVO in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media,

distribution modalities, and any other aspects of the programme, with the National Competent Authority.
The educational programme is aimed at increasing the awareness about the potential immune mediated adverse events associated with OPDIVO use, how to manage them and to enhance the awareness of patients or their caregivers on the signs and symptoms relevant to the early those adverse events.
The MAH shall ensure that in each Member State where OPDIVO is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use OPDIVO have access to/are provided with the following educational package:

- Physician educational material
- Patient alert card

The physician educational material should contain:
- The Summary of Product Characteristics
- Adverse Reaction Management Guide

The Adverse Reaction Management Guide shall contain the following key elements:

- Relevant information (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable) for the following safety concerns:
  - Immune-related pneumonitis
  - Immune-related colitis
  - Immune-related hepatitis
  - Immune-related nephritis or renal dysfunction
  - Immune-related endocrinopathies
  - Immune related rash
  - Other immune-related ARs

- Details on how to minimise the safety concern through appropriate monitoring and management

- **The patient alert card** shall contain the following key messages:

- That OPDIVO treatment may increase the risk of:
  - Immune-related pneumonitis
  - Immune-related colitis
  - Immune-related hepatitis
  - Immune-related nephritis or renal dysfunction
  - Immune-related endocrinopathies
  - Immune related rash
  - Other immune-related ARs

- Signs or symptoms of the safety concern and when to seek attention from a HCP

- Contact details of the OPDIVO prescriber

- **Obligation to conduct post-authorisation measures**

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

Description	Due date
1. Post-authorisation efficacy study (PAES): The MAH should submit the final Study report for study CA209037: a Randomized, Open-Label, Phase 3 Trial of nivolumab vs Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy.	The final clinical study report should be submitted by 30th June 2016

2. Post-authorisation efficacy study (PAES): The MAH should submit an updated OS data for Study CA209066: a Phase 3, randomized, double-blind study of nivolumab vs dacarbazine in subjects with BRAF wild type, previously untreated, unresectable or metastatic melanoma.	The updated data/study report should be submitted by 31st December 2015
3. The value of biomarkers to predict the efficacy of nivolumab should be further explored, specifically: 1. To continue the exploration of the optimal cut-off for PD-L1 positivity based on current assay method used to further elucidate its value as predictive of nivolumab efficacy. These analyses will be conducted in Studies CA 209037 and CA209066 in patients with advanced melanoma. 2. To further investigate the value biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut-offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, etc.) as predictive of nivolumab efficacy. These additional biomarker analyses are occurring in the context of Study CA209-038 and Study CA209-066. 3. To further investigate at post-approval the relation between PDL-1 and PDL-2 expression in Phase 1 (CA209009, CA209038 and CA209064). 4. To further investigate the associative analyses between PDL-1 and PDL-2 expression conducted in Study CA209-066. 5. To further investigate at post-approval the possible change in PD-L1 status of the tumour during treatment and/or tumour progression in Studies CA209-009, CA209-038 and CA209-064.	 30th September 2015 30th September 2017 31st March 2017 31st December 2017 30th September 2017

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

OPDIVO 10 mg/mL concentrate for solution for infusion
nivolumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of concentrate contains 10 mg of nivolumab.
Each vial of 4 mL contains 40 mg of nivolumab.
Each vial of 10 mL contains 100 mg of nivolumab.

3. LIST OF EXCIPIENTS

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

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

40 mg/4 mL
100 mg/10 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1014/001 40 mg vial
EU/1/15/1014/002 100 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

OPDIVO 10 mg/mL sterile concentrate
nivolumab
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/4 mL
100 mg/10 mL

6. OTHER

For single use only.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

OPDIVO 10 mg/mL concentrate for solution for infusion
nivolumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What OPDIVO is and what it is used for

OPDIVO is a medicine used to treat advanced melanoma (a type of skin cancer) in adults. It contains the active substance nivolumab, which is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body.

Nivolumab attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the melanoma cells.

2. What you need to know before you use OPDIVO

You should not be given OPDIVO
- if you are **allergic** to nivolumab or any of the other ingredients of this medicine (listed in section 6 "Contents of the pack and other information"). **Talk to your doctor** if you are not sure.

Warnings and precautions
Talk to your doctor before using OPDIVO as it may cause:
- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Diarrhoea** (watery, loose or soft stools) or any symptoms of **inflammation of the intestines** (colitis), such as stomach pain and mucus or blood in stool.
- **Inflammation of the liver (hepatitis).** Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, or tiredness.
- **Inflammation or problems with your kidneys.** Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.

- **Problems with your hormone producing glands** (including the pituitary, the thyroid and adrenal glands) that may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache and visual disturbances.
- **Diabetes** (symptoms include excessive thirst, the passing of a greatly increased amount of urine, increase in appetite with a loss of weight, feeling tired, drowsy, weak, depressed, irritable and generally unwell) or **diabetes ketoacidosis** (acid in the blood produced from diabetes).
- **Inflammation of the skin** that can lead to rash and itching.

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

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

Check with your doctor or nurse before you are given OPDIVO if:
- you have an **autoimmune disease** (a condition where the body attacks its own cells);
- you have **melanoma of the eye**;
- you were previously given ipilimumab, another medicine for treating melanoma, and experienced **serious side effects** because of that medicine.

Children and adolescents
OPDIVO should not be used in children and adolescents below 18 years of age.

Other medicines and OPDIVO
Before you are given OPDIVO, tell your doctor if you are taking any medicines that suppress your immune system, such as corticosteroids, since these medicines may interfere with the effect of OPDIVO. However, once you are treated with OPDIVO, your doctor may give you corticosteroids to reduce any possible side effects that you may have during your treatment and this will not impact the effect of the medicine.
Tell your doctor if you are taking or have recently taken any other medicines. **Do not take any other medicines** during your treatment without talking to your doctor first.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or think you might be, if you are planning to become pregnant, or if you are breast-feeding.

Do not use OPDIVO if you are pregnant unless your doctor specifically tells you to. The effects of OPDIVO in pregnant women are not known, but it is possible that the active substance, nivolumab, could harm an unborn baby.
- You must use **effective contraception** while you are being treated with OPDIVO, if you are a woman who could become pregnant.
- If you become pregnant while using OPDIVO **tell your doctor**.

It is not known whether nivolumab gets into breast milk. A risk to the breast-fed infant cannot be excluded. **Ask your doctor** if you can breast-feed during or after treatment with OPDIVO.

Driving and using machines
Nivolumab is unlikely to affect your ability to drive or use machines; however, use caution when performing these activities until you are sure that nivolumab does not adversely affect you.

OPDIVO contains sodium
Tell your doctor if you are on a low-sodium (low-salt) diet before you are given OPDIVO. This medicine contains 2.5 mg sodium per mL of concentrate.

3. How to use OPDIVO

How much OPDIVO is given
The amount of OPDIVO you will be given will be calculated based on your body weight. The recommended dose is 3 mg of nivolumab per kilogram of your body weight.
Depending on your dose, the appropriate amount of OPDIVO will be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection before use. More than one vial of OPDIVO may be necessary to obtain the required dose.

How OPDIVO is given
You will receive treatment with OPDIVO in a hospital or clinic, under the supervision of an experienced doctor.

OPDIVO will be given to you as an infusion (a drip) into a vein (intravenously) over a period of 60 minutes, every 2 weeks. Your doctor will continue giving you OPDIVO for as long as you keep benefitting from it or until you no longer tolerate the treatment.

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

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

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

4. Possible side effects

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

Be aware of important symptoms of inflammation. OPDIVO acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening and need treatment or withdrawal of nivolumab.

The following side effects have been reported in clinical trials with nivolumab:

Very common (may affect more than 1 in 10 people)
- Diarrhoea (watery, loose or soft stools), nausea
- Skin rash, itching
- Feeling tired or weak

Common (may affect up to 1 in 10 people)
- Infections of the upper respiratory tract
- Underactive thyroid gland, which can cause tiredness or weight gain, overactive thyroid gland, which can cause rapid heart rate, sweating and weight loss
- High sugar levels in the blood (hyperglycaemia)
- Low levels of sodium in the blood (hyponatraemia), decreased appetite
- Inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs; headache, dizziness
- High blood pressure (hypertension)

- Inflammation of the lungs (pneumonitis), characterised by coughing and difficulty breathing, shortness of breath (dyspnoea), cough
- Inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), vomiting, stomach pain, constipation
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning
- Pain in the muscles, bones and joints
- Fever, oedema (swelling)
- Allergic reaction, reactions related to the infusion of the medicine

Uncommon (may affect up to 1 in 100 people)
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, acid in the blood produced from diabetes (diabetic ketoacidosis), diabetes
- A temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome); loss of the protective sheath around nerves (demyelination); a condition in which the muscles become weak and tire easily (myasthenic syndrome); inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain
- Inflammation of the eye, which causes pain and redness, vision problems or blurry vision
- Changes in the rhythm or rate of the heart beat
- Inflammation of the pancreas
- Severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme); skin disease with thickened patches of red skin, often with silvery scales (psoriasis); skin condition of the face where the nose and cheeks are unusually red (rosacea)
- Inflammation of the kidney, kidney failure.

Tell your doctor immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

Changes in test results
OPDIVO may cause changes in the results of tests carried out by your doctor. These include:
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch.

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

5. How to store OPDIVO

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

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

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

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

6. Contents of the pack and other information

What OPDIVO contains

- The active substance is nivolumab.
  Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.
  Each vial contains either 40 mg (in 4 mL) or 100 mg (in 10 mL) of nivolumab.

- The other ingredients are sodium citrate dihydrate, sodium chloride (see section 2 "OPDIVO contains sodium"), mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid and water for injections.

What OPDIVO looks like and contents of the pack
OPDIVO concentrate for solution for infusion (sterile concentrate) is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.

It is available in packs containing either 1 vial of 4 mL or 1 vial of 10 mL.

Not all pack sizes may be marketed.

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This leaflet was last revised in

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

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The following information is intended for healthcare professionals only:

Preparation and administration of OPDIVO

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

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

- The **total nivolumab dose** in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The **volume of OPDIVO concentrate** to prepare the dose (mL) = the total dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

Preparing the infusion
Take care to ensure aseptic handling when you prepare the infusion. The infusion should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents.

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

STEP 1
- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake the vial. OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.
- Withdraw the required volume of OPDIVO concentrate using an appropriate sterile syringe.

STEP 2
- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. Gently mix the infusion by manual rotation. Do not shake.

Administration
OPDIVO infusion must not be administered as an intravenous push or bolus injection.
Administer the OPDIVO infusion **intravenously over a period of 60 minutes**.

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

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

OPDIVO infusion is compatible with:
- PVC containers
- Polyolefin containers
- Glass bottles

- PVC infusion sets
- In-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

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

Storage conditions and shelf life
Unopened vial
OPDIVO must be **stored in a refrigerator** (2°C to 8°C). The vials must be kept in the original package in order to protect from light. OPDIVO should not be frozen.

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

OPDIVO infusion
OPDIVO infusion must be completed within 24 hours of preparation. If not used immediately, the solution may be stored under refrigeration conditions (2°C-8°C) and protected from light for up to 24 hours [a maximum of 4 hours of the total 24 hours can be at room temperature (20°C-25°C) and room light]. Other in-use storage time and conditions are the responsibility of the user.

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