

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

Nivolumab BMS 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, colourless 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

Nivolumab BMS is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy 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 Nivolumab BMS 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 Nivolumab BMS

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold Nivolumab BMS until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue Nivolumab BMS
Immune-related colitis	Grade 2 or 3 diarrhoea or colitis	Withhold Nivolumab BMS until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue Nivolumab BMS
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold Nivolumab BMS 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 Nivolumab BMS
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold Nivolumab BMS until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue Nivolumab BMS
Immune-related endocrinopathies	Symptomatic endocrinopathies (including hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency and diabetes)	Withhold Nivolumab BMS until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Nivolumab BMS 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 Nivolumab BMS

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.

Nivolumab BMS 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.

Patients treated with Nivolumab BMS must be given the patient alert card and be informed about the risks of Nivolumab BMS (see also package leaflet).

Special populations

Paediatric population

The safety and efficacy of Nivolumab BMS 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). Data from patients 75 years of age or older are too limited to draw conclusions on this population.

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. Nivolumab BMS must be administered with caution in patients with moderate (total bilirubin $> 1.5 \times$ to $3 \times$ the upper limit of normal [ULN] and any AST) or severe (total bilirubin $> 3 \times$ ULN and any AST) hepatic impairment.

Method of administration

Nivolumab BMS is for intravenous 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 .

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

The total dose of Nivolumab BMS 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.

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 infiltrates), 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. 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.

Immune-related endocrinopathies

Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis have been observed with nivolumab treatment.

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 or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the clinical trials of NSCLC (see sections 4.5 and 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.

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.

Patient Alert Card

All prescribers of Nivolumab BMS must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of Nivolumab BMS therapy with the patient. The patient will be provided with the Patient Alert Card with each prescription.

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 Nivolumab BMS.

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 studies in squamous NSCLC (CA209017 and CA209063), the most frequent adverse reactions ($\geq 10\%$ of patients) were fatigue (33%), decreased appetite (15%), and nausea (12%). 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=248) of CA209017 and CA209063 are presented in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in patients with squamous NSCLC treated with nivolumab 3 mg/kg (CA209017 and CA209063)

Infections and infestations	
Uncommon	bronchitis, upper respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Immune system disorders	
Uncommon	anaphylactic reaction, hypersensitivity, infusion related reaction
Endocrine disorders	
Common	hypothyroidism
Uncommon	adrenal insufficiency, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite
Nervous system disorders	
Common	peripheral neuropathy, headache, dizziness
Uncommon	myasthenic syndrome, polyneuropathy
Cardiac disorders	
Uncommon	tachycardia
Vascular disorders	
Uncommon	vasculitis
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis, dyspnoea, cough
Uncommon	lung infiltration
Gastrointestinal disorders	
Very common	nausea
Common	diarrhoea, stomatitis, vomiting, abdominal pain, constipation, dry mouth
Uncommon	colitis, duodenal ulcer
Skin and subcutaneous tissue disorders	
Common	rash, pruritus
Uncommon	urticaria
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain, ^a arthralgia
Uncommon	polymyalgia rheumatica
Renal and urinary disorders	
Uncommon	tubulointerstitial nephritis, renal failure
General disorders and administration site conditions	
Very common	fatigue
Common	pyrexia, oedema
Investigations	
Very common	increased AST, ^b increased ALT, ^b increased alkaline phosphatase, ^b increased creatinine, ^b decreased lymphocytes, ^b decreased platelet count, ^b decreased haemoglobin, ^b hypercalcaemia, ^b hypocalcaemia, ^b hyperkalaemia, ^b hypokalaemia, ^b hypomagnesaemia, ^b hyponatraemia ^b
Common	increased total bilirubin, ^b decreased absolute neutrophil count, ^b hypermagnesaemia, ^b hypernatraemia ^b
Uncommon	Increased lipase, increased amylase

^a 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.

^b 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 NSCLC studies (CA209017 and CA209063, see section 5.1). The management guidelines for these adverse reactions are described in section 4.4.

Immune-related pneumonitis

In CA209017 and CA209063, the incidence of pneumonitis, including interstitial lung disease, was 5.2% (13/248). Grade 2 and Grade 3 cases were reported in 2.8% (7/248) and 1.6% (4/248) of patients, respectively. No Grade 4 or 5 cases reported in these studies. In the phase 1 study MDX1106-03, pneumonitis, including a Grade 4 case in 1 patient, was reported in 3/37 patients (8.1%) with NSCLC receiving nivolumab 3 mg/kg.

Median time to onset was 11.6 weeks (range: 2.6-85.1). Eleven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.1 mg/kg (range: 0.5-4.0) for a median total duration of 4.3 weeks (range: 0.6-13.1). Eight patients, including the 4 patients with a Grade 3 case, required permanent discontinuation of nivolumab due to pneumonitis. Resolution occurred in all 13 patients with a median time to resolution of 3.9 weeks (range: 0.6-13.4).

Immune-related colitis

In CA209017 and CA209063, the incidence of diarrhoea or colitis was 9.3% (23/248). Grade 2 and Grade 3 cases were reported in 2% (5/248) and 1.6% (4/248) of patients, respectively. No Grade 4 or 5 cases were reported in these studies.

Median time to onset was 5.6 weeks (range: 0.1-91.0). Three patients, including 2 patients with a Grade 3 case, received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.6 mg/kg (range: 0.4-1.3) for a median duration of 2.0 weeks (range: 1.4-14.1). One patient required permanent discontinuation of nivolumab due to Grade 3 diarrhoea. Resolution occurred in 19 patients (83%) with a median time to resolution of 2.0 weeks (range: 0.1-31.0).

Immune-related hepatitis

In CA209017 and CA209063, the incidence of liver function test abnormalities was 1.2% (3/248). Grade 2 cases were reported in 0.4% (1/248) of patients. No Grade 3-5 cases were reported in these studies.

Median time to onset was 25.1 weeks (range: 4.1-31.1). None of these patients received high-dose corticosteroids. One patient required permanent discontinuation of nivolumab due to Grade 2 increases in transaminases. Resolution occurred in 2 patients (67%) with a median time to resolution of 4.1 weeks (range: 2.9-22.3⁺); ⁺ denotes a censored observation.

Immune-related nephritis and renal dysfunction

In CA209017 and CA209063, the incidence of nephritis or renal dysfunction was 3.2% (8/248). Grade 2 and Grade 3 cases were reported in 1.2% (3/248) and 0.4% (1/248) of patients, respectively. No Grade 4 or 5 nephritis or renal dysfunction was reported in these studies.

Median time to onset was 10.5 weeks (range: 2.1-27.0). Two patients, including the one patient with a Grade 3 case (tubulointerstitial nephritis), received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 0.8 mg/kg (range: 0.5-1.2) for a median duration of 5.3 weeks (range: 0.9-9.7). Resolution occurred in 5 patients (71%), including the Grade 3 case, with a median time to resolution of 5.9 weeks (range: 0.7- 37.6⁺); ⁺ denotes a censored observation.

Immune-related endocrinopathies

In CA209017 and CA209063, the incidence of thyroid disorders, including hypothyroidism or thyroiditis, was 4.4% (11/248). Grade 2 cases were reported in 3.6% (9/248) of patients. No Grade 3-5 thyroid disorders were reported. The incidence of adrenal insufficiency was 0.4% (1/248; Grade 3). There were no reports of hypophysitis, diabetes mellitus, or diabetic ketoacidosis in these studies.

Median time to onset of these endocrinopathies was 17.8 weeks (range: 6.1-33.1). Three patients, including the one patient with Grade 3 adrenal insufficiency, received high-dose corticosteroids (at least 40 mg prednisone equivalents) at a median initial dose of 1.1 mg/kg (range: 0.5-1.3) for 2.7 weeks (range: 0.6-4.6). The Grade 3 case required permanent discontinuation of nivolumab. Resolution occurred in 6 patients (50%) with a median time to resolution of 20.6 weeks (0.4-47.6⁺); ⁺ denotes a censored observation.

Immune-related rash

In CA209017 and CA209063, the incidence of rash was 12.1% (30/248). Grade 2 and Grade 3 cases were reported in 1.6% (4/248) and 0.8% (2/248) of patients, respectively. No Grade 4 or 5 rash was reported in these studies.

Median time to onset was 8.1 weeks (range: 0.3-51.9). None of these patients received high-dose corticosteroids. Two patients (1 with Grade 2 rash and 1 with Grade 3 rash) required permanent discontinuation of nivolumab. Resolution occurred in 24 patients (83%), including the 2 patients with a Grade 3 case, with a median time to resolution of 5.7 weeks (range: 0.1- 46.9⁺); ⁺ denotes a censored observation.

Infusion reactions

In CA209017 and CA209063, the incidence of hypersensitivity/infusion reactions was 1.6% (4/248). Grade 3 anaphylactic reaction and Grade 4 hypersensitivity were each reported in 1 patient; both of these cases led to discontinuation and resolved with treatment.

Laboratory abnormalities

In CA209017 and CA209063, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 13.2% for decreased lymphocytes, 9% for hyponatraemia, 2.9% for hypercalcaemia and hyperkalaemia, 2.5% for decreased haemoglobin (all Grade 3), 2.0% for hypokalaemia, 1.6% for decreased neutrophil count, 1.3% for hypomagnesaemia, 1.2% for hypocalcaemia, 0.8% for increased total bilirubin, and 0.4% for increased AST, decreased platelet, hypermagnesaemia, and hypernatraemia. There was no worsening to Grade 3 or 4 in increased ALT, increased alkaline phosphatase, and increased creatinine.

In study CA209017, hypercalcaemia was more frequently reported in the nivolumab group (31/130, 24%) than in the docetaxel group (9/124, 7%). The exact cause is not known. Although hyperparathyroidism was not reported in CA209017, immune-related hyperparathyroidism might be considered especially if associated with hypophosphataemia (reported in 6 hypercalcemic patients in this study).

Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response to nivolumab. Of the 497 patients who were treated with nivolumab 3 mg/kg every 2 weeks and evaluable for the presence of anti-product-antibodies, 51 (10.3%) patients tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. Only 4 (0.8%) patients were persistent positive. Neutralising antibodies were detected in only 5 (1.0% of the total) of the positive anti-product-antibody patients. There was no evidence of altered pharmacokinetic 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. docetaxel (CA209017)

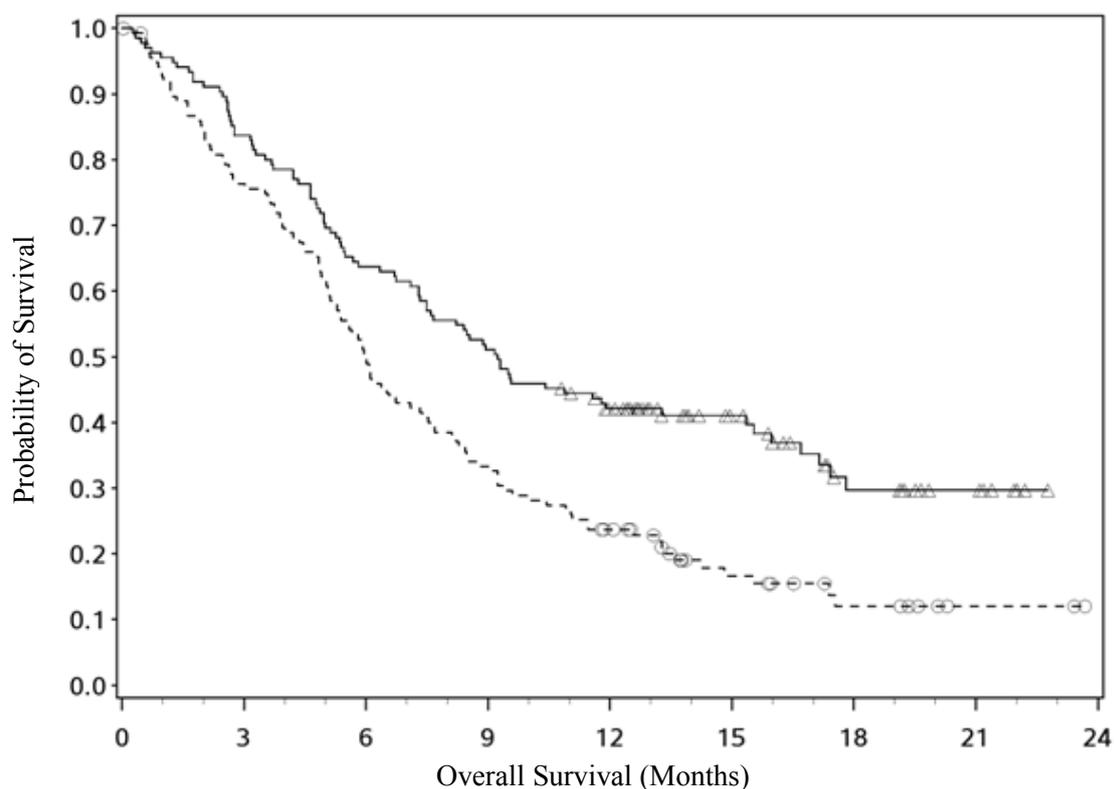
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209017). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients were enrolled regardless of their PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (N = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m² every 3 weeks. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. The primary efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed objective response rate (ORR) and progression-free survival (PFS). In addition, symptom improvement and overall health status were assessed using the Lung Cancer Symptom Score (LCSS) average symptom burden index and the EQ-5D Visual Analogue Scale (EQ-VAS), respectively.

Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 39-85) with 44% ≥65 years of age and 11% ≥75 years of age. The majority of patients were white (93%) and male (76%). Thirty-one percent had progressive disease reported as the best response to their most recent prior regimen and 45% received nivolumab within 3 months of completing their most recent prior regimen. Baseline ECOG performance status score was 0 (24%) or 1 (76%).

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

Figure 1: Kaplan-Meier curves of OS (CA209017)



Number of Subjects at Risk

Nivolumab 3 mg/kg

135 113 86 69 52 31 15 7 0

Docetaxel

137 103 68 45 30 14 7 2 0

—△— Nivolumab 3 mg/kg (events : 86/135), median and 95% CI : 9.23 (7.33, 13.27)

--○-- Docetaxel (events : 113/137), median and 95% CI : 6.01 (5.13, 7.33)

The observed OS benefit was consistently demonstrated across subgroups of patients. 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 1%, 5% or 10%). However, the role of this biomarker (PD-L1 expression) has not been fully elucidated.

Study CA209017 included a limited number of patients ≥ 75 years (11 in the nivolumab group and 18 in the docetaxel group). Nivolumab showed numerically less effect on OS (HR 1.85; 95% CI: 0.76, 4.51), PFS (HR=1.76; 95%-CI: 0.77, 4.05) and ORR (9.1% vs 16.7%). Because of the small sample size, no definitive conclusions can be drawn from these data.

Efficacy results are shown in Table 3.

Table 3: Efficacy results (CA209017)

	nivolumab (n = 135)	docetaxel (n = 137)
Overall survival		
Events	86 (63.7)	113 (82.5)
Hazard ratio		0.59
96.85% CI		(0.43, 0.81)
p-value		0.0002
Median (95% CI) months	9.23 (7.33, 13.27)	6.01 (5.13, 7.33)
Rate (95% CI) at 12 months	42.1 (33.7, 50.3)	23.7 (16.9, 31.1)
Confirmed objective response		
(95% CI)	27 (20.0%) (13.6, 27.7)	12 (8.8%) (4.6, 14.8)
Odds ratio (95% CI)		2.64 (1.27, 5.49)
p-value		0.0083
Complete response (CR)	1 (0.7%)	0
Partial response (PR)	26 (19.3%)	12 (8.8%)
Stable disease (SD)	39 (28.9%)	47 (34.3%)
Median duration of response		
Months (range)	Not reached (2.9 - 20.5 ⁺)	8.4 (1.4 ⁺ - 15.2 ⁺)
Median time to response		
Months (range)	2.2 (1.6 - 11.8)	2.1 (1.8 - 9.5)
Progression-free survival		
Events	105 (77.8)	122 (89.1)
Hazard ratio		0.62
95% CI		(0.47, 0.81)
p-value		< 0.0004
Median (95% CI) (months)	3.48 (2.14, 4.86)	2.83 (2.10, 3.52)
Rate (95% CI) at 12 months	20.8 (14.0, 28.4)	6.4 (2.9, 11.8)

The rate of disease-related symptom improvement, as measured by LCSS, was similar between the nivolumab group (18.5%) and the docetaxel group (21.2%). The average EQ-VAS increased over time for both treatment groups, indicating better overall health status for patients remaining on treatment.

Single-arm phase 2 study (CA209063)

Study CA209063 was a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous-NSCLC after two or more lines of therapy; otherwise similar inclusion criteria as study CA209017 were applied. Nivolumab 3 mg/kg showed an overall response rate of 14.5% (95% CI: 8.7-22.2%), a median OS of 8.21 months (95% CI: 6.05-10.9 months), and a median PFS of 1.87 months (95% CI 1.77-3.15 months). The PFS was measured by RECIST version 1.1. The estimated 1-year survival rate was 41%.

Safety and efficacy in elderly patients

No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from patients 75 years of age or older are too limited to draw conclusions on this population.

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 m²; n = 379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 m²; n = 179), or severe (GFR < 30 and ≥ 15 mL/min/1.73 m²; n = 2) renal impairment compared to patients with normal renal function (GFR ≥ 90 mL/min/1.73 m²; 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 $1.0 \times$ to $1.5 \times$ 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 \leq 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 $> 1.5 \times$ to $3 \times$ ULN and any AST) or severe hepatic impairment (total bilirubin $> 3 \times$ 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. Nivolumab BMS 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 Nivolumab BMS has been demonstrated for 24 hours at 2°C to 8°C 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 Nivolumab BMS 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 Nivolumab BMS concentrate to prepare the dose (mL) = the total dose in mg, divided by 10 (the Nivolumab BMS 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.

Nivolumab BMS 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. Nivolumab BMS 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 Nivolumab BMS concentrate for particulate matter or discoloration. Do not shake the vial. Nivolumab BMS concentrate is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.
- Withdraw the required volume of Nivolumab BMS 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

Nivolumab BMS infusion must not be administered as an intravenous push or bolus injection.

Administer the Nivolumab BMS infusion intravenously over a period of 60 minutes.

Nivolumab BMS 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).

Nivolumab BMS 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/1/15/1026/001-002

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 Nivolumab BMS 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 Nivolumab BMS 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 Nivolumab BMS is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Nivolumab BMS 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 Nivolumab BMS 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 Nivolumab BMS 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 an updated OS data for Study CA209017: a Phase 3, randomized study of nivolumab vs docetaxel in subjects with advanced or metastatic squamous NSCLC who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen.	The updated data should be submitted by 31 st December 2015

<p>2. The value of biomarkers to predict the efficacy of nivolumab should be further explored, specifically:</p> <ol style="list-style-type: none"> 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. 	<p>30th September 2015</p> <p>30th September 2017</p> <p>31st March 2017</p> <p>31st December 2017</p> <p>30th September 2017</p>
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ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nivolumab BMS 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/1/15/1026/001 40 mg vial
EU/1/15/1026/002 100 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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

Nivolumab BMS 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

Nivolumab BMS 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.

It is important that you keep the Alert Card with you during treatment.

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

1. What Nivolumab BMS is and what it is used for

Nivolumab BMS is a medicine used to treat advanced non-small cell lung cancer (a type of lung 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 lung cancer cells.

2. What you need to know before you use Nivolumab BMS

You should not be given Nivolumab BMS

- 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 Nivolumab BMS 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 **diabetic 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 Nivolumab BMS,
- or stop your treatment with Nivolumab BMS 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 Nivolumab BMS if:

- you have been told that your **cancer has spread to your brain**
- you have an **autoimmune disease** (a condition where the body attacks its own cells);
- you have any history of **inflammation of the lungs**;
- you have been taken **medicines to suppress your immune system.**

Children and adolescents

Nivolumab BMS should not be used in children and adolescents below 18 years of age.

Other medicines and Nivolumab BMS

Before you are given Nivolumab BMS, 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 Nivolumab BMS. However, once you are treated with Nivolumab BMS, 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 Nivolumab BMS if you are pregnant unless your doctor specifically tells you to. The effects of Nivolumab BMS 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 Nivolumab BMS and for at least 5 months following the last dose of Nivolumab BMS, if you are a woman who could become pregnant.
- If you become pregnant while using Nivolumab BMS **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 Nivolumab BMS.

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.

Nivolumab BMS contains sodium

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

You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregivers.

3. How to use Nivolumab BMS

How much Nivolumab BMS is given

The amount of Nivolumab BMS 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 Nivolumab BMS 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 Nivolumab BMS may be necessary to obtain the required dose.

How Nivolumab BMS is given

You will receive treatment with Nivolumab BMS in a hospital or clinic, under the supervision of an experienced doctor.

Nivolumab BMS 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 Nivolumab BMS for as long as you keep benefitting from it or until you no longer tolerate the treatment.

If you miss a dose of Nivolumab BMS

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

If you stop using Nivolumab BMS

Stopping your treatment may stop the effect of the medicine. Do not stop treatment with Nivolumab BMS 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. Nivolumab BMS 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)

- Decreased appetite
- Nausea
- Feeling tired or weak

Common (may affect up to 1 in 10 people)

- Underactive thyroid gland which can cause tiredness or weight gain
- Inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs, headache, dizziness

- Inflammation of the lungs (pneumonitis), characterised by coughing and difficulty breathing, shortness of breath (dyspnoea), cough
- Diarrhoea (watery, loose or soft stools), mouth ulcers and cold sores (stomatitis), vomiting, stomach pain, constipation, dry mouth
- Skin rash, itching
- Pain in the muscles, bones and joints
- Fever, oedema (swelling)

Uncommon (may affect up to 1 in 100 people)

- Bronchitis, infections of the upper respiratory tract
- A disease causing the inflammation or enlargement of a lymph node (Kikuchi lymphadenitis)
- Allergic reaction, reactions related to the administration of the medicine
- Adrenal glands not working properly, inflammation of the thyroid gland
- A condition in which the muscles become weak and tire easily (myasthenic syndrome), damage to the nerves in different parts of the body that can cause decreased feeling or affect movement
- Fast heart rate
- Inflammation of blood vessels
- Fluid in the lungs
- Inflammation of the intestines (colitis), ulcer of the small intestines
- Hives (itchy, bumpy rash)
- Inflammation of muscles causing pain or stiffness
- Kidney disease, 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

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

- 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)
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase in your blood, higher blood levels of bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- Abnormal levels of calcium, potassium, magnesium, or sodium in your blood
- An increased level of the enzyme that breaks down lipids 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 Nivolumab BMS

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 Nivolumab BMS 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 "Nivolumab BMS contains sodium"), mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid and water for injections.

What Nivolumab BMS looks like and contents of the pack

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

The following information is intended for healthcare professionals only:

Preparation and administration of Nivolumab BMS

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 Nivolumab BMS 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 Nivolumab BMS concentrate** to prepare the dose (mL) = the total dose in mg, divided by 10 (the Nivolumab BMS 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.

Nivolumab BMS 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. Nivolumab BMS 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 Nivolumab BMS concentrate for particulate matter or discoloration. Do not shake the vial. Nivolumab BMS concentrate is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.
- Withdraw the required volume of Nivolumab BMS 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

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

Nivolumab BMS 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).

Nivolumab BMS 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

Nivolumab BMS 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. Nivolumab BMS should not be frozen.

Do not use Nivolumab BMS 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.

Nivolumab BMS infusion

Nivolumab BMS 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.