Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: http://www.gmc-uk.org/mobile/14327

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to licence such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

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

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

Special populations

Paediatric population
The safety and efficacy of Nivolumab 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 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

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

The total dose of Nivolumab 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 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. 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 must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of Nivolumab 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 embryofoetal 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.

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 (≥ 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 (≥ 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 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	histocytic 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.

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)

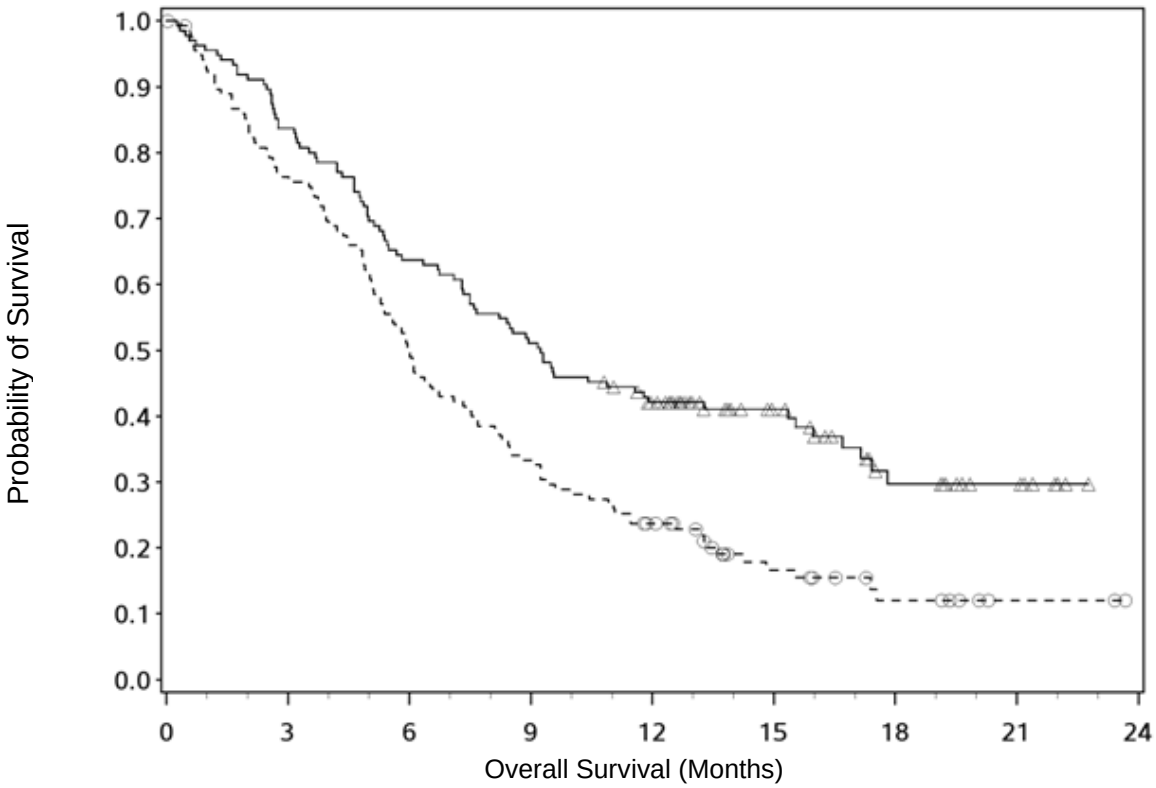
The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced or metastatic squamous NSCLC were evaluated in a phase 3, randomised, open-label study (CA209017). The study included patients (18 years or older) who have experienced disease progression during or after one 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/m^2 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	27 (20.0%)	12 (8.8%)
(95% CI)	(13.6, 27.7)	(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 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. Nivolumab 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 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

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.

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 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 concentrate to prepare the dose (mL) = the total dose in mg, divided by 10 (the Nivolumab 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 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 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 concentrate for particulate matter or discoloration. Do not shake the vial. Nivolumab concentrate is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.
- Withdraw the required volume of Nivolumab 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 infusion must not be administered as an intravenous push or bolus injection.
Administer the Nivolumab infusion intravenously over a period of 60 minutes.
Nivolumab 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 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. SCIENTIFIC OPINION HOLDER

Bristol-Myers Squibb Pharmaceutical Limited
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. EAMS NUMBER

15105/0002

9. DATE OF SCIENTIFIC OPINION

19 June 2015

Additional information:

Each prescribing oncologist will have to complete a short **Application Form** to ensure eligibility within the scheme and to collect anonymised patient data.

An **Informed Consent Form** (ICF) will be provided to be completed with the patient.

A **Letter of Agreement** will be signed by the prescribing oncologist for each individual patient.

BMS will arrange a site visit for the purposes of training and delivery of the programme materials, including in particular the following:

- **Adverse Reaction Management Guide**
  This guide will ensure understanding of the immunologic aetiology of important adverse reactions, the requirement for more frequent monitoring and/or unique interventions and the guidelines for the management of adverse reactions.
- **Patient Alert Card**
  This is a wallet-sized card to be carried at all times to show at all medical visits to HCPs other than the prescriber (e.g., emergency HCPs). It has contact details of the treating physician and it alerts other physicians that the patient is treated with nivolumab.

Every two weeks following commencement of treatment, updated patient data will be collected in a **Case Report Form** (CRF).

Contact information:

To register a patient for the EAMS programme, please

- either email to EAMS@bms.com
- or follow the link from the Bristol-Myers Squibb website for UK EAMS Squamous NSCLC patients: http://www.bms.com/clinical_trials/investigator_sponsored_research/Pages/expanded-access-program.aspx; this link will take you to an application form to ensure eligibility within the scheme (see above)

Additional contact:
Bristol-Myers Squibb Medical Information on 0800 731 1736 or medical.information@bms.com