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 license (marketing authorisation) in this indication 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/guidance/ethical_guidance/14316.asp

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 license 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'.

In this updated treatment protocol (31/05/2018), additional information has been included in section 4.8 (safety data) and 6 (storage conditions) – identified by red text.

For further updates of the safety information, please refer to the product information of Opdivo (nivolumab) on the EMA website:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf

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 as monotherapy is indicated for the treatment of adult patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma after two or more prior systemic therapies.

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

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 dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 or 3 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[a] as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 3 myocarditis	Permanently discontinue treatment
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse

Events Version 4.0 (NCI-CTCAE v4).
[a] Recommendation for the use of hormone replacement therapy is provided in section 4.4.

Nivolumab should be permanently discontinued for:
Grade 4 or recurrent Grade 3 adverse reactions;
Persistent Grade 2 or 3 adverse reactions despite management.

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

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).

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 m.

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 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 or

recurrence 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 monotherapy (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 monotherapy (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 monotherapy (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 transaminase or total bilirubin elevation, nivolumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 transaminase or total bilirubin elevation, nivolumab should be withheld. Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab must be permanently discontinued.
Immune-related nephritis and renal dysfunction
Severe nephritis and renal dysfunction have been observed with nivolumab monotherapy (see section 4.8).

Patients should be monitored for signs and symptoms of nephritis or renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.

For Grade 4 serum creatinine elevation, 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 (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), diabetes mellitus, and diabetic ketoacidosis have been observed with nivolumab monotherapy (see section 4.8).

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

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

For symptomatic Grade 2 adrenal insufficiency, nivolumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed. Nivolumab must be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised.

For symptomatic Grade 2 or 3 hypophysitis, 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. Nivolumab must be permanently discontinued for life-threatening (Grade 4) hypophysitis. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.

For symptomatic diabetes, 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. Nivolumab must be permanently discontinued for life-threatening diabetes.

Immune-related skin adverse reactions
Severe rash has been observed with nivolumab as monotherapy (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 methylprednisolone equivalents.

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

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 monotherapy or nivolumab combined with ipilimumab in clinical trials across doses and tumour types: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenic syndrome, encephalitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, and rhabdomyolysis. Cases of Vogt-Koyanagi-Harada syndrome have been reported post-marketing (see section 4.8).

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, 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.

Rare cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab should be withheld or discontinued (see section 4.2), and appropriate treatment instituted.

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients.

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

Special populations
Patients with history of chronic or recurrent autoimmune disease, interstitial lung disease or pulmonary fibrosis, symptomatic brain metastases, diverticulitis, or symptomatic gastrointestinal ulcerative disease were excluded from the pivotal trial in gastric cancer (see section 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

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 provided in the Physician Pack. The prescriber must discuss the risks of nivolumab therapy with the patient and provide a Patient Alert Card to each patient prior to starting treatment.

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 fetus. 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
In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumour types (n = 2578), with minimum follow up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (30%), rash (17%), pruritus (13%), diarrhoea (13%), 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 for patients treated with nivolumab monotherapy (n = 2578) 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), not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions

Infections and infestations	
Common	upper respiratory tract infection
Uncommon	pneumonia[a], bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Very common	neutropaenia[a,b]
Uncommon	eosinophilia
Immune system disorders	

Common	infusion related reaction[c], hypersensitivity[c]
Rare	anaphylactic reaction[c]
Not known	solid organ transplant rejection
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism
Uncommon	adrenal insufficiency, hypopituitarism, hypophysitis, thyroiditis, diabetes mellitus,
Rare	diabetic ketoacidosis
Metabolism and nutrition disorders	
Common	decreased appetite
Uncommon	dehydration, metabolic acidosis
Not known	tumour lysis syndrome[i]
Hepatobiliary disorders	
Uncommon	hepatitis[c]
Rare	cholestasis
Nervous system disorders	
Common	peripheral neuropathy, headache, dizziness
Uncommon	Polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,c]
Eye disorders	
Uncommon	uveitis, blurred vision, dry eye
Not known	Vogt-Koyanagi-Harada syndrome[h]
Cardiac disorders	
Uncommon	tachycardia
Rare	arrhythmia (including ventricular arrhythmia)[d], atrial fibrillation, myocarditis[a,f]
Vascular disorders	
Common	hypertension
Rare	vasculitis
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis[a,c], dyspnoea[a], cough
Uncommon	pleural effusion
Rare	lung infiltration
Gastrointestinal disorders	
Very common	diarrhoea, nausea
Common	colitis[a], stomatitis, vomiting, abdominal pain, constipation, dry mouth
Uncommon	pancreatitis, gastritis
Rare	duodenal ulcer
Skin and subcutaneous tissue disorders	
Very common	rash[e], pruritus
Common	vitiligo, dry skin, erythema, alopecia
Uncommon	erythema multiforme, psoriasis, rosacea, urticaria
Rare	toxic epidermal necrolysis[a,f], Stevens-Johnson syndrome[a,f]
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain[g], arthralgia
Uncommon	polymyalgia rheumatica, arthritis
Rare	Sjogren's syndrome, myopathy, myositis (including polymyositis)[a,f], rhabdomyolysis[a,f]
Renal and urinary disorders	

Uncommon	tubulointerstitial nephritis, renal failure (including acute kidney injury) [a,c]
General disorders and administration site conditions	
Very common	fatigue
Common	pyrexia, oedema (including peripheral oedema)
Uncommon	pain, chest pain
Investigations[b]	
Very common	increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, hypocalcaemia, increased creatinine, , hyperglycaemia[c], lymphopaenia, leucopaenia, thrombocytopaenia, anaemia, hypercalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia
Common	increased total bilirubin, hypoglycaemia, hypermagnesaemia, hypernatraemia, weight decreased

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

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

[c] Life-threatening cases have been reported in completed or ongoing clinical studies.

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

[e] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.

[f] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

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

[h] Post-marketing event (also see section 4.4)

[i] Reported in clinical studies and in the post-marketing setting.

Description of selected adverse reactions

Nivolumab is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. The management guidelines for these adverse reactions are described in section 4.4.

Immune-related pneumonitis

The incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.4% (87/2578). The majority of cases were Grade 1 or 2 in severity reported in 0.8% (21/2578) and 1.7% (44/2578) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (19/2578) and <0.1% (1/2578) of patients respectively. Grade 5 cases were reported in <0.1% (2/2578) of patients. Median time to onset was 3.6 months (range: 0.2-19.6). Resolution occurred in 63 patients (72.4%) with a median time to resolution of 6.1 weeks (range: 0.1^{+}-96.7^{+}); $^{+}$ denotes a censored observation.

Immune-related colitis

The incidence of diarrhoea, colitis, or frequent bowel movements was 13.1% (339/2578). 2578. The majority of cases were Grade 1 or 2 in severity reported in 8.5% (220/2578) and 3.0% (78/2578) of patients respectively. Grade 3 cases were reported in 1.6% (41/2578) of patients. No Grade 4 or 5 cases were reported. Median time to onset was 1.8 months (range: 0.0-26.6). Resolution occurred in 296 patients (88.1%) with a median time to resolution of 2.1 weeks (range: 0.1-124.4^{+}).

Immune-related hepatitis
The incidence of liver function test abnormalities was 6.7% (173/2578). The majority of cases were Grade 1 or 2 in severity reported in 3.5% (91/2578) and 1.2% (32/2578) of patients respectively. Grade 3 and 4 cases were reported in 1.6% (41/2578) and 0.3% (9/2578) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.1 months (range: 0.0-27.6). Resolution occurred in 132 patients (76.7%) with a median time to resolution of 5.9 weeks (range: 0.1-82.6+).

Immune-related nephritis and renal dysfunction
The incidence of nephritis or renal dysfunction was 2.8% (71/2578). The majority of cases were Grade 1 or 2 in severity reported in 1.6% (41/2578) and 0.7% (18/2578) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (11/2578) and <0.1% (1/2578) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported. Median time to onset was 2.3 months (range: 0.0-18.2). Resolution occurred in 42 patients (61.8%) with a median time to resolution of 12.1 weeks (range: 0.3+-79.1+).

Immune-related endocrinopathies
The incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 9.6% (248/2578). The majority of cases were Grade 1 or 2 in severity reported in 4.2% (107/2578) and 5.4% (139/2578) of patients respectively. Grade 3 thyroid disorders were reported in < 0.1% (2/2578) of patients. Hypophysitis (1 Grade 1, 2 Grade 2, 5 Grade 3 and 1 Grade 4), hypopituitarism (4 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency) (1 Grade 1, 9 Grade 2, and 5 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus) (3 Grade 2 and 1 Grade 3), and diabetic ketoacidosis (2 Grade 3) were reported. No Grade 5 cases were reported. Median time to onset of these endocrinopathies was 2.8 months (range: 0.3-29.1). Resolution occurred in 117 patients (42.9%). Time to resolution ranged from 0.4 to 144.1+ weeks.

Immune-related skin reactions
The incidence of rash was26.4% (680/2578). The majority of cases were Grade 1 in severity reported in 20.1% (518/2578) of patients. Grade 2 and Grade 3 cases were reported in 5.1% (131/2578) and 1.2% (31/2578) of patients respectively. No Grade 4 or 5 cases were reported. Median time to onset was 1.4 months (range: 0.0-27.9). Resolution occurred in 428 patients (63.8%) with a median time to resolution of 17.1 weeks (0.1-150.1+).

Rare cases of SJS and TEN some of them with fatal outcome have been observed (see sections 4.2 and 4.4).

Infusion reactions
The incidence of hypersensitivity/infusion reactions was 4.7% (121/2578), including 6 Grade 3 and 2 Grade 4 cases.

Laboratory abnormalities
The proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 5.2% for anaemia (all Grade 3), 1.0 % for thrombocytopaenia, 1.0% for leucopaenia, 10.0% for lymphopaenia, 1.1% for neutropaenia, 2.1% for increased alkaline phosphatase, 2.7% for increased AST, 2.2% for increased ALT, 1.2% for increased total bilirubin, 0.9% for increased creatinine, 3.8% for hyperglycaemia, 1.0% for hypoglycaemia, 3.5% for increased amylase, 7.9% for increased lipase, 6.4% for hyponatraemia, 1.8% for hyperkalaemia, 1.5% for hypokalaemia, 1.2% for hypercalcaemia, 0.7% for hypermagnesaemia, 0.5% for hypomagnesaemia, 0.7% for hypocalcaemia, and 0.1% for hypernatraemia.

Immunogenicity
Of the 2022 patients who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 231 patients (11.4%) tested positive for treatment-emergent anti-nivolumab antibodies with fifteen patients (0.7%) testing positive for neutralising antibodies.

Although the clearance of nivolumab was increased by 24% when anti-nivolumab-antibodies were present, there was no evidence of loss of efficacy or altered toxicity profile in the presence of anti-nivolumab antibodies based on the pharmacokinetic and exposure-response analyses.

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

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 double-blind phase 3 study (ONO-4538-12/CA209316)

The safety and efficacy of nivolumab monotherapy for the treatment of advanced or recurrent gastric cancer (including GEJ cancer) were evaluated in a phase 3, randomised, double-blind study (ONO-4538-12/CA209316). The study included adult patients previously treated with two or more regimens and whose disease was refractory to or who were intolerant of standard therapy. Patients had ECOG performance status of 0 or 1 and were enrolled regardless of PD-L1 expression level. Patients with history of chronic or recurrent autoimmune disease, interstitial lung disease or pulmonary fibrosis, symptomatic brain metastases, diverticulitis, or symptomatic gastrointestinal ulcerative disease were excluded from the study.

A total of 493 patients were randomised to receive nivolumab (n=330) or placebo (163 patients; of these, 161 patients received at least one dose) administered over 60 minutes every 2 weeks. Randomisation was stratified by location (Japan vs. Korea vs. Taiwan), ECOG performance status (0 vs. 1), and the number of organs with metastases (≤1 vs. ≥2). Nivolumab-treated patients with disease progression per RECIST version 1.1 were allowed to continue treatment until a second RECIST assessment of progressive disease provided that they were receiving a clinical benefit, tolerating nivolumab, and maintaining a stable ECOG performance status score. Tumour assessments were conducted every 6 weeks for the first year and then every 12 weeks thereafter. The primary outcome measure was overall survival (OS). Additional outcome measures included investigator-assessed progression-free survival (PFS) and objective response rate (ORR).

Baseline characteristics were balanced between treatment groups. In the nivolumab group, the median age was 62 years (range: 20 to 83 years), with 141/330 (43%) ≥65 years of age and 30/330 (9%) ≥75 years of age; the majority of patients were male (69%). Disease characteristics were balanced between treatment groups. In the nivolumab group, 41% of patients had recurrent disease, 82% of patients had gastric and 9% had GEJ as the primary site of disease, and 73% had an ECOG score of 1. All patients had received at least 2 prior treatment regimens and most nivolumab-treated patients had received prior fluoropyrimidine, platinum, or taxane therapy.

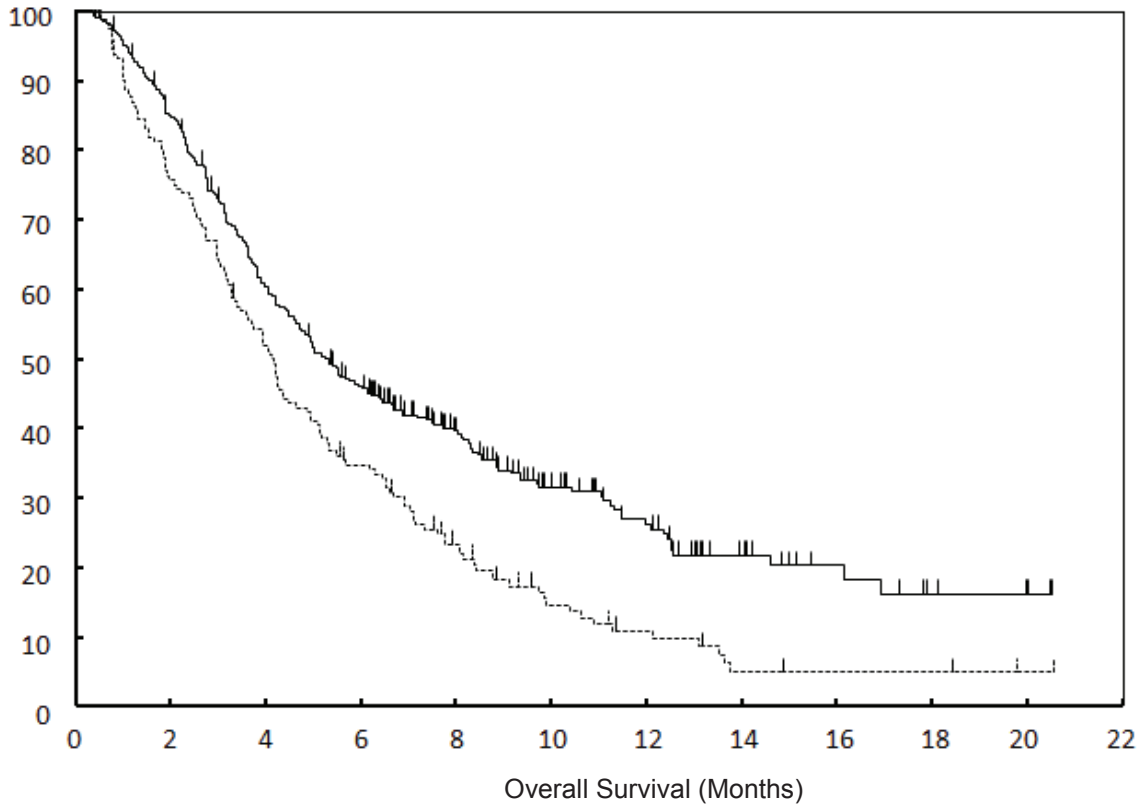
With a minimum duration of follow-up of approximately 6 months, nivolumab demonstrated a statistically significant improvement in OS compared with placebo. Efficacy results are shown in Table 3 and Figure 1.

Table 3: Efficacy results (ONO-4538-12/CA209316)

	Nivolumab (n=330)	Placebo (n=163)
Overall Survival		
Events (%)	226 (68.5%)	141 (86.5%)
Hazard ratio[a] (95% CI)	0.63 (0.51, 0.78)	
p-value[b]	<0.0001[c]	
Median (95% CI)	5.26 (4.60, 6.37)	4.14 (3.42, 4.86)
Rate (95% CI) at 6 months	46.1 (40.5, 51.4)	34.7 (27.4, 42.1)
Rate (95% CI) at 12 months	26.2 (20.7, 32.0)	10.9 (6.2, 17.0)
Progression-Free Survival		
Events (%)	253 (76.7%)	145 (89.0%)
Hazard ratio[a] (95% CI)	0.60 (0.49, 0.75)	
p-value[b]	<0.0001	
Median (95% CI)	1.61 (1.54, 2.30)	1.45 (1.45, 1.54)
Rate (95% CI) at 6 months	20.2 (15.7, 25.1)	6.8 (3.3, 11.8)
Objective Response Rate[c]	30 (11.2%)	0
(95% CI)	(7.7, 15.6)	(0.0, 2.8)
p-value[e]	<0.0001	
Complete response (CR)	0	0
Partial response (PR)	30 (11.2%)	0
Stable disease (SD)	78 (29.1%)	33 (25.2%)
Disease control rate[d]	108 (40.3%)	33 (25.2%)
Median time to response		
Months (range)	1.61 (1.4 to 7.0)	NA
Median duration of response[f]		
Months (95% CI)	9.53 (6.14, 9.82)	NA
% with duration 6 months (95% CI)[g]	75.0 (52.2, 88.0)	NA

[a] Based on a stratified proportional hazards model.
[b] Based on a one-sided stratified log-rank test.
[c] ORR (CR + PR) in patients with measurable target lesions at baseline (nivolumab: n=268; placebo: n=131).
[d] Based on the stratified Cochran-Mantel-Haenszel test.
[e] Disease control rate (DCR) consists of CR+PR+SD.
[f] Based on Kaplan-Meier estimation.

Figure 1: Kaplan-Meier curves of OS (ONO-4538-12/CA209316)



Number of Subjects at Risk

Nivolumab											
330	275	192	141	94	56	38	19	10	5	3	0
Placebo											
163	121	82	53	32	16	10	4	3	3	1	0

——— Nivolumab 3 mg/kg - - - - - Placebo

Overall survival benefit in nivolumab-treated patients was observed regardless of tumour PD-L1 expression. The observed OS benefit was consistently demonstrated across subgroups of patients, including age, gender, baseline ECOG performance status (0 vs. 1), tumour site (gastric vs. GEJ), and histologic type.

Open-label phase 1/2 study (CA209032)

Efficacy was also evaluated in a phase 1/2 study conducted in Europe and the United States, which included a cohort of 42 patients treated with Nivolumab monotherapy 3 mg/kg for gastric cancer (16/42; 38%) or GEJ cancer (26/42; 62%) and who had received at least 2 prior systemic regimens. Inclusion criteria were similar and efficacy was consistent in this study and ONO-4538-12/CA209316. At a minimum follow-up of 17 months, the median OS was 8.48 months (95% CI: 3.35, 15.01), with an OS rate at 12 months of 45% (95% CI: 29, 60). Investigator-assessed confirmed ORR was 16.7% (95% CI: 7.0, 31.4).

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, malignant neoplasms of lymphoid tissue and malignant neoplasms of the central nervous system (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 7.9 mL/h, 25.0 days, and 86.6 g/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, solid 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
3 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 8 hours at 20°C-25°C and room light (this 8-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.

The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

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.

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. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white 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. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 0.9 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 Pharmaceuticals Limited
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. EAMS NUMBER

15105/0008

9. DATE OF SCIENTIFIC OPINION

20 December 2017

10. DATE OF LAST REVISION

31 May 2018

Additional information

Each prescribing Oncologist will have to register on the BMS FastTrack online portal at https://fasttrack.bms.com/.

An **Informed Consent Form** (ICF) will be provided by BMS via the Fast Track portal to be completed with the patient.

A **Letter of Agreement** (LOA) is required to be signed by the prescribing Oncologist and a legal representative from the trust. The LoA will also be provided via the Fast Track online portal.

BMS will arrange training (including adverse event training) and delivery of the programme materials, including 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 by the patient 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 being treated with nivolumab. This will be given to the patient before starting treatment.

The prescribing Oncologist (or designee registered on the Fast Track portal) will be required to request drug re-supplies via the BMS Fast Track online portal every four weeks (except for the first re-supply which will be after two weeks) to order the next two treatment cycles of nivolumab for their patient. The order should be placed at least two weeks before the next planned cycle is due.

In addition to pharmacovigilance data, additional data will be collected on clinical efficacy and quality of life on a voluntary basis subject to additional patient consent.

The prescribing Oncologist is requested to inform BMS if a patient discontinues treatment by completing a discontinuation form (available on Fast Track portal) with the patient's last date of treatment.

Contact information

To initiate the registration process for EAMS the prescribing Oncologist is required to register on the BMS FastTrack online portal at https://fasttrack.bms.com.

Upon registering his/her intent to participate in the EAMS, the prescribing Oncologist will be able to download a patient informed consent form and supporting information to use in consenting the patient from the BMS FastTrack online portal (https://fasttrack.bms.com): 'NPP', then 'EAMS' should be selected from the FastTrack menu.

To register a patient:

To register a patient and request enrolment, the prescribing Oncologist is required to log into the BMS FastTrack online portal, confirm that informed consent has been obtained, and then enter the patient's details. Upon approval of the enrolment by BMS the prescribing Oncologist may proceed to request drug supply from BMS by following the process on the FastTrack portal. BMS will assign a unique patient identification number via the portal (request #) to be used in any future communication including reporting adverse events.

For NHS England only - additional requirement for registering a patient:

Following notification from BMS of eligibility approval, the HCP must complete a Blueteq form online and register their patient with NHS England, which is located at https://www.Blueteq-secure.co.uk/trust/. Once the Blueteq form has been completed, an approval email will be received by the user and pharmacy stating the request has been approved, also stating an EAMS number. This must be provided to BMS once received. If this is not received, BMS will prompt the HCP to provide the EAMS number prior to drug supply.

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