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:
https://www.gov.uk/apply-for-the-early-access-to-medicines-scheme-eams

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'.

MHRA
March 2015

Information for the healthcare professionals:

1 NAME OF THE MEDICINAL PRODUCT

Pembrolizumab (MK-3475) 50 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 50 mg of pembrolizumab.

After reconstitution, 1 mL of solution contains 25 mg of pembrolizumab.

Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype) produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white lyophilised powder, free from visible foreign matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care agents including ipilimumab, and when indicated a V-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor or mitogen-activated protein kinase (MEK) enzyme inhibitor.

4.2 Posology and method of administration

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

Posology

The recommended dose of pembrolizumab is 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

Dose Modifications (See also section 4.4)

Withhold pembrolizumab for any of the following:

- Grade 2 pneumonitis (Grade 2; US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3))
- Grade 2 or 3 colitis
- Symptomatic hypophysitis
- Grade 2 nephritis
- Grade 3 hyperthyroidism
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times

upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction

Resume pembrolizumab in patients whose adverse reactions recover to Grade 0-1.
Permanently discontinue pembrolizumab for any of the following:

- Any life-threatening adverse reaction
- Grade 3 or 4 pneumonitis
- Grade 3 or 4 nephritis
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions (see 4.4 Warnings and Precautions)
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions that do not recover to Grade 0-1 within 12 weeks after last dose of pembrolizumab
- Any severe or Grade 3 treatment-related adverse reaction that recurs.

Paediatric Use

Safety and effectiveness of pembrolizumab have not been established in paediatric patients. However, paediatric patients from the age of 12 years may be prescribed pembrolizumab in the EAMS.

Special populations

Elderly Use
Of the 411 melanoma patients treated with pembrolizumab, 39% were 65 years and over. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

Renal Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is needed for patients with renal impairment *[see section 5.2].*

Hepatic Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is needed for patients with mild hepatic impairment [total bilirubin (TB) less than or equal to ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST]. Pembrolizumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment *[see section 4.4].*

Method of administration
- Administer infusion solution intravenously, using an infusion pump over 30 minutes with a window of -5 and +10 minutes through a peripheral line or in-dwelling catheter containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- Unused infusion solution for injection should not be used for another infusion of the same subject or different subject.

For instruction on reconstitution and dilution 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

Immune-Mediated Pneumonitis
Pneumonitis occurred in 12 (2.9%) of 411 melanoma patients, including Grade 2 or 3 cases in 8 (1.9%) and 1 (0.2%) patients, respectively. The median time to development of pneumonitis was 5 months (range 0.3 weeks-9.9 months). The median duration was 4.9 months (range 1 week-14.4 months). Five of eight patients with Grade 2 and the one patient with Grade 3 pneumonitis required initial treatment with high-dose systemic corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. The median initial dose of high-dose corticosteroid treatment was 63.4 mg/day of prednisone or equivalent with a median duration of treatment of 3 days (range 1-34) followed by a corticosteroid taper. Pneumonitis led to discontinuation of pembrolizumab in 3 (0.7%) patients. Pneumonitis completely resolved in seven of the nine patients with Grade 2-3 pneumonitis.

Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids for Grade 2 or greater pneumonitis. Withhold pembrolizumab for moderate (Grade 2) pneumonitis, and permanently discontinue pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis *[see Dose Modifications (4.2) and Undesirable Effects (4.8)].*

Immune-Mediated Colitis
Colitis (including microscopic colitis) occurred in 4 (1%) of 411 patients, including Grade 2 or 3 cases in 1 (0.2%) and 2 (0.5%) patients, respectively. The median time to onset of colitis was 6.5 months (range 2.3-9.8). The median duration was 2.6 months (range 0.6 weeks-3.6 months). All three patients with Grade 2 or 3 colitis were treated with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) with a median initial dose of 70 mg/day of prednisone or equivalent; the median duration of initial treatment was 7 days (range 4-41), followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of pembrolizumab due to colitis. All four patients with colitis experienced complete resolution of the event.

Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold pembrolizumab for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue pembrolizumab for life-threatening (Grade 4) colitis *[see Dose Modifications (4.2) and Undesirable Effects (4.8)].*

Immune-Mediated Hepatitis
Hepatitis (including autoimmune hepatitis) occurred in 2 (0.5%) of 411 patients, including a Grade 4 case in 1 (0.2%) patient. The time to onset was 22 days for the case of Grade 4 hepatitis which lasted 1.1 months. The patient with Grade 4 hepatitis permanently discontinued pembrolizumab and was treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) systemic corticosteroids followed by a corticosteroid taper. Both patients with hepatitis experienced complete resolution of the event.

Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab *[see Dose Modifications (4.2) and Undesirable Effects (4.8)].*

Immune-Mediated Endocrinopathies
Hypophysitis occurred in 2 (0.5%) of 411 patients, consisting of one Grade 2 and one Grade 4 case (0.2% each). The time to onset was 1.7 months for the patient with Grade 4 hypophysitis and 1.3 months for the patient with Grade 2 hypophysitis. Both patients were treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) corticosteroids followed by a corticosteroid taper and remained on a physiologic replacement dose.

Monitor for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency). Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold pembrolizumab for moderate (Grade 2) hypophysitis, withhold or discontinue pembrolizumab for severe (Grade 3) hypophysitis, and permanently discontinue pembrolizumab for life-threatening (Grade 4) hypophysitis *[see Dose Modifications (4.2) and Undesirable Effects (4.8)]*.

Hyperthyroidism occurred in 5 (1.2%) of 411 patients, including Grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients, respectively. The median time to onset was 1.5 months (range 0.5 to 2.1). The median duration was 2.8 months (range 0.9 to 6.1). One of two patients with Grade 2 and the one patient with Grade 3 hyperthyroidism required initial treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of pembrolizumab due to hyperthyroidism. All five patients with hyperthyroidism experienced complete resolution of the event.

Hypothyroidism occurred in 34 (8.3%) of 411 patients, including a Grade 3 case in 1 (0.2%) patient. The median time to onset of hypothyroidism was 3.5 months (range 0.7 weeks to 19 months). All but two of the patients with hypothyroidism were treated with long-term thyroid hormone replacement therapy. The other two patients only required short-term thyroid hormone replacement therapy. No patient received corticosteroids or discontinued pembrolizumab for management of hypothyroidism.

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Administer corticosteroids for Grade 3 or greater hyperthyroidism, withhold pembrolizumab for severe (Grade 3) hyperthyroidism, and permanently discontinue pembrolizumab for life-threatening (Grade 4) hyperthyroidism. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids [*see Dose modifications (4.2) and Undesirable effects (4.8)*].

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in 0.1% of patients across clinical studies with pembrolizumab in approximately 5000 patients. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold pembrolizumab in cases of severe hyperglycemia until metabolic control is achieved.

Renal Failure and Immune-Mediated Nephritis
Nephritis occurred in 3 (0.7%) patients, consisting of one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%), one Grade 3 and one Grade 4. The time to onset of autoimmune nephritis was 11.6 months after the first dose of pembrolizumab (5 months after the last dose) and lasted 3.2 months; this patient did not have a biopsy. Acute interstitial nephritis was confirmed by renal biopsy in two patients with Grades 3-4 renal failure. All three patients fully recovered renal function with treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper.

Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold pembrolizumab for moderate (Grade 2) nephritis, and permanently discontinue pembrolizumab for severe (Grade 3), or life-threatening (Grade 4) nephritis *[see Dose Modifications (4.2) and Undesirable Effects (4.8)].*

Other Immune-Mediated Adverse Reactions
Other clinically important immune-mediated adverse reactions can occur.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of 411 patients treated with pembrolizumab in Trial P001: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and adrenal insufficiency.

Across clinical studies with pembrolizumab in approximately 2000 patients, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients: myasthenic syndrome, optic neuritis, and rhabdomyolysis.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude

other causes. Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Restart pembrolizumab if the adverse reaction remains at Grade 1 or less. Permanently discontinue pembrolizumab for any severe or Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction *[see Dose Modifications (4.2), Interaction with other medicinal products and other forms of interaction (4.5) and Undesirable Effects (4.8)].*

Infusion-Related Reactions
Across clinical studies with pembrolizumab in approximately 5000 patients, severe infusion-related reactions have been reported in less than 0.1% of patients. For severe infusion reactions, stop infusion and permanently discontinue pembrolizumab [*Posology and Method of Administration (4.2)*]. Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

4.5 Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab.

The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-mediated adverse reactions [*Special Warnings and Precautions for Use (4.4)*].

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary
Based on its mechanism of action, pembrolizumab may cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PDL-1 signalling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with pembrolizumab and for at least 4 months following the last dose of pembrolizumab.

Animal Data
Animal reproduction studies have not been conducted with pembrolizumab to evaluate its effect on reproduction and fetal development, but an assessment of the effects on reproduction was provided. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering pembrolizumab during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signalling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice.

Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

Nursing Mothers
It is not known whether pembrolizumab is excreted in human milk. No studies have been conducted to assess the impact of pembrolizumab on milk production or its presence in breast milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with pembrolizumab.

Fertility

Fertility studies have not been conducted with pembrolizumab. In 1 month and 6 month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

4.7 Effects on ability to drive and use machines

Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab (see section 4.8).

4.8 Undesirable effects

The following adverse reactions are discussed in greater detail in 4.4.

- Immune-mediated pneumonitis
- Immune-mediated colitis
- Immune-mediated hepatitis
- Immune-mediated hypophysitis
- Renal failure and immune-mediated nephritis
- Immune-mediated hyperthyroidism and hypothyroidism
- Other immune-mediated adverse reactions
- Infusion-related reactions

Clinical Trials Experience
The data described in 4.4 Warnings and Precautions section reflect exposure to pembrolizumab in Trial P001, an uncontrolled, open-label, multiple cohort trial in which 411 patients with unresectable or metastatic melanoma received pembrolizumab at either 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks, in which the median duration of exposure to pembrolizumab was 6.2 months (range 1 day to 24.6 months) with a median of 10 doses (range 1 to 51). The study population characteristics were: median age of 61 years (range 18-94), 39% age 65 years or older, 60% male, 97% white, 73% with M1c disease, 8% with brain metastases, 35% with elevated LDH, 54% with prior exposure to ipilimumab, and 47% with two or more prior systemic therapies for advanced or metastatic disease.

Pembrolizumab was discontinued for adverse events (regardless of their relationship to treatment) in 9% of the 411 patients. Adverse events reported in at least two patients that led to discontinuation of pembrolizumab were: pneumonitis, renal failure, and pain.

Serious adverse events occurred in 36% of patients receiving pembrolizumab. The most frequent serious adverse events reported in 2% or more of patients were renal failure, dyspnoea, pneumonia, and cellulitis.

Table 1 presents adverse events identified from analyses of the 89 patients with unresectable or metastatic melanoma who received pembrolizumab 2 mg/kg every three weeks in one cohort of Trial 1. Of the 89 patients in this cohort, the median age was 59 years (range 18-88), 33% were age 65 years or older, 53% were male, 98% were white, 44% had an elevated LDH, 84% had Stage M1c disease, 8% had brain metastases, and 70% received two or more prior therapies for advanced or metastatic disease. The median duration of exposure to pembrolizumab was 6.2 months (range 1 day to 15.3 months) with a median of nine doses (range 1 to 23). Fifty-one percent of patients were exposed to pembrolizumab for greater than 6 months and 21% for greater than 1 year.

Pembrolizumab was discontinued for adverse events in 6% of the 89 patients. The most common adverse events (reported in at least 20% of patients) were fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhoea.

Table 1: Adverse Events in ≥10% of Patients with Unresectable or Metastatic Melanoma treated at 2 mg/kg every three weeks

Adverse Event	All Grades (%)	Grade 3* (%)
General Disorders and Administration Site Conditions		
Fatigue	47	7
Peripheral oedema	17	1
Chills	14	0
Pyrexia	11	0
Gastrointestinal Disorders		
Nausea	30	0
Constipation	21	0
Diarrhoea	20	0
Vomiting	16	0
Abdominal pain	12	0
Respiratory, Thoracic And Mediastinal Disorders		
Cough	30	1
Dyspnoea	18	2
Skin And Subcutaneous Tissue Disorders		
Pruritus	30	0
Rash	29	0
Vitiligo	11	0
Metabolism and Nutrition Disorders		
Decreased appetite	26	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	20	0
Pain in extremity	18	1
Myalgia	14	1
Back pain	12	1
Nervous System Disorders		
Headache	16	0
Dizziness	11	0
Blood and Lymphatic System Disorders		
Anaemia	14	5
Psychiatric Disorders		
Insomnia	14	0
Infections and Infestations		
Upper respiratory tract infection	11	1

* There were no Grade 5 adverse reactions reported. Of the ≥10% adverse reactions, none was reported as Grade 4. Other Grade 3-4 events reported in at least 2 patients were pneumonia (3%), dehydration (3%), hyponatraemia (2%), muscular weakness (2%), and tumour pain (2%).

Other clinically important adverse reactions observed in up to 10% of patients treated with pembrolizumab were:

Infections and infestations: sepsis

Table 2: Worsening of Laboratory Abnormalities from Baseline in ≥20% of Patients with Unresectable or Metastatic Melanoma treated at 2 mg/kg every three weeks

Laboratory Test	All Grades (%)	Grades 3-4 (%)
Chemistry		
Hyperglycaemia	40	2*
Hyponatraemia	35	9
Hypoalbuminaemia	34	0
Hypertriglyceridemia	25	0
Increased Aspartate Aminotransferase	24	2*
Hypocalcaemia	24	1
Haematology		
Anaemia	55	8*

* Grade 4 abnormalities in this table limited to hyperglycaemia, increased aspartate aminotransferase, and anaemia (one patient each)

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Because trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In this analysis, none of the 97 patients who were treated with 2 mg/kg every 3 weeks tested positive for treatment-emergent anti-pembrolizumab antibodies.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to pembrolizumab with the incidences of antibodies to other products may be misleading.

4.9 Overdose

There is no information on overdosage with pembrolizumab.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies ATC code: Not yet assigned.

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Mechanism of Action
Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour

growth.

Pharmacodynamic effects
In peripheral blood of patients with advanced melanoma who received pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every 2 weeks or 3 weeks, an increased percentage of activated (i.e., HLA-DR+) CD4+ and CD8+ T-cells was observed after treatment at all doses and schedules without an increase in the circulating T-lymphocyte number.

Clinical studies
The efficacy of pembrolizumab was investigated in a multicentre, open-label, randomized (1:1), dose-comparative, activity-estimating cohort of Trial P001. Key eligibility criteria were ECOG stage 0-1 and unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; a history of severe immune-mediated adverse reactions with ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; previous severe hypersensitivity to other monoclonal antibodies; a history of pneumonitis or interstitial lung disease; and any active infection requiring therapy, including HIV or hepatitis B or C. Patients were randomized to receive 2 mg/kg (n=89) or 10 mg/kg (n=84) of pembrolizumab every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumour status was performed every 12 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded independent central review and duration of response.

Among the 173 patients enrolled, the median age was 61 years (36% age 65 or older); 60% male; 97% White; and 66% and 34% with an ECOG performance status 0 and 1, respectively. Disease characteristics were BRAF V600 mutation (17%), elevated lactate dehydrogenase (39%), M1c (82%), brain metastases (9%), and two or more prior therapies for advanced or metastatic disease (73%).

The ORR was 24% (95% confidence interval: 15, 34) in the 2 mg/kg arm, consisting of 1 complete response and 20 partial responses. Among the 21 patients with an objective response, 3 (14%) had progression of disease 2.8, 2.9, and 8.2 months after initial response. The remaining 18 patients (86%) had ongoing responses with durations ranging from 1.4+ to 8.5+ months, which included 8 patients with ongoing responses of 6 months or longer. One additional patient developed two new asymptomatic lesions at the first tumour assessment concurrent with a 75% decrease in overall tumour burden; pembrolizumab was continued and this reduction in tumour burden was durable for 5+ months.

There were objective responses in patients with and without BRAF V600 mutation-positive melanoma. Similar ORR results were observed in the 10 mg/kg arm.

5.2 Pharmacokinetic properties

The pharmacokinetics of pembrolizumab was studied in 479 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population pharmacokinetic analysis, the mean [% coefficient of variation (CV%)] clearance (CL) is 0.22 L/day (28%) and the mean (CV%) elimination half-life (t1/2) is 26 days (24%). Steady-state concentrations of pembrolizumab should be reached by 18 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation should be 2.1-fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve at steady state (AUCss) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Specific Populations: The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The CL of pembrolizumab increased with increasing body weight; the resulting exposure differences were adequately addressed by the administration of a weight-based

dose. The following factors had no clinically important effect on the CL of pembrolizumab: age (range 18-94 years), gender, renal impairment, mild hepatic impairment, and tumour burden. The effect of race could not be assessed due to limited data available in non-White patients.

Renal Impairment: The effect of renal impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n=210), moderate (eGFR 30 to 59 mL/min/1.73m^2; n=43), or severe (eGFR 15 to 29 mL/min/1.73m^2; n=2) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73m^2; n=221) renal function. No clinically important differences in the CL of pembrolizumab were found between patients with renal impairment and patients with normal renal function *[see 4.2].*

Hepatic Impairment: The effect of hepatic impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (TB less than or equal to ULN and AST greater than ULN or TB between 1 and 1.5 times ULN and any AST; n=59) compared to patients with normal hepatic function (TB and AST less than or equal to ULN; n=410). No clinically important differences in the CL of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment *[see 4.2].*

5.3 Preclinical safety data

In animal models, inhibition of PD-1 signalling resulted in an increased incidence of infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
Sucrose
Polysorbate-80
Hydrochloric acid (for pH adjustment) and/or
Sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial: 1 year

The product does not contain preservative. The reconstituted and/or diluted product should be used immediately. If not used immediately, reconstituted and diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, reconstituted vials and/or IV bags may be stored under refrigeration at 2°C to 8 °C for up to 20 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

For storage conditions after reconstitution or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Pembrolizumab powder for solution for intravenous infusion is a sterile, non-pyrogenic lyophilized powder supplied in a single-use Type I glass vial containing 50 mg of pembrolizumab.

Pembrolizumab is provided in a 15 mL Type I glass vial with a grey bromobutyl stopper and an aluminium seal with an avocado coloured flip-off cap.

6.6 Special precautions for disposal and other handling

Preparation

- Aseptic technique must be strictly observed throughout the preparation procedure preferably in a biologic safety cabinet or hood since no anti-microbial preservative is present in the solutions.
- Equilibrate the vial of pembrolizumab to room temperature. Prior to reconstitution, the vial of lyophilized powder can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Aseptically add 2.3 mL of Sterile Water for Injection by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.
- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. Reconstituted pembrolizumab is a clear to slightly opalescent, colourless to slightly yellow solution. Discard reconstituted vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.
- Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection.
- Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Reconstituted and Diluted Solutions

- The product does not contain a preservative. The reconstituted and/or diluted product should be used immediately.
- If not used immediately, reconstituted and diluted solutions of pembrolizumab may be stored either:
    - at room temperature for no more than 4 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
    - or under refrigeration at 2°C to 8 °C for up to 20 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

- Do not freeze.

7 SCIENTIFIC OPINION HOLDER

Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire
EN11 9BU
UK

8 EAMS NUMBER

00025/0626

9 DATE OF SCIENTIFIC OPINION

9th March 2015

Additional information:

- Each prescribing oncologist will be provided with a **physician pack** containing all the relevant documents needed to manage patients receiving pembrolizumab under EAMS.
- As each patient signs the Informed Consent Form, they must be issued with a **Patient Alert Card**. This is credit-card sized and patients must be instructed to carry it with them at all times. It summarises the important side effects which they need to seek assistance for. In addition it alerts any other healthcare professional that may treat them, that the patient is receiving pembrolizumab through an early access scheme, with details of their own oncologist, specialist nurse, out of hours contact details and the Company's contact details.
- Prescribers will be provided with guidance on managing Adverse Events including immune-related adverse events and dose management.
- A dose calculator is provided.

Contact information:

pembrolizumabEAMS@merck.com

Telephone number for MSD Medical Information: 01992 467272