



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

Introduction

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

<http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm>

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) in this indication and is to be used in combination with another medicine prescribed off-label. The information is provided to assist the doctor in prescribing off-label medicines. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:

https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of the combination therapy in this new indication. As such this is a scientific opinion and should not be regarded as an indication licensed by the MHRA or a future commitment by the MHRA to license such indication.

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'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document

For further updates of the safety information, please refer to the product information of the combination products on the electronic Medicines Compendium (eMC) website:

<https://www.medicines.org.uk/emc>.

Information for the healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Avelumab 20 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 20 mg of avelumab.
One vial of 10 mL contains 200 mg of avelumab.

Avelumab is a human monoclonal IgG1 antibody directed against the immunomodulatory cell surface ligand protein PD-L1 and produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless to slightly yellow solution. The solution pH is in the range of 5.0 - 5.6 and the osmolality is between 270 and 330 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

Avelumab in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the treatment of cancer.

Posology

The recommended dose of avelumab in combination with axitinib is 800 mg administered intravenously over 60 minutes every 2 weeks and axitinib 5 mg orally taken twice daily (12 hours apart) with or without food until disease progression or unacceptable toxicity.

Administration of avelumab should continue according to the recommended schedule until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms, no change in performance status for greater than two weeks, and no need for salvage therapy, could continue treatment.

For information on the posology of axitinib, please refer to axitinib (Inlyta®) product information.

Premedication

Patients have to be premedicated with an antihistamine and with paracetamol prior to the first 4 infusions of avelumab. If the fourth infusion is completed without an infusion-related reaction, premedication for subsequent doses should be administered at the discretion of the physician.

Treatment modifications

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability; see Table 1.

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

Table 1: Guidelines for withholding or discontinuation of avelumab

Treatment-related adverse reaction	Severity*	Treatment modification
Infusion-related reactions	Grade 1 infusion-related reaction	Reduce infusion rate by 50%
	Grade 2 infusion-related reaction	Withhold until adverse reactions recover to Grade 0-1; restart infusion with a 50% slower rate
	Grade 3 or Grade 4 infusion-related reaction	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold until adverse reactions recover to Grade 0-1
	Grade 3 or Grade 4 pneumonitis or recurrent Grade 2 pneumonitis	Permanently discontinue
Hepatitis For details on axitinib dose modifications for hepatitis, see below	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	Withhold until adverse reactions recover to Grade 0-1
	AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN	Permanently discontinue
Colitis	Grade 2 or Grade 3 colitis or diarrhoea	Withhold until adverse reactions recover to Grade 0-1
	Grade 4 colitis or diarrhoea or recurrent Grade 3 colitis	Permanently discontinue
Pancreatitis	Suspected pancreatitis	Withhold
	Confirmed pancreatitis	Permanently discontinue
Myocarditis	Suspected myocarditis	Withhold
	Confirmed myocarditis	Permanently discontinue
Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, hyperglycaemia)	Grade 3 or Grade 4 endocrinopathies	Withhold until adverse reactions recover to Grade 0-1
Nephritis and renal dysfunction	Serum creatinine more than 1.5 and up to 6 times ULN	Withhold until adverse reactions recover to Grade 0-1
	Serum creatinine more than 6 times ULN	Permanently discontinue
Other immune-related adverse reactions (including myositis, hypopituitarism, uveitis, Guillain-Barré syndrome)	For any of the following: <ul style="list-style-type: none"> Grade 2 or Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above. 	Withhold until adverse reactions recover to Grade 0-1
	For any of the following: <ul style="list-style-type: none"> Life threatening or Grade 4 adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy) Recurrent Grade 3 immune-related adverse reaction Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks Persistent Grade 2 or Grade 3 immune-mediate adverse reactions lasting 12 weeks or longer 	Permanently discontinue

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.03)

Hepatitis: Treatment modifications for avelumab and axitinib

If ALT or AST ≥ 3 times ULN but < 5 times ULN or total bilirubin ≥ 1.5 times ULN but < 3 times ULN, both avelumab and axitinib should be withheld until these adverse reactions recover to Grades 0-1. If persistent (greater than 5 days), corticosteroid therapy (prednisone or equivalent) followed by a taper should be considered. Rechallenge with avelumab or axitinib or sequential rechallenge with both avelumab and axitinib after recovery should be considered. Dose reduction according to the axitinib product information should be considered if rechallenging with axitinib.

If ALT or AST ≥ 5 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN or total bilirubin ≥ 3 times ULN, both avelumab and axitinib should be permanently discontinued and corticosteroid therapy should be considered.

Dose modification advice for axitinib when used in combination with avelumab

When avelumab is administered in combination with axitinib, please refer to the axitinib product information for recommended dose modifications for axitinib.

Special populations

Elderly

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

Paediatric population

The safety and efficacy of avelumab in children and adolescents below 18 years of age have not been established.

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment (see section 5.2). There are insufficient data in patients with severe renal impairment for dosing recommendations.

Hepatic impairment

No dose adjustment is needed for patients with mild hepatic impairment (see section 5.2). There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations.

Method of administration

Avelumab is for intravenous infusion only. It must not be administered as an intravenous push or bolus injection.

Avelumab has to be diluted with either sodium chloride 9 mg/mL (0.9%) solution for injection or with sodium chloride 4.5 mg/mL (0.45%) solution for injection. It is administered over 60 minutes as an intravenous infusion using a sterile, non-pyrogenic, low protein binding 0.2 micrometre in line or add on filter.

For instructions on the preparation and administration of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
ECOG performance status > 1
Newly diagnosed brain metastases or symptomatic brain metastases requiring steroids
Use of investigational drug(s) or other experimental interventions within 30 days

4.4 Special warnings and precautions for use

Infusion-related reactions

Infusion-related reactions, which might be severe, have been reported in patients receiving avelumab (see section 4.8).

Patients should be monitored for signs and symptoms of infusion related reactions including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria.

For Grade 3 or Grade 4 infusion-related reactions, the infusion should be stopped and avelumab should be permanently discontinued (see section 4.2).

For Grade 1 infusion-related reactions, the infusion rate should be slowed by 50% for the current infusion. For patients with Grade 2 infusion-related reactions, the infusion should be temporarily discontinued until Grade 1 or resolved, then the infusion will restart with a 50% slower infusion rate (see section 4.2).

In case of recurrence of Grade 1 or Grade 2 infusion-related reaction, the patient may continue to receive avelumab under close monitoring, after appropriate infusion rate modification and premedication with paracetamol and antihistamine (see section 4.2).

In clinical trials, 98.6% (433/439) of patients with infusion-related reactions had a first infusion related reaction during the first 4 infusions of which 2.7% (12/439) were Grade \geq 3. In the remaining 1.4% (6/439) of patients, infusion-related reactions occurred after the first 4 infusions and all were of Grade 1 or Grade 2.

Immune-related adverse reactions

Most immune-related adverse reactions with avelumab were reversible and managed with temporary or permanent discontinuation of avelumab, administration of corticosteroids and/or supportive care.

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, avelumab should be withheld and corticosteroids administered. If corticosteroids are used to treat an adverse reaction, a taper of at least 1-month duration should be initiated upon improvement.

In patients, whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants may be considered.

Immune-related pneumonitis

Immune-related pneumonitis occurred in patients treated with avelumab. One fatal case has been reported in patients receiving avelumab (see section 4.8).

Patients should be monitored for signs and symptoms of immune-related pneumonitis and causes other than immune-related pneumonitis should be ruled out. Suspected pneumonitis should be confirmed with radiographic imaging.

Corticosteroids should be administered for Grade \geq 2 events (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper).

Avelumab should be withheld for Grade 2 immune related pneumonitis until resolution, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 immune related pneumonitis (see section 4.2).

Immune related hepatitis

Immune-related hepatitis occurred in patients treated with avelumab. Two fatal cases have been reported in patients receiving avelumab (see section 4.8).

Patients should be monitored for changes in liver function and symptoms of immune-related hepatitis and causes other than immune-related hepatitis should be ruled out.

Corticosteroids should be administered for Grade \geq 2 events (initial dose 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper).

Avelumab should be withheld for Grade 2 immune-related hepatitis until resolution and permanently discontinued for Grade 3 or Grade 4 immune-related hepatitis (see section 4.2).

Immune-related colitis

Immune-related colitis has been reported in patients receiving avelumab (see section 4.8).

Patients should be monitored for signs and symptoms of immune-related colitis and causes other than immune-related colitis should be ruled out. Corticosteroids should be administered for Grade \geq 2 events (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper).

Avelumab should be withheld for Grade 2 or Grade 3 immune-related colitis until resolution, and permanently discontinued for Grade 4 or recurrent Grade 3 immune-related colitis (see section 4.2).

Immune-related pancreatitis

Immune-related pancreatitis has been reported in patients receiving avelumab. Two fatal cases have been reported in patients receiving avelumab in combination with axitinib (see section 4.8).

Patients should be monitored for signs and symptoms of immune-related pancreatitis. In symptomatic patients, obtain gastroenterology consultation and laboratory investigations (including imaging) to ensure the initiation of appropriate measures at an early stage. Corticosteroids should be administered for immune-related pancreatitis (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper).

Avelumab should be withheld in the event of suspected immune-related pancreatitis. Avelumab should be permanently discontinued if immune-related pancreatitis is confirmed (see section 4.2).

Immune-related myocarditis

Immune-related myocarditis has been reported in patients receiving avelumab. Two fatal cases have been reported in patients receiving avelumab in combination with axitinib (see section 4.8).

A baseline electrocardiogram (ECG) is recommended. Patients should be monitored for signs and symptoms of possible immune-related myocarditis such as fatigue, chest pain, dyspnoea, palpitations, oedema or hypotension. In symptomatic patients, obtain cardiologic consultation and laboratory investigations to ensure the initiation of appropriate measures at an early stage. In addition to signs and symptoms, a diagnosis of immune-related myocarditis may include one or more of the following: new ECG abnormalities, increased troponin, cardiac imaging abnormalities or histopathology findings consistent with myocarditis. Corticosteroids should be administered for immune-related myocarditis (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper). If no improvement within 24 hours on corticosteroids, consider additional immunosuppression (e.g., mycophenolate, infliximab, anti-thymocyte globulin).

Avelumab should be withheld in the event of suspected immune-related myocarditis. Avelumab should be permanently discontinued if immune-related myocarditis is confirmed (see section 4.2).

Immune-related endocrinopathies

Immune-related thyroid disorders, immune-related adrenal insufficiency, and Type 1 diabetes mellitus have been reported in patients receiving avelumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of endocrinopathies. Avelumab should be withheld for Grade 3 or Grade 4 endocrinopathies until resolution (see section 4.2).

Thyroid disorders (hypothyroidism/hyperthyroidism)

Thyroid disorders can occur at any time during treatment (see section 4.8).

Patients should be monitored 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. Hypothyroidism should be managed with replacement therapy and hyperthyroidism with anti-thyroid medicinal product, as needed.

Avelumab should be withheld for Grade 3 or Grade 4 thyroid disorders (see section 4.2).

Adrenal insufficiency

Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment. Corticosteroids should be administered (1 to 2 mg/kg/day prednisone intravenously or oral equivalent) for Grade \geq 3 adrenal insufficiency followed by a taper until a dose of less than or equal to 10 mg/day has been reached.

Avelumab should be withheld for Grade 3 or Grade 4 symptomatic adrenal insufficiency (see section 4.2).

Type 1 diabetes mellitus

Avelumab can cause Type 1 diabetes mellitus, including diabetic ketoacidosis (see section 4.8).

Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Initiate treatment with insulin for Type 1 diabetes mellitus. Avelumab should be withheld and anti-hyperglycaemics in patients with Grade \geq 3 hyperglycaemia should be administered. Treatment with avelumab should be resumed when metabolic control is achieved on insulin replacement therapy.

Immune-related nephritis and renal dysfunction

Avelumab can cause immune-related nephritis (see section 4.8).

Patients should be monitored for elevated serum creatinine prior to and periodically during treatment. Corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) should be administered for Grade \geq 2 nephritis. Avelumab should be withheld for Grade 2 or Grade 3 nephritis until resolution to \leq Grade 1 and permanently discontinued for Grade 4 nephritis.

Other immune-related adverse reactions

Other clinically important immune-related adverse reactions were reported in less than 1% of patients: myositis, hypopituitarism, uveitis, and Guillain-Barré syndrome (see section 4.8).

For suspected immune-related adverse reactions, ensure adequate evaluation to confirm aetiology or to rule out other causes. Based on the severity of the adverse reaction, avelumab should be withheld and corticosteroids to be administered. Avelumab should be resumed when the immune-related adverse reaction returns to Grade 1 or less following corticosteroid taper. Avelumab should be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for Grade 4 immune-related adverse reaction (see section 4.2).

Hepatotoxicity

Hepatotoxicity occurred in patients treated with avelumab in combination with axitinib with higher frequencies of Grade 3 and Grade 4 ALT and AST elevation compared to avelumab alone (see section 4.8).

Patients should be more frequently monitored for changes in liver function and symptoms as compared to when avelumab is used as monotherapy.

Avelumab should be withheld for Grade 2 hepatotoxicity until resolution and permanently discontinued for Grade 3 or Grade 4 hepatotoxicity. Corticosteroids should be considered for Grade \geq 2 events (see section 4.2).

Patients excluded from clinical studies

Patients with the following conditions were excluded from clinical trials: active central nervous system (CNS) metastasis; active or a history of autoimmune disease; a history of other malignancies within the last 5 years; organ transplant; conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been conducted with avelumab.

Avelumab is primarily metabolised through catabolic pathways, therefore, it is not expected that avelumab will have pharmacokinetic drug-drug interactions with other medicinal products.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should be advised to avoid becoming pregnant while receiving avelumab and should use effective contraception during treatment with avelumab and for at least 1 month after the last dose of avelumab.

Pregnancy

There are no or limited data from the use of avelumab in pregnant women.

Animal reproduction studies have not been conducted with avelumab. However, in murine models of pregnancy, blockade of PD-L1 signalling has been shown to disrupt tolerance to the fetus and to result in an increased fetal loss (see section 5.3). These results indicate a potential risk, based on its mechanism of

action, that administration of avelumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.

Human IgG1 immunoglobulins are known to cross the placental barrier. Therefore, avelumab has the potential to be transmitted from the mother to the developing fetus. It is not recommended to use avelumab during pregnancy unless the clinical condition of the woman requires treatment with avelumab.

Breast-feeding

It is unknown whether avelumab is excreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded.

Breast-feeding women should be advised not to breast-feed during treatment and for at least 1 month after the last dose due to the potential for serious adverse reactions in breast-fed infants.

Fertility

The effect of avelumab on male and female fertility is unknown.

Although studies to evaluate the effect of avelumab on fertility have not been conducted, there were no notable effects in the female reproductive organs in monkeys based on 1-month and 3-month repeat-dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Avelumab has negligible influence on the ability to drive and use machines. Fatigue has been reported following administration of avelumab (see section 4.8). Patients should be advised to use caution when driving or operating machinery until they are certain that avelumab does not adversely affect them.

4.8 Undesirable effects

Avelumab is most frequently associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of avelumab (see "Description of selected adverse reactions" below).

Summary of the safety profile

The safety of avelumab in combination with axitinib has been evaluated in 489 patients with advanced RCC receiving 10 mg/kg avelumab every 2 weeks and axitinib 5 mg orally twice daily in two clinical studies.

In this patient population, the most common adverse reactions were diarrhoea (62.8%), hypertension (49.3%), fatigue (42.9%), nausea (33.5%), dysphonia (32.7%), decreased appetite (26.0%), hypothyroidism (25.2%), cough (23.7%), headache (21.3%), dyspnoea (20.9%), and arthralgia (20.9%).

Tabulated list of adverse reactions

Adverse reactions reported for 489 patients with advanced RCC treated in 2 clinical studies with avelumab in combination with axitinib are presented in Table 2. In these studies, avelumab was administered at 10 mg/kg every 2 weeks and axitinib 5 mg orally twice daily.

These reactions are presented by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in patients treated with avelumab in combination with axitinib in clinical studies B9991002 and B9991003

Frequency	Adverse reactions
Infections and infestations	
Uncommon	Rash pustular
Blood and lymphatic system disorders	
Common	Anaemia, thrombocytopenia
Uncommon	Lymphopenia, eosinophilia

Immune system disorders	
Common	Hypersensitivity
Endocrine disorders	
Very common	Hypothyroidism
Common	Hyperthyroidism, adrenal insufficiency, thyroiditis
Uncommon	Autoimmune thyroiditis, hypophysitis
Metabolism and nutrition disorders	
Very common	Decreased appetite
Common	Hyperglycaemia
Uncommon	Diabetes mellitus, Type 1 diabetes mellitus
Nervous system disorders	
Very common	Headache, dizziness
Common	Neuropathy peripheral
Cardiac disorders	
Uncommon	Myocarditis
Vascular disorders	
Very common	Hypertension
Common	Hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Very common	Dysphonia, cough, dyspnoea
Common	Pneumonitis
Gastrointestinal disorders	
Very common	Diarrhoea, nausea, constipation, vomiting, abdominal pain
Common	Dry mouth, colitis
Uncommon	Autoimmune colitis, autoimmune pancreatitis, enterocolitis, ileus, pancreatitis necrotizing
Hepatobiliary disorders	
Common	Hepatic function abnormal
Uncommon	Hepatitis, hepatotoxicity, immune-mediated hepatitis, liver disorder
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Rash pruritic, rash maculo-papular, pruritus generalized, dermatitis acneiform, erythema, rash macular, rash papular, rash erythematous, dermatitis, eczema, rash generalized
Uncommon	Drug eruption, erythema multiforme, psoriasis
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, back pain, myalgia
Renal and urinary disorders	
Common	Acute kidney injury
General disorders and administrative site conditions	
Very common	Fatigue, chills, asthenia, pyrexia
Common	Oedema peripheral, influenza like illness
Investigations	
Very common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased
Common	Blood creatinine increased, amylase increased, lipase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood thyroid stimulating hormone decreased, transaminases increased
Uncommon	Liver function test increased
Injury, poisoning and procedural complications	
Very common	Infusion related reaction

The following additional adverse reactions were reported in clinical trials of avelumab monotherapy: anaphylactic reaction (uncommon), Guillain-Barré Syndrome (uncommon), uveitis (uncommon), myositis (uncommon), tubulo-interstitial nephritis (uncommon), systemic inflammatory response syndrome (uncommon).

Description of selected adverse reactions

Data for the immune-related adverse reactions for avelumab as a monotherapy are based on 1,650 patients in the phase I study EMR100070-001 in other solid tumours and 88 patients in study EMR100070-003 and for avelumab in combination with axitinib are based on 489 patients in study B9991002 and B9991003 (see section 5.1).

The management guidelines for these adverse reactions are described in section 4.4.

Immune-related pneumonitis

In patients treated with avelumab as monotherapy, 1.2% (21/1,738) of patients developed immune-related pneumonitis. Of these patients there was 1 (0.1%) patient with a fatal outcome, 1 (0.1%) patient with Grade 4, and 5 (0.3%) patients with Grade 3 immune-related pneumonitis.

The median time to onset of immune-related pneumonitis was 2.5 months (range: 3 days to 11 months). The median duration was 7 weeks (range: 4 days to more than 4 months).

Avelumab was discontinued in 0.3% (6/1,738) of patients due to immune-related pneumonitis. All 21 patients with immune-related pneumonitis were treated with corticosteroids and 17 (81%) of the 21 patients were treated with high-dose corticosteroids for a median of 8 days (range: 1 day to 2.3 months). Immune-related pneumonitis resolved in 12 (57%) of the 21 patients at the time of data cut off.

In patients treated with avelumab in combination with axitinib, 0.6% (3/489) of patients developed immune-related pneumonitis. Of these patients, none experienced immune-related pneumonitis Grade \geq 3.

The median time to onset of immune-related pneumonitis was 3.7 months (range: 2.7 months to 8.6 months). The median duration was 2.6 months (range: 3.3 weeks to more than 7.9 months). Immune-related pneumonitis did not lead to discontinuation of avelumab in any patient. All 3 patients with immune-related pneumonitis were treated with high-dose corticosteroids for a median of 3.3 months (range: 3 weeks to 22.3 months). Immune-related pneumonitis resolved in 2 (66.7%) of the 3 patients at the time of data cut-off.

Immune-related hepatitis

In patients treated with avelumab as monotherapy, 0.9% (16/1,738) of patients developed immune-related hepatitis. Of these patients, there were 2 (0.1%) patients with a fatal outcome, and 11 (0.6%) patients with Grade 3 immune-related hepatitis.

The median time to onset of immune-related hepatitis was 3.2 months (range: 1 week to 15 months). The median duration was 2.5 months (range: 1 day to more than 7.4 months).

Avelumab was discontinued in 0.5% (9/1,738) of patients due to immune-related hepatitis. All 16 patients with immune-related hepatitis treated with corticosteroids and 15 (94%) of the 16 patients received high-dose corticosteroids for a median of 14 days (range: 1 day to 2.5 months). Immune-related hepatitis resolved in 9 (56%) of the 16 patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, 6.3% (31/489) of patients developed immune-related hepatitis. Of these patients, there were 18 (3.7%) patients with Grade 3 and 3 (0.6%) patients with Grade 4 immune-related hepatitis.

The median time to onset of immune-related hepatitis was 2.3 months (range: 2.1 weeks to 14.5 months). The median duration was 2.1 weeks (range: 2 days to 8.9 months).

Avelumab was discontinued in 4.7% (23/489) of patients due to immune-related hepatitis. All 31 patients with immune-related hepatitis were treated for hepatitis including 30 (96.8%) patients treated with corticosteroids and 1 patient with a non-steroidal immunosuppressant. Twenty-eight (90.3%) of the 31 patients received high-dose corticosteroids for a median of 2.4 weeks (range: 1 day to 10.2 months). Immune-related hepatitis resolved in 27 (87.1%) of the 31 patients at the time of data cut-off.

Immune-related colitis

In patients treated with avelumab as monotherapy, 1.5% (26/1,738) of patients developed immune-related colitis. Of these patients, there were 7 (0.4%) patients with Grade 3 immune-related colitis.

The median time to onset of immune-related colitis was 2.1 months (range: 2 days to 11 months). The median duration was 6 weeks (range: 1 day to more than 14 months).

Avelumab was discontinued in 0.5% (9/1,738) of patients due to immune-related colitis. All 26 patients with immune-related colitis were treated with corticosteroids and 15 (58%) of the 26 patients received high-dose corticosteroids for a median of 19 days (range: 1 day to 2.3 months). Immune-related colitis resolved in 18 (70%) of 26 patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, 2.7% (13/489) of patients developed immune-related colitis. Of these patients, there were 9 (1.8%) patients with Grade 3 immune-related colitis.

The median time to onset of immune-related colitis was 5.1 months (range: 2.3 weeks to 14 months). The median duration was 1.6 weeks (range: 1 day to more than 9 months).

Avelumab was discontinued in 0.4% (2/489) of patients due to immune-related colitis. All 13 patients with immune-related colitis were treated with corticosteroids and 12 (92.3%) of the 13 patients received high-dose corticosteroids for a median of 2.3 weeks (range: 5 days to 4.6 months). Immune-related colitis resolved in 10 (76.9%) of 13 patients at the time of data cut-off.

Immune-related pancreatitis

No cases of immune-related pancreatitis were reported among 1,738 patients treated with avelumab as monotherapy across clinical trials in multiple tumour types.

In patients treated with avelumab in combination with axitinib, 0.4% (2/489) of patients developed immune-related pancreatitis. Of these patients, there was 1 (0.2%) patients with a fatal outcome and 1 (0.2%) patient with Grade 4 immune-related pancreatitis.

The median time to onset of immune-related pancreatitis was 3.2 months (range: 2.5 to 3.9 months). The median duration was 2.1 months (range: more than 1.3 to 2.1 months).

Avelumab was discontinued in 0.4% (2/489) of patients due to immune-related pancreatitis. All patients with immune-related pancreatitis were treated with high-dose corticosteroids for a median of 1.2 months (range: 1.3 weeks to 2.1 months). Immune-related pancreatitis resolved in 1 (0.2%) of 2 patients at the time of data cut-off.

After the data cut-off, 1 additional patient developed immune-related pancreatitis with fatal outcome.

Immune-related myocarditis

No cases of immune-related myocarditis were reported among 1,738 patients treated with avelumab as monotherapy across clinical trials in multiple tumour types.

In patients treated with avelumab in combination with axitinib, 0.6% (3/489) of patients developed immune-related myocarditis. Of these patients, there were 2 (0.4%) patients with a fatal outcome and 1 (0.2%) patient with Grade 3 immune-related myocarditis.

The median time to onset of immune-related myocarditis was 4.1 weeks (range: 3.9 to 4.1 weeks). The median duration was not estimable (range: more than 1 day to more than 5.6 months).

Avelumab was discontinued in 0.6% (3/489) of patients due to immune-related myocarditis. Two of the 3 patients with immune-related myocarditis were treated with high-dose corticosteroids for a median of 9.8 months (range: 1.9 weeks to 19.2 months). One patient did not receive any corticosteroids due to the fulminant course of the adverse reaction. The Grade 3 event of immune-related myocarditis was not resolved at the time of data cut-off.

Immune-related endocrinopathies

Thyroid disorders

In patients treated with avelumab as monotherapy, 6% (98/1,738) of patients developed immune-related thyroid disorders, including 90 (5%) patients with hypothyroidism, 7 (0.4%) with hyperthyroidism, and 4

(0.2%) with thyroiditis. Of these patients, there were 3 (0.2%) patients with Grade 3 immune-related thyroid disorders.

The median time to onset of thyroid disorders was 2.8 months (range: 2 weeks to 13 months). The median duration was not estimable (range: 1 day to more than 26 months).

Avelumab was discontinued in 0.1% (2/1,738) of patients due to immune-related thyroid disorders. Thyroid disorders resolved in 7 (7%) of the 98 patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, 24.7% (121/489) of patients developed immune-related thyroid disorders, including 111 (22.7%) patients with hypothyroidism, 17 (3.5%) with hyperthyroidism, and 7 (1.4%) with thyroiditis. Of these patients, there were 2 (0.4%) patients with Grade 3 immune-related thyroid disorders.

The median time to onset of thyroid disorders was 2.8 months (range: 3.6 weeks to 19.3 months). The median duration was not estimable (range: 8 days to more than 23.9 months).

Avelumab was discontinued in 0.2% (1/489) of patients due to immune-related thyroid disorders. Thyroid disorders resolved in 15 (12.4%) of the 121 patients at the time of data cut-off.

Adrenal insufficiency

In patients treated with avelumab as monotherapy, 0.5% (8/1,738) of patients developed immune-related adrenal insufficiency. Of these patients, there was 1 (0.1%) patient with Grade 3 immune-related adrenal insufficiency.

The median time to onset of immune-related adrenal insufficiency was 2.5 months (range: 1 day to 8 months). The median duration was not estimable (range: 2 days to more than 6 months).

Avelumab was discontinued in 0.1% (2/1,738) of patients due to immune-related adrenal insufficiency. All 8 patients with immune-related adrenal insufficiency were treated with corticosteroids, 4 (50%) of the 8 patients received high-dose systemic corticosteroids (≥ 40 mg prednisone or equivalent) followed by a taper for a median of 1 day (range: 1 day to 24 days). Adrenal insufficiency resolved in 1 patient with corticoid treatment at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, 1.8% (9/489) of patients developed immune-related adrenal insufficiency. Of these patients, there were 2 (0.4%) patients with Grade 3 immune-related adrenal insufficiency.

The median time to onset of immune-related adrenal insufficiency was 5.5 months (range: 3.6 weeks to 8.7 months). The median duration was 2.8 months (range: 3 days to more than 15.5 months).

Immune-related adrenal insufficiency did not lead to discontinuation of avelumab in any patient. Eight (88.9%) patients with immune-related adrenal insufficiency were treated with corticosteroids and 2 (25%) of the 8 patients received high-dose corticosteroids (≥ 40 mg prednisone or equivalent) for a median of 8 days (range: 5 days to 11 days). Adrenal insufficiency resolved in 4 (44.4%) of the 9 patients at the time of data cut-off.

Type 1 diabetes mellitus

In patients treated with avelumab as monotherapy, Type 1 diabetes mellitus without an alternative aetiology occurred in 0.1% (2/1,738) of patients including two Grade 3 reactions that led to permanent discontinuation of avelumab.

In patients treated with avelumab in combination with axitinib, Type 1 diabetes mellitus without an alternative aetiology occurred in 1.0% (5/489) of patients. Of these patients, there was 1 (0.2%) patient with Grade 3 Type 1 diabetes mellitus.

The median time to onset of Type 1 diabetes mellitus was 1.9 months (range: 1.1 months to 7.3 months).

Avelumab was discontinued in 0.2% (1/489) of patients due to Type 1 diabetes mellitus. All 5 patients with Type 1 diabetes mellitus were treated with insulin. Type 1 diabetes mellitus did not resolve in any of the patients at the time of data cut-off.

Immune-related nephritis and renal dysfunction

In patients treated with avelumab as monotherapy, immune-related nephritis occurred in 0.1% (1/1,738) of patients receiving avelumab leading to permanent discontinuation of avelumab.

In patients treated with avelumab in combination with axitinib, immune-related nephritis occurred in 0.4% (2/489) of patients. Both patients had Grade 3 immune-related nephritis.

The median time to onset of immune-related nephritis was 1.2 months (range: 2.9 weeks to 1.8 months). The median duration was 1.3 weeks (range: more than 4 days to 1.3 weeks).

Immune-related nephritis did not lead to discontinuation of avelumab in any patient. Both patients with immune-related nephritis were treated with high-dose corticosteroids for a median of 1.1 weeks (range: 3 days to 1.9 weeks). Immune-related nephritis resolved in 1 (50%) of the 2 patients at the time of data cut-off.

Hepatotoxicity (in combination with axitinib)

In patients treated with avelumab in combination with axitinib, Grades 3 and Grade 4 increased ALT and increased AST were reported in 9% and 7% of patients.

In patients with ALT \geq 3 times ULN (Grades 2-4, n=82), ALT resolved to Grades 0-1 in 92%.

Among the 73 patients who were rechallenged with either avelumab (59%) or axitinib (85%) monotherapy or with both (55%), 66% had no recurrence of ALT \geq 3 times ULN.

Hypertension (in combination with axitinib)

In patients treated with avelumab in combination with axitinib, Grade 3 hypertension was reported in 26% (127/489) of patients. Additional antihypertensive medications were required in 81.1% (103/127) of patients with Grade 3 hypertension. Hypertension was uncontrolled in 20.5% (26/127) of patients with Grade 3 hypertension at the time of data cut-off. Patients should be monitored for hypertension and appropriate antihypertensive medications prescribed to achieve adequate blood pressure control. In case hypertension persists despite the use of antihypertensive medications, an axitinib dose reduction should be considered according to the axitinib product information.

Immunogenicity

Of 1,738 patients treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks, 1,627 were evaluable for treatment-emergent anti-drug antibodies (ADA) and 96 (5.9%) tested positive. In ADA positive patients, there may be an increased risk for infusion-related reactions (about 40% and 25% in ADA ever-positive and ADA never-positive patients, respectively). Based on data available, including the low incidence of immunogenicity, the impact of ADA on pharmacokinetics, efficacy and safety is uncertain, while the impact of neutralizing antibodies (nAb) is unknown.

Of the 480 patients with at least one valid ADA result at any time point treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily, 453 were evaluable for treatment-emergent ADA and 66 (14.6%) tested positive. A new ADA method with improved sensitivity and drug tolerance was used in the RCC population. Overall, there was no evidence of altered pharmacokinetic profile, increased incidence of infusion reactions or effects on efficacy with anti-avelumab antibody development.

Reporting of suspected adverse reactions

All observed or volunteered adverse reactions regardless of causal relationship with the EAMS products must be reported as described in Section 11 of the EAMS Treatment Protocol. Adverse events (serious and non-serious) are reported to Merck from the time the patient has taken the first dose of EAMS product administered, until withdrawal or the end of EAMS. Adverse events occurring after the active reporting period has ended should be reported to the Merck if the responsible physician becomes aware of them and believes they have at least a reasonable possibility of being related to EAMS. Adverse events (serious and non-serious) should be reported to Merck on an EAMS adverse event report form.

The contact details for reporting adverse events are:

Email: ICSR_UKI@merckgroup.com

Telephone: 0208 818 7373

4.9 Overdose

Three patients were reported to be overdosed with 5% to 10% above the recommended dose of avelumab. The patients had no symptoms, did not require any treatment for the overdose, and continued on avelumab therapy.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions. The treatment is directed to the management of symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, monoclonal antibodies, ATC code: L01XC31.

Mechanism of action

Avelumab is a human immunoglobulin G1 (IgG1) monoclonal antibody directed against programmed death ligand 1 (PD-L1). Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the programmed death 1 (PD-1) and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic CD8⁺ T cells, resulting in the restoration of anti-tumour T cell responses.

Avelumab has also shown to induce natural killer (NK) cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC).

Clinical efficacy and safety

Renal cell carcinoma (study B9991003)

The efficacy and safety of avelumab in combination with axitinib was evaluated in study B9991003, a randomized, multicentre, open-label study of avelumab in combination with axitinib in 886 patients with untreated advanced or metastatic RCC.

Patients were included irrespective of prognostic risk groups or tumour PD-L1 expression and had to have at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 that was not been previously irradiated. Patients were required to have a clear cell component. PD-L1 status was determined by immunohistochemistry.

Patients with prior systemic therapy directed at advanced or metastatic RCC; prior systemic immunotherapy treatment with IL-2, IFN- α , anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies, or active brain metastasis were excluded.

Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0 vs. 1) and region (United States vs. Canada/Western Europe vs. the rest of the world). Patients were randomized (1:1) to one of the following treatment arms:

- Avelumab 10 mg/kg intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily orally (N=442). Patients who tolerated axitinib 5 mg twice daily without Grade 2 or greater axitinib-related adverse events for 2 consecutive weeks could increase to 7 mg and then subsequently to 10 mg twice daily. Axitinib could be interrupted or reduced to 3 mg twice daily and subsequently to 2 mg twice daily to manage toxicity.
- Sunitinib 50 mg once daily orally for 4 weeks followed by 2 weeks off (N=444) until radiographic or clinical progression or unacceptable toxicity.

Treatment with avelumab and axitinib continued until RECIST v1.1-defined progression of disease by Blinded Independent Central Review (BICR) assessment or unacceptable toxicity. Administration of avelumab and axitinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at baseline, after randomisation at 6 weeks, then every 6 weeks thereafter up to 18 months after randomisation, and every 12 weeks thereafter until documented confirmed disease progression by BICR.

The primary efficacy endpoints were progression-free survival (PFS), as assessed by BICR using RECIST v1.1 and overall survival (OS) in patients with PD-L1-positive tumours (PD-L1 expression level $\geq 1\%$). The key secondary endpoints were PFS based on BICR assessment per RECIST v1.1 and OS irrespective of PD-L1 expression. Additional secondary endpoints included objective response (OR), time to response (TTR) and duration of response (DOR).

The study population characteristics were: median age of 61 years (range: 27.0 to 88.0), 38% of patients were 65 years or older, 75% were male, 75% were White, and the ECOG performance score was 0 (63%) or 1 (37%).

Patient distribution by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups was 21% favourable, 62% intermediate, and 16% poor. Patient distribution by Memorial Sloan-Kettering Cancer Center (MSKCC) risk groups was 22% favourable, 65% intermediate, and 11% poor.

The study included 270 (61%) and 290 (65%) patients with PD-L1-positive tumours randomized to avelumab in combination with axitinib and sunitinib, respectively. Median PFS was 13.8 months (95% CI: 11.1, NE) and 7.2 months (95% CI: 5.7, 9.7) for patients with PD-L1-positive tumours randomized to avelumab in combination with axitinib and sunitinib, respectively. Since PFS was statistically significant in patients with PD-L1-positive tumours (HR: 0.61 [95% CI: 0.48, 0.79], 2-sided p-value = 0.0001), it was then tested in all patients irrespective of PD-L1 expression and a statistically significant improvement in PFS in all patients was also demonstrated.

Efficacy results for all patients irrespective of PD-L1 expression (full analysis set) are presented in Table 3 and Figure 1. At the time of the first interim analysis, the OS data were still immature. The observed HR was 0.78 (95% CI: 0.554, 1.084).

Table 3: Efficacy results from study B9991003 – patients irrespective of PD-L1 expression

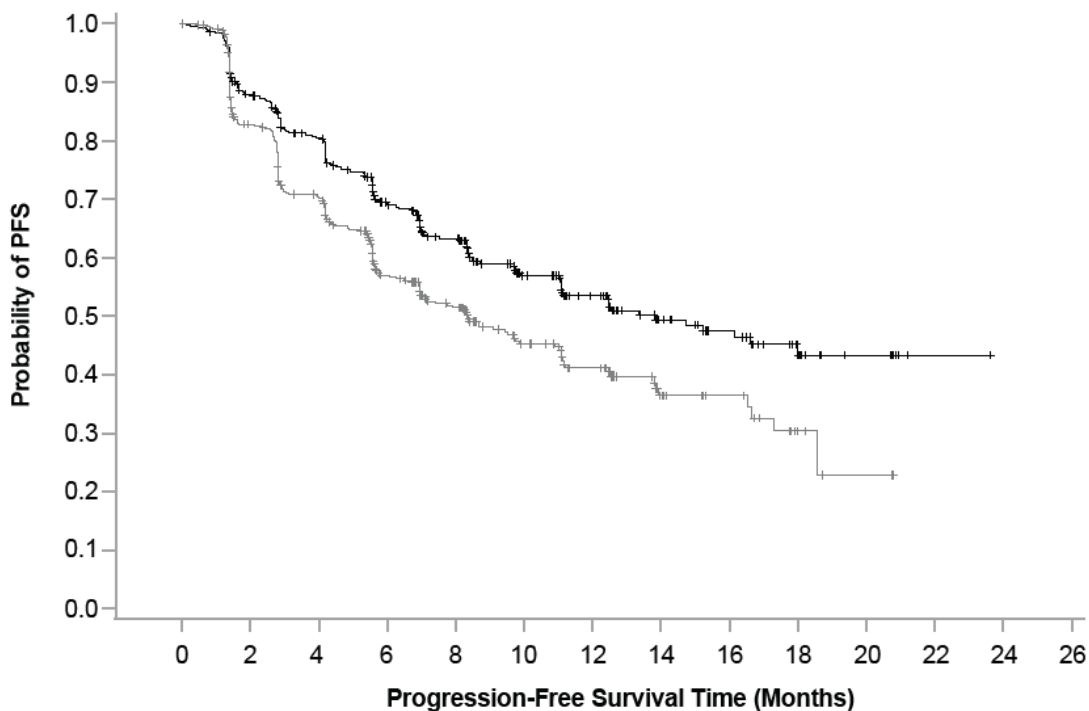
Efficacy endpoints (Based on BICR assessment)	Avelumab plus axitinib (N=442)	Sunitinib (N=444)
Progression-free survival (PFS)		
Events (%)	180 (41)	216 (49)
Median in months (95% CI)	13.8 (11.1, NE)	8.4 (6.9, 11.1)
Hazard ratio (95% CI)	0.69 (0.56, 0.84)	
p-value*	0.0002	
12-month PFS rate by K-M, (95% CI)**	53.5% (47.8, 58.8)	41.2% (35.4, 46.8)
18-month PFS rate by K-M, (95% CI)**	45.2% (0.38, 0.52)	30.4% (0.22, 0.39)
Confirmed objective response rate (ORR)		
Objective response rate (ORR) n (%)	227 (51.4)	114 (25.7)
(95% CI)	46.6, 56.1	21.7, 30.0
Complete response (CR) n (%)	15 (3.4)	8 (1.8)
Partial response (PR) n (%)	212 (48.0)	106 (23.9)
Time to response (TTR)		
Median, months (range)	2.6 (1.2, 13.8)	3.2 (1.2, 11.6)
Duration of response (DOR)		
Median, months (95% CI)	NE (NE, NE)	NE (11.2, NE)

BICR: Blinded Independent Central Review; CI: Confidence interval; NE: Not estimable.

* 2-sided p-value based on stratified log-rank.

** Cis are derived using the log-log transformation with back transformation to untransformed scale.

Figure 1: Kaplan-Meier estimates for progression-free survival based on BICR assessment in patients irrespective of PD-L1 expression



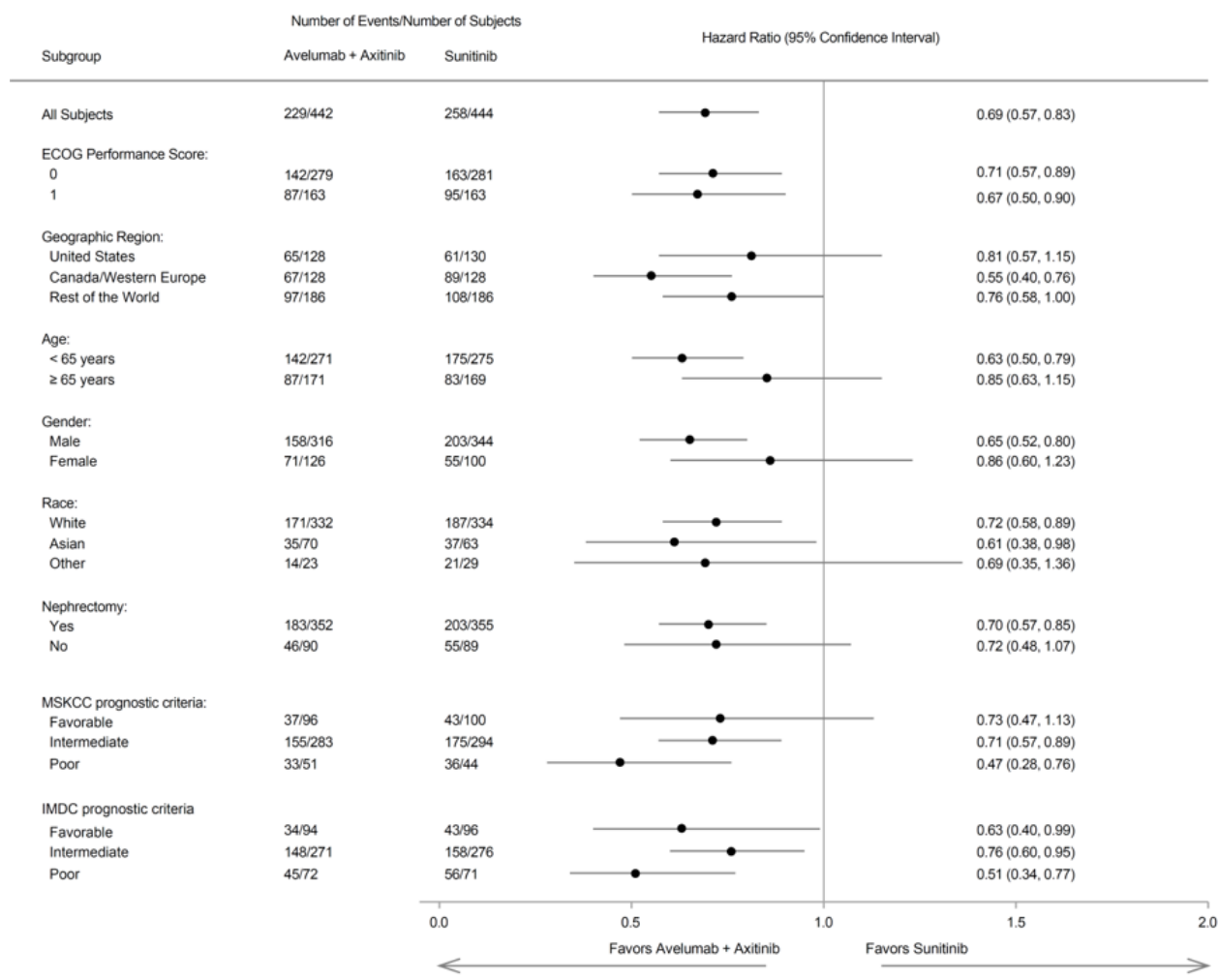
No. at risk

Avelumab + Axitinib:	442	364	321	250	193	127	94	57	42	24	8	1	0
Sunitinib:	444	329	271	192	144	90	64	29	20	8	2	0	0

—+—+ Avelumab + Axitinib: (N=442, Events=180, Median=13.8 months, 95% CI (11.1, NE))
 - - - - Sunitinib: (N=444, Events=216, Median=8.4 months, 95% CI (6.9, 11.1))

Improvement of PFS was observed across all pre-specified subgroups including risk groups based on IMDC and MSKCC criteria (Figure 2).

Figure 2: Forest plot of progression-free survival based on BICR assessment in patients irrespective of PD-L1 expression



5.2 Pharmacokinetic properties

Avelumab pharmacokinetics (PK) was assessed using a population PK approach for avelumab as monotherapy and avelumab in combination with axitinib.

Based on a population PK analysis for avelumab as monotherapy and in combination with axitinib, there are no expected clinically meaningful differences in exposure of avelumab between settings administered every 2 weeks at 800 mg or 10 mg/kg.

Distribution

Avelumab is expected to be distributed in the systemic circulation and to a lesser extent in the extracellular space. The volume of distribution at steady state was 4.72 L.

Consistent with a limited extravascular distribution, the volume of distribution of avelumab at steady state is small. As expected for an antibody, avelumab does not bind to plasma proteins in a specific manner.

Elimination

Based on a population pharmacokinetic analysis from 1,629 patients, the value of total systemic clearance (CL) is 0.59 L/day. In the supplemental analysis, avelumab CL was found to decrease over time: the largest mean maximal reduction (% coefficient of variation [CV%]) from baseline value with different tumour types was approximately 32.1% (CV 36.2%).

Steady-state concentrations of avelumab were reached after approximately 4 to 6 weeks (2 to 3 cycles) of repeated dosing at 10 mg/kg every 2-weeks, and systemic accumulation was approximately 1.25-fold.

The elimination half-life ($t_{1/2}$) at the recommended dose is 6.1 days based on the population PK analysis.

Linearity/non-linearity

The exposure of avelumab increased dose-proportionally in the dose range of 10 mg/kg to 20 mg/kg every 2 weeks.

When avelumab 10 mg/kg was administered in combination with axitinib 5 mg, the respective exposures of avelumab and axitinib were unchanged compared to the single agents. There was no evidence to suggest a clinically relevant change of avelumab clearance over time in patients with advanced RCC.

Special populations

A population pharmacokinetic analysis suggested no difference in the total systemic clearance of avelumab based on age, gender, race, PD-L1 status, tumour burden, renal impairment and mild or moderate hepatic impairment.

Total systemic clearance increases with body weight. Steady-state exposure was approximately uniform over a wide range of body weights (30 to 204 kg) for body weight normalised dosing.

Renal impairment

No clinically important differences in the clearance of avelumab were found between patients with mild (glomerular filtration rate (GFR) 60 to 89 mL/min, Cockcroft-Gault Creatinine Clearance (CrCL); n=623), moderate (GFR 30 to 59 mL/min, n=320) and patients with normal (GFR \geq 90 mL/min, n=671) renal function.

Avelumab has not been studied in patients with severe renal impairment (GFR 15 to 29 mL/min).

Hepatic impairment

No clinically important differences in the clearance of avelumab were found between patients with mild hepatic impairment (bilirubin \leq ULN and AST $>$ ULN or bilirubin between 1 and 1.5 times ULN, n=217) and normal hepatic function (bilirubin and AST \leq ULN, n=1,388) in a population PK analysis. Hepatic impairment was defined by National Cancer Institute (NCI) criteria of hepatic dysfunction.

Avelumab has not been studied in patients with moderate hepatic impairment (bilirubin between 1.5 and 3 times ULN) or severe hepatic impairment (bilirubin $>$ 3 times ULN).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity in Cynomolgus monkeys administered intravenously doses of 20, 60 or 140 mg/kg once a week for 1 month and 3 months, followed by a 2-month recovery period after the 3-month dosing period. Perivascular mononuclear cell cuffing was observed in the brain and spinal cord of monkeys treated with avelumab at \geq 20 mg/kg for 3 months. Although there was no clear dose-response relationship, it cannot be excluded that this finding was related to avelumab treatment.

Animal reproduction studies have not been conducted with avelumab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the fetus throughout pregnancy. 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. These results indicate a potential risk that administration of avelumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.

No studies have been conducted to assess the potential of avelumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with avelumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the female reproductive organs. Many of the male monkeys used in these studies were sexually immature and thus no explicit conclusions regarding effects on male reproductive organs can be made.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Glacial acetic acid
Polysorbate 20
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

2 years

After opening

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

After preparation of infusion

Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at 20°C to 25°C and room light. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the diluted solution should be infused immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

10 mL of concentrate in a vial (Type I glass) with a halobutyl rubber stopper and an aluminium seal fitted with a removable plastic cap.
Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Avelumab is compatible with polyethylene, polypropylene, and ethylene vinyl acetate infusion bags, glass bottles, polyvinyl chloride infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 micrometre.

Handling instructions

An aseptic technique for the preparation of the solution for infusion should be used.

- The vial should be visually inspected for particulate matter and discoloration. Avelumab is a clear, colourless to slightly yellow solution. If the solution is cloudy, discoloured, or contains particulate matters, the vial should be discarded.
- An infusion bag of appropriate size (preferably 250 mL) containing either sodium chloride 9 mg/mL (0.9%) solution for injection or with sodium chloride 4.5 mg/mL (0.45%) solution for injection should be used. The required volume of avelumab should be withdrawn from the vial(s) and transferred to the infusion bag. Any partially used or empty vials have to be discarded.

- The diluted solution should be mixed by gently inverting the bag in order to avoid foaming or excessive shearing of the solution.
- The solution should be inspected to ensure it is clear, colourless, and free of visible particles. The diluted solution should be used immediately once prepared.
- Do not co-administer other medicinal products through the same intravenous line. Administer the solution for infusion using a sterile, non-pyrogenic, low-protein binding 0.2 micrometre in-line or add-on filter as described in section 4.2.

After administration of avelumab, the line should be flushed with either sodium chloride 9 mg/mL (0.9%) solution for injection or with sodium chloride 4.5 mg/mL (0.45%) solution for injection.

Do not freeze or shake the diluted solution. If refrigerated, allow the diluted solution in the intravenous bags to come to room temperature prior to use.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Merck Serono Limited
Bedfont Cross
Stanwell Road
Feltham
Middlesex
TW14 8NX

8. EAMS NUMBER

11648/0002

9. DATE OF SCIENTIFIC OPINION

12 July 2019

Additional information

EAMS registration

To register a patient with the EAMS, healthcare professionals (HCPs) will need to register on the Inceptua portal: <https://portal.inceptua.com/#/login>

Once registered they will be able to complete a Patient Access Form, drug supply information and agreement on their responsibilities within the EAMS.

Further information and documentation are available within the Inceptua EAMS portal.

Merck/Pfizer will be able to arrange the required training on adverse event reporting and risk minimisation for immune related toxicities. To gain access to this training please contact either EAMS-RCC@merckgroup.com or EAMS-RCC@pfizer.com

Documents for patients

HCPs will be provided with the following documents to give to patients to help minimise the risk of immune-related adverse reactions:

- Treatment protocol – Information for patients
- Information for Patients Brochure
- Patient Alert card, a wallet-size card for the patient to carry

The **Information for Patients Brochure** is designed to highlight the key immune related adverse events and their symptoms.

Patients should be advised to always carry the **Patient Alert Card**, with them and show it at all medical visits to other healthcare professionals.

- Please direct the patient to complete all relevant sections of the card, including contact information for the prescriber, patient, and any caregiver who plays a role in helping the patient. This card can be especially helpful in visits to emergency healthcare facilities, where the patient may be unknown.
- Please take a moment to ensure patients understand how to use the Alert Card. Show that it contains summary information about treatment and how to appropriately manage adverse reactions. Emphasise to patients the importance of completing the card and carrying it at while on treatment.
- Most importantly, patients should be reminded that if they do experience an adverse reaction, they should seek medical attention immediately and undergo prompt treatment.

Contact information

Contact details for reporting adverse events

Email: ICSR_UKI@merckgroup.com

Telephone: 0208 818 7373

Contact details for Medical Information

Email: medinfo.uk@merckgroup.com