Final Professional Information

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

Bavencio 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.

Contains sugar (sweetener) D-Mannitol 51 mg/ml

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 285 and 350 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).

Bavencio is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy.

Bavencio 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

Avelumab Monotherapy:

The recommended dose of Bavencio as monotherapy is 800 mg administered intravenously over 60 minutes every 2 weeks.

Administration of Bavencio should continue according to the recommended schedule until disease progression or unacceptable toxicity.

Avelumab in combination with axitinib:

The recommended dose of Bavencio 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.

For information on the posology of axitinib, please refer to the axitinib product information.

Premedication

Patients have to be premedicated with an antihistamine and with paracetamol prior to the first 4 infusions of Bavencio.

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 Bavencio

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 Bavencio in combination with axitinib, 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

Treatment-related adverse reaction	**Severity***	**Treatment modification**
	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
Skin reactions	Grade 3 rash	Withhold until adverse reactions recover to Grade 0-1
	Grade 4 or recurrent Grade 3 rash or confirmed Stevens–Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN)	Permanently discontinue
Other immune-related adverse reactions (including myositis, hypopituitarism, uveitis, myasthenia gravis, myasthenic syndrome, Guillain-Barré syndrome)	For any of the following: • 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: • 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)

Treatment modifications when Bavencio is used in combination with axitinib

If ALT or AST ≥ 3 times ULN but < 5 times ULN or total bilirubin ≥ 1.5 times ULN but < 3 times ULN, both Bavencio and axitinib should be withheld until these adverse reactions recover to Grades 0-1.

If persistent (greater than 5 days), corticosteroid therapy with prednisone or equivalent followed by a taper should be considered.

Rechallenge with Bavencio or axitinib or sequential rechallenge with both Bavencio 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 Bavencio and axitinib should be permanently discontinued and corticosteroid therapy should be considered.

Dose modification advice for axitinib when used with Bavencio

When Bavencio 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 Bavencio in children and adolescents below 18 years of age have not been established. Currently available data of Bavencio are described in section 5.1 but no recommendation on a posology can be made.

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

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

Bavencio 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.

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 temporary 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 ≥ 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.

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune related adverse reactions following immune checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

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 ≥ 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 ≥ 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 ≥ 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).

Patients should be monitored for signs and symptoms of immune-related myocarditis. In symptomatic patients, obtain cardiologic consultation and laboratory investigations to ensure the initiation of appropriate measures at an early stage.

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, additional immunosuppression (e.g., mycophenolate, infliximab, anti-thymocyte globulin) should be considered.

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 ≥ 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 ≥ 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 ≥ 2 nephritis.

Avelumab should be withheld for Grade 2 or Grade 3 nephritis until resolution to ≤ 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, myasthenia gravis, myasthenic syndrome, cystitis noninfective, sarcoidosis 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 (in combination with axitinib)

Hepatotoxicity occurred in patients treated with avelumab in combination with axitinib with higher-than-expected 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 ≥ 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.

Avelumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Sodium content

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

4.5 Interactions 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 foetus and to result in an increased foetal 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 foetal harm, including increased rates of abortion or still birth.

Human IgG1 immunoglobulins are known to cross the placental barrier.

Therefore, avelumab has the potential to be transmitted from the mother to the developing foetus. It is not recommended to use avelumab during pregnancy unless the clinical condition of the woman requires treatment with avelumab.

Breastfeeding

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.

Breastfeeding women should be advised not to breastfeed during treatment and for at least 1 month after the last dose due to the potential for serious adverse reactions in breastfed 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

a) Summary of the safety profile

Avelumab is 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).

The most common adverse reactions with avelumab were fatigue (30.0%), nausea (23.6%), diarrhoea (18.5%), constipation (18.1%), decreased appetite (17.6%), infusion-related reactions (15.9%), vomiting (15.6%), and weight decreased (14.5%).

The most common Grade ≥ 3 adverse reactions were anaemia (5.6%), hypertension (3.9%), hyponatraemia (3.6%), dyspnoea (3.5%), and abdominal pain (2.6%). Serious

adverse reactions were immune-related adverse reactions and infusion-related reaction (see section 4.4).

b) Tabulated summary of adverse reactions

The adverse reactions are listed for use of avelumab as monotherapy and combination therapy.

These reactions are presented by system organ class and frequency.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Monotherapy

The safety of avelumab as monotherapy has been evaluated in 2082 patients with solid tumours including metastatic MCC or locally advanced or metastatic UC receiving 10 mg/kg every 2 weeks of avelumab in clinical studies.

Table 2: Adverse reactions in patients treated with avelumab as monotherapy

Frequency	**Adverse reactions**
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Lymphopenia, thrombocytopenia
Uncommon	Eosinophilia§
Immune system disorders	
Uncommon	Hypersensitivity, drug hypersensitivity, sarcoidosis**
Rare	Anaphylactic reaction, Type I hypersensitivity
Endocrine disorders	
Common	Hypothyroidism*, hyperthyroidism*
Uncommon	Adrenal insufficiency*, autoimmune thyroiditis*, thyroiditis*, autoimmune hypothyroidism*
Rare	Adrenocortical insufficiency acute*, hypopituitarism*
Metabolism and nutrition disorders	
Very common	Decreased appetite
Common	Hyponatraemia
Uncommon	Hyperglycaemia*

Frequency	**Adverse reactions**
Rare	Diabetes mellitus*, Type 1 diabetes mellitus*
Nervous system disorders	
Common	Headache, dizziness, neuropathy peripheral
Uncommon	Myasthenia gravis†, myasthenic syndrome†
Rare	Guillain-Barré Syndrome*, Miller Fisher syndrome*
Eye disorders	
Rare	Uveitis*
Cardiac disorders	
Rare	Myocarditis*
Vascular disorders	
Common	Hypertension
Uncommon	Hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnoea
Common	Pneumonitis*
Rare	Interstitial lung disease*
Gastrointestinal disorders	
Very common	Nausea, diarrhoea, constipation, vomiting, abdominal pain
Common	Dry mouth
Uncommon	Ileus, colitis*
Rare	Pancreatitis*, autoimmune colitis*, enterocolitis*, autoimmune pancreatitis*, enteritis*, proctitis*
Hepatobiliary disorders	
Uncommon	Autoimmune hepatitis*
Rare	Acute hepatic failure*, hepatic failure*, hepatitis*, hepatotoxicity*
Skin and subcutaneous tissue disorders	
Common	Pruritus*, rash*, dry skin, rash maculo-papular*
Uncommon	Eczema, dermatitis, rash pruritic*, psoriasis*, erythema*, rash erythematous*, rash generalised*, rash macular*, rash papular*
Rare	Erythema multiforme*, purpura*, vitiligo*, pruritus generalised*, dermatitis exfoliative*, pemphigoid*, dermatitis psoriasiform*, drug eruption*, lichen planus*
Musculoskeletal and connective tissue disorders	
Very common	Back pain, arthralgia
Common	Myalgia
Uncommon	Myositis*, rheumatoid arthritis*
Rare	Arthritis*, polyarthritis*, oligoarthritis*
Renal and urinary disorders	
Uncommon	Renal failure*, nephritis*
Rare	Tubulo-interstitial nephritis*, cystitis noninfective*
General disorders and administrative site conditions	
Very common	Fatigue, pyrexia, oedema peripheral
Common	Asthenia, chills, influenza like illness
Rare	Systemic inflammatory response syndrome*
Investigations	
Very common	Weight decreased
Common	Blood creatinine increased, blood alkaline phosphatase increased, lipase increased, gamma-glutamyltransferase increased, amylase increased

Frequency	Adverse reactions
Uncommon	Alanine aminotransferase (ALT) increased*, aspartate aminotransferase (AST) increased*, blood creatine phosphokinase increased*
Rare	Transaminases increased*, thyroxine free decreased*, blood thyroid stimulating hormone increased*
Injury, poisoning and procedural complications	
Very common	Infusion related reaction

* Immune-related adverse reaction based on medical review

** Sarcoidosis was observed in clinical trials in patients receiving avelumab in combination with platinum-based chemotherapy

† Adverse reactions occurred in estimated 4 000 patients exposed to avelumab monotherapy beyond the pooled analysis.

§ Reaction only observed from study EMR 100070-003 (Part B) after the data cut-off of the pooled analysis, hence frequency estimated

Combination therapy:

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%).

Table 3: Adverse reactions in patients treated with avelumab in combination with axitinib

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

Frequency	**Adverse reactions**
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
Uncommon	Myasthenia gravis, myasthenic syndrome
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

c) Description of selected adverse reactions

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

Immune related pneumonitis

In patients treated with avelumab as monotherapy, 1.3% (28/2 082) of patients developed immune related pneumonitis.
Of these patients, there was 1 (less than 0.1%) patient with a fatal outcome, 1 (less than 0.1%) patient with Grade 4, and 6 (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 13.8 months). The median duration was 8.1 weeks (range: 4 days to more than 4.9 months).

Avelumab was discontinued in 0.4% (9/2 082) of patients due to immune-related pneumonitis. All 28 patients with immune-related pneumonitis were treated with corticosteroids and 21 (75%) of the 28 patients were treated with high dose corticosteroids for a median of 9 days (range: 1 day to 2.3 months). Immune related pneumonitis resolved in 18 (64.3%) of the 28 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 ≥ 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, 1.0% (21/2 082) of patients developed immune related hepatitis.
Of these patients, there were 2 (0.1%) patients with a fatal outcome, and 16 (0.8%) patients with Grade 3 immune related hepatitis.

The median time to onset of immune related hepatitis was 3.3 months (range: 9 days to 14.8 months). The median duration was 2.5 months (range: 1 day to more than 7.4 months).

Avelumab was discontinued in 0.6% (13/2 082) of patients due to immune related hepatitis. All 21 patients with immune related hepatitis were treated with corticosteroids and 20 (95.2%) of the 21 patients received high dose corticosteroids for a median of 17 days (range: 1 day to 4.1 months). Immune related hepatitis resolved in 12 (57.1%) of the 21 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% (31/2 082) of patients developed immune related colitis.
Of these patients, there were 10 (0.5%) patients with Grade 3 immune related colitis.

The median time to onset of immune related colitis was 2.0 months (range: 2 days to 11.5 months). The median duration was 5.9 weeks (range: 1 day to more than 14 months).

Avelumab was discontinued in 0.5% (11/2 082) of patients due to immune related colitis. All 31 patients with immune related colitis were treated with corticosteroids and 19 (61.3%) of the 31 patients received high dose corticosteroids for a median of 19 days (range: 1 day to 2.3 months). Immune related colitis resolved in 22 (71%) of 31 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
In patients treated with avelumab as monotherapy, immune related pancreatitis occurred in less than 1% (1/4 000) of patients across clinical trials in multiple tumour types and in 0.6% (3/489) of patients receiving avelumab in combination with axitinib including 2 (0.4%) patients with fatal outcome.

Immune-related myocarditis
In patients treated with avelumab as monotherapy, immune related myocarditis occurred in less than 1% (5/4 000) of patients across clinical trials in multiple tumour types and in 0.6% (3/489) of patients receiving avelumab in combination with axitinib including 2 (0.4%) patients with fatal outcome.

Immune related endocrinopathies

Thyroid disorders

In patients treated with avelumab as monotherapy, 6.7% (140/2 082) of patients developed immune related thyroid disorders, including 127 (6.1%) patients with hypothyroidism, 23

(1.1%) with hyperthyroidism, and 7 (0.3%) with thyroiditis. Of these patients, there were 4 (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 12.8 months). The median duration was not estimable (range: 3 days to more than 27.6 months).

Avelumab was discontinued in 0.2% (4/2 082) of patients due to immune related thyroid disorders. Thyroid disorders resolved in 14 (10%) of the 140 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% (11/2 082) of patients developed immune related adrenal insufficiency. Of these patients, there was 1 (less than 0.1%) patient with Grade 3 immune related adrenal insufficiency.

The median time to onset of immune related adrenal insufficiency was 3.3 months (range: 1 day to 7.6 months).
The median duration was not estimable (range: 2 days to more than 10.4 months).

Avelumab was discontinued in 0.1% (2/2 082) of patients due to immune related adrenal insufficiency. All 11 patients with immune related adrenal insufficiency were treated with corticosteroids, and 5 (45.5%) of the 11 patients received high dose systemic corticosteroids (≥ 40 mg prednisone or equivalent) for a median of 2 days (range: 1 day to 24 days). Adrenal insufficiency resolved in 3 (27.3%) of patients 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 0.2% (5/2 082) of patients.

All 5 patients experienced Grade 3 Type 1 diabetes mellitus.

The median time to onset of Type 1 diabetes mellitus was 3.3 months (range: 1 day to 18.7 months). The median duration was not estimable (range: 14 days to more than 4.8 months).

Avelumab was discontinued in 0.1% (2/2 082) of patients due to Type 1 diabetes mellitus. Type 1 diabetes mellitus resolved in 2 (40%) patients at the time of data cut off.

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 0.3% (7/2 082) of patients.

There was 1 (less than 0.1%) patient with Grade 3 immune related nephritis.

The median time to onset of immune related nephritis was 2.4 months (range: 7.1 weeks to 21.9 months). The median duration was 6.1 months (range: 9 days to 6.1 months).

Avelumab was discontinued in 0.2% (4/2 082) of patients due to immune related nephritis. All 7 patients with immune related nephritis were treated with corticosteroids. 6 (85.7%) of those 7 patients with immune related nephritis were treated with high dose corticosteroids for a median of 2.5 weeks (range: 6 days to 2.8 months). Immune related nephritis resolved in 4 (57.1%) patients at the time of data cut off.

In patients treated with avelumab in combination with axitinib, immune related nephritis occurred in 0.4% (2/489) of patients. Of these patients, there were 2 (0.4%) patients with 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. All 2 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, respectively.

In patients with ALT ≥ 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 ≥ 3 times ULN.

Immunogenicity

For study EMR107000-003 in the MCC population, out of 204 patients (88 from Part A and 116 from Part B) with at least one valid anti-drug antibodies (ADA) result at any time point treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks, 189 (79 from Part A and 110 from Part B) were evaluable for treatment-emergent ADA and 16 (8.5%) (7 from Part A and 9 from Part B) tested positive.

For study B9991001 in the UC population, out of 344 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 plus BSC, 325 were evaluable for treatment emergent ADA and 62 (19.1%) tested positive.

For study B9991002 and study B9991003 in the RCC population, out of 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.

Overall, there was no evidence of altered pharmacokinetic profile, increased incidence of infusion reactions or effects on efficacy with anti avelumab antibody development. The impact of neutralizing antibodies (nAb) is unknown.

d) Paediatric population

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

e) Other special populations

Elderly

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

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Health care providers are requested to report any suspected adverse drug reaction to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) & eReporting platform (who-umc.org) found on SAHRPA website.

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 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: A30.5 Biologicals, Others

ATC code: L01FF04

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

Merkel cell carcinoma (study EMR100070-003)

The efficacy and safety of avelumab was investigated in the single arm, multi-centre study EMR100070-003 with two parts. Part A was conducted in patients with histologically confirmed metastatic MCC, whose disease had progressed on or after chemotherapy administered for distant metastatic disease, with a life expectancy of more than 3 months. Part B included patients with histologically confirmed metastatic MCC who were treatment-naïve to systemic therapy in the metastatic setting.

Patients with active or a history of 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 were excluded.

Patients received avelumab at a dose of 10 mg/kg every 2 weeks 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.

Tumour response assessments were performed every 6 weeks, as assessed by an Independent Endpoint Review Committee (IERC) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.

Study 003 Part A – previously-treated patients
The major efficacy outcome measure was confirmed best overall response (BOR); secondary efficacy outcome measures included duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

An efficacy analysis was conducted in all 88 patients after a minimum follow-up of 36 months. Patients received a median of 7 doses of avelumab (range: 1 dose to 95 doses), and the median duration of treatment was 17 weeks (range: 2 weeks to 208 weeks).

Of the 88 patients, 65 (74%) were male, the median age was 73 years (range 33 years to 88 years), 81 (92%) patients were Caucasian, and 49 (56%) patients and 39 (44%) patients

with an Eastern Cooperative Oncology Group (ECOG) performance status 0 and 1, respectively.

Overall, 52 (59%) patients were reported to have had 1 prior anti-cancer therapy for MCC, 26 (30%) with 2 prior therapies, and 10 (11%) with 3 or more prior therapies. Forty-seven (53%) of the patients had visceral metastases.

Table 4 summarises efficacy endpoints in patients receiving avelumab at the recommended dose for study EMR100070-003, Part A with a minimum follow-up of 36 months. Overall survival was evaluated in an analysis with a minimum follow-up of 44 months.
The median OS was 12.6 months (95% CI 7.5, 17.1).

Table 4: Response to avelumab 10 mg/kg every 2 weeks in patients with metastatic MCC in study EMR100070-003 (Part A)*

Efficacy endpoints (Part A) (per RECIST v1.1, IERC)	**Results (N=88)**
Objective response rate (ORR)	
Response rate, CR+PR** n (%)	29 (33.0%)
(95% CI)	(23.3, 43.8)
Confirmed best overall response (BOR)	
Complete response (CR)** n (%)	10 (11.4%)
Partial response (PR)** n (%)	19 (21.6%)
Duration of response (DOR)[a]	
Median, months	40.5
(95% CI)	(18, not estimable)
Minimum, maximum (months)	2.8, 41.5+
≥ 6 months by K-M, (95% CI)	93% (75, 98)
≥ 12 months by K-M, (95% CI)	71% (51, 85)
≥ 24 months by K-M, (95% CI)	67% (47, 82)
≥ 36 months by K-M, (95% CI)	52% (26, 73)
Progression-free survival (PFS)	
Median PFS, months	2.7
(95% CI)	(1.4, 6.9)
6-month PFS rate by K-M, (95% CI)	40% (29, 50)
12-month PFS rate by K-M, (95% CI)	29% (19, 39)
24-month PFS rate by K-M, (95% CI)	26% (17, 36)
36-month PFS rate by K-M, (95% CI)	21% (12, 32)

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid

Tumours; IERC: Independent Endpoint Review Committee; K-M:

Kaplan-Meier; +denotes a censored value

* Efficacy data with a minimum follow-up of 36 months (cut-off date 14 September 2018)

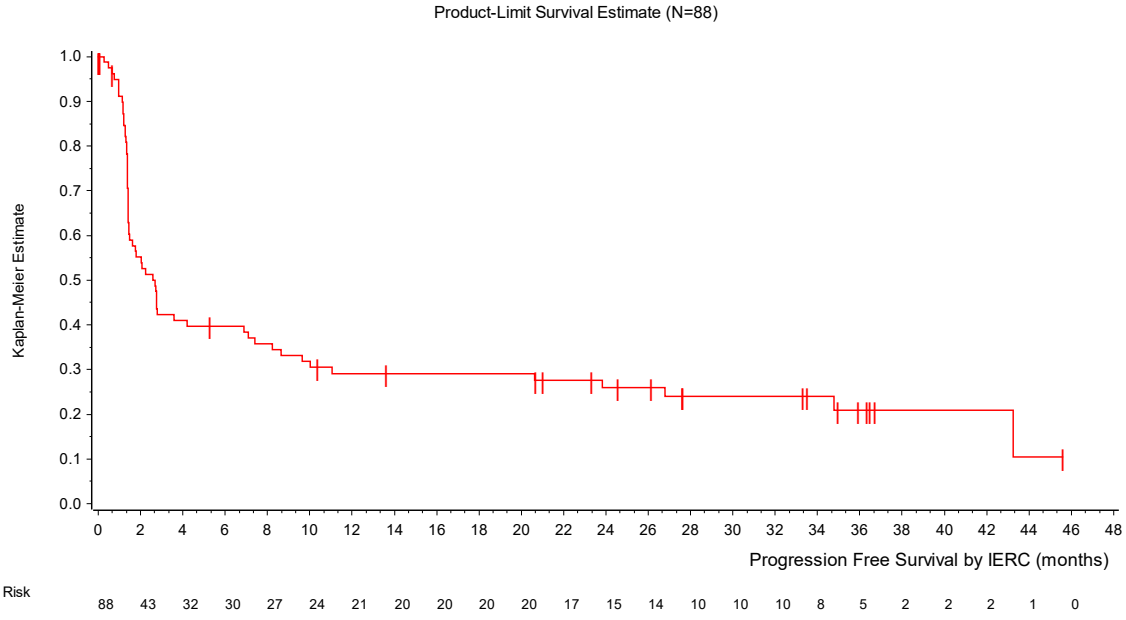
** CR or PR was confirmed at a subsequent tumour assessment

[a] Based on number of patients with confirmed response (CR or PR)

The median time to response was 6 weeks (range: 6 weeks to 36 weeks) after the first dose of avelumab. Twenty-two out of 29 (76%) patients with response were reported to have responded within 7 weeks after the first dose of avelumab.

The Kaplan-Meier estimates of PFS of the 88 patients (Part A) with metastatic MCC is presented in Figure 1.

Figure 1: Kaplan-Meier estimates of progression-free survival (PFS) per RECIST v1.1, IERC (Part A, minimum follow-up of 36 months)



Tumour samples were evaluated for PD-L1 tumour cell expression, and for Merkel cell polyomavirus (MCV) using an investigational immunohistochemistry (IHC) assay. Table 5

summarises the objective response rates by the PD-L1 expression and MCV status of patients with metastatic MCC in study EMR100070-003 (Part A).

Table 5: Objective response rates by PD-L1 expression and MCV tumour status in patients with metastatic MCC in study EMR100070-003 (Part A)

	Avelumab ORR (95% CI)*
PD-L1 expression at cut-off of ≥ 1%	N=74[a]
Positive (n=58)	36.2% (24.0, 49.9)
Negative (n=16)	18.8% (4.0, 45.6)
IHC-MCV tumour status	N=77[b]
Positive (n=46)	28.3% (16.0, 43.5)
Negative (n=31)	35.5% (19.2, 54.6)

IHC: Immunohistochemistry; MCV: Merkel cell polyomavirus; ORR: objective response rate
* ORR (cut-off date 14 September 2018)
[a] Based on data from patients evaluable for PD-L1
[b] Based on data from patients evaluable for MCV by immunohistochemistry (IHC)

Study 003 Part B – patients who have not received systemic therapy in the metastatic setting

The major efficacy outcome measure was durable response, defined as objective response (complete response (CR) or partial response (PR)) with a duration of at least 6 months; secondary outcome measures included BOR, DOR, PFS, and OS.

The primary analysis for Part B included 116 patients who received at least one dose of avelumab with a minimum follow-up of 15 months at the time of the data cut-off (cut-off date 02 May 2019).

Of the 116 patients, 81 (70%) were male, the median age was 74 years (range: 41 to 93 years), 75 (65%) were white, and 72 (62%) and 44 (38%) had an ECOG performance status of 0 and 1 respectively.

Table 6 summarises the primary analysis of efficacy endpoints including an estimate of the 24-month rates by Kaplan-Meier for DOR, and PFS in patients receiving avelumab at the recommended dose for study EMR100070-003, Part B.

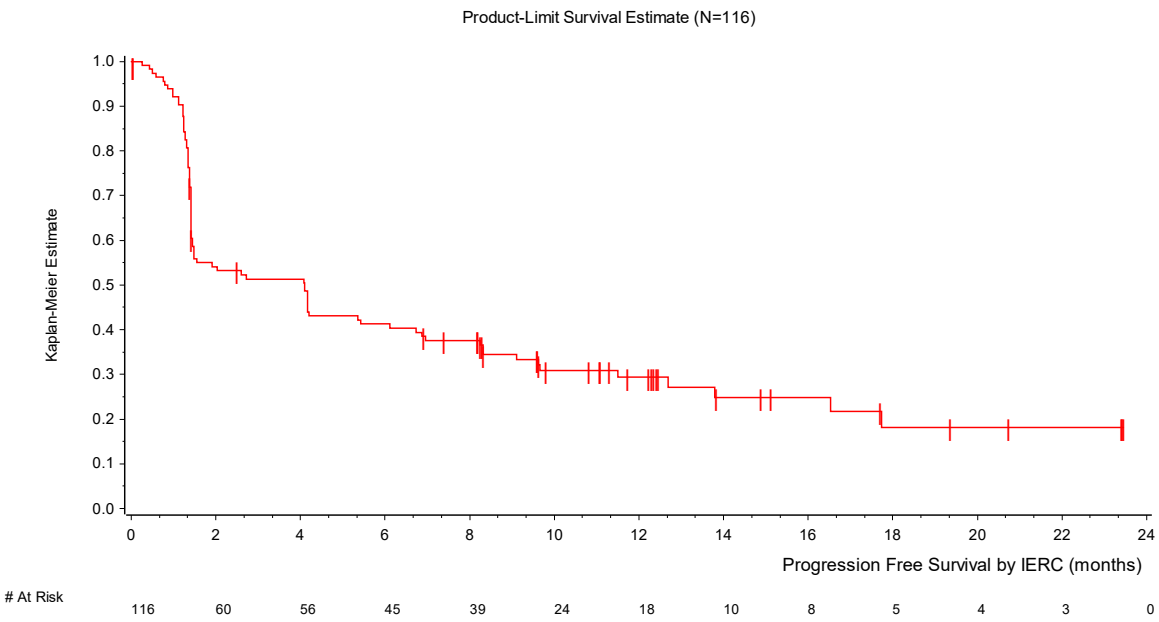
Table 6: Primary analysis of response to avelumab 10 mg/kg every 2 weeks in patients with metastatic MCC in study EMR100070-003 (Part B)*

Efficacy endpoints (Part B) (per RECIST v1.1, IERC)	Results (N=116)
Durable response	
≥ 6 months	30.2%
(95% CI)	(22.0, 39.4)
Objective response rate (ORR)	
Response rate, CR+PR** n (%)	46 (39.7%)
(95% CI)	(30.7, 49.2)
Confirmed best overall response (BOR)	
Complete response (CR)** n (%)	19 (16.4%)
Partial response (PR)** n (%)	27 (23.3%)
Duration of response (DOR)[a]	
Median, months	18.2
(95% CI)	(11.3, not estimable)
Minimum, maximum (months)	1.2, 28.3
≥ 3 months by K-M, (95% CI)	89% (75, 95)
≥ 6 months by K-M, (95% CI)	78% (63, 87)
≥ 12 months by K-M, (95% CI)	66% (50, 78)
≥ 18 months by K-M, (95% CI)	52% (34, 67)
≥ 24 months by K-M, (95% CI)	45% (25, 63)
Progression-free survival (PFS)	
Median PFS, months	4.1
(95% CI)	(1.4, 6.1)
3-month PFS rate by K-M, (95% CI)	51% (42, 60)
6-month PFS rate by K-M, (95% CI)	41% (32, 50)
12-month PFS rate by K-M, (95% CI)	31% (23, 40)
24-month PFS rate by K-M, (95% CI)	20% (12, 30)

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; K-M: Kaplan-Meier
* Efficacy data with a minimum follow-up of 15 months (cut-off date 02 May 2019)
** CR or PR was confirmed at a subsequent tumour assessment
a Based on number of patients with confirmed response (CR or PR)

Figure 2 presents the Kaplan-Meier estimates for PFS from the primary analysis with 116 patients enrolled into Part B with a minimum follow-up of 15 months.

Figure 2: Kaplan-Meier estimates of progression-free survival (PFS) per RECIST v1.1, IERC (Part B, N=116)



Tumour samples were evaluated for PD-L1 tumour cell expression, and for MCV using an investigational IHC assay. Table 7 summarises the objective response rates by PD-L1 expression and MCV status of patients with metastatic MCC in study EMR100070-003 (Part B).

Table 7: Objective response rates by PD-L1 expression and MCV tumour status in patients with metastatic MCC in study EMR100070-003 (Part B)

	Avelumab ORR (95% CI)*
PD-L1 expression at cut-off of ≥ 1%	N=108[a]
Positive (n=21)	61.9% (38.4, 81.9)
Negative (n=87)	33.3% (23.6, 44.3)
IHC-MCV tumour status	N=107[b]
Positive (n=70)	34.3% (23.3, 46.6)
Negative (n=37)	48.6% (31.9, 65.6)

IHC: Immunohistochemistry; MCV: Merkel cell polyomavirus; ORR: objective response rate
* ORR (cut-off date 02 May 2019)
[a] Based on data from patients evaluable for PD-L1
[b] Based on data from patients evaluable for MCV by IHC

Locally advanced or metastatic urothelial carcinoma (study B9991001)

The efficacy and safety of avelumab was demonstrated in study B9991001, a randomised, multi centre, open label study conducted in 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma whose disease had not progressed with 4-6

cycles of first line platinum-based induction chemotherapy. Patients with autoimmune disease or a medical condition that required immunosuppression were excluded.

Randomization was stratified by best response to chemotherapy (CR/PR vs. stable disease [SD]) and site of metastasis (visceral vs. non visceral) at the time of initiating first line induction chemotherapy. Patients were randomised (1:1) to receive either avelumab 10 mg/kg intravenous infusion every 2 weeks plus best supportive care (BSC) or BSC alone.

Administration of avelumab was permitted beyond Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 defined progression of disease by Blinded Independent Central Review (BICR) if the patient was clinically stable and considered to be deriving clinical benefit by the investigator.
Assessment of tumour status was performed at baseline, 8 weeks after randomization, then every 8 weeks up to 12 months after randomization, and every 12 weeks thereafter until documented confirmed disease progression based on BICR assessment per RECIST v1.1.

Demographic and baseline characteristics were generally well balanced between the avelumab plus BSC and the BSC alone arm. Baseline characteristics were a median age of 69 years (range: 32 to 90), 66% of patients were 65 years or older, 77% were male, 67% were White, and the ECOG PS was 0 (61%) or 1 (39%) for both arms.

For first line induction chemotherapy, 56% of patients received cisplatin plus gemcitabine, 38% of patients received carboplatin plus gemcitabine and 6% of patients received cisplatin plus gemcitabine and carboplatin plus gemcitabine (i.e. these patients received one or more cycles of each combination).
Best response to first line induction chemotherapy was CR or PR (72%) or SD (28%). Sites of metastasis prior to chemotherapy were visceral (55%) or non-visceral (45%). Fifty one percent of patients had PD L1 positive tumours.

Six percent of patients in the avelumab plus BSC arm and 44% of patients in the BSC alone arm received another PD 1/PD L1 checkpoint inhibitor after discontinuation of treatment.

The primary efficacy outcome measure was overall survival (OS) in all randomized patients and in patients with PD L1 positive tumours. Progression free survival (PFS) based on BICR assessment per RECIST v1.1 was an additional efficacy outcome measure. Efficacy outcomes were measured from time of randomisation after 4 to 6 cycles of platinum-based induction chemotherapy.

The PD L1 status of the tumour was assessed using the Ventana PD L1 (SP263) assay. PD L1 positivity was defined as ≥ 25% of tumour cells stained for PD L1; or ≥ 25% of immune cells stained for PD L1 if > 1% of the tumour area contained immune cells; or 100% of immune cells stained for PD L1 if = 1% of the tumour area contained immune cells.

At the pre-specified interim analysis (cut-off date 21 October 2019), study B9991001 met its primary endpoint for OS in both coprimary populations: in all randomized patients with a median OS of 21.4 months (95% CI: 18.9, 26.1; HR 0.69, 95% CI: 0.556, 0.863) in the avelumab plus BSC arm and with a median OS of 14.3 months (95% CI: 12.9, 17.8) in the BSC alone arm. For patients with PD L1 positive tumours the median OS was not reached (95% CI: 20.3, not reached; HR 0.56, 95%, CI: 0.404, 0.787) in the avelumab plus BSC arm and the median OS in the BSC alone arm was 17.1 months (95% CI: 13.5, 23.7). Updated OS results with a data cut-off date of 19 January 2020 and PFS data with a cut-off date of 21 October 2019 are presented in Table 8 and in Figure 3 and Figure 4 below.

Table 8: Efficacy results by PD-L1 expression in study B9991001

Efficacy endpoints	**Avelumab plus BSC** (N=350)	**BSC** (N=350)	**Avelumab plus BSC** (N=189)	**BSC** (N=169)	**Avelumab plus BSC** (N=139)	**BSC** (N=131)
	All randomized patients		**PD-L1-positive tumours**		**PD-L1-negative tumours**[c]	
Overall survival (OS)[a]						
Events (%)	156 (44.6)	190 (54.3)	68 (36.0)	85 (50.3)	80 (57.6)	80 (61.1)
Median in months (95% CI)	22.1 (19.0, 26.1)	14.6 (12.8, 17.8)	NE (20.6, NE)	17.5 (13.5, 31.6)	18.9 (13.3, 22.1)	13.4 (10.4, 17.3)
Hazard ratio (95% CI)	0.70 (0.564, 0.862)		0.60 (0.439, 0.833)		0.83 (0.603, 1.131)	
2-sided p-value[d]	0.0008		0.0019		-	
Progression-free survival (PFS)[b, e, f]						
Events (%)	225 (64.3)	260 (74.3)	109 (57.7)	130 (76.9)	103 (74.1)	99 (75.6)
Median in months (95% CI)	3.7 (3.5, 5.5)	2.0 (1.9, 2.7)	5.7 (3.7, 7.4)	2.1 (1.9, 3.5)	3.0 (2.0, 3.7)	1.9 (1.9, 2.1)
Hazard ratio (95% CI)	0.62 (0.519, 0.751)		0.56 (0.431, 0.728)		0.63 (0.474, 0.847)	
2-sided p-value[d]	< 0.0001		< 0.0001		-	

CI: Confidence interval; K-M: Kaplan-Meier, NE: not estimable

Note: 72 patients (22 patients on avelumab plus BSC arm and 50 patients on BSC alone arm) had a tumour with an unknown PD-L1 status

[a] OS cut-off date 19 January 2020

[b] PFS cut-off date 21 October 2019

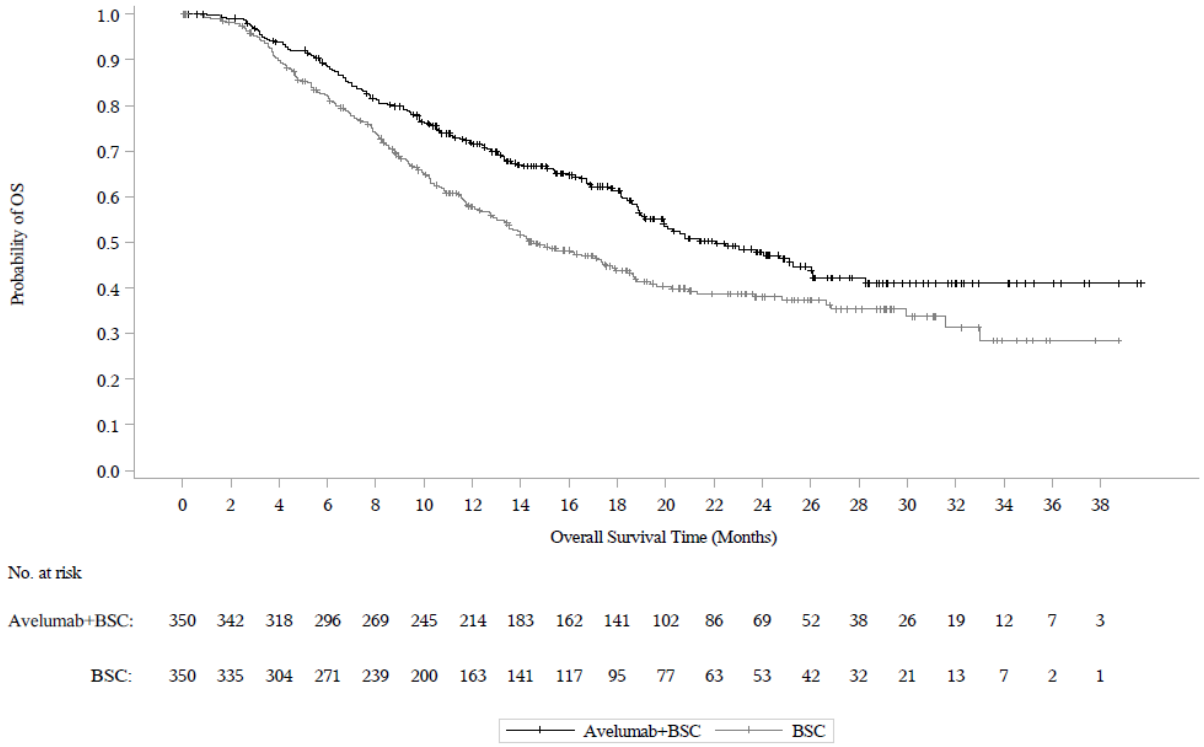
[c] PD-L1-negative population analyses were exploratory, and no formal test was performed

[d] p-value based on stratified log-rank

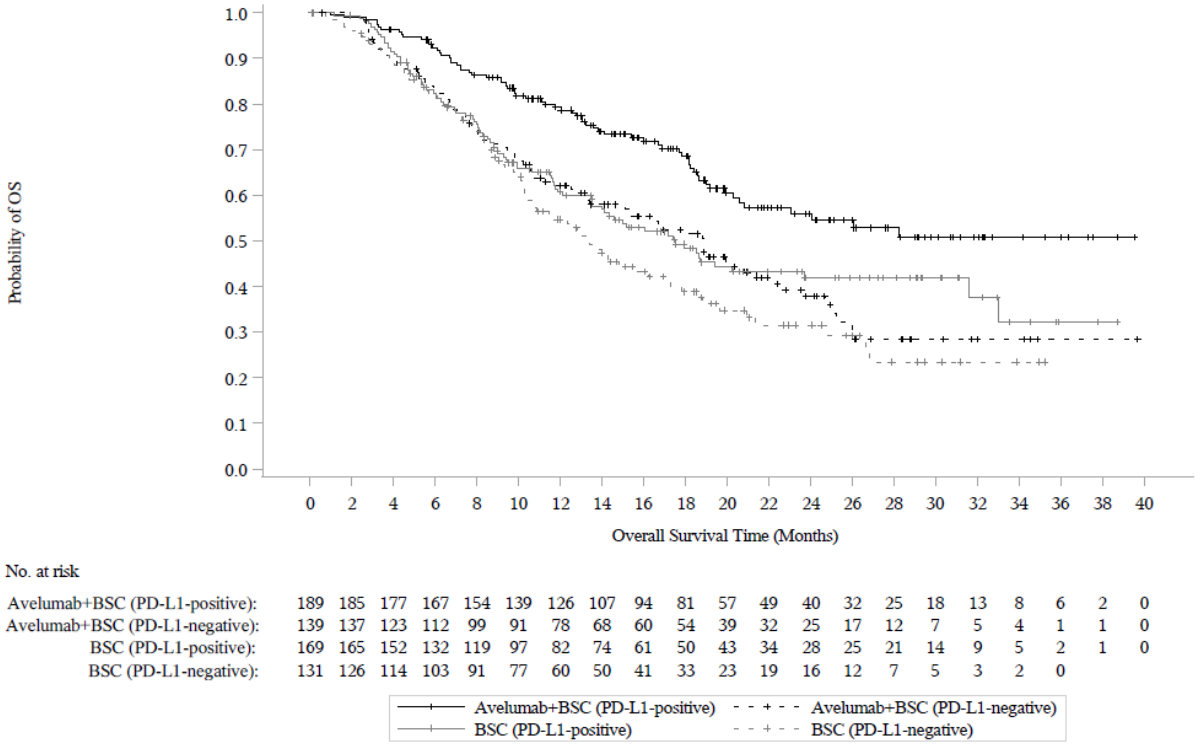
[e] Based on BICR assessment per RECIST v1.1

[f] PFS censoring reasons follow the hierarchy in sequential order: no adequate baseline assessment, start of new anti-cancer therapy, event after 2 or more missing assessments, withdrawal of consent, lost to follow-up, no adequate post-baseline tumour assessment, ongoing without an event

Figure 3: Kaplan-Meier estimates for overall survival (OS) by PD-L1 expression (cut-off date 19 January 2020) - Full analysis set



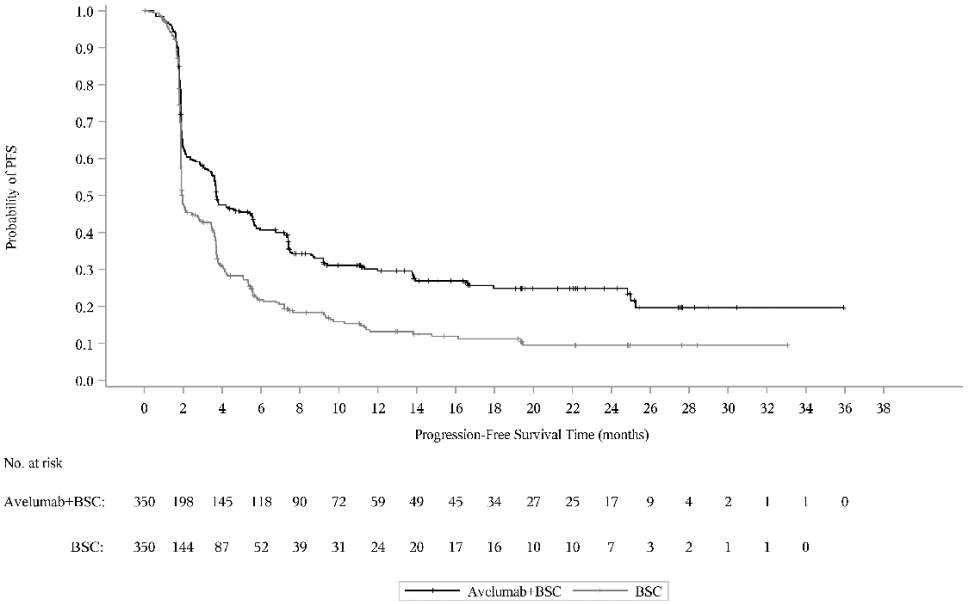
(A): All randomized patients

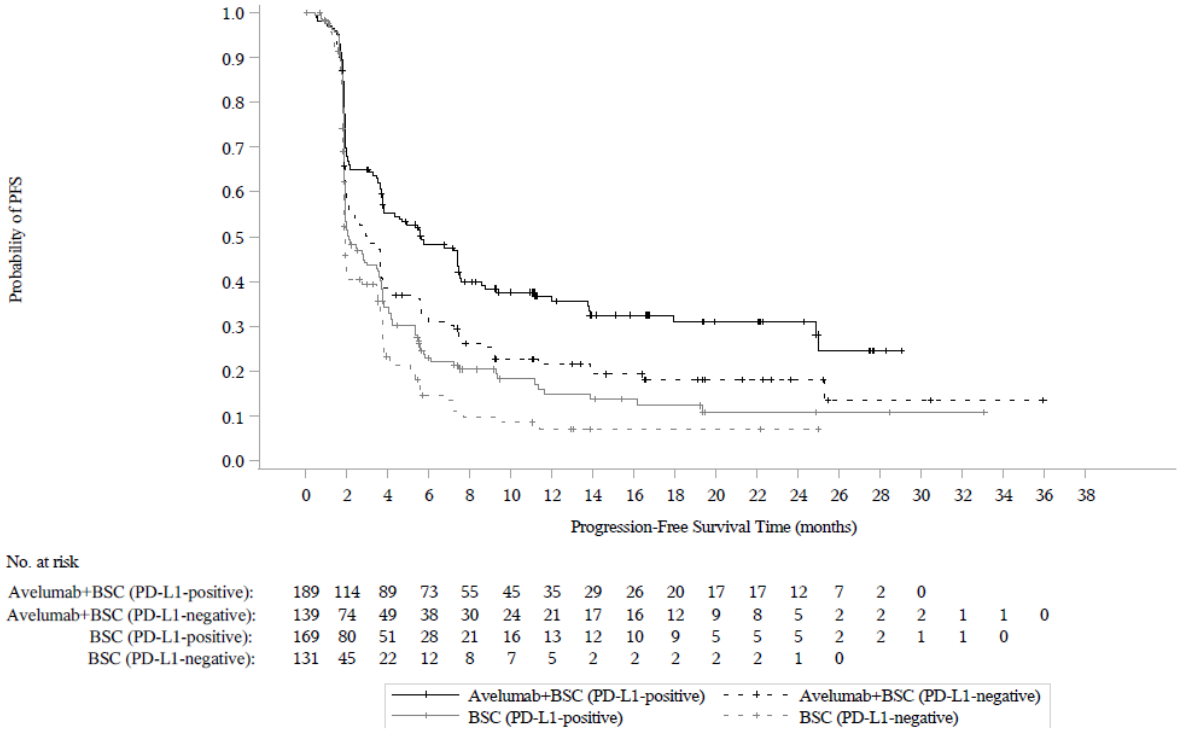


(B): Patients by PD-L1 expression

Figure 4: Kaplan-Meier estimates for progression-free survival (PFS) by PD-L1 expression based on BICR assessment (RECIST v1.1) (cut-off date 21 October 2019) - Full analysis set

(A): All randomized patients





(B): Patients by PD-L1 expression

Renal cell carcinoma (study B9991003)

The efficacy and safety of avelumab in combination with axitinib was demonstrated in study B9991003, a randomised, multi-centre, open-label study of avelumab in combination with

axitinib in 886 patients with untreated advanced or metastatic RCC with a clear-cell component.

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 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; active autoimmune disease that might deteriorate when receiving an immunostimulatory agents; a history of other malignancies within the last 5 years; organ transplant were ineligible.

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 randomised (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 based on investigator's assessment of the patient's benefit-risk and clinical condition, including performance status, clinical symptoms, adverse events and laboratory data. The majority (n=160, 71.4%) of the patients with progressive disease continued treatment with both medicinal products after progression. 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 the first-line treatment of patients with advanced RCC who have PD-L1-positive tumours (PD-L1 expression level ≥ 1%).
The key secondary endpoints were PFS based on BICR assessment per RECIST v1.1 and OS irrespective of PD-L1 expression. PD-L1 status was determined by immunohistochemistry.
Additional secondary endpoints included objective response (OR), time to response (TTR) and duration of response (DOR).

Study population characteristics: 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.

Efficacy results are presented in Table 9 and Figure 5 based on a data cut-off date of 28 January 2019. With a median OS follow-up of 19 months, OS data were immature with 27% deaths. The observed hazard ratio (HR) for OS was 0.80 (95% CI: 0.616, 1.027) for avelumab in combination with axitinib compared to sunitinib.

Table 9: Efficacy results from study B9991003 in patients irrespective of PD-L1 expression

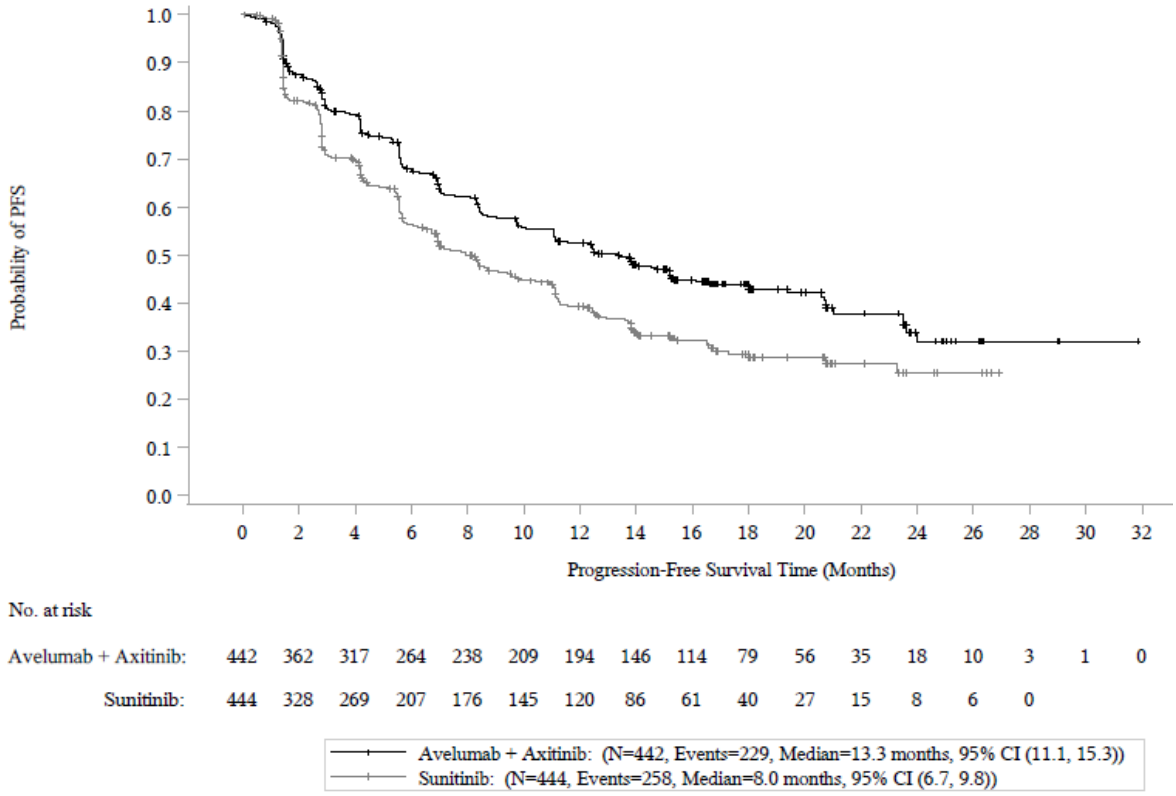
Efficacy endpoints (Based on BICR assessment)	**Avelumab plus axitinib** (N=442)	**Sunitinib** (N=444)
Progression-free survival (PFS)		
Events (%)	229 (52)	258 (58)
Median in months (95% CI)	13.3 (11.1, 15.3)	8.0 (6.7, 9.8)
Hazard ratio (95% CI)	0.69 (0.574, 0.825)	
p-value*	< 0.0001	
12-month PFS rate by K-M, (95% CI)**	52.4% (47.4, 57.2)	39.2% (34.1, 44.2)
18-month PFS rate by K-M, (95% CI)**	43.9% (38.8, 49.0)	29.3% (24.2, 34.6)
Confirmed objective response rate (ORR)		
Objective response rate (ORR) n (%)	232 (52.5)	121 (27.3)
(95% CI)	47.7, 57.2	23.2, 31.6
Complete response (CR) n (%)	17 (3.8)	9 (2.0)
Partial response (PR) n (%)	215 (48.6)	112 (25.2)
Time to response (TTR)		
Median, months (range)	2.7 (1.2, 20.7)	4.0 (1.2, 18.0)
Duration of response (DOR)		
Median, months (95% CI)	18.5 (17.8, NE)	NE (16.4, NE)

BICR: Blinded Independent Central Review; CI: Confidence interval; K-M: Kaplan-Meier; NE: Not estimable

* 1-sided p-value based on stratified log-rank

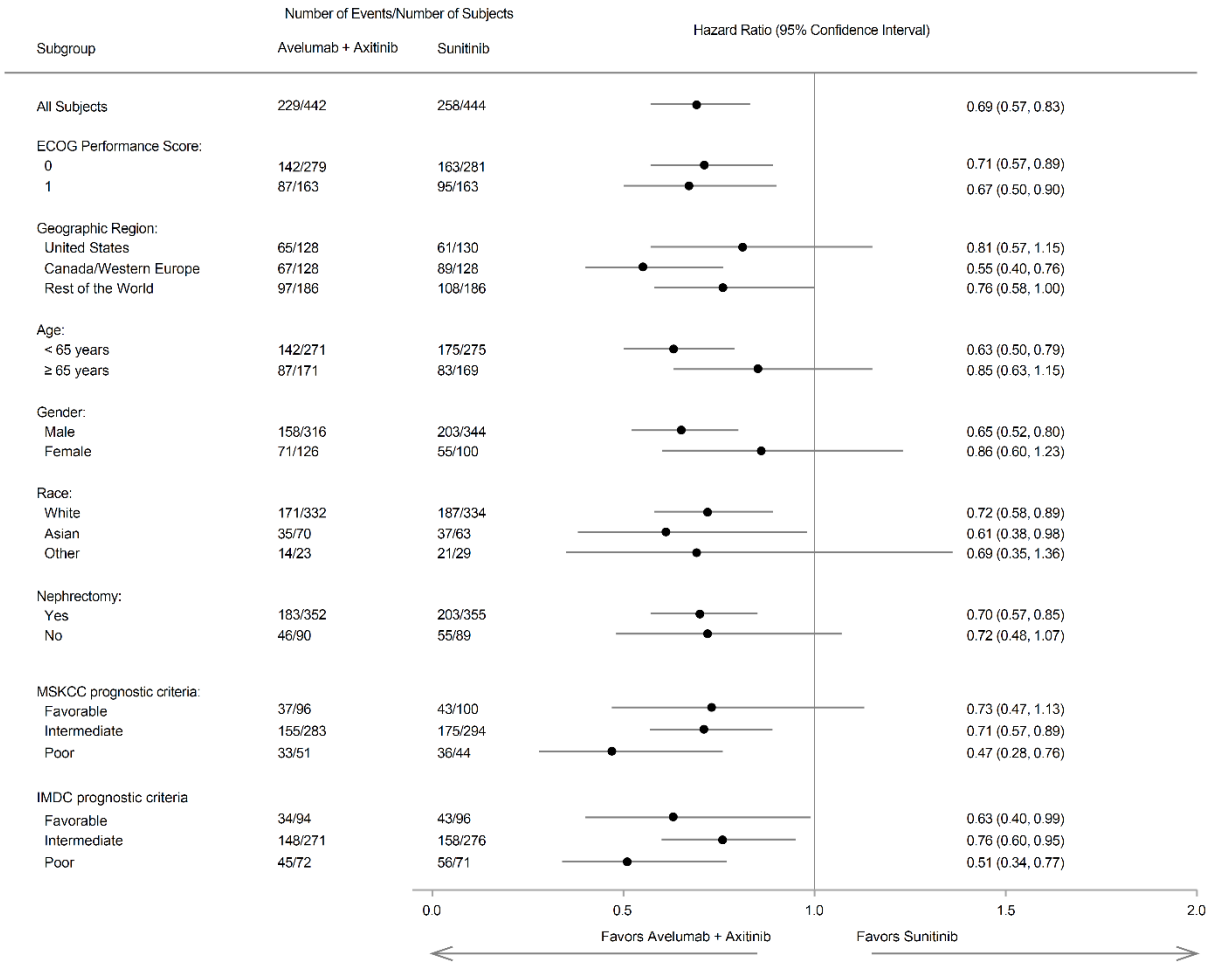
** CIs are derived using the log-log transformation with back transformation to untransformed scale

Figure 5: Kaplan-Meier estimates for progression-free survival based on BICR assessment in patients irrespective of PD-L1 expression



Improvement of PFS was observed across pre-specified subgroups.

Figure 6: Forest plot of progression-free survival based on BICR assessment in patients irrespective of PD-L1 expression



Paediatric population

Study MS100070-0306 was a multi-centre, open-label, Phase I/II study to evaluate the dose, safety and tolerability, antitumour activity, pharmacokinetic, and pharmacodynamics of avelumab in paediatric patients from birth to less than 18 years of age with refractory or relapsed solid tumours including central nervous system (CNS) tumours and lymphoma for which no standard therapy is available or for which the patient was not eligible for the existing therapy.

The study enrolled 21 paediatric patients with an age ranged from 3 to 17 years (11 patients ≤ 12 years and 10 patients > 12 years) receiving either 10 mg/kg (N=6) or 20 mg/kg (N=15) avelumab intravenously every 2 weeks until confirmed progression, death,

or unacceptable toxicity.

The primary tumour categories were soft tissue/bone sarcoma (N=12), CNS malignancies (N=8), and gastro-intestinal (GI) carcinoma (N=1).

There was no complete response (CR) or partial response (PR) in this study as assessed according to RECIST 1.1.

The European Medicines Agency has waived the obligation to submit the results of studies with Bavencio in all subsets of the paediatric population for the treatment of Merkel cell carcinoma, urothelial carcinoma, and renal cell carcinoma (see section 4.2 for information on paediatric use).

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 (t½) 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 ≥ 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 ≤ ULN and AST > ULN or bilirubin between 1 and 1.5 times ULN, n=217) and normal hepatic function (bilirubin and AST ≤ 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).

Paediatric population

The pharmacokinetics of avelumab was evaluated in 21 children and adolescents from 3 years to 17 years in study MS100070-306 receiving either 10 mg/kg (N=6) or 20 mg/kg (N=15) avelumab intravenously every 2 weeks until confirmed progression, death, or unacceptable toxicity.

The paediatric PK parameters and the corresponding PK profiles for all patients were evaluated according to dosing and stratified by bodyweight.

The exposure in paediatric patients receiving 20 mg/kg avelumab were similar or higher compared to those in adults receiving 10 mg/kg or 800 mg avelumab. In paediatric patients receiving 10 mg/kg avelumab the exposure was lower compared to those in adults.

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 for1 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 ≥ 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 foetus throughout pregnancy.

Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk that administration of avelumab during pregnancy could cause foetal 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

D-Mannitol; acetic acid glacial; polysorbate 20; sodium hydroxide; water for injection

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

3 years

After opening

From a microbiological point of view, unless the method of dilution precludes the risk of 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.

After preparation of infusion

Chemical and physical in-use stability of the diluted solution has been demonstrated as follows:

Infusion solution	**Storage at 2°C to 8°C protected from light**	**Storage at 20°C to 25°C and room light**
Sodium chloride 9 mg/mL (0.9%) solution for injection	96 hours	72 hours
Sodium chloride 4.5 mg/mL (0.45%) solution for injection	24 hours	24 hours

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 grey halobutyl rubber stopper and an aluminium seal fitted with a yellow removable plastic cap.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Bavencio 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. Bavencio 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 Bavencio 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 Bavencio, 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. HOLDER OF CERTIFICATE FOR REGISTRATION

Merck (Pty) Ltd

1 Friesland Drive

Longmeadow Business Estate South

Modderfontein, 1645

Tel: +27 (0)11 372 5000

8. REGISTRATION NUMBER

61/30.5/0848

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 March 2026

10. DATE OF REVISION OF TEXT