1. NAME OF THE MEDICINAL PRODUCT

Bavencio 200 mg/10mL 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 285 and 350 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Bavencio is indicated for the first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy.

Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) (see section 5.1).

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 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.

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
	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

Treatment-related adverse reaction	Severity*	Treatment modification
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.

<u>*Special populations*</u>

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.

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

None.

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).

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 ≥ 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 immunerelated 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 immunerelated myocarditis. Avelumab should be permanently discontinued if immunerelated 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 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.

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 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 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 foetus. 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 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 as monotherapy has been evaluated in 1,738 patients with solid tumours including metastatic MCC receiving 10 mg/kg every 2 weeks of avelumab in clinical studies. In this patient population, the most common adverse reactions with avelumab were fatigue (32.4%), nausea (25.1%), diarrhoea (18.9%), decreased appetite (18.4%), constipation (18.4%), infusion-related reactions (17.1%), weight decreased (16.6%), and vomiting (16.2%).

The most common Grade ≥ 3 adverse reactions were anaemia (6.0%), dyspnoea (3.9%), and abdominal pain (3.0%). Serious adverse reactions were immune-related adverse reactions and infusion-related reaction (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions reported for avelumab as monotherapy in patients with metastatic MCC, or locally advanced or metastatic UC are presented in Table 2. In all studies, avelumab was administered at 10 mg/kg every 2 weeks.

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.

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

Frequency	Adverse reactions
Infections and infestations	
Very common	Urinary tract infection
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Lymphopenia
Uncommon	Thrombocytopenia, eosinophilia§
Immune system disorders	
Uncommon	Drug hypersensitivity, hypersensitivity anaphylactic reaction, Type I hypersensitivity
Endocrine disorders	
Common	Hypothyroidism*

Frequency	Adverse reactions
Uncommon	Adrenal insufficiency*, hyperthyroidism*, thyroiditis*, autoimmune thyroiditis*, adrenocortical insufficiency acute*, autoimmune hypothyroidism*, hypopituitarism*
Metabolism and nutrition disorders	
Very common	Decreased appetite
Uncommon	Diabetes mellitus*, Type 1 diabetes mellitus*, hyperglycemia*
Nervous system disorders	
Common	Headache, dizziness, neuropathy peripheral
Uncommon	Guillain-Barré Syndrome*, myasthenia gravis†, myasthenic syndrome†, Miller Fisher syndrome*
Eye disorders	
Uncommon	Uveitis*
Cardiac disorders	
Rare	Myocarditis*
Vascular disorders	
Common	Hypertension, hypotension
Uncommon	Flushing
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnoea
Common	Pneumonitis*
Uncommon	Interstitial lung disease
Gastrointestinal disorders	
Very common	Nausea, diarrhoea, constipation, vomiting, abdominal pain
Common	Dry mouth
Uncommon	Colitis*, autoimmune colitis*, enterocolitis*, ileus, autoimmune pancreatitis*, enteritis*, proctitis
Rare	Pancreatitis*
Hepatobiliary disorders	
Uncommon	Autoimmune hepatitis*, acute hepatic failure*, hepatic failure*, hepatitis*, hepatotoxicity*
Skin and subcutaneous tissue disorders	
Common	Rash*, pruritus*, rash maculo-papular*, dry skin
Uncommon	Rash pruritic*, erythema*, rash generalised*, psoriasis*, rash erythematous*, rash macular*, rash papular*, dermatitis exfoliative*, erythema multiforme*, pemphigoid*, pruritus generalised*, eczema, dermatitis, vitiligo*, purpura*, dermatitis psoriasiform*, drug eruption*, lichen planus*
Musculoskeletal and connective tissue disorders	
Very common	Back pain, arthralgia
Common	Myalgia
Uncommon	Myositis*, arthritis*, polyarthritis*, oligoarthritis*, rheumatoid arthritis*
Renal and urinary disorders	
Uncommon	Tubulo-interstitial nephritis*, renal failure*, nephritis*
General disorders and administrative site conditions	
Very common	Fatigue, pyrexia, oedema peripheral
Common	Asthenia, chills, influenza like illness
Uncommon	Systemic inflammatory response syndrome*
Investigations	
Very common	Weight decreased
Common	Gamma-glutamyltransferase increased, blood alkaline phosphatase increased, amylase increased, lipase increased, blood creatinine increased

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

* Immune-related adverse reaction based on medical review

† *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

Renal cell carcinoma

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 two clinical studies with avelumab in combination with axitinib are presented in Table 3.

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.

Table 3: 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

Frequency	Adverse reactions
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

Description of selected adverse reactions

Data for immune-related adverse reactions for avelumab as a monotherapy are based on 1,650 patients in the phase I study EMR100070-001 in 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 who received avelumab (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 ≥ 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
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% (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. 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
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). A new ADA method with improved sensitivity and drug tolerance for evaluating treatment-emergent ADA in patients treated with avelumab as monotherapy was used for study B9991001. Of the 344 patients 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. Based on data available, including the low incidence of immunogenicity, the impact of ADA on pharmacokinetics, efficacy and safety is uncertain, 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. Thenew ADA method with improved sensitivity 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.

4.9 Overdose

There are limited experiences with overdose with avelumab in clinical studies. 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: 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 study EMR100070-003 with two parts. Part A was a single-arm, multi-centre study 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.

For Part A, the major efficacy outcome measure was confirmed best overall response (BOR); secondary efficacy outcome measures included duration of response (DOR), and progression-free survival (PFS).

For Part A, the efficacy analysis was conducted in all 88 patients after a minimum follow-up of 18 months Patients received a median of 7 doses of avelumab (range: 1 dose to 61 doses), and the median duration of treatment was 17 weeks (range: 2 weeks to 132 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 3 summarises efficacy endpoints in patients receiving avelumab at the recommended dose for study EMR100070-003, Part A.

Table 3: 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	NR
(95% CI)	(18, not estimable)
Minimum, maximum, months	2.8, 24.9+
≥ 6 months by K-M, (95% CI)	93% (75, 98)
≥ 12 months by K-M, (95% CI)	71% (51, 85)
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)

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; K-M: Kaplan-Meier; NR: Not reached; +denotes a censored value

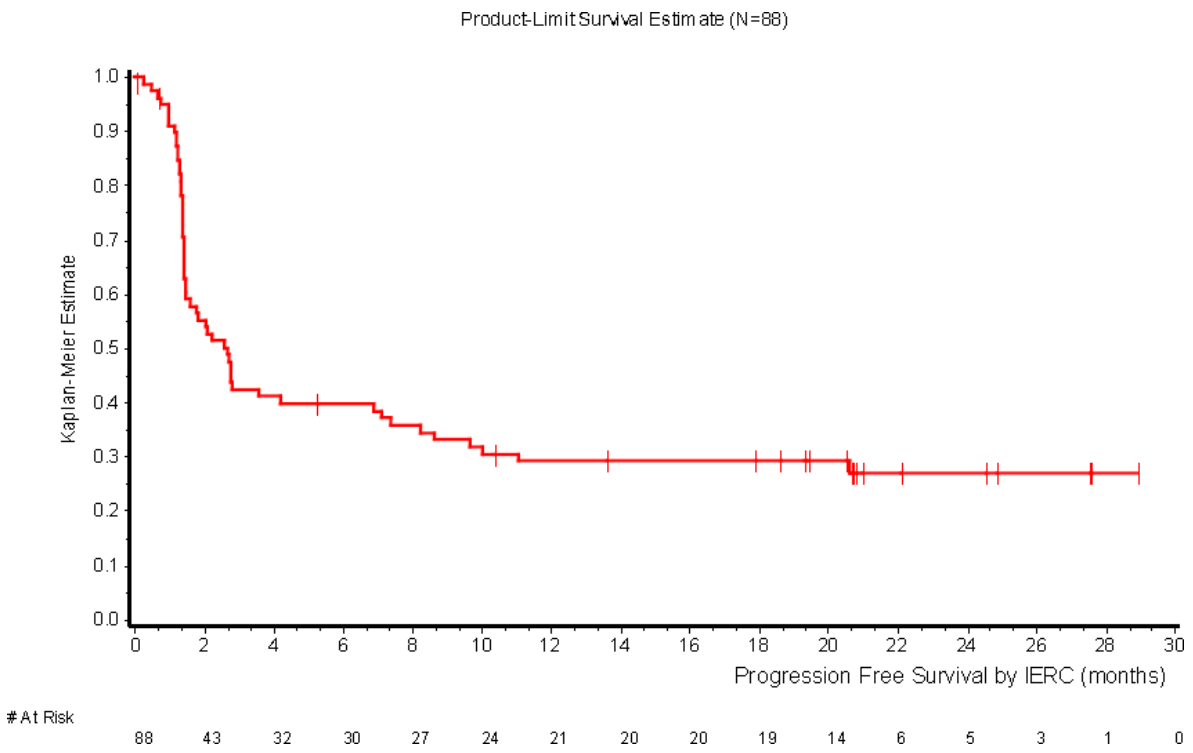
* CR or PR was confirmed at a subsequent tumour assessment

[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)



Tumour samples were evaluated for PD-L1 tumour cell expression, and for Merkel cell polyomavirus (MCV) using an investigational immunohistochemistry (IHC) assay. Table 4 summarises 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 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)
PD-L1 expression at cut-off of 5%	N=74[a]
Positive (n=19)	57.9% (33.5, 79.7)
Negative (n=55)	23.6% (13.2, 37.0)
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
[a] Based on data from patients evaluable for PD-L1
[b] Based on data from patients evaluable for MCV by immunohistochemistry (IHC)

The clinical utility of PD-L1 as a predictive biomarker in MCC has not been established.

For Part B, 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.

For Part B, an interim analysis of efficacy was conducted with 39 patients who received at least one dose. Of those, 30 (77%) were males, the median age was 75 years (range: 47 years to 88 years), 33 (85%) patients were Caucasian, and 31 (79%) patients and 8 (21%) patients had an ECOG performance status 0 and 1, respectively. Twenty-nine patients had at least 13 weeks of follow-up at the time of the

data cut-off.

Table 6 summarises efficacy endpoints in patients receiving avelumab at the recommended dose for study EMR100070-003, Part B.

Table 6: 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
Objective response rate (ORR)	(N=29)
Response rate, CR+PR* n (%)	18 (62.1%)
(95% CI)	(42.3, 79.3)
Confirmed best overall response (BOR)	(N=29)
Complete response (CR)* n (%)	4 (13.8%)
Partial response (PR)* n (%)	14 (48.3%)
Duration of response (DOR)[a]	(N=29)
Median, months	NR
(95% CI)	(4.0, not estimable)
Minimum, maximum. months	1.2+, 8.3+
≥ 3 months by K-M, (95% CI)	93% (61, 99)
Progression-free survival (PFS)	(N=39)
Median PFS, months	9.1
(95% CI)	(1.9, not estimable)
3-month PFS rate by K-M, (95% CI)	67% (48, 80)

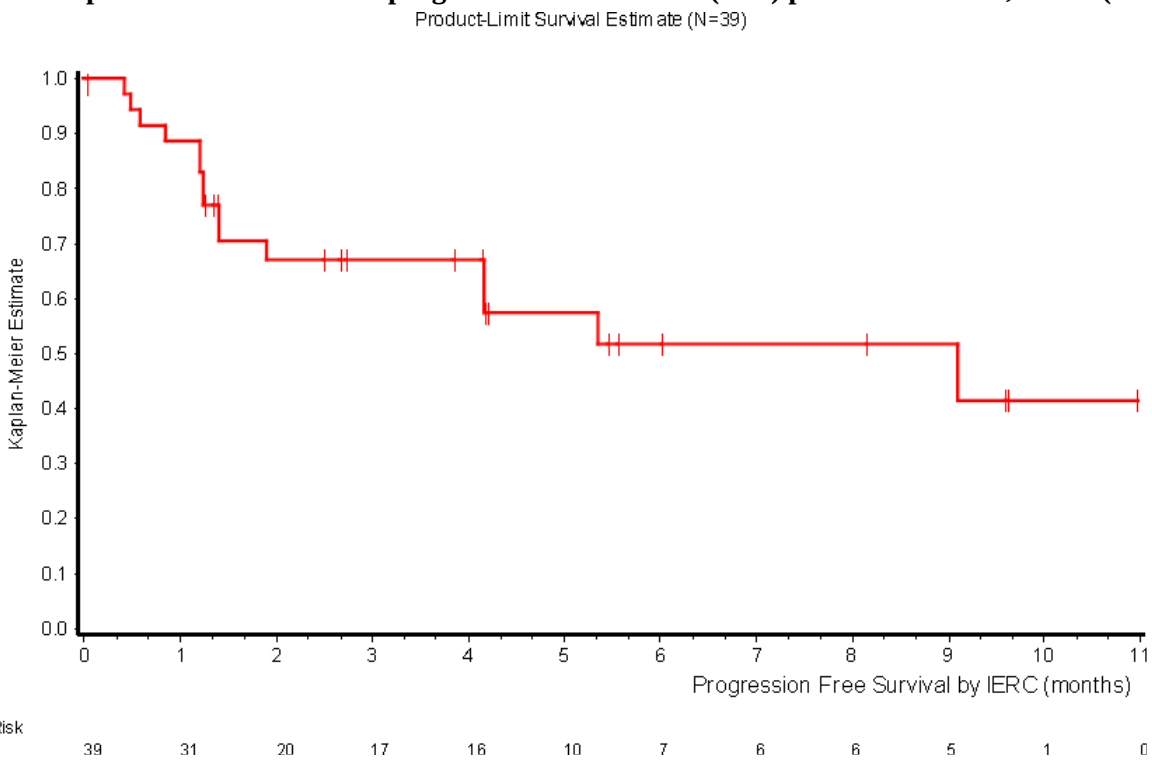
CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; K-M: Kaplan-Meier; NR: Not reached; +denotes a censored value

* 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 for the 39 patients enrolled into Part B who received at least one dose of study drug prior to the data cut-off for the interim analysis.

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



B)

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

Treatment with avelumab continued until Response Evaluation Criteria in Solid Tumours (RECIST) v1.1-defined progression of disease by Blinded Independent Central Review (BICR) assessment or *unacceptable toxicity. Administration of avelumab 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, 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.
Efficacy results are presented below.

Table 7: Efficacy results from study B9991001

Efficacy endpoints	{Tradename} plus BSC (N=350)	BSC (N=350)
Overall survival (OS)[1]		
Events (%)	145 (41.4)	179 (51.1)
Median in months (95% CI)	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)
Hazard ratio (95% CI)	0.69 (0.556, 0.863)	
2-sided p-value*	0.0010	
12-month OS rate by K-M (95% CI)**	71.3% (66.0, 76.0)	58.4% (52.7, 63.7)
18-month OS rate by K-M (95% CI)**	61.3% (55.4, 66.7)	43.8% (37.8, 49.7)
Progression-free survival (PFS)***[2]		
Events (%)	225 (64.3)	260 (74.3)
Median in months (95% CI)	3.7 (3.5, 5.5)	2.0 (1.9, 2.7)
Hazard ratio (95% CI)	0.62 (0.519, 0.751)	
2-sided p-value*	< 0.0001	

CI: Confidence interval; K-M: Kaplan-Meier
** p-value based on stratified log-rank*
*** CIs are derived using the log-log transformation with back transformation to untransformed scale*

*** *based on BICR assessment per RECIST v1.1*

Figure 3: Kaplan-Meier estimates for overall survival (OS) - Full analysis set

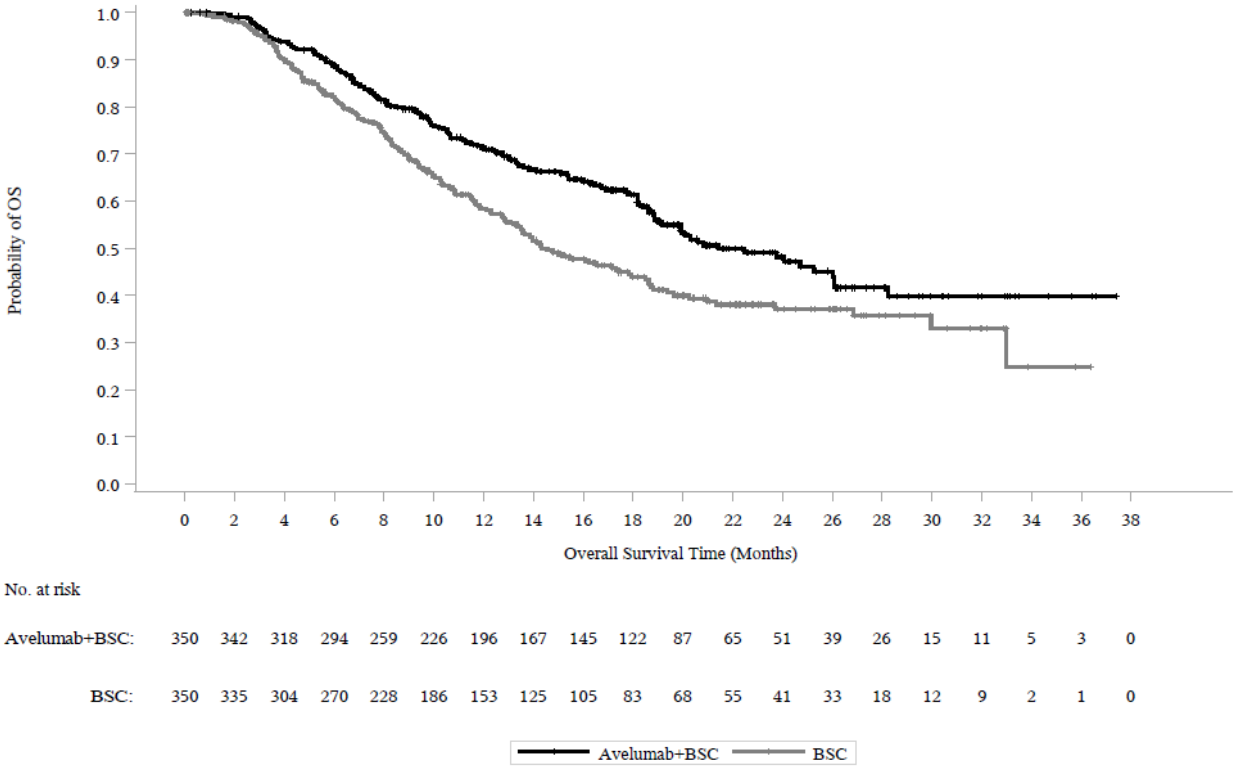
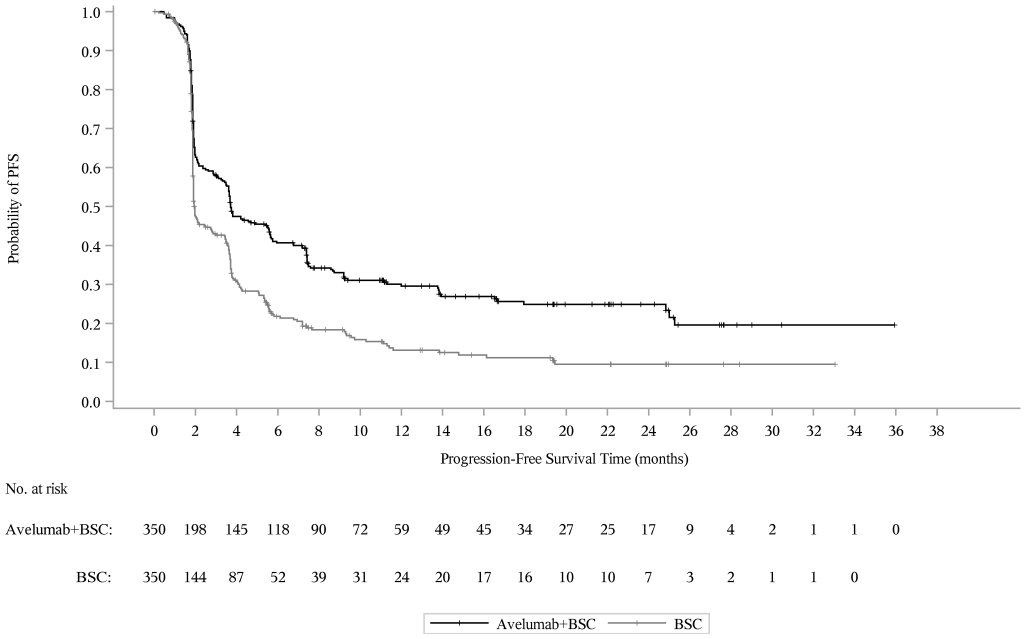
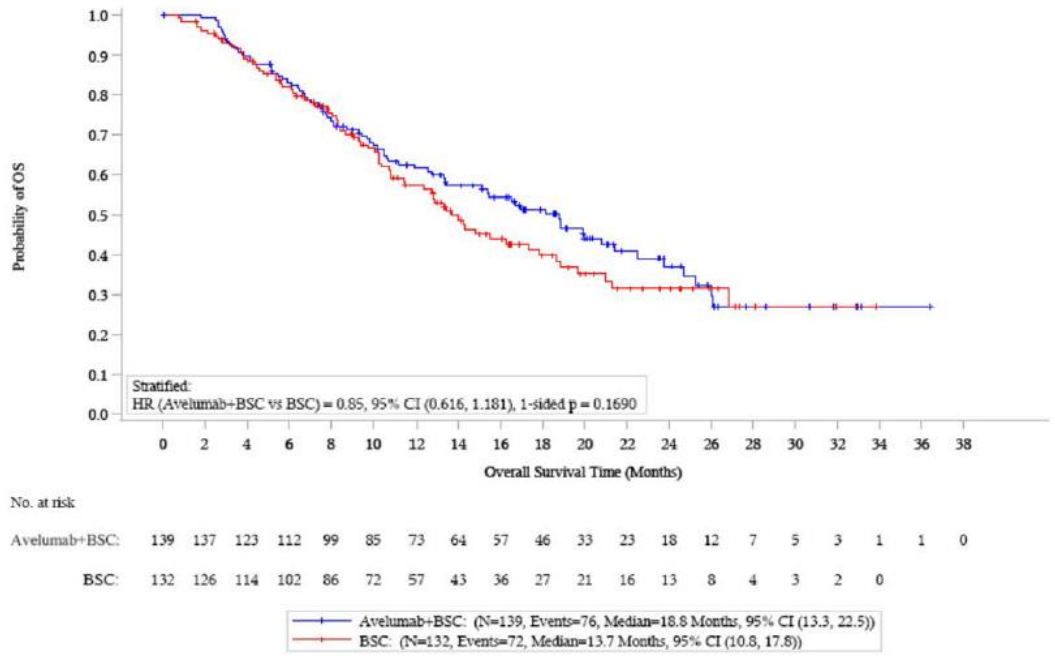


Figure 4: Kaplan-Meier estimates for progression-free survival (PFS) based on BICR assessment (RECIST v1.1) - Full analysis set



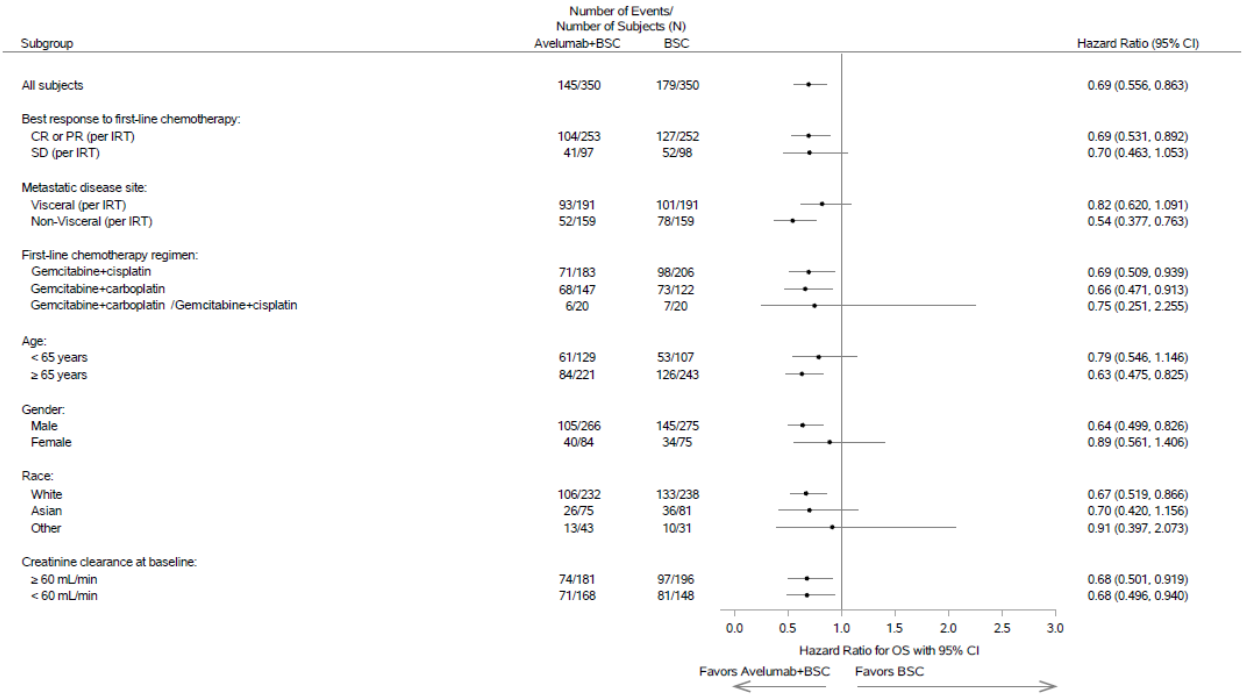
In addition, a statistically significant improvement in OS was demonstrated in patients with PD-L1-positive tumours for avelumab plus BSC compared to BSC alone (HR 0.56; 95% CI: 0.40, 0.79; 2-sided p-value 0.0007). The median OS was not reached (95% CI: 20.3 months, not reached) in the avelumab plus BSC arm, and 17.1 months (95% CI: 13.5, 23.7) in the BSC alone arm. In an exploratory analysis of patients with PD-L1-negative tumours (n=271, 39%), the OS hazard ratio was 0.85 (95% CI: 0.62, 1.18).

Figure 5: Kaplan-Meier Plot of Overall Survival – Subjects with PD-L1 Negative Tumours in the Full Analysis Set (Protocol B9991001)



Consistent results were observed across pre-specified subgroups, including best response to first-line induction chemotherapy, sites of metastasis, as shown in Figure 6.

Figure 6: Forest plot of overall survival (OS) by subgroups - Full analysis set



Patient reported outcomes (PRO)
Patient reported outcomes of physical and emotional disease related symptoms, treatment side effects, and function and well-being were collected using the FACT/NCCN Bladder Symptom Index (FBlSI-18). No detrimental effects were observed when adding avelumab maintenance therapy to BSC compared to BSC alone as measured by FBlSI-18 during treatment period.

Renal cell carcinoma (study B9991003)
The efficacy and safety of avelumab in combination with axitinib was demonstrated in study B9991003, a randomised, multicentre, 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 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.

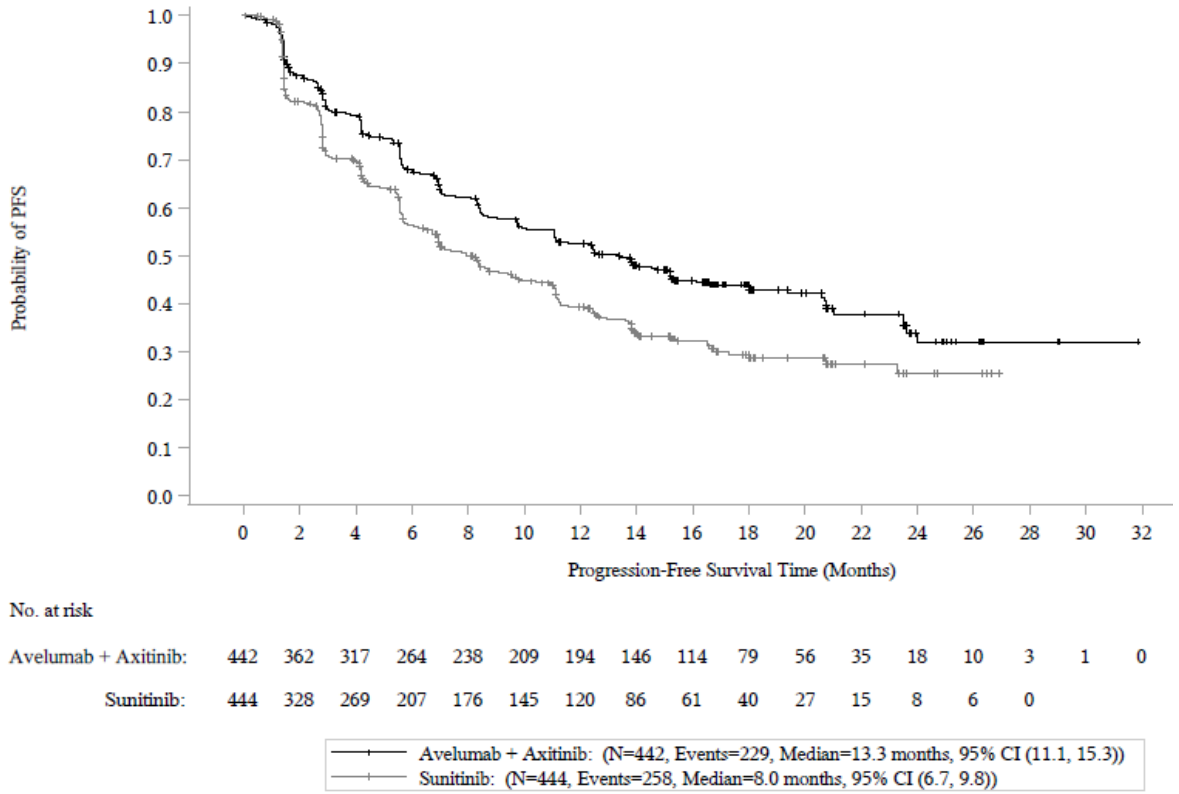
Efficacy results are presented in Table 7 and Figure 3 based on a data cut-off date of 28 January 2019. With a median OS follow-up of 19 months, OS data were immature with 27% deaths. The observed hazard ratio (HR) for OS was 0.80 (95% CI: 0.616, 1.027) for avelumab in combination with axitinib compared to sunitinib.

Table 8: 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)

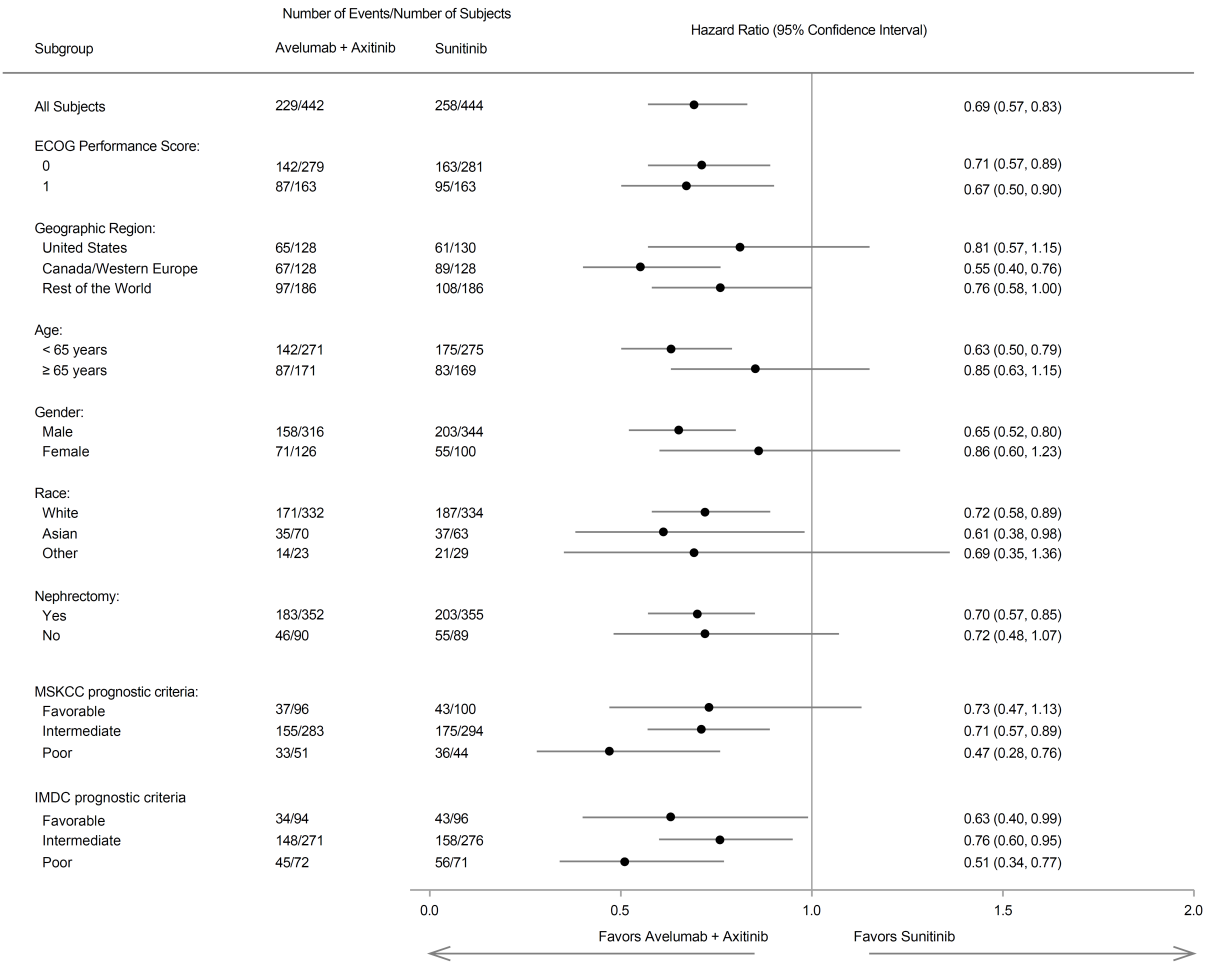
BICR: Blinded Independent Central Review; CI: Confidence interval; NE: Not estimable.
* 1-sided p-value based on stratified log-rank.
** CIs are derived using the log-log transformation with back transformation to untransformed scale.

Figure 7: 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 8: 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 ($t_{½}$) 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).

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

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

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

After preparation of infusion
The product does not contain a preservative.
If avelumab is not infused immediately, the diluted solution can be stored up to 8 hours at room temperature (up to 25°C) or up to 24 hours at 2°C to 8°C in the refrigerator. If refrigerated, allow the diluted solution to come to room temperature prior to administration.
This storage time includes the storage of the infusion solution in the infusion bag and the duration of infusion.
Do not freeze or shake the diluted solution.

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

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. PRODUCT OWNER

Merck Europe B.V
Gustav Mahlerplein 102
Amsterdam, The Netherlands

8. DATE OF REVISION OF THE TEXT

August 2022 CCDS V7