

BAVENCIO

1. NAME OF THE MEDICINAL PRODUCT

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.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic Merkel Cell Carcinoma

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

Locally Advanced or Metastatic Urothelial Carcinoma

First-Line Maintenance Treatment of Urothelial Carcinoma

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

Previously-Treated Urothelial Carcinoma

Bavencio is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Advanced Renal Cell Carcinoma

Bavencio in combination with axitinib is indicated for the first-line treatment of 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

Recommended Dosage for MCC

The recommended dose of Bavencio is 800 mg or 10 mg/kg body weight, according to treating physician's discretion, administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

Recommended Dosage for UC

The recommended dose of Bavencio is 800 mg or 10 mg/kg body weight, according to treating physician's discretion, administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

Recommended Dosage for RCC

The recommended dose of Bavencio is 800 mg or 10 mg/kg body weight, according to treating physician's discretion, administered as an intravenous infusion over 60 minutes every 2 weeks in combination with axitinib 5 mg orally taken twice daily (12 hours apart) with or without food until disease progression or unacceptable toxicity.

When axitinib is used in combination with Bavencio, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of two weeks or longer. Review the Full Prescribing Information for axitinib prior to initiation.

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

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

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

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. Re-challenge with Bavencio or axitinib or sequential re-challenge with both Bavencio and axitinib after recovery should be considered. Dose reduction according to the axitinib product information should be considered if re-challenging 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.

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 \geq 3. In the remaining 1.4% (6/439) of patients, infusion-related reactions occurred after the first 4 infusions and all were of Grade 1 or Grade 2.

Immune-related adverse reactions

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

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, avelumab should be withheld and corticosteroids administered. If corticosteroids are used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement.

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

Immune-related pneumonitis

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

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

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

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

Immune-related hepatitis

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

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

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

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

Immune-related colitis

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

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

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

Immune-related pancreatitis

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

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

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

Immune-related myocarditis

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

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 \geq 3 adrenal insufficiency followed by a taper until a dose of less than or equal to 10 mg/day has been reached.

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

Type 1 diabetes mellitus

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

Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Initiate treatment with insulin for Type 1 diabetes mellitus. Avelumab should be withheld and anti-hyperglycaemics in patients with Grade ≥ 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 \leq Grade 1 and permanently discontinued for Grade 4 nephritis.

Other immune-related adverse reactions

Other clinically important immune-related adverse reactions were reported in less than 1% of patients: myositis, hypopituitarism, uveitis, 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.

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been conducted with avelumab.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

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

Pregnancy

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

Animal reproduction studies have not been conducted with avelumab. However, in murine models of pregnancy, blockade of PD-L1 signalling has been shown to disrupt tolerance to the 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 most frequently associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of avelumab (see “Description of selected adverse reactions” below).

Merkel cell carcinoma

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 88 patients with metastatic MCC and for 1,650 patients in a phase I study in solid tumours are presented in Table 2. In both 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in patients treated with avelumab as monotherapy in clinical study EMR10070-003 and adverse reactions from a phase I study (EMR10070-001) in solid tumours

Frequency	Adverse reactions
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*
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*
Nervous system disorders	
Common	Headache, dizziness, neuropathy peripheral
Uncommon	Guillain-Barré Syndrome*, myasthenia gravis [†] , myasthenic 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*
Gastrointestinal disorders	
Very common	Nausea, diarrhoea, constipation, vomiting, abdominal pain
Common	Dry mouth
Uncommon	Colitis*, autoimmune colitis*, enterocolitis*, ileus
Rare	Pancreatitis*
Hepatobiliary disorders	
Uncommon	Autoimmune hepatitis*, acute hepatic failure*, hepatic failure*, hepatitis*
Skin and subcutaneous tissue disorders	
Common	Rash*, pruritus*, rash maculo-papular*, dry skin

Frequency	Adverse reactions
Uncommon	Rash pruritic*, erythema*, rash generalised*, psoriasis*, rash erythematous*, rash macular*, rash papular*, dermatitis exfoliative*, erythema multiforme*, pemphigoid*, pruritus generalised*, eczema, dermatitis
Musculoskeletal and connective tissue disorders	
Very common	Back pain, arthralgia
Common	Myalgia
Uncommon	Myositis*
Renal and urinary disorders	
Uncommon	Tubulo-interstitial 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
Uncommon	Alanine aminotransferase (ALT) increased*, aspartate aminotransferase (AST) increased*, blood creatine phosphokinase increased*, transaminases increased*
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

Locally Advanced or Metastatic Urothelial Carcinoma

First-Line Maintenance Treatment of Urothelial Carcinoma

The safety of avelumab was evaluated in study B9991001 where patients received avelumab 10 mg/kg every 2 weeks plus best supportive care (BSC) (N=344) or BSC alone (N=345). Patients with autoimmune diseases or conditions requiring systemic immunosuppression were excluded.

In the avelumab plus BSC arm, 47% were exposed to avelumab for > 6 months and 28% were exposed for > 1 year.

The median age of patients treated with avelumab plus BSC was 69 years (range: 37 to 90), 63% of patients were 65 years or older, 76% were male, 67% were White, and the ECOG performance score was 0 (61%) or 1 (39%).

A fatal adverse reaction (sepsis) occurred in one (0.3%) of patients receiving avelumab plus BSC.

Serious adverse reactions occurred in 28% of patients receiving avelumab plus BSC. Serious adverse reactions in ≥ 1% of patients included urinary tract infection (including kidney infection, pyelonephritis, and urosepsis) (6.1%), pain (including abdominal, back, bone, flank, extremity, and pelvic pain) (3.2%), acute kidney injury (1.7%), haematuria (1.5%), sepsis (1.2%), and infusion-related reaction (1.2%).

Permanent discontinuation due to an adverse reaction of avelumab plus BSC occurred in 12% of patients. Adverse reactions resulting in permanent discontinuation of avelumab in > 1% of patients were myocardial infarction (including acute myocardial infarction and troponin T increased) (1.5%) and infusion-related reaction (1.2%).

Dose interruptions due to an adverse reaction, excluding temporary interruptions of avelumab infusions due to infusion-related reactions, occurred in 41% of patients receiving avelumab plus BSC. Adverse reactions leading to interruption of avelumab in > 2% of patients were urinary tract infection (including

pyelonephritis) (4.7%) and blood creatinine increased (including acute kidney injury, renal impairment, and renal failure) (3.8%).

The most common adverse reactions ($\geq 20\%$) in patients receiving avelumab plus BSC were fatigue, musculoskeletal pain, urinary tract infection, and rash.

Thirty-one (9%) patients treated with avelumab plus BSC received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction.

Table 3 summarizes adverse reactions that occurred in $\geq 10\%$ of patients treated with avelumab plus BSC.

Table 3: Adverse Reactions ($\geq 10\%$) of Patients Receiving avelumab plus BSC (Study B9991001)

Adverse Reactions	AVELUMAB plus BSC (N=344)		BSC (N=345)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
General Disorders and Administration Site Conditions				
Fatigue ^a	35	1.7	13	1.7
Pyrexia	15	0.3	3.5	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ^b	24	1.2	15	2.6
Arthralgia	16	0.6	6	0
Skin and Subcutaneous Tissue Disorders				
Rash ^c	20	1.2	2.3	0
Pruritus	17	0.3	1.7	0
Infections and Infestations				
Urinary tract infection ^d	20	6	11	3.8
Gastrointestinal Disorders				
Diarrhea	17	0.6	4.9	0.3
Constipation	16	0.6	9.0	0
Nausea	16	0.3	6	0.6
Vomiting	13	1.2	3.5	0.6
Respiratory, Thoracic and Mediastinal Disorders				
Cough ^e	14	0.3	4.6	0
Metabolism and Nutrition Disorders				
Decreased appetite	14	0.3	7	0.6
Endocrine disorders				
Hypothyroidism	12	0.3	0.6	0
Injury, Poisoning and Procedural Complications				
Infusion-related reaction	10	0.9	0	0

^a Fatigue is a composite term that includes fatigue, asthenia and malaise.

^b Musculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain.

^c Rash is a composite term that includes rash, rash maculo-papular, erythema, dermatitis acneiform, eczema, erythema multiforme, rash erythematous, rash macular, rash papular, rash pruritic, drug eruption and lichen planus.

^d Urinary tract infection is a composite term that includes urinary tract infection, urosepsis, cystitis, kidney infection, pyuria, pyelonephritis, bacteriuria, pyelonephritis acute, urinary tract infection bacterial, and Escherichia urinary tract infection.

^e Cough is a composite term that includes cough and productive cough.

Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Infusion-related reactions occurred in 10% (Grade 3: 0.9%) of patients treated with avelumab plus BSC.

Table 4: Selected Laboratory Abnormalities Worsening from Baseline Occurring in $\geq 10\%$ of Patients Receiving avelumab plus BSC (Study B9991001)

Laboratory Abnormality	AVELUMAB plus BSC*		BSC*	
	Any Grade %	Grade 3-4 %	Any Grade %	Grade 3-4 %
Chemistry				
Blood triglycerides increased	34	2.1	28	1.2
Alkaline phosphatase increased	30	2.9	20	2.3
Blood sodium decreased	28	6	20	2.6
Lipase increased	25	8	16	6
Aspartate aminotransferase (AST) increased	24	1.7	12	0.9
Blood potassium increased	24	3.8	16	0.9
Alanine aminotransferase (ALT) increased	24	2.6	12	0.6
Blood cholesterol increased	22	1.2	16	0.3
Serum amylase increased	21	5	12	1.8
CPK increased	19	2.4	12	0
Phosphate decreased	19	3.2	15	1.2
Hematology				
Hemoglobin decreased	28	4.4	18	3.2
White blood cell decreased	20	0.6	10	0
Platelet count decreased	18	0.6	12	0.3

*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Avelumab plus BSC group (range: 339 to 344 patients) and BSC group (range: 329 to 341 patients).

Previously-Treated Urothelial Carcinoma

The safety of avelumab was evaluated in 242 patients with locally advanced or metastatic UC receiving avelumab at 10 mg/kg every 2 weeks in the UC cohorts of the EMR100070-001 trial. Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. The median duration of exposure to avelumab was 12 weeks (range: 2 weeks to 92 weeks).

Fourteen patients (6%) who were treated with avelumab experienced either pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.

Grade 1-4 serious adverse reactions were reported in 41% of patients. The most frequent serious adverse reactions reported in $\geq 2\%$ of patients were urinary tract infection/urosepsis, abdominal pain, musculoskeletal pain, creatinine increased/renal failure, dehydration, haematuria/urinary tract haemorrhage, intestinal obstruction/small intestine obstruction, and pyrexia.

Permanent discontinuation due to an adverse reaction for avelumab occurred in 12% of patients. The adverse reaction that resulted in permanent discontinuation in $> 1\%$ of patients was fatigue.

Dose interruptions due to an adverse reaction, excluding temporary interruptions due to infusion-related reactions, occurred in 29% of patients receiving avelumab. Adverse reactions leading to interruption of Bavencio in $> 1\%$ of patients were diarrhoea, fatigue, dyspnoea, urinary tract infection, and rash.

The most common Grade 3 and 4 adverse reactions ($\geq 3\%$) were anaemia, fatigue, hyponatremia, hypertension urinary tract infection, and musculoskeletal pain.

The most common adverse reactions ($\geq 20\%$) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

Eleven (4.5%) patients received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction.

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 5.

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

Table 5: 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
Uncommon	Myasthenia gravis, myasthenic syndrome
Cardiac disorders	
Uncommon	Myocarditis
Vascular disorders	
Very common	Hypertension
Common	Hypotension, flushing

Frequency	Adverse reactions
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 (see section 5.1).

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

Immune-related pneumonitis

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

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

Avelumab was discontinued in 0.3% (6/1,738) of patients due to immune-related pneumonitis. All 21 patients with immune-related pneumonitis were treated with corticosteroids and 17 (81%) of the 21 patients were treated with high-dose corticosteroids for a median of 8 days (range: 1 day to

2.3 months). Immune-related pneumonitis resolved in 12 (57%) of the 21 patients at the time of data cut-off.

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

The median time to onset of immune-related pneumonitis was 3.7 months (range: 2.7 months to 8.6 months). The median duration was 2.6 months (range: 3.3 weeks to more than 7.9 months).

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

Immune-related hepatitis

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

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

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

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

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

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

Immune-related colitis

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

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

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

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

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

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

Immune-related pancreatitis

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 anti-drug antibodies (ADA) method with improved sensitivity for evaluating treatment-emergent ADA in patients treated with avelumab as a single agent was used for study B9991001.

Of the 344 patients treated with Bavencio 10 mg/kg as an intravenous infusion every 2 weeks plus BSC, 325 were evaluable for treatment-emergent anti-drug antibodies (ADA) and 62 (19.1%) tested positive in the B9991001 study. Based on data available, including the low incidence of immunogenicity, the impact of ADA on pharmacokinetics, efficacy and safety is uncertain, while the impact of neutralizing antibodies (nAb) is unknown.

Of the 480 patients with at least one valid ADA result at any time point treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily, 453 were evaluable for treatment-emergent ADA and 66 (15%) tested positive in the B9991002 and B9991003 studies. The new 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.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il/>

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

Clinical efficacy and safety

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), and 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 6 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 6: 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 (%) (95% CI)	29 (33.0%) (23.3, 43.8)
Confirmed best overall response (BOR) Complete response (CR)** n (%) Partial response (PR)** n (%)	10 (11.4%) 19 (21.6%)
Duration of response (DOR)^a Median, months (95% CI) Minimum, maximum (months) ≥ 6 months by K-M, (95% CI) ≥ 12 months by K-M, (95% CI) ≥ 24 months by K-M, (95% CI) ≥ 36 months by K-M, (95% CI)	40.5 (18, not estimable) 2.8, 41.5+ 93% (75, 98) 71% (51, 85) 67% (47, 82) 52% (26, 73)
Progression-free survival (PFS) Median PFS, months (95% CI) 6-month PFS rate by K-M, (95% CI) 12-month PFS rate by K-M, (95% CI) 24-month PFS rate by K-M, (95% CI) 36-month PFS rate by K-M, (95% CI)	2.7 (1.4, 6.9) 40% (29, 50) 29% (19, 39) 26% (17, 36) 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

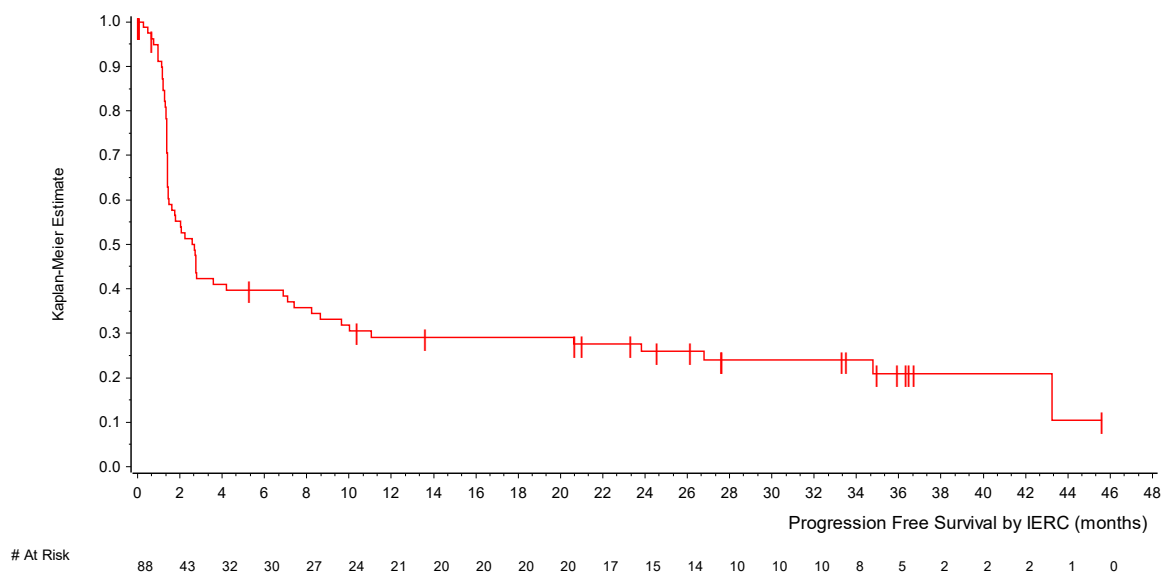
^a Based on number of patients with confirmed response (CR or PR)

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 curve 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)

Product-Limit Survival Estimate (N=88)



Tumour samples were evaluated for PD-L1 tumour cell expression, and for Merkel cell polyomavirus (MCV) using an investigational immunohistochemistry (IHC) assay. Table 7 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 7: 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 8 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 8: 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 (95% CI)	30.2% (22.0, 39.4)
Objective response rate (ORR) Response rate, CR+PR** n (%) (95% CI)	46 (39.7%) (30.7, 49.2)
Confirmed best overall response (BOR) Complete response (CR)** n (%) Partial response (PR)** n (%)	19 (16.4%) 27 (23.3%)
Duration of response (DOR)^a Median, months (95% CI) Minimum, maximum (months) ≥ 3 months by K-M, (95% CI) ≥ 6 months by K-M, (95% CI) ≥ 12 months by K-M, (95% CI) ≥ 18 months by K-M, (95% CI) ≥ 24 months by K-M, (95% CI)	18.2 (11.3, not estimable) 1.2, 28.3 89% (75, 95) 78% (63, 87) 66% (50, 78) 52% (34, 67) 45% (25, 63)
Progression-free survival (PFS) Median PFS, months (95% CI) 3-month PFS rate by K-M, (95% CI) 6-month PFS rate by K-M, (95% CI) 12-month PFS rate by K-M, (95% CI) 24-month PFS rate by K-M, (95% CI)	4.1 (1.4, 6.1) 51% (42, 60) 41% (32, 50) 31% (23, 40) 20% (12, 30)

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; K-M: Kaplan-Meier

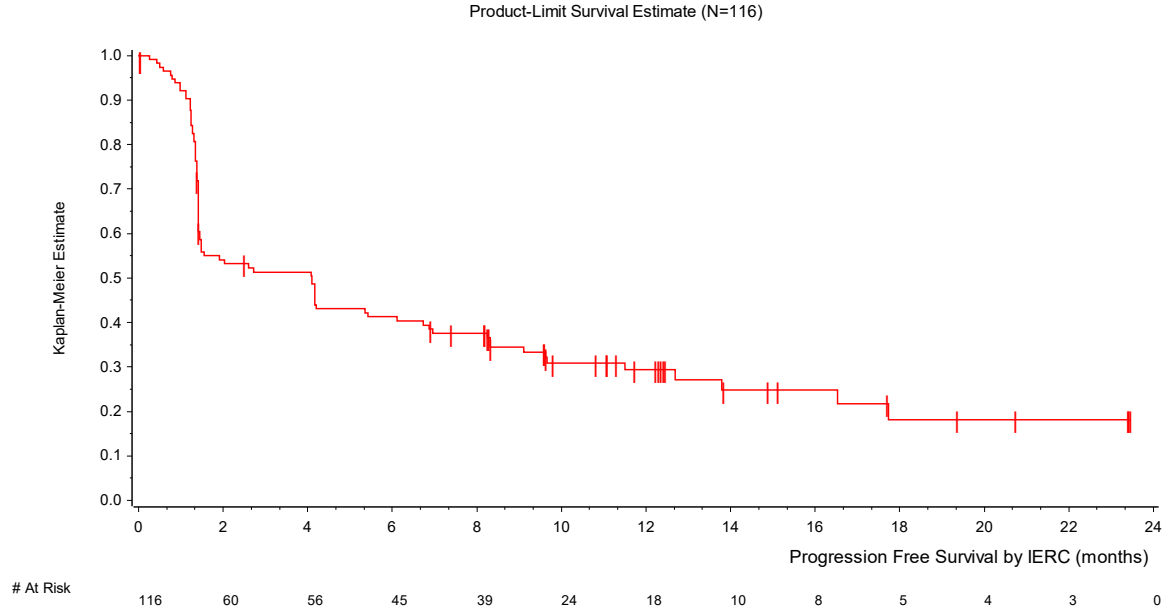
* Efficacy data with a minimum follow-up of 15 months (cut-off date 02 May 2019)

** 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 curve 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 9 summarises the objective response rates by PD-L1 expression and MCV status of patients with metastatic MCC in study EMR100070-003 (Part B).

Table 9: 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 $\geq 1\%$	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

First-Line Maintenance Treatment of Urothelial Carcinoma

The efficacy and safety of Bavencio was demonstrated in the B9991001 study (NCT02603432), a randomized, multi-center, open-label study conducted in 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing 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 chemotherapy. Patients were randomized (1:1) to receive either Bavencio 10 mg/kg intravenous infusion every 2 weeks plus best

supportive care (BSC) or BSC alone. Treatment was initiated within 4-10 weeks after the last dose of chemotherapy.

Treatment with BAVENCIO continued until RECIST v1.1-defined progression of disease by Blinded Independent Central Review (BICR) assessment or unacceptable toxicity. Administration of BAVENCIO was permitted beyond RECIST-defined disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Assessment of tumor 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.

Baseline characteristics were well-balanced between arms. Overall, the median age was 69 years (range: 32 to 90), with 66% of patients ≥ 65 years of age and 24% of patients ≥ 75 years of age. Most patients were male (77%). The majority of patients were White (67%) and 22% were Asian. Baseline ECOG PS was 0 (61%) or 1 (39%).

Fifty-six percent (56%) of patients received prior gemcitabine plus cisplatin, 38% of patients received prior gemcitabine plus carboplatin, and 6% of patients received prior gemcitabine plus cisplatin and gemcitabine plus carboplatin. Best response to first-line chemotherapy was CR or PR (72%) or SD (28%). Sites of metastasis prior to chemotherapy were visceral (55%) or non-visceral (45%). Fifty-one (51%) of patients had PD-L1-positive-tumors, 39% of patients had PD-L1-negative tumors, and 10% of patients had unknown PD-L1 tumor status. Six percent (6%) of patients received another PD-1/PD-L1 checkpoint inhibitor after discontinuation of treatment in the Bavencio plus BSC arm and 44% of patients in the BSC arm.

The major efficacy outcome measure was overall survival (OS) in all randomized patients and patients with PD-L1-positive tumors. The trial demonstrated a statistically significant improvement in OS for patients randomized to Bavencio plus BSC as compared with BSC alone (Table 10 and Figure 3). Consistent results were observed across the pre-specified subgroup of CR/PR versus SD to first-line chemotherapy.

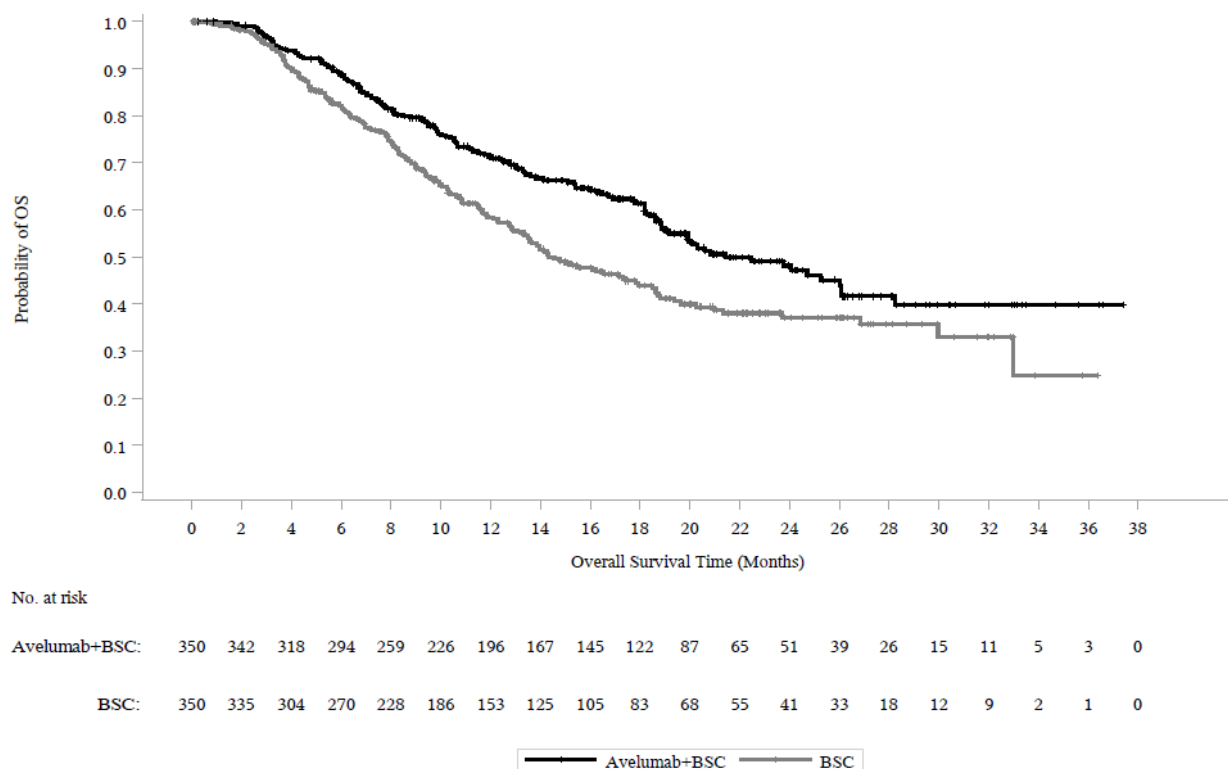
Table 10: Efficacy Results from the B9991001 study

Efficacy Endpoints	Bavencio plus BSC (N=350)	BSC (N=350)
Overall Survival (OS)		
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 (0.56, 0.86)	
2-sided p-value*	0.001	

BSC: Best supportive care; CI: Confidence interval.

* p-value based on stratified log-rank.

Figure 3: Kaplan-Meier Estimates for OS from the B9991001 study



In the prespecified endpoint of OS among patients with PD-L1-positive tumours (n=358, 51%), the hazard ratio was 0.56 (95% CI: 0.40, 0.79; 2-sided p-value <0.001) for patients randomized to Bavencio plus BSC versus BSC alone. 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).

Previously-treated Urothelial Carcinoma

The efficacy and safety of Bavencio was demonstrated in the UC cohorts of the EMR100070-001 trial, an open-label, single-arm, multi-center study that included 242 patients with locally advanced or metastatic urothelial carcinoma (UC) with disease progression on or after platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Patients with active or history of central nervous system metastasis; other malignancies within the last 5 years; organ transplant; conditions requiring therapeutic immune suppression; or active infection with HIV, hepatitis B, or hepatitis C were excluded. Patients with autoimmune disease, other than type 1 diabetes, vitiligo, psoriasis, or thyroid disease that did not require immunosuppressive treatment, were excluded. Patients were included regardless of their PD-L1 status.

Patients received Bavencio at a dose of 10 mg/kg intravenously every 2 weeks until radiographic or clinical progression or unacceptable toxicity. Tumour response assessments were performed every 6 weeks. Efficacy outcome measures included confirmed overall response rate (ORR), as assessed by an Independent Endpoint Review Committee (IERC) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, and duration of response (DOR). Efficacy was evaluated in patients who were followed for a minimum of both 13 weeks and 6 months at the time of data cut-off.

Baseline demographic and disease characteristics for the 226 patients with a minimum of 13 weeks of follow-up were median age 68 years (range: 30 to 89), 72% male, 80% White, and 34% and 66% of patients had an ECOG performance status 0 and 1, respectively. Forty-four percent of patients had non-bladder urothelial carcinoma including 23% of patients with upper tract disease, and 83% of patients had visceral metastases (baseline target and/or non-target lesions present outside of the lymph nodes). Nine (4%) patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy only. Forty-seven percent of patients only received prior cisplatin-based regimens, 32% received only prior carboplatin-based regimens, and 20% received both cisplatin and carboplatin-

based regimens. At baseline, 17% of patients had a haemoglobin < 10 g/dL and 34% of patients had liver metastases.

Efficacy results are presented in Table 11. The median time to response was 2.0 months (range: 1.3 to 11.0) among patients followed for either ≥ 13 weeks or ≥ 6 months. Using a clinical trial assay to assess PD-L1 staining, with 16% of patients not evaluable, there were no clear differences in response rates based on PD-L1 tumour expression. Among the total 30 responding patients followed for ≥ 13 weeks, 22 patients (73%) had an ongoing response of 6 months or longer and 4 patients (13%) had ongoing responses of 12 months or longer. Among the total 26 responding patients followed for ≥ 6 months, 22 patients (85%) had ongoing responses of 6 months or longer and 4 patients (15%) had ongoing responses of 12 months or longer.

Table 11: Efficacy Results of the UC Cohorts in the EMR100070-001 Trial

Efficacy Endpoints	≥ 13 Weeks Follow-Up (N=226)	≥ 6 Months Follow-Up (N=161)
Confirmed Overall Response Rate (ORR)		
Overall Response Rate n (%) (95% CI)	30 (13.3%) (9.1, 18.4)	26 (16.1%) (10.8, 22.8)
Complete Response (CR) n (%)	9 (4.0%)	9 (5.6%)
Partial Response (PR) n (%)	21 (9.3%)	17 (10.6%)
Duration of Response (DOR)		
Median, months (range)	NE (1.4+ to 17.4+)	NE (1.4+ to 17.4+)

CI: Confidence interval; NE: Not estimable; + denotes a censored value

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 $\geq 1\%$). 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).

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

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

Efficacy results are presented in Table 12 and Figure 4 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 12: Efficacy results from study B9991003 in patients irrespective of PD-L1 expression

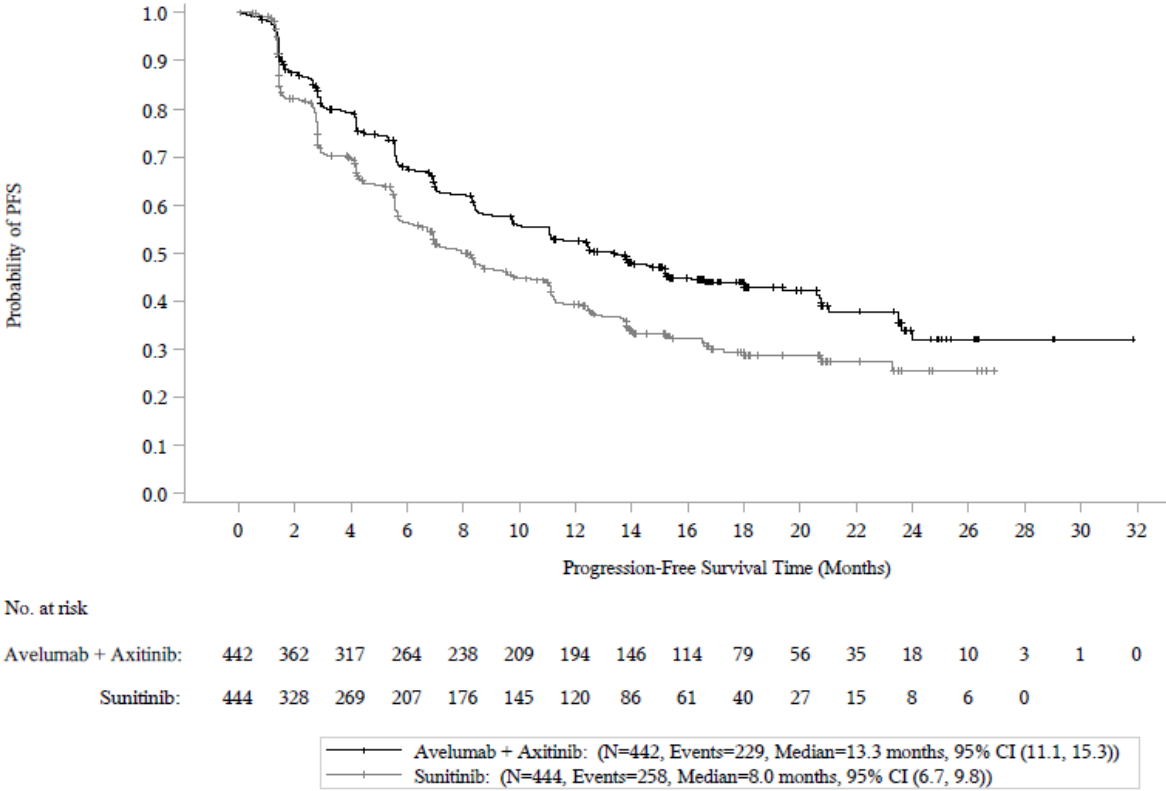
Efficacy endpoints (Based on BICR assessment)	Avelumab plus axitinib (N=442)	Sunitinib (N=444)
Progression-free survival (PFS)		
Events (%)	229 (52)	258 (58)
Median in months (95% CI)	13.3 (11.1, 15.3)	8.0 (6.7, 9.8)
Hazard ratio (95% CI)	0.69 (0.574, 0.825)	
p-value*	< 0.0001	
12-month PFS rate by K-M, (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.

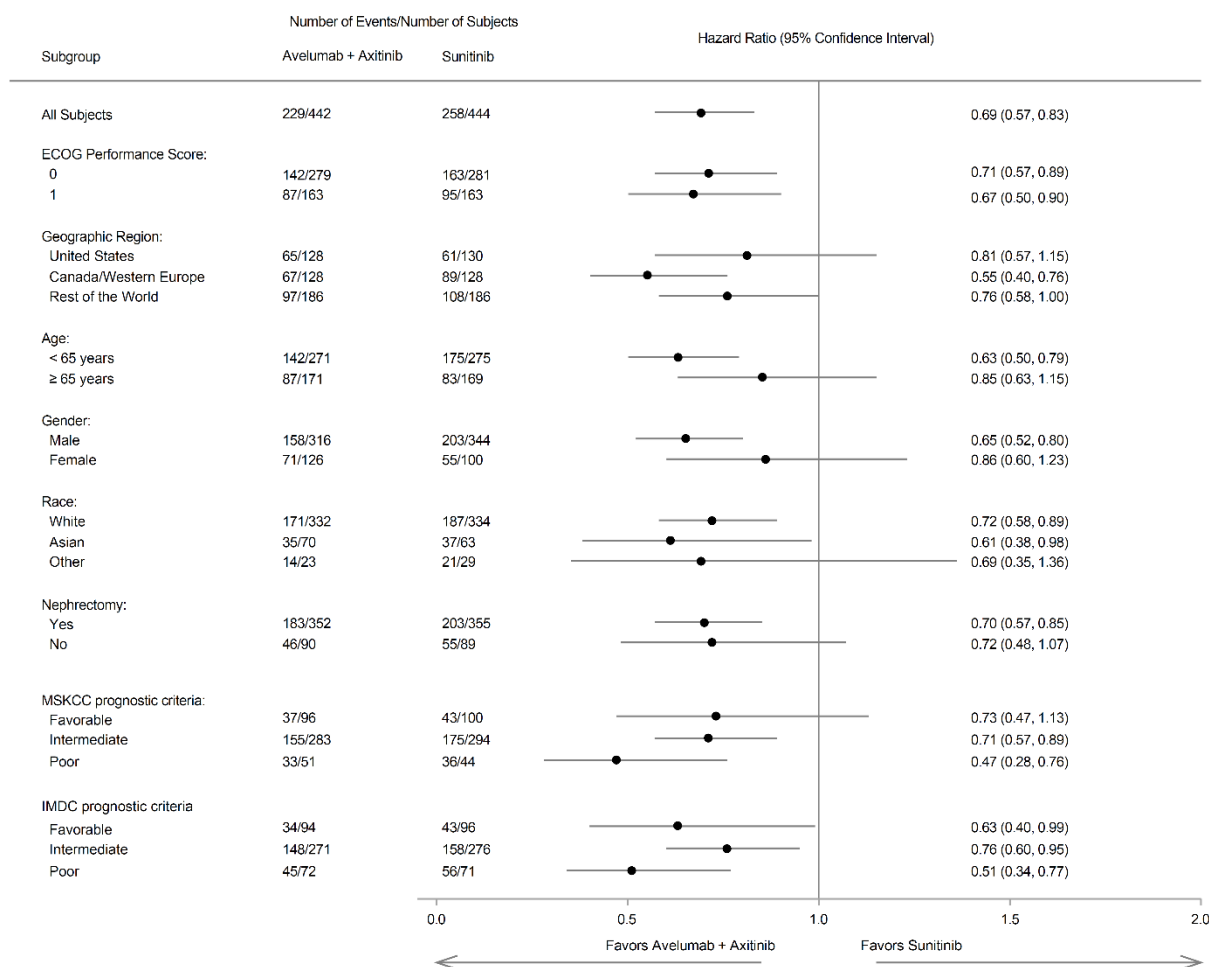
** CIs are derived using the log-log transformation with back transformation to untransformed scale.

Figure 4: 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 5: Forest plot of progression-free survival based on BICR assessment in patients irrespective of PD-L1 expression



5.2 Pharmacokinetic properties

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

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

Distribution

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

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

Elimination

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

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

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

Linearity/non-linearity

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

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

Special populations

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

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

Renal impairment

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

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

Hepatic impairment

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

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

5.3 Preclinical safety data

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

Animal reproduction studies have not been conducted with avelumab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the 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
Glacial acetic acid
Polysorbate 20
Sodium hydroxide
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

After opening

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

After preparation of infusion

Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at room temperature and room light. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the diluted solution should be infused immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than a total of 24 hours under refrigerated conditions (2° C to 8°C) or up to 8 hours at room temperature (20°C to 25°C). If refrigerated, allow the vial and/or intravenous bag to come to room temperature prior to use.

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.

Disposal

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

7. MANUFACTURER

Merck Serono S.A.
Succursale d'Aubonne,
Zone Industrielle de l'Ourietaz,
1170 Aubonne,
Switzerland

8. REGISTRATION HOLDER

Merck Serono Ltd.
18 Hakishon St.,
Yavne 81220
Israel

9. LICENSE NUMBER

159 77 35284 00

10. DATE OF REVISION OF THE TEXT

Revised in December 2020.