ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 285 and 350 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

Treatment-related adverse reaction	Severity*	Treatment modification
Nephritis and renal dysfunction	Serum creatinine more than 1.5 and up to 6 times ULN	Withhold until adverse reactions recover to Grade 0-1
	Serum creatinine more than 6 times ULN	Permanently discontinue
Skin reactions	Grade 3 rash	Withhold until adverse reactions recover to Grade 0-1
	Grade 4 or recurrent Grade 3 rash or confirmed Stevens–Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN)	Permanently discontinue
Other immune-related adverse reactions (including myositis, hypopituitarism, uveitis, myasthenia gravis, myasthenic syndrome, Guillain-Barré syndrome)	For any of the following: • Grade 2 or Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above	Withhold until adverse reactions recover to Grade 0-1
	For any of the following: • Life threatening or Grade 4 adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy) • Recurrent Grade 3 immune-related adverse reaction • Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks • Persistent Grade 2 or Grade 3 immune-mediate adverse reactions lasting 12 weeks or longer	Permanently discontinue

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

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

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

Dose modification advice for axitinib when used with Bavencio
When Bavencio is administered in combination with axitinib, please refer to the axitinib product information for recommended dose modifications for axitinib.

Special populations

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

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

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

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

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

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

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

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

Immune-related pneumonitis

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

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

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

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

Immune-related hepatitis

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

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

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

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

Immune-related colitis

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

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

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

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

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

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

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

Patients should be monitored for signs and symptoms of immune-related myocarditis. In symptomatic patients, obtain cardiologic consultation and laboratory investigations to ensure the initiation of appropriate measures at an early stage. Corticosteroids should be administered for immune-related myocarditis (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper). If no improvement within 24 hours on corticosteroids, additional immunosuppression (e.g., mycophenolate, infliximab, anti-thymocyte globulin) should be considered.

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

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

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

Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Hypothyroidism should be managed with replacement therapy and hyperthyroidism with anti-thyroid medicinal product, as needed.

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

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

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

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

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

Immune-related nephritis and renal dysfunction
Avelumab can cause immune-related nephritis (see section 4.8).

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

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

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

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

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

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

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

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

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

4.5 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

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

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

The most common Grade ≥ 3 adverse reactions were anaemia (5.6%), hypertension (3.9%), hyponatraemia (3.6%), dyspnoea (3.5%), and abdominal pain (2.6%). Serious adverse reactions were immune-related adverse reactions and infusion-related reaction (see section 4.4).

Tabulated list of adverse reactions
The safety of avelumab as monotherapy has been evaluated in 2 082 patients with solid tumours including metastatic MCC or locally advanced or metastatic UC receiving 10 mg/kg every 2 weeks of avelumab in clinical studies (see Table 2).

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**
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Lymphopenia, thrombocytopenia
Uncommon	Eosinophilia[§]
Immune system disorders	
Uncommon	Hypersensitivity, drug hypersensitivity, sarcoidosis**
Rare	Anaphylactic reaction, Type I hypersensitivity
Endocrine disorders	
Common	Hypothyroidism*, hyperthyroidism*
Uncommon	Adrenal insufficiency*, autoimmune thyroiditis*, thyroiditis*, autoimmune hypothyroidism*
Rare	Adrenocortical insufficiency acute*, hypopituitarism*
Metabolism and nutrition disorders	
Very common	Decreased appetite
Common	Hyponatraemia
Uncommon	Hyperglycaemia*
Rare	Diabetes mellitus*, Type 1 diabetes mellitus*
Nervous system disorders	
Common	Headache, dizziness, neuropathy peripheral
Uncommon	Myasthenia gravis[†], myasthenic syndrome[†]
Rare	Guillain-Barré Syndrome*, Miller Fisher syndrome*
Eye disorders	
Rare	Uveitis*
Cardiac disorders	
Rare	Myocarditis*
Vascular disorders	
Common	Hypertension
Uncommon	Hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnoea
Common	Pneumonitis*
Rare	Interstitial lung disease*
Gastrointestinal disorders	
Very common	Nausea, diarrhoea, constipation, vomiting, abdominal pain
Common	Dry mouth
Uncommon	Ileus, colitis*
Rare	Pancreatitis*, autoimmune colitis*, enterocolitis*, autoimmune pancreatitis*, enteritis*, proctitis*
Hepatobiliary disorders	
Uncommon	Autoimmune hepatitis*
Rare	Acute hepatic failure*, hepatic failure*, hepatitis*, hepatotoxicity*

Frequency	Adverse reactions
Skin and subcutaneous tissue disorders	
Common	Pruritus*, rash*, dry skin, rash maculo-papular*
Uncommon	Eczema, dermatitis, rash pruritic*, psoriasis*, erythema*, rash erythematous*, rash generalised*, rash macular*, rash papular*
Rare	Erythema multiforme*, purpura*, vitiligo*, pruritus generalised*, dermatitis exfoliative*, pemphigoid*, dermatitis psoriasiform*, drug eruption*, lichen planus*
Musculoskeletal and connective tissue disorders	
Very common	Back pain, arthralgia
Common	Myalgia
Uncommon	Myositis*, rheumatoid arthritis*
Rare	Arthritis*, polyarthritis*, oligoarthritis*
Renal and urinary disorders	
Uncommon	Renal failure*, nephritis*
Rare	Tubulo-interstitial nephritis*, cystitis noninfective*
General disorders and administrative site conditions	
Very common	Fatigue, pyrexia, oedema peripheral
Common	Asthenia, chills, influenza like illness
Rare	Systemic inflammatory response syndrome*
Investigations	
Very common	Weight decreased
Common	Blood creatinine increased, blood alkaline phosphatase increased, lipase increased, gamma-glutamyltransferase increased, amylase increased
Uncommon	Alanine aminotransferase (ALT) increased*, aspartate aminotransferase (AST) increased*, blood creatine phosphokinase increased*
Rare	Transaminases increased*, thyroxine free decreased*, blood thyroid stimulating hormone increased*
Injury, poisoning and procedural complications	
Very common	Infusion related reaction

* Immune-related adverse reaction based on medical review

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

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

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

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
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

Frequency	Adverse reactions
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 2 082 patients including 1 650 patients in the phase I study EMR100070-001 in solid tumours, 88 patients in study EMR100070-003 in MCC, and 344 patients in study B9991001 in UC, and for avelumab in combination with axitinib are based on 489 patients in studies B9991002 and B9991003 in RCC (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, 1.3% (28/2 082) of patients developed immune-related pneumonitis. Of these patients, there was 1 (less than 0.1%) patient with a fatal outcome, 1 (less than 0.1%) patient with Grade 4, and 6 (0.3%) patients with Grade 3 immune-related pneumonitis.

The median time to onset of immune-related pneumonitis was 2.5 months (range: 3 days to 13.8 months). The median duration was 8.1 weeks (range: 4 days to more than 4.9 months).

Avelumab was discontinued in 0.4% (9/2 082) of patients due to immune-related pneumonitis. All 28 patients with immune-related pneumonitis were treated with corticosteroids and 21 (75%) of the 28 patients were treated with high-dose corticosteroids for a median of 9 days (range: 1 day to 2.3 months). Immune-related pneumonitis resolved in 18 (64.3%) of the 28 patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, 0.6% (3/489) of patients developed immune-related pneumonitis. Of these patients, none experienced immune-related pneumonitis Grade $\geq$ 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, 1.0% (21/2 082) of patients developed immune-related hepatitis. Of these patients, there were 2 (0.1%) patients with a fatal outcome, and 16 (0.8%) patients with Grade 3 immune-related hepatitis.

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

Avelumab was discontinued in 0.6% (13/2 082) of patients due to immune-related hepatitis. All 21 patients with immune-related hepatitis were treated with corticosteroids and 20 (95.2%) of the 21 patients received high-dose corticosteroids for a median of 17 days (range: 1 day to 4.1 months). Immune-related hepatitis resolved in 12 (57.1%) of the 21 patients at the time of data cut-off.

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

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

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

Immune-related colitis
In patients treated with avelumab as monotherapy, 1.5% (31/2 082) of patients developed immune-related colitis. Of these patients, there were 10 (0.5%) patients with Grade 3 immune-related colitis.

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

Avelumab was discontinued in 0.5% (11/2 082) of patients due to immune-related colitis. All 31 patients with immune-related colitis were treated with corticosteroids and 19 (61.3%) of the 31 patients received high-dose corticosteroids for a median of 19 days (range: 1 day to 2.3 months). Immune-related colitis resolved in 22 (71%) of 31 patients at the time of data cut-off.

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

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

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

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

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

Immune-related endocrinopathies

Thyroid disorders

In patients treated with avelumab as monotherapy, 6.7% (140/2 082) of patients developed immune-related thyroid disorders, including 127 (6.1%) patients with hypothyroidism, 23 (1.1%) with hyperthyroidism, and 7 (0.3%) with thyroiditis. Of these patients, there were 4 (0.2%) patients with Grade 3 immune-related thyroid disorders.

The median time to onset of thyroid disorders was 2.8 months (range: 2 weeks to 12.8 months). The median duration was not estimable (range: 3 days to more than 27.6 months).

Avelumab was discontinued in 0.2% (4/2 082) of patients due to immune-related thyroid disorders. Thyroid disorders resolved in 14 (10%) of the 140 patients at the time of data cut-off.

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

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

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

Adrenal insufficiency

In patients treated with avelumab as monotherapy, 0.5% (11/2 082) of patients developed immune-related adrenal insufficiency. Of these patients, there was 1 (less than 0.1%) patient with Grade 3 immune-related adrenal insufficiency.

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

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

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

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

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

Type 1 diabetes mellitus

In patients treated with avelumab as monotherapy, Type 1 diabetes mellitus without an alternative aetiology occurred in 0.2% (5/2 082) of patients. All 5 patients experienced Grade 3 Type 1 diabetes mellitus.

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

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

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

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

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

Immune-related nephritis and renal dysfunction
In patients treated with avelumab as monotherapy, immune-related nephritis occurred in 0.3% (7/2 082) of patients. There was 1 (less than 0.1%) patient with Grade 3 immune-related nephritis.

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

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

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

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

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

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

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

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

Immune checkpoint inhibitor class effects
There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with avelumab: pancreatic exocrine insufficiency, coeliac disease.

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

For study B9991001 in the UC population, out of 344 patients with at least one valid ADA result at any time point treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks plus BSC, 325 were evaluable for treatment-emergent ADA and 62 (19.1%) tested positive.

For study B9991002 and study B9991003 in the RCC population, out of 480 patients with at least one valid ADA result at any time point treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily, 453 were evaluable for treatment-emergent ADA and 66 (14.6%) tested positive.

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

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: L01FF04.

Mechanism of action
Avelumab is a human immunoglobulin G1 (IgG1) monoclonal antibody directed against programmed death ligand 1 (PD-L1). Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the programmed death 1 (PD-1) and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic $CD8^+$ T-cells, resulting in the restoration of anti-tumour T-cell responses. Avelumab has also shown to induce natural killer (NK) cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC).

Clinical efficacy and safety

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

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

Patients received avelumab at a dose of 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms, no change in performance status for greater than two weeks, and no need for salvage therapy could continue treatment.

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

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

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

Of the 88 patients, 65 (74%) were male, the median age was 73 years (range 33 years to 88 years), 81 (92%) patients were Caucasian, and 49 (56%) patients and 39 (44%) patients with an Eastern Cooperative Oncology Group (ECOG) performance status 0 and 1, respectively.

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

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

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

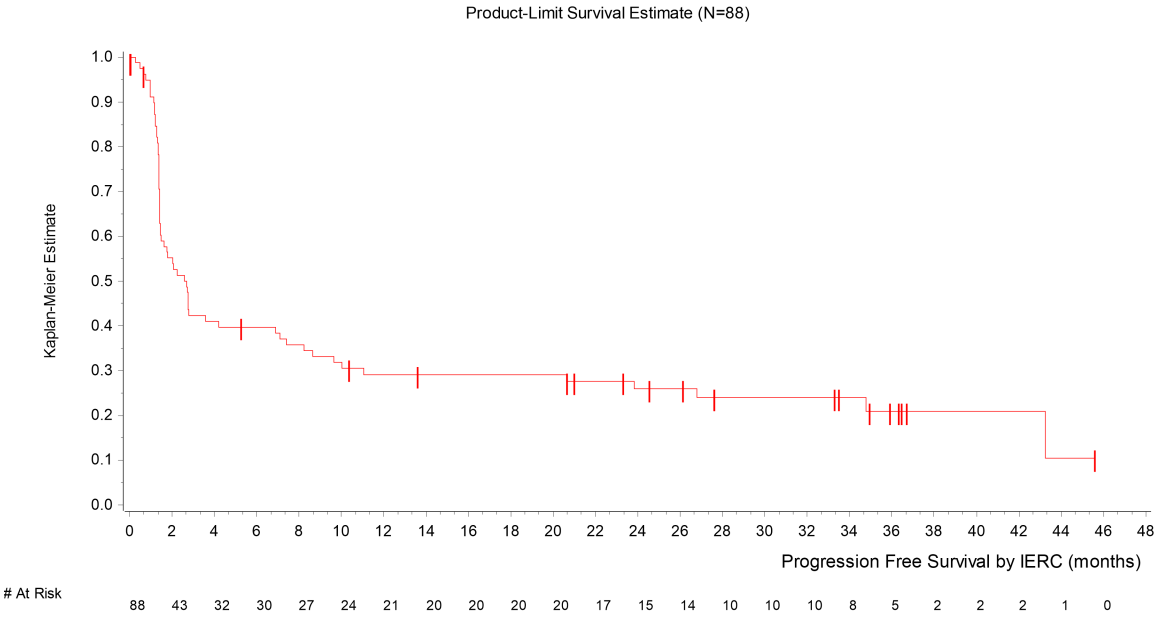
Efficacy endpoints (Part A) (per RECIST v1.1, IERC)	Results (N=88)
Objective response rate (ORR)	
Response rate, CR+PR** n (%)	29 (33.0%)
(95% CI)	(23.3, 43.8)
Confirmed best overall response (BOR)	
Complete response (CR)** n (%)	10 (11.4%)
Partial response (PR)** n (%)	19 (21.6%)
Duration of response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

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; K-M: Kaplan-Meier; +denotes a censored value
* Efficacy data with a minimum follow-up of 36 months (cut-off date 14 September 2018)
** CR or PR was confirmed at a subsequent tumour assessment
[a] Based on number of patients with confirmed response (CR or PR)

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

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

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



Tumour samples were evaluated for PD-L1 tumour cell expression, and for Merkel cell polyomavirus (MCV) using an investigational immunohistochemistry (IHC) assay. Table 5 summarises the objective response rates by the PD-L1 expression and MCV status of patients with metastatic MCC in study EMR100070-003 (Part A).

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

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

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

Study 003 Part B – patients who have not received systemic therapy in the metastatic setting
The major efficacy outcome measure was durable response, defined as objective response (complete response (CR) or partial response (PR)) with a duration of at least 6 months; secondary outcome measures included BOR, DOR, PFS, and OS.

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

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

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

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

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

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

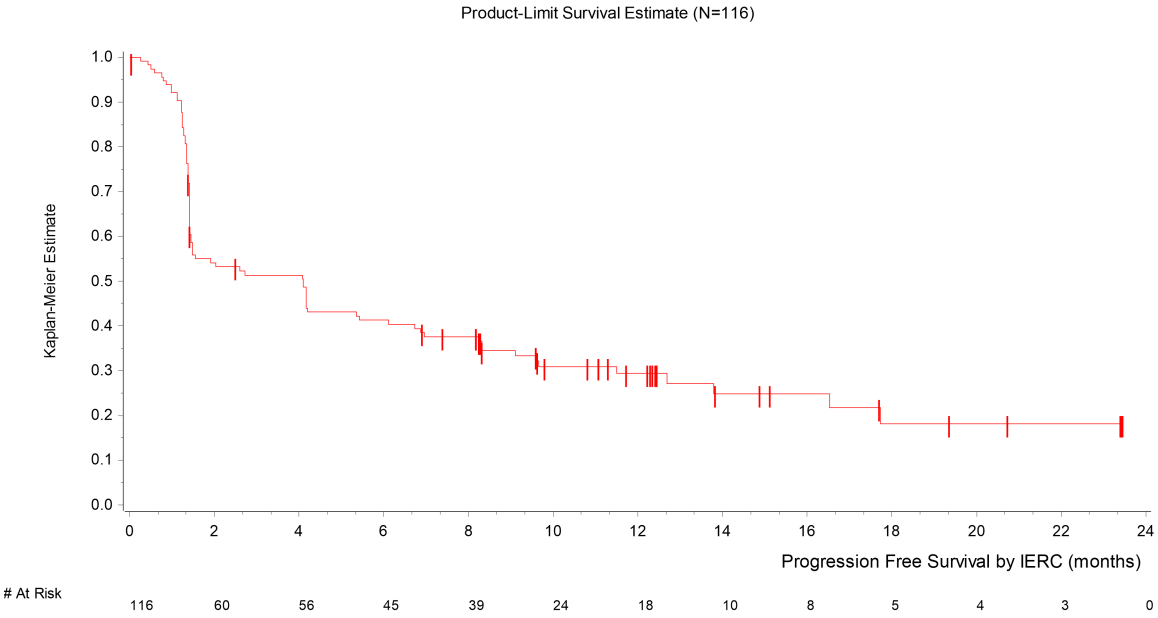
* Efficacy data with a minimum follow-up of 15 months (cut-off date 02 May 2019)

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

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

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

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



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

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

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

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

Locally advanced or metastatic urothelial carcinoma (study B9991001)
The efficacy and safety of avelumab was demonstrated in study B9991001, a randomised, multi-centre, open-label study conducted in 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma whose disease had not progressed with 4-6 cycles of first-line platinum-based induction chemotherapy. Patients with autoimmune disease or a medical condition that required immunosuppression were excluded.

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

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

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

For first-line induction chemotherapy, 56% of patients received cisplatin plus gemcitabine, 38% of patients received carboplatin plus gemcitabine and 6% of patients received cisplatin plus gemcitabine and carboplatin plus gemcitabine (i.e. these patients received one or more cycles of each combination). Best response to first-line induction chemotherapy was CR or PR (72%) or SD (28%). Sites of metastasis prior to chemotherapy were visceral (55%) or non-visceral (45%). Fifty-one percent of patients had PD-L1-positive tumours. Six percent of patients in the avelumab plus BSC arm and 44% of patients in the BSC alone arm received another PD-1/PD-L1 checkpoint inhibitor after discontinuation of treatment.

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

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

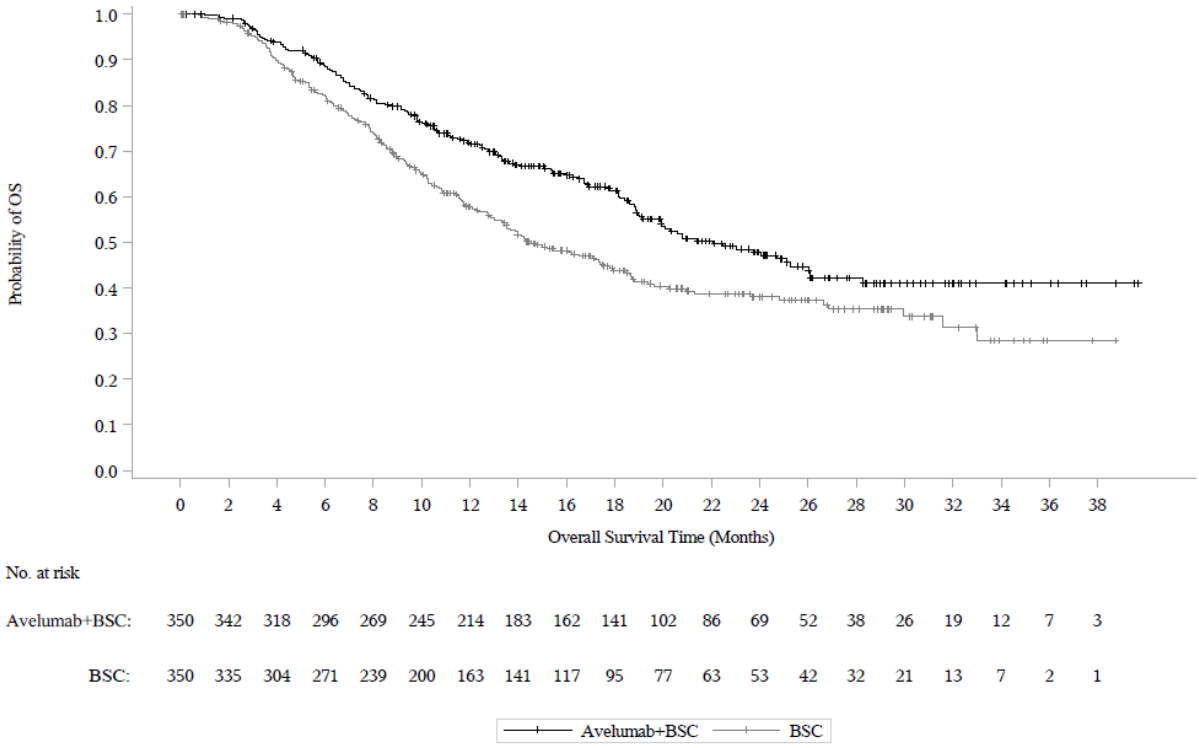
At the pre-specified interim analysis (cut-off date 21 October 2019), study B9991001 met its primary endpoint for OS in both coprimary populations: in all randomized patients with a median OS of 21.4 months (95% CI: 18.9, 26.1; HR 0.69, 95% CI: 0.556, 0.863) in the avelumab plus BSC arm and with a median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

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

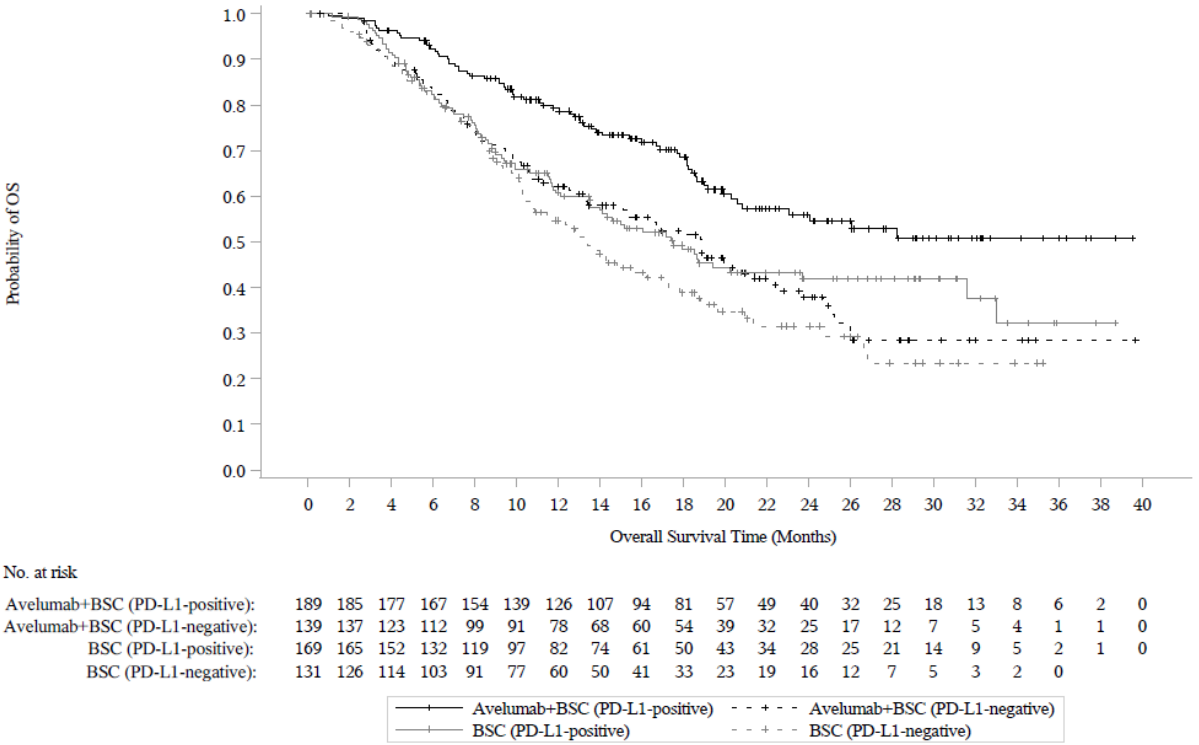
Efficacy endpoints	Avelumab plus BSC (N=350)	BSC (N=350)	Avelumab plus BSC (N=189)	BSC (N=169)	Avelumab plus BSC (N=139)	BSC (N=131)
	All randomized patients		**PD-L1-positive tumours**		**PD-L1-negative tumours**[c]	
Overall survival (OS)[a]						
Events (%)	156 (44.6)	190 (54.3)	68 (36.0)	85 (50.3)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

CI: Confidence interval; K-M: Kaplan-Meier, NE: not estimable
Note: 72 patients (22 patients on avelumab plus BSC arm and 50 patients on BSC alone arm) had a tumour with an unknown PD-L1 status
[a] OS cut-off date 19 January 2020
[b] PFS cut-off date 21 October 2019
[c] PD-L1-negative population analyses were exploratory and no formal test was performed
[d] p-value based on stratified log-rank
[e] Based on BICR assessment per RECIST v1.1
[f] PFS censoring reasons follow the hierarchy in sequential order: no adequate baseline assessment, start of new anti-cancer therapy, event after 2 or more missing assessments, withdrawal of consent, lost to follow-up, no adequate post-baseline tumour assessment, ongoing without an event

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

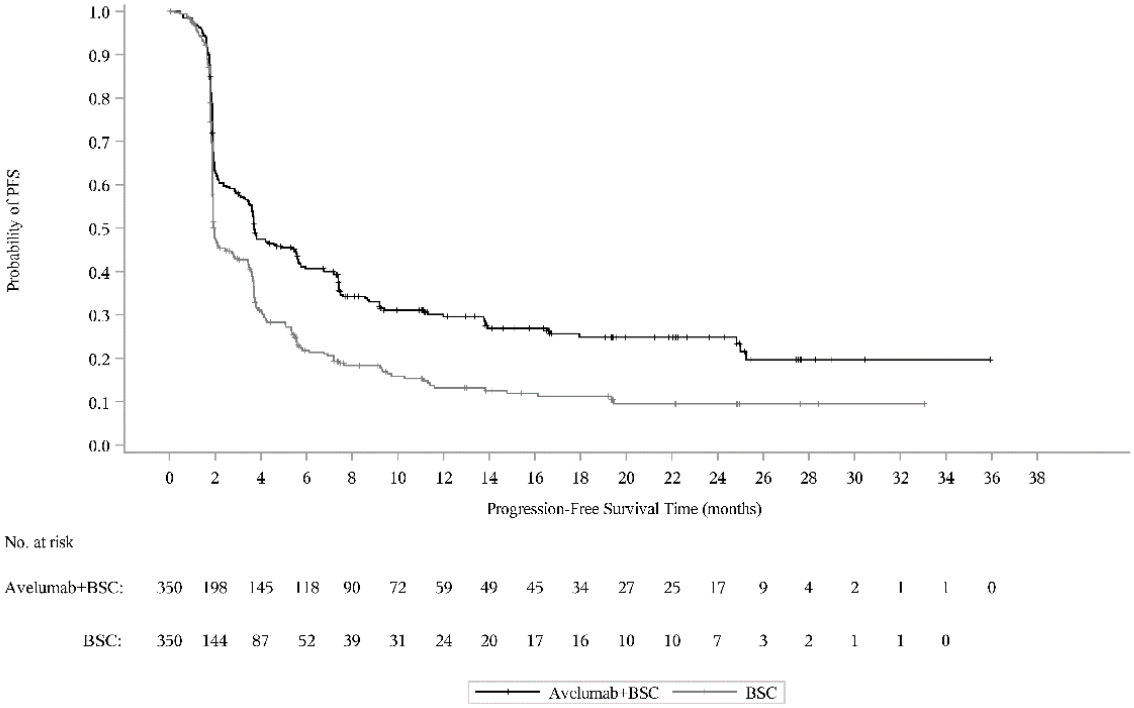


(A): All randomized patients

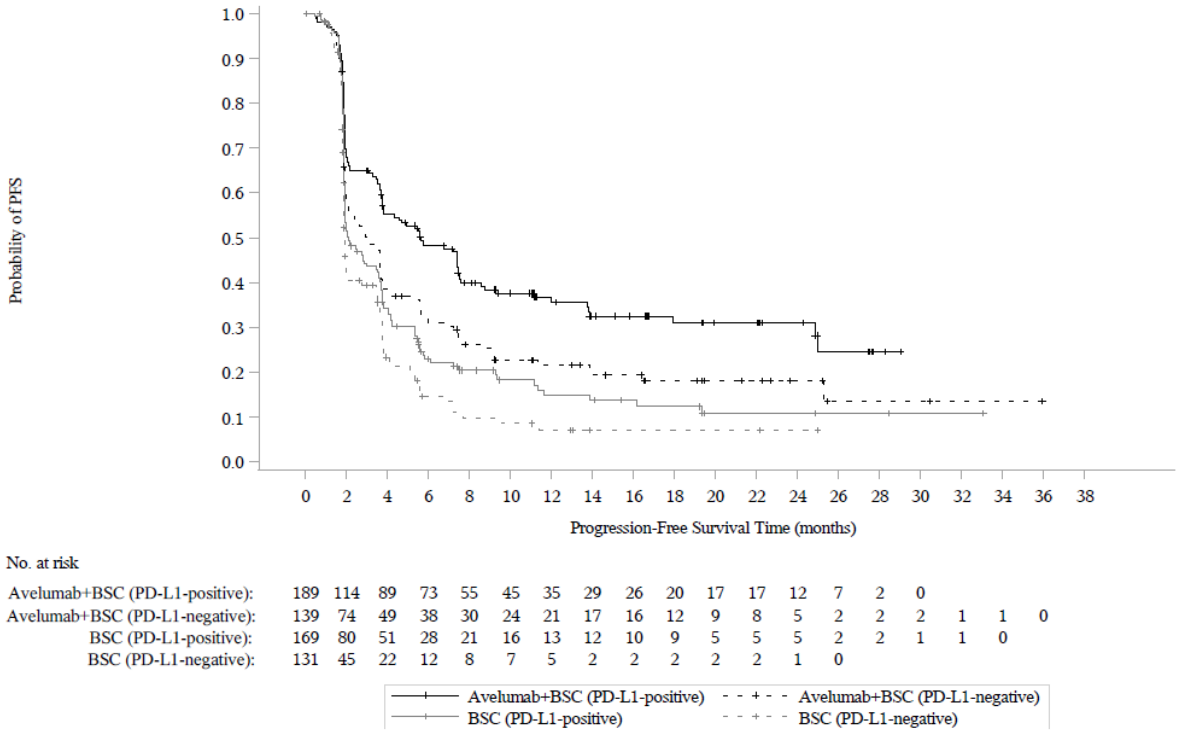


(B): Patients by PD-L1 expression

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



(A): All randomized patients



(B): Patients by PD-L1 expression

Renal cell carcinoma (study B9991003)

The efficacy and safety of avelumab in combination with axitinib was demonstrated in study B9991003, a randomised, multi-centre, open-label study of avelumab in combination with axitinib in 886 patients with untreated advanced or metastatic RCC with a clear-cell component.

Patients were included irrespective of prognostic risk groups or tumour PD-L1 expression and had to have at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 that was not been previously irradiated. Patients with prior systemic therapy directed at advanced or metastatic RCC; prior systemic immunotherapy treatment with IL-2, IFN-α, anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies, or active brain metastasis; active autoimmune disease that might deteriorate when receiving an immunostimulatory agents; a history of other malignancies within the last 5 years; organ transplant were ineligible.

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

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

Treatment with avelumab and axitinib continued until RECIST v1.1-defined progression of disease by Blinded Independent Central Review (BICR) assessment or unacceptable toxicity. Administration of avelumab and axitinib was permitted beyond RECIST-defined disease progression based on investigator's assessment of the patient's benefit-risk and clinical condition, including performance status, clinical symptoms, adverse events and laboratory data. The majority (n=160, 71.4%) of the patients with progressive disease continued treatment with both medicinal products after progression. Assessment of tumour status was performed at baseline, after randomisation at 6 weeks, then every 6 weeks thereafter up to 18 months after randomisation, and every 12 weeks thereafter until documented confirmed disease progression by BICR.

The primary efficacy endpoints were progression-free survival (PFS), as assessed by BICR using RECIST v1.1 and overall survival (OS) in the first-line treatment of patients with advanced RCC who have PD-L1-positive tumours (PD-L1 expression level ≥ 1%). The key secondary endpoints were PFS based on BICR assessment per RECIST v1.1 and OS irrespective of PD-L1 expression. PD-L1 status was determined by immunohistochemistry. Additional secondary endpoints included objective response (OR), time to response (TTR) and duration of response (DOR).

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

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

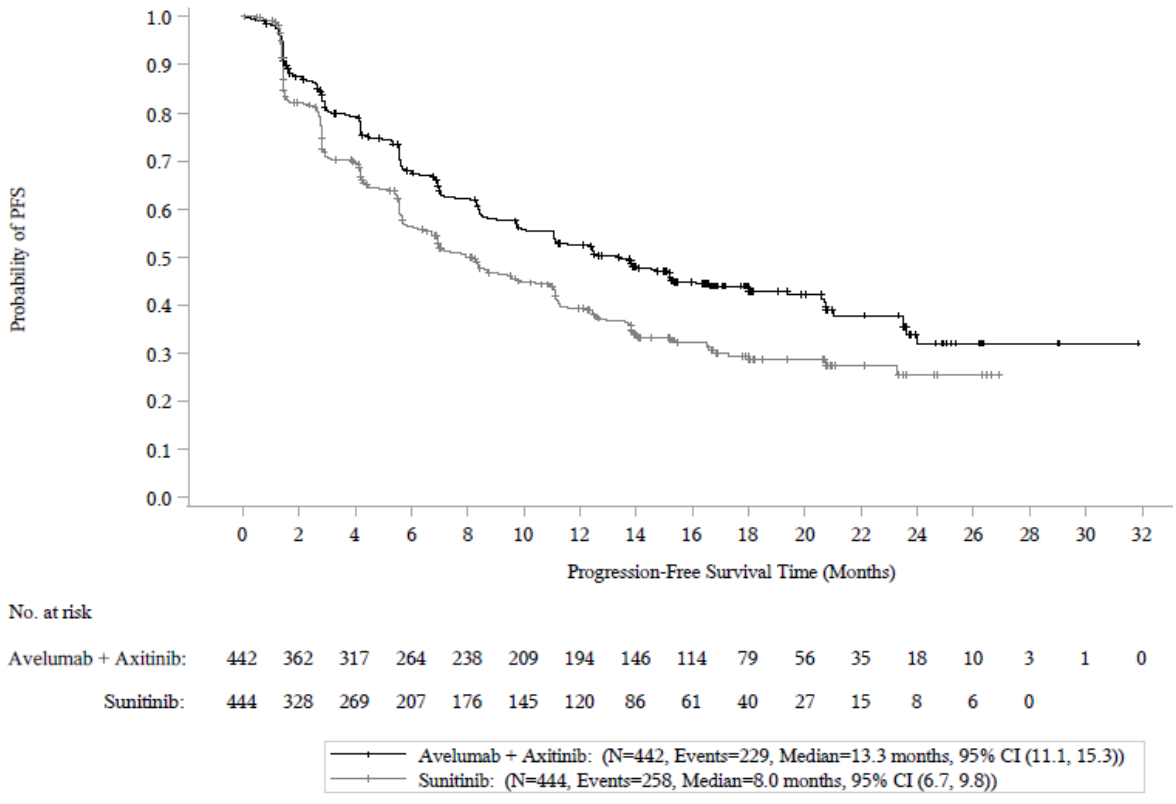
Efficacy results are presented in Table 9 and Figure 5 based on a data cut-off date of 28 January 2019. With a median OS follow-up of 19 months, OS data were immature with 27% deaths. The observed hazard ratio (HR) for OS was 0.80 (95% CI: 0.616, 1.027) for avelumab in combination with axitinib compared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

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

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

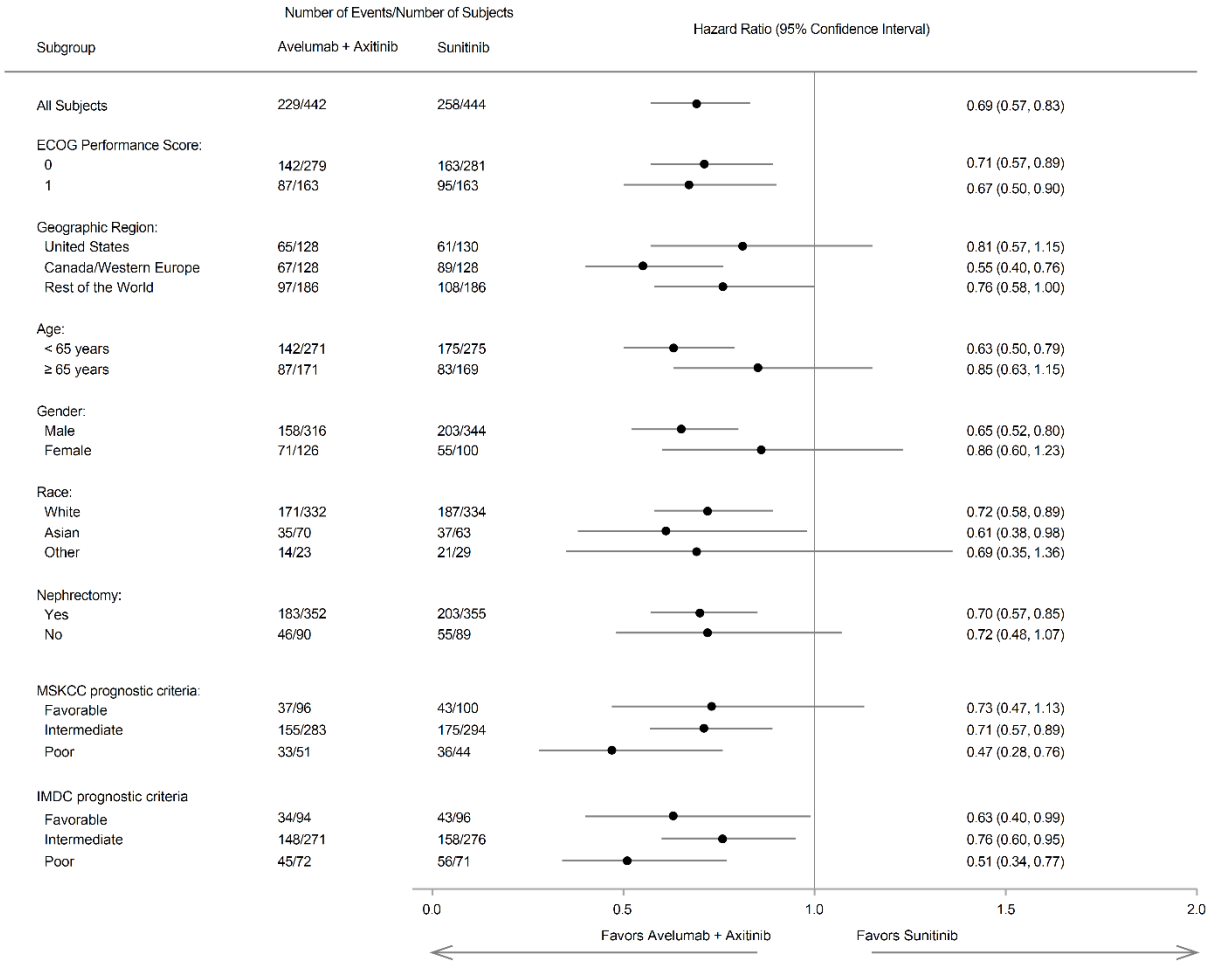
BICR: Blinded Independent Central Review; CI: Confidence interval; K-M: Kaplan-Meier; NE: Not estimable
* 1-sided p-value based on stratified log-rank
** CIs are derived using the log-log transformation with back transformation to untransformed scale

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



Improvement of PFS was observed across pre-specified subgroups.

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



Paediatric population

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

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

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

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

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

5.2 Pharmacokinetic properties

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

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

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

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

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

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

The elimination half-life ($t_{½}$) 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 $\geq$ 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 ≤ ULN and AST > ULN or bilirubin between 1 and 1.5 times ULN, n=217) and normal hepatic function (bilirubin and AST ≤ ULN, n=1 388) in a population PK analysis. Hepatic impairment was defined by National Cancer Institute (NCI) criteria of hepatic dysfunction.

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

Paediatric population
The pharmacokinetics of avelumab was evaluated in 21 children and adolescents from 3 years to 17 years in study MS100070-0306 receiving either 10 mg/kg (N=6) or 20 mg/kg (N=15) avelumab intravenously every 2 weeks until confirmed progression, death, or unacceptable toxicity.

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

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity in Cynomolgus monkeys administered intravenously doses of 20, 60 or 140 mg/kg once a week for1 month and 3 months, followed by a 2-month recovery period after the 3-month dosing period. Perivascular mononuclear cell cuffing was observed in the brain and spinal cord of monkeys treated with avelumab at ≥ 20 mg/kg for 3 months. Although there was no clear dose-response relationship, it cannot be excluded that this finding was related to avelumab treatment.

Animal reproduction studies have not been conducted with avelumab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk that administration of avelumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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
3 years

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

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

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

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the diluted solution should be infused immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

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

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

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. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1214/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 2017
Date of latest renewal: 23 July 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Merck Serono SA
Succursale de Corsier-sur-Vevey
Chemin du Fenil - Zone Industrielle B
1804 Corsier-sur-Vevey
Switzerland

Name and address of the manufacturer(s) responsible for batch release

Merck Serono S.p.A.
Via Delle Magnolie 15 (loc. frazione Zona Industriale)
70026 - Modugno (BA)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Bavencio in each Member State the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness and providing information concerning the signs and symptoms of certain important identified risks of avelumab, including immune-related pneumonitis, hepatitis, colitis, pancreatitis, myocarditis, thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, nephritis and renal dysfunction, myositis, hypopituitarism, uveitis, Guillain-Barre syndrome and infusion related reactions, and how to manage them.

The MAH shall ensure that in each Member State where Bavencio is marketed, all patients/carers who are expected to use Bavencio have access to/are provided with the following educational package:

- Patient Information Brochure
- Patient Alert Card

The patient educational material should contain

- Package leaflet
- Patient Information brochure
- Patient Alert Card

The Patient Information brochure shall contain the following key messages:

- Brief introduction to the tool and its purpose
- Brief introduction to Bavencio treatment
- Recommendation to consult the package leaflet
- Information that avelumab can cause serious side effects during or after treatment, that need to be treated right away and warning message on the importance of being aware of signs and symptoms while receiving avelumab treatment
- Reminder of the importance to consult their doctor before any change of treatment or in case of side effect

The Patient Alert Card shall contain the following key messages:

- Brief introduction to avelumab (indication and purpose of this tool)
- Description of the main signs and symptoms of the following safety concerns and reminder of the importance of notifying their treating physician immediately if symptoms occur, persist or worsen:
    - Immune-Related Pneumonitis
    - Immune-Related Hepatitis
    - Immune-Related Colitis
    - Immune-Related Pancreatitis
    - Immune-Related Myocarditis
    - Immune-Related Endocrinopathies (diabetes mellitus, thyroid disorders, adrenal insufficiency)
    - Immune-related nephritis and renal dysfunction
    - Other immune-related adverse reactions including myositis, hypopituitarism, uveitis, myasthenia gravis/myasthenic syndrome, and Guillain-Barre Syndrome
    - Infusion-Related Reactions
- Warning message for patients on the importance of consulting their doctor immediately in case they develop any of the listed signs and symptoms and on the important not attempting to treat themselves.
- Reminder to carry the Patient Alert Card at all times and to show it to all healthcare professionals that may treat them.
- The card should also prompt to enter contact details of the physician and include a warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Bavencio.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bavencio 20 mg/mL concentrate for solution for infusion
avelumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: Mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

200 mg/10 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after dilution
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1214/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bavencio 20 mg/mL sterile concentrate
avelumab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg/10 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Bavencio 20 mg/mL concentrate for solution for infusion
avelumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bavencio is and what it is used for
2. What you need to know before you use Bavencio
3. How to use Bavencio
4. Possible side effects
5. How to store Bavencio
6. Contents of the pack and other information

1. What Bavencio is and what it is used for

Bavencio contains the active substance avelumab, a monoclonal antibody (a type of protein) that attaches to a specific target in the body called PD-L1.

PD-L1 is found on the surface of certain tumour cells, and helps protect them from the immune system (the body's natural defences). Bavencio binds to PD-L1, and blocks this protective effect, allowing the immune system to attack the tumour cells.

Bavencio is used in adults to treat:
- Merkel cell carcinoma (MCC)**, a rare type of skin cancer**, when it is metastatic (has spread to other parts of the body).
- Urothelial carcinoma (UC), **a cancer that originates in the urinary tract**, when it is advanced or metastatic (has spread beyond the urinary bladder or to other parts of the body). Bavencio is used as maintenance treatment if the tumour has not grown after so called platinum-based chemotherapy as the first treatment.
- Renal cell carcinoma (RCC)**, a type of kidney cancer**, when it is advanced (has spread beyond the kidney or to other parts of the body).

For renal cell cancer, Bavencio is to be used in combination with axitinib.

It is important that you also read the package leaflet for the medicine containing axitinib. If you have any questions about axitinib, ask your doctor.

2. What you need to know before you use Bavencio

Do not use Bavencio
if you are allergic to avelumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Blood tests and weight checks:
Your doctor will check your general health before and during treatment with Bavencio.
You will have blood tests during your treatment and your doctor will monitor your weight before and during treatment.

Talk to your doctor before receiving Bavencio:
It may cause side effects (see section 4). Please note that in some cases symptoms may be delayed, and may develop after your last dose. If you suffer from any of these you should **seek urgent medical attention:**

- infusion-related reactions;
- problems due to inflammation of your lungs (pneumonitis);
- inflammation of your liver (hepatitis) or other liver problems;
- inflammation of your intestines (colitis), diarrhoea (watery, loose or soft stools) or more bowel movements than usual;
- inflammation of your pancreas (pancreatitis);
- inflammation of your heart (myocarditis);
- problems with your hormone producing glands (the thyroid, adrenal and pituitary glands) that may affect how these glands work;
- Type 1 diabetes, including a serious, sometimes life-threatening problem due to acid in the blood produced from diabetes (diabetic ketoacidosis);
- problems with your kidneys;
- inflammation of your muscles (myositis);
- problems due to inflammation of your lungs, skin, eyes and/or lymph nodes (sarcoidosis).

If you experience any of these symptoms when taking Bavencio **do not** try to treat them on your own with other medicines. Your doctor may

- give you other medicines in order to prevent complications and reduce your symptoms,
- withhold the next dose of Bavencio,
- or stop your treatment with Bavencio altogether.

Check with your doctor or nurse before you receive Bavencio if:

- you have an autoimmune disease (a condition where the body attacks its own cells);
- you have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS);
- you have ever had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV);
- you receive medicines to suppress your immune system;
- you have had an organ transplant.

Bavencio acts on your immune system. It may cause inflammation in parts of your body. Your risk of these side effects may be higher if you already have an autoimmune disease (a condition where the body attacks its own cells). You may also experience frequent flares of your autoimmune disease, which in the majority of cases are mild.

Children and adolescents
Bavencio has not been studied in children and adolescents below 18 years of age.

Other medicines and Bavencio
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy
Bavencio can cause harm to your unborn baby. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

You must not use Bavencio if you are pregnant unless your doctor specifically recommends it.

If you are a woman who could become pregnant, you must use effective contraceptives while you are being treated with Bavencio and for at least 1 month after your last dose.

Breast-feeding
If you are breast-feeding, tell your doctor.

Do not breast-feed while receiving Bavencio and for at least 1 month after your last dose.

It is unknown if Bavencio passes into your breast milk. A risk to the breast-fed child cannot be excluded.

Driving and using machines
Do not drive or use machines after you have received Bavencio if you are not feeling well enough. Tiredness is a very common side effect of Bavencio and can affect your ability to drive or to use machines.

Bavencio has a low sodium content
Bavencio contains less than 1 mmol sodium (23 mg) in each dose and therefore is essentially sodium-free.

3. How to use Bavencio

You will receive Bavencio in a hospital or clinic, under the supervision of an experienced doctor.

How much Bavencio you will receive
The recommended dose of avelumab is 800 mg every 2 weeks. Your doctor will decide how many treatments you need.

How you will receive Bavencio
You will receive Bavencio as an infusion (a drip) into a vein (intravenously) over a period of 1 hour. Bavencio will be added to an infusion bag containing a sodium chloride solution before use.

Before you receive Bavencio
For at least the first 4 treatments, you will receive paracetamol and an antihistamine before being given Bavencio, to help to prevent possible side effects related to the infusion. Depending on how your body responds to treatment, your doctor may decide to continue giving you these medicines before all of your Bavencio treatments.

If you miss a dose of Bavencio
It is very important for you to keep all your appointments to receive Bavencio. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop receiving Bavencio
Do not stop treatment with Bavencio unless you have discussed this with your doctor. Stopping your treatment may stop the effect of the medicine.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some side effects may happen weeks or months after your last dose.

Bavencio acts on your immune system and may cause inflammation in parts of your body (see section 2). Inflammation may cause serious damage to your body and some inflammatory conditions may lead to death and need treatment or withdrawal of Bavencio.

Seek urgent medical attention if you experience inflammation in any part of your body or if you have any of the following signs or symptoms, or if they get worse.

- Signs of infusion-related reactions such as **shortness of breath or wheezing**, **chills or shaking**, **bumpy rash or skin wheals**, **flushing**, **low blood pressure (**dizziness, fatigue, nausea) **feve**r, **back pain**, and **abdominal pain**. This is very common.

- Signs of inflammation of hormone producing glands (which may affect how the glands work) may include **extreme tiredness**, **rapid heartbeat**, **increased sweating**, **changes in mood or behaviour**, such as irritability or forgetfulness, **feeling cold**, **very low blood pressure (**fainting, dizziness, fatigue, nausea), **weight change** or **headache**. This is very common for thyroid gland, common for adrenal glands, and uncommon for pituitary gland.

- Signs of inflammation of the lungs (pneumonitis) may be **breathing difficulties** or **cough**. This is common.

- Signs of inflammation of the intestines (colitis) may include **diarrhoea** (loose stools) or **more bowel movements than usual**, **blood in your stools or dark, tarry, sticky stools**, or **severe stomach (abdomen) pain** or **tenderness**. This is common.

- Signs of liver problems, including inflammation of the liver (hepatitis) may include **yellowing of your skin** (jaundice) or the **whites of your eyes**, **severe nausea or vomiting**, **pain on the right side of your stomach area** (abdomen), **drowsiness**, **dark urine** (tea coloured), **bleeding or bruising more easily than normal**, **feeling less hungry than usual**, **tiredness** or **abnormal liver function tests**. This is common.

- Signs of inflammation of the pancreas (pancreatitis) may include **abdominal pain**, **nausea** and **vomiting**. This is uncommon.

- Signs of inflammation of the heart (myocarditis) may include **trouble breathing**, **dizziness** or **fainting**, **fever**, **chest pain** and **chest tightness** or **flu like symptoms**. This is uncommon.

- Signs of type 1 diabetes including diabetic ketoacidosis may include **feeling more hungry** or **thirsty than usual**, **needing to urinate more often**, **weight loss**, and **feeling tired** or **having difficulty thinking clearly, breath that smells sweet** or **fruity, feeling sick** or **being sick, stomach pain,** and **deep** or **fast breathing**. This is uncommon.

- Signs of inflammation of the kidney may include **abnormal kidney function tests**, **urinating less than usual**, **blood in your urine**, or **swelling in your ankles**. This is uncommon.

- Signs of inflammation of the muscles (myositis) may include **muscle pain** or **weakness**. This is uncommon.

- Signs of inflammation associated with **a build-up of inflammatory cells** in various organs and tissues, most commonly the lungs (sarcoidosis). This is uncommon.

Do not try to treat yourself with other medicines.

Other side effects

Some side effects may not have symptoms and may only be discovered through blood tests.

The following side effects have been reported in clinical trials with avelumab alone:

Very common (may affect more than 1 in 10 people)
- Decrease in the number of red blood cells
- Nausea, loose stools, constipation, vomiting
- Belly pain, back pain, joint pain
- Cough, shortness of breath
- Feeling tired or weak
- Fever
- Swelling in the arms, feet or legs
- Weight loss, feeling less hungry

Common (may affect up to 1 in 10 people)
- Decrease in the number of a type of white blood cells (lymphocytes)
- Decrease in the number of platelets in the blood
- Increases in blood pressure
- Low level of sodium
- Headache, dizziness
- Feeling cold
- Dryness in the mouth
- Increased liver enzymes in the blood
- Increased pancreatic enzymes in the blood
- Skin rash, itching
- Muscle pain
- Flu-like illness (includes feeling of fever, muscle aches)
- Numbness, tingling, weakness, burning sensation in arms or legs

Uncommon (may affect up to 1 in 100 people)
- Redness in the skin
- Bowel occlusion
- Red, itchy, scaly patches on the skin, dry skin
- Decreases in blood pressure
- Increased muscle enzyme in the blood
- Increase in the number of a type of white blood cells (eosinophils)
- Inflammation of the joints (rheumatoid arthritis)
- Myasthenia gravis, myasthenic syndrome, an illness that can cause muscle weakness

Rare (may affect up to 1 in 1 000 people)
- Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

The following side effects have been reported in clinical trials with avelumab in combination with axitinib:

Very common (may affect more than 1 in 10 people)
- Loose stools, nausea, constipation, vomiting
- Increases in blood pressure
- Feeling tired or weak

- Hoarseness, cough, shortness of breath
- Feeling less hungry, weight loss
- Headache, dizziness
- Joint pain, back pain, belly pain, muscle pain
- Increased liver enzymes in the blood
- Feeling cold
- Skin rash, itching
- Fever

Common (may affect up to 1 in 10 people)
- Red, itchy, scaly patches on the skin, acne-like rash
- Swelling in the arms, feet or legs
- Dryness in the mouth
- Increased pancreatic enzymes in the blood
- Decreased kidney function
- Decrease in the number of red blood cells
- Decreases in blood pressure
- Increased glucose in the blood
- Flu-like illness (includes feeling of fever, muscle aches)
- Increased muscle enzyme in the blood
- Decrease in the number of platelets in the blood
- Numbness, tingling, weakness, burning sensation in arms or legs
- Redness in the skin

Uncommon (may affect up to 1 in 100 people)
- Decrease in the number of a type of white blood cells (lymphocytes)
- Increase in the number of a type of white blood cells (eosinophils)
- Bowel occlusion
- Myasthenia gravis, myasthenic syndrome, an illness that can cause muscle weakness

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bavencio

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package in order to protect from light.

Do not store any unused portion of the concentrate or of the diluted infusion solution for reuse.

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

6. Contents of the pack and other information

What Bavencio contains

The active substance is avelumab.

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

The other ingredients are mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, water for injections (see section 2 “Bavencio has a low sodium content”).

What Bavencio looks like and contents of the pack
Bavencio is a clear, colourless to slightly yellow concentrate for solution for infusion (sterile concentrate).

The pack size is 1 glass vial per carton.

Marketing Authorisation Holder
Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer
Merck Serono S.p.A.
Via Delle Magnolie 15 (loc. frazione Zona Industriale)
70026 - Modugno (BA)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Handling instructions

Preparation and administration
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 be 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 infusion using a sterile, non-pyrogenic, low-protein binding 0.2 micrometre in-line or add-on filter.

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.

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