AUSTRALIAN PRODUCT INFORMATION – BAVENCIO® (avelumab) concentrated solution for injection (intravenous infusion)

1. NAME OF THE MEDICINE

avelumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL vial contains 200 mg of avelumab.

Each mL of concentrate contains 20 mg of avelumab.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

BAVENCIO is indicated for the treatment of adults and paediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC). This indication is approved based on tumour response rate, duration of response in a single arm study.

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

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

4.2. DOSE AND METHOD OF ADMINISTRATION

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

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.

Dosage

Merkel cell carcinoma

The recommended dose of BAVENCIO as monotherapy is either 10 mg/kg body weight or 800 mg administered intravenously over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

Urothelial carcinoma

The recommended dose of BAVENCIO as monotherapy is 800 mg administered intravenously over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

Renal cell carcinoma

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.

Treatment modifications

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

Detailed guidelines for the management of immune-mediated adverse reactions are described in Section 4.4.

Table 1: Recommended treatment modifications of BAVENCIO for the management of adverse reactions

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	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

Adverse Reaction	Severity	Treatment modification
Myocarditis	Suspected myocarditis	Withhold
	Confirmed myocarditis	Permanently discontinue
Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, hyperglycaemia)	Grade 3 or Grade 4 endocrinopathies	Withhold until adverse reactions recover to Grade 0-1
Nephritis and renal dysfunction	Serum creatinine more than 1.5 and up to 6 times ULN	Withhold until adverse reactions recover to Grade 0-1
	Serum creatinine more than 6 times ULN	Permanently discontinue
Other immune-mediated adverse reactions (including see Section 4.4 “Other immune-mediated adverse reactions”)	For any of the following: • Grade 2 or Grade 3 clinical signs or symptoms of an immune-mediated 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-mediated 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-mediated adverse reactions lasting 12 weeks or longer	Permanently discontinue

Note: toxicity grades are in accordance with 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.

Special populations

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. 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. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations.

Administration

BAVENCIO is administered over 60 minutes as an intravenous infusion using a sterile, non-pyrogenic, low-protein binding 0.2 µm in-line or add-on filter.

BAVENCIO has to be diluted with either 0.9% or 0.45% sodium chloride solution prior to infusion.

BAVENCIO infusion must not be administered as an intravenous push or bolus injection.

Compatibilities

BAVENCIO is compatible with either 0.9% or 0.45% sodium chloride solution.

BAVENCIO is compatible with 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 µm.

BAVENCIO must not be mixed with other medicinal products except those mentioned above.

Handling instructions

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

The vial should be visually inspected for particulate matter and discolouration. BAVENCIO is a clear, colourless to slightly yellow solution. If the solution is cloudy, discoloured, or contains particulate matter, the vial has to be discarded.

An infusion bag of appropriate size (preferable 250 mL) containing either 0.9% or 0.45% sodium chloride solution 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 drugs through the same intravenous line.

Administer the infusion as described above.

After administration of BAVENCIO, the line should be flushed with either 0.9% or 0.45% sodium chloride solution.

4.3. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infusion-related reactions

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

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.

For Grade 1 infusion-related reactions, the infusion rate should be slowed by 50% for the current infusion. For patients with Grade 2 infusion-related reactions, the infusion should be temporarily discontinued until Grade 1 or resolved, then the infusion will restart with a 50% slower infusion rate, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

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 DOSE AND METHOD OF ADMINISTRATION.

Immune-mediated adverse reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients treated with avelumab.

While immune-mediated adverse reactions usually occur during treatment, symptoms can also manifest after discontinuation.

Immune-mediated adverse reactions affecting more than one body system can occur simultaneously, such as myositis, myocarditis, and myasthenia gravis (Triple-M syndrome), in patients treated with avelumab or other PD-1/PD-L1 inhibitors. Institute medical management promptly, including specialty consultation as appropriate.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients for signs and symptoms of immune-mediated adverse reactions.

Most immune-mediated adverse reactions occurring during treatment with avelumab as a single agent or in combination with axitinib were reversible and managed with temporary or permanent discontinuation of avelumab, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions have also occurred after the last dose of avelumab.

For suspected immune-mediated 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-mediated adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants may be considered.

Patients with pre-existing autoimmune disease (AID)

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

Important immune-mediated adverse reactions listed in this section below are not inclusive of all possible immune-mediated reactions.

Immune-mediated pneumonitis

Immune-mediated pneumonitis including fatal outcome has been reported in patients receiving avelumab, see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Patients should be monitored for signs and symptoms of pneumonitis and causes other than immune-mediated 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 - 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper).

Avelumab should be withheld for Grade 2 immune-mediated pneumonitis until resolution, and permanently discontinued for Grade 3 or Grade 4 or recurrent Grade 2 immune-mediated pneumonitis, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Immune-mediated hepatitis

Immune-mediated hepatitis including fatal outcome has been reported in patients receiving avelumab, see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Patients should be monitored for changes in liver function and symptoms of immune-mediated hepatitis. Causes other than immune-mediated hepatitis should be ruled out. Corticosteroids should be administered for Grade ≥2 events (initial dose 1 - 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper).

Avelumab should be withheld for Grade 2 immune-mediated hepatitis until resolution and permanently discontinued for Grade 3 or Grade 4 immune-mediated hepatitis, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

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.

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.

Immune-mediated colitis

Immune-mediated colitis has been reported in patients receiving avelumab, see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

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

Avelumab should be withheld for Grade 2 or Grade 3 immune-mediated colitis until resolution, and permanently discontinued for Grade 4 or recurrent Grade 3 immune-mediated colitis, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Immune-mediated pancreatitis

Immune-mediated pancreatitis including fatal outcome has been reported in patients receiving avelumab, see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Patients should be monitored for signs and symptoms of immune-mediated 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-mediated 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-mediated pancreatitis. Avelumab should be permanently discontinued if immune-mediated pancreatitis is confirmed, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Immune-mediated myocarditis

Immune-mediated myocarditis including fatal outcome has been reported in patients receiving avelumab, see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Patients should be monitored for signs and symptoms of immune-mediated 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-mediated 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-mediated myocarditis. Avelumab should be permanently discontinued if immune-mediated myocarditis is confirmed, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Immune-mediated endocrinopathies

Immune-mediated thyroid disorders and immune-mediated adrenal insufficiency, and Type 1 diabetes mellitus have been reported in patients receiving avelumab, see Section 4.8

ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Patients should be monitored for clinical signs and symptoms of endocrinopathies. Avelumab should be withheld for Grade 3 or Grade 4 endocrinopathies until resolution.

Thyroid disorders (hypothyroidism/hyperthyroidism)

Thyroid disorders can occur at any time during treatment. 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 drug as needed.

For suspected immune-mediated 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-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Avelumab should be withheld for any Grade 3 immune-mediated adverse reaction that recurs and for Grade 4 immune-mediated adverse reaction, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Adrenal insufficiency

Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment. Corticosteroids should be administered (1 - 2 mg/kg/day prednisone i.v. 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 DOSE AND METHOD OF ADMINISTRATION.

Type 1 diabetes mellitus

Avelumab can cause Type 1 diabetes mellitus, including diabetic ketoacidosis, see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

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 or insulin in patients with Grade ≥ 3 hyperglycaemia should be administered. Treatment with avelumab should be resumed when metabolic control is achieved on insulin replacement therapy or anti-hyperglycaemics.

Immune-mediated nephritis and renal dysfunction

Avelumab can cause immune-mediated nephritis, see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

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.

Major Adverse Cardiovascular Events (MACE)

BAVENCIO in combination with axitinib can cause severe and fatal cardiovascular events. Consider baseline and periodic evaluations of left ventricular ejection fraction. Monitor for signs and symptoms of cardiovascular events. Discontinue BAVENCIO and axitinib for Grade 3-4 cardiovascular events.

MACE occurred in 7% of patients with advanced RCC treated with BAVENCIO in combination with axitinib compared to 3.4% treated with sunitinib in JAVELIN Renal 101. These events included death due to cardiac events (1.4%), Grade 3-4 myocardial infarction (2.8%), and Grade 3-4 congestive heart failure (1.8%). Median time to onset of MACE was 4.2 months (range: 2 days to 24.5 months).

Other immune-mediated adverse reactions

Other clinically important immune-mediated adverse reactions were reported in clinical studies or in post-marketing use of avelumab: myositis, hypopituitarism, uveitis, myasthenia gravis, myasthenic syndrome, Guillain-Barré syndrome, sclerosing cholangitis, arthritis, polymyalgia rheumatica, Sjögren's syndrome, neutropenia, gastritis, and sarcoidosis, see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

The following clinically significant, immune-mediated adverse reactions have been reported with avelumab or other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: autoimmune haemolytic anaemia (AIHA), systemic inflammatory response syndrome (SIRS).

For suspected immune-mediated 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-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper.

Avelumab should be permanently discontinued for any other Grade 3 immune-mediated adverse reactions that recur and for any Grade 4 treatment-related adverse reactions except for endocrinopathies controlled with hormone replacement, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Patients excluded from clinical studies

Patients with the following conditions were excluded from clinical trials: active central nervous system (CNS) metastasis or treated within 2 months; active or a history of autoimmune disease; a history of other malignancies within the last 5 years except basal or squamous cell carcinoma of the skin or cervical carcinoma in situ; organ transplant; conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C.

Paediatric Use

Merkel cell carcinoma

The safety and efficacy of BAVENCIO have been established in paediatric patients age 12 years and older. Use of BAVENCIO in this age group is supported by evidence from adequate and well-controlled studies of BAVENCIO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of avelumab, that drug exposure is generally similar

between adults and paediatric patients age 12 years and older for monoclonal antibodies, and that the course of MCC is sufficiently similar in adults and paediatric patients to allow extrapolation of data in adults to paediatric patients. The recommended dose in paediatric patients 12 years of age or greater is the same as that in adults.

The safety and efficacy of BAVENCIO in children less than 12 years of age have not been established.

Urothelial carcinoma

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

Renal cell carcinoma

The safety and efficacy of BAVENCIO in combination with axitinib in children and adolescents below 18 years of age have not been established.

Use in the Elderly

Merkel cell carcinoma

Clinical studies of BAVENCIO in MCC did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Urothelial carcinoma

Of the 350 patients randomised to BAVENCIO 10 mg/kg plus BSC in the JAVELIN Bladder 100 trial, 63% were 65 years or older and 24% were 75 years or older. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

Renal cell carcinoma

Of the 434 patients who received BAVENCIO 10 mg/kg administered in combination with axitinib 5 mg twice daily in the JAVELIN Renal 101 trial, 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety or efficacy were reported between elderly patients and younger patients.

Immunosuppressed/Organ Transplant Patients

Efficacy and safety have not been studied in immunosuppressed patients or in patients with a history of organ transplantation.

Effects on laboratory tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been conducted with avelumab in humans.

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

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on 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 male and female reproductive organs in monkeys following IV administration at up to 140 mg/kg weekly for 3 months (yielding 25 times the serum AUC in patients at the recommended clinical dose of 10 mg/kg or 800 mg every two weeks).

Use in Pregnancy (Category D)

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. 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.

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.

Use in Lactation

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 breastfeed during treatment and for 1 month after the last dose of avelumab due to the potential for serious adverse reactions in breastfed infants.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Avelumab has no or negligible influence on the ability to drive and use machines. Fatigue has been reported following administration of avelumab, see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Avelumab is associated with immune-mediated 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.

For immune-mediated adverse reactions and infusion-related reactions, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

All tables in Section 4.8 are presented by system organ class, preferred term, frequency, and grade of severity. 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).

Merkel cell carcinoma

Summary of the safety profile

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

In this patient population, the most common adverse reactions with avelumab were fatigue (32.4%), nausea (25.1%), diarrhoea (18.9%), decreased appetite (18.4%), constipation (18.4%), infusion-related reactions (17.1%), weight decrease (16.6%), and vomiting (16.2%). The most common Grade ≥ 3 adverse reactions were anaemia (6.0%), dyspnoea (3.9%), and abdominal pain (3.0%).

Tabulated list of adverse reactions

Adverse reactions reported for 88 patients with mMCC treated with avelumab 10 mg/kg in study EMR100070-003 and adverse reactions reported for 1,650 patients in a phase I study (EMR100070-001) in other solid tumours are presented in Table 2.

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

	Adverse Reactions	**Avelumab (N = 1738)**	
Frequency category		**All Grades n (%)**	**Grade ≥ 3 n (%)**
	Blood and lymphatic system disorder		
Very common	Anaemia	259 (14.9)	104 (6.0)
	Endocrine disorders		
Common	Hypothyroidism*	88 (5.1)	3 (0.2)
Uncommon	Adrenal insufficiency*	8 (0.5)	1 (0.1)
Uncommon	Hyperthyroidism*,#	7 (0.4)	0
Uncommon	Thyroiditis*,#	2 (0.1)	0
Uncommon	Autoimmune thyroiditis*,#	2 (0.1)	0
Uncommon	Adrenocortical insufficiency acute*,#	1 (0.1)	0
Uncommon	Autoimmune hypothyroidism*,#	2 (0.1)	0
Uncommon	Hypopituitarism*,#	1 (0.1)	0
	Eye disorders		
Uncommon	Uveitis*,#	1 (0.1)	0
	Gastrointestinal disorders		
Very common	Nausea	437 (25.1)	27 (1.6)
Very common	Diarrhoea[a]	329 (18.9)	22 (1.3)

	Adverse Reactions	Avelumab (N = 1738)	
Frequency category		**All Grades n (%)**	**Grade ≥ 3 n (%)**
Very common	Constipation	320 (18.4)	17 (1.0)
Very common	Vomiting	281 (16.2)	31 (1.8)
Very common	Abdominal pain	250 (14.4)	52 (3.0)
Uncommon	Colitis*	5 (0.3)	4 (0.2)
Uncommon	Autoimmune colitis*,#	1 (0.1)	0
Uncommon	Enterocolitis*,#	1 (0.1)	0
	General disorders and administration site conditions		
Very common	Fatigue	563 (32.4)	51 (2.9)
Very common	Pyrexia[b]	237 (13.6)	5 (0.3)
Very common	Oedema peripheral	206 (11.9)	8 (0.5)
Common	Chills#,[b]	169 (9.7)	1 (0.1)
	Hepatobiliary disorders		
Uncommon	Autoimmune hepatitis*	5 (0.3)	4 (0.2)
Uncommon	Acute hepatic failure*,#	1 (0.1)	1 (0.1)
Uncommon	Hepatic failure*,#	1 (0.1)	1 (0.1)
Uncommon	Hepatitis*,#	1 (0.1)	1 (0.1)
	Immune system disorders		
Uncommon	Drug hypersensitivity#,[b]	8 (0.5)	0
Uncommon	Hypersensitivity#,[b]	6 (0.3)	0
Uncommon	Anaphylactic reaction[b]	2 (0.1)	2 (0.1)
Uncommon	Type I hypersensitivity#,[b]	1 (0.1)	0
	Injury, Poisoning and Procedural Complications		
Very common	Infusion related reaction[b]	297 (17.1)	10 (0.6)
	Investigations		
Very common	Weight decreased	288 (16.6)	12 (0.7)
Common	Lipase increased	45 (2.6)	29 (1.7)
Uncommon	Aspartate aminotransferase (AST) increased*,#	10 (0.6)	3 (0.2)
Uncommon	Alanine aminotransferase (ALT) increased*,#	9 (0.5)	4 (0.2)
Uncommon	Blood creatine phosphokinase increased*	5 (0.3)	3 (0.2)
Uncommon	Transaminases increased*	2 (0.1)	2 (0.1)
	Metabolism and nutrition disorders		
Very common	Decreased appetite	320 (18.4)	19 (1.1)
Uncommon	Diabetes mellitus*,#	1 (0.1)	1 (0.1)
Uncommon	Type 1 diabetes mellitus*,#	1 (0.1)	1 (0.1)

	Adverse Reactions	Avelumab (N = 1738)	
Frequency category		**All Grades n (%)**	**Grade ≥ 3 n (%)**
	Musculoskeletal and connective tissue disorders		
Very common	Back pain	205 (11.8)	24 (1.4)
Very common	Arthralgia	180 (10.4)	18 (1.0)
Uncommon	Myositis*	5 (0.3)	2 (0.1)
	Nervous system disorders		
Common	Headache	160 (9.2)	7 (0.4)
Common	Dizziness	129 (7.4)	2 (0.1)
Uncommon	Guillain-Barre Syndrome*,#	1 (0.1)	1 (0.1)
Uncommon	Myasthenia gravis*,§, myasthenic syndrome*,§	4 (0.1)	2 (0.05)
	Renal and urinary disorders		
Uncommon	Tubulointerstitial nephritis*,#	1 (0.1)	0
	Respiratory, thoracic and mediastinal disorders		
Very common	Cough#	240 (13.8)	2 (0.1)
Very common	Dyspnoea	229 (13.2)	68 (3.9)
Common	Pneumonitis*	21 (1.2)	7 (0.4)
	Skin and subcutaneous tissue disorders		
Common	Rash*,#	40 (2.3)	1 (0.1)
Common	Pruritus*,#	26 (1.5)	0
Common	Rash maculo-papular*,#	20 (1.2)	0
Uncommon	Rash pruritic*,#	7 (0.4)	0
Uncommon	Erythema*,#	5 (0.3)	0
Uncommon	Rash generalised*,#	5 (0.3)	0
Uncommon	Rash erythematous*,#	4 (0.2)	0
Uncommon	Rash macular*,#	3 (0.2)	0
Uncommon	Rash papular*,#	2 (0.1)	0
Uncommon	Dermatitis exfoliative*,#	1 (0.1)	0
Uncommon	Erythema multiforme*,#	1 (0.1)	0
Uncommon	Pemphigoid*,#	1 (0.1)	0
Uncommon	Pruritus generalised*,#	1 (0.1)	0
	Vascular disorders		
Common	Hypertension	166 (9.6)	75 (4.3)

* Immune-mediated adverse reaction based on medical review

Single or no SAEs

§ Adverse reactions occurred in estimated 4000 patients exposed to avelumab monotherapy beyond the pooled analysis.

[a] Frequencies presented in the table represents all events of diarrhoea (all causalities) including immune-mediated diarrhoea: 21 (1.2%); Grade ≥ 3: 4 (0.2%); serious: 4 (0.2%)

[b] Frequencies presented in the table represents all events (all causalities) including infusion-related adverse reaction based on predefined definition

Pyrexia: 62 (3.6%); Grade ≥ 3: 0 (0%), serious: 3 (0.2%)

Chills: 94 (5.4%); Grade ≥ 3: 0 (0%), serious: 1 (0.1%)

Infusion related reaction: 296 (17.0%), Grade ≥ 3: 10 (0.6%), serious: 15 (0.9%)

Drug hypersensitivity: 5 (0.3%), Grade ≥ 3: 0 (0%), serious: 0 (0%)

Hypersensitivity: 3 (0.2%), Grade ≥ 3: 0 (0%), serious: 0 (0%)

Anaphylactic reaction: 1 (0.1%), Grade ≥ 3: 1 (0.1%), serious: 1 (0.1%)

Type I hypersensitivity: (0.1%), Grade ≥ 3: 0 (0%), serious: 1 (0.1%)

Urothelial carcinoma

Summary of the safety profile

In study B9991001 (N=344), the most common adverse reactions (preferred term/composite term) with avelumab were fatigue (35.5%), musculoskeletal pain (23.5%), urinary tract infection (20.3%), rash (20.1%), pruritus (17.2%), diarrhoea (16.6%), constipation (16.3%), arthralgia (16.3%), nausea (15.7%), pyrexia (14.8%), cough (14.0%), decreased appetite (13.7%), vomiting (12.5%), hypothyroidism (11.6%), and infusion-related reactions (10.2%). The most common Grade ≥ 3 adverse reaction was urinary tract infection (5.8%).

Tabulated list of adverse reactions

Table 3 and Table 4 describe the adverse reactions reported in 344 patients with locally advanced or metastatic UC receiving avelumab 10 mg/kg every 2 weeks plus best supportive care (BSC) in study B9991001.

Table 3: Adverse reactions* in ≥ 1% of patients receiving avelumab + BSC in study B9991001

System Organ Class and Preferred Term/ Clustered Preferred Term	Avelumab + BSC (N=344)		BSC (N=345)	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
General disorders and administration site conditions				
Fatigue[a]	122 (35.5)	6 (1.7)	46 (13.3)	6 (1.7)
Pyrexia	51 (14.8)	1 (0.3)	12 (3.5)	0
Chills	28 (8.1)	0	3 (0.9)	0
Gastrointestinal disorders				
Diarrhoea	57 (16.6)	2 (0.6)	17 (4.9)	1 (0.3)
Constipation	56 (16.3)	2 (0.6)	31 (9.0)	0
Nausea	54 (15.7)	1 (0.3)	22 (6.4)	2 (0.6)
Vomiting	43 (12.5)	4 (1.2)	12 (3.5)	2 (0.6)
Colitis	6 (1.7)	2 (0.6)	0	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[b]	81 (23.5)	4 (1.2)	51 (14.8)	9 (2.6)
Arthralgia	56 (16.3)	2 (0.6)	19 (5.5)	0
Arthritis	5 (1.5)	1 (0.3)	0	0
Skin and subcutaneous tissue disorders				
Rash[c]	69 (20.1)	4 (1.2)	8 (2.3)	0
Pruritus	59 (17.2)	1 (0.3)	6 (1.7)	0
Infections and infestations				
Urinary tract infection[d]	70 (20.3)	20 (5.8)	38 (11.0)	13 (3.8)
Respiratory, thoracic and mediastinal disorders				
Cough[e]	48 (14.0)	1 (0.3)	16 (4.6)	0
Dyspnoea	23 (6.7)	5 (1.5)	11 (3.2)	2 (0.6)

System Organ Class and Preferred Term/ Clustered Preferred Term	Avelumab + BSC (N=344)		BSC (N=345)	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Pneumonitis	9 (2.6)	1 (0.3)	0	0
Metabolism and nutrition disorders				
Decreased appetite	47 (13.7)	1 (0.3)	23 (6.7)	2 (0.6)
Hyperglycaemia	13 (3.8)	6 (1.7)	8 (2.3)	1 (0.3)
Endocrine disorders				
Hypothyroidism	40 (11.6)	1 (0.3)	2 (0.6)	0
Hyperthyroidism	21 (6.1)	0	1 (0.3)	0
Adrenal insufficiency	5 (1.5)	0	0	0
Injury, poisoning and procedural complications				
Infusion-related reaction	35 (10.2)	3 (0.9)	0	0
Investigations				
Alanine aminotransferase increased	18 (5.2)	5 (1.5)	2 (0.6)	0
Aspartate aminotransferase increased	13 (3.8)	3 (0.9)	2 (0.6)	0
Blood thyroid stimulating hormone increased	4 (1.2)	0	0	0
Renal and urinary disorders				
Renal failure	6 (1.7)	0	4 (1.2)	3 (0.9)
Vascular disorders				
Hypotension	6 (1.7)	0	0	0
Immune system disorders				
Hypersensitivity	5 (1.5)	0	0	0

* Adverse reactions include immune-mediated adverse reactions, infusion-related reactions, and adverse events in the avelumab + BSC arm for which the frequency is ≥10% and higher than in the BSC alone arm (between arm difference ≥5% for all grades or ≥2% for Grade 3 and above).

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

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

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

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

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

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.

Subjects reporting more than one adverse event within a preferred term or clustered preferred term are counted only once in that term.

Table 4: Adverse reactions in < 1% of patients receiving avelumab + BSC in study B9991001

System Organ Class and Preferred Term/ Clustered Preferred Term	Avelumab + BSC (N=344)		BSC (N=345)	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Skin and subcutaneous tissue disorders				
Psoriasis	3 (0.9)	0	0	0
Purpura	2 (0.6)	0	0	0
Vitiligo	2 (0.6)	0	0	0
Dermatitis psoriasiform	1 (0.3)	0	0	0
Gastrointestinal disorders				
Pancreatitis	2 (0.6)	0	1 (0.3)	1 (0.3)

Proctitis	2 (0.6)	0	0	0
Autoimmune pancreatitis	1 (0.3)	1 (0.3)	0	0
Enteritis	1 (0.3)	1 (0.3)	0	0
Musculoskeletal and connective tissue disorders				
Myositis	2 (0.6)	2 (0.6)	0	0
Polyarthritis	2 (0.6)	0	0	0
Oligoarthritis	1 (0.3)	1 (0.3)	0	0
Rheumatoid arthritis	1 (0.3)	1 (0.3)	0	0
Endocrine disorders				
Autoimmune thyroiditis	3 (0.9)	0	0	0
Autoimmune hypothyroidism	1 (0.3)	0	0	0
Thyroiditis	1 (0.3)	0	1 (0.3)	0
Renal and urinary disorders				
Nephritis	3 (0.9)	0	0	0
Tubulointerstitial nephritis	1 (0.3)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Interstitial lung disease	3 (0.9)	0	0	0
Hepatobiliary disorders				
Autoimmune hepatitis	1 (0.3)	1 (0.3)	0	0
Hepatotoxicity	1 (0.3)	1 (0.3)	0	0
Metabolism and nutrition disorders				
Diabetes mellitus	2 (0.6)	2 (0.6)	0	0
Eye disorders				
Uveitis	1 (0.3)	0	0	0
Investigations				
Thyroxine free decreased	1 (0.3)	0	0	0

After the end of on-treatment period, the following adverse drug reactions were reported in the avelumab + BSC arm: Miller Fisher syndrome - 1 (0.3%).
After the end of on-treatment period, the following adverse drug reactions were reported in the BSC arm: uveitis - 1 (0.3%), diabetes mellitus - 1 (0.3%).
The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event within a preferred term or clustered preferred term are counted only once in that term.

Renal cell carcinoma

Summary of the safety profile

The safety of avelumab in combination with axitinib has been evaluated in a total of 434 patients in study B9991003, a randomised, open-label study in which 873 patients with treatment-naïve advanced RCC received avelumab 10 mg/kg intravenously every 2 weeks in combination with axitinib 5 mg orally twice daily (n=434) or sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks off (n=439).

Tabulated list of adverse reactions

The adverse reactions presented in Table 5 and Table 6 describe the safety profile for avelumab in combination with axitinib in 434 patients with RCC.

Table 5: Adverse reactions* ≥ 1% of patients receiving avelumab in combination with axitinib in study B9991003

System Organ Class and Preferred Term/ Clustered Preferred Term	Avelumab + Axitinib (N = 434)		Sunitinib (N = 439)	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Gastrointestinal disorders				
Diarrhoea	270 (62.2)	29 (6.7)	209 (47.6)	12 (2.7)
Colitis[a]	9 (2.1)	6 (1.4)	1 (0.2)	1 (0.2)
Vascular disorders				
Hypertension[b]	217 (50.0)	113 (26.0)	161 (36.7)	78 (17.8)
Flushing	7 (1.6)	0	3 (0.7)	0
Respiratory, thoracic and mediastinal disorders				
Dysphonia	135 (31.1)	2 (0.5)	15 (3.4)	0
Dyspnoea[c]	101 (23.3)	13 (3.0)	77 (17.5)	13 (3.0)
Pneumonitis	5 (1.2)	0	1 (0.2)	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[d]	161 (37.1)	11 (2.5)	126 (28.7)	13 (3.0)
Arthralgia	85 (19.6)	4 (0.9)	51 (11.6)	3 (0.7)
Investigations				
Weight decreased	86 (19.8)	13 (3.0)	32 (7.3)	4 (0.9)
Alanine aminotransferase increased	75 (17.3)	26 (6.0)	50 (11.4)	11 (2.5)
Aspartate aminotransferase increased	63 (14.5)	17 (3.9)	52 (11.8)	9 (2.1)
Blood thyroid stimulating hormone increased	30 (6.9)	0	16 (3.6)	1 (0.2)
Transaminases increased	5 (1.2)	2 (0.5)	3 (0.7)	1 (0.2)
Skin and subcutaneous tissue disorders				
Rash[e]	102 (23.5)	3 (0.7)	71 (16.2)	2 (0.5)
Pruritus[f]	61 (14.1)	0	22 (5.0)	0
Erythema	14 (3.2)	0	14 (3.2)	0
Urticaria	7 (1.6)	1 (0.2)	2 (0.5)	1 (0.2)
Endocrine disorders				
Hypothyroidism	108 (24.9)	1 (0.2)	65 (14.8)	1 (0.2)
Hyperthyroidism	24 (5.5)	3 (0.7)	6 (1.4)	0
Adrenal insufficiency	13 (3.0)	5 (1.2)	1 (0.2)	0
Thyroiditis[g]	10 (2.3)	0	0	0
General disorders and administration site conditions				
Chills	69 (15.9)	1 (0.2)	33 (7.5)	0
Pyrexia	56 (12.9)	0	64 (14.6)	2 (0.5)
Injury, poisoning and procedural complications				
Infusion-related reaction	53 (12.2)	7 (1.6)	0	0
Metabolism and nutrition disorders				
Hyperglycaemia	20 (4.6)	4 (0.9)	13 (3.0)	3 (0.7)
Renal and urinary disorders				
Acute kidney injury	14 (3.2)	6 (1.4)	12 (2.7)	8 (1.8)
Hepatobiliary disorders				
Hepatic function abnormal	7 (1.6)	5 (1.2)	3 (0.7)	2 (0.5)
Immune system disorders				
Hypersensitivity	7 (1.6)	0	1 (0.2)	0

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.03 (NCI CTCAE v4.03)

*Adverse reactions include immune-mediated Adverse Reactions, infusion-related reactions, and adverse events in ≥ 10% of patients receiving avelumab in combination with axitinib and at a higher incidence than in the sunitinib arm (between arm difference of ≥ 5% [All Grades] or ≥ 2% [Grades 3-4]) (study B9991003)

[a]Colitis is a composite term that includes Colitis and Autoimmune colitis

[b]Hypertension is a composite term that includes Hypertension and Hypertensive crisis

[c]Dyspnoea is a composite term that includes Dyspnoea, Dyspnoea exertional and Dyspnoea at rest
[d]Musculoskeletal pain is a composite term that includes Musculoskeletal pain, Back pain, Pain in extremity, Myalgia and Neck pain
[e]Rash is a composite term that includes Rash, Rash generalised, Rash macular, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash Papular and Rash Pustular
[f]Pruritus is a composite term that includes Pruritus and Pruritus generalised
[g]Thyroiditis is a composite term that includes Thyroiditis and Autoimmune thyroiditis

Table 6: Adverse reactions* in < 1% of patients receiving avelumab in combination with axitinib in study B9991003

System Organ Class and Preferred Term/ Clustered Preferred Term	Avelumab + Axitinib (N = 434)		Sunitinib (N = 439)	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Hepatobiliary disorders				
Hepatitis	2 (0.5)	0	0	0
Hepatotoxicity	2 (0.5)	2 (0.5)	1 (0.2)	0
Immune-mediated hepatitis	1 (0.2)	0	0	0
Liver disorder	1 (0.2)	1 (0.2)	1 (0.2)	0
Investigations				
Blood thyroid stimulating hormone decreased	3 (0.7)	0	4 (0.9)	0
Liver function test increased	1 (0.2)	1 (0.2)	0	0
Metabolism and nutrition disorders				
Diabetes mellitus	2 (0.5)	0	1 (0.2)	1 (0.2)
Type 1 diabetes mellitus	2 (0.5)	0	0	0
Nervous system disorders				
Myasthenia gravis/myasthenic syndrome[a]	2(0.4)	1 (0.2)	0	0
Cardiac disorders				
Myocarditis	2 (0.5)	2 (0.5)	0	0
Gastrointestinal disorders				
Autoimmune pancreatitis	1 (0.2)	1 (0.2)	0	0
Pancreatitis necrotising	1 (0.2)	1 (0.2)	0	0
Endocrine disorders				
Hypophysitis	1 (0.2)	0	0	0

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.03 (NCI CTCAE v4.03)
*Adverse reactions include immune-mediated Adverse Reactions and infusion-related reactions (JAVELIN Renal 101 Trial)
[a] Adverse reaction identified in the pooled advanced RCC population (N = 489) after the cut-off date.

Drug eruption was reported in one patient receiving avelumab in combination with axitinib in study B9991002.

Description of selected adverse reactions

Data for the following adverse reactions for avelumab as monotherapy are based on 1650 patients in study EMR100070-001 in other 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 PHARMACODYNAMIC PROPERTIES).

The management guidelines for these adverse reactions are described in Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Infusion-related reactions

In patients treated with avelumab as monotherapy, 24.6% (513/2082) of patients experienced infusion-related reactions. Of these, 97.7% (501/513) of patients with infusion-related reactions had a first infusion-related reaction during the first 4 infusions of which 2.7% (14/513) were Grade ≥ 3. In the remaining 2.3% (12/513) of patients, infusion-related reactions occurred after the first 4 infusions and all were of Grade 1 or Grade 2.

Immune-mediated pneumonitis

In patients treated with avelumab as monotherapy, 1.3% (28/2082) of patients developed immune-mediated 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, 6 (0.3%) patients with Grade 3, immune-mediated pneumonitis.

The median time to onset of immune-mediated 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% (9/2082) of patients due to immune-mediated pneumonitis. All 28 patients with immune-mediated 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-mediated 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-mediated pneumonitis. Of these patients, none experienced immune-mediated pneumonitis Grade ≥ 3.

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

Immune-mediated hepatitis

In patients treated with avelumab as monotherapy, 1.0% (21/2082) of patients developed immune-mediated hepatitis. Of these patients there were 2 (0.1%) patients with a fatal outcome, 16 (0.8%) patients with Grade 3 immune-mediated hepatitis.

The median time to onset of immune-mediated 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% (13/2082) of patients due to immune-mediated hepatitis. All 21 patients with immune-mediated hepatitis 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-mediated hepatitis resolved in 12 (57.1%) of 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-mediated hepatitis. Of these patients, there were 18 (3.7%) patients with Grade 3 and 3 (0.6%) patients with Grade 4 immune-mediated hepatitis.

The median time to onset of immune-mediated 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-mediated hepatitis. All 31 patients with immune-mediated 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-mediated hepatitis resolved in 27 (87.1%) of the 31 patients at the time of data cut-off.

Immune-mediated pancreatitis

In patients treated with avelumab as monotherapy, immune-mediated 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-mediated myocarditis

In patients treated with avelumab as monotherapy, immune-mediated 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-mediated colitis

In patients treated with avelumab as monotherapy, 1.5% (31/2082) of patients developed immune-mediated colitis. Of these patients there were 10 (0.5%) patients with Grade 3 immune-mediated colitis.

The median time to onset of immune-mediated 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% (11/2082) patients due to immune-mediated colitis. All 31 patients with immune-mediated 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-mediated 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-mediated colitis. Of these patients, there were 9 (1.8%) patients with Grade 3 immune-mediated colitis.

The median time to onset of immune-mediated 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-mediated colitis. All 13 patients with immune-mediated 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-mediated colitis resolved in 10 (76.9%) of 13 patients at the time of data cut-off.

Immune-mediated endocrinopathies

Thyroid disorders

In patients treated with avelumab as monotherapy, 6.7% (140/2082) of patients developed immune-mediated thyroid disorders. Of these patients, there were 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-mediated 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% (4/2082) of patients due to immune-mediated 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-mediated 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-mediated 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-mediated 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% (11/2082) of patients developed immune-mediated adrenal insufficiency. Of these patients, there was 1 (less than 0.1%) patient with Grade 3 immune-mediated adrenal insufficiency.

The median time to onset of immune-mediated 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% (2/2082) patients due to immune-mediated adrenal insufficiency. All 11 patients with immune-mediated adrenal insufficiency were treated with corticosteroids, 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%) patients with corticoid treatment at the time of data cut-off.

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

The median time to onset of immune-mediated 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-mediated adrenal insufficiency did not lead to discontinuation of avelumab in any patient. Eight (88.9%) patients with immune-mediated 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

Type 1 diabetes mellitus without an alternative aetiology occurred in 0.2% (5/2082) 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% (2/2082) 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-mediated nephritis and renal dysfunction

Immune-mediated nephritis occurred in 0.3% (7/2082) of patients. There was 1 (less than 0.1%) patient with Grade 3 immune-mediated nephritis.

The median time to onset of immune-mediated 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% (4/2082) of patients due to immune-mediated nephritis. All 7 patients with immune-mediated nephritis were treated with corticosteroids. 6 (85.7%) of those 7 patients with immune-mediated nephritis were treated with high-dose corticosteroids for a median of 2.5 weeks (range: 6 days to 2.8 months). Immune-mediated nephritis resolved in 4 (57.1%) patients at the time of data cut-off.

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

The median time to onset of immune-mediated 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-mediated nephritis did not lead to discontinuation of avelumab in any patient. The 2 patients with immune-mediated nephritis were treated with high-dose corticosteroids for a median of 1.1 weeks (range: 3 days to 1.9 weeks). Immune-mediated 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, Grade 3 and Grade 4 increased ALT and increased AST were reported in 9% and 7% of patients respectively. In patients with ALT ≥3 times ULN (Grades 2-4, n=82), ALT resolved to Grades 0-1 in 92%.

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

Immunogenicity

For study EMR100070-003 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. The treatment-emergent neutralising antibody (nAb) incidence rate is 5 of 81 (6.2%) evaluable patients in study EMR100070-003 Part A, and 8 of 111 (7.2%) evaluable patients in Part B.

For study B9991001 in the UC population, out of 344 patients treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks plus BSC and that had a valid ADA result at any time, 326 were evaluable for treatment-emergent ADA and 62 (19.0%) tested positive. Of the 66 patients evaluable for nAb, 60 (90.9%) tested positive.

For study B9991003 in the RCC population, out of 433 patients treated with avelumab and axitinib, 411 were evaluable for treatment-emergent ADA and 66 (16.1%) patients tested positive. Of the 421 patients evaluable for nAb, 51 (12.1%) tested positive.

Overall, the development of treatment-emergent ADA did not appear to alter the risk of infusion-related reactions. Based on the available data, no other meaningful impact of ADA and/or nAb has been identified on pharmacokinetics, safety, or efficacy, although these assessments are limited by the low rate of immunogenicity.

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 and aplastic anaemia.

Post-marketing experience

Blood and lymphatic system disorders: neutropenia*.

Gastrointestinal disorders: gastritis*.

Hepatobiliary disorders: sclerosing cholangitis*.

Immune system disorders: sarcoidosis*.

Injury, poisoning and procedural complications: cytokine release syndrome (under “infusion-related reaction”).

Musculoskeletal and connective tissue disorders: arthritis* (including immune-mediated arthritis), Sjögren's syndrome*, tenosynovitis, polymyalgia rheumatica*, and myositis* (including polymyositis).
* Immune-mediated adverse reaction based on medical review

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

There are limited experiences with overdose with avelumab in clinical studies.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other antineoplastic agents, monoclonal antibodies.
ATC code: L01FF04

Mechanism of action

PD-L1 may be expressed on tumour cells and/or tumour-infiltrating immune cells and can contribute to the inhibition of the anti-tumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Avelumab is a fully 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. In syngeneic mouse tumour models, blocking PD-L1 activity resulted in decreased tumour growth.

Avelumab has also been shown to induce NK cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro*.

Avelumab (anti-PD-L1) and axitinib (a receptor tyrosine kinase inhibitor of the vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3) target different immunomodulatory pathways. Axitinib reduced the proliferation of immune suppressive cells and enhanced tumour infiltration of immune effector cells in mouse models. Axitinib also inhibited VEGF-mediated endothelial cell proliferation and survival, and tumour growth, *in vitro* and in mouse tumour xenograft models. Compared to either drug alone, co-administration of a PD-1 pathway inhibitor and a VEGF pathway blocker resulted in

enhanced biological activity and improved anti-tumour responses in mouse models and patients with advanced RCC.

Clinical trials

Merkel cell carcinoma (study EMR100070-003)

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

Patients with active central nervous system (CNS) metastasis or treated less than 2 months prior to enrolment, active or a history of any 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

For Part A, 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 evaluated in all 88 patients after a minimum of 36 months follow-up after the last patient-initiated treatment. 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 (73.9%) were male, the median age was 72.5 years (range 33 years to 88 years), 81 (92.0%) patients were Caucasian, and 49 (55.7%) patients and 39 (44.3%) patients with an ECOG performance status 0 and 1, respectively.

Overall, 52 (59.1%) of the patients were reported to have had 1 prior anti-cancer therapy for MCC, 26 (29.5%) with 2 prior therapies, 10 (11%) with 3 or more prior therapies. Forty-seven (53.4%) of the patients had visceral metastases.
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 (75.9%) patients with a response responded within 7 weeks after the first dose of avelumab.

Responses were observed in patients regardless of PD-L1 expression and/or Merkel cell polyomavirus status.

Table 7 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 7: Response to avelumab 10 mg/kg every 2 weeks in patients with mMCC in study EMR100070-003 (Part A)*

Efficacy Endpoints (per RECIST v1.1, IERC)	Results (N = 88)
Objective Response Rate (ORR)	
Response Rate, CR+PR** n (%) (95% CI)	29 (33.0%) (23.3, 43.8)
Confirmed Best Overall Response (BOR)	
Complete Response (CR)** n (%)	10 (11.4%)
Partial Response (PR)** n (%)	19 (21.6%)
Duration of Response (DOR)[a]	
Median, months (95% CI)	40.5 (18.0, not estimated)
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)

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)

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

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

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 2 May 2019).

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

Responses were observed in patients regardless of PD L1 expression and/or Merkel cell polyomavirus status.

Table 8 summarises the primary analysis of efficacy endpoints including an estimate of the 24-month rates by Kaplan-Meier for DOR and PFS in patients receiving avelumab at the recommended dose for study EMR100070-003, Part B.

Table 8: Primary analysis of response to avelumab 10 mg/kg every 2 weeks in patients with metastatic MCC in study EMR100070-003 (Part B)*

Efficacy endpoints (Part B) (per RECIST v1.1, IERC)	**Results** (N=116)
Durable response	
≥ 6 months	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	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)

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 2 May 2019)

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

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

Urothelial carcinoma (study B9991001)

The efficacy and safety of BAVENCIO 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 first-line platinum-based induction chemotherapy. Patients with autoimmune disease or a medical condition that required immunosuppression were excluded.

Randomisation 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 BAVENCIO 10 mg/kg intravenous infusion every 2 weeks plus best supportive care (BSC) or BSC alone.

Treatment with BAVENCIO continued until RECIST v1.1 defined progression of disease by Blinded Independent Central Review (BICR) assessment or unacceptable toxicity. Administration of BAVENCIO was permitted beyond RECIST defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at baseline, 8 weeks after randomisation, then every 8 weeks up to 12 months after randomisation, 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 BAVENCIO 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 BAVENCIO plus BSC arm and 44% of patients in the BSC alone received another PD-1/PD-L1 checkpoint inhibitor after discontinuation of treatment.

The primary efficacy outcome measure was overall survival (OS) in all randomised patients and in patients with PD-L1-positive tumours.

Progression-free survival (PFS) based on BICR assessment per RECIST v1.1 was an additional efficacy outcome measure.

Efficacy outcomes were measured from time of randomisation after 4 to 6 cycles of platinum-based induction chemotherapy.

Efficacy results from study B9991001 are presented below.

Table 9: Efficacy results from study B9991001

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

CI: Confidence interval; K-M: Kaplan-Meier
* p-value based on stratified log-rank
** CIs are derived using the log-log transformation with back transformation to untransformed scale
*** based on BICR assessment per RECIST v1.1

Figure 1: Kaplan-Meier estimates for overall survival (OS) - Full analysis set

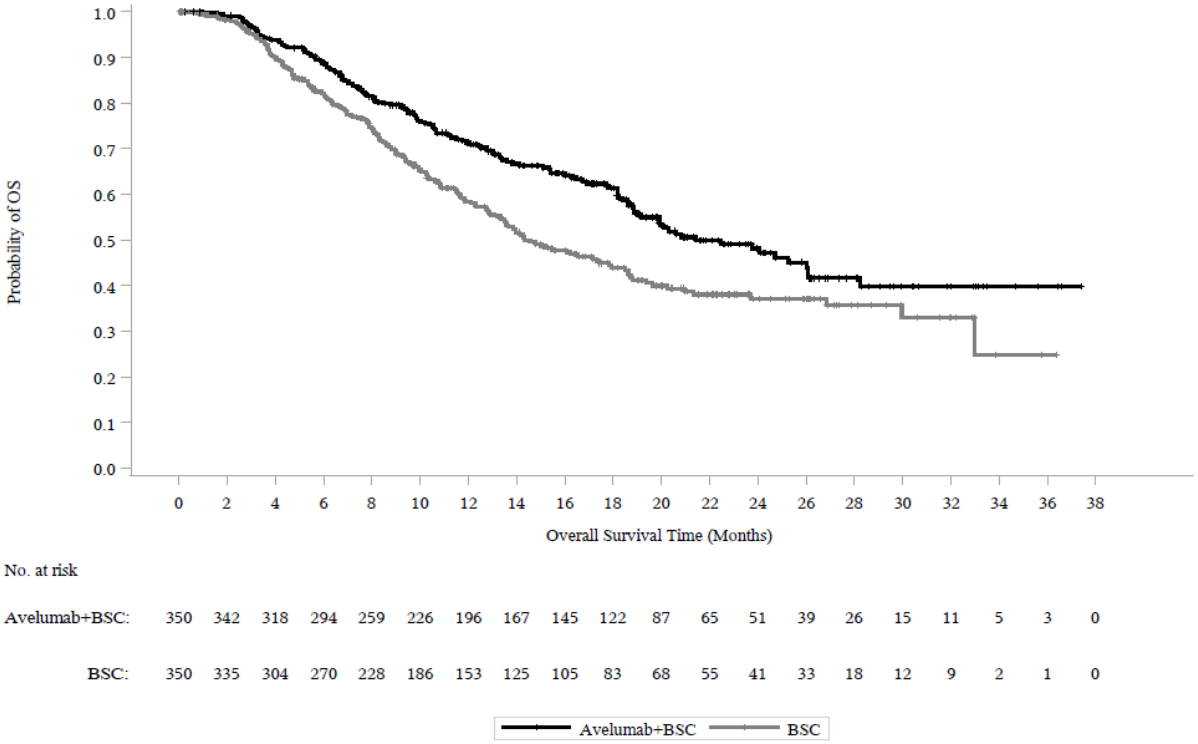
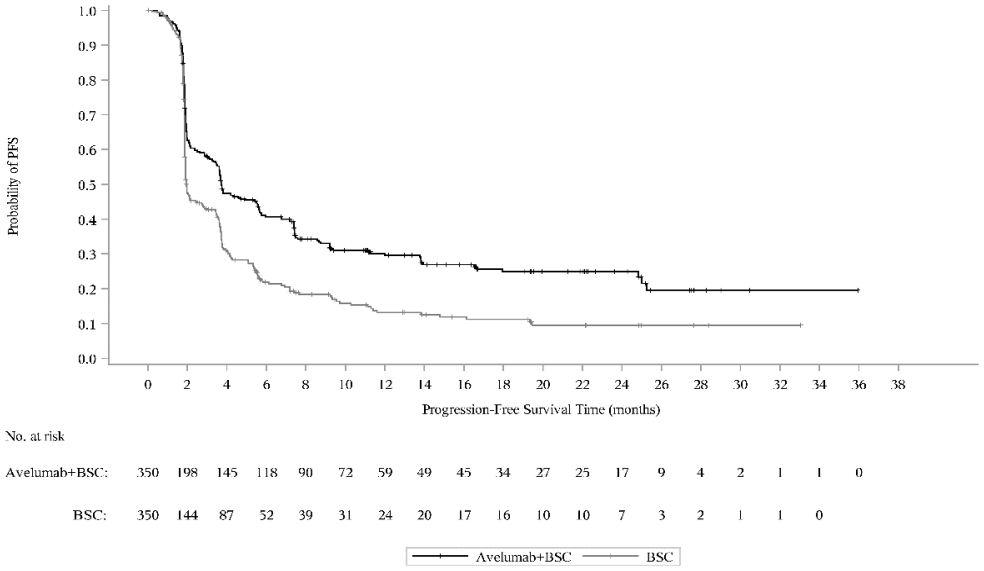


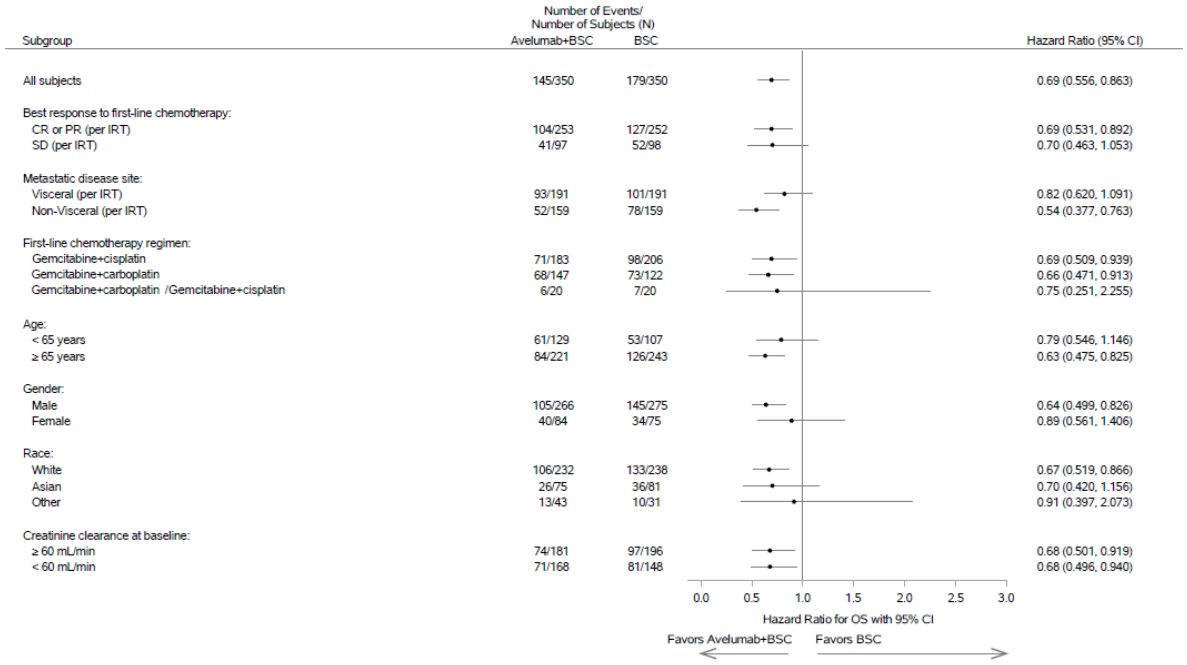
Figure 2: Kaplan-Meier estimates for progression free survival (PFS) based on BICR assessment (RECIST v1.1) - Full analysis set



In addition, a statistically significant improvement in OS was demonstrated in patients with PD-L1-positive tumours for BAVENCIO plus BSC compared to BSC alone (HR 0.56; 95% CI: 0.40, 0.79; 2-sided p-value 0.0007). The median OS was not reached (95% CI: 20.3 months, not reached) in the BAVENCIO plus BSC arm, and 17.1 months (95% CI: 13.5, 23.7) in the BSC alone arm. Consistent results were observed across pre-specified subgroups, including

best response to first-line induction chemotherapy, and sites of metastasis as shown in Figure 3.

Figure 3: Forest plot of overall survival by subgroups - Full analysis set



Patient reported outcomes (PRO)

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

Renal cell carcinoma (study B9991003)

The efficacy and safety of avelumab in combination with axitinib was demonstrated in study B9991003 (NCT02684006), a randomised (1:1), multi-centre, open-label study of avelumab in combination with axitinib in patients with untreated advanced RCC. Patients were included irrespective of tumour PD-L1 expression.

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

Randomisation 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 to receive avelumab 10 mg/kg intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily until disease progression or unacceptable toxicity.

A total of 886 patients were randomised: 442 to the avelumab in combination with axitinib arm and 444 to the sunitinib arm.

The primary efficacy endpoints were progression-free survival (PFS), as assessed by a Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumours (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 a BICR assessment per RECIST v.1.1 and OS irrespective of PD-L1 expression. PD-L1 status was determined by immunohistochemistry. Additional secondary endpoints included objective response (OR), time to response (TTR) and duration of response (DOR).

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

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

The first tumour assessments were conducted 6 weeks after randomisation and continued every 6 weeks up to 18 months after randomisation, and every 12 weeks thereafter until confirmed disease progression.

Efficacy results in patients irrespective of PD-L1 expression are presented in Table 10 and Figure 4.

Table 10: Efficacy results of study B9991003 – full analysis set

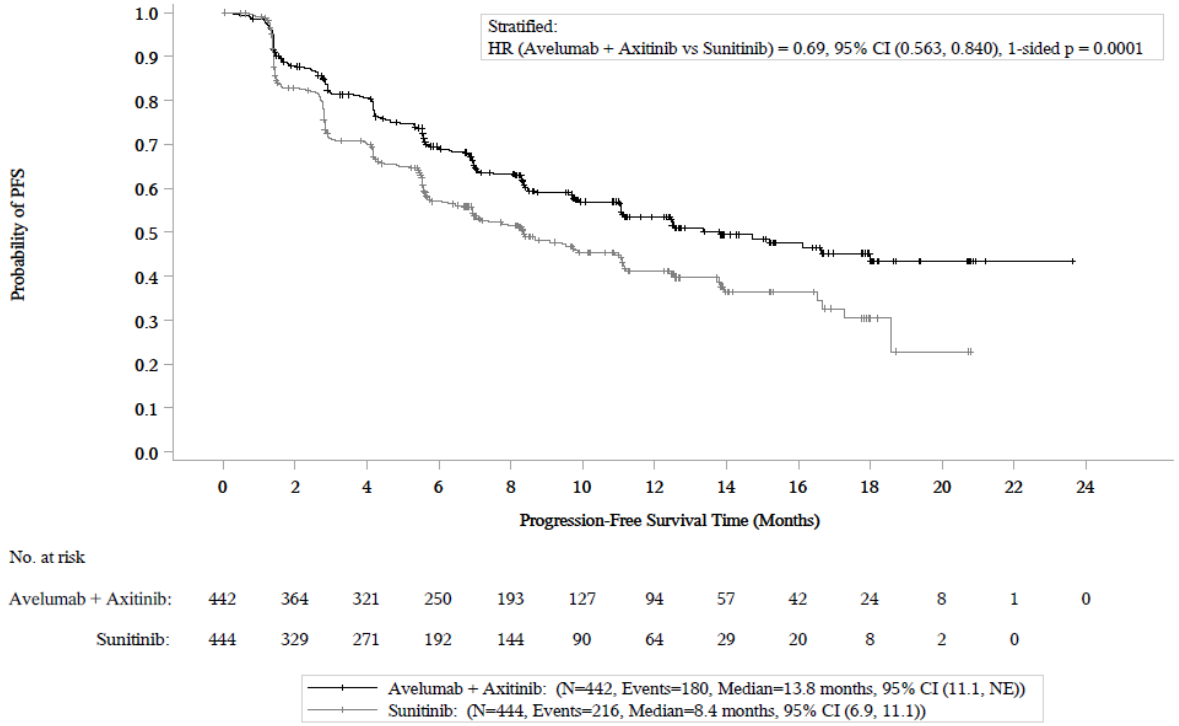
Efficacy endpoints (based on BICR assessment)	**Avelumab + axitinib (N = 442)**	**Sunitinib (N=444)**
Progression-free survival (PFS)		
Events (%)	180 (41)	216 (49)
Median in months (95% CI)	13.8 (11.1, NE)	8.4 (6.9, 11.1)
Hazard ratio (95% CI)	0.69 (0.56, 0.84)	
p-value*	0.0001	
12-month PFS rate by K-M (95% CI)**	53.5% (47.8, 58.8)	41.2% (35.4, 46.8)
18-month PFS rate by K-M (95% CI)**	45.2% (0.38, 0.52)	30.4% (0.22, 0.39)
Confirmed objective response rate (ORR)		
Objective response rate n (%)	227 (51.4)	114 (25.7)
(95% CI)	(46.6, 56.1)	(21.7, 30.0)
Complete response (CR) n (%)	15 (3)	8 (2)
Partial response (PR) n (%)	212 (48)	106 (24)
Stable disease (SD) n (%)	131 (29.6)	202 (45.5)
Disease control rate (DCR) n (%)	366 (82.8)	326 (73.4)
Progressive disease (PD) n (%)	51 (11.5)	83 (18.7)
Time to response (TTR)		
Median, months (range)	2.6 (1.2, 13.8)	3.2 (1.2, 11.6)
Duration of response (DOR)		
Median, months (95% CI)	NE (NE, NE)	NE (11.2, NE)

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

At the time of the first interim analysis, the OS data were still immature. The observed HR was 0.78 (95% CI: 0.554, 1.084) in favour of avelumab in combination with axitinib. Median OS was not yet reached in either treatment arms. The probability of being alive at 12 months

was 86.3% (95%CI: 82.2%, 89.5%) for the avelumab plus axitinib arm and 83.0% (95% CI: 78.8%, 86.5%) for the sunitinib arm.

Figure 4: Kaplan-Meier estimates for PFS based on BICR assessment – full analysis set



A statistically significant improvement in PFS was observed in both patients with PD-L1-positive tumours and all patients irrespective of PD-L1 expression who received the combination of avelumab with axitinib, with a 39% and 31% reduction of the risk of progression or death as compared to patients treated with sunitinib, respectively. Improvement of PFS was observed across all risk groups based on IMDC and MSKCC.

5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetics of avelumab as monotherapy have been determined by non-compartmental analyses and a population PK analysis in which patients received avelumab up to 20 mg/kg were studied while the majority of them received dose of 10 mg/kg every 2 weeks, which equates to the recommended avelumab dose. The pharmacokinetics of avelumab in combination with axitinib were also assessed using a population PK approach.

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

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 4.12 L.

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

Elimination

Based on a population pharmacokinetic analysis from 2171 patients treated with avelumab monotherapy, the value of total systemic clearance (CL) is 0.66 L/day.

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

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

Linearity/non-linearity

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

Based on a population PK analysis, there are no expected clinically meaningful differences in exposure of avelumab administered every 2 weeks at 800 mg or 10 mg/kg.

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.

<u>Renal impairment</u>

No clinically important differences in the clearance of avelumab were found between patients with mild (glomerular filtration rate [GFR] 60 to 89 mL/min, n = 623), moderate (GFR 30 to 59 mL/min, n = 320) and patients with normal (GFR greater than or equal to 90 mL/min, n = 671) renal function.

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

<u>Hepatic impairment</u>

No clinically important differences in the clearance of avelumab were found between patients with mild hepatic impairment (bilirubin less than or equal to the ULN and AST greater than ULN or bilirubin between 1 and 1.5 times ULN, n = 217), or moderate hepatic impairment (bilirubin between 1.5 and 3 times ULN, n = 4), and normal hepatic function (bilirubin and AST less than or equal to ULN, n = 1,388) in a population PK analysis.

Avelumab has not been studied in patients with severe hepatic impairment (bilirubin greater than 3 times ULN).

Paediatric population

The pharmacokinetics of avelumab at a dose of 10 mg/kg intravenously was evaluated in 3 adolescents (12 - 17 years old) in study MS100070-0306. The exposures in these patients appeared to be similar to those in adults receiving 10 mg/kg or 800 mg avelumab.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted to assess the genotoxic potential of avelumab. As a large protein molecule, avelumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No studies have been conducted to assess the carcinogenic potential of avelumab.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

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

6.2. INCOMPATIBILITIES

This medicine must not be mixed with other medicines except those mentioned in Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

6.3. SHELF LIFE

Unopened vial

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After opening

BAVENCIO should be diluted and infused immediately.

After preparation of infusion

BAVENCIO does not contain a preservative. The diluted solution should be infused immediately, unless dilution has taken place in controlled and validated aseptic conditions.

If BAVENCIO is not used immediately, store the diluted solution of BAVENCIO, either:

- At room temperature and room light for up to 8 hours. This includes room temperature storage of the infusion in the infusion bag and the duration of infusion.

- At 2°C to 8°C (Refrigerate. Do not freeze) for up to 24 hours at the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze or shake the diluted solution.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C - 8°C). Do not freeze.

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

Product is for single use in one patient only. Discard any residue.

For storage conditions after dilution of the medicine, see Section 6.3 SHELF LIFE.

6.5. NATURE AND CONTENTS OF CONTAINER

10 mL of concentrated solution for intravenous infusion in a 16 mL vial (Type I glass) with a halobutyl rubber stopper and an aluminium seal fitted with a removable plastic cap.

Pack size of 1 vial.

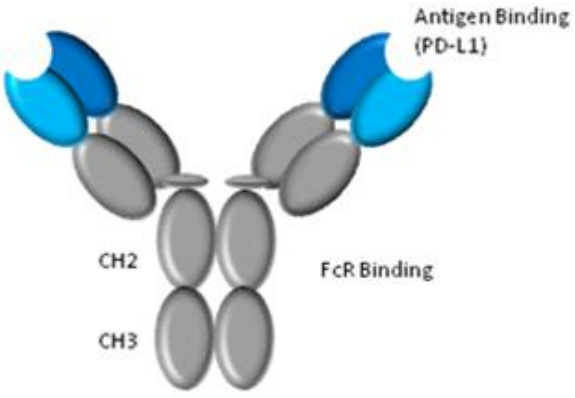
6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7. PHYSICOCHEMICAL PROPERTIES

The solution pH is in the range of 5.0 - 5.6 and the osmolality is between 285 and 350 mOsm/kg.

Chemical structure



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.

CAS number

1537032-82-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

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Macquarie Park NSW 2113
Merck Medical Information: 1800 633 463

9. DATE OF FIRST APPROVAL

3 January 2018

10. DATE OF REVISION

28 October 2025

Summary table of changes

Section changed	Summary of new information
4.4, 4.8	Addition of immune-mediated adverse reaction “sarcoidosis”
4.4	Addition of warning statements for immune-mediated adverse reactions including the co-occurrence of myositis, myocarditis, and myasthenia gravis (Triple-M syndrome)