HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BAVENCIO safely and effectively. See full prescribing information for BAVENCIO.

BAVENCIO® (avelumab) injection, for intravenous use
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------

Indication and Usage (1.1)	09/2023
Warnings and Precautions (5.1, 5.2)	09/2023

----------INDICATIONS AND USAGE----------

BAVENCIO is a programmed death ligand-1 (PD-L1) blocking antibody indicated for:

Merkel Cell Carcinoma (MCC)

- Adults and pediatric patients 12 years and older with metastatic MCC. (1.1, 14.1)

Urothelial Carcinoma (UC)

- Maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy. (1.2, 14.2)
- Patients with locally advanced or metastatic UC who:
  - Have disease progression during or following platinum-containing chemotherapy. (1.2, 14.2)
  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.2, 14.2)

Renal Cell Carcinoma (RCC)

- First-line treatment, in combination with axitinib, of patients with advanced RCC. (1.3, 14.3)

----------DOSAGE AND ADMINISTRATION----------

- Premedicate for the first 4 infusions and subsequently as needed. (2.1)
- Merkel Cell Carcinoma: 800 mg every 2 weeks. (2.2)
- Urothelial Carcinoma; 800 mg every 2 weeks. (2.3)
- Renal Cell Carcinoma: 800 mg every 2 weeks in combination with axitinib 5 mg orally twice daily. (2.4)

Administer BAVENCIO as an intravenous infusion over 60 minutes.

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 200 mg/10 mL (20 mg/mL) solution in single-dose vial. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Immune-Mediated Adverse Reactions (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and may result in solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue based on severity and type of reaction.
- Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue BAVENCIO based on severity of reaction. (5.2)
- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Major adverse cardiovascular events: Optimize management of cardiovascular risk factors. Discontinue BAVENCIO in combination with axitinib for Grade 3-4 events. (5.4)
- Embryo-fetal toxicity: BAVENCIO can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.5, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 20%) in patients were:

- MCC:
  - Fatigue, musculoskeletal pain, infusion-related reaction, rash, nausea, constipation, cough, and diarrhea. (6.1)
- UC:
  - Maintenance treatment: fatigue, musculoskeletal pain, urinary tract infection, and rash. (6.1)
  - Previously-treated: fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection. (6.1)
- RCC (with axitinib): diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext. 5563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Merkel Cell Carcinoma

BAVENCIO (avelumab) is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).

1.2 Locally Advanced or Metastatic Urothelial Carcinoma

First-Line Maintenance Treatment of Urothelial Carcinoma

BAVENCIO is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy *[see Clinical Studies (14.2)]*.

Previously-treated Urothelial Carcinoma

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

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *[see Clinical Studies (14.2)]*.

1.3 Advanced Renal Cell Carcinoma

BAVENCIO in combination with axitinib is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC) *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Premedication

Premedicate patients with an antihistamine and with acetaminophen prior to the first 4 infusions of BAVENCIO. Premedication should be administered for subsequent BAVENCIO doses based upon clinical judgment and presence/severity of prior infusion reactions *[see Dosage and Administration (2.5) and Warnings and Precautions (5.2)]*.

2.2 Recommended Dosage for MCC

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

2.3 Recommended Dosage for UC

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

2.4 Recommended Dosage for RCC

The recommended dose of BAVENCIO is 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks in combination with axitinib 5 mg orally taken twice daily (12 hours apart) with or without food until disease progression or unacceptable toxicity.
When axitinib is used in combination with BAVENCIO, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of two weeks or longer. Review the Full Prescribing Information for axitinib prior to initiation.

2.5 Dose Modifications

No dose reduction for BAVENCIO is recommended. In general, withhold BAVENCIO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Dosage modifications for BAVENCIO for adverse reactions that require management different from these general guidelines are summarized in Table 1.

Table 1: Recommended Monotherapy Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[a]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver For liver enzyme elevations in patients treated with combination therapy, see Table 2	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[a]
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[b]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold[a]

Adverse Reaction	Severity*	Dosage Modification
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold[a]
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrosis, DRESS = drug rash with eosinophilia and systemic symptoms
* Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
[a] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating corticosteroids.
[b] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue BAVENCIO based on recommendations for hepatitis where there is no tumor involvement of the liver.

Table 2 presents dosage modifications that are different from those described above in Table 1 for BAVENCIO used as monotherapy or in the Full Prescribing Information for the drug administered in combination.

Table 2: Recommended Specific Dosage Modifications for Adverse Reactions for Combination Therapy *[see Warnings and Precautions (5.1)]*

Treatment	Adverse Reaction	Severity*	Dosage Modification
BAVENCIO in combination with axitinib	Liver enzyme elevations	ALT or AST at least 3 times ULN but less than 10 times ULN without concurrent total bilirubin at least 2 times ULN	Withhold both BAVENCIO and axitinib until adverse reactions recover to Grades 0-1[a] Consider rechallenge with BAVENCIO or axitinib or sequential rechallenge with both BAVENCIO and axitinib after recovery**
		ALT or AST at least 10 times ULN or more than 3 times ULN with concurrent total bilirubin at least 2 times ULN	Permanently discontinue both BAVENCIO and axitinib[a]

* Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
** Dose reduction according to the axitinib Full Prescribing Information should be considered if rechallenging with axitinib.
[a] Consider corticosteroid therapy

2.6 Preparation and Administration

Preparation

- Visually inspect vial for particulate matter and discoloration. BAVENCIO is a clear, colorless to slightly yellow solution. Discard vial if the solution is cloudy, discolored, or contains particulate matter.
- Withdraw the required volume of BAVENCIO from the vial(s) and inject it into a 250 mL infusion bag containing either 0.9% Sodium Chloride Injection or 0.45% Sodium Chloride Injection.
- Gently invert the bag to mix the diluted solution and avoid foaming or excessive shearing.
- Inspect the solution to ensure it is clear, colorless, and free of visible particles.
- Discard any partially used or empty vials.

Storage of diluted BAVENCIO solution

Protect from light.

Store diluted BAVENCIO solution:

- At room temperature up to 77°F (25°C) for no more than 4 hours from the time of dilution.

Or

- Under refrigeration at 36°F to 46°F (2°C to 8°C) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze or shake diluted solution.

Administration

- Administer the diluted solution over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron).
- Do not co-administer other drugs through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

Injection: 200 mg/10 mL (20 mg/mL), clear, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

BAVENCIO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue BAVENCIO depending on severity *[see Dosage and Administration (2.5)]*. In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic

immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

BAVENCIO can cause immune-mediated pneumonitis. Immune-mediated pneumonitis occurred in 1.1% (21/1854) of patients receiving BAVENCIO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%) and Grade 2 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% and withholding of BAVENCIO in 0.3% of patients.

Systemic corticosteroids were required in all (21/21) patients with pneumonitis. Pneumonitis resolved in 57% (12/21) of the patients. Of the 5 patients in whom BAVENCIO was withheld for pneumonitis, 5 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of pneumonitis.

With other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-Mediated Colitis

BAVENCIO can cause immune-mediated colitis. The primary component of the immune-mediated colitis consisted of diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 1.5% (27/1854) of patients receiving BAVENCIO, including Grade 3 (0.4%) and Grade 2 (0.8%) adverse reactions. Colitis led to permanent discontinuation of BAVENCIO in 0.5% and withholding of BAVENCIO in 0.4% of patients.

Systemic corticosteroids were required in all (27/27) patients with colitis. Colitis resolved in 70% (19/27) of the patients. Of the 8 patients in whom BAVENCIO was withheld for colitis, 5 reinitiated treatment with BAVENCIO after symptom improvement; of these, 40% had recurrence of colitis.

Hepatotoxicity and Immune-Mediated Hepatitis

BAVENCIO as a single agent

BAVENCIO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 1.1% (20/1854) of patients receiving BAVENCIO, including fatal (0.1%), Grade 3 (0.8%), and Grade 2 (0.2%) adverse reactions. Hepatitis led to permanent discontinuation of BAVENCIO in 0.6% and withholding of BAVENCIO in 0.2% of patients.

Systemic corticosteroids were required in all (20/20) patients with hepatitis. Hepatitis resolved in 60% (12/20) of the patients. Of the 4 patients in whom BAVENCIO was withheld for hepatitis,

4 reinitiated treatment with BAVENCIO after symptom improvement; of these, 25% had recurrence of hepatitis.

BAVENCIO with Axitinib
BAVENCIO in combination with axitinib can cause hepatotoxicity with higher than expected frequencies of Grade 3 and 4 ALT and AST elevation compared to BAVENCIO alone. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy. For elevated liver enzymes, interrupt BAVENCIO and axitinib and consider administering corticosteroids as needed *[see Dosage and Administration (2.5)]*.

In patients treated with BAVENCIO in combination with axitinib in the advanced RCC trials, increased ALT and increased AST were reported in 9% (Grade 3) and 7% (Grade 4) of patients. 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 BAVENCIO (n=3) or axitinib (n=25) administered as a single agent or with both (n=45), recurrence of ALT ≥3 times ULN was observed in no patient receiving BAVENCIO, 6 patients receiving axitinib, and 15 patients receiving both BAVENCIO and axitinib. Twenty-two (88%) patients with a recurrence of ALT ≥3 ULN subsequently recovered to Grade 0-1 from the event. Immune-mediated hepatitis was reported in 7% of patients, including 4.9% with Grade 3 or 4 immune-mediated hepatitis. Hepatotoxicity led to permanent discontinuation in 6.5% and immune-mediated hepatitis led to permanent discontinuation of either BAVENCIO or axitinib in 5.3% of patients. Thirty-four patients were treated with corticosteroids and one patient was treated with a non-steroidal immunosuppressant. Resolution of hepatitis occurred in 31 of the 35 patients at the time of data cut-off.

Immune-Mediated Endocrinopathies
Adrenal Insufficiency
BAVENCIO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO depending on severity *[see Dosage and Administration (2.5)]*.

Immune-mediated adrenal insufficiency occurred in 0.6% (11/1854) of patients receiving BAVENCIO, including Grade 3 (0.1%), and Grade 2 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.1% of patients.

Systemic corticosteroids were required in all (11/11) patients with adrenal insufficiency. Adrenal insufficiency resolved in 18% (2/11) of patients. Of the 2 patients in whom BAVENCIO was withheld for adrenal insufficiency, none reinitiated treatment with BAVENCIO.

Hypophysitis
BAVENCIO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated.

Withhold or permanently discontinue BAVENCIO depending on severity *[see Dosage and Administration (2.5)]*.

Immune-mediated pituitary disorders occurred in 0.1% (1/1854) of patients receiving BAVENCIO which was a Grade 2 (0.1%) adverse reactions. Hypopituitarism did not lead to withholding of BAVENCIO in this patient. Systemic corticosteroids were not required in this patient.

Thyroid Disorders
BAVENCIO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold or permanently discontinue BAVENCIO depending on severity *[see Dosage and Administration (2.5)]*.

Thyroiditis occurred in 0.2% (4/1854) of patients receiving BAVENCIO, including Grade 2 (0.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation or withholding of BAVENCIO in any patients. No patients with thyroiditis required systemic corticosteroids. Thyroiditis did not resolve in any patients (0/4).

Hyperthyroidism occurred in 0.4% (8/1854) of patients receiving BAVENCIO, including Grade 2 (0.3%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of BAVENCIO in any patients and led to withholding of BAVENCIO in 0.1% of patients. Systemic corticosteroids were required in 25% (2/8) of patients with hyperthyroidism. Hyperthyroidism resolved in 88% (7/8) of the patients. Of the 2 patients in whom BAVENCIO was withheld for hyperthyroidism, 2 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of hyperthyroidism.

Hypothyroidism occurred in 5% (97/1854) of patients receiving BAVENCIO, including Grade 3 (0.2%) and Grade 2 (3.6%) adverse reactions. Hypothyroidism led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.4% of patients. Systemic corticosteroids were required in 6% (6/97) of patients with hypothyroidism. Hypothyroidism resolved in 6% (6/97) of the patients. Of the 8 patients in whom BAVENCIO was withheld for hypothyroidism, none reinitiated BAVENCIO.

Type I Diabetes Mellitus, which can present with Diabetic Ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO depending on severity *[see Dosage and Administration (2.5)]*.

Immune-mediated Type I diabetes mellitus occurred in 0.2% (3/1854) of patients receiving BAVENCIO, including Grade 3 (0.2%) adverse reactions. Type I diabetes mellitus led to permanent discontinuation of BAVENCIO in 0.1% of patients. Type I diabetes mellitus did not lead to withholding of BAVENCIO in any patient. Systemic corticosteroids were not required in any patient with Type I diabetes mellitus. Type I diabetes mellitus resolved in no patient and all patients required ongoing insulin treatment.

Immune-Mediated Nephritis with Renal Dysfunction
BAVENCIO can cause immune-mediated nephritis.

Immune-mediated nephritis with renal dysfunction occurred in 0.1% (2/1854) of patients receiving BAVENCIO, including Grade 3 (0.1%) and Grade 2 (0.1%) adverse reactions. Nephritis with renal dysfunction led to permanent discontinuation of BAVENCIO in 0.1% of patients. Nephritis did not lead to withholding of BAVENCIO in any patient.

Systemic corticosteroids were required in 100% of patients with nephritis with renal dysfunction. Nephritis with renal dysfunction resolved in 50% of the patients.

Immune-Mediated Dermatologic Adverse Reactions
BAVENCIO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson Syndrome, DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue BAVENCIO depending on severity *[see Dosage and Administration (2.5)]*.

Immune-mediated dermatologic adverse reactions occurred in 6% (108/1854) of patients receiving BAVENCIO, including Grade 3 (0.1%) and Grade 2 (1.9%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of BAVENCIO in 0.3% of patients and withholding of BAVENCIO in 0.4% of patients.

Systemic corticosteroids were required in 25% (27/108) of patients with dermatologic adverse reactions. One patient required the addition of tacrolimus to high-dose corticosteroids. Dermatologic adverse reactions resolved in 46% (50/108) of the patients. Of the 8 patients in whom BAVENCIO was withheld for dermatologic adverse reactions, 4 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of dermatologic adverse reaction.

Other Immune-Mediated Adverse Reactions
The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% (unless otherwise noted) in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis**,** vasculitis.

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae including renal failure), arthritis, polymyalgia rheumatic.

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

5.2 Infusion-Related Reactions

BAVENCIO can cause severe or life-threatening infusion-related reactions *[see Adverse Reactions (6.1)]*. Premedicate with antihistamine and acetaminophen prior to the first 4 infusions. Monitor patients for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions *[see Dosage and Administration (2.5) and Adverse Reactions (6.1)]*.

Infusion-related reactions occurred in 26% of patients treated with BAVENCIO including 3 (0.2%) Grade 4 and 10 (0.5%) Grade 3 infusion-related reactions. Ninety-three percent of patients received premedication with antihistamine and acetaminophen. Eleven (85%) of the 13 patients with Grade ≥ 3 reactions were treated with intravenous corticosteroids. Fifteen percent of patients had infusion-related reactions that occurred after the BAVENCIO infusion was completed.

5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 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. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. 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 a randomized trial, 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).

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking BAVENCIO, inform the patient of the potential risk to a fetus. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least one month after the last dose of BAVENCIO *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*
- Infusion-related reactions *[see Warnings and Precautions (5.2)]*
- Complications of allogeneic HSCT *[see Warnings and Precautions (5.3)]*
- Major adverse cardiovascular events *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to BAVENCIO 10 mg/kg intravenously every 2 weeks as a single agent in 1854 patients enrolled in the JAVELIN Merkel 200 and JAVELIN Solid Tumor trials and to BAVENCIO 10 mg/kg intravenously every 2 weeks in combination with axitinib 5 mg orally twice daily in 489 patients enrolled in the JAVELIN Renal 100 and JAVELIN Renal 101 trials. In the BAVENCIO monotherapy population, 25% of patients were exposed for ≥ 6 months and 9% were exposed for ≥ 12 months. The population characteristics of BAVENCIO in combination with axitinib are shown below. When BAVENCIO was used in combination with axitinib, 70% of patients were exposed for ≥ 6 months and 31% were exposed for ≥ 12 months. The following criteria were used to classify an adverse reaction as immune-mediated: onset within 90 days after last dose of BAVENCIO, no spontaneous resolution within 7 days of onset, treatment with corticosteroids or

other immunosuppressant or hormone replacement therapy, biopsy consistent with immune-mediated reaction, and no other clear etiology.

Metastatic Merkel Cell Carcinoma

The safety of BAVENCIO was evaluated in 204 patients enrolled in the JAVELIN Merkel 200 trial with metastatic MCC. Patients received BAVENCIO 10 mg/kg intravenously every 2 weeks or 800 mg intravenously every 2 weeks until disease progression or unacceptable toxicity.

The median duration of exposure to BAVENCIO was 4.1 months (range: 2 weeks to 48 months). *[see Clinical Studies (14.1)]*.

Serious adverse reactions occurred in 52% of patients receiving BAVENCIO. The most frequent serious adverse reactions (≥ 2% of patients) were general physical health deterioration, anemia, abdominal pain, acute kidney injury, sepsis, hyponatremia, and infusion-related reaction.

Permanent discontinuation of BAVENCIO due to an adverse reaction occurred in 27% of patients. The most frequent adverse reactions (> 1% of patients) that resulted in permanent discontinuation were infusion-related reaction, anemia, increased ALT, and increased AST.

Dosage interruptions of BAVENCIO due to an adverse reaction, excluding temporary interruptions due to infusion-related reactions, occurred in 29% of patients. The most frequent adverse reactions (> 1% of patients) that required dosage interruption were nasopharyngitis, anemia, diarrhea, lung infection, and ALT increased.

The most common adverse reactions (≥ 20%) that occurred in patients receiving BAVENCIO were fatigue, musculoskeletal pain, infusion-related reaction, rash, nausea, constipation, cough, and diarrhea.

Table 3 and Table 4 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in patients receiving BAVENCIO.

Table 3: Adverse Reactions in ≥ 10% of Patients with Metastatic MCC Receiving BAVENCIO in the JAVELIN Merkel 200 Trial

Adverse Reactions	BAVENCIO (N=204)	
	All Grades %	Grade 3-4 %
General Disorders		
Fatigue[a]	47	2.9
Infusion-related reaction[b]	26	0.5
Edema[c]	17	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	29	1.5
Arthralgia	13	0.5
Skin and Subcutaneous Tissue Disorders		
Rash[e]	25	0
Pruritus[f]	16	0.5
Gastrointestinal Disorders		
Nausea	23	0
Constipation	22	0.5
Diarrhea[g]	21	1
Abdominal pain[h]	16	3.4
Vomiting	12	1
Respiratory, Thoracic and Mediastinal Disorders		
Cough	22	0
Dyspnea[i]	15	1
Metabolism and Nutrition Disorders		
Decreased appetite	18	3.4
Decreased weight	16	0.5
Vascular Disorders		
Hypertension	11	6

[a] Includes fatigue and asthenia.
[b] Includes infusion-related reaction, chills, pyrexia, back pain, hypotension, drug hypersensitivity, dyspnea, flushing and hypersensitivity.
[c] Includes peripheral edema, peripheral swelling, and genital edema.
[d] Includes musculoskeletal pain, back pain, pain in extremity, myalgia, musculoskeletal pain, and neck pain.
[e] Includes rash, erythema, rash maculo-papular, rash pruritic, dermatitis bullous, rash erythematous, and rash macular.
[f] Includes pruritus and pruritus generalized.
[g] Includes diarrhea and colitis.
[h] Includes abdominal pain, abdominal pain upper, and abdominal pain lower.
[i] Includes dyspnea and dyspnea exertional.

Other clinically significant adverse reactions in < 10% of patients receiving BAVENCIO in the JAVELIN Merkel 200 trial were dizziness, headache, transaminase increased, creatine phosphokinase increased, and tubulointerstitial nephritis.

Table 4: Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients with Metastatic MCC Receiving BAVENCIO in the JAVELIN Merkel 200 Trial

Laboratory Tests	Any Grade %[a]	Grade 3-4 %[a]
Hematology		
Lymphocyte count decreased	51	16
Hemoglobin decreased	40	6
Platelet count decreased	23	1.5
Chemistry		
Aspartate aminotransferase (AST) increased	31	3
Alanine aminotransferase (ALT) increased	22	3.5
Lipase increased	21	5

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (range: 185 to 199 patients).

Locally Advanced or Metastatic Urothelial Carcinoma

First-Line Maintenance Treatment of Urothelial Carcinoma

The safety of BAVENCIO was evaluated in the JAVELIN Bladder 100 trial where patients received BAVENCIO 10 mg/kg every 2 weeks plus best supportive care (BSC) (N=344) or BSC alone (N=345). Patients with autoimmune diseases or conditions requiring systemic immunosuppression were excluded.

In the BAVENCIO plus BSC arm, 47% were exposed to BAVENCIO for > 6 months and 28% were exposed for > 1 year *[see Clinical Studies (14.2)]*.

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

A fatal adverse reaction (sepsis) occurred in one (0.3%) patient receiving BAVENCIO plus BSC.

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

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

Dose interruptions due to an adverse reaction, excluding temporary interruptions of BAVENCIO infusions due to infusion-related reactions, occurred in 41% of patients receiving BAVENCIO

plus BSC. Adverse reactions leading to interruption of BAVENCIO in > 2% of patients were urinary tract infection (including pyelonephritis) (4.7%) and blood creatinine increased (including acute kidney injury, renal impairment, and renal failure) (3.8%).

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

Thirty-one (9%) patients treated with BAVENCIO plus BSC received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5)]*.

Table 5 summarizes adverse reactions that occurred in ≥ 10% of patients treated with BAVENCIO plus BSC.

Table 5: Adverse Reactions (≥ 10%) of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

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

[a] Fatigue is a composite term that includes fatigue, asthenia and malaise.
[b] Musculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain.
[c] Rash is a composite term that includes rash, rash maculo-papular, erythema, dermatitis acneiform, eczema, erythema multiforme, rash erythematous, rash macular, rash papular, rash pruritic, drug eruption and lichen planus.
[d] Urinary tract infection is a composite term that includes urinary tract infection, urosepsis, cystitis, kidney infection, pyuria, pyelonephritis, bacteriuria, pyelonephritis acute, urinary tract infection bacterial, and Escherichia urinary tract infection.
[e] Cough is a composite term that includes cough and productive cough.

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

Table 6: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 10% of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

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

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

Previously-treated Urothelial Carcinoma

The safety of BAVENCIO was evaluated in 242 patients with locally advanced or metastatic UC receiving BAVENCIO at 10 mg/kg every 2 weeks in the UC cohorts of the JAVELIN Solid Tumor trial. Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. The median duration of exposure to BAVENCIO was 12 weeks (range: 2 weeks to 92 weeks) *[see Clinical Studies (14.2)]*.

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

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

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

Dose interruptions due to an adverse reaction, excluding temporary interruptions due to infusion-related reactions, occurred in 29% of patients receiving BAVENCIO. Adverse reactions leading to interruption of BAVENCIO in > 1% of patients were diarrhea, fatigue, dyspnea, urinary tract infection, and rash.

The most common Grade 3 and 4 adverse reactions (≥ 3%) were anemia, fatigue, hyponatremia, hypertension, urinary tract infection, and musculoskeletal pain.

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

Eleven (4.5%) patients received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5)]*.

Advanced Renal Cell Carcinoma

The safety of BAVENCIO was evaluated in JAVELIN Renal 101. Patients with autoimmune disease other than type I diabetes mellitus, vitiligo, psoriasis, or thyroid disorders not requiring immunosuppressive treatment were excluded. Patients received BAVENCIO 10 mg/kg every 2 weeks administered in combination with axitinib 5 mg twice daily (N=434) or sunitinib 50 mg once daily for 4 weeks followed by 2 weeks off (N=439).

In the BAVENCIO plus axitinib arm, 70% were exposed to BAVENCIO for ≥ 6 months and 29% were exposed for ≥ 1 year in JAVELIN Renal 101 *[see Clinical Studies (14.3)]*.

The median age of patients treated with BAVENCIO in combination with axitinib was 62 years (range: 29 to 83), 38% of patients were 65 years or older, 71% were male, 75% were White, and the ECOG performance score was 0 (64%) or 1 (36%).

Fatal adverse reactions occurred in 1.8% of patients receiving BAVENCIO in combination with axitinib. These included sudden cardiac death (1.2%), stroke (0.2%), myocarditis (0.2%), and necrotizing pancreatitis (0.2%).

Serious adverse reactions occurred in 35% of patients receiving BAVENCIO in combination with axitinib. Serious adverse reactions in ≥ 1% of patients included diarrhea (2.5%), dyspnea (1.8%), hepatotoxicity (1.8%), venous thromboembolic disease (1.6%), acute kidney injury (1.4%), and pneumonia (1.2%).

Permanent discontinuation due to an adverse reaction of either BAVENCIO or axitinib occurred in 22% of patients: 19% BAVENCIO only, 13% axitinib only, and 8% both drugs. The most common adverse reactions (> 1%) resulting in permanent discontinuation of BAVENCIO or the combination were hepatotoxicity (6%) and infusion-related reaction (1.8%).

Dose interruptions or reductions due to an adverse reaction, excluding temporary interruptions of BAVENCIO infusions due to infusion-related reactions, occurred in 76% of patients receiving BAVENCIO in combination with axitinib. This includes interruption of BAVENCIO in 50% of patients. Axitinib was interrupted in 66% and dose reduced in 19% of patients. The most common adverse reaction (> 10%) resulting in interruption of BAVENCIO was diarrhea (10%) and the most common adverse reactions resulting in either interruption or dose reduction of axitinib were diarrhea (19%), hypertension (18%), palmar-plantar erythrodysesthesia (18%), and hepatotoxicity (10%).

The most common adverse reactions (≥ 20%) in patients receiving BAVENCIO in combination with axitinib were diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain, and headache.

Forty-eight (11%) patients treated with BAVENCIO in combination with axitinib received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5)]*.

Table 7 summarizes adverse reactions that occurred in ≥ 20% of BAVENCIO in combination with axitinib-treated patients.

Table 7: Adverse Reactions (≥ 20%) of Patients Receiving BAVENCIO in Combination with Axitinib (JAVELIN Renal 101 Trial)

Adverse Reactions	BAVENCIO plus Axitinib (N=434)		Sunitinib (N=439)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal Disorders				
Diarrhea[a]	62	8	48	2.7
Nausea	34	1.4	39	1.6
Mucositis[b]	34	2.8	35	2.1
Hepatotoxicity[c]	24	9	18	3.6
Abdominal pain[d]	22	1.4	19	2.1
General Disorders and Administration Site Conditions				
Fatigue[e]	53	6	54	6
Vascular Disorders				
Hypertension[f]	50	26	36	17
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[g]	40	3.2	33	2.7
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	33	6	34	4
Rash[h]	25	0.9	16	0.5
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	31	0.5	3.2	0
Dyspnea[i]	23	3	16	1.8
Cough	23	0.2	19	0
Metabolism and Nutrition Disorders				
Decreased appetite	26	2.1	29	0.9
Endocrine Disorders				
Hypothyroidism	25	0.2	14	0.2
Nervous System Disorders				
Headache	21	0.2	16	0.2

[a] Diarrhea is a composite term that includes diarrhea, autoimmune colitis, and colitis.
[b] Mucositis is a composite term that includes mucosal inflammation and stomatitis.
[c] Hepatotoxicity is a composite term that includes ALT increased, AST increased, autoimmune hepatitis, bilirubin conjugated, bilirubin conjugated increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis fulminant, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, liver disorder, liver injury, and transaminases increased.
[d] Abdominal pain is a composite term that includes abdominal pain, flank pain, abdominal pain upper, and abdominal pain lower.
[e] Fatigue is a composite term that includes fatigue and asthenia.
[f] Hypertension is a composite term that includes hypertension and hypertensive crisis.
[g] Musculoskeletal pain is a composite term that includes musculoskeletal pain, musculoskeletal chest pain, myalgia, back pain, bone pain, musculoskeletal discomfort, neck pain, spinal pain, and pain in extremity.
[h] Rash is a composite term that includes rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash erythematous, rash papular, and rash pustular.

[i] Dyspnea is a composite term that includes dyspnea, dyspnea exertional and dyspnea at rest.

Other clinically important adverse reactions that occurred in less than 20% of patients in JAVELIN Renal 101 included arthralgia, weight decreased, and chills.

Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Infusion-related reactions occurred in 12% (Grade 3: 1.6%; no Grade 4) of patients treated with BAVENCIO in combination with axitinib.

Table 8 summarizes selected laboratory abnormalities that occurred in ≥ 20% of BAVENCIO in combination with axitinib-treated patients.

Table 8: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients Receiving BAVENCIO in Combination with Axitinib (JAVELIN Renal 101 Trial)

Laboratory Abnormality	BAVENCIO plus Axitinib*		Sunitinib*	
	Any Grade %	Grade 3-4 %	Any Grade %	Grade 3-4 %
Chemistry				
Blood triglycerides increased	71	13	48	5
Blood creatinine increased	62	2.3	68	1.4
Blood cholesterol increased	57	1.9	22	0.7
Alanine aminotransferase increased (ALT)	50	9	46	3.2
Aspartate aminotransferase increased (AST)	47	7	57	3.2
Blood sodium decreased	38	9	37	10
Lipase increased	37	14	25	7
Blood potassium increased	35	3	28	3.9
Blood bilirubin increased	21	1.4	23	1.4
Hematology				
Platelet count decreased	27	0.7	80	15
Hemoglobin decreased	21	2.1	65	8

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: BAVENCIO in combination with axitinib group (range: 413 to 428 patients) and sunitinib group (range: 405 to 433 patients).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of BAVENCIO in pregnant women *[see Clinical Pharmacology (12.1)]*. Animal studies have demonstrated that inhibition of the

PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death *[see Data]*. Human IgG1 immunoglobulins (IgG1) are known to cross the placenta. Therefore, BAVENCIO has the potential to be transmitted from the mother to the developing fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with BAVENCIO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering BAVENCIO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to BAVENCIO may increase the risk of developing immune-related disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of avelumab in human milk, the effects on the breastfed infant, or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise a lactating woman not to breastfeed during treatment and for at least one month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO.

8.4 Pediatric Use

The safety and effectiveness of BAVENCIO have been established in pediatric patients aged 12 years and older for metastatic MCC. 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 pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MCC is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients

12 years of age or greater is the same as that in adults *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

Safety and effectiveness of BAVENCIO have not been established in pediatric patients less than 12 years of age.

8.5 Geriatric Use

Metastatic Merkel Cell Carcinoma

Of the 204 patients with MCC who received BAVENCIO in the JAVELIN Merkel 200 trial, 78% were 65 years or older and 43% were 75 years or older. No overall differences in safety or efficacy were observed between elderly patients and younger patients.

Locally Advanced or Metastatic Urothelial Carcinoma

Of the 344 patients randomized 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.

Advanced Renal Cell Carcinoma

Of the 434 patients randomized to 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.

11 DESCRIPTION

Avelumab is a programmed death ligand1 (PD-L1) blocking antibody. Avelumab is a human IgG1 lambda monoclonal antibody produced in Chinese hamster ovary cells and has a molecular weight of approximately 147 kDa.

BAVENCIO (avelumab) Injection for intravenous use is a sterile, preservative-free, non-pyrogenic, clear, colorless to slightly yellow solution. Each single-dose vial contains 200 mg avelumab in 10 mL (20 mg/mL). Each mL contains 20 mg avelumab, D-mannitol (51 mg), glacial acetic acid (0.6 mg), polysorbate 20 (0.5 mg), sodium hydroxide (0.3 mg), and Water for Injection. The pH range of the solution is 5.0 – 5.6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PD-L1 may be expressed on tumor cells and tumor-infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor 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 binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This interaction releases the inhibitory effects of PD-L1 on the immune response resulting in the restoration of immune responses, including anti-tumor immune responses. Avelumab has also been shown to

induce antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

12.2 Pharmacodynamics

Based on exposure efficacy and exposure safety relationships, there are no expected clinically meaningful differences in the safety or efficacy of BAVENCIO administered every 2 weeks at 800 mg or 10 mg/kg in patients with metastatic Merkel cell carcinoma, in patients with urothelial carcinoma and in patients with advanced renal cell carcinoma.

12.3 Pharmacokinetics

Avelumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent BAVENCIO and BAVENCIO in combination with axitinib. There are no expected clinically meaningful differences in exposure of avelumab administered every 2 weeks at 800 mg or 10 mg/kg in both settings.

BAVENCIO as a single agent

The pharmacokinetics of avelumab as a single agent was studied in 1629 patients who received doses ranging from 1 to 20 mg/kg every 2 weeks. The data showed that the exposure of avelumab increased dose-proportionally in the dose range of 10 to 20 mg/kg every 2 weeks. Steady-state concentrations of avelumab were reached after approximately 4 to 6 weeks (2 to 3 cycles) of repeated dosing, and the systemic accumulation was approximately 1.25-fold. The geometric mean volume of distribution at steady state for a subject receiving 10 mg/kg was 4.72 L. The primary elimination mechanism of avelumab is proteolytic degradation. Based on population pharmacokinetic analyses in patients with solid tumors, the total systemic clearance was 0.59 L/day and the terminal half-life was 6.1 days in patients receiving 10 mg/kg. In a post hoc analysis, avelumab clearance was found to decrease over time in patients with MCC, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline value of approximately 32.1% (36.2%), which is not considered clinically important. There was no evidence to suggest a change of avelumab clearance over time in patients with UC.

BAVENCIO with axitinib

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

Specific Populations

Body weight was positively correlated with total systemic clearance in population pharmacokinetic analyses. No clinically meaningful differences in pharmacokinetics were observed in the clearance of avelumab based on age; sex; race; PD-L1 status; tumor burden; mild [calculated creatinine clearance (CLcr) 60 to 89 mL/min, n=623 as estimated by the Cockcroft-Gault formula], moderate [CLcr 30 to 59 mL/min, n=320], or severe [CLcr 15 to 29 mL/min, n=4] renal impairment; and mild [bilirubin less than or equal to ULN and AST greater than ULN or bilirubin between 1 and 1.5 times ULN, n=217] or moderate [bilirubin between 1.5 and 3 times ULN, n=4] hepatic impairment. There are limited data from patients with severe hepatic impairment [bilirubin greater than 3 times ULN, n=1], and the effect of severe hepatic

impairment on the pharmacokinetics of avelumab is unknown. In patients with advanced UC or advanced RCC, BAVENCIO clearance in patients who tested positive for treatment-emergent ADA was approximately 15% higher as compared to clearance in patients who tested negative for treatment-emergent ADA.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of BAVENCIO or of other avelumab products.

ADA responses with BAVENCIO 10 mg/kg as an intravenous infusion every 2 weeks were monitored during the respective treatment periods in each trial. The ADA responses are listed in Table 9.

Table 9: BAVENCIO ADA Incidence

Trial Name*	ADA
JAVELIN Merkel 200 Part A	8.9% (7/79)
JAVELIN Merkel 200 Part B	8.2% (9/110)
JAVELIN Bladder 100	19.1% (62/325)
JAVELIN Solid Tumor, UC	18.1% (41/226)
JAVELIN Renal 100 and 101	15% (66/453)

* Details of each treatment regimen are described in Section 14 *[see Clinical Studies (14)]*.
ADA: anti-avelumab antibodies; UC: urothelial carcinoma

In JAVELIN Merkel 200 trial, neutralizing antibodies were detected in 5 out of 7 (Part A), and 8 out of 9 (Part B) patients with treatment-emergent ADAs, respectively.

There was no clinically meaningful impact of ADA development on pharmacokinetics. The effect of ADA on the efficacy or safety could not be determined due to the low occurrence of ADAs.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Fertility studies have not been conducted with avelumab; however, an assessment of male and female reproductive organs was included in 3-month repeat-dose toxicity study in Cynomolgus monkeys. Weekly administration of avelumab did not result in any notable effects in the male and female reproductive organs.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit

markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Metastatic Merkel Cell Carcinoma

The efficacy and safety of BAVENCIO was demonstrated in the JAVELIN Merkel 200 trial (NCT02155647), an open-label, single--arm, multi-center study conducted in patients with histologically confirmed metastatic MCC. This trial consisted of two parts; Part A enrolled patients with metastatic MCC whose disease had progressed on or after chemotherapy administered for distant metastatic disease, and Part B enrolled patients with metastatic MCC who were treatment-naïve. The trial excluded patients with autoimmune disease; medical conditions requiring systemic immunosuppression; prior organ or allogeneic stem cell transplantation; prior treatment with anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies; CNS metastases; infection with HIV, hepatitis B, or hepatitis C; or ECOG performance score ≥ 2.

Patients received BAVENCIO 10 mg/kg as an intravenous infusion over 60 minutes 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 2 weeks, and no need for salvage therapy, could continue treatment. Tumor response assessments were performed every 6 weeks.

The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by a blinded independent central review committee (IRC) and IRC-assessed duration of response.

Previously-treated Merkel Cell Carcinoma

A total of 88 patients were enrolled in Part A. Baseline patient characteristics were a median age of 73 years (range: 33 to 88), 74% of patients were male, 92% were White, and the ECOG performance score was 0 (56%) or 1 (44%). Seventy-five percent of patients were 65 years or older, 35% were 75 or older, and 3% were 85 or older. Sixty-five percent of patients were reported to have had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies. Fifty-three percent of patients had visceral metastases. Sixty-six percent were PD-L1-positive (≥ 1% of tumor cells), 18% were PD-L1 negative, and 16% had non-evaluable results by an investigational immunohistochemistry assay. Archival tumor samples were evaluated for Merkel cell polyomavirus (MCV) using an investigational assay; of the 77 patients with evaluable results, 52% had evidence of MCV.

Efficacy results are summarized in Table 10. Responses were observed in patients regardless of tumor PD-L1 expression or presence of MCV.

Table 10: Efficacy Results from the JAVELIN Merkel 200 Trial in Previously-Treated Patients with Metastatic MCC (Part A)

Efficacy Endpoints	BAVENCIO (N=88)
Overall Response Rate (ORR)	
Overall response rate, n (%)	29 (33%)
(95% CI)	(23, 44)
Complete responses, n (%)	10 (11%)
Partial responses, n (%)	19 (22%)
Duration of Response (DOR)	N=29
Median DOR in months (range)	40.5 (2.8, 41.5+)
Patients with DOR ≥ 6 months, n (%)	26 (90%)
Patients with DOR ≥ 12 months, n (%)	19 (66%)

CI: Confidence interval.

Treatment-naïve Merkel Cell Carcinoma

A total of 116 patients were enrolled in Part B. Baseline patient characteristics were median age of 74 years (range: 41 to 93); 70% of patients were male; 65% were White, 31% were unknown or not collected, 2.6% were Asian, and 1.7% were Black; ECOG performance score was 0 (62%) or 1 (38%). Eighteen percent of patients were PD-L1-positive (≥ 1% of tumor cells), 75% were PD-L1-negative, and 7% had non-evaluable results by an investigational immunohistochemistry assay. Sixty percent of patients had Merkel cell polyomavirus (MCV).

Efficacy results are presented in Table 11. Responses were observed in patients regardless of tumor PD-L1 expression or presence of MCV.

Table 11: Efficacy Results of the JAVELIN Merkel 200 Trial in Patients with Treatment-Naïve Metastatic MCC (Part B)

Efficacy Endpoints	BAVENCIO (N=116)
Overall Response Rate (ORR)	
Overall response rate, n (%)	46 (40%)
(95% CI)	(31, 49)
Complete responses, n (%)	19 (16%)
Partial responses, n (%)	27 (23%)
Duration of Response (DOR)	N=46
Median DOR in months, (range)	18.2 (1.2+, 28.3+)
Patients with DOR ≥ 6 months, n (%)	35 (76%)
Patients with DOR ≥ 12 months, n (%)	24 (52%)

CI: Confidence interval.

14.2 Locally Advanced or Metastatic Urothelial Carcinoma

First-Line Maintenance Treatment of Urothelial Carcinoma

The efficacy and safety of BAVENCIO was demonstrated in the JAVELIN Bladder 100 trial (NCT02603432), a randomized, multi-center, open-label study conducted in 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing chemotherapy. Patients with autoimmune disease or a medical condition that required immunosuppression were excluded.

Randomization was stratified by best response to chemotherapy (CR/PR vs. stable disease [SD]) and site of metastasis (visceral vs. non-visceral) at the time of initiating first-line chemotherapy. Patients were randomized (1:1) to receive either BAVENCIO 10 mg/kg intravenous infusion every 2 weeks plus best supportive care (BSC) or BSC alone. Treatment was initiated within 4-10 weeks after the last dose of chemotherapy.

Treatment with BAVENCIO continued until RECIST v1.1-defined progression of disease by Blinded Independent Central Review (BICR) assessment or unacceptable toxicity. Administration of BAVENCIO was permitted beyond RECIST-defined disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at baseline, 8 weeks after randomization, then every 8 weeks up to 12 months after randomization, and every 12 weeks thereafter until documented confirmed disease progression based on BICR assessment per RECIST v1.1.

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

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

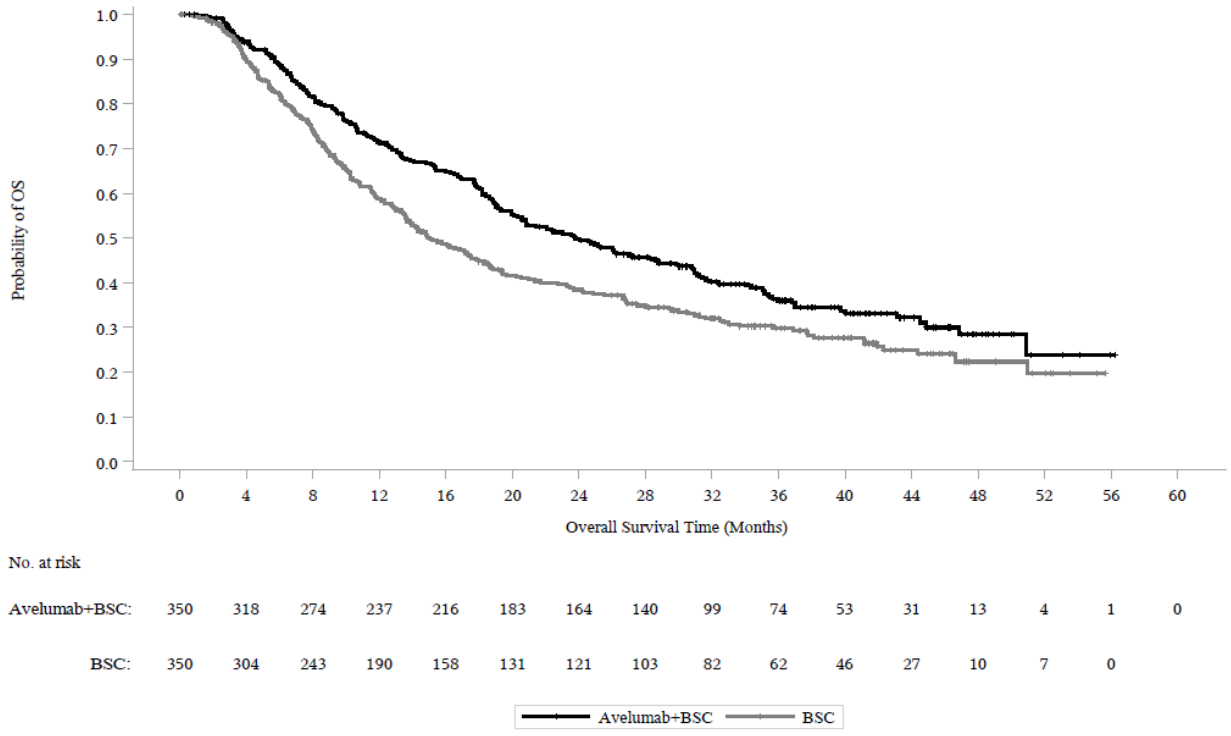
The major efficacy outcome measure was overall survival (OS) in all randomized patients and patients with PD-L1-positive tumors. The results from a pre-specified interim analysis demonstrated a statistically significant improvement in OS for patients randomized to BAVENCIO plus BSC as compared with BSC alone. An updated OS analysis was conducted when 452 deaths were observed. Consistent results were observed across the pre-specified subgroups of CR/PR versus SD to first-line chemotherapy.

Table 12: Efficacy Results from the JAVELIN Bladder 100 Trial

Efficacy Endpoints	BAVENCIO plus BSC (N=350)	BSC (N=350)
Primary OS		
Events (%)	145 (41.4)	179 (51.1)
Median in months (95% CI)	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)
Hazard ratio (95% CI)	0.69 (0.56, 0.86)	
p-value*	0.001	
Updated OS		
Events (%)	215 (61.4)	237 (67.7)
Median in months (95% CI)	23.8 (19.9, 28.8)	15.0 (13.5, 18.2)
Hazard ratio (95% CI)	0.76 (0.63, 0.92)	

BSC: Best supportive care; CI: Confidence interval; OS: overall survival.
* p-value based on 2-sided stratified log-rank.

Figure 1: K-M Estimates for Updated OS from the JAVELIN Bladder 100 Trial



In the pre-specified endpoint of OS among patients with PD-L1-positive tumors (n=358, 51%), the hazard ratio was 0.69 (95% CI: 0.52, 0.90) in the updated OS analysis for patients

randomized to BAVENCIO plus BSC versus BSC alone. In an exploratory analysis of patients with PD-L1-negative tumors (n=270, 39%), the updated OS hazard ratio was 0.82 (95% CI: 0.62, 1.09).

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

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

Baseline demographic and disease characteristics for the 226 patients with a minimum of 13 weeks of follow-up were median age 68 years (range: 30 to 89), 72% male, 80% White, and 34% and 66% of patients had an ECOG performance status 0 and 1, respectively. Forty-four percent of patients had non-bladder urothelial carcinoma including 23% of patients with upper tract disease, and 83% of patients had visceral metastases (baseline target and/or non-target lesions present outside of the lymph nodes). Nine (4%) patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy only. Forty-seven percent of patients only received prior cisplatin-based regimens, 32% received only prior carboplatin-based regimens, and 20% received both cisplatin and carboplatin-based regimens. At baseline, 17% of patients had a hemoglobin < 10 g/dL and 34% of patients had liver metastases.

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

Table 13: Efficacy Results of the UC Cohorts in the JAVELIN Solid Tumor Trial

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

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

14.3 Advanced Renal Cell Carcinoma

The efficacy and safety of BAVENCIO in combination with axitinib was demonstrated in the JAVELIN Renal 101 trial (NCT02684006), a randomized, multicenter, open-label, study of BAVENCIO in combination with axitinib in 886 patients with untreated advanced RCC regardless of tumor PD-L1 expression [intent-to-treat (ITT) population]. Patients with autoimmune disease or conditions requiring systemic immunosuppression were excluded.

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 randomized (1:1) to one of the following treatment arms:

- BAVENCIO 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 BAVENCIO and axitinib continued until RECIST v1.1-defined progression of disease by Blinded Independent Central Review (BICR) assessment or unacceptable toxicity. Administration BAVENCIO and axitinib 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 tumor status was performed at baseline, after randomization at 6 weeks, then every 6 weeks thereafter up to 18 months after randomization, and every 12 weeks thereafter until documented confirmed disease progression by BICR.

Baseline characteristics were a median age of 61 years (range: 27 to 88), 38% of patients were 65 years or older, 75% were male, 75% were White, and the ECOG PS was 0 (63%) or 1 (37%), respectively. Patient distribution by International Metastatic Renal Cell Carcinoma Database (IMDC) risk groups was 21% favorable, 62% intermediate, and 16% poor.

The major efficacy outcome measures were progression-free survival (PFS), as assessed by an BICR using RECIST v1.1 and overall survival (OS) in patients with PD-L1-positive tumors using a clinical trial assay (PD-L1 expression level ≥ 1%). Since PFS was statistically significant in patients with PD-L1-positive tumors [HR 0.61 (95% CI: 0.48, 0.79)], it was then tested in the ITT population and a statistically significant improvement in PFS in the ITT population was also demonstrated.

With a median overall survival follow-up of 19 months, overall survival data were immature with 27% deaths in the ITT population.

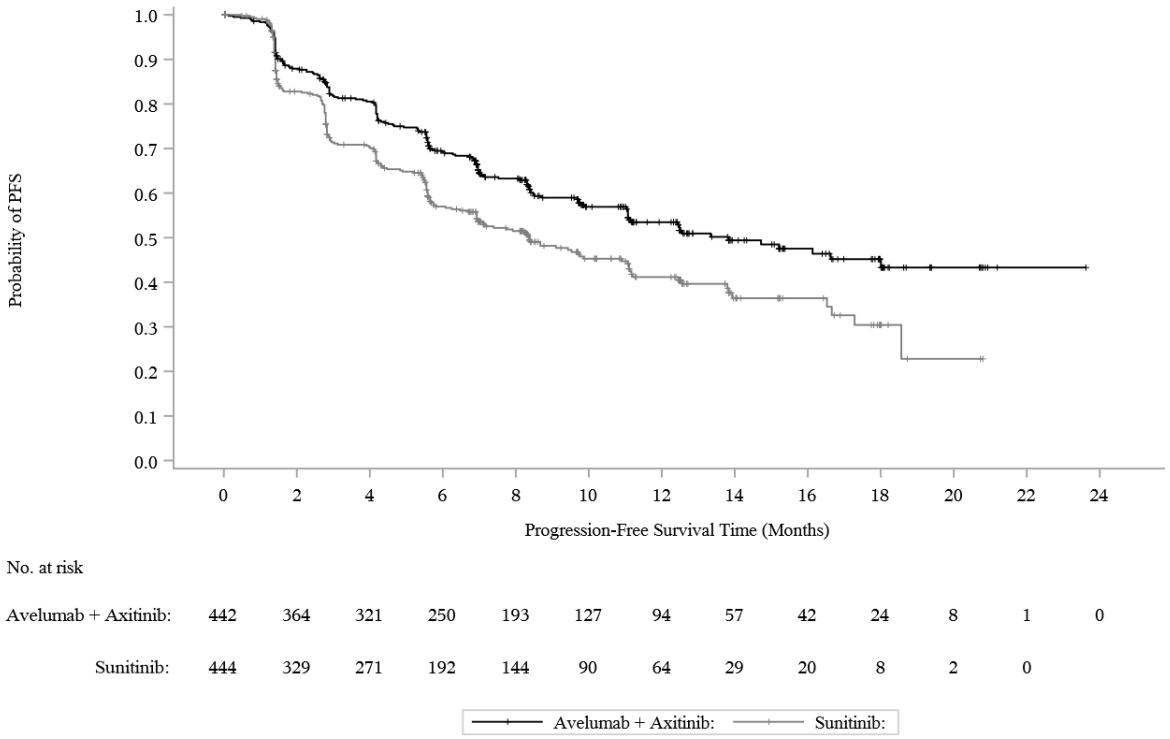
Efficacy results are presented in Table 14 and Figure 2.

Table 14: Efficacy Results from JAVELIN Renal 101 Trial - ITT

Efficacy Endpoints (Based on BICR Assessment)	**BAVENCIO plus 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*	0.0002	
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 (3.4)	8 (1.8)
Partial Response (PR) n (%)	212 (48)	106 (24)

BICR: Blinded Independent Central Review; CI: Confidence interval; NE: Not estimable.
* p-value based on 2-sided stratified log-rank.

Figure 2: K-M Estimates for PFS based on BICR Assessment – ITT



16 HOW SUPPLIED/STORAGE AND HANDLING

BAVENCIO (avelumab) Injection is a sterile, preservative-free, and clear, colorless to slightly yellow solution for intravenous infusion supplied as a single-dose vial of 200 mg/10 mL (20 mg/mL), individually packed into a carton (NDC 44087-3535-1).

Store refrigerated at 36°F to 46°F (2°C to 8°C) in original package to protect from light.

Do not freeze or shake the vial.

The vial stopper is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions requiring corticosteroids or hormone replacement therapy, including, but not limited to:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.1)]*.

- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions (5.1)]*.
- Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.1)]*.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of skin rash, itchy skin, rash with tiny spots and bumps, reddening of skin, blisters or peeling *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions
Advise patients to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT
Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.3)]*.

Major Adverse Cardiovascular Events
Advise patients receiving BAVENCIO in combination with axitinib to contact their healthcare provider immediately for signs or symptoms of cardiovascular events including but not limited to new or worsening chest discomfort, dyspnea, or peripheral edema *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity
Advise females of reproductive potential that BAVENCIO can cause fetal harm. Instruct females of reproductive potential to use effective contraception during and for at least one month after the last dose of BAVENCIO *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.1, 8.3)]*.

Lactation
Advise nursing mothers not to breastfeed while taking BAVENCIO and for at least one month after the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
EMD Serono, Inc.
Rockland, MA 02370
U.S.A.

Marketed by:
EMD Serono, Inc., MA, USA

US License No: 1773

Product of Switzerland

BAVENCIO is a trademark of Merck KGaA, Darmstadt, Germany

MEDICATION GUIDE

BAVENCIO® (buh-VEN-see-oh)
(avelumab)
injection

What is the most important information I should know about BAVENCIO?

BAVENCIO is a medicine that may treat certain cancers by working with your immune system. BAVENCIO can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death**.** You can have more than one of these problem at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you get any new or worsening signs or symptoms, including:

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach-area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than

Hormone gland problems.

- headache that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems.

- decrease in your amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

Skin problems.

- rash
- itching
- skin blistering or peeling
- painful sores or ulcers in mouth or nose, throat, or genital area
- fever or flu-like symptoms
- swollen lymph nodes

Problems can also happen in other organs and tissues. These are not all of the signs or symptoms of immune system problems that can happen with BAVENCIO. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:

- chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs

- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising.

Infusion-related reactions can sometimes be severe or life-threatening. Signs and symptoms of infusion-related reactions may include:

- chills or shaking
- hives
- flushing
- shortness of breath or wheezing
- dizziness
- feel like passing out
- fever
- back pain
- stomach area (abdomen) pain

Complications, including graft-versus-host-disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with BAVENCIO. Your healthcare provider will monitor you for these complications.

Heart problems. When BAVENCIO is used with the medicine axitinib, severe heart problems can happen and can lead to death. Signs and symptoms of heart problems may include:

- swelling of your stomach area (abdomen), legs, hands, feet, or ankles
- shortness of breath
- nausea or vomiting
- new or worsening chest discomfort, including pain or pressure
- weight gain
- pain or discomfort in your arms, back, neck, or jaw
- breaking out in a cold sweat
- feeling lightheaded or dizzy

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during your treatment with BAVENCIO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with BAVENCIO if you have severe side effects.

What is BAVENCIO?

BAVENCIO is a prescription medicine used to treat:

- a type of skin cancer called Merkel cell carcinoma (MCC) in adults and children 12 years of age and older. BAVENCIO may be used when your skin cancer has spread.
- a type of cancer in the bladder or urinary tract called urothelial carcinoma (UC) when it has spread or cannot be removed by surgery (advanced UC). BAVENCIO may be used:
  - as maintenance treatment when your cancer has responded or stabilized after you have received platinum-containing chemotherapy as your first treatment.
  - when you have received platinum-containing chemotherapy, and it did not work or is no longer working.
- a type of kidney cancer called renal cell carcinoma (RCC). BAVENCIO may be used with the medicine axitinib as your first treatment when your kidney cancer has spread or cannot be removed by surgery (advanced RCC).

It is not known if BAVENCIO is safe and effective in children under the age of 12.

Before you receive BAVENCIO, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- have heart problems or high blood pressure
- have diabetes

- have a high cholesterol level in your blood
- are pregnant or plan to become pregnant. BAVENCIO can harm your unborn baby.
  Females who are able to become pregnant:
  - You should use an effective method of birth control during your treatment and for at least 1 month after the last dose of BAVENCIO. Talk to your healthcare provider about birth control methods that you can use during this time.
- are breastfeeding or plan to breastfeed. It is not known if BAVENCIO passes into your breast milk. Do not breastfeed during treatment and for at least 1 month after the last dose of BAVENCIO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive BAVENCIO?

- Your healthcare provider will give you BAVENCIO into your vein through an intravenous (IV) line over 60 minutes.
- BAVENCIO is usually given every 2 weeks.
- Your healthcare provider will give you medicines before the first 4 infusions and then as needed to help reduce infusion reactions.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for certain side effects.
- If you miss an appointment, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of BAVENCIO?

BAVENCIO can cause serious side effects, including:

- **See "What is the most important information I should know about BAVENCIO?"**

The most common side effects of BAVENCIO in people with MCC include:

- feeling tired
- muscle and bone pain
- infusion-related reactions including chills, fever, and back pain
- rash
- nausea
- constipation
- cough
- diarrhea

The most common side effects of BAVENCIO as maintenance treatment in people with UC whose cancer responded or stabilized after platinum-containing chemotherapy as first treatment include:

- feeling tired
- muscle and bone pain
- urinary tract infection
- rash

The most common side effects of BAVENCIO in people with UC after platinum-containing chemotherapy that did not work, or is no longer working, include:

- feeling tired
- infusion-related reactions including chills, fever, back pain, redness, and shortness of breath
- muscle and bone pain
- nausea
- decreased appetite
- urinary tract infection

The most common side effects of BAVENCIO when given with axitinib in people with RCC include:

- diarrhea
- feeling tired
- high blood pressure
- muscle and bone pain
- nausea
- mouth sores
- hoarseness
- decreased appetite
- low levels of thyroid hormone
- rash
- liver problems
- cough
- shortness of breath

- blisters or rash on the palms of your hands and soles of your feet
- stomach area (abdomen) pain
- headache

These are not all the possible side effects of BAVENCIO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of BAVENCIO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about BAVENCIO that is written for health professionals.

What are the ingredients in BAVENCIO?

Active ingredient: avelumab

Inactive ingredients: D-mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, and Water for Injection

Manufactured by: EMD Serono, Inc. One Technology Place, Rockland, MA 02370 USA, U.S. License No. 1773.
Marketed by: EMD Serono, Inc., MA, USA.
BAVENCIO is a trademark of Merck KGaA, Darmstadt, Germany.

For more information, call toll-free 1-844-826-8371 or go to www.bavencio.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 09/2023