FOR THE FIRST-LINE TREATMENT OF ADVANCED

RCC

BAVENCIO® avelumab Injection 20 mg/mL + Inlyta® axitinib 1mg and 5mg tablets

Dosing guidelines and some suggested management strategies for BAVENCIO in combination with INLYTA

Therapy Management Guide

INDICATION

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

SELECTED SAFETY INFORMATION

BAVENCIO (avelumab)

BAVENCIO can cause **immune-mediated pneumonitis**, including fatal cases. Monitor patients for signs and symptoms of pneumonitis, and evaluate suspected cases with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis. Pneumonitis occurred in 1.2% of patients, including one (0.1%) patient with fatal, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

INLYTA (axitinib)

Hypertension including **hypertensive crisis** has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

BAVENCIO® (avelumab) IN COMBINATION WITH INLYTA® (axitinib) DOSING

Recommended dosage of BAVENCIO

800 MG IV INFUSION

GIVEN OVER **60 MINUTES**

EVERY **2 WEEKS**

in combination with

Recommended dosage of INLYTA

5 MG ORALLY TAKEN **TWICE DAILY** WITH OR WITHOUT FOOD

Administer doses **12 hours apart**
Swallow whole with a glass of water

UNTIL DISEASE PROGRESSION OR UNACCEPTABLE TOXICITY

- 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
- When INLYTA is used in combination with BAVENCIO, dose escalation of INLYTA above the initial 5-mg dose may be considered at intervals of two weeks or longer
  - Review the full Prescribing Information for INLYTA prior to initiation

SELECTED SAFETY INFORMATION

BAVENCIO (avelumab)

BAVENCIO can cause **hepatotoxicity and immune-mediated hepatitis**, including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater hepatitis. Withhold BAVENCIO for moderate (Grade 2) immune-mediated hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% of patients, including two (0.1%) patients with fatal, and 11 (0.6%) with Grade 3.

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INLYTA (axitinib)

Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk for, or who have a history of, these events.

Hemorrhagic events, including fatal events, have been reported. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

Management of some AEs may require temporary interruption or permanent discontinuation and/or dose reduction

- The dose of INLYTA may be increased or reduced based on individual safety or tolerability
- Film-coated tablets in 2 different strengths (5 mg and 1 mg) allow for titration
- Do not break apart INLYTA tablets

If a **dose reduction** from the starting dose is required:

- Reduce dose to **3 mg twice daily**
- Reduce dose to **2 mg twice daily** if additional dose reduction is required

Dose increase criteria: Patients tolerate INLYTA for at least 2 consecutive weeks with no AEs >Grade 2 and are normotensive without antihypertension medication.

- Dose may be increased to **7 mg twice daily** if patients meet dose increase criteria at the starting dose
- Dose may be further increased to **10 mg twice daily** if patients meet the dose increase criteria at the 7-mg dose

Other dosing considerations:

- For patients with moderate hepatic impairment, or for patients on a strong CYP3A4/5 inhibitor, decrease the INLYTA dose by approximately half
- Avoid strong CYP3A4/5 inhibitors. If unavoidable, reduce the dose
- Avoid strong CYP3A4/5 inducers and, if possible, avoid moderate CYP3A4/5 inducers
- Patients should not eat grapefruit, drink grapefruit juice, or take St John's wort while taking INLYTA
- Stop treatment with INLYTA at least 2 days prior to elective surgery. Do not re-administer INLYTA for at least 2 weeks following major surgery and until adequate wound healing

SELECTED SAFETY INFORMATION

BAVENCIO (avelumab)

BAVENCIO in combination with INLYTA can cause **hepatotoxicity** with higher than expected frequencies of Grade 3 and 4 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy. Withhold BAVENCIO and INLYTA for moderate (Grade 2) hepatotoxicity and permanently discontinue the combination for severe or life-threatening (Grade 3 or 4) hepatotoxicity. Administer corticosteroids as needed. In patients treated with BAVENCIO in combination with INLYTA, Grades 3 and 4 increased ALT and AST occurred in 9% and 7% of patients, respectively, and immune-mediated hepatitis occurred in 7% of patients, including 4.9% with Grade 3 or 4.

INLYTA (axitinib)

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

BAVENCIO® Injection 20 mg/mL avelumab + Inlyta® 1mg and 5mg tablets axitinib

PREPARATION AND ADMINISTRATION OF BAVENCIO® (avelumab)

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

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 coadminister other drugs** through the same intravenous line

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

IMPORTANT SAFETY INFORMATION

BAVENCIO (avelumab)

BAVENCIO can cause **immune-mediated pneumonitis**, including fatal cases. Monitor patients for signs and symptoms of pneumonitis, and evaluate suspected cases with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis. Pneumonitis occurred in 1.2% of patients, including one (0.1%) patient with fatal, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

BAVENCIO can cause **hepatotoxicity and immune-mediated hepatitis**, including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater hepatitis. Withhold BAVENCIO for moderate (Grade 2) immune-mediated hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% of patients, including two (0.1%) patients with fatal, and 11 (0.6%) with Grade 3.

BAVENCIO in combination with INLYTA can cause **hepatotoxicity** with higher than expected frequencies of Grade 3 and 4 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy. Withhold BAVENCIO and INLYTA for moderate (Grade 2) hepatotoxicity and permanently discontinue the combination for severe or life-threatening (Grade 3 or 4) hepatotoxicity. Administer corticosteroids as needed. In patients treated with BAVENCIO in combination with INLYTA, Grades 3 and 4 increased ALT and AST occurred in 9% and 7% of patients, respectively, and immune-mediated hepatitis occurred in 7% of patients, including 4.9% with Grade 3 or 4.

BAVENCIO can cause **immune-mediated colitis**. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold BAVENCIO for moderate or severe (Grade 2 or 3) colitis until resolution. Permanently discontinue for life-threatening (Grade 4) or recurrent (Grade 3) colitis upon reinitiation of BAVENCIO. Immune-mediated colitis occurred in 1.5% of patients, including seven (0.4%) with Grade 3.

INLYTA (axitinib)

Hypertension including **hypertensive crisis** has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk for, or who have a history of, these events.

Hemorrhagic events, including fatal events, have been reported. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

INLYTA has the potential to adversely affect **wound healing.** Withhold INLYTA for at least 2 days prior to elective surgery. Do not administer INLYTA for at least 2 weeks following major surgery and until adequate wound healing. The safety of resuming INLYTA after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. If signs or symptoms occur, permanently discontinue treatment.

BAVENCIO® (avelumab) Injection 20 mg/mL + Inlyta® (axitinib) 1mg and 5mg tablets

IMPORTANT SAFETY INFORMATION

BAVENCIO (avelumab)

BAVENCIO can cause **immune-mediated endocrinopathies**, including adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus.

Monitor patients for signs and symptoms of **adrenal insufficiency** during and after treatment, and administer corticosteroids as appropriate. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Adrenal insufficiency was reported in 0.5% of patients, including one (0.1%) with Grade 3.

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage hypothyroidism with hormone replacement therapy and hyperthyroidism with medical management. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders. Thyroid disorders, including hypothyroidism, hyperthyroidism, and thyroiditis, were reported in 6% of patients, including three (0.2%) with Grade 3.

Type 1 diabetes mellitus including diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold BAVENCIO and administer antihyperglycemics or insulin in patients with severe or life-threatening (Grade ≥3) hyperglycemia, and resume treatment when metabolic control is achieved. Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% of patients, including two cases of Grade 3 hyperglycemia.

BAVENCIO can cause **immune-mediated nephritis and renal dysfunction**. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to Grade 1 or lower. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis. Immune-mediated nephritis occurred in 0.1% of patients.

BAVENCIO can result in **other severe and fatal immune-mediated adverse reactions** involving any organ system during treatment or after treatment discontinuation. For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending on the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high-dose corticosteroids, and initiate hormone replacement therapy, if appropriate. Resume BAVENCIO when the immune-mediated adverse reaction remains at

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INLYTA (axitinib)

Monitor for **proteinuria** before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment with INLYTA.

INLYTA in combination with BAVENCIO® (avelumab) can cause **hepatotoxicity** with higher than expected frequencies of Grades 3 and 4 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used for monotherapy. Consider withholding INLYTA and/or BAVENCIO, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

For patients with moderate **hepatic impairment,** the starting dose of INLYTA should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

INLYTA in combination with BAVENCIO can cause severe and fatal **major adverse cardiovascular events (MACE).** Consider baseline and periodic evaluations of left ventricular ejection fraction and monitor for signs and symptoms of cardiovascular events. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue INLYTA and BAVENCIO for Grade 3 or 4 cardiovascular events.

INLYTA can cause **fetal harm.** Advise patients of the potential risk to the fetus and to use effective contraception.

Avoid strong **CYP3A4/5 inhibitors.** If unavoidable, reduce the dose of INLYTA. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

IMPORTANT SAFETY INFORMATION

BAVENCIO® avelumab Injection 20 mg/mL + Inlyta® axitinib 1mg and 5mg tablets

BAVENCIO (avelumab)

Grade 1 or lower following a corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening (Grade 4) immune-mediated adverse reaction. The following clinically significant immune-mediated adverse reactions occurred in less than 1% of 1738 patients treated with BAVENCIO as a single agent or in 489 patients who received *BAVENCIO in combination with INLYTA*: myocarditis including fatal cases, pancreatitis including fatal cases, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response.

BAVENCIO can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. 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 (Grade 1) or moderate (Grade 2) infusion-related reactions. Permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

BAVENCIO in combination with INLYTA can cause **major adverse cardiovascular events (MACE)** including severe and fatal 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 INLYTA for Grade 3-4 cardiovascular events. MACE occurred in 7% of patients with advanced RCC treated with BAVENCIO in combination with INLYTA compared to 3.4% treated with sunitinib. 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%).

BAVENCIO can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

ADVERSE REACTIONS (BAVENCIO + INLYTA)

Fatal adverse reactions occurred in 1.8% of patients with **advanced renal cell carcinoma (RCC)** receiving BAVENCIO in combination with INLYTA. These included sudden cardiac death (1.2%), stroke (0.2%), myocarditis (0.2%), and necrotizing pancreatitis (0.2%).

The most common adverse reactions (all grades, ≥20%) in patients with **advanced RCC** receiving BAVENCIO in combination with INLYTA (vs sunitinib) were diarrhea (62% vs 48%), fatigue (53% vs 54%), hypertension (50% vs 36%), musculoskeletal pain (40% vs 33%), nausea (34% vs 39%), mucositis (34% vs 35%), palmar-plantar erythrodysesthesia (33% vs 34%), dysphonia (31% vs 3.2%), decreased appetite (26% vs 29%), hypothyroidism (25% vs 14%), rash (25% vs 16%), hepatotoxicity (24% vs 18%), cough (23% vs 19%), dyspnea (23% vs 16%), abdominal pain (22% vs 19%), and headache (21% vs 16%).

Selected laboratory abnormalities (all grades, ≥20%) worsening from baseline in patients with **advanced RCC** receiving BAVENCIO in combination with INLYTA (vs sunitinib) were blood triglycerides increased (71% vs 48%), blood creatinine increased (62% vs 68%), blood cholesterol increased (57% vs 22%), alanine aminotransferase increased (ALT) (50% vs 46%), aspartate aminotransferase increased (AST) (47% vs 57%), blood sodium decreased (38% vs 37%), lipase increased (37% vs 25%), blood potassium increased (35% vs 28%), platelet count decreased (27% vs 80%), blood bilirubin increased (21% vs 23%), and hemoglobin decreased (21% vs 65%).

BAVENCIO® (avelumab) + INLYTA® (axitinib) ADVERSE REACTIONS PROFILE

In the JAVELIN Renal 100 Trial---a Phase 3, randomized, open-label, multicenter study (N=873)[1]

- **Fatal adverse reactions** occurred in **1.8%** of patients receiving BAVENCIO in combination with INLYTA. 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 INLYTA. 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%)
- **An oral prednisone dose equivalent to ≥40 mg daily** was administered for an immune-mediated adverse reaction to **11%** (48) of patients treated with BAVENCIO in combination with INLYTA

Adverse reactions (≥20%) in patients receiving BAVENCIO + INLYTA

Adverse Reactions	BAVENCIO + INLYTA (n=434)		Sunitinib (n=439)	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Diarrhea*	62	8	48	2.7
Nausea	34	1.4	39	1.6
Mucositis†	34	2.8	35	2.1
Hepatotoxicity‡	24	9	18	3.6
Abdominal pain§	22	1.4	19	2.1
General Disorders and Administration Site Conditions				
Fatigue‖	53	6	54	6
Vascular Disorders				
Hypertension¶	50	26	36	17
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain#	40	3.2	33	2.7
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	33	6	34	4
Rash**	25	0.9	16	0.5
Respiratory, Thoracic, and Mediastinal Disorders				
Dysphonia	31	0.5	3.2	0
Dyspnea††	23	3.0	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

*Diarrhea is a composite term that includes diarrhea, autoimmune colitis, and colitis. †Mucositis is a composite term that includes mucosal inflammation and stomatitis. ‡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. §Abdominal pain is a composite term that includes abdominal pain, flank pain, abdominal pain upper, and abdominal pain lower. ‖Fatigue is a composite term that includes fatigue and asthenia. ¶Hypertension is a composite term that includes hypertension and hypertensive crisis. #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. **Rash is a composite term that includes rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash erythematous, rash papular, and rash pustular. ††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 the patients in the JAVELIN Renal 101 Trial included arthralgia, weight decreased, and chills
- Patients received premedication with an antihistamine 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 INLYTA

Study design: The efficacy and safety of BAVENCIO in combination with INLYTA was studied in the JAVELIN Renal 101 Trial, a Phase 3, randomized, open-label, multicenter study of BAVENCIO in combination with INLYTA in 886 patients with previously untreated advanced RCC with clear-cell component, ≥1 measurable lesion defined by RECIST v1.1, and an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1. These patients were included regardless of tumor PD-L1 expression (intent-to-treat population). Patients with autoimmune disease other than type 1 diabetes mellitus, vitiligo, psoriasis, or thyroid disorders not requiring immunosuppressive treatment were excluded. Randomization was stratified according to ECOG 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 INLYTA 5 mg twice daily orally (n=442), or sunitinib 50 mg once daily orally for 4 weeks followed by 2 weeks off (n=444), until radiographic or clinical progression or unacceptable toxicity, with dose modifications permitted. The primary endpoints were PFS and OS in patients with PD-L1 positive tumors (PD-L1 expression level ≥1% of immune cells staining within the tumor area of the tested tissue sample by Ventana PD-L1 [SP263] assay [2]). Key secondary endpoints were PFS and OS in the ITT population, with objective response rate as an additional secondary endpoint. Safety was also an outcome measure. If PFS was statistically significant in patients with PD-L1 positive tumors, it was then tested in the ITT population. Administration of BAVENCIO and INLYTA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Assessment of tumor status was performed by Blinded Independent Central Review (BICR) using RECIST v1.1 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.

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BAVENCIO® (avelumab) AND INLYTA® (axitinib) LABORATORY ABNORMALITIES

In the JAVELIN Renal 101 Trial—a Phase 3, randomized, open-label, multicenter study (N=873)[1]

Selected laboratory abnormalities worsening from baseline occurring in ≥20% of patients receiving BAVENCIO + INLYTA

Laboratory Abnormality	BAVENCIO + INLYTA*		Sunitinib*	
	Any Grade %	Grades 3-4 %	Any Grade %	Grades 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	3.0	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 1 on-study laboratory measurement available: the BAVENCIO in combination with INLYTA group (range: 413 to 428 patients) and the sunitinib group (range: 405 to 433 patients).

Discontinuation rates due to adverse reactions

- **22%** of patients permanently discontinued treatment with either BAVENCIO or INLYTA due to an adverse reaction
- **8%** of patients permanently discontinued both BAVENCIO + INLYTA due to adverse reactions compared to 13.4% with sunitinib[1]
- **19%** of patients permanently discontinued treatment with BAVENCIO alone due to adverse reactions
- **13%** of patients permanently discontinued treatment with INLYTA alone due to adverse reactions
- 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 modifications due to adverse reactions

- 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 INLYTA
  - BAVENCIO was interrupted in 50% of patients
  - INLYTA was interrupted in 66% of patients 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 INLYTA were diarrhea (19%), hypertension (18%), palmar-plantar erythrodysesthesia (18%), and hepatotoxicity (10%)

The data described in the BAVENCIO WARNINGS AND PRECAUTIONS section reflect exposure to BAVENCIO® (avelumab) 10 mg/kg intravenously every 2 weeks as a single agent in 1738 patients enrolled in 2 trials and to BAVENCIO 10 mg/kg intravenously every 2 weeks in combination with INLYTA® (axitinib) 5 mg orally twice daily in 489 patients enrolled in the JAVELIN Renal 100 and JAVELIN Renal 101 trials.

BAVENCIO® (avelumab)
IMMUNE-MEDIATED PNEUMONITIS

Clinical trial experience

- BAVENCIO can cause immune-mediated pneumonitis, including fatal cases
- Pneumonitis occurred in 1.2% of patients receiving BAVENCIO, including one (0.1%) patient with fatal, one (0.1%) with Grade 4, and five (0.3%) with Grade 3 pneumonitis
- Immune-mediated pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% of patients
- Among the 21 patients with immune-mediated pneumonitis, the median time to onset was 2.5 months (range: 3 days to 11 months) and the median duration of pneumonitis was 7 weeks (range: 4 days to 4+ months)
- All 21 patients were treated with systemic corticosteroids; 17 (81%) of the 21 patients received high-dose corticosteroids for a median of 8 days (range: 1 day to 2.3 months). Resolution of pneumonitis occurred in 12 (57%) of the 21 patients at the time of data cut-off

Monitor patients for signs and symptoms of pneumonitis, including

- New or worsening cough
- Shortness of breath
- Chest pain

Monitor patients for signs and symptoms of pneumonitis and evaluate patients with suspected pneumonitis with radiographic imaging.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

BAVENCIO (avelumab)
IMMUNE-MEDIATED PNEUMONITIS

Assess the severity of the adverse reaction[2]

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental activities of daily living (ADL)	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)

Modify treatment based on severity

Corticosteroids	Grade 2	Grade 3 or 4 or recurrent Grade 2
For Grade 2 or greater, administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper).	Withhold BAVENCIO for moderate pneumonitis. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of pneumonitis after corticosteroid taper.	Permanently discontinue for severe or life-threatening pneumonitis. Permanently discontinue for recurrent moderate pneumonitis.

BAVENCIO® (avelumab)
HEPATOTOXICITY AND IMMUNE-MEDIATED HEPATITIS (BAVENCIO as a single agent)

Clinical trial experience

- BAVENCIO can cause immune-mediated hepatitis, including fatal cases

BAVENCIO as a single agent

- Immune-mediated hepatitis occurred in 0.9% of patients receiving BAVENCIO, including two (0.1%) patients with fatal, and 11 (0.6 %) patients with Grade 3 immune-mediated hepatitis
- Immune-mediated hepatitis led to permanent discontinuation of BAVENCIO in 0.5% of patients
- Among the 16 patients with immune-mediated hepatitis, the median time to onset was 3.2 months (range: 1 week to 15 months), and the median duration of hepatitis was 2.5 months (range: 1 day to 7.4+ months)
- All 16 patients were treated with corticosteroids; 15 (94%) of the 16 patients received high-dose corticosteroids for a median of 14 days (range: 1 day to 2.5 months)
- Resolution of hepatitis occurred in nine (56%) of the 16 patients at the time of data cut-off

Monitor patients for signs and symptoms of hepatitis, including

- Yellowing of your skin or the whites of your eyes
- Pain on the right side of your stomach-area (abdomen)
- Drowsiness
- Severe nausea or vomiting
- Bleeding or bruising more easily than normal
- Dark urine (tea colored)

Monitor patients for abnormal liver tests prior to and periodically during treatment.

BAVENCIO (avelumab)
HEPATOTOXICITY AND IMMUNE-MEDICATED HEPATITIS (BAVENCIO as a single agent)

Assess the severity of the adverse reaction[2]

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Alanine aminotransferase (ALT) increased >ULN - 3.0 x ULN	ALT increased >3.0 - 5.0 x ULN	ALT increased >5.0 - 20.0 x ULN	ALT increased >20.0 x ULN
Aspartate aminotransferase (AST) increased >ULN - 3.0 x ULN	AST increased >3.0 - 5.0 x ULN	AST increased >5.0 - 20.0 x ULN	AST increased >20.0 x ULN
Blood bilirubin increased >ULN - 1.5 x ULN	Blood bilirubin increased >1.5 - 3.0 x ULN	Blood bilirubin increased >3.0 - 10.0 x ULN	Blood bilirubin increased >10.0 x ULN

Modify treatment based on severity

Corticosteroids	Grade 2	Grade 3 or 4
For Grade 2 or greater, administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper).	AST or ALT more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal: Withhold BAVENCIO for moderate immune-mediated hepatitis until resolution. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of hepatitis after corticosteroid taper.	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal: Permanently discontinue for severe or life-threatening immune-mediated hepatitis.

BAVENCIO® (avelumab)

HEPATOTOXICITY AND IMMUNE-MEDIATED HEPATITIS [BAVENCIO with INLYTA® (axitinib)]

Clinical trial experience

BAVENCIO with INLYTA

- BAVENCIO in combination with INLYTA can cause hepatotoxicity with higher than expected frequencies of Grade 3 and 4 ALT and AST elevation
- In patients treated with BAVENCIO in combination with INLYTA in the advanced RCC trials, Grades 3 and 4 increased ALT and increased AST were reported in 9% and 7% of patients, respectively
- In patients with ALT ≥3 times ULN (Grades 2-4, n=82), ALT resolved to Grades 0-1 in 92%. Among the 73 patients who were rechallenged with either BAVENCIO (59%) or INLYTA (85%) monotherapy or with both (55%), 66% had no recurrence of ALT ≥3 times ULN
- 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 INLYTA in 5.3% of patients
- Among the 35 patients with immune-mediated hepatitis, the median time to onset was 2.8 months (range: 2.1 weeks to 14.5 months), and the median duration of hepatitis was 15 days (range: 2 days to 9 months)
- Thirty-four patients were treated with corticosteroids and one patient was treated with a non-steroidal immunosuppressant; 33 patients received high-dose corticosteroids for a median of 21 days (range: 4 days to 3 months)
- Resolution of hepatitis occurred in 31 of the 35 patients at the time of data cut-off

Monitor patients for signs and symptoms of hepatitis, including

- Yellowing of your skin or the whites of your eyes
- Dark urine (tea colored)
- Drowsiness
- Pain on the right side of your stomach-area (abdomen)
- Severe nausea or vomiting
- Bleeding or bruising more easily than normal

Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy.

Assess the severity of the adverse reaction[2]

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Alanine aminotransferase (ALT) increased >ULN - 3.0 x ULN	ALT increased >3.0 - 5.0 x ULN	ALT increased >5.0 - 20.0 x ULN	ALT increased >20.0 x ULN
Aspartate aminotransferase (AST) increased >ULN - 3.0 x ULN	AST increased >3.0 - 5.0 x ULN	AST increased >5.0 - 20.0 x ULN	AST increased >20.0 x ULN
Blood bilirubin increased >ULN - 1.5 x ULN	Blood bilirubin increased >1.5 - 3.0 x ULN	Blood bilirubin increased >3.0 - 10.0 x ULN	Blood bilirubin increased >10.0 x ULN

Modify treatment based on severity

Administer corticosteroids as needed.

Grade 2	Grade 3 or 4
If ALT or AST ≥3 times ULN but <5 times ULN or total bilirubin ≥1.5 times ULN but <3 times ULN: Withhold both BAVENCIO and INLYTA until these adverse reactions recover to Grades 0-1. If persistent (greater than 5 days), consider corticosteroid therapy (initial dose of 0.5 to 1 mg/kg/day prednisone or equivalent followed by a taper). Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with INLYTA, dose reduce per the INLYTA dose modification guidelines on page 3.	If ALT or AST ≥5 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN or total bilirubin ≥3 times ULN: Permanently discontinue both BAVENCIO and INLYTA and consider corticosteroid therapy (initial dose 1 to 2 mg/kg/day prednisone or equivalent followed by a taper).

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

BAVENCIO® avelumab Injection 20 mg/mL + Inlyta® axitinib 1mg and 5mg tablets

BAVENCIO® (avelumab)
IMMUNE-MEDIATED COLITIS

Clinical trial experience

- BAVENCIO can cause immune-mediated colitis
- Immune-mediated colitis occurred in 1.5% of patients receiving BAVENCIO, including seven (0.4%) patients with Grade 3 colitis
- Immune-mediated colitis led to permanent discontinuation of BAVENCIO in 0.5% of patients
- Among the 26 patients with immune-mediated colitis, the median time to onset was 2.1 months (range: 2 days to 11 months) and the median duration of colitis was 6 weeks (range: 1 day to 14+ months)
- All 26 patients were treated with corticosteroids; 15 (58%) of the 26 patients received high-dose corticosteroids for a median of 19 days (range: 1 day to 2.3 months)
- Resolution of colitis occurred in 18 (70%) of the patients at the time of data cut-off

Monitor patients for signs and symptoms of colitis, including

- Diarrhea (loose stools) or more bowel movements than usual
- Blood in your stools or dark, tarry, sticky stools
- Severe stomach-area (abdomen) pain or tenderness

Assess the severity of the adverse reaction[2]

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated

Modify treatment based on severity

Corticosteroids	Grade 2 or 3	Grade 4 or recurrent Grade 3
For Grade 2 or greater, administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper).	Withhold BAVENCIO for moderate or severe diarrhea or colitis until resolution. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of colitis or diarrhea after corticosteroid taper.	Permanently discontinue BAVENCIO for life-threatening or recurrent severe diarrhea or colitis upon reinitiation of BAVENCIO.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

BAVENCIO (avelumab)
IMMUNE-MEDIATED ENDOCRINOPATHIES - ADRENAL INSUFFICIENCY

Clinical trial experience

- BAVENCIO can cause immune-mediated endocrinopathies, including adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus

Adrenal insufficiency

- Adrenal insufficiency occurred in 0.5% of patients receiving BAVENCIO, including one patient (0.1%) with Grade 3 adrenal insufficiency
- Immune-mediated adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% of patients
- Among the 8 patients with immune-mediated adrenal insufficiency, the median time to onset was 2.5 months (range: 1 day to 8 months)
- All eight patients were treated with corticosteroids; four (50%) of the eight patients received high-dose corticosteroids for a median of 1 day (range: 1 day to 24 days)

Monitor patients during and after treatment for signs and symptoms of adrenal insufficiency, including

- Increased sweating
- Changes in mood or behavior, such as irritability or forgetfulness
- Fatigue
- Weight loss
- Hypotension
- Dizziness or fainting
- Nausea or vomiting
- Abdominal pain

BAVENCIO® (avelumab)

IMMUNE-MEDIATED ENDOCRINOPATHIES - ADRENAL INSUFFICIENCY

Assess the severity of the adverse reaction[2]

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

Modify treatment based on severity

Corticosteroids	Grade 3 or 4
Administer corticosteroids as appropriate for adrenal insufficiency.	Withhold BAVENCIO for severe or life-threatening adrenal insufficiency. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of endocrinopathies after corticosteroid taper.

BAVENCIO (avelumab)

IMMUNE-MEDIATED ENDOCRINOPATHIES - THYROID DISORDERS

Clinical trial experience

Thyroid disorders (hypothyroidism/hyperthyroidism)

- BAVENCIO can cause immune-mediated thyroid disorders. Thyroid disorders can occur at any time during treatment
- Immune-mediated thyroid disorders occurred in 6% of patients receiving BAVENCIO, including 3 (0.2%) Grade 3 immune-mediated thyroid disorders
- Immune-mediated thyroid disorders led to discontinuation of BAVENCIO in 0.1% of patients
- Hypothyroidism occurred in 90 (5%) patients; hyperthyroidism in seven (0.4%) patients; and thyroiditis in four (0.2%) patients treated with BAVENCIO
- Among the 98 patients with immune-mediated thyroid disorders, the median time to onset was 2.8 months (range: 2 weeks to 13 months) and the median duration was not estimable (range: 6 days to more than 26 months)
- Immune-mediated thyroid disorders resolved in seven (7%) of the 98 patients

Monitor patients for signs and symptoms of thyroid disorders, including

- Tachycardia
- Increased sweating
- Weight gain or weight loss
- Feeling more hungry or thirsty than usual
- Hair loss
- Changes in mood or behavior, such as irritability or forgetfulness
- Feeling cold

Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation.

BAVENCIO® (avelumab)

IMMUNE-MEDIATED ENDOCRINOPATHIES - THYROID DISORDERS

Assess the severity of the adverse reaction[2]

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental activities of daily living (ADL)	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

Modify treatment based on severity

Any grade hypothyroidism	Any grade hyperthyroidism	Grade 3 or 4
Manage hypothyroidism with hormone-replacement therapy.	Initiate medical management for control of hyperthyroidism.	Withhold BAVENCIO for severe or life-threatening thyroid disorders. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of endocrinopathies after corticosteroid taper.

BAVENCIO (avelumab)

IMMUNE-MEDIATED ENDOCRINOPATHIES - TYPE 1 DIABETES MELLITUS

Clinical trial experience

Type 1 diabetes mellitus

- BAVENCIO can cause type 1 diabetes mellitus, including diabetic ketoacidosis
- Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% of patients, including two cases of Grade 3 hyperglycemia that led to permanent discontinuation of BAVENCIO

Monitor patients for hyperglycemia or other signs and symptoms of diabetes

Assess the severity of the adverse reaction[2]

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Fasting glucose value >ULN - 160 mg/dL; fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences

Modify treatment based on severity

Grade 3 or 4
Withhold BAVENCIO and administer anti-hyperglycemics or insulin in patients with severe or life-threatening hyperglycemia. Resume treatment with BAVENCIO when metabolic control is achieved on insulin replacement or anti-hyperglycemics.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

BAVENCIO® (avelumab)
IMMUNE-MEDIATED NEPHRITIS AND RENAL DYSFUNCTION

Clinical trial experience

- BAVENCIO can cause immune-mediated nephritis
- Immune-mediated nephritis occurred in 0.1% of patients receiving BAVENCIO; BAVENCIO was permanently discontinued in this patient

Monitor patients for elevated serum creatinine prior to, and periodically during, treatment, as well as signs and symptoms, including

- Decrease in the amount of urine
- Swelling in the ankles
- Blood in the urine
- Loss of appetite

Assess the severity of the adverse reaction[2]

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated

Modify treatment based on severity

Corticosteroids	Grade 2 or 3	Grade 4
For Grade 2 or greater, administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper).	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal (ULN): Withhold BAVENCIO for moderate or severe nephritis until resolution to ≤Grade 1. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of nephritis and renal dysfunction after corticosteroid taper.	Serum creatinine more than 6 times the ULN: Permanently discontinue BAVENCIO for life-threatening nephritis.

BAVENCIO (avelumab)
OTHER IMMUNE-MEDIATED ADVERSE REACTIONS

Clinical trial experience

- BAVENCIO can result in severe and fatal immune-mediated adverse reactions
  - These immune-mediated reactions may involve any organ system. Most immune-mediated reactions initially manifest during treatment with BAVENCIO; however, immune-mediated adverse reactions can occur after discontinuation of BAVENCIO
- The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% of patients who received BAVENCIO as a single agent or in 489 patients who received BAVENCIO in combination with INLYTA: immune-mediated myocarditis including fatal cases, pancreatitis including fatal cases, immune-mediated myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response
- The following clinically significant, immune-mediated adverse reactions have been reported with other products in this class: bullous dermatitis, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, hypophysitis, iritis, and encephalitis

Monitor for signs and symptoms of problems in other organs, including

- Severe muscle weakness
- Swelling of the feet and legs
- Trouble breathing
- Changes in eyesight
- Tiredness, sleepiness
- Chest pain and tightness
- Fever, flu like symptoms
- Changes in heartbeat, such as beating fast, or seeming to skip a beat, or pounding sensation
- Severe or persistent muscle or joint pains
- Dizziness or fainting
- Skin rash, blisters or peeling

For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes.

BAVENCIO® (avelumab)
OTHER IMMUNE-MEDIATED ADVERSE REACTIONS

Modify treatment based on severity

Depending upon the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high dose corticosteroids, and if appropriate, initiate hormone replacement therapy.

For any of the following: • Moderate or severe clinical signs or symptoms of an immune-mediated adverse reaction not described above • Grade 3 or 4 endocrinopathies	Withhold BAVENCIO pending clinical evaluation. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of other immune-mediated adverse reactions after corticosteroid taper.
For any of the following: • Life-threatening adverse reaction (excluding endocrinopathies) • Recurrent severe immune-mediated adverse reaction • Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks • Persistent Grade 2 or 3 immune-mediated adverse reactions lasting 12 weeks or longer	Permanently discontinue.

BAVENCIO (avelumab)
INFUSION-RELATED REACTIONS

Clinical trial experience

- BAVENCIO can cause severe or life-threatening infusion-related reactions
- Infusion-related reactions occurred in 25% of patients treated with BAVENCIO, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions
- Ninety-three percent of patients received premedication with antihistamine and acetaminophen
- Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids
- Fourteen percent of patients had infusion-related reactions that occurred after the BAVENCIO infusion was completed

Monitor patients for signs and symptoms of infusion-related reactions, including

- Pyrexia
- Chills
- Flushing
- Hypotension
- Dyspnea
- Wheezing
- Back pain
- Abdominal pain
- Urticaria

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.

Assess the severity of the adverse reaction[2]

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

Modify treatment based on severity

Grade 1 or 2	Grade 3 or 4
Interrupt or slow the rate of infusion.	Stop the infusion and permanently discontinue BAVENCIO for severe or life-threatening infusion-related reactions.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

BAVENCIO® Injection 20 mg/mL avelumab + Inlyta® 1mg and 5mg tablets axitinib

BAVENCIO® (avelumab)

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Clinical trial experience

- BAVENCIO in combination with INLYTA can cause severe and fatal cardiovascular events
- MACE occurred in 7% of patients with advanced RCC treated with BAVENCIO in combination with INLYTA 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)

MONITOR

Consider baseline and periodic evaluations of left ventricular ejection fraction.

Monitor for signs and symptoms of cardiovascular events.

Signs and symptoms of heart problems may include:

- Swelling of your stomach-area, legs, hands, feet or ankles
- Chest discomfort, including pain or pressure
- Breaking out in a cold sweat
- Shortness of breath
- Weight gain
- Feeling lightheaded or dizzy
- Nausea or vomiting
- Pain or discomfort in your arms, back, neck, or jaw

Assess the severity of the adverse reaction[2]

Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia.

Modify treatment based on severity

Grade 3 or 4

Discontinue BAVENCIO and INLYTA for Grade 3-4 cardiovascular events.

BAVENCIO (avelumab)

EMBRYO-FETAL TOXICITY

Clinical trial experience

- 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

Assess the severity of the adverse reaction[2]

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.

It is not known whether BAVENCIO is 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.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

INLYTA® (axitinib)
HYPERTENSION AND HYPERTENSIVE CRISIS

- Hypertension including hypertensive crisis has been observed with INLYTA
- The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of INLYTA treatment and blood pressure increases have been observed as early as 4 days after starting INLYTA
- Blood pressure should be well controlled prior to initiating INLYTA

MONITOR AND MODIFY

Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensive medications, reduce the INLYTA dose.

Discontinue INLYTA if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

If INLYTA is interrupted, patients receiving anti-hypertensive medications should be monitored for hypotension.

ARTERIAL AND VENOUS THROMBOEMBOLIC EVENTS

- Arterial and venous thrombotic events have been observed with INLYTA and can be fatal
- Use INLYTA with caution in patients who are at risk for, or who have a history of, these events
- INLYTA has not been studied in patients who had an arterial thromboembolic event within the previous 12 months or a venous thromboembolic event within the previous 6 months

INLYTA (axitinib)
HEMORRHAGE

- Hemorrhagic events, including fatal events, have been reported with INLYTA
- INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients

MODIFY

If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

CARDIAC FAILURE

- Cardiac failure has been observed with INLYTA and can be fatal

MONITOR

Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA.

MANAGEMENT

Management of cardiac failure may require permanent discontinuation of INLYTA.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

BAVENCIO® avelumab Injection 20 mg/mL + Inlyta® axitinib 1mg and 5mg tablets

INLYTA® (axitinib)

GASTROINTESTINAL PERFORATION AND FISTULA FORMATION

- Gastrointestinal perforation and fistula, including death, have occurred with INLYTA
- Use with caution in patients at risk for gastrointestinal perforation or fistula

MONITOR

Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment with INLYTA.

THYROID DYSFUNCTION

- Hypothyroidism requiring thyroid hormone replacement and hyperthyroidism have been reported with INLYTA

MONITOR

Monitor thyroid function before initiation of and periodically throughout treatment with INLYTA.

MANAGEMENT

Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain euthyroid state.

INLYTA (axitinib)

RISK OF IMPAIRED WOUND HEALING

- INLYTA has the potential to adversely affect wound healing

MODIFY

Withhold INLYTA for at least 2 days prior to elective surgery. Do not administer INLYTA for at least 2 weeks following major surgery and until adequate wound healing. The safety of resuming INLYTA after resolution of wound healing complications has not been established.

REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME

- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed with INLYTA

MONITOR

RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances.

Mild to severe hypertension may be present.

Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS.

MODIFY

Discontinue INLYTA in patients developing RPLS. The safety of reinitiating INLYTA therapy in patients previously experiencing RPLS is not known.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

INLYTA® (axitinib)
PROTEINURIA

- Proteinuria has been observed with INLYTA

MONITOR

Monitor for proteinuria before initiation of, and periodically throughout, treatment.

MODIFY

For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

HEPATOTOXICITY

- INLYTA in combination with BAVENCIO® (avelumab) can cause hepatotoxicity with higher than expected frequencies of Grades 3 and 4 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation

MONITOR

Consider more frequent monitoring of liver enzymes as compared to when the drugs are used for monotherapy.

MODIFY

Consider withholding INLYTA and/or BAVENCIO, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

INLYTA (axitinib)
HEPATIC IMPAIRMENT

- The systemic exposure to INLYTA was higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function
- No starting dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A)

MONITOR

Based on the pharmacokinetic data, the INLYTA starting dose should be reduced by approximately half in patients with baseline moderate hepatic impairment (Child-Pugh class B). The subsequent doses can be increased or decreased based on individual safety and tolerability.

INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

INLYTA® (axitinib)
MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

- INLYTA in combination with avelumab can cause severe and fatal cardiovascular events

MONITOR

Consider baseline and periodic evaluations of left ventricular ejection fraction and monitor for signs and symptoms of cardiovascular events.

MANAGEMENT

Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia.

MODIFY

Discontinue INLYTA and BAVENCIO for Grade 3 or 4 cardiovascular events.

INLYTA (axitinib)
EMBRYO-FETAL TOXICITY

- Based on its mechanism of action and findings from animal studies, INLYTA can cause fetal harm when administered to a pregnant woman
- Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with INLYTA and for 1 week after the last dose
- There are no data on the presence of INLYTA in human milk, or its effects on the breastfed child or on milk production
- Because of the potential for serious adverse reactions in a breastfed child from INLYTA, advise lactating women not to breastfeed during treatment and for 2 weeks after the final dose
- Advise males with female partners of reproductive potential to use effective contraception during treatment with INLYTA and for 1 week after the last dose

Please see Important Safety Information on pages 5-7. Click for the full Prescribing Information for BAVENCIO and the full Prescribing Information for INLYTA, or visit BAVENCIO.com.

BAVENCIO® avelumab Injection 20 mg/mL + Inlyta® axitinib 1mg and 5mg tablets

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