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 **severe and fatal immune-mediated adverse reactions** in any organ system or issue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

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.

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)

No dose reduction for BAVENCIO is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue BAVENCIO depending on severity. 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. 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 (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

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.

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.

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 can cause **immune-mediated pneumonitis**. Withhold BAVENCIO for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

INLYTA (axitinib)

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

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 **severe and fatal immune-mediated adverse reactions** in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

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.

No dose reduction for BAVENCIO is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue BAVENCIO depending on severity. 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. 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 (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

BAVENCIO can cause **immune-mediated pneumonitis**. Withhold BAVENCIO for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

BAVENCIO can cause **immune-mediated colitis**. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus 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. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Systemic corticosteroids were required in all (26/26) patients with colitis.

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.

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

IMPORTANT SAFETY INFORMATION

BAVENCIO® (avelumab)

BAVENCIO can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue BAVENCIO based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% (16/1738) of patients, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (16/16) patients with hepatitis.

BAVENCIO **in combination with INLYTA** 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. Withhold or permanently discontinue both BAVENCIO and INLYTA based on severity of AST, ALT, or total bilirubin elevation, and consider administering corticosteroids as needed. Consider rechallenge with BAVENCIO or INLYTA, or sequential rechallenge with both BAVENCIO and INLYTA, after recovery. In patients treated with BAVENCIO in combination with INLYTA in the advanced RCC trials, increased ALT and increased AST were reported in 9% (Grade 3) and 7% (Grade 4) of patients. Immune-mediated hepatitis was reported in 7% of patients including 4.9% with Grade 3 or 4 immune-mediated hepatitis. Thirty-four patients were treated with corticosteroids and one patient was treated with a non-steroidal immunosuppressant.

BAVENCIO can cause primary or secondary **immune-mediated adrenal insufficiency**. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients, including Grade 3 (0.1%) and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency.

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 BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction.

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 BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism.

INLYTA® (axitinib)

INLYTA in combination with BAVENCIO 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)

BAVENCIO can cause **immune-mediated 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 for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 0.1% (2/1738) of patients, including Grade 3 (0.1%) adverse reactions.

BAVENCIO can cause **immune-mediated nephritis with renal dysfunction**. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction. Systemic corticosteroids were required in this patient.

BAVENCIO can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (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 BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions.

BAVENCIO can result in **other immune-mediated adverse reactions**. Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. For **myocarditis**, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4. For **neurological toxicities**, withhold BAVENCIO for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

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 Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids.

Fatal and other serious **complications of allogeneic hematopoietic stem cell transplantation (HSCT)** can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. 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.

BAVENCIO (avelumab)

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. Permanently 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 in a randomized trial. 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.

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%)

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)
IMPORTANT INFORMATION ON WARNINGS AND PRECAUTIONS

- The data below and on the following pages related to immune-mediated adverse reactions and infusion-related reactions are based on data from over 1700 patients treated with BAVENCIO 10 mg/kg across multiple tumor types, the majority of whom were treated with BAVENCIO monotherapy
- This included exposure to BAVENCIO as a single agent in 1738 patients enrolled in the JAVELIN Merkel 200 and JAVELIN Solid Tumor Trials and to BAVENCIO in combination with INLYTA (axitinib) in 489 patients enrolled in the JAVELIN Renal 100 and JAVELIN Renal 101 Trials

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 and 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, they can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies

Monitor and Assess

- 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

General 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 on the following pages

General Corticosteroid Management

- 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 (eg, endocrinopathies and dermatologic reactions) are discussed on the following pages

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

Clinical trial experience

- BAVENCIO can cause immune-mediated pneumonitis
- Across clinical studies,* immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients receiving BAVENCIO, including:
  - Fatal (0.1%) adverse reactions
  - Grade 4 (0.1%) adverse reactions
  - Grade 3 (0.3%) adverse reactions
  - 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

Monitor patients for signs and symptoms of pneumonitis, including

Cough	Shortness of breath	Chest pain

Assess the severity of the adverse reaction[2]

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

ADL, activities of daily living.

Modify treatment based on severity

Withhold†	Permanently discontinue
For Grade 2	For Grade 3 or 4

- 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.

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.
†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.

BAVENCIO® (avelumab)
IMMUNE-MEDIATED COLITIS

Clinical trial experience

- BAVENCIO can cause immune-mediated colitis
- Across clinical studies,* immune-mediated colitis occurred in 1.5% (26/1738) of patients receiving BAVENCIO, including:
  - Grade 3 (0.4%) adverse reactions
  - Grade 2 (0.7%) adverse reactions
- Colitis led to permanent discontinuation of BAVENCIO in 0.5% and withholding of BAVENCIO in 0.5% of patients
- Systemic corticosteroids were required in all (26/26) patients with colitis
- Colitis resolved in 69% (18/26) 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

Monitor patients for signs and symptoms of colitis, including

Diarrhea	Stools that are black, tarry, sticky, or have blood or mucus	Severe abdominal pain

- 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

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated

Modify treatment based on severity

Withhold†	Permanently discontinue
For Grade 2 or 3	For Grade 4

- 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

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

†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.

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

Clinical trial experience

- BAVENCIO can cause immune-mediated hepatitis **(BAVENCIO as a single agent)**
- Across clinical studies,* immune-mediated hepatitis occurred in 0.9% (16/1738) of patients receiving BAVENCIO, including:
  - Fatal (0.1%) adverse reactions
  - Grade 3 (0.6%) adverse reactions
  - Grade 2 (0.1%) adverse reactions
- Hepatitis led to permanent discontinuation of BAVENCIO in 0.5% and withholding of BAVENCIO in 0.2% of patients
- Systemic corticosteroids were required in all (16/16) patients with hepatitis
- Hepatitis resolved in 56% (9/16) of the patients
- Of the 3 patients in whom BAVENCIO was withheld for hepatitis, 3 reinitiated treatment with BAVENCIO after symptom improvement
  - Of these, none had recurrence of hepatitis

Monitor patients for signs and symptoms of hepatitis, including

Jaundice	Severe nausea or vomiting	Pain on the right side of abdomen
Dark urine	Easy bruising or bleeding	

- Evaluate liver enzymes at baseline and periodically during treatment

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic, intervention not indicated	Moderate symptoms; medical intervention indicated	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; severe decompensated liver function (eg, coagulopathy, encephalopathy, coma)

Modify treatment based on severity

	Withhold†	Permanently discontinue
Hepatitis with no tumor involvement of the liver	For AST or ALT increases >3 and up to 8 times ULN, or total bilirubin increases >1.5 and up to 3 times ULN	For AST or ALT >8 times ULN or total bilirubin >3 times ULN
Hepatitis with tumor involvement of the liver‡	If baseline AST or ALT is >1 and up to 3 times ULN and increases to >5 and up to 10 times ULN, or baseline AST or ALT is >3 and up to 5 times ULN and increases to >8 and up to 10 times ULN	For AST or ALT increases to >10 times ULN or total bilirubin increases to >3 times ULN

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

- 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

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

†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.

‡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.

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

BAVENCIO® (avelumab)

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

Clinical trial experience

- 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
- 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

Monitor patients for signs and symptoms of hepatitis, including

Jaundice	Severe nausea or vomiting	Pain on the right side of abdomen
Dark urine	Easy bruising or bleeding	

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

Modify treatment based on severity

Withhold both BAVENCIO and INLYTA until adverse reactions recover to Grades 0-1*	Permanently discontinue both BAVENCIO and INLYTA*
For ALT or AST at least 3 times ULN but less than 10 times ULN without concurrent total bilirubin at least 2 times ULN	For ALT or AST at least 10 times ULN or more than 3 times ULN with concurrent total bilirubin at least 2 times ULN
Consider rechallenge with BAVENCIO or axitinib or sequential rechallenge with both BAVENCIO and axitinib after recovery†	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

*Consider corticosteroid therapy.
†Dose reduction according to the axitinib Full Prescribing Information should be considered if rechallenging with axitinib.

BAVENCIO (avelumab)

IMMUNE-MEDIATED ENDOCRINOPATHIES: ADRENAL INSUFFICIENCY

Clinical trial experience

- BAVENCIO can cause primary or secondary adrenal insufficiency
- Across clinical studies,* immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients receiving BAVENCIO, including:
  - Grade 3 (0.1%) adverse reactions
  - Grade 2 (0.3%) 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 (8/8) patients with adrenal insufficiency
- Adrenal insufficiency did not resolve in any patient (0/8)
- Of the 2 patients in whom BAVENCIO was withheld for adrenal insufficiency, none reinitiated treatment with BAVENCIO

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

Fatigue	Weight loss or weight gain	Dizziness or fainting
Hair loss	Changes in mood or behavior	

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
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

Grade 2 or higher	Grade 3-4
Initiate symptomatic treatment, including hormone replacement, as clinically indicated	Withhold BAVENCIO for adrenal insufficiency until clinically stable, or permanently discontinue depending on severity

- 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

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

BAVENCIO® (avelumab)
IMMUNE-MEDIATED ENDOCRINOPATHIES: HYPOPHYSITIS

Clinical trial experience

- BAVENCIO can cause immune-mediated hypophysitis. Hypophysitis can cause hypopituitarism
- Across clinical studies,* immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients receiving BAVENCIO, including:
  - 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

Hypophysitis can present with acute symptoms associated with mass effect, such as

Headache	Photophobia	Visual field defects

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

ADL, activities of daily living.

Modify treatment based on severity

Any grade	Grade 3-4
Initiate hormone replacement as clinically indicated	Withhold BAVENCIO until clinically stable, or permanently discontinue depending on severity

- 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

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

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: THYROID DISORDERS

Clinical trial experience

- BAVENCIO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism
- Across clinical studies,* thyroiditis occurred in 0.2% (4/1738) 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)
- Across clinical studies,* hyperthyroidism occurred in 0.4% (7/1738) 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 29% (2/7) of patients with hyperthyroidism
  - Hyperthyroidism resolved in 86% (6/7) 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
- Across clinical studies,* hypothyroidism occurred in 5% (90/1738) of patients receiving BAVENCIO, including:
  - Grade 3 (0.2%) adverse reactions
  - Grade 2 (3.7%) adverse reactions
  - Hypothyroidism led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.5% of patients
  - Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism
  - Hypothyroidism resolved in 4% (4/90) of the patients
  - Of the 8 patients in whom BAVENCIO was withheld for hypothyroidism, none reinitiated BAVENCIO

Monitor patients for signs and symptoms of thyroid disorders, including

Tachycardia	Increased sweating	Fatigue
Weight gain or weight loss	Unusual thirst or hunger	Hair loss
Feeling cold	Constipation	Changes in mood or behavior

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression or replacement therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

ADL, activities of daily living.

Modify treatment based on severity

Any grade hypothyroidism or hyperthyroidism	Grade 3-4
Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated	Withhold BAVENCIO until clinically stable, or permanently discontinue depending on severity

- 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

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

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

BAVENCIO® (avelumab)

IMMUNE-MEDIATED ENDOCRINOPATHIES: TYPE 1 DIABETES MELLITUS, WHICH CAN PRESENT WITH DIABETIC KETOACIDOSIS

Clinical trial experience

- Type 1 diabetes mellitus, which can present with diabetic ketoacidosis
- Across clinical studies,* immune-mediated type 1 diabetes mellitus occurred in 0.1% (2/1738) of patients receiving BAVENCIO, including:
  - Grade 3 (0.1%) adverse reactions
- Type 1 diabetes mellitus led to permanent discontinuation of BAVENCIO in these two patients
- Type 1 diabetes mellitus did not lead to withholding of BAVENCIO in any patient
- Systemic corticosteroids were not required in any patient with Type 1 diabetes mellitus
- Type 1 diabetes mellitus resolved in no patient and all patients required ongoing insulin treatment

Monitor patients for hyperglycemia or other signs and symptoms of diabetes

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

Modify treatment based on severity

Hyperglycemia
Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO until clinically stable or permanently discontinue depending on severity

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

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BAVENCIO (avelumab)

IMMUNE-MEDIATED NEPHRITIS WITH RENAL DYSFUNCTION

Clinical trial experience

- BAVENCIO can cause immune-mediated nephritis
- Across clinical studies,* immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients receiving BAVENCIO, including:
  - Grade 2 (0.1%) adverse reactions
- Nephritis with renal dysfunction led to permanent discontinuation of BAVENCIO in this patient
- Nephritis did not lead to withholding of BAVENCIO in any patient
- Systemic corticosteroids were required in this patient
- Nephritis with renal dysfunction did not resolve in this patient

Evaluate creatinine at baseline and periodically during treatment

Assess the severity of the adverse reaction[2]

Grade 1 creatinine increased	Grade 2 creatinine increased	Grade 3 creatinine increased	Grade 4 creatinine increased
>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

ULN, upper limit of normal.

Modify treatment based on severity

Withhold†	Permanently discontinue
For Grade 2 or 3 increased blood creatinine	For Grade 4 increased blood creatinine

- 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

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

†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.

BAVENCIO® (avelumab)
IMMUNE-MEDIATED DERMATOLOGIC ADVERSE REACTIONS

Clinical trial experience

- BAVENCIO can cause immune-mediated rash or dermatitis
- Exfoliative dermatitis, including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies
- Across clinical studies,* immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients receiving BAVENCIO, including:
  - Grade 3 (0.1%) adverse reactions
  - Grade 2 (2.0%) 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 29% (26/90) of patients with dermatologic adverse reactions
  - One patient required the addition of tacrolimus to high-dose corticosteroids
- Dermatologic adverse reactions resolved in 41% (37/90) of the patients
- Of the 7 patients in whom BAVENCIO was withheld for dermatologic adverse reactions, 3 reinitiated treatment with BAVENCIO after symptom improvement
  - Of these, none had recurrence of dermatologic adverse reaction

Monitor patients for signs and symptoms of rash or dermatitis

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

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
–	–	SJS - skin sloughing covering <10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, and mucous membrane detachment)	SJS - skin sloughing covering 10% to 30% BSA with associated signs TEN - skin sloughing covering ≥30% BSA with associated symptoms

BSA, body surface area.

Modify treatment based on severity

Withhold†	Permanently discontinue
For suspected SJS, TEN, or DRESS	For confirmed SJS, TEN, or DRESS

- Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes
- 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

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

†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.

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BAVENCIO (avelumab)
OTHER IMMUNE-MEDIATED ADVERSE REACTIONS

Clinical trial experience

- 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 reaction

Other immune-mediated 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

- For myocarditis, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4 adverse reactions
- For neurological toxicities, withhold BAVENCIO for Grade 2* and permanently discontinue for Grade 3 or Grade 4 adverse reactions

*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.

BAVENCIO® (avelumab)

INFUSION-RELATED REACTIONS

Clinical trial experience

- BAVENCIO can cause severe or life-threatening infusion-related reactions
- Across clinical studies,* infusion-related reactions occurred in 25% of patients, including:
  - 3 (0.2%) Grade 4 infusion-related reactions
  - 9 (0.5%) Grade 3 infusion-related reactions
- 93% of patients received premedication with antihistamine and acetaminophen
- 11 (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids
- 14% of patients had infusion-related reactions that occurred after BAVENCIO infusion was completed
- 25.3% (439/1738) of patients experienced infusion-related reactions[1]
- The onset of infusion-related reactions was mostly at the initial infusions[1]:
  - 20.1% of patients experienced their first infusion-related reaction during the first infusion (n=1738 patients at risk)
  - 4.7% of patients experienced their first infusion-related reaction during their second infusion (n=1306 patients at risk)
  - 1.5% of patients experienced their first infusion-related reaction during their third infusion (n=1144 patients at risk)
  - 0.6% of patients experienced their first infusion-related reaction during their fourth infusion (n=937 patients at risk)
  - 0.7% of patients experienced their first infusion-related reaction during their fifth infusion or a subsequent infusion (n=841 patients at risk)

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

Pyrexia	Chills	Flushing
Hypotension	Dyspnea	Wheezing
Back pain	Abdominal pain	Urticaria

- Premedicate with an antihistamine and with acetaminophen prior to the first 4 infusions of BAVENCIO and subsequently as needed

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Mild transient reaction; infusion interruption is not indicated; intervention is not indicated	Therapy or infusion interruption is indicated but the reaction responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications are indicated for less than 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

IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.

Modify treatment based on severity

Grade 1-2	Grade 3-4
Interrupt or slow the rate of infusion	Stop the infusion and permanently discontinue BAVENCIO

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

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)

COMPLICATIONS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Clinical trial experience

- 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

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 patients for signs and symptoms of MACE

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 (abdomen), legs, hands, feet, or ankles
- New or worsening 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

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.

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.

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.

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.

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)

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

References: 1. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380(12):1103-1115. **2.** Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. National Institutes of Health website. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed January 5, 2021.

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.

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