EMD SERONO

INDICATIONS AND IMPORTANT SAFETY INFORMATION

AVELUMAB SAFETY DECK

SECTION 1:
Immune-Mediated Adverse Reactions

SECTION 2:
Infusion-Related Reactions and Safety Summaries for Approved Indications

Please see the full BAVENCIO® (avelumab) US Prescribing Information available at https://www.emdserono.com/us-en/pi/bavencio-pi.pdf

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FDA-Approved Indications

Metastatic Merkel cell carcinoma

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

First-line maintenance treatment of urothelial carcinoma

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

Previously-treated urothelial carcinoma

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

- have disease progression during or following platinum-containing chemotherapy
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Advanced renal cell carcinoma

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

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Important Safety Information

- Avelumab 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 avelumab is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue avelumab depending on severity**. In general, withhold avelumab for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue avelumab 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 avelumab 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.
- Avelumab can cause **immune-mediated pneumonitis**. Withhold avelumab for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.1% (21/1854) 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.
- Avelumab 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 avelumab for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (27/1854) of patients, including Grade 3 (0.4%) and Grade 2 (0.8%) adverse reactions. Systemic corticosteroids were required in all (27/27) patients with colitis.

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Important Safety Information, Continued

- Avelumab can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue avelumab 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 avelumab as a single agent in 1.1% (20/1854) of patients, including fatal (0.1%), Grade 3 (0.8%), and Grade 2 (0.2%) adverse reactions. Systemic corticosteroids were required in all (20/20) patients with hepatitis.
- Avelumab **in combination with axitinib** can cause **hepatotoxicity** with higher than expected frequencies of Grade 3 and 4 ALT and AST elevation compared to avelumab alone. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy. Withhold or permanently discontinue both avelumab and axitinib based on severity of AST, ALT, or total bilirubin elevation, and consider administering corticosteroids as needed. Consider rechallenge with avelumab or axitinib, or sequential rechallenge with both avelumab and axitinib, after recovery. In patients treated with avelumab 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. 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.
- Avelumab 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 avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.6% (11/1854) of patients, including Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in all (11/11) patients with adrenal insufficiency.
- Avelumab 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 avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1854) of patients, which was a Grade 2 (0.1%) adverse reaction.

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Important Safety Information, Continued

- Avelumab 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 avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1854) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (8/1854) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 25% (2/8) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (97/1854) of patients, including Grade 3 (0.2%) and Grade 2 (3.6%) adverse reactions. Systemic corticosteroids were required in 6% (6/97) of patients with hypothyroidism.
- Avelumab 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 avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 0.2% (3/1854) of patients, including Grade 3 (0.2%) adverse reactions.
- Avelumab can cause **immune-mediated nephritis with renal dysfunction**. Withhold avelumab for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine. Immune-mediated nephritiswith renal dysfunction occurred in 0.1% (2/1854) of patients, including Grade 3 (0.1%) and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required all (2/2) patients with nephritis with renal dysfunction.
- Avelumab 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 avelumab for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 6% (108/1854) of patients, including Grade 3 (0.1%) and Grade 2 (1.9%) adverse reactions. Systemic corticosteroids were required in 25% (27/108) of patients with dermatologic adverse reactions.
- Avelumab 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 avelumab or were reported with the use of other PD-1/PD-L1 blocking antibodies. For **myocarditis**, permanently discontinue avelumab for Grade 2, Grade 3, or Grade 4. For **neurological toxicities**, withhold avelumab for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

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Important Safety Information, Continued

- Avelumab 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 avelumab for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 26% of patients, including three (0.2%) Grade 4 and ten (0.5%) Grade 3 infusion-related reactions. Eleven (85%) of the 13 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.
- Avelumab **in combination with axitinib** 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 avelumab and axitinib for Grade 3-4 cardiovascular events. MACE occurred in 7% of patients with advanced RCC treated with avelumab in combination with axitinib 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%).
- Avelumab 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 avelumab and for at least 1 month after the last dose of avelumab. It is not known whether avelumab 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 avelumab due to the potential for serious adverse reactions in breastfed infants.
- **The most common adverse reactions** (all grades, ≥20%) in patients with **metastatic Merkel cell carcinoma (MCC)** were fatigue (47%), musculoskeletal pain (29%), infusion-related reaction (26%), rash (25%), nausea (23%), constipation (22%), cough (22%), and diarrhea (21%).
- **Laboratory abnormalities** worsening from baseline (all grades, ≥20%) in patients with **metastatic MCC** were decreased lymphocyte count (51%), decreased hemoglobin (40%), increased aspartate aminotransferase (31%), decreased platelet count (23%), increased alanine aminotransferase (22%), and increased lipase (21%).

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Important Safety Information, Continued

- A **fatal adverse reaction** (sepsis) occurred in one (0.3%) patient with **locally advanced or metastatic urothelial carcinoma (UC)** receiving avelumab + best supportive care (BSC) as first-line maintenance treatment. In patients with previously treated locally advanced or metastatic UC, fourteen patients (6%) who were treated with avelumab experienced either pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.
- **The most common adverse reactions** (all grades, ≥20%) in patients with **locally advanced or metastatic UC** receiving avelumab + BSC (vs BSC alone) as first-line maintenance treatment were fatigue (35% vs 13%), musculoskeletal pain (24% vs 15%), urinary tract infection (20% vs 11%), and rash (20% vs 2.3%). In patients with previously treated locally advanced or metastatic UC receiving avelumab, the most common adverse reactions (all grades, ≥20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.
- **Selected laboratory abnormalities** worsening from baseline (all grades, ≥20%) in patients with **locally advanced or metastatic UC** receiving avelumab + BSC (vs BSC alone) as first-line maintenance treatment were blood triglycerides increased (34% vs 28%), alkaline phosphatase increased (30% vs 20%), blood sodium decreased (28% vs 20%), lipase increased (25% vs 16%), aspartate aminotransferase (AST) increased (24% vs 12%), blood potassium increased (24% vs 16%), alanine aminotransferase (ALT) increased (24% vs 12%), blood cholesterol increased (22% vs 16%), serum amylase increased (21% vs 12%), hemoglobin decreased (28% vs 18%), and white blood cell decreased (20% vs 10%).
- **Fatal adverse reactions** occurred in 1.8% of patients with **advanced renal cell carcinoma (RCC)** receiving avelumab in combination with axitinib. 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 avelumab in combination with axitinib (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 avelumab in combination with axitinib (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%).

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Immune-Mediated Adverse Reactions

SECTION 2:
Infusion-Related Reactions and Safety Summaries for Approved Indications

- Introduction
- IM Pneumonitis
- IM Colitis
- IM Hepatitis
- IM Endocrinopathies
- IM Nephritis
- IM Dermatologic ARs
- Other IM ARs

Introduction

Introduction	Onset	Management
Avelumab is a monoclonal antibody that belongs to a class of drugs that bind to either PD-1 or PD-L1, blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated ARs. Important immune-mediated ARs listed under Warnings and Precautions **may not include all possible severe and fatal immune-mediated reactions**. Immune-mediated ARs, which may be severe or fatal, can occur in any organ system or tissue.	Immune-mediated ARs can occur at **any time after starting treatment** with a PD-1/PD-L1 blocking antibody. While immune-mediated ARs usually manifest during treatment with PD-1/PD-L1 blocking antibodies, **immune-mediated ARs can also manifest after discontinuation** of PD-1/PD-L1 blocking antibodies.	Early identification and management of immune-mediated ARs 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 ARs. **Evaluate** liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated ARs, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

AR, adverse reaction; PD-1, programmed death-receptor 1; PD-L1, programmed death-ligand 1.

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Introduction

● Avelumab monotherapy (1) ○ Avelumab monotherapy (2) ○ Avelumab + BSC (Bladder 100) ○ Avelumab + axitinib (Renal 101)

Immune-related AEs with avelumab monotherapy in advanced solid tumors from the pooled analysis of data from the Phase 1 JAVELIN Solid Tumor and Phase 2 JAVELIN Merkel 200 trials

- With avelumab monotherapy, 247/1738 patients (14.2%) experienced 379 irAEs with median occurrence of 1 (range, 1–10 irAEs); 71 patients (4.1%) had >1 irAE. These were Grade ≥3 in 39 patients (2.2%) and considered serious in 43 patients (2.5%)
- After an irAE, 39/247 patients (15.8%) had **1 dose interruption** and 9 patients (3.6%) had **≥2 dose interruptions**; irAEs led to treatment **discontinuation** in 34 patients (2.0%)
- 109 patients (44.1%) were **treated with a systemic corticosteroid** for irAEs:
  - 71 (28.7%) with ≥40 mg of prednisone or equivalent
  - 35 (14.2%) with <40 mg of prednisone or equivalent
- 5 patients (2.0%) were treated with a nonsteroidal immunosuppressant medication
- At data analysis, 134/379 irAEs (35.3%) had resolved
- The median time to resolution of all events was not estimable (range: 1–783+ days)

Patients with active or a history of any autoimmune disease or immune deficiencies (except patients with type 1 diabetes mellitus, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment) were not eligible.
AE, adverse event; AR, adverse reaction; irAE, immune-related adverse event.
Kelly K, et al. Cancer. 2018;124(9):2010–2017.

Introduction

○ Avelumab monotherapy (1) ● Avelumab monotherapy (2) ○ Avelumab + BSC (Bladder 100) ○ Avelumab + axitinib (Renal 101)

Immune-related AEs with avelumab monotherapy in advanced solid tumors from the pooled analysis of data from the Phase 1 JAVELIN Solid Tumor and Phase 2 JAVELIN Merkel 200 trials

irAE, n(%)[a]	Avelumab (N=1854)			
	Any Grade	Grade 3	Grade 4	Grade 5
Any irAE	247 (14.2)	32 (1.8)	4 (0.2)	3 (0.2)
Rash	90 (5.2)	1 (0.1)	0	0
Colitis	27 (1.5)	7 (0.4)	0	0
Pneumonitis	21 (1.1)	5 (0.3)	1 (0.1)	1 (0.1)
Hepatitis	20 (1.1)	15 (0.8)	0	2 (0.1)
Endocrinopathies	106 (6.1)	6 (0.3)	0	0
Thyroid disorders	109 (5.9)	3 (0.2)	0	0
Adrenal insufficiency	11 (0.6)	1 (0.1)	0	0
Type 1 diabetes mellitus	3 (0.2)	4 (0.2)	0	0
All other irAEs	19 (1.1)	5 (0.3)	3 (0.2)	0
Blood CPK increased	5 (0.3)	1 (0.1)	2 (0.1)	0
Myositis	5 (0.3)	1 (0.1)	1 (0.1)	0
Psoriasis	5 (0.3)	1 (0.1)	0	0
Guillain-Barré syndrome	1 (0.1)	1 (0.1)	0	0
Systemic inflammatory response syndrome	1 (0.1)	1 (0.1)	0	0

a, categories with an incidence of irAEs of Grade ≥3 are shown (graded according to NCI-CTCAE v5.0).
AE, adverse event; AR, adverse reaction; CPK, creatine phosphokinase; irAE, immune-related adverse event; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Event.
Kelly K, et al. Cancer. 2018;124(9):2010–2017.

Introduction

○ Avelumab monotherapy (1) ○ Avelumab monotherapy (2) ● Avelumab + BSC (Bladder 100) ○ Avelumab + axitinib (Renal 101)

Immune-related AEs of any grade occurring in ≥1% or Grade ≥3 irAEs occurring in ≥0.5% with avelumab + BSC in the Phase 3 JAVELIN Bladder 100 trial

	Avelumab + BSC (N=344)	
	All Grades	Grade 3
Any irAE, %	**29.4**	**7.0**
Hypothyroidism	10.2	0.3
Rash	4.9	0.3
Hyperthyroidism	4.7	0
Rash maculopapular	2.3	0.3
Pruritis	2.0	0
Pneumonitis	1.5	0.3
Colitis	0.9	0.6
Increased ALT	0.9	0.9
Increased AST	0.6	0.6
Hyperglycemia	0.9	0.9
Myositis	0.6	0.6

AE, adverse event; ALT, alanine aminotransferase; AR, adverse reaction; AST, aspartate aminotransferase; irAE, immune-related adverse event.
Powles T, et al. Presented at ASCO 2020. Abstract LBA1.

Introduction

○ Avelumab monotherapy (1) ○ Avelumab monotherapy (2) ○ Avelumab + BSC (Bladder 100) ● Avelumab + axitinib (Renal 101)

Select immune-mediated AEs observed with avelumab in combination with axitinib in the Phase 3 JAVELIN Renal 101 trial

- In the avelumab plus axitinib group, the incidence of irAEs of any grade was 38.2%, and the incidence of Grade ≥3 irAEs was 9.0%. Thyroid disorders were the most common irAEs occurring in 107 patients (24.7%)[1]

irAE, %	Avelumab + Axitinib (n=434)[2]		
	All Grades	Grade 3	Grade 4
All immune-related AEs	35	8	1
Hypothyroidism	21	<1	0
Liver function test abnormalities	5	4	<1
Adrenal insufficiency	2	1	0
Diarrhea	2.5	1	0
Acute kidney injury	1.4	1	0
Colitis	1	1	0
Hepatotoxicity	1.8	1	0

Patients with an active or a history of any autoimmune disease and current or previous use of glucocorticoids or other immunosuppressants within 7 days before randomization were not eligible.[1]
AE, adverse event; AR, adverse reaction; irAE, immune-related AE.
1. Motzer RJ ,et al. N Engl J Med. 2019;380:1103–1115; 2. Motzer RJ, et al. Ann Oncol. 2018;29(suppl_8[abstr LBA6_PR]).

Introduction

No dose reduction for avelumab is recommended. Withhold or permanently discontinue avelumab depending on severity.

General Dose Modification Guidelines	
Withhold Avelumab	**Permanently Discontinue Avelumab**
• Grade 3	• Life-threatening (Grade 4) immune-mediated ARs • Recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment • An inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids

- If avelumab 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 ARs are not controlled with corticosteroid therapy.

Toxicity management guidelines for ARs that do not necessarily require systemic corticosteroids* are discussed in the following sections.

* Endocrinopathies and dermatologic reactions.
AR, adverse reaction.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Pneumonitis

Pneumonitis is defined as a focal or diffuse inflammation of the lung parenchyma with or without dry cough.[1]

NCI-CTCAE v5.0 Grade	Severity	Definition[1]
Grade 1	*mild*	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	*moderate*	Symptomatic; medical intervention indicated; limiting instrumental ADL
Grade 3	*severe*	Severe symptoms; limiting self-care ADL; oxygen indicated
Grade 4	*life-threatening*	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)

Monitor for new or worsening signs and symptoms of pneumonitis, including[2]:

- Cough
- Shortness of breath
- Chest pain

Per study protocol, immune-mediated pneumonitis was defined with PTs* coded to the MedDRA v21.0 or v22.0, requiring use of corticosteroids and no clear alternative explanation.[3,4]

* Interstitial lung disease, Pneumonitis, and Acute interstitial pneumonitis were considered SMQ/PTs for immune-mediated pneumonitis in JAVELIN clinical studies.[4,5]

ADL, activities of daily living; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Event, PT, preferred term, SMQ, Standard MedDRA Query.

1. CTCAE, Version 5.0. National Institutes of Health. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed August 14, 2024;
2. BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf; 3. JAVELIN Merkel 200 protocol; 4. JAVELIN Renal 101 protocol.

Immune-Mediated Pneumonitis

Avelumab can cause immune-mediated pneumonitis, including fatal cases.

Immune-Mediated Pneumonitis with Avelumab Monotherapy (N=1854)		
Incidence	1.1% (21/1854) of patients	Grade 2: 0.6%; Grade 3: 0.3%; Grade 4: 0.1%; fatal: 0.1%
Permanent discontinuation of avelumab due to immune-mediated pneumonitis	0.3%	
Withholding of avelumab due to immune-mediated pneumonitis	0.3%	
Systemic corticosteroid treatment	All 21 patients	
Resolution of pneumonitis	57% (12/21) of patients	
Reinitiated treatment with avelumab after symptom improvement	5/5 patients	Of these, none had recurrence

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

Based on the pooled analysis of 1854 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Pneumonitis

The **US Prescribing Information** describes the following management of immune-mediated pneumonitis:

Withhold Avelumab	Permanently Discontinue Avelumab
• **Grade 2** Resume in patients with complete or partial resolution (Grade 0–1) 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	• **Grade 3–4**

- If avelumab 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 ARs are not controlled with corticosteroid therapy.

PI, prescribing information.
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Immune-Mediated Colitis

Colitis is characterized by inflammation of the colon.[1]

NCI-CTCAE v5.0 Grade	Severity	Definition[1]
Grade 1	*mild*	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	*moderate*	Abdominal pain; mucus or blood in stool
Grade 3	*severe*	Severe abdominal pain; peritoneal signs
Grade 4	*life-threatening*	Life-threatening consequences; urgent intervention indicated

Monitor for new or worsening signs and symptoms, including intestinal problems[2]:

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

Per study protocol, immune-mediated colitis was defined with HLTs/PTs* coded to the MedDRA v21.0 or v22.0, requiring use of corticosteroids and no clear alternative explanation.[3,4]

* Acute hemorrhagic ulcerative colitis, Allergic colitis, Autoimmune colitis, Colitis, Colitis erosive, Colitis ischemic, Colitis microscopic, Colitis psychogenic, Colitis ulcerative, Crohn's disease, Enterocolitis hemorrhagic, Eosinophilic colitis, Inflammatory bowel disease, Necrotizing colitis, Neutropenic colitis, Pseudopolyposis, Diarrhea, Diarrhea hemorrhagic, Diarrhea neonatal, Enterocolitis were considered the SMQ/PTs for immune-mediated colitis in JAVELIN clinical studies.[3,4]

ADL, activities of daily living; HLT, high-level term; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Event; PT, preferred term, SMQ, Standard MedDRA Query.

1. CTCAE, Version 5.0. National Institutes of Health. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed August 14, 2024; 2. BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf; 3. JAVELIN Merkel 200 protocol; 4. JAVELIN Renal 101 protocol.

Immune-Mediated Colitis

Definition | **Incidence** | PI-based management

Avelumab can cause immune-mediated colitis; the primary component consisted of diarrhea.

Immune-Mediated Colitis with Avelumab Monotherapy (N=1854)		
Incidence	1.5% (27/1854) of patients	Grade 2: 0.8%; Grade 3: 0.4%
Permanent discontinuation of avelumab due to immune-mediated colitis	0.5%	
Withholding of avelumab due to immune-mediated colitis	0.4%	
Systemic corticosteroid treatment	All 27 patients	
Resolution of colitis	70% (19/27) of patients	
Reinitiated avelumab after symptom improvement	5/8 patients	Recurrence: 40% of patients

- 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.

Based on the pooled analysis of 1854 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
CMV, cytomegalovirus.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Colitis

The **US Prescribing Information** describes the following management of immune-mediated colitis:

Withhold Avelumab	Permanently Discontinue Avelumab
• **Grade 2 or 3** Resume in patients with complete or partial resolution (Grade 0–1) 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	• **Grade 4**

- If avelumab 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 ARs are not controlled with corticosteroid therapy.

AR, adverse reaction; PI, prescribing information.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Hepatotoxicity and Immune-Mediated Hepatitis

NCI-CTCAE v5.0 Grade	Severity	Definition[1]
Grade 1	*mild*	AST or ALT >ULN–3.0X ULN and/or total bilirubin >ULN–1.5X ULN[2,3]
Grade 2	*moderate*	AST or ALT >3.0–5.0X ULN and/or total bilirubin >1.5–3.0X ULN[2]
Grade 3**	*severe*	AST or ALT >5.0–20.0X ULN and/or total bilirubin >3.0–10.0X ULN[2]
Grade 4**	*life-threatening*	AST or ALT >20.0X ULN and/or total bilirubin >10.0X ULN[2]

Monitor for new or worsening signs and symptoms of hepatitis[2]:

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

With avelumab in combination with axitinib, consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy.

Per study protocol, immune-mediated hepatitis was defined with PTs* coded to the MedDRA v19.0 or v21.0, requiring use of corticosteroids and no clear alternative explanation.[3,4]

* Acute hepatic failure, Alanine aminotransferase increased, Aspartate aminotransferase increased, Autoimmune hepatitis, Hepatic enzyme increased, Hepatic failure, Hepatitis, Hepatitis acute, Hepatotoxicity, Liver disorder, Liver function test abnormal, Liver injury, and Transaminases increased.[3,4]; ** In JAVELIN Renal 101, Grade 3/4 was considered AST or ALT >5X ULN and/or total bilirubin >3X ULN.[4]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Event, PI, prescribing information; PT, preferred term; ULN, upper limit of normal.

1. CTCAE, Version 5.0. National Institutes of Health. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed August 14, 2024;
2. BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf; 3. JAVELIN Merkel 200 protocol; 4. JAVELIN Renal 101 protocol.

Hepatotoxicity and Immune-Mediated Hepatitis

● Avelumab monotherapy ○ Avelumab + axitinib imARs ○ Avelumab + axitinib hepatotoxicity

Avelumab can cause immune-mediated hepatitis.

Immune-Mediated Hepatitis with Avelumab Monotherapy (N=1854)		
Incidence	1.1% (20/1854) of patients	Grade 2: 0.2%; Grade 3: 0.8%; fatal: 0.1%
Permanent discontinuation of avelumab due to immune-mediated hepatitis	0.6%	
Withholding of avelumab due to immune-mediated hepatitis	0.2%	
Systemic corticosteroid treatment	All 20 patients	
Resolution of hepatitis	60% (12/20) of patients	
Reinitiated treatment with avelumab after symptom improvement	4/4 patients	Of these, 25% had recurrence

Based on the pooled analysis of 1854 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Hepatotoxicity and Immune-Mediated Hepatitis

○ Avelumab monotherapy ● Avelumab + axitinib imARs ○ Avelumab + axitinib hepatotoxicity

Avelumab in combination with axitinib can cause immune-mediated hepatitis.

Immune-Mediated Hepatitis with Avelumab + Axitinib (N=489)		
Incidence of increased AST/ALT	7% of patients	Grade 3/4: 4.9%
Permanent discontinuation of either treatment due to immune-mediated hepatitis	5.3%	
Systemic corticosteroid treatment	34/35 patients	
Non-steroidal immunosuppressant treatment	1/35 patients	
Resolution of hepatitis	31/35 of patients at data cut-off	

Based on the JAVELIN Renal 101 trial.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; imARs, immune-mediated adverse reactions.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Hepatotoxicity and Immune-Mediated Hepatitis

○ Avelumab monotherapy ○ Avelumab + axitinib imARs ● Avelumab + axitinib hepatotoxicity

Avelumab in combination with axitinib can cause hepatotoxicity with higher than expected frequencies of Grade 3 and 4 ALT and AST elevation compared to avelumab alone.

Immune-Mediated Hepatotoxicity with Avelumab + Axitinib (N=489)		
Incidence	Grade 3: 9%; Grade 4: 7%	
Permanent discontinuation of both treatments due to immune-mediated hepatotoxicity	6.5%	
Resolution of hepatoxicity	ALT resolved to Grades 0/1 in 92% of patients	
Reinitiated treatment with avelumab or axitinib after symptom improvement	73/82 patients	Recurrence: 0/3 patients rechallenged with avelumab, 6/25 patients rechallenged with axitinib, 15/45 patients rechallenged with avelumb + axtinib 88% patients with a recurrence of ALT ≥3 ULN subsequently recovered to Grade 0–1

Based on the JAVELIN Renal 101 trial.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Hepatotoxicity and Immune-Mediated Hepatitis

The **US Prescribing Information** describes the following management of hepatotoxicity and immune-mediated hepatitis:

	Withhold Avelumab[a]	Permanently Discontinue Treatment
Avelumab monotherapy[1]	**No tumor involvement of the liver** AST/ALT increases to 3–8X ULN or, total bilirubin increases to 1.5–3X ULN	**No tumor involvement of the liver** AST/ALT increases to >8X ULN or, total bilirubin increases to >3X ULN
	Tumor involvement of the liver[b] Baseline AST/ALT is 1–3X ULN and increases to 5–10X ULN or, baseline AST/ALT is 3-5X ULN and increases to 8–10X ULN	**Tumor involvement of the liver[b]** AST/ALT increases to >10X ULN or, total bilirubin increases to >3X ULN
Avelumab + axitinib combination therapy	**Withhold both avelumab and axitinib until ARs recover to Grades 0–1[c]** ALT/AST of ≥3 and <10X ULN without concurrent total bilirubin ≥2X ULN; consider rechallenge with axitinib and/or avelumab or sequential rechallenge with both avelumab and axitinib after recovery[d]	**Permanently discontinue both avelumab and axitinib[c] if:** ALT/AST ≥10X ULN or >3X ULN with concurrent total bilirubin ≥2X ULN

- If avelumab 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 ARs are not controlled with corticosteroid therapy.

a, Resume in patients with complete or partial resolution (Grade 0–1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating corticosteroids; b, If AST and ALT are ≤ULN at baseline, withhold or permanently discontinue avelumab based on recommendations for hepatitis where there is no tumor involvement of the liver; c, Consider corticosteroid therapy; d, Dose reduction according to the axitinib full PI should be considered if rechallenging with axitinib.

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

BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Endocrinopathies

● Adrenal insufficiency ○ Hypophysitis ○ Thyroid disorders ○ Type 1 diabetes mellitus

Adrenal insufficiency is a disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and, in some cases, the hormone aldosterone.[1]

NCI-CTCAE v5.0 Grade	Severity	Definition[1]
Grade 1	*mild*	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	*moderate*	Moderate symptoms; medical intervention indicated
Grade 3	*severe*	Severe symptoms; hospitalization indicated
Grade 4	*life-threatening*	Life-threatening consequences; urgent intervention indicated

Monitor for new or worsening signs and symptoms of adrenal insufficiency, including[2]:

- Increased sweating
- Fatigue
- Weight loss
- Dizziness or fainting
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Per study protocol, immune-mediated adrenal insufficiency was defined with HLTs/PTs* coded to the MedDRA v21.0 or v22.0, requiring use of corticosteroids and no clear alternative explanation.[3,4]

* Addison's disease, Adrenal androgen deficiency, Adrenal atrophy, Adrenal insufficiency, Adrenal suppression, Adrenocortical insufficiency acute, Glucocorticoid deficiency, Hypoaldosteronism, Mineralocorticoid deficiency, Primary adrenal insufficiency, Secondary adrenocortical insufficiency, and Steroid withdrawal syndrome were considered SMQ/PTs for immune-mediated adrenal insufficiency in pooled safety analysis.[3] HLT, high-level term; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PT, preferred term; SMQ, Standard MedDRA Query.

1. CTCAE, Version 5.0. National Institutes of Health. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed August 14, 2024;
2. BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf; 3. JAVELIN Merkel 200 protocol; 4. JAVELIN Renal 101 protocol.

Immune-Mediated Endocrinopathies

○ Adrenal insufficiency ● Hypophysitis ○ Thyroid disorders ○ Type 1 diabetes mellitus

Hypophysitis is a disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood.[1]

NCI-CTCAE v5.0 Grade	Severity	Definition[1]
Grade 1	*mild*	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	*moderate*	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	*severe*	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL
Grade 4	*life-threatening*	Life-threatening consequences; urgent intervention indicated

Monitor for new or worsening signs and symptoms of hypophysitis, including[2]:

- Headache
- Photophobia
- Visual field defects

ADL, activities of daily living; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.

1. CTCAE, Version 5.0. National Institutes of Health. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed August 14, 2024;
2. BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Endocrinopathies

○ Adrenal insufficiency ○ Hypophysitis ● Thyroid disorders ○ Type 1 diabetes mellitus

Thyroid disorders (hypothyroidism/hyperthyroidism) are characterized by a decrease/increase in production of thyroid hormone by the thyroid gland.[1]

NCI-CTCAE v5.0 Grade	Severity	Definition[1]
Grade 1	*mild*	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	*moderate*	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL
Grade 3	*severe*	Severe symptoms; limiting self care ADL; hospitalization indicated
Grade 4	*life-threatening*	Life-threatening consequences; urgent intervention indicated

Monitor for new or worsening signs and symptoms of thyroid disorders, including[2]:

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

Per study protocol, immune-mediated thyroid disorders were defined with HLTs/PTs* coded to the MedDRA v21.0 or v22.0, requiring use of corticosteroids and no clear alternative explanation.[3,4]

* Autoimmune hypothyroidism, Hypothyroidic goiter, Hypothyroidism, Myxedema, Primary hypothyroidism, Secondary hypothyroidism, Tertiary hypothyroidism, Thyroid atrophy, Transient hypothyroxinemia of prematurity, Basedow's disease, Hyperthyroidism, Marine-Lenhart syndrome, Primary hyperthyroidism, Secondary hyperthyroidism, Thyroid dermatopathy, Thyrotoxic crisis, Thyrotoxic periodic paralysis, Toxic goiter, Toxic nodular goiter, Autoimmune thyroiditis, Thyroiditis, Thyroiditis acute, Thyroiditis chronic, Thyroiditis fibrous chronic, Thyroiditis subacute were considered SMQ/PTs for immune-mediated thyroid disorders in pooled safety analysis.[1]

ADL, activities of daily living; HLT, high-level term; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Event; PT, preferred term; SMQ, Standard MedDRA Query.

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Immune-Mediated Endocrinopathies

○ Adrenal insufficiency ○ Hypophysitis ○ Thyroid disorders ● Type 1 diabetes mellitus

Type I diabetes mellitus is defined as requiring insulin therapy and/or use of corticosteroids and no clear alternative explanation.[1]

NCI-CTCAE v5.0 Grade	Severity	Definition[1]
Grade 1	*mild*	Abnormal glucose above baseline with no medical intervention
Grade 2	*moderate*	Change in daily management from baseline for a diabetic; oral anti-glycemic agent initiated; workup for diabetes
Grade 3	*severe*	Insulin therapy initiated; hospitalization indicated
Grade 4	*life-threatening*	Life-threatening consequences; urgent intervention indicated

Monitor patients for hyperglycemia or other signs and symptoms of diabetes[2]

Per study protocol, immune-mediated Type 1 diabetes mellitus was defined with HLTs/PTs* coded to the MedDRA v21.0 or v22.0, requiring use of corticosteroids and no clear alternative explanation.[3,4]

* Type I Diabetes mellitus, Latent autoimmune diabetes in adults, Diabetic ketoacidosis, Diabetes Mellitus, and Hyperglycemia were considered SMQ/PTs for immune-mediated type I diabetes mellitus in pooled safety analysis.[1] MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Event; PT, preferred term; SMQ, Standard MedDRA Query; ULN, upper limit of normal.

1. CTCAE, Version 5.0. National Institutes of Health. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed August 14, 2024;
2. BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf; 3. JAVELIN Merkel 200 protocol; 4. JAVELIN Renal 101 protocol.

Immune-Mediated Endocrinopathies

● **Adrenal insufficiency** ○ **Hypophysitis** ○ **Thyroid disorders** ○ **Type 1 diabetes mellitus**

Avelumab can cause immune-mediated endocrinopathies, including primary or secondary adrenal insufficiency.

Immune-Mediated Adrenal Insufficiency with Avelumab Monotherapy (N=1854)		
Incidence	0.6% (11/1854) of patients	Grade 2: 0.4%; Grade 3: 0.1%
Permanent discontinuation of avelumab due to immune-mediated adrenal insufficiency	0.1%	
Withholding of avelumab due to immune-mediated adrenal insufficiency	0.1%	
Systemic corticosteroid treatment	All 11 patients	
Resolution of adrenal insufficiency	2/11 patients	
Reinitiated treatment with avelumab after symptom improvement	0/2	

Based on the pooled analysis of 1854 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Endocrinopathies

○ Adrenal insufficiency ● Hypophysitis ○ Thyroid disorders ○ Type 1 diabetes mellitus

Avelumab can cause immune-mediated hypophysitis, which can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism.

Immune-Mediated Pituitary Disorders with Avelumab Monotherapy (N=1854)		
Incidence	0.1% (1/1854) of patients	Grade 2: 0.1%
Hypopituitarism did not lead to withholding of avelumab in this patient		
Systemic corticosteroids were not required in this patient		

Based on the pooled analysis of 1854 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Endocrinopathies

○ Adrenal insufficiency ○ Hypophysitis ● Thyroid disorders ○ Type 1 diabetes mellitus

Avelumab can cause immune-mediated endocrinopathies, including thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism.

Immune-Mediated Endocrinopathy with Avelumab Monotherapy (N=1854)	Thyroiditis		Hyperthyroidism		Hypothyroidism	
Incidence	0.2% (4/1854) of patients	Grade 2: 0.1%	0.4% (8/1854) of patients	Grade 2: 0.3%	5% (97/1854) of patients	Grade 2: 3.6%; Grade 3: 0.2%
Permanent discontinuation of avelumab due to immune-mediated thyroid disorders	0 patients		0 patients		0.1%	
Withholding of avelumab due to immune-mediated thyroid disorders	0 patients		0.1%		0.4%	
Systemic corticosteroid treatment	0/4 patients		25% (2/8) of patients		6% (6/97) of patients	
Resolution	0/4 patients		88% (7/8) of patients		6% (6/97) of patients	
Reinitiated treatment with avelumab after symptom improvement	0 patients		2/2 patients	Of these, none had recurrence	0/8 patients	

Based on the pooled analysis of 1854 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Endocrinopathies

○ Adrenal insufficiency ○ Hypophysitis ○ Thyroid disorders ● Type 1 diabetes mellitus

Avelumab can cause immune-mediated endocrinopathies, including Type 1 diabetes mellitus which can present with diabetic ketoacidosis.

Immune-Mediated Type I Diabetes Mellitus with Avelumab Monotherapy (N=1854)		
Incidence	0.2% (3/1854) of patients	Grade 3: 0.2%
Permanent discontinuation of avelumab due to immune-mediated Type I diabetes mellitus	0.1%	
Systemic corticosteroids were not required in any patient with Type I diabetes mellitus		
Type I diabetes mellitus did not resolve, and all patients required ongoing insulin treatment		
Hyperglycemia did not lead to withholding of avelumab in any patient		

Based on the pooled analysis of 1854 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
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Immune-Mediated Endocrinopathies

● Adrenal insufficiency ○ Hypophysitis ○ Thyroid disorders ○ Type 1 diabetes mellitus

The **US Prescribing Information** describes the following management of adrenal insufficiency:

Symptomatic Treatment	Withhold Avelumab
• **Grade ≥2 adrenal insufficiency** Initiate symptomatic treatment, including hormone replacement, as clinically indicated	• **Grade 3 or 4** Withhold until clinically stable or permanently discontinue depending on severity

- If avelumab 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 ARs are not controlled with corticosteroid therapy.

PI, prescribing information.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Endocrinopathies

○ Adrenal insufficiency ● Hypophysitis ○ Thyroid disorders ○ Type 1 diabetes mellitus

The **US Prescribing Information** describes the following management of hypophysitis:

Hormone Replacement	Withhold Avelumab
• **Any grade hypophysitis** Initiate hormone replacement as clinically indicated	• **Grade 3 or 4** Withhold until clinically stable or permanently discontinue depending on severity

- If avelumab 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 ARs are not controlled with corticosteroid therapy.

PI, prescribing information.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Endocrinopathies

○ Adrenal insufficiency ○ Hypophysitis ● Thyroid disorders ○ Type 1 diabetes mellitus

The **US Prescribing Information** describes the following management of thyroid disorders:

Hormone Replacement	Withhold Avelumab
• **Any grade hypothyroidism/hyperthyroidism** Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated	• **Grade 3 or 4** Withhold until clinically stable or permanently discontinue depending on severity

- If avelumab 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 ARs are not controlled with corticosteroid therapy.

PI, prescribing information.
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Immune-Mediated Endocrinopathies

○ Adrenal insufficiency ○ Hypophysitis ○ Thyroid disorders ● Type 1 diabetes mellitus

The **US Prescribing Information** describes the following management of diabetes mellitus:

Insulin Treatment	Withhold Avelumab
• **Any grade hyperglycemia** Initiate treatment with insulin as clinically indicated	• **Grade 3 or 4** Withhold until clinically stable or permanently discontinue depending on severity

PI, prescribing information.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Nephritis with Renal Dysfunction

NCI-CTCAE v5.0 Grade	Severity	Definition[1]
Grade 1	*mild*	Creatinine increased >ULN–1.5X ULN
Grade 2	*moderate*	Creatinine increased >1.5–3.0X baseline; >1.5–3.0X ULN
Grade 3	*severe*	Creatinine increased >3.0X baseline; >3.0–6.0X ULN; hospitalization indicated
Grade 4	*life-threatening*	Creatinine increased >6.0X ULN; life-threatening consequences; dialysis indicated

Monitor for new or worsening signs and symptoms of nephritis with renal dysfunction, including[2]:

- Decreased amount of urine
- Blood in urine
- Swelling of ankles
- Loss of appetite

Per study protocol, immune-mediated nephritis with renal dysfunction was defined with HLTs/PTs* coded to the MedDRA v21.0 or v22.0, requiring use of corticosteroids and no clear alternative explanation.[3,4]

* Acute renal failure, Renal failure, and Renal impairment. Autoimmune nephritis, Lupus nephritis, Nephritis, Nephritis hemorrhagic, Perinephritis, Tubulointerstitial nephritis, and Uveitis.

HLTs, high-level terms; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Event; PI, prescribing information; PT, preferred term; SMQ, Standard MedDRA Query; ULN, upper limit of normal.

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2. BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf; 3. JAVELIN Merkel 200 protocol; 4. JAVELIN Renal 101 protocol.

Immune-Mediated Nephritis with Renal Dysfunction

Avelumab can cause immune-mediated nephritis.

Immune-Mediated Nephritis with Avelumab Monotherapy (N=1854)		
Incidence	0.1% (2/1854) of patients	Grade 2: 0.1% Grade 3: 0.1%
Permanent discontinuation of avelumab due to nephritis with renal dysfunction	0.1%	
Withholding of avelumab due to nephritis with renal dysfunction	0 patients	
Systemic corticosteroid treatment	100% patient	
Resolution of nephritis with renal dysfunction	50% patients	

Based on the pooled analysis of 1854 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
PI, prescribing information.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Nephritis with Renal Dysfunction

The **US Prescribing Information** describes the following management of immune-mediated nephritis with renal dysfunction:

Withhold Avelumab	Permanently Discontinue Avelumab
• **Grade 2 or 3 increased blood creatinine** Resume in patients with complete or partial resolution (Grade 0–1) 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	• **Grade 4 increased blood creatinine**

- If avelumab 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 ARs are not controlled with corticosteroid therapy.

PI, prescribing information.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Dermatologic ARs

Exfoliative dermatitis, including SJS, DRESS, and TEN has occurred with PD-1/PD-L1 blocking antibodies[1]

NCI-CTCAE v5.0 Grade	Severity	Definition[2]
Grade 1	*mild*	-
Grade 2	*moderate*	-
Grade 3	*severe*	Skin sloughing covering <10% BSA (SJS) with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)
Grade 4	*life-threatening*	Skin sloughing covering 10-30% BSA (SJS) or ≥30% BSA (TEN) with associated symptoms (e.g., erythema, purpura, or epidermal detachment)

Monitor for new or worsening signs and symptoms of dermatologic ARs, including[1]:

- 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

AR, adverse reaction; BSA, body surface area; DRESS, drug rash with eosinophilia and systemic symptoms; PD-1, programmed death-receptor 1; PD-L1, programmed death-ligand 1; SJS; Stevens-Johnson syndrome, TEN, toxic epidermal necrosis.

1. BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf; 2. CTCAE, Version 5.0. National Institutes of Health. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed August 14, 2024.

Immune-Mediated Dermatologic ARs

Avelumab can cause immune-mediated dermatologic ARs, including immune-mediated rash or dermatitis. Exfoliative dermatitis, including SJS, DRESS, and TEN, has occurred with PD-1/PD-L1 blocking antibodies.

Immune-Mediated Dermatologic ARs with Avelumab Monotherapy (N=1854)		
Incidence	6% (108/1854) of patients	Grade 2: 1.9%; Grade 3: 0.1%
Permanent discontinuation of avelumab due to immune-mediated dermatologic ARs	0.3%	
Withholding of avelumab due to immune-mediated dermatologic ARs	0.4%	
Systemic corticosteroid treatment	25% (27/108) of patients (One patient required the addition of tacrolimus to high-dose corticosteroid)	
Resolution of dermatologic ARs	46% (50/108) of patients	
Reinitiated treatment with avelumab after symptom improvement	4/8 patients	Of these patients, none had recurrence

Based on the pooled analysis of 1854 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
AR, adverse reaction; DRESS, drug rash with eosinophilia and systemic symptoms; PD-1, programmed death-receptor 1; PD-L1, programmed death-ligand 1; PI, prescribing information; SJS, Stevens-Johnson syndrome, TEN, toxic epidermal necrosis.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Immune-Mediated Dermatologic ARs

The **US Prescribing Information** describes the following management of immune-mediated dermatologic ARs:

Withhold Avelumab	Permanently Discontinue Avelumab
• **Suspected SJS, TEN, or DRESS** 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	• **Confirmed SJS, TEN, or DRESS**

- Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes
- If avelumab 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 ARs are not controlled with corticosteroid therapy.

DRESS, drug rash with eosinophilia and systemic symptoms; PI, prescribing information; SJS, Stevens-Johnson syndrome, TEN, toxic epidermal necrosis.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Other Immune-Mediated ARs

Monitor for new or worsening signs and symptoms of problems in other organs, including:

- Chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- Confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- Double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- Persistent or severe muscle pain or weakness, muscle cramps

AR, adverse reaction.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Other Immune-Mediated ARs

Clinically significant immune-mediated ARs occurred at an incidence of <1% of patients (unless otherwise noted) in patients who received avelumab 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 ARs.

- **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 ARs, 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, other transplant (including corneal graft) rejection.

AR, adverse reaction; PD-1, programmed death-receptor 1; PD-L1, programmed death-ligand 1.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Other Immune-Mediated ARs

The **US Prescribing Information** describes the following management of the other immune-mediated ARs observed with avelumab:

Permanently Discontinue Avelumab

- **Grade ≥2 myocarditis**

Withhold Avelumab

- **Grade 2 Neurological Toxicities**

Resume in patients with complete or partial resolution (Grade 0–1) 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

Permanently Discontinue Avelumab

- **Grade 3 or 4 neurological toxicities**

- If avelumab 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 ARs are not controlled with corticosteroid therapy.

AR, adverse reaction.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

SECTION 1:

Immune-Mediated Adverse Reactions

SECTION 2:

Infusion-Related Reactions and Safety Summaries for Approved Indications

- IRRs
- MCC
- UC
- RCC

Infusion-Related Reactions

NCI-CTCAE v5.0	Severity	Definition[1]
Grade 1	*mild*	Mild transient reaction; infusion interruption not indicated; intervention not indicated
Grade 2	*moderate*	Therapy or infusion interruption indicated but the reaction responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications are indicated for ≤24 hours
Grade 3	*severe*	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
Grade 4	*life-threatening*	Life-threatening consequences; urgent intervention indicated

Monitor for signs and symptoms, including[2]:

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

Premedication

Premedicate patients with an antihistamine and with acetaminophen prior to the first 4 infusions of avelumab.

Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

In the pooled safety analyses, AEs considered potential IRRs[3]:

1. They included AEs identified by MedDRA PTs, i.e., IRR, drug hypersensitivity, anaphylactic reaction, hypersensitivity, and Type I hypersensitivity that had an onset that was on: the day of avelumab infusion (during or after the infusion) **or** the day after the avelumab infusion (irrespective of resolution date; 'IRR diagnoses')

2. All AEs identified by MedDRA PTs describing the most commonly observed signs and symptoms of IRRs in association with avelumab therapy, i.e., pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria that had an onset that was on: the day of avelumab infusion (during or after infusion) **and** the event resolved with an end date within 2 days after onset ('IRR symptoms')

AE, adverse event; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities, PT, preferred terms.

1. CTCAE, Version 5.0. National Institutes of Health. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed August 14, 2024;
2. BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf; 3. JAVELIN Merkel 200 protocol.

Infusion-Related Reactions

Avelumab can cause severe or life-threatening infusion-related reactions

With avelumab monotherapy

- IRRs occurred in 26% (482/1854) of patients treated with avelumab, including:
  - Grade 3 IRRs: 10 (0.5%) patients
  - Grade 4 IRRs: 3 (0.2%) patients
- 93% of patients received premedication with antihistamine and acetaminophen
- 11/13 patients (85%) with Grade ≥3 reactions were treated with IV corticosteroids
- 15% of patients had IRRs that occurred after the avelumab infusion was completed

Based on the pooled analysis of 1854 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
IRR, infusion-related reaction; IV, intravenous; NCI-CTCAE; National Cancer Institute-Common Terminology Criteria for Adverse Events.

1. BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Infusion-Related Reactions

Avelumab can cause severe or life-threatening infusion-related reactions

JAVELIN Bladder 100

- Four (1.2%) patients in the avelumab + BSC arm of the JAVELIN Bladder 100 trial experienced serious IRRs and all were discontinued from study treatment.
- Serious AEs with avelumab + BSC included IRRs (1.2%).
- AEs causing permanent discontinuation of avelumab treatment included IRRs (1.2%).

	Avelumab + BSC (N=344)‡	
	All Grades	Grade ≥3*
Subjects with IRR (composite term), n(%)**	74 (21.5)	3 (0.9)
IRR (preferred term), n(%)	34 (10)	3 (0.9)

- Premedication with an antihistamine and acetaminophen was received prior to each infusion.
- The first IRR was typically following the first or second infusion of avelumab, only 8/344 patients who received avelumab had a first IRR at a later infusion.

JAVELIN Renal 101

- The most common ARs (>1%) resulting in permanent discontinuation of avelumab or the combination in the JAVELIN Renal 101 trial included infusion-related reaction (1.8%).†

	Avelumab in combination with axitinib (N=434)†	
	All Grades	Grade ≥3
IRR (preferred term), n(%)	52 (12)	7 (1.6)
IRR (composite term), n(%)	121 (27.9)	7 (1.6)

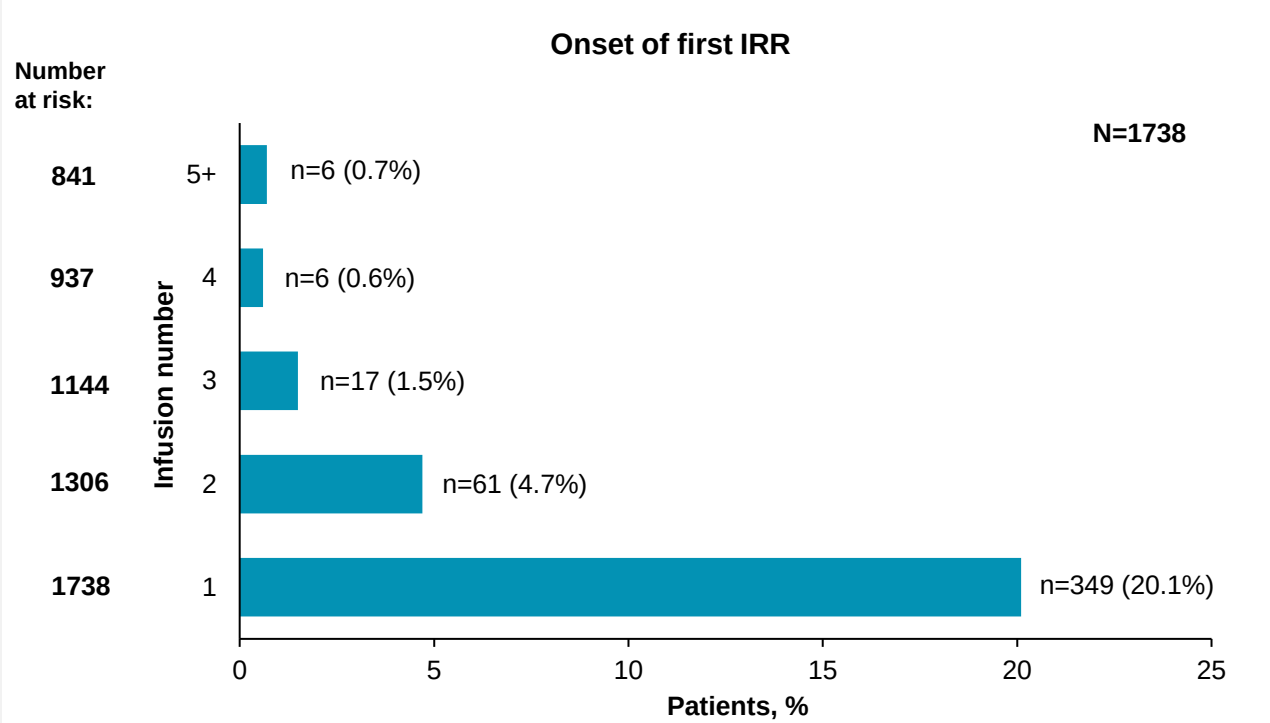
- Premedication with an antihistamine and acetaminophen was received prior to each infusion.

* All Grade ≥3 IRRs were considered Grade 3; ** Included one or more of the preferred terms: IRR, drug hypersensitivity, hypersensitivity, chills, pyrexia, back pain, and hypotension; † Based on the analysis of 434 patients receiving avelumab + axitinib in the JAVELIN Renal 101 trial; ‡ Based on the analysis of 344 patients receiving avelumab + BSC in the JAVELIN Bladder 100 trial.
AE, adverse event; AR, adverse reaction; BSC, best supportive care; IRR, infusion-related reaction; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.03.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Infusion-Related Reactions

○ Incidence (1) ○ Incidence (2) ● Kinetics ○ Kinetics with premedication

Onset of IRRs occurred mostly during the first infusions of avelumab monotherapy



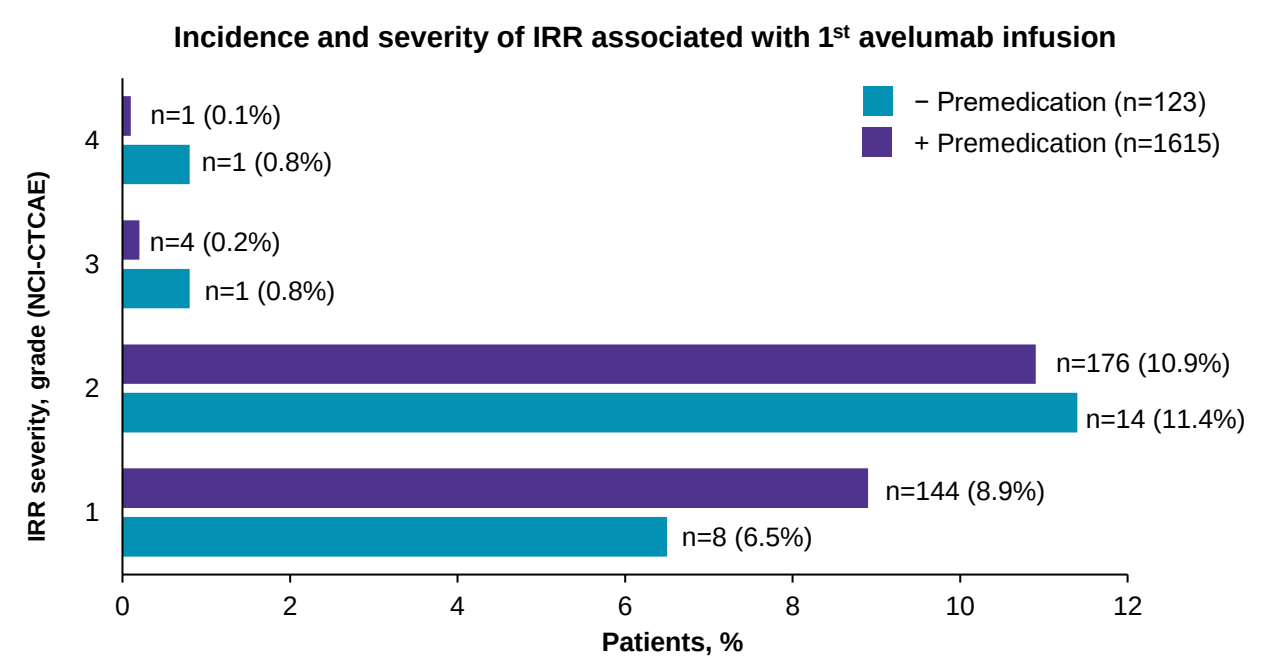
- In the 439 of 1754 patients that experienced an IRR:
  - 79.5% had an IRR at the time of first infusion
  - 98.6% had onset within the first 4 infusions
  - 14.4% and 3.9%, respectively, had at least 2 or 3 infusions with IRRs

Based on the pooled analysis of 1738 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
IRR, infusion-related reaction.
1. Kelly K, et al. Cancer 2018;124:2010.

Infusion-Related Reactions

○ Incidence (1) ○ Incidence (2) ○ Kinetics ● Kinetics with premedication

Premedication appeared to decrease severity, but not incidence, of IRRs with avelumab monotherapy



- **Incidence of IRR during 1st infusion:**
  - 24/123 (19.5%) patients without premedication
  - 325/1615 (20.1%) patients after premedication

Based on the pooled analysis of 1738 patients receiving avelumab monotherapy in JAVELIN Solid Tumor and JAVELIN Merkel 200 trials.
IRR, infusion-related reaction; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.
1. Kelly K, et al. Cancer 2018;124:2010.

Infusion-Related Reactions

The **US Prescribing Information** describes the following management of infusion-related reactions:

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

PI, prescribing information.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Metastatic Merkel Cell Carcinoma

In the JAVELIN Merkel 200 study (N=204):

Serious ARs occurred in 52% of patients, including the following ARs in ≥2% of patients:

- General physical health deterioration
- Anemia
- Abdominal pain
- Acute kidney injury
- Sepsis
- Hyponatremia
- Infusion-related reaction

27% patients permanently discontinued avelumab due to an AR, including the following ARs in >1% of patients:

- Infusion-related reaction
- Anemia
- Increased ALT
- Increased AST

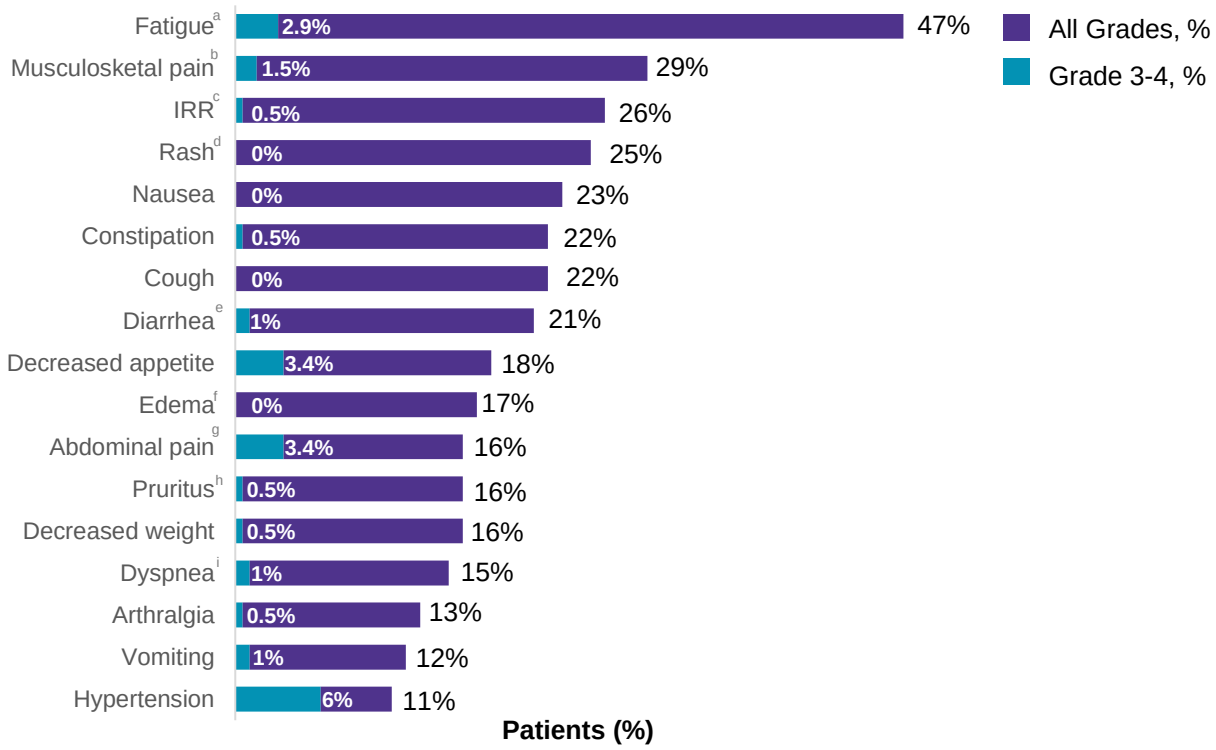
29% patients temporarily discontinued avelumab for an AR*

Most common AR (>1% of patients) requiring dose interruption was nasopharyngitis, anemia, lung infection, and increased ALT

* Excluding temporary dose interruption for IRRs where infusion was restarted the same day.
AE, adverse event; AR, adverse reaction; IRR, infusion-related reaction.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Metastatic Merkel Cell Carcinoma

ARs in ≥10% of patients with metastatic MCC in JAVELIN Merkel 200 study (N=204)



[a] Includes fatigue and asthenia

[b] Includes musculoskeletal pain, back pain, pain in extremity, myalgia, and neck pain

[c] Includes infusion-related reaction, chills, pyrexia, back pain, hypotension, drug hypersensitivity, dyspnea, flushing and hypersensitivity

[d] Includes rash, erythema, rash maculo-papular, rash pruritic, dermatitis bullous, rash erythematous, and rash macular

[e] Includes diarrhea and colitis

[f] Includes peripheral edema, peripheral swelling, and genital edema

[g] Includes abdominal pain, abdominal pain upper, and abdominal pain lower

[h] Includes pruritus and pruritus generalized

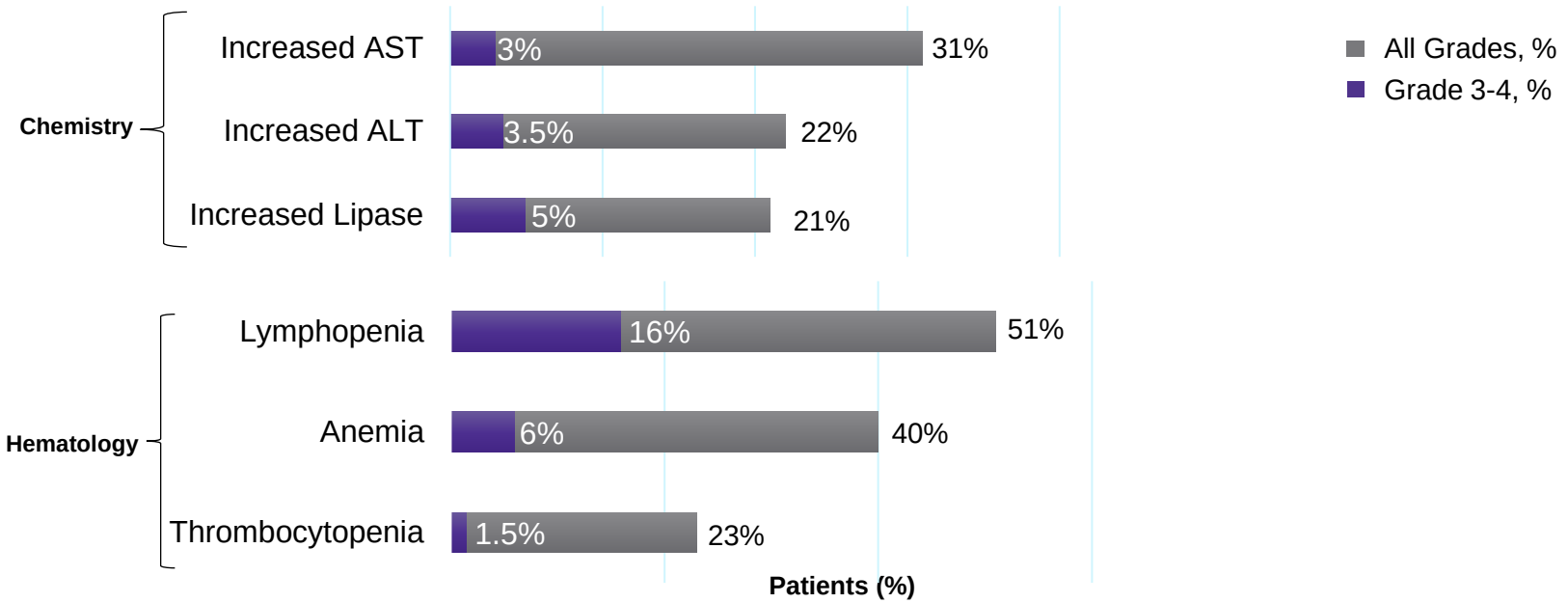
[i] Includes dyspnea and dyspnea exertional

AR, adverse reaction; IRR, infusion-related reaction; MCC, Merkel cell carcinoma.

BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Metastatic Merkel Cell Carcinoma

Selected treatment-emergent† laboratory abnormalities in patients with metastatic MCC receiving avelumab in JAVELIN Merkel 200 study (N=204)



*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (range: 185 to 199 patients).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; MCC, Merkel cell carcinoma.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Locally Advanced or Metastatic Urothelial Carcinoma

In the JAVELIN Bladder 100 study (N=689):

A fatal AR (sepsis) occurred in one (0.3%) patient receiving avelumab + BSC.

Serious ARs occurred in 28% of patients receiving avelumab + BSC. Serious ARs reported in ≥1% of patients:

- UTI (including kidney infection, pyelonephritis, and urosepsis) (6.1%)
- Pain (including abdominal, back, bone, flank, extremity, and pelvic pain) (3.2%)
- Acute kidney injury (1.7%)
- Hematuria (1.5%)
- Sepsis (1.2%)
- IRR (1.2%)

Thirty-one (9%) patients treated with avelumab + BSC received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated AR.

Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. IRRs occurred in 10% of patients treated with avelumab + BSC (Grade 3: 0.9%).

Permanent discontinuation due to ARs resulting in permanent discontinuation of avelumab in >1% of patients included:

- Myocardial infarction (including acute myocardial infarction and troponin T increased) (1.5%)
- IRR (1.2%)

Dose interruptions due to an AR, excluding temporary interruptions of avelumab infusions due to IRRs, occurred in 41% of patients receiving avelumab + BSC.

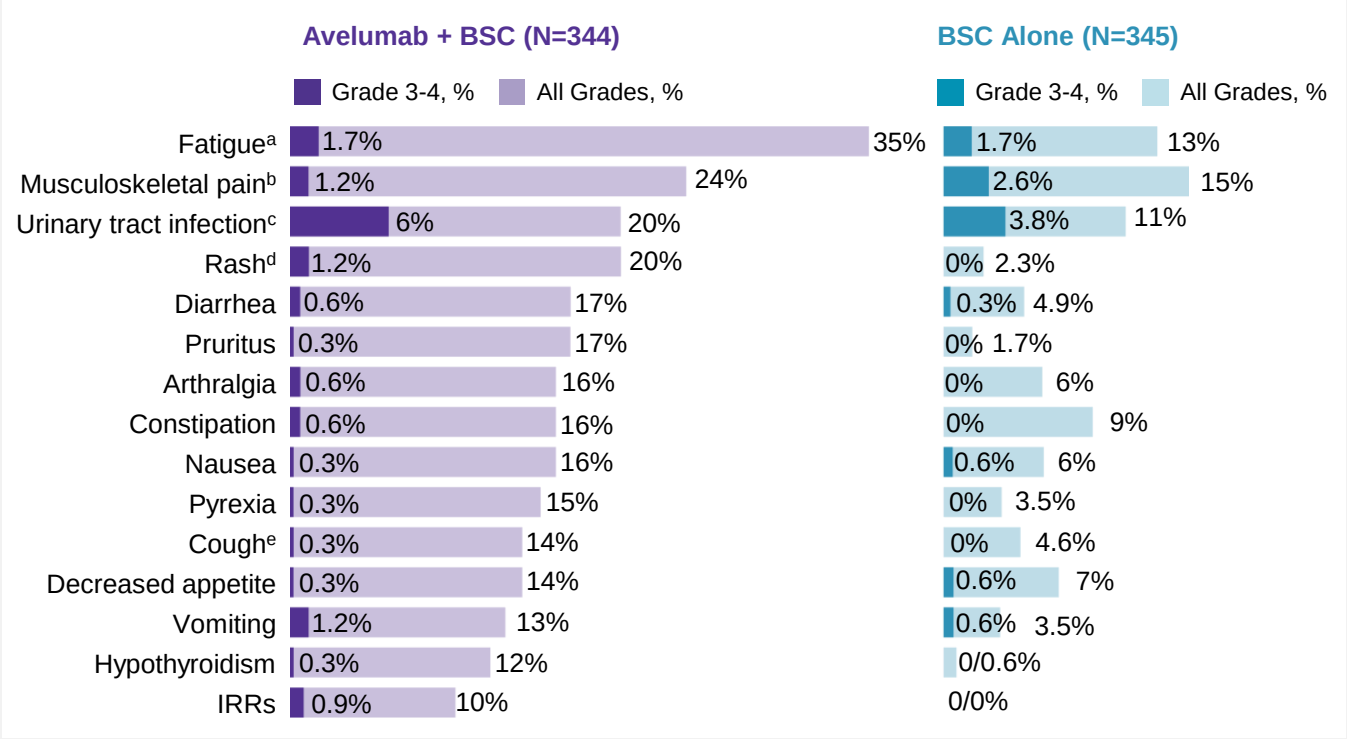
ARs leading to **interruption** of avelumab in >2% of patients:

- Urinary tract infection (including pyelonephritis) (4.7%)
- Blood creatinine increased (including acute kidney injury, renal impairment, and renal failure) (3.8%)

1L, first-line; AR, adverse reaction; BSC, best supportive care; IRR, infusion-related reaction; UTI, urinary tract infection.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Locally Advanced or Metastatic Urothelial Carcinoma

ARs (≥10%) of patients receiving avelumab + BSC vs BSC alone from the JAVELIN Bladder 100 trial (N=689)



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

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

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

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

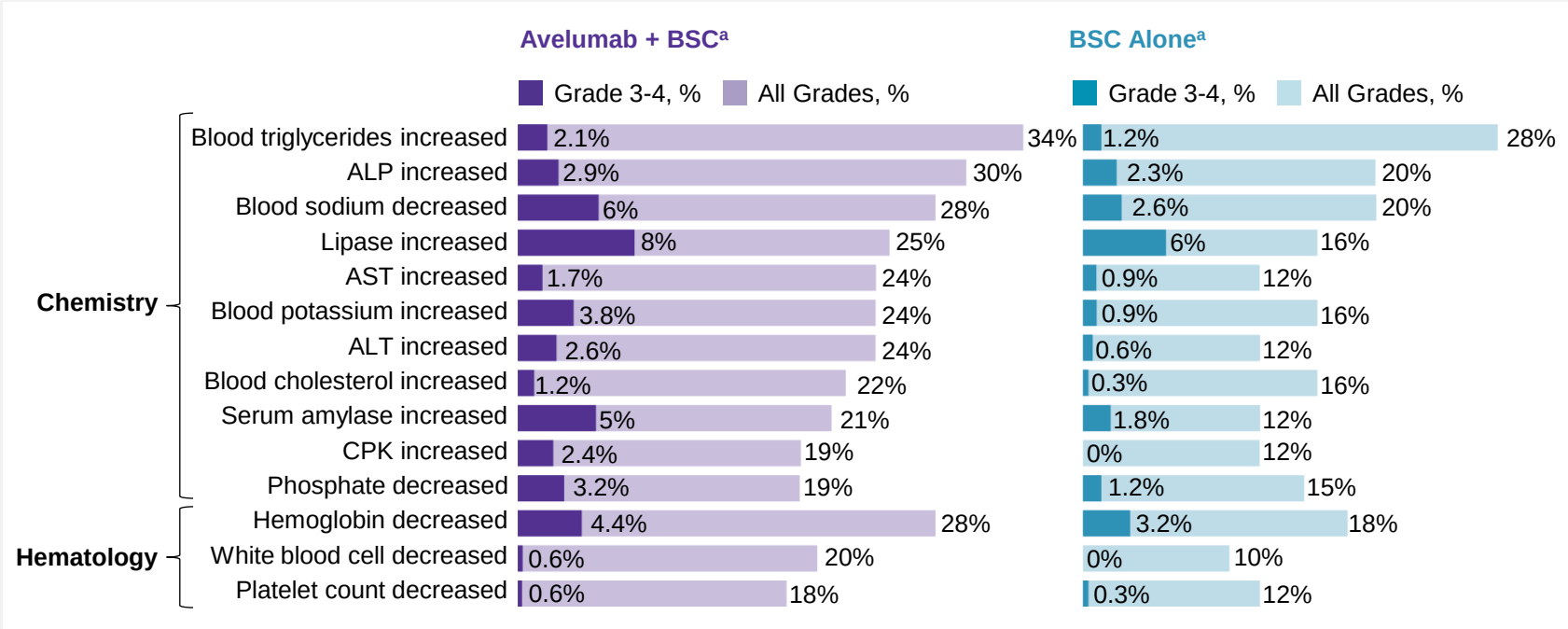
[e] Cough is a composite term that includes cough and productive cough.

1L, first-line; AR, adverse reaction; BSC, best supportive care; IRR, infusion-related reaction.

BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Locally Advanced or Metastatic Urothelial Carcinoma

Selected laboratory abnormalities worsening from baseline occurring in ≥10% of patients receiving avelumab + BSC vs BSC alone in the JAVELIN Bladder 100 trial (N=689)



[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Avelumab plus BSC group (range: 339 to 344 patients) and BSC group (range 329 to 341 patients).
1L, first-line; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSC, best supportive care; CPK, creatinine phosphokinase.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Locally Advanced or Metastatic Urothelial Carcinoma

In the UC cohorts of the JAVELIN Solid Tumor study (N=242):

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

Grade 1–4 **serious** ARs were reported in 41% of patients. **Serious ARs reported in ≥2%** of patients:

- UTI/urosepsis
- Abdominal pain
- Musculoskeletal pain
- Creatinine increased/renal failure
- Dehydration
- Hematuria/urinary tract hemorrhage
- Intestinal obstruction/small intestine obstruction
- Pyrexia

Most common Grade 3 and 4 (≥3%) ARs:

- Anemia
- Fatigue
- Hyponatremia
- Hypertension
- UTI
- Musculoskeletal pain

Eleven (4.5%) patients received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated AR.

12% patients **permanently discontinued** avelumab for Grade 1–4 ARs.

- AR that resulted in **permanent discontinuation in >1%** of patients:
  - Fatigue

29% patients **temporarily discontinued** avelumab for ARs*

- ARs resulting in **temporary discontinuation in >1%** of patients:
  - Diarrhea
  - Fatigue
  - Dyspnea
  - UTI
  - Rash

* Excluding temporary dose interruption for IRRs where infusion was restarted the same day.
2L, second-line; AE, adverse event; AR, adverse reaction; UTI, urinary tract infection.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

First-line Advanced Renal Cell Carcinoma, in Combination with Axitinib

Serious ARs/ discontinuations | ARs | Laboratory abnormalities

In the JAVELIN Renal 101 study (N=873)[1]:

- **Fatal ARs** occurred in 1.8% of patients receiving avelumab in combination with axitinib
  - These included sudden cardiac death (1.2%), stroke (0.2%), myocarditis (0.2%), and necrotizing pancreatitis (0.2%)
- **Serious ARs** occurred in 35% of patients receiving avelumab in combination with axitinib
  - Serious ARs reported 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%)
- 48 (11%) patients treated with avelumab in combination with axitinib received an **oral prednisone dose equivalent to ≥40 mg daily** for an immune-mediated AR
- Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. **IRRs** occurred in 12% (Grade 3: 1.6%; no Grade 4) of patients treated with avelumab in combination with axitinib

Permanent Discontinuation, Dose Interruptions, or Dose Reductions	n=434
Permanent discontinuation due to an AR of:	
Either avelumab or axitinib	**22%**
Avelumab only	**19%**
Axitinib only	**13%**
Both avelumab and axitinib	**8%**
Dose interruptions or reductions due to an AR[a]:	
Dose interruption or reduction in patients receiving avelumab + axitinib	**76%**
Interruption of avelumab	**50%**
Interruption of axitinib	**66%**
Dose reduction of axitinib	**19%**

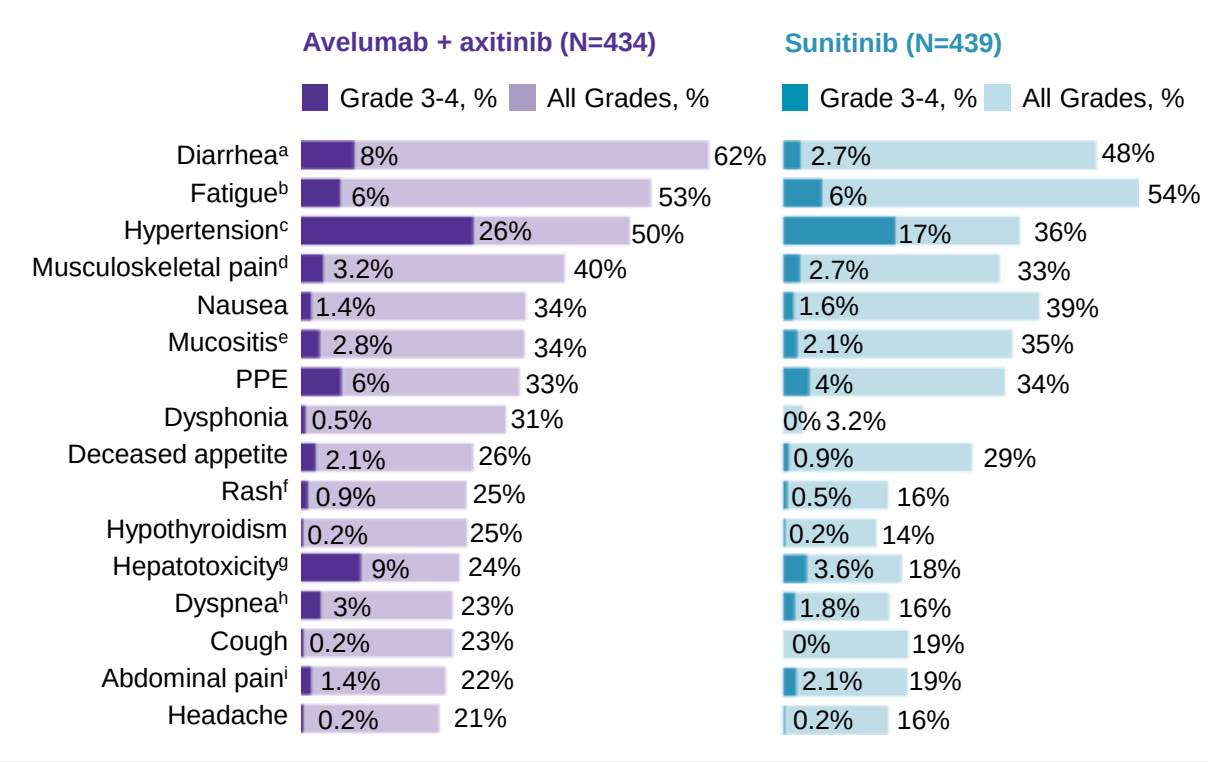
- The most common ARs (>1%) resulting in **permanent discontinuation** of avelumab or the combination were hepatoxicity (6%) and infusion-related reaction (1.8%)
- The most common AR (>10%) resulting in **interruption of avelumab** was diarrhea (10%)
- The most common ARs resulting in **either interruption or dose reduction of axitinib** were diarrhea (19%), hypertension (18%), palmar-plantar erythrodysesthesia (18%), and hepatotoxicity (10%)

[a] Excluding temporary interruptions of avelumab infusions due to infusion-related reactions.
AR, adverse reaction; IRR, infusion-related reaction.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

First-line Advanced Renal Cell Carcinoma, in Combination with Axitinib

Serious ARs/ discontinuations | **ARs** | Laboratory abnormalities

ARs (≥20%) of patients receiving avelumab in combination with axitinib in the JAVELIN Renal 101 Trial[1]



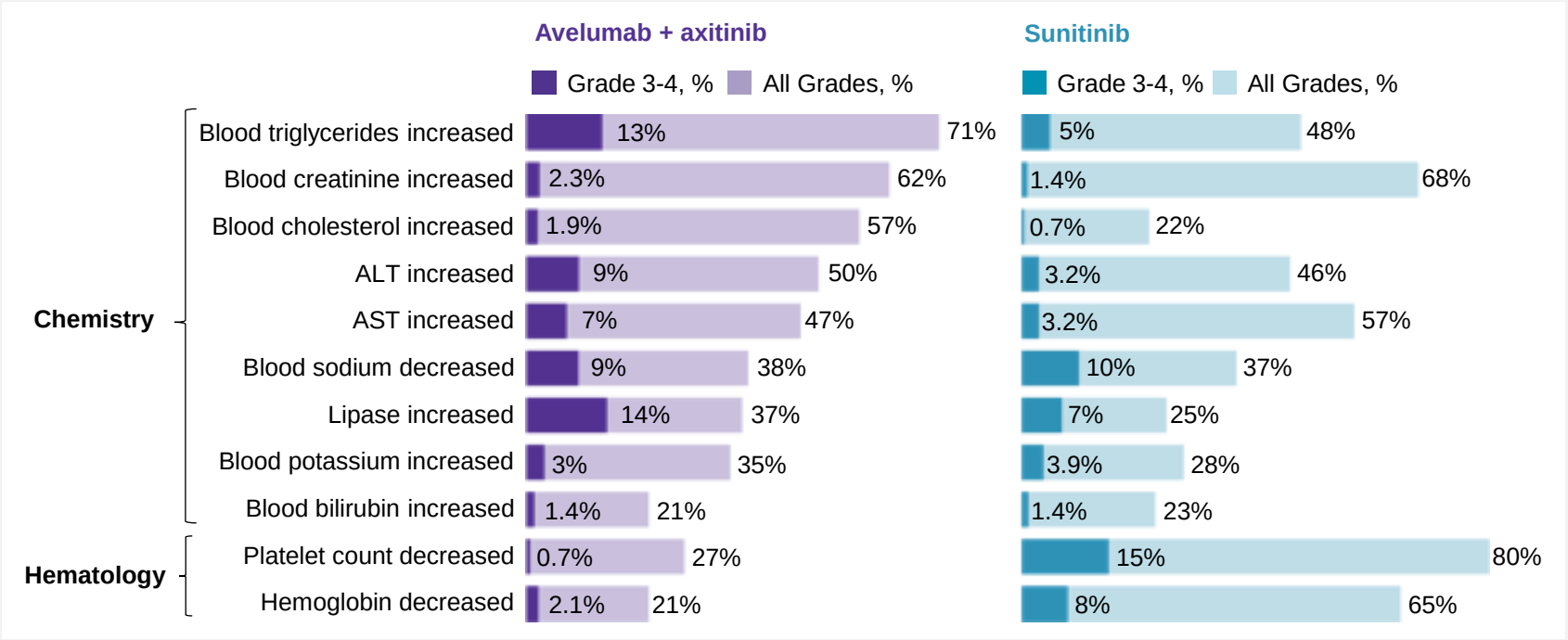
Other clinically important ARs that occurred in less than 20% of patients in JAVELIN Renal 101 trial included arthralgia, weight decreased, and chills

[a] Diarrhea is a composite term that includes diarrhea, autoimmune colitis, and colitis.
[b] Fatigue is a composite term that includes fatigue and asthenia.
[c] Hypertension is a composite term that includes hypertension and hypertensive crisis.
[d] 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.
[e] Mucositis is a composite term that includes mucosal inflammation and stomatitis.
[f] Rash is a composite term that includes rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash erythematous, rash papular, and rash pustular.
[g] 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, transaminases increased.
[h] Dyspnea is a composite term that includes dyspnea, dyspnea exertional, and dyspnea at rest.
[i] Abdominal pain is a composite term that includes abdominal pain, flank pain, abdominal pain upper, and abdominal pain lower.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

First-line Advanced Renal Cell Carcinoma, in Combination with Axitinib

Selected laboratory abnormalities worsening from baseline occurring in ≥20% of patients receiving avelumab in combination with axitinib[a] in the JAVELIN Renal 101 Trial[1]



[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Avelumab in combination with axitinib group (range: 413 to 428 patients) and sunitinib group (range: 405 to 433 patients).
ALT, alanine transaminase; AST, aspartate transaminase.
BAVENCIO® (avelumab) Prescribing Information, https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

INDICATIONS AND IMPORTANT SAFETY INFORMATION

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SECTION 1:
Immune-Mediated Adverse Reactions

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Infusion-Related Reactions and Safety Summaries for Approved Indications

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- IM Pneumonitis
- IM Colitis
- IM Hepatitis
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- Other IM ARs

INDICATIONS AND IMPORTANT SAFETY INFORMATION

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SECTION 1:

Immune-Mediated Adverse Reactions

SECTION 2:

Infusion-Related Reactions and Safety Summaries for Approved Indications

- **IRR**
- **MCC**
- **UC**
- **RCC**