



NURSE HANDBOOK

A comprehensive resource for Advanced Practice Providers and other oncology specialists

CREATED IN PARTNERSHIP WITH ONCOLOGY CERTIFIED NURSES®

BAVENCIO® (avelumab) 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.

NCCN
CATEGORY 1

National Comprehensive Cancer Network® (NCCN®) Recommendation

Avelumab (BAVENCIO) is a **recommended NCCN CATEGORY 1** immunotherapy maintenance option for both cisplatin-eligible and -ineligible patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed on first-line platinum-containing chemotherapy.¹

Category 1=Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

SELECTED SAFETY INFORMATION

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.

Please see Selected Safety Information throughout. Click for the full [Prescribing Information](#) and [Medication Guide](#), or visit BAVENCIO.com.

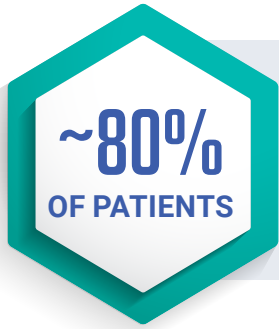
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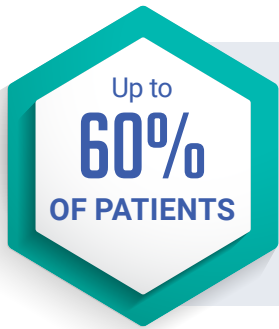
This handbook provides important information as you care for patients who have been prescribed BAVENCIO[®] (avelumab) as maintenance treatment after their locally advanced or metastatic UC did not progress with first-line platinum-containing chemotherapy. This handbook can be used as your go-to for BAVENCIO-related information. It discusses JAVELIN Bladder 100 Trial data, Warnings and Precautions, adverse reactions, dosing and administration, and dose modifications. A discussion guide has also been included at the end of this handbook to help facilitate conversations with your patients about their treatment questions and needs.

Despite eligibility, many US patients with locally advanced or metastatic UC are not treated with 1L platinum-containing chemotherapy²⁻⁴



are eligible for 1L platinum-containing chemotherapy, according to established guidelines.³⁻⁶

~50% of patients receiving treatment for locally advanced or metastatic UC are eligible for **cisplatin-based chemotherapy**^{3,4}



in the United States treated for locally advanced or metastatic UC **NEVER receive systemic therapy, including platinum-containing chemotherapy.**²

Platinum-containing chemotherapy followed by 1L maintenance: A proven approach⁷⁻⁹

In randomized trials in patients with locally advanced or metastatic UC who received any 1L platinum-containing chemotherapy,

~8 IN 10 PATIENTS
achieved disease control^{10,11}



Subsequent 1L maintenance treatment may extend the overall survival benefit in patients who do not progress on 1L chemotherapy (CR, PR, or SD).^{8,12}

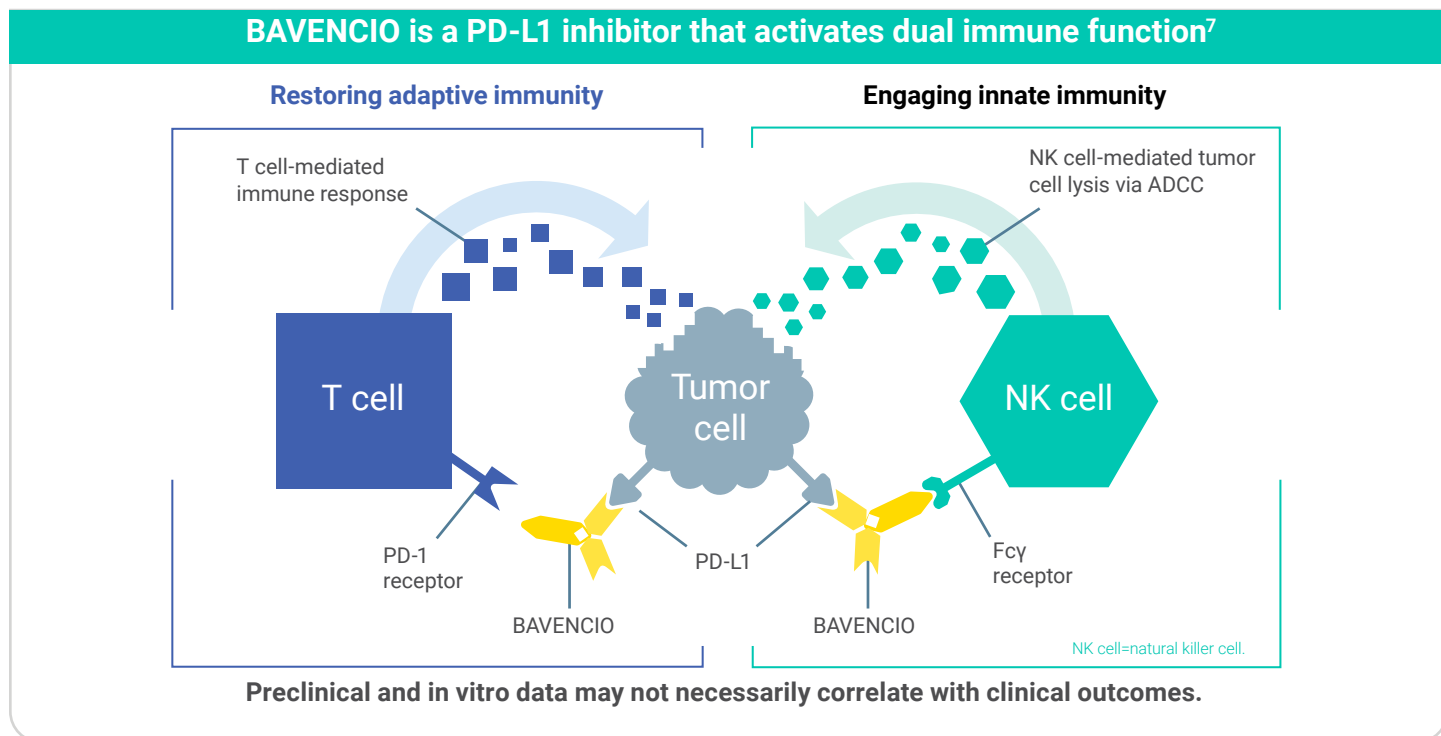
1L=first line; CR=complete response; PR=partial response; SD=stable disease; UC=urothelial carcinoma.

Please see Selected Safety Information throughout. Click for the full [Prescribing Information](#) and [Medication Guide](#), or visit [BAVENCIO.com](#).

 **BAVENCIO**[®]
avelumab Injection
20 mg/mL

What is BAVENCIO and its mechanism of action?

BAVENCIO maintenance therapy is not 2L treatment. It is part of a 1L treatment regimen, including platinum-containing chemotherapy followed by maintenance therapy.⁷



ADAPTIVE IMMUNE RESPONSE

BAVENCIO has been shown to release the suppression of the T cell-mediated antitumor immune response by blocking the interaction of PD-L1 with PD-1 receptors in preclinical models⁷

INNATE IMMUNE RESPONSE

BAVENCIO has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro⁷

1L=first line; 2L=second line; PD-1=programmed death-1 receptor; PD-L1=programmed death ligand-1.

SELECTED SAFETY INFORMATION

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.

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BAVENCIO[®]
avelumab
Injection
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Clinical data

JAVELIN Bladder 100 Trial: Study design

A Phase 3, randomized, open-label, multicenter study in patients (N=700; n=350 for each arm [BAVENCIO + BSC^a vs BSC alone]) with unresectable, locally advanced or metastatic UC that did not progress (patients achieved CR, PR, or SD) with 1L platinum-containing chemotherapy.^b Patients were randomized 1:1 to receive either BAVENCIO 10 mg/kg IV infusion every 2 weeks + BSC or BSC alone, and treated until disease progression or unacceptable toxicity. The major efficacy outcome measure was OS in all randomized patients and patients with PD-L1–positive tumors. **Key eligibility criteria** included unresectable locally advanced or metastatic UC, ≥ 1 measurable lesion defined by RECIST v1.1, 4-6 cycles of platinum-containing chemotherapy (gemcitabine + cisplatin and/or gemcitabine + carboplatin), and ECOG PS 0 or 1. Patients with autoimmune diseases or medical conditions requiring systemic immunosuppression were excluded.^{7,10}

JAVELIN BLADDER 100 PRIMARY ANALYSIS: BAVENCIO + BSC demonstrated superior OS vs BSC alone⁷

Median follow-up: **19.6 months** (95% CI: 18.0, 20.6) in the BAVENCIO + BSC arm; 19.2 months (95% CI: 17.4, 21.6) in the BSC-alone arm¹³

BAVENCIO + BSC demonstrated a median OS of **21.4 months** (95% CI: 18.9, 26.1) vs **14.3 months** (95% CI: 12.9, 17.9) with BSC alone (n=350 in each arm); HR 0.69 (95% CI: 0.56, 0.86)

2-sided P-value^c=0.001

The pre-planned interim analysis was considered the primary analysis since the primary endpoint was met.^{8,14}

^aBSC was administered as deemed appropriate by the treating physician and could include treatment with antibiotics, nutritional support, and other patient management approaches with palliative intent (excludes systemic antitumor therapy).¹⁰

^bCisplatin and/or carboplatin + gemcitabine.⁷

^cP-value based on stratified log-rank.¹⁰

1L=first line; BSC=best supportive care; CI=confidence interval; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HR=hazard ratio; IV=intravenous; PD-L1=programmed death ligand-1; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; UC=urothelial carcinoma.

SELECTED SAFETY INFORMATION

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 1.1% (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.

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% (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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 **BAVENCIO**[®]
avelumab Injection
20 mg/mL

LONG-TERM ANALYSIS (3+ years): Consistent OS results were observed⁷

Median follow-up: **38.0 months** (95% CI: 36.1, 40.5) in the BAVENCIO + BSC arm; 39.6 months (95% CI: 36.2, 41.7) in the BSC-alone arm^{8,14}

BAVENCIO + BSC
n=350



BSC ALONE
n=350



	BAVENCIO + BSC	BSC alone
95% CI	19.9, 28.8	13.5, 18.2
HR (95% CI)	0.76 (0.63, 0.92)	

Long-term OS results in PD-L1–positive patients^{7,a} (n=358, 51% of patients): HR 0.69 (95% CI: 0.52, 0.90)

PD-L1–negative tumors (exploratory analysis; n=270, 39% of patients): OS HR 0.82 (95% CI: 0.62, 1.09)

An updated OS analysis was conducted when 452 deaths were observed. The follow-up OS analysis was prespecified, but no formal hypothesis testing was performed given that the OS endpoint was met in the initial interim analysis.^{7,8}

LONG-TERM EXPLORATORY ANALYSIS: mOS of ~30 months from start of 1L platinum-containing chemotherapy¹⁴

BAVENCIO + BSC
n=350



BSC ALONE
n=350



	BAVENCIO + BSC	BSC alone
95% CI	25.2, 34.0	19.0, 23.5
HR (95% CI)	0.77 (0.64, 0.92)	

LIMITATIONS: This is an exploratory, post hoc analysis of OS data, inclusive of platinum-containing chemotherapy (4-6 cycles), treatment-free interval (4-10 weeks, per trial protocol), randomized study treatment with BAVENCIO + BSC or BSC alone, and subsequent therapy. This analysis only includes patients who did not progress on first-line platinum-containing chemotherapy and subsequently enrolled in the JAVELIN Bladder 100 trial. Safety data are not available pre-randomization. No conclusions can be drawn from this OS analysis.

^aUsing the VENTANA PD-L1 (SP263) assay, PD-L1–positive status was defined as PD-L1 expression in $\geq 25\%$ of tumor cells or in $\geq 25\%$ or 100% of tumor-associated immune cells if the percentage of immune cells was $>1\%$ or $\leq 1\%$, respectively. If none of these criteria were met, PD-L1 status was considered negative.¹⁰

1L=first line; BSC=best supportive care; CI=confidence interval; HR=hazard ratio; mOS=median overall survival; PD-L1=programmed death ligand-1.

SELECTED SAFETY INFORMATION

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 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.

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 0.6% (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.

Patient-reported outcomes from JAVELIN Bladder 100: A prespecified secondary endpoint¹⁵

- Baseline characteristics of enrolled patients (N=700) were generally well balanced between arms and between the overall and PD-L1-positive populations

Among patients in the BAVENCIO + BSC and BSC-alone arms (n=350 for each),
**overall and average per-assessment completion rates for PRO analyses
among eligible patients at each scheduled visit were**

>90% FOR MOST OF THE TREATMENT PERIOD

FBISI-18

- FBISI-18 measured **symptoms and QOL** in the past 7 days in bladder cancer patients
- FBISI-18 subscales comprise disease-related symptoms, including physical (DRS-P; pain, weight loss, urination, weakness, dizziness, meeting family needs, appetite, erection in males, and sleep), emotional (DRS-E; worrying about disease worsening and sadness), treatment side effects (TSEs; nausea, lack of energy, feeling ill, bowel control, and bother of TSE), and functional well-being (FWB; ability to enjoy life and contentment with QOL)
- Ranges for each FBISI-18 score: total, 0-72; DRS-P, 0-36; DRS-E, 0-8; TSE, 0-20; and FWB, 0-8. Descriptive statistics were calculated for FBISI-18 total score and subscales
- Estimates of clinically important differences and changes for group comparisons: total, 3-6; DRS-P, 2-3; TSE, 1-2; and DRS-E and FWB, one each
- Estimates of significant changes in individual patients: total, 3-9; DRS-P, 2-6; DRS-E, 1-3; TSE, 2-5; and FWB, 2-4

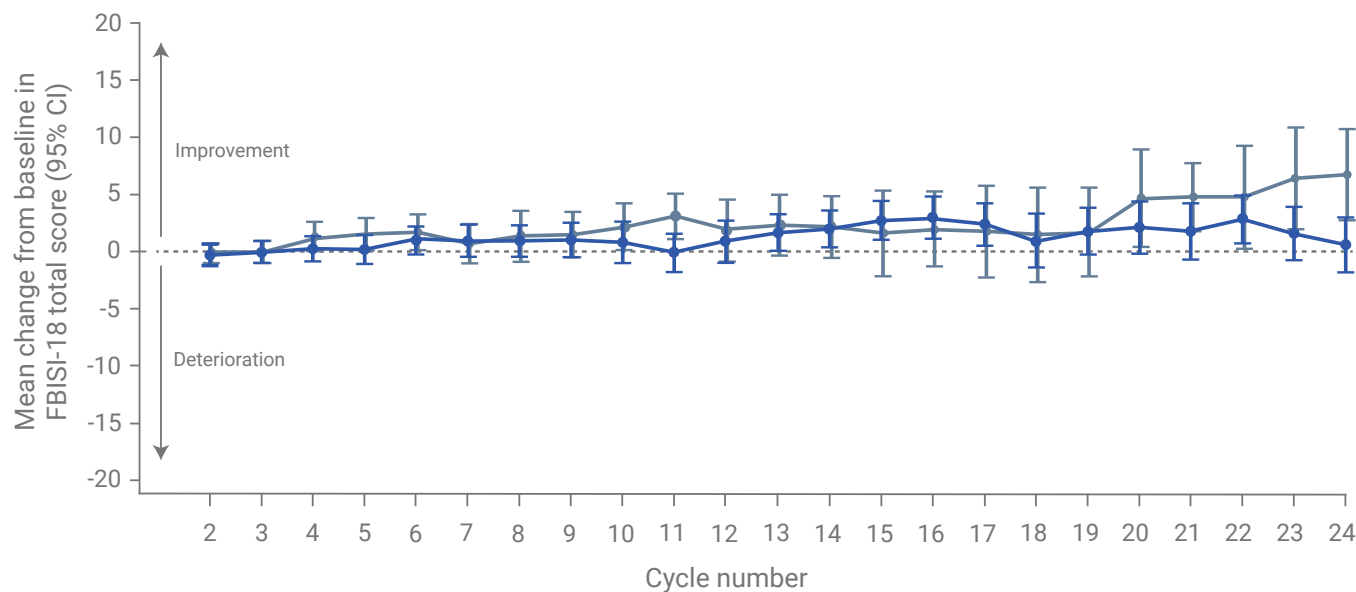
1L=first line; BSC=best supportive care; FBISI-18=Functional Assessment of Cancer Therapy Bladder Symptom Index-18; PD-L1=programmed death ligand-1; PRO=patient-reported outcome; QOL=quality of life.

SELECTED SAFETY INFORMATION

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% (1/1854) of patients, which was a Grade 2 (0.1%) adverse reaction.

FBISI-18 analysis in the overall population¹⁵

- At baseline (after completion of chemotherapy but before the start of maintenance treatment) in the overall population, FBISI-18 total scores appeared to be similar between the BAVENCIO + BSC arm (mean, 53.3; SD, 9.6) and the BSC-alone arm (mean, 52.7; SD, 9.3)
- The mean change from baseline on treatment appeared relatively stable, with most values at or above baseline and most corresponding CIs including the baseline value



No. of patients^a

	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
BAVENCIO + BSC	310	269	240	202	178	160	144	132	123	120	103	96	87	80	67	63	57	47	42	43	38	35	33
BSC	297	223	155	120	109	85	68	55	49	47	43	36	32	28	26	23	21	18	16	16	15	14	10

Figure recreated from Grivas P, et al. *Eur Urol.* 2023;83(4):320-328.

LIMITATIONS OF THIS PRO ASSESSMENT:

- Open-label trial design and the limited number of patients providing data at later time points
 - The limited number of patients at later cycles was prominent in the control arm, mainly due to progression events, which may limit the interpretation of longer-term PROs
- The FBISI-18 instrument was validated in patients with bladder cancer, but some items may be less relevant for advanced disease in the maintenance setting
- All analyses were not adjusted for multiple testing, hindering their overall interpretation
- The methodology of this assessment does not allow conclusions based on this data

^aNumber of patients who completed the baseline assessment and the assessment at the respective cycle. Data for on-treatment visits that had 10 or more patients in both arms are shown. For the BAVENCIO + BSC and BSC-alone arms, 333 and 330 patients responded to one or more items at baseline, respectively.

BSC=best supportive care; CI=confidence interval; FBISI-18=Functional Assessment of Cancer Therapy Bladder Symptom Index-18; PRO=patient-reported outcome; SD=standard deviation.

SELECTED SAFETY INFORMATION

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% (4/1854) 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.

BAVENCIO: An established safety profile⁸

PRIMARY ANALYSIS¹⁰

TRARs (77.3% of patients)

16.6% of patients had a Grade ≥ 3 TRAR

irARs (29.4% of patients)

7.0% of patients had a Grade ≥ 3 irAR

Treatment discontinuation due to ARs: **11.9%**

Treatment discontinuation due to TRARs: **9.6%**

LONG-TERM ANALYSIS⁸

TRARs (78.2% of patients)

19.5% of patients had a Grade ≥ 3 TRAR

irARs (32.3% of patients)

7.6% of patients had a Grade ≥ 3 irAR

Treatment discontinuation due to ARs: **14.2%**

Treatment discontinuation due to TRARs: **11.6%**

NO NEW SAFETY SIGNALS OBSERVED IN THE LONG-TERM ANALYSIS (MEDIAN FOLLOW-UP, ≥ 38 MONTHS)⁸

NEARLY **20%** of patients were still receiving treatment with BAVENCIO after 2 years (median duration, 5.8 months)⁸

irAR=immune-mediated adverse reaction;
TRAR=treatment-related adverse reaction.

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20 mg/mL

PRIMARY ANALYSIS: Adverse reactions⁷

Fatal adverse reaction

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

Serious adverse reactions

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

Infusion-related reactions

Patients received premedication with an antihistamine and acetaminophen prior to each infusion. Infusion-related reactions occurred in **10% of patients** treated with BAVENCIO + BSC (Grade 3: 0.9%)

Oral steroid use

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



PRIMARY ANALYSIS: Adverse reactions (≥10%) of patients receiving BAVENCIO + BSC⁷

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

^aFatigue is a composite term that includes fatigue, asthenia, and malaise.

^bMusculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain.

^cRash is a composite term that includes rash, rash maculopapular, erythema, dermatitis acneiform, eczema, erythema multiforme, rash erythematous, rash macular, rash papular, rash pruritic, drug eruption, and lichen planus.

^dUrinary 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.

^eCough is a composite term that includes cough and productive cough.

BSC=best supportive care.

PRIMARY ANALYSIS: Selected laboratory abnormalities worsening from baseline occurring in $\geq 10\%$ of patients receiving BAVENCIO + BSC⁷

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

^aEach test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: BAVENCIO + BSC group (range: 339-344 patients) and BSC group (range: 329-341 patients).
BSC=best supportive care.

BAVENCIO dosing, preparation, storage, and administration⁷

Recommended dosage



- **BAVENCIO is administered as an 800-mg intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity**
- BAVENCIO is supplied in 200 mg/10 mL vials; therefore, 4 vials are used for the recommended 800-mg dose

Premedication



- Premedicate patients with an antihistamine and with acetaminophen **prior to the first 4 infusions of BAVENCIO**
- Premedication should be administered for subsequent BAVENCIO doses based on clinical judgment and presence/severity of prior infusion reactions

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**, 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 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 the 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

SELECTED SAFETY INFORMATION

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 0.2% (3/1854) of patients, including Grade 3 (0.2%) adverse reactions.

Please see Selected Safety Information throughout. Click for the full [Prescribing Information](#) and [Medication Guide](#), or visit [BAVENCIO.com](#).

Important information on selected adverse reactions with BAVENCIO® (avelumab)⁷

- The data below and on the following pages related to immune-mediated adverse reactions and infusion-related reactions are based on data from 1854 patients enrolled in the JAVELIN Merkel 200 and JAVELIN Solid Tumor trials across multiple tumor types, the majority of whom were treated with BAVENCIO monotherapy
- This included 204 patients with metastatic MCC (JAVELIN Merkel 200 Trial) and 242 patients with locally advanced and metastatic UC (JAVELIN Solid Tumor Trial)

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



Advise your patients that the adverse reactions listed in this guide are not all the possible side effects of treatment. Ask your patients to contact their cancer care team right away if they notice any signs or symptoms of adverse reactions. They may report side effects to FDA at 1-800-FDA-1088.

Immune-mediated pneumonitis

Clinical trial experience (across the development program)

- BAVENCIO® (avelumab) can cause immune-mediated pneumonitis
- Across clinical studies,^a immune-mediated pneumonitis occurred in 1.1% (21/1854) 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

Median time to onset

2.5 months

Range: 3 days to 11 months¹⁶

Median duration

1.75 months

Range: 4 days to 4+ months¹⁶

MONITOR

Monitor patients for signs and symptoms of pneumonitis, including

Cough	Shortness of breath	Chest pain
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ASSESS

Assess the severity of the adverse reaction⁵

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)

MODIFY

Modify treatment based on severity

Withhold ^b	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

^aThese data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

^bResume 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.

ADL=activities of daily living.

Immune-mediated colitis

Clinical trial experience (across the development program)

- BAVENCIO® (avelumab) can cause immune-mediated colitis
- Across clinical studies,^a immune-mediated colitis occurred in 1.5% (27/1854) of patients receiving BAVENCIO, including:
 - Grade 3 (0.4%) adverse reactions
 - Grade 2 (0.8%) adverse reactions
- Colitis led to permanent discontinuation of BAVENCIO in 0.5% and withholding of BAVENCIO in 0.4% of patients
- Systemic corticosteroids were required in all (27/27) patients with colitis
- Colitis resolved in 70% (19/27) of the patients
- Of the 8 patients in whom BAVENCIO was withheld for colitis, 5 reinitiated treatment with BAVENCIO after symptom improvement
 - Of these, 40% had recurrence of colitis

Median time to onset

2.1
months

Range: 2 days to 11 months¹⁶

Median duration

1.5
months

Range: 1 day to 14+ months¹⁶

MONITOR

Monitor patients for signs and symptoms of colitis, including

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

Assess the severity of the adverse reaction⁵

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

Modify treatment based on severity

Withhold ^b	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

^aThese data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

^bResume 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.

Hepatotoxicity and immune-mediated hepatitis

Clinical trial experience (across the development program)

- BAVENCIO® (avelumab) can cause immune-mediated hepatitis
- Across clinical studies,^a immune-mediated hepatitis occurred in 1.1% (20/1854) of patients receiving BAVENCIO, including:
 - Fatal (0.1%) adverse reactions
 - Grade 3 (0.8%) adverse reactions
 - Grade 2 (0.2%) adverse reactions
- Hepatitis led to permanent discontinuation of BAVENCIO in 0.6% and withholding of BAVENCIO in 0.2% of patients
- Systemic corticosteroids were required in all (20/20) patients with hepatitis
- Hepatitis resolved in 60% (12/20) of the patients
- Of the 4 patients in whom BAVENCIO was withheld for hepatitis, 4 reinitiated treatment with BAVENCIO after symptom improvement
 - Of these, 25% had recurrence of hepatitis

Median time to onset

3.2 months

Range: 1 week to 15 months¹⁶

Median duration

2.5 months

Range: 1 day to 7.4+ months¹⁶

MONITOR

Monitor patients for signs and symptoms of pneumonitis, 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

Assess the severity of the adverse reaction⁵

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

Modify treatment based on severity

	Withhold ^b	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^c	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

- 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

^aThese data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

^bResume 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.

^cIf 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.

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

Please see Selected Safety Information throughout. Click for the full [Prescribing Information](#) and [Medication Guide](#), or visit [BAVENCIO.com](#).



Immune-mediated endocrinopathies: adrenal insufficiency

Clinical trial experience (across the development program)

- BAVENCIO® (avelumab) can cause primary or secondary adrenal insufficiency
- Across clinical studies,^a immune-mediated adrenal insufficiency occurred in 0.6% (11/1854) of patients receiving BAVENCIO, including:
 - Grade 3 (0.1%) adverse reactions
 - Grade 2 (0.4%) adverse reactions
- Adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.1% of patients
- Systemic corticosteroids were required in all (11/11) patients with adrenal insufficiency
- Adrenal insufficiency resolved in 18% (2/11) of patients
- Of the 2 patients in whom BAVENCIO was withheld for adrenal insufficiency, none reinitiated treatment with BAVENCIO

Median time to onset

2.5 months

Range: 1 day to 8 months¹⁶

MONITOR

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

Assess the severity of the adverse reaction⁵

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

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

^aThese data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

Immune-mediated endocrinopathies: hypophysitis

Clinical trial experience (across the development program)

- BAVENCIO® (avelumab) can cause immune-mediated hypophysitis. Hypophysitis can cause hypopituitarism
- Across clinical studies,^a immune-mediated pituitary disorders occurred in 0.1% (1/1854) 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

MONITOR		
Hypophysitis can present with acute symptoms associated with mass effect, such as		
Headache	Photophobia	Visual field defects

ASSESS			
Assess the severity of the adverse reaction ⁵			
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

MODIFY	
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

^aThese data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

ADL=activities of daily living.

Immune-mediated endocrinopathies: thyroid disorders

Clinical trial experience (across the development program)

- BAVENCIO® (avelumab) can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism
- Across clinical studies,^a thyroiditis occurred in 0.2% (4/1854) of patients receiving BAVENCIO, including:
 - Grade 2 (0.1%) adverse reactions
 - Thyroiditis did not lead to permanent discontinuation or withholding of BAVENCIO in any patients
 - No patients with thyroiditis required systemic corticosteroids
 - Thyroiditis did not resolve in any patients (0/4)
- Across clinical studies,^a hyperthyroidism occurred in 0.4% (8/1854) of patients receiving BAVENCIO, including:
 - Grade 2 (0.3%) adverse reactions
 - Hyperthyroidism did not lead to permanent discontinuation of BAVENCIO in any patients and led to withholding of BAVENCIO in 0.1% of patients
 - Systemic corticosteroids were required in 25% (2/8) of patients with hyperthyroidism
 - Hyperthyroidism resolved in 88% (7/8) of the patients
 - Of the 2 patients in whom BAVENCIO was withheld for hyperthyroidism, 2 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of hyperthyroidism
- Across clinical studies,^a hypothyroidism occurred in 5% (97/1854) of patients receiving BAVENCIO, including:
 - Grade 3 (0.2%) adverse reactions
 - Grade 2 (3.6%) adverse reactions
 - Hypothyroidism led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.4% of patients
 - Systemic corticosteroids were required in 6% (6/97) of patients with hypothyroidism
 - Hypothyroidism resolved in 6% (6/97) of the patients
 - Of the 8 patients in whom BAVENCIO was withheld for hypothyroidism, none reinitiated BAVENCIO

Median time to onset

2.8 months

Range: 3.6 weeks to 19.3 months¹⁴

Median duration

NE

Range: 8 days to more than 23.9 months¹⁴

MONITOR

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

Assess the severity of the adverse reaction¹⁷

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

MODIFY

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

^aThese data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

ADL=activities of daily living; NE=not estimable.

Please see Selected Safety Information throughout. Click for the full [Prescribing Information](#) and [Medication Guide](#), or visit [BAVENCIO.com](#).

BAVENCIO[®]
avelumab Injection
20 mg/mL

Immune-mediated endocrinopathies: type 1 diabetes mellitus, which can present with diabetic ketoacidosis

Clinical trial experience (across the development program)

- Type 1 diabetes mellitus, which can present with diabetic ketoacidosis
- Across clinical studies,^a immune-mediated type 1 diabetes mellitus occurred in 0.2% (3/1854) of patients receiving BAVENCIO® (avelumab), including:
 - Grade 3 (0.2%) adverse reactions
- Type 1 diabetes mellitus led to permanent discontinuation of BAVENCIO in 0.1% of 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

Monitor patients for hyperglycemia or other signs and symptoms of diabetes

ASSESS

Assess the severity of the adverse reaction¹⁷

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

Modify treatment based on severity

Hyperglycemia

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

^aThese data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

Immune-mediated nephritis with renal dysfunction

Clinical trial experience (across the development program)

- BAVENCIO® (avelumab) can cause immune-mediated nephritis
- Across clinical studies,^a immune-mediated nephritis with renal dysfunction occurred in 0.1% (2/1854) of patients receiving BAVENCIO, including:
 - Grade 3 (0.1%) adverse reactions
 - Grade 2 (0.1%) adverse reactions
- Nephritis with renal dysfunction led to permanent discontinuation of BAVENCIO in 0.1% of patients
- Nephritis did not lead to withholding of BAVENCIO in any patient
- Systemic corticosteroids were required in 100% of patients with nephritis with renal dysfunction
- Nephritis with renal dysfunction resolved in 50% of the patients

MONITOR

Evaluate creatinine at baseline and periodically during treatment

ASSESS

Assess the severity of the adverse reaction¹⁷

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

MODIFY

Modify treatment based on severity

Withhold ^b	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

^aThese data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

^bResume 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.

ULN=upper limit of normal.

Immune-mediated dermatologic adverse reactions

Clinical trial experience (across the development program)

- BAVENCIO® (avelumab) 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,^a immune-mediated dermatologic adverse reactions occurred in 6% (108/1854) of patients receiving BAVENCIO, including:
 - Grade 3 (0.1%) adverse reactions
 - Grade 2 (1.9%) adverse reactions
- Dermatologic adverse reactions led to permanent discontinuation of BAVENCIO in 0.3% of patients and withholding of BAVENCIO in 0.4% of patients
- Systemic corticosteroids were required in 25% (27/108) of patients with dermatologic adverse reactions
 - One patient required the addition of tacrolimus to high-dose corticosteroids
- Dermatologic adverse reactions resolved in 46% (50/108) of the patients
- Of the 8 patients in whom BAVENCIO was withheld for dermatologic adverse reactions, 4 reinitiated treatment with BAVENCIO after symptom improvement
 - Of these, none had recurrence of dermatologic adverse reaction

MONITOR

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

Assess the severity of the adverse reaction¹⁷

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

MODIFY

Modify treatment based on severity

Withhold ^b	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

^aThese data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

^bResume 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.

BSA=body surface area; DRESS=drug reaction with eosinophilia and systemic symptoms; PD-1=programmed death-1 receptor; PD-L1=programmed death ligand-1; SJS=Stevens Johnson Syndrome; TEN=toxic epidermal necrolysis.

Other immune-mediated adverse reactions

Clinical trial experience (across the development program)

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received BAVENCIO® (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 adverse reactions

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, other transplant (including corneal graft) rejection

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

^aResume 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.

PD-1=programmed death-1 receptor; PD-L1=programmed death ligand-1.

Infusion-related reactions

Clinical trial experience (across the development program)

- BAVENCIO® (avelumab) can cause severe or life-threatening infusion-related reactions
- Across clinical studies,^a infusion-related reactions occurred in 26% (482/1854; all grades) of patients, including:
 - 3 (0.2%) Grade 4 infusion-related reactions
 - 10 (0.5%) Grade 3 infusion-related reactions
- 93% (1724/1854) of patients received premedication with antihistamine and acetaminophen
- 11 (85%) of the 13 patients with Grade ≥3 reactions were treated with intravenous corticosteroids
- 15% (278/1854) of patients had infusion-related reactions that occurred after BAVENCIO infusion was completed

MONITOR

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

Assess the severity of the adverse reaction¹⁷

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

MODIFY

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

^aThese data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

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

Complications of allogeneic hematopoietic stem cell transplantation (HSCT)

Clinical trial experience (across the development program)

- Fatal and other serious complications can occur in patients who receive 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

MONITOR

Follow patients closely for evidence of transplant-related complications and intervene promptly

ASSESS

Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT

Embryo-fetal toxicity

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.

PD-1=programmed death-1 receptor; PD-L1=programmed death ligand-1.

CoverOne[®] patient support

CoverOne[®] provides access and reimbursement support services to help eligible patients^a gain appropriate access to BAVENCIO[®] (avelumab).

^aEligibility requirements and restrictions may apply.

We recognize that each patient's situation is different, and are dedicated to helping eligible BAVENCIO patients one at a time

Please contact us at 1-844-8COVER1 if you have any questions.

CoverOne[®]



Call: 1-844-8COVER1
(1-844-826-8371)

Monday—Friday
8:00 AM—5:00 PM ET



Fax: 1-800-214-7295



Visit: CoverOne.com

Patient discussion guide

It's important to check in with your patients about how they are doing with BAVENCIO® (avelumab).

The questions below are examples of conversation starters to help with any questions or concerns regarding treatment.

- ✓ How are you feeling about your treatment?
- ✓ Do you have any questions about the side effects we discussed?
- ✓ Have you experienced any new or worsening signs or symptoms we discussed?
- ✓ Do you need assistance with insurance coverage or cost of treatment?
- ✓ Do you have any questions about your next infusion?
- ✓ Do you have any questions about advanced urothelial carcinoma?



Advise your patients that the adverse reactions listed in this guide are not all the possible side effects of treatment. Ask your patients to contact their cancer care team right away if they notice any signs or symptoms of adverse reactions. They may report side effects to FDA at 1-800-FDA-1088.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.4.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed May 15, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2. Kearney M, Zhang L, Hubscher E, et al. Undertreatment in patients with advanced urothelial cancer: systematic literature review and meta-analysis. *Future Oncol.* 2023. Epub ahead of print. doi:10.2217/fon-2023-0298 3. Cathomas R, Lorch A, Bruins HM, et al. The 2021 updated European Association of Urology guidelines on metastatic urothelial carcinoma. *Eur Urol.* 2022;81(1):95-103. 4. Galsky MD, Hahn NM, Rosenberg J, et al. 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Superior OS vs BSC alone demonstrated in **one of the largest Phase 3 trials** (N=700), with follow-up data of 38 months^{8,10,18-23}



3+ years of follow-up data^{7,8}



Updated exploratory mOS: nearly 30 months from start of first-line chemotherapy^{14,b}



Established safety profile: no new safety signals observed in the follow-up period⁷



Low rates of treatment discontinuations and Grade ≥ 3 treatment-related ARs⁷



In an analysis of QOL according to PROs from JAVELIN Bladder 100, **similar results were seen with BAVENCIO + BSC** vs BSC alone¹⁵

BAVENCIO warnings and precautions

- Severe and fatal immune-mediated adverse reactions
 - Immune-mediated pneumonitis
 - Immune-mediated colitis
 - Hepatotoxicity and immune-mediated hepatitis
 - Immune-mediated endocrinopathies
 - Immune-mediated nephritis with renal dysfunction
 - Immune-mediated dermatologic adverse reactions
 - Other immune-mediated adverse reactions
- Infusion-related reactions
- Complications of allogeneic hematopoietic stem cell transplantation
- Embryo-fetal toxicity

See Safety Profile for more information on BAVENCIO warnings and precautions.

^aCategory 1=Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

^bExploratory, post hoc analysis of OS data, inclusive of platinum-containing chemotherapy (4-6 cycles), treatment-free interval (4-10 weeks, per trial protocol), randomized study treatment with BAVENCIO + BSC or BSC alone, and subsequent therapy. This analysis only includes patients who did not progress on first-line platinum-containing chemotherapy and subsequently enrolled in the JAVELIN Bladder 100 trial. Safety data are not available pre-randomization. No conclusions can be drawn from this OS analysis.

BSC=best supportive care; IO=immunotherapy; NCCN=National Comprehensive Cancer Network; OS=overall survival; PROs=patient-reported outcomes; QOL=quality of life; UC=urothelial carcinoma.

Most common adverse reactions

The most common adverse reactions ($\geq 20\%$) in patients receiving BAVENCIO + BSC vs BSC alone were:

- Fatigue (35% vs 13%)
- Musculoskeletal pain (24% vs 15%)
- Urinary tract infection (20% vs 11%)
- Rash (20% vs 2.3%)



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Please see Selected Safety Information throughout. Click for the full [Prescribing Information](#) and [Medication Guide](#), or visit [BAVENCIO.com](#).