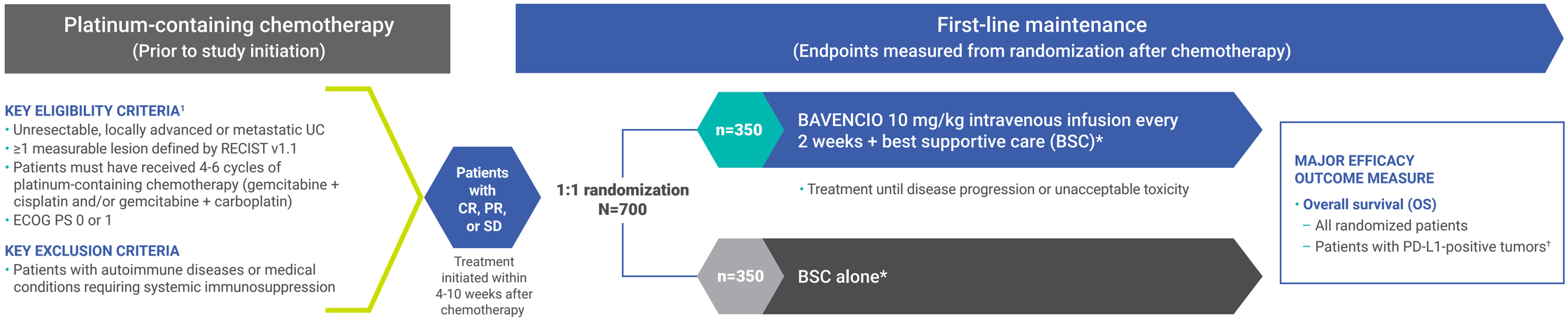
# JAVELIN Bladder 100 Trial

**JAVELIN Bladder 100 Trial**—a Phase 3, randomized, open-label, multicenter study in patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing chemotherapy (N=700)[1]

## Study design: JAVELIN Bladder 100 regimen with BAVENCIO® (avelumab) as first-line maintenance treatment




- Stratified by best response to chemotherapy (CR/PR [72%] vs SD [28%] per RECIST v1.1) and site of metastasis (visceral [55%] vs nonvisceral, including bone metastasis [45%]) assessed at the time of initiating first-line platinum-containing chemotherapy[1]
- First-line chemotherapy regimens included prior gemcitabine plus cisplatin (56%), prior gemcitabine plus carboplatin (38%), and prior gemcitabine plus cisplatin and gemcitabine plus carboplatin (6%)
- Administration of BAVENCIO was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator
- Assessment of tumor status was performed at baseline, 8 weeks after randomization, then every 8 weeks up to 12 months after randomization, and every 12 weeks thereafter until documented confirmed disease progression based on BICR assessment per RECIST v1.1

*BSC 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); †PD-L1 expression was assessed in tumor samples using the VENTANA PD-L1 (SP263) assay.[1]

BICR=blinded independent central review; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group (ECOG) Performance Status; PD-L1=programmed death ligand-1; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

# 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.

**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.

**Please see Selected Safety Information throughout and full Prescribing Information here.**

**JAVELIN Bladder 100 Trial**—a Phase 3, randomized, open-label, multicenter study in patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing chemotherapy (N=700)[1]

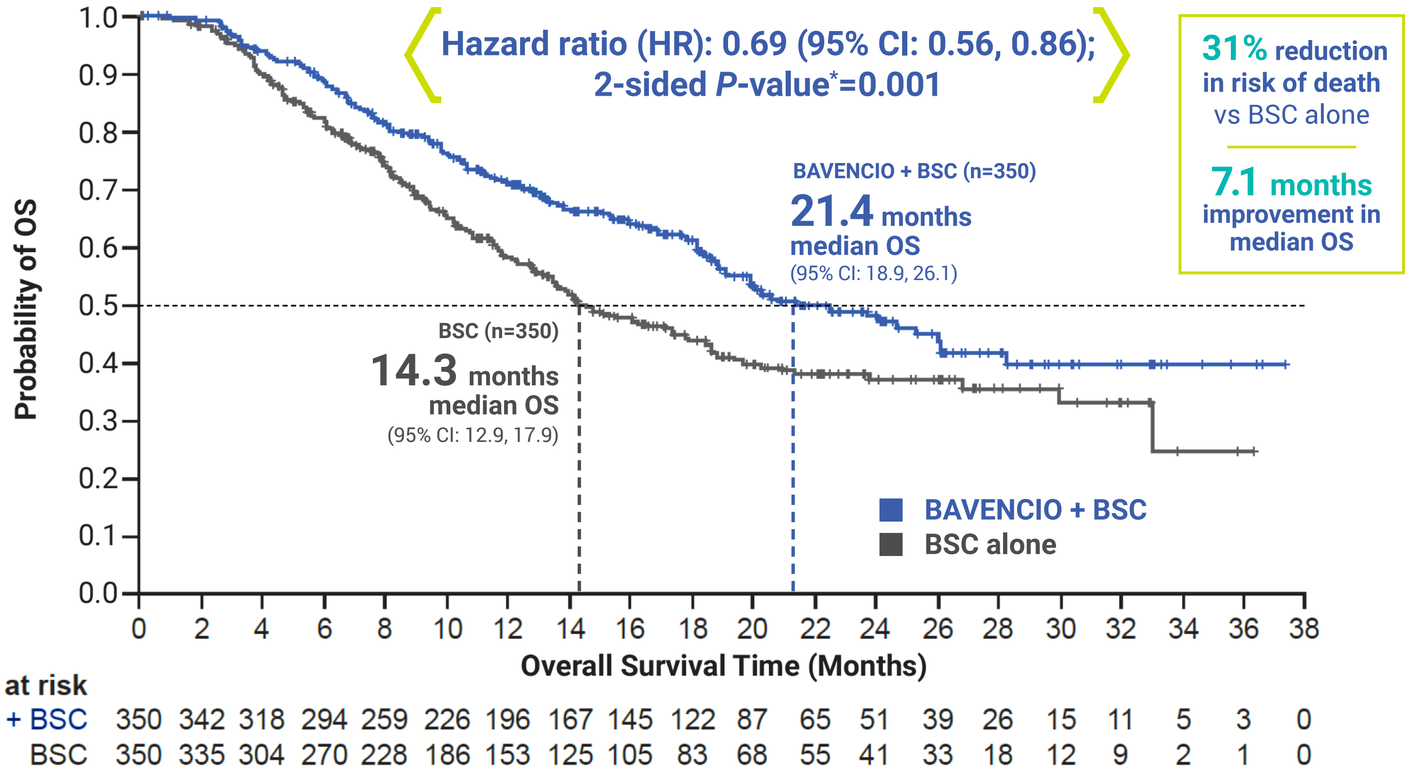
# BAVENCIO® (avelumab) + best supportive care (BSC) demonstrated superior overall survival (OS) vs BSC alone[1]

## Primary OS analysis: OS in all randomized patients (major efficacy outcome measure), data cutoff October 21, 2019[1]

**4-6 Cycles**
Platinum-containing chemotherapy[1]

**4-10 Weeks**
Treatment-free interval

OS was measured post-randomization (after chemotherapy and treatment-free interval)[1]




| No. at risk | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BAVENCIO + BSC | 350 | 342 | 318 | 294 | 259 | 226 | 196 | 167 | 145 | 122 | 87 | 65 | 51 | 39 | 26 | 15 | 11 | 5 | 3 | 0 |
| BSC | 350 | 335 | 304 | 270 | 228 | 186 | 153 | 125 | 105 | 83 | 68 | 55 | 41 | 33 | 18 | 12 | 9 | 2 | 1 | 0 |

### OS in patients with PD-L1-positive tumors† (major efficacy outcome measure)

- BAVENCIO + BSC demonstrated statistically significant improvement in OS vs BSC alone in patients with PD-L1-positive tumors (n=358, 51%); the OS hazard ratio was 0.56 (95% CI: 0.40, 0.79; 2-sided *P*-value <0.001)*

### OS in patients with PD-L1-negative tumors† (exploratory analysis)

- In patients with PD-L1-negative tumors (n=270, 39%), the OS hazard ratio was 0.85 (95% CI: 0.62, 1.18)

†Using the VENTANA PD-L1 (SP263) assay, PD-L1-positive status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively. If none of these criteria were met, PD-L1 status was considered negative.[1]

- A pre-planned interim analysis (IA) occurred with a data cut-off of October 21, 2019. The IA was considered as the primary analysis of the trial since the primary endpoint was met[2]
- Among all randomized patients, consistent results were observed across the prespecified subgroup of CR/PR vs SD to first-line chemotherapy
- Median duration of follow-up was 19.6 months (95% CI: 18.0, 20.6) in the BAVENCIO + BSC arm and 19.2 months (95% CI: 17.4, 21.6) in the BSC arm alone[2]
- 44% of patients in the BSC arm received another PD-1/PD-L1 checkpoint inhibitor as subsequent therapy vs 6% of patients in the BAVENCIO + BSC arm

**P*-value based on stratified log-rank.
CI=confidence interval; PD-1=programmed death-1 receptor; PD-L1=programmed death ligand-1.

## 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 1.2% (21/1738) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

BAVENCIO can cause **immune-mediated colitis**. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Systemic corticosteroids were required in all (26/26) patients with colitis.

## FOLLOW-UP OVERALL SURVIVAL RESULTS

**LIMITATIONS:** Although the follow-up overall survival (OS) analysis was prespecified, no formal hypothesis testing was performed given that the OS endpoint was met in the initial interim analysis. Therefore, no conclusions can be drawn from the follow-up OS analysis.[2]

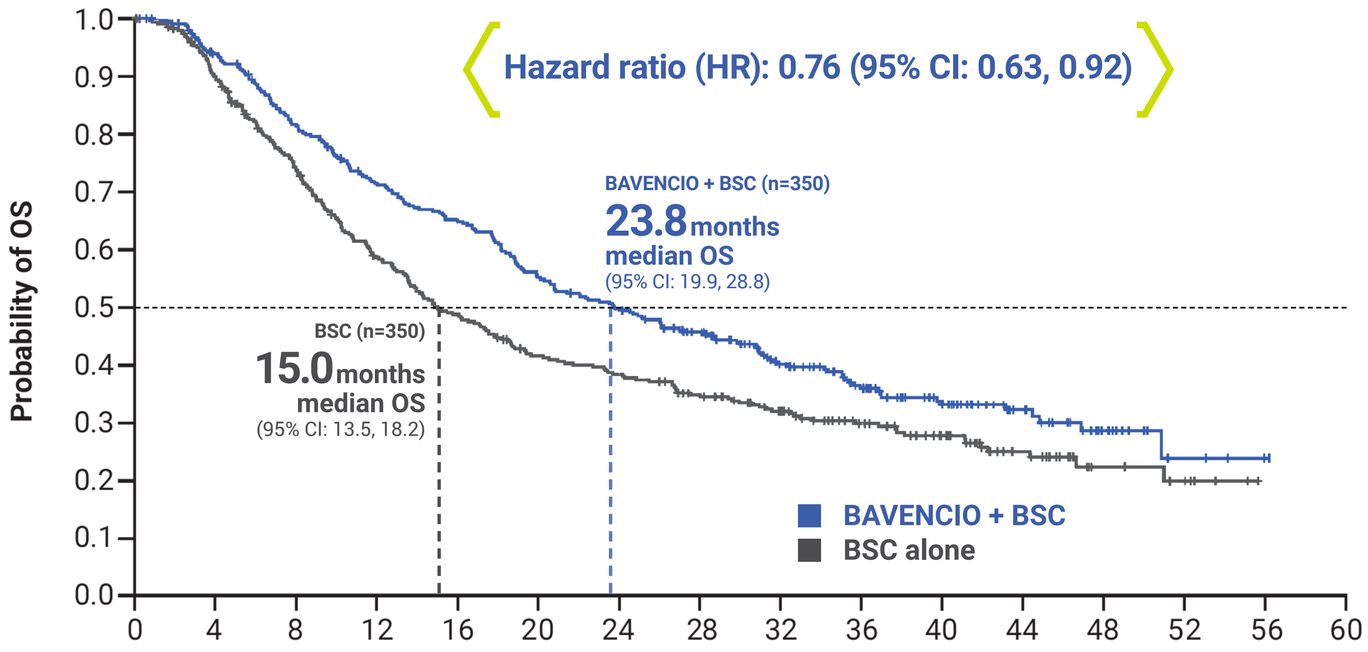
# Follow-up OS analysis: BAVENCIO + BSC vs BSC alone[3]

**OS in all randomized patients, data cutoff June 4, 2021[3]**

**4-6 Cycles**
Platinum-containing chemotherapy[1]

**4-10 Weeks**
Treatment-free interval

OS was measured post-randomization (after chemotherapy and treatment-free interval)[1]




| No. at risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BAVENCIO + BSC | 350 | 318 | 274 | 237 | 216 | 183 | 164 | 140 | 99 | 74 | 53 | 31 | 13 | 4 | 1 | 0 |
| BSC | 350 | 304 | 243 | 190 | 158 | 131 | 121 | 103 | 82 | 62 | 46 | 27 | 10 | 7 | 0 | |

### Follow-up OS results in patients with PD-L1-positive tumors*

- In patients with PD-L1-positive tumors (n=358, 51%); the OS hazard ratio was 0.69 (95% CI: 0.52, 0.90)[3]

### Follow-up OS results in patients with PD-L1-negative tumors* (exploratory analysis)

- In patients with PD-L1-negative tumors (n=270, 39%), the OS hazard ratio was 0.82 (95% CI: 0.62, 1.09)[3]

*Using the VENTANA PD-L1 (SP263) assay, PD-L1-positive status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively. If none of these criteria were met, PD-L1 status was considered negative.[1]

- Median duration of follow-up was 38.0 months (95% CI: 36.1, 40.5) in the BAVENCIO + BSC arm and 39.6 months (95% CI: 36.2, 41.7) in the BSC arm alone[2]
- 53% of patients in the BSC arm received another PD-1/PD-L1 checkpoint inhibitor as subsequent therapy vs 11% of patients in the BAVENCIO + BSC arm[2]

BSC, best supportive care; CI=confidence interval; PD-1=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 0.9% (16/1738) of patients, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (16/16) patients with hepatitis.

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

# BAVENCIO® (avelumab)—an established safety profile

**The WARNINGS AND PRECAUTIONS were established based on data from over 1700 patients treated with BAVENCIO 10 mg/kg across multiple tumor types, the majority of whom were treated with BAVENCIO monotherapy.**

## Summary of warnings and precautions

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

**Early identification and management of immune-mediated adverse reactions are essential** to ensure safe use of PD-1/PD-L1 blocking antibodies.

- Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions
- Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment
- In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection
- Institute medical management promptly, including specialty consultation as appropriate

**No dose reduction for BAVENCIO is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue BAVENCIO depending on severity**.

- In general, withhold BAVENCIO for severe (Grade 3) immune-mediated adverse reactions
- Permanently discontinue BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids
- In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade ≤1
  - Upon improvement to Grade ≤1, initiate corticosteroid taper and continue to taper over ≥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

**(Summary of warnings and precautions continues on next page)**

## 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% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction.

BAVENCIO can cause **immune-mediated thyroid disorders**. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism.

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## Summary of warnings and precautions (cont'd)

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

BAVENCIO can cause **immune-mediated colitis**.
- The primary component of immune-mediated colitis consisted of diarrhea
- Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies
- Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis
- Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions
- Systemic corticosteroids were required in all (26/26) patients with colitis

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

**(Summary of warnings and precautions continues on next page)**

## 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 0.1% (2/1738) of patients, including Grade 3 (0.1%) adverse reactions.

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

BAVENCIO can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions.

**Please see Selected Safety Information throughout and full Prescribing Information here.**

# BAVENCIO® (avelumab)—an established safety profile

**The WARNINGS AND PRECAUTIONS were established based on data from over 1700 patients treated with BAVENCIO 10 mg/kg across multiple tumor types, the majority of whom were treated with BAVENCIO monotherapy.**

## Summary of warnings and precautions (cont'd)

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

BAVENCIO can cause **immune-mediated hypophysitis**.
- Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects
- Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated
- Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity
- Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction

BAVENCIO can cause **immune-mediated thyroid disorders**.
- Thyroiditis can present with or without endocrinopathy
- Hypothyroidism can follow hyperthyroidism
- Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated
- Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity
- Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions
- Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions
  - Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism
- Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions
  - Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism

**(Summary of warnings and precautions continues on next page)**

## SELECTED SAFETY INFORMATION

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

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## Summary of warnings and precautions (cont'd)

BAVENCIO can cause **immune-mediated type I diabetes mellitus**, which can present with diabetic ketoacidosis.
- Monitor patients for hyperglycemia or other signs and symptoms of diabetes
- Initiate treatment with insulin as clinically indicated
- Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity
- Immune-mediated type I diabetes mellitus occurred in 0.1% (2/1738) of patients, including Grade 3 (0.1%) adverse reactions

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

BAVENCIO can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis.
- Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies
- Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes
- Withhold BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS
- Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions
- Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions

BAVENCIO can result in **other immune-mediated adverse reactions**.
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- For **myocarditis**, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4
- For **neurological toxicities**, withhold BAVENCIO for Grade 2 and permanently discontinue for Grade 3 or Grade 4

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## Summary of warnings and precautions (cont'd)

BAVENCIO can cause severe or life-threatening **infusion-related reactions**.
- Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions
- Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria
- Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions
- Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions
- Infusion-related reactions occurred in 25% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions
- Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids

Fatal and other serious **complications of allogeneic hematopoietic stem cell transplantation (HSCT)** can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.
- Follow patients closely for evidence of transplant-related complications and intervene promptly
- Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT

BAVENCIO 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

## SELECTED SAFETY INFORMATION

BAVENCIO can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids.

Fatal and other serious **complications of allogeneic hematopoietic stem cell transplantation (HSCT)** can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

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**Primary analysis, data cutoff October 21, 2019**[1]

**JAVELIN Bladder 100 Trial**—a Phase 3, randomized, open-label, multicenter study in patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing chemotherapy (N=689)[1]

# BAVENCIO® (avelumab)—adverse reaction profile

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

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

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

- 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%)

## Adverse reactions (≥10%) of patients receiving BAVENCIO + BSC

| 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* | 35 | 1.7 | 13 | 1.7 |
| Pyrexia | 15 | 0.3 | 3.5 | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Musculoskeletal pain† | 24 | 1.2 | 15 | 2.6 |
| Arthralgia | 16 | 0.6 | 6 | 0 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Rash‡ | 20 | 1.2 | 2.3 | 0 |
| Pruritus | 17 | 0.3 | 1.7 | 0 |
| **Infections and Infestations** | | | | |
| Urinary tract infection§ | 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‖ | 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 |

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

†Musculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain.

‡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.

§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.

‖Cough is a composite term that includes cough and productive cough.

**Please see Selected Safety Information throughout and full Prescribing Information here.**

**Primary analysis, data cutoff October 21, 2019**[1]

**JAVELIN Bladder 100 Trial**—a Phase 3, randomized, open-label, multicenter study in patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing chemotherapy (N=689)[1]

# BAVENCIO® (avelumab)—adverse reaction profile (cont'd)

## Discontinuation rates due to an adverse reaction

- In the BAVENCIO + best supportive care (BSC) arm (n=344), permanent discontinuation due to an adverse reaction occurred in **12%** of patients
  - Adverse reactions resulting in permanent discontinuation of BAVENCIO in >1% of patients were myocardial infarction (including acute myocardial infarction and troponin T increased) **(1.5%)** and infusion-related reaction **(1.2%)**

## Dose interruptions due to an adverse reaction

- In the BAVENCIO + BSC arm (n=344), dose interruptions due to an adverse reaction, excluding temporary interruptions of BAVENCIO infusions due to infusion-related reactions, occurred in **41%** of patients
  - Adverse reactions leading to interruption of BAVENCIO in >2% of patients were urinary tract infection (including pyelonephritis) **(4.7%)** and blood creatinine increased (including acute kidney injury, renal impairment, and renal failure) **(3.8%)**

## Selected laboratory abnormalities worsening from baseline occurring in ≥10% of patients receiving BAVENCIO + BSC

| Laboratory Abnormality | BAVENCIO + BSC* | | BSC* | |
|---|---|---|---|---|
| | Any Grade % | Grades 3-4 % | Any Grade % | 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 |

*Each 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 to 344 patients) and BSC group (range: 329 to 341 patients).

**References: 1.** Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2020;383(13):1218-1230. **2.** Data on file. Pfizer Inc., New York, NY. **3.** BAVENCIO [prescribing information]. Rockland, MA: EMD Serono, Inc; New York, NY: Pfizer Inc.

## SELECTED SAFETY INFORMATION

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.

A **fatal adverse reaction** (sepsis) occurred in one (0.3%) patient with **locally advanced or metastatic urothelial carcinoma (UC)** receiving BAVENCIO + 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 BAVENCIO 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 BAVENCIO + 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 BAVENCIO, 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** (all grades, ≥20%) in patients with **locally advanced or metastatic UC** receiving BAVENCIO + 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%).

**Please see Selected Safety Information throughout and full Prescribing Information here.**



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