BAVENCIO® (avelumab) in Combination With Axitinib

For the first-line treatment of patients with advanced renal cell carcinoma (RCC)

January 2024| US-AVE-01337

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

Important Notices

- Avelumab has been approved by the FDA and is under investigation for the treatment of various diseases. Efficacy and safety of avelumab are still under investigation for various indications. Regulatory approval is dependent on the completion of the study programs and review by the FDA. Clinical trial information is available at www.clinicaltrials.gov.
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Table of Contents

FDA-Approved Indication

Advanced renal cell carcinoma

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

BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf .

Menu

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Avelumab and Axitinib

Mechanism of Action

Avelumab and Axitinib: One Treatment Regimen, Two Different MOAs

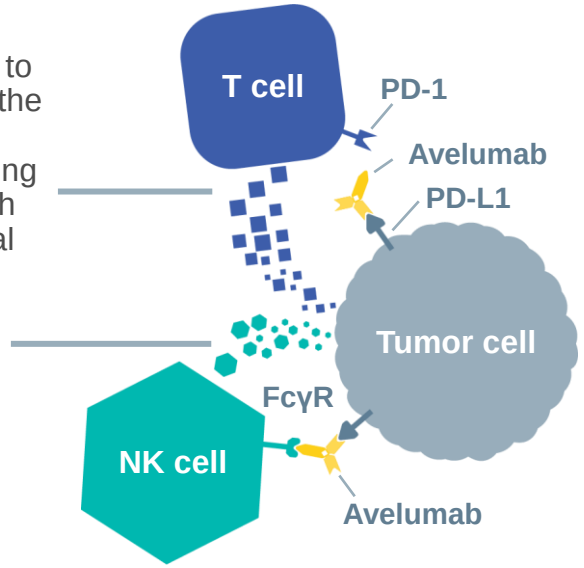
The combination of an immune checkpoint inhibitor and TKI therapy acts on 2 pathways[1]

Avelumab and the PD-L1 pathway

RCC is an immunogenic tumor in which PD-L1 expression can contribute to the inhibition of the antitumor response.[2-4]

Avelumab 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 models.[3-6]

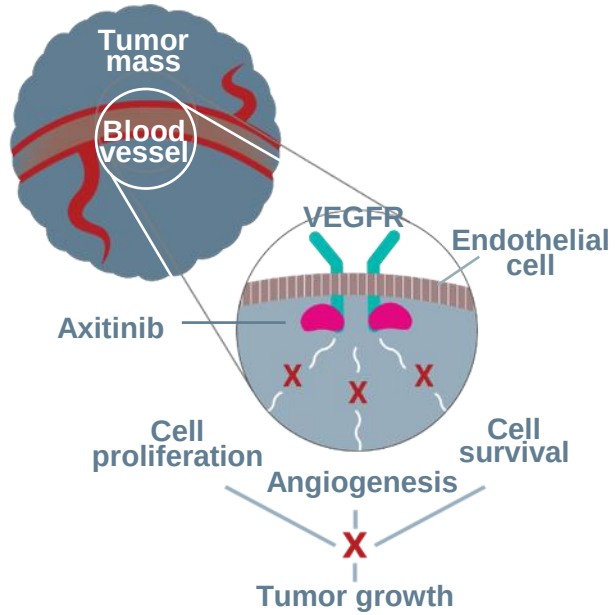
Avelumab has also been shown to induce NK-cell-mediated direct tumor cell lysis via ADCC in vitro.[4,6-8]



Axitinib and the VEGF pathway

RCC is a highly vascular tumor in which VEGF plays a key role. VEGF acts on 3 receptors: VEGFR-1, -2, and -3, which are implicated in pathologic angiogenesis, tumor growth, and cancer progression.[9,10]

Axitinib has been shown to inhibit receptor tyrosine kinases, including VEGFR-1, VEGFR-2, and VEGFR-3. VEGF-mediated endothelial cell proliferation and survival were inhibited by axitinib in vitro and in mouse models. Axitinib was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in mouse models.[10]



Preclinical and in vitro data may not necessarily correlate with clinical outcomes.

ADCC, antibody-dependent cell-mediated cytotoxicity; FcγR, Fc receptor; MOAs, mechanisms of action; NK, natural killer; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

References: 1. Motzer RJ, et al. *N Engl J Med.* 2019;380(12):1103-1115. **2.** Itsumi M, Tatsugami K. *Clin Dev Immunol.* 2010;2010:284581. doi: 10.1155/2010/284581. **3.** Dolan DE, Gupta S. *Cancer Control.* 2014;21(3):231-237. **4.** BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf. **5.** Dahan R, et al. *Cancer Cell.* 2015;28(3):285-295. **6.** Hamilton G, Rath B. *Expert Opin Biol Ther.* 2017;17(4):515-523. **7.** Kohrt HE, et al. *Immunotherapy.* 2012;4(5):511-527. **8.** Boyerinas B, et al. *Cancer Immunol Res.* 2015;3(10):1148-1157. **9.** Qian CN, et al. *Cancer.* 2009;115(suppl 10):2282-2289. **10.** INLYTA® Prescribing Information. Pfizer, Inc. US; 2022.

Menu

JAVELIN Renal 101

Study Design

Avelumab in Combination With Axitinib Was Studied in the First-Line Treatment of Patients With Advanced RCC[1-3]

In the JAVELIN Renal 101 Trial — A Phase 3, Randomized, Open-label, Multicenter Study (N=886)

Study design

N=886

Key Inclusion Criteria:

- Previously untreated advanced RCC with clear-cell component
- ≥1 measurable lesion defined by RECIST v1.1
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0 or 1)

Key Exclusion Criteria:

- Patients with autoimmune disease other than type I diabetes mellitus, vitiligo, psoriasis, or thyroid disorders not requiring immunosuppressive treatment

1:1 randomization
Stratified by ECOG PS (0 vs 1) and geographic region[a]

n=442
Avelumab 10 mg/kg intravenous infusion every 2 weeks + axitinib 5 mg orally twice daily

- Until radiographic or clinical progression or unacceptable toxicity
- Dose modifications permitted

n=444
Sunitinib 50 mg orally once daily 4 weeks on, 2 weeks off

Outcome Measures

Primary Endpoints

- Progression-free survival (PFS)[b,] and overall survival (OS) in patients with PD-L1-positive tumors[c]

Key Secondary Endpoints

- PFS[b,d] and OS in the ITT population

Additional Secondary Endpoints

ORR, safety, PK, biomarkers, PROs

- Administration of avelumab and axitinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator[1]
- Assessment of tumor status was performed at baseline, after randomization at 6 weeks, then every 6 weeks thereafter up to 18 months after randomization, and every 12 weeks thereafter until documented confirmed disease progression by BICR[1]

If PFS was statistically significant in patients with PD-L1-positive tumors, it was then tested in the intent-to-treat (ITT) population, which included patients regardless of tumor PD-L1 expression[1]

BICR, Blinded Independent Central Review; ITT, intent-to-treat; ORR, objective response rate; PK, pharmacokinetics; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors.
a, United States vs Canada/Western Europe vs the rest of the world.[1] b, Assessed by a BICR using RECIST v1.1.[1] c, PD-L1 expression level ≥1% of immune cells staining positive within the tumor area of the tested tissue sample by Ventana PD-L1 (SP263) assay (Ventana Medical Systems).[1,2] d, Per investigator assessment.[1]

References: 1. BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf. **2.** Motzer RJ, et al. *N Engl J Med.* 2019;380(12):1103-1115. **3.** NCT02684006. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02684006. Updated June 29, 2020. Accessed July 28, 2020.

Menu

JAVELIN Renal 101

Study Results

Avelumab in Combination With Axitinib Was Studied in the First-Line Treatment of Patients With Advanced RCC[1,2]

In the JAVELIN Renal 101 Trial — A Phase 3, Randomized, Open-label, Multicenter Study (N=886)

Selected Baseline Characteristics (N=886)[1]	
Median age, years (range)	61 (27, 88)
≥65 years, %	38
Male, %	75
White, %	75
ECOG PS, %	
0	63
1	37
Prognostic risk group according to IMDC, %[a]	
Favorable	21
Intermediate	62
Poor	16

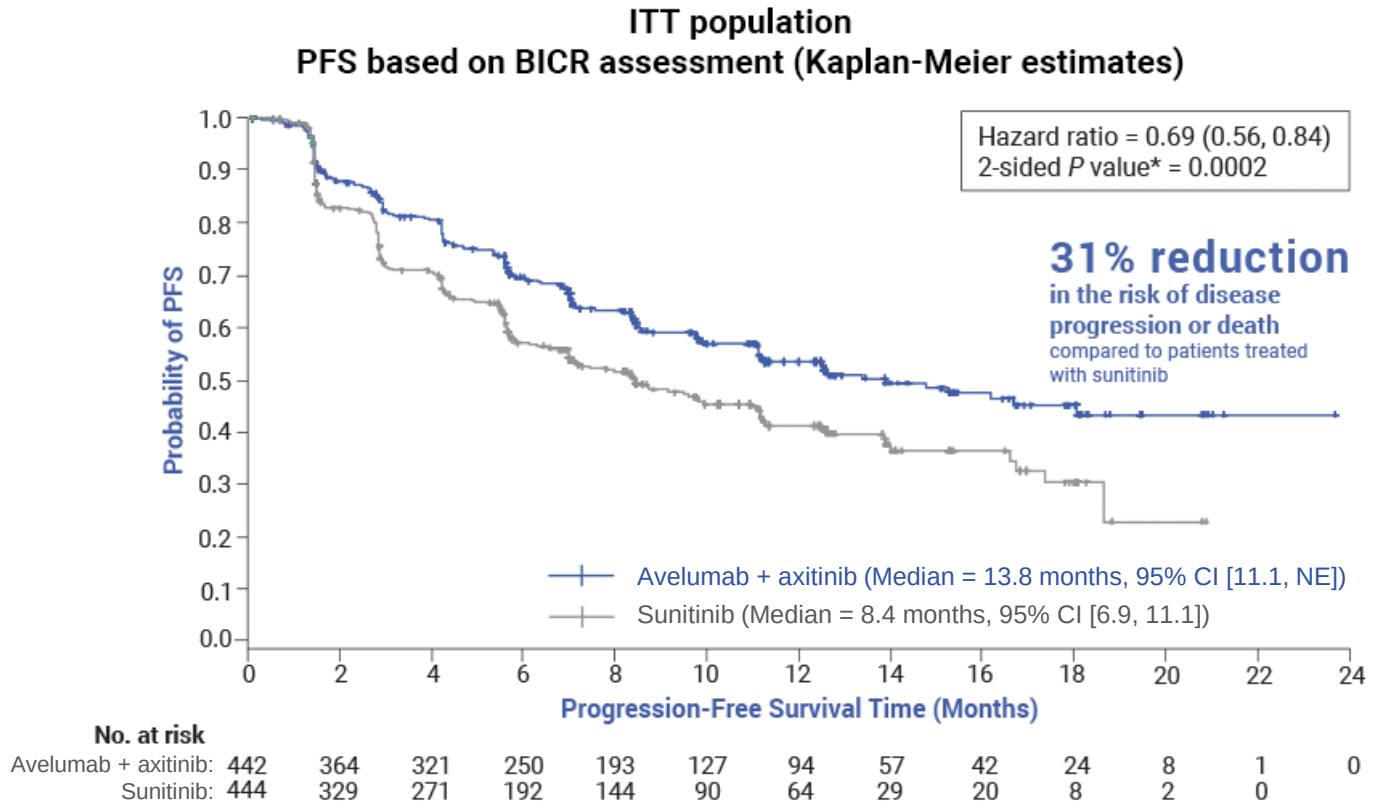
- IMDC risk groups were classified based on 6 prognostic factors that impact survival[2]
- IMDC risk scores were defined according to the number of the following risk factors present[2]:
  - Karnofsky Performance Status score of less than 80, time from initial diagnosis to randomization of less than 1 year, hemoglobin level below the LLN range, corrected serum calcium level above the ULN range, absolute neutrophil count above the ULN range, and platelet count above the ULN
- Patients with favorable risk had an IMDC score of 0, those with intermediate risk had a score of 1 or 2, and those with poor risk had a score of 3 to 6[2]

ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; LLN, lower limit of normal; ULN, upper limit of normal.
a, Not reported, <1%. Percentages may not total 100 because of rounding.[2]

References: 1. BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf. **2.** Motzer RJ, et al. *N Engl J Med.* 2019;380(12):1103-1115.

Avelumab in Combination With Axitinib Demonstrated an Improvement in PFS vs Sunitinib[1,2]

In the JAVELIN Renal 101 Trial – A Phase 3, Randomized, Open-label, Multicenter Study (N=886)



Since PFS was statistically significant in patients with PD-L1 positive tumors (HR 0.61 [95% CI: 0.48, 0.79]), it was then tested in the ITT population and a statistically significant improvement in PFS in the ITT population was also demonstrated.

BICR, Blinded Independent Central Review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; PD-L1, programmed death ligand-1; PFS, progression free survival.
a, *P* value based on stratified log-rank.

References: 1. BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.
2. NCT02684006. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02684006. Updated June 29, 2020. Accessed July 28, 2020.

Avelumab in Combination With Axitinib Efficacy Results[1,2]

In the JAVELIN Renal 101 Trial – A Phase 3, Randomized, Open-label, Multicenter Study (N=886)

Efficacy results from JAVELIN Renal 101 Trial–ITT population

Efficacy Endpoints (Based on BICR Assessment)	Avelumab + Axitinib (n=442)	Sunitinib (n=444)
Progression-Free Survival (PFS)		
Events (%)	180 (41)	216 (49)
Median in months (95% CI)	13.8 (11.1, NE)	8.4 (6.9, 11.1)
Hazard ratio (95% CI)	0.69 (0.56, 0.84)	
2-sided *P*-value[a]	0.0002	
Confirmed Objective Response Rate (ORR)		
Objective response rate, n (%)	227 (51.4)	114 (25.7)
(95% CI)	(46.6, 56.1)	(21.7, 30.0)
Complete response, n (%)	15 (3.4)	8 (1.8)
Partial response, n (%)	212 (48)	106 (24)

Overall survival (OS)

With a median OS follow-up of 19 months, OS data were immature with 27% deaths in the ITT population[1]

BICR, Blinded Independent Central Review; CI, confidence interval; ITT, intention-to-treat; NE, not estimable.
a, *P* value based on stratified log-rank.[1]

References: 1. BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf. **2.** NCT02684006. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02684006. Updated July 30, 2019. Accessed July 28, 2020.

Adverse Reactions

In the JAVELIN Renal 101 Trial — A Phase 3, Randomized, Open-label, Multicenter Study (N=873)

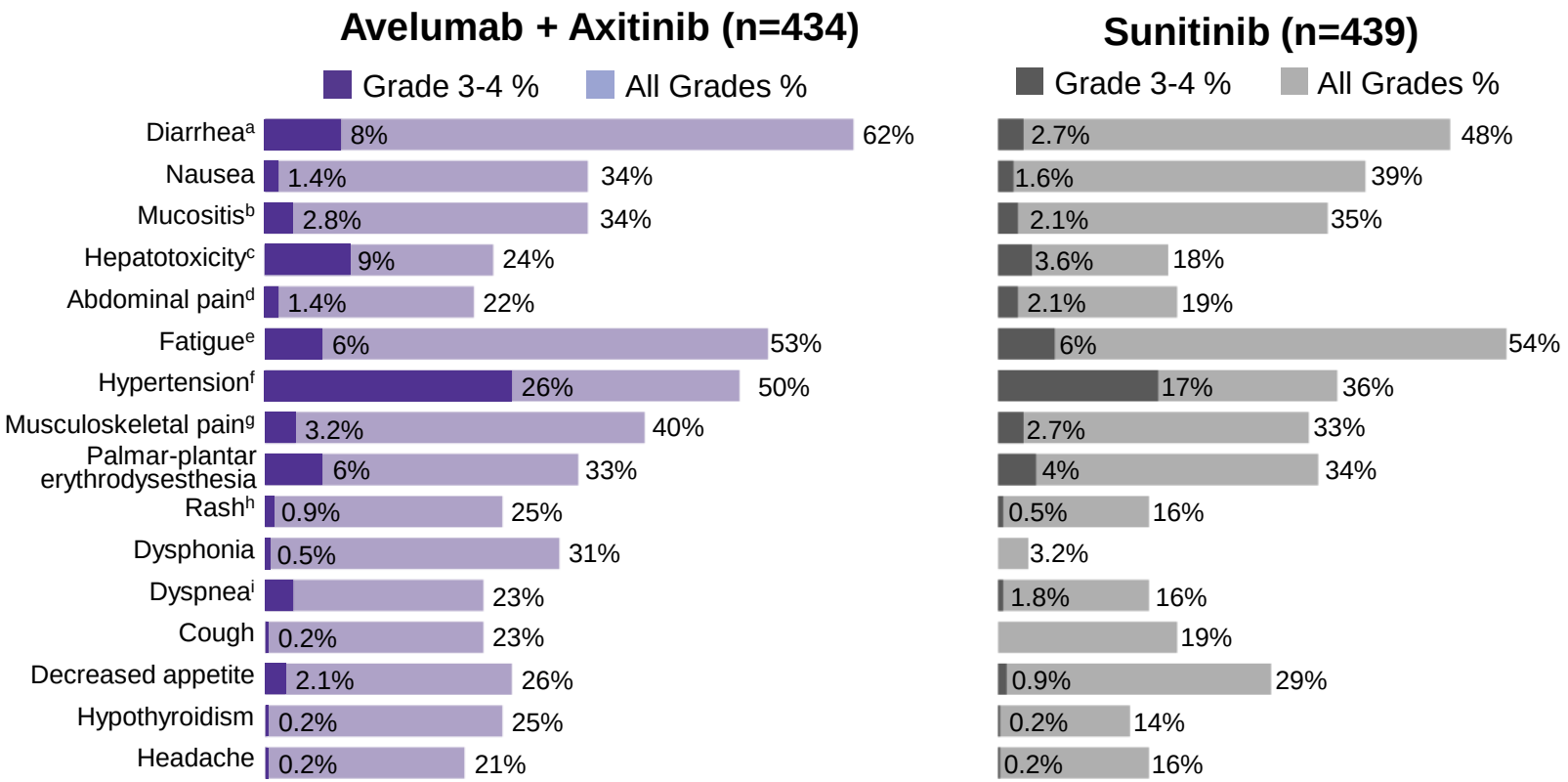
- Fatal adverse reactions occurred in 1.8% of patients receiving avelumab in combination with axitinib
  - These included sudden cardiac death (1.2%), stroke (0.2%), myocarditis (0.2%), and necrotizing pancreatitis (0.2%)
- Serious adverse reactions occurred in 35% of patients receiving avelumab in combination with axitinib
  - Serious adverse reactions reported in ≥1% of patients included diarrhea (2.5%), dyspnea (1.8%), hepatotoxicity (1.8%), venous thromboembolic disease (1.6%), acute kidney injury (1.4%), and pneumonia (1.2%)
- Forty-eight (11%) patients treated with avelumab in combination with axitinib received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction
- Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Infusion-related reactions occurred in 12% (Grade 3: 1.6%; no Grade 4) of patients treated with avelumab in combination with axitinib

Reference: BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Adverse Reactions

In the JAVELIN Renal 101 Trial — A Phase 3, Randomized, Open-label, Multicenter Study (N=873)

Adverse Reactions (≥20%) of patients receiving avelumab in combination with axitinib



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

[a] Diarrhea is a composite term that includes diarrhea, autoimmune colitis, and colitis.

[b] Mucositis is a composite term that includes mucosal inflammation and stomatitis.

[c] Hepatotoxicity is a composite term that includes ALT increased, AST increased, autoimmune hepatitis, bilirubin conjugated, bilirubin conjugated increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis fulminant, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, liver disorder, liver injury, transaminases increased.

[d] Abdominal pain is a composite term that includes abdominal pain, flank pain, abdominal pain upper, and abdominal pain lower.

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

[f] Hypertension is a composite term that includes hypertension and hypertensive crisis.

[g] Musculoskeletal pain is a composite term that includes musculoskeletal pain, musculoskeletal chest pain, myalgia, back pain, bone pain, musculoskeletal discomfort, neck pain, spinal pain, and pain in extremity.

[h] Rash is a composite term that includes rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash erythematous, rash papular, and rash pustular.

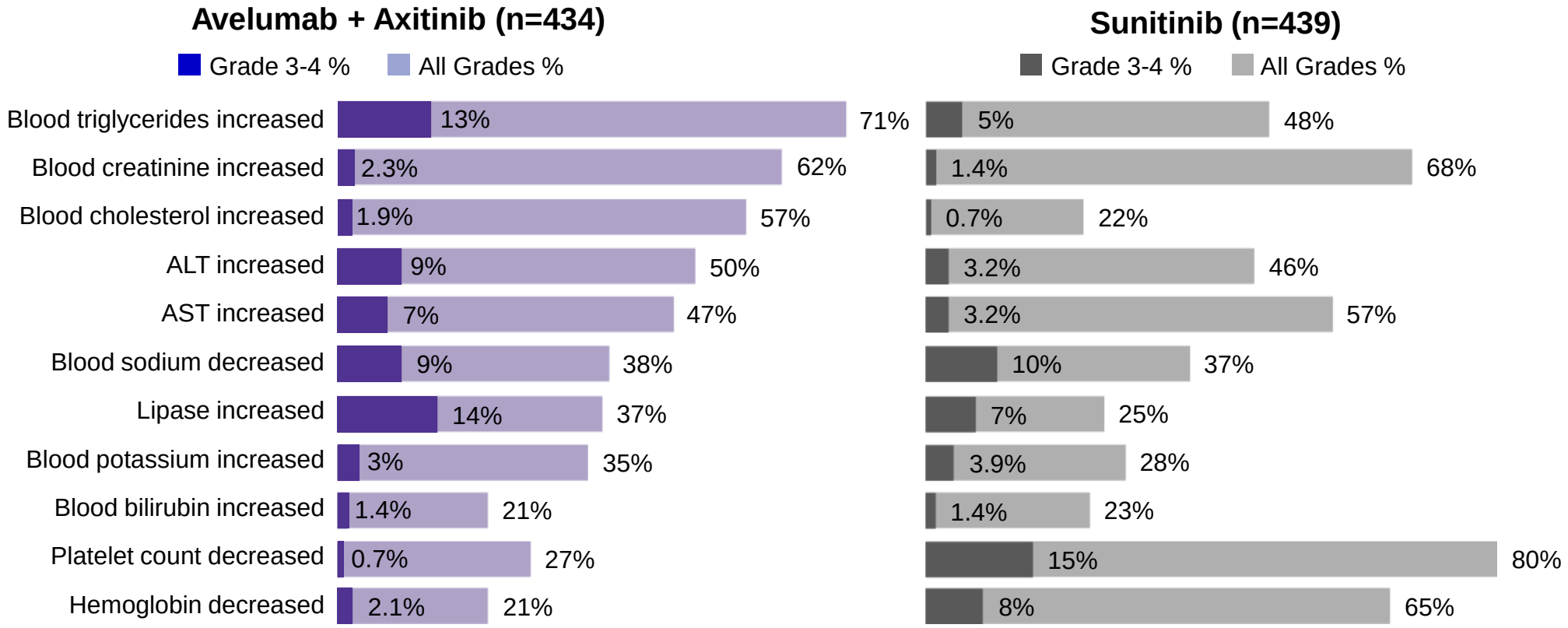
[i] Dyspnea is a composite term that includes dyspnea, dyspnea exertional, and dyspnea at rest.

Reference: BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Laboratory Abnormalities

In the JAVELIN Renal 101 Trial — A Phase 3, Randomized, Open-label, Multicenter Study (N=873)

Selected laboratory abnormalities worsening from baseline occurring in ≥20% of patients receiving avelumab in combination with axitinib[a]



ALT, alanine aminotransferase; AST, aspartate aminotransferase.
a, Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Avelumab in combination with axitinib group (range: 413 to 428 patients) and sunitinib group (range: 405 to 433 patients).

Reference: BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Dose Modification Rates due to Adverse Reactions

In the JAVELIN Renal 101 Trial — A Phase 3, Randomized, Open-label, Multicenter Study (N=873)

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

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

a, Excluding temporary interruptions of avelumab infusions due to infusion-related reactions.

Reference: BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Dosing

Administration and Dose Modifications

Recommended Dosage for Avelumab in Combination With Axitinib

- The recommended dose of avelumab is 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks in combination with axitinib 5 mg orally taken twice daily (12 hours apart) with or without food until disease progression or unacceptable toxicity
- When axitinib is used in combination with avelumab, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of two weeks or longer
  - Review the full Prescribing Information for axitinib prior to initiation

Adverse reaction management

Management of some adverse reactions may require temporary interruption or permanent discontinuation of either or both medicines

Premedication

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

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

Reference: BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Axitinib Dose and Administration

- The recommended starting dosage of axitinib is 5 mg orally taken twice daily (12 hours apart) with or without food in combination with avelumab 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. When axitinib is used in combination with avelumab, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of two weeks or longer.

Dose Titration

Dose can be increased or decreased based on individual safety and tolerability

Half-life

The half-life of axitinib ranges from 2.5 to 6.1 hours

- For patients with moderate hepatic impairment, or for patients on a strong CYP3A4/5 inhibitor, decrease the axitinib dose by approximately half
- Swallow whole with a glass of water

Reference: INLYTA® Prescribing Information. Pfizer, Inc. US; 2022.

Axitinib Recommended Dose Modifications

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

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

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

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

Dose increase criteria: Patients tolerate axitinib for at least 2 consecutive weeks with no AEs >Grade 2 and are normotensive without anti-hypertension medication

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

AE, adverse event.

Reference: INLYTA® Prescribing Information. Pfizer, Inc. US; 2022.

Axitinib Recommended Dose Modifications (cont'd)

In patients being treated with axitinib in combination with avelumab

Liver enzyme elevations

- If ALT or AST ≥3 times ULN but <10 times ULN without concurrent bilirubin ≥2 times ULN, withhold axitinib and avelumab until resolution to Grades 0–1. Consider rechallenge with axitinib and/or avelumab
- If ALT or AST increases to >3 times ULN with concurrent total bilirubin ≥2 times ULN or ALT or AST ≥10 times ULN, permanently discontinue axitinib and avelumab

Diarrhea

- If Grade 1–2, initiate symptomatic medications
- If Grade 3, interrupt axitinib and initiate symptomatic medications. If diarrhea is controlled, axitinib may be resumed at either the same dose or reduced by 1 dose level
- If Grade 4, withhold axitinib until resolution to Grade <2, then restart axitinib dose reduced by 1 dose level

Review the Full Prescribing Information for additional dose modifications for avelumab

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

Reference: INLYTA® Prescribing Information. Pfizer, Inc. US; 2022.

Axitinib Other Dosing Considerations

- For patients with moderate hepatic impairment, or for patients on a strong CYP3A4/5 inhibitor, decrease the axitinib dose by approximately half
- Avoid strong CYP3A4/5 inhibitors. If unavoidable, reduce the dose of axitinib
- Avoid strong CYP3A4/5 inducers and, if possible, avoid moderate CYP3A4/5 inducers
- Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided
- Stop treatment with axitinib at least 2 days prior to elective surgery. Do not re-administer axitinib for at least 2 weeks following major surgery and until adequate wound healing

Reference: INLYTA® Prescribing Information. Pfizer, Inc. US; 2022.

Summary of Warnings and Precautions

BAVENCIO® (avelumab) Summary of Warnings and Precautions

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to avelumab 10 mg/kg intravenously every 2 weeks as a single agent in 1854 patients enrolled in 2 trials and to avelumab 10 mg/kg intravenously every 2 weeks in combination with axitinib 5 mg orally twice daily in 489 patients enrolled in the JAVELIN Renal 100 and JAVELIN Renal 101 trials.

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**
- **Major adverse cardiovascular events**
- **Embryo-fetal toxicity**

Reference: BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Avelumab Summary of Warnings and Precautions

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

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies	• Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions • Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment • In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection • Institute medical management promptly, including specialty consultation as appropriate
No dose reduction for avelumab is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue avelumab depending on severity	• In general, withhold avelumab for severe (Grade 3) immune-mediated adverse reactions • Permanently discontinue avelumab for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids • In general, if avelumab requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy • Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections

Reference: BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Avelumab Summary of Warnings and Precautions (cont'd)

Avelumab can cause immune-mediated pneumonitis	• Withhold avelumab for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis • Immune-mediated pneumonitis occurred in 1.1% (21/1854) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions • Systemic corticosteroids were required in all (21/21) patients with pneumonitis
Avelumab can cause immune-mediated colitis	• The primary component of immune-mediated colitis consisted of diarrhea • Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis • In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies • Withhold avelumab for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis • Immune-mediated colitis occurred in 1.5% (27/1854) of patients, including Grade 3 (0.4%) and Grade 2 (0.8%) adverse reactions • Systemic corticosteroids were required in all (27/27) patients with colitis

Reference: BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Avelumab Summary of Warnings and Precautions (cont'd)

Avelumab can cause hepatotoxicity and immune-mediated hepatitis	• Withhold or permanently discontinue avelumab based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation • Immune-mediated hepatitis occurred with avelumab as a single agent in 1.1% (20/1854) of patients, including fatal (0.1%), Grade 3 (0.8%), and Grade 2 (0.2%) adverse reactions • Systemic corticosteroids were required in all (20/20) patients with hepatitis
Avelumab in combination with axitinib can cause hepatotoxicity with higher than expected frequencies of Grade 3 and 4 ALT and AST elevation compared to avelumab alone	• Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy • Withhold or permanently discontinue both avelumab and axitinib based on severity of AST, ALT, or total bilirubin elevation, and consider administering corticosteroids as needed • Consider rechallenge with avelumab or axitinib, or sequential rechallenge with both avelumab and axitinib, after recovery • In patients treated with avelumab in combination with axitinib in the advanced RCC trials, increased ALT and increased AST were reported in 9% (Grade 3) and 7% (Grade 4) of patients • Immune-mediated hepatitis was reported in 7% of patients including 4.9% with Grade 3 or 4 immune-mediated hepatitis • Thirty-four patients were treated with corticosteroids and one patient was treated with a non-steroidal immunosuppressant

Reference: BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Avelumab Summary of Warnings and Precautions (cont'd)

Avelumab can cause primary or secondary immune-mediated adrenal insufficiency	• For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated • Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity • Immune-mediated adrenal insufficiency occurred in 0.6% (11/1854) of patients, including Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions • Systemic corticosteroids were required in all (11/11) patients with adrenal insufficiency
Avelumab can cause immune-mediated hypophysitis	• Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects • Hypophysitis can cause hypopituitarism • Initiate hormone replacement, as clinically indicated • Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity • Immune-mediated pituitary disorders occurred in 0.1% (1/1854) of patients, which was a Grade 2 (0.1%) adverse reaction

Reference: BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf.

Avelumab Summary of Warnings and Precautions (cont'd)

Avelumab can cause immune-mediated thyroid disorders	• Thyroiditis can present with or without endocrinopathy • Hypothyroidism can follow hyperthyroidism • Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated • Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity • Thyroiditis occurred in 0.2% (4/1854) of patients, including Grade 2 (0.1%) adverse reactions • Hyperthyroidism occurred in 0.4% (8/1854) of patients, including Grade 2 (0.3%) adverse reactions • Systemic corticosteroids were required in 25% (2/8) of patients with hyperthyroidism • Hypothyroidism occurred in 5% (97/1854) of patients, including Grade 3 (0.2%) and Grade 2 (3.6%) adverse reactions • Systemic corticosteroids were required in 6% (6/97) of patients with hypothyroidism
Avelumab can cause immune-mediated type I diabetes mellitus, which can present with diabetic ketoacidosis	• Monitor patients for hyperglycemia or other signs and symptoms of diabetes • Initiate treatment with insulin as clinically indicated • Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity • Immune-mediated type I diabetes mellitus occurred in 0.2% (3/1854) of patients, including Grade 3 (0.2%) adverse reactions

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Avelumab Summary of Warnings and Precautions (cont'd)

Avelumab can cause immune-mediated nephritis with renal dysfunction	• Withhold avelumab for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine • Immune-mediated nephritis with renal dysfunction occurred in 0.1% (2/1854) of patients, including Grade 3 (0.1%) and Grade 2 (0.1%) adverse reactions • Systemic corticosteroids were required in all (2/2) patients with nephritis with renal dysfunction
Avelumab can cause immune-mediated dermatologic adverse reactions, including rash or dermatitis	• Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies • Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes • Withhold avelumab for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS • Immune-mediated dermatologic adverse reactions occurred in 6% (108/1854) of patients, including Grade 3 (0.1%) and Grade 2 (1.9%) adverse reactions • Systemic corticosteroids were required in 25% (27/108) of patients with dermatologic adverse reactions
Avelumab can result in other immune-mediated adverse reactions	• Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received avelumab or were reported with the use of other PD-1/PD-L1 blocking antibodies • For **myocarditis**, permanently discontinue avelumab for Grade 2, Grade 3, or Grade 4 • For **neurological toxicities**, withhold avelumab for Grade 2 and permanently discontinue for Grade 3 or Grade 4

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Avelumab Summary of Warnings and Precautions (cont'd)

Avelumab can cause severe or life-threatening infusion-related reactions	• Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions • Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria • Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions • Permanently discontinue avelumab for Grade 3 or Grade 4 infusion-related reactions • Infusion-related reactions occurred in 26% of patients, including 3 (0.2%) Grade 4 and 10 (0.5%) Grade 3 infusion-related reactions • Eleven (85%) of the 13 patients with Grade ≥3 reactions were treated with intravenous corticosteroids
Complications of allogeneic hematopoietic stem cell transplantation (HSCT)	• 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 vs risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT

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Avelumab Summary of Warnings and Precautions (cont'd)

Avelumab in combination with axitinib can cause major adverse cardiovascular events (MACE) including severe and fatal events	• Consider baseline and periodic evaluations of left ventricular ejection fraction • Monitor for signs and symptoms of cardiovascular events • Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia • Permanently discontinue avelumab and axitinib for Grade 3-4 cardiovascular events • MACE occurred in 7% of patients with advanced RCC treated with avelumab in combination with axitinib compared to 3.4% treated with sunitinib in a randomized trial • These events included death due to cardiac events (1.4%), Grade 3-4 myocardial infarction (2.8%), and Grade 3-4 congestive heart failure (1.8%)
Avelumab can cause fetal harm when administered to a pregnant woman	• Advise patients of the potential risk to a fetus including the risk of fetal death • Advise females of childbearing potential to use effective contraception during treatment with avelumab and for at least 1 month after the last dose of avelumab • It is not known whether avelumab is excreted in human milk • Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of avelumab due to the potential for serious adverse reactions in breastfed infants

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