CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761049Orig1s009

Trade Name:	**Bavencio injection, for intravenous use**
Generic or Proper Name:	(avelumab)
Sponsor:	EMD Serono
Approval Date:	June 30, 2020
Indication:	For the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

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761049Orig1s009

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APPLICATION NUMBER:

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APPROVAL LETTER

BLA 761049/S-009

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
REQUIREMENT

EMD Serono, Inc.
Attention: Jennifer L. Stevens, JD
Executive Director
US Hub Lead/Global Regulatory Program Lead
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Stevens:

Please refer to your supplemental biologics license application dated April 7, 2020, received April 7, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Bavencio (avelumab) Injection.

This Prior Approval supplemental biologics application provides for a new indication for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

We also refer to your biologics license application (BLA) 761078, approved May 9, 2017, under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART E FULFILLED

As noted above, we approved BLA 761078 under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses (21 CFR 601.41) and required further adequate and well-controlled clinical trials to verify and describe the clinical benefit of avelumab. Therefore, you were required to conduct postmarketing requirement 3201-1. Because BLA 761078 was administratively closed on the date of its approval, all submissions and reports for BLA 761078 were addressed to BLA 761049.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated April 7, 2020, containing the final report for the following postmarketing requirement listed in the May 17, 2019, approval letter for BLA 761078.

3201-1	Conduct "Javelin Bladder 100: A Phase 3, Multicenter, Multinational, Randomized, Open-label Parallel-arm Study of Avelumab Plus Best Supportive Care Versus Best Supportive Care Alone as a Maintenance Treatment in patients with Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion of First-line Platinum-containing Chemotherapy" and provide a final report, datasets, and revised labeling.

We have reviewed your submission and conclude that the above requirement was fulfilled.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Approval of this supplement fulfills your requirement made under 21 CFR 601.41 for BLA 761078.

We remind you that there is a postmarketing commitment listed in the May 9, 2017, approval letter for BLA 761078 that is still open.

In addition, we remind you that the required postmarketing study (PMR 3185-1) for BLA 761049, under the accelerated approval regulations (21 CFR 601.41), remains open.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for this application because necessary studies are impossible or highly impracticable in children. Urothelial carcinoma occurs, for the most part, in the adult population. The incidence of this cancer type in pediatric patients is extremely rare and as such, clinical pediatric studies are impossible or highly impracticable.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since avelumab was approved on March 23, 2017, we have become aware of a signal of increased incidence of adverse events in patients with treatment-induced anti-drug antibodies leading to dose reduction and discontinuation of avelumab, and infusion related reactions observed in clinical trials. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess this signal of serious risk of increased adverse events.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3882 -1 Reanalyze anti-drug antibodies (ADA) in the stored samples from 249 avelumab-treated patients with urothelial cancer (UC) (Study EMR100070-001) and 88 avelumab-treated patients with Merkel cell carcinoma (MCC) (Study EMR100070-003 Part A) that are evaluable for treatment-emergent ADA with the new ADA method. Using the updated treatment-emergent ADA data from the above two studies and emerging treatment-emergent ADA data from approximately 350 patients with UC in Study B9991001, assess the effect of treatment-emergent ADA on safety endpoints in patients with metastatic MCC or locally advanced or metastatic UC. The final report should include the following analyses and datasets:

a) Individual trial analyses assessing the effects of ADA on safety as the numbers of treatment-emergent adverse events (TEAEs), Grade 3-4 TEAEs, serious TEAEs, TEAEs leading to discontinuation, and infusion-related reactions (IRRs).

b) The ADA rate; median time to detection of ADA; median duration of ADA positivity in months, and the numbers of doses (before/after first detection of ADA and total) received in patients with treatment-emergent ADA.

c) Effect of “early” ADA (e.g., based on ADA at Week 5 or at another early visit with adequate justification) on safety outcome measures (TEAEs), Grade 3-4 TEAEs, serious TEAEs, TEAEs leading to discontinuation, and IRRs) in individual trials.

For all analyses performed, include the following information in the final study report: the model codes and output listings; all datasets as a SAS transport files (*.xpt); and a description of each data item in a define.xml file.

The timetable you submitted on June 17, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	09/2020
Final Report Submission:	03/2021

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocols to Pfizer's IND 126217, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3882 - 2 Submit the final overall survival analysis and datasets from clinical trial JAVELIN Bladder 100 titled; *A phase 3 Multicenter, Multinational, Randomized, Open Label, Parallel-Arm Study of Avelumab Plus Best Supportive Care Versus Best Supportive Care Alone As a Maintenance Treatment in Patients With Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion of First-Line Platinum-Containing Chemotherapy,* to provide additional efficacy data for avelumab as maintenance treatment in patients with advanced or metastatic urothelial cancer that may inform product labeling.

The timetable you submitted on June 17, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	06/2021
Final Report Submission:	12/2021

Submit clinical protocols to Pfizer's IND 126217 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Rajesh Venugopal, Senior Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Director
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMNA IBRAHIM
06/30/2020 04:13:51 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761049Orig1s009

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BAVENCIO safely and effectively. See full prescribing information for BAVENCIO.

BAVENCIO® (avelumab) injection, for intravenous use
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------
Indication and Usage (1.2) 06/2020

----------INDICATIONS AND USAGE----------
BAVENCIO is a programmed death ligand-1 (PD-L1) blocking antibody indicated for:
Merkel Cell Carcinoma (MCC)
- Adults and pediatric patients 12 years and older with metastatic MCC. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1, 14.1)

Urothelial Carcinoma (UC)
- Maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy. (1.2, 14.2)
- Patients with locally advanced or metastatic UC who:
  - Have disease progression during or following platinum-containing chemotherapy. (1.2 14.2)
  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.2, 14.2)

Renal Cell Carcinoma (RCC)
- First-line treatment, in combination with axitinib, of patients with advanced RCC. (1.3, 14.3)

----------DOSAGE AND ADMINISTRATION----------
- Premedicate for the first 4 infusions and subsequently as needed. (2.1)
- Merkel Cell Carcinoma: 800 mg every 2 weeks. (2.2)
- Urothelial Carcinoma; 800 mg every 2 weeks. (2.3)
- Renal Cell Carcinoma: 800 mg every 2 weeks in combination with axitinib 5 mg orally twice daily. (2.4)

Administer BAVENCIO as an intravenous infusion over 60 minutes

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 200 mg/10 mL (20 mg/mL) solution in single-dose vial. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Immune-mediated pneumonitis: Withhold for moderate pneumonitis; permanently discontinue for severe, life-threatening, or recurrent moderate pneumonitis. (5.1)
- Hepatotoxicity and immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate hepatitis; permanently discontinue for severe or life-threatening hepatitis. (5.2)
- Immune-mediated colitis: Withhold for moderate or severe colitis; permanently discontinue for life-threatening or recurrent severe colitis. (5.3)
- Immune-mediated endocrinopathies: Withhold for severe or life-threatening endocrinopathies. (5.4)
- Immune-mediated nephritis and renal dysfunction: Withhold for moderate or severe nephritis and renal dysfunction; permanently discontinue for life-threatening nephritis or renal dysfunction. (5.5)
- Infusion-related reactions: Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe or life-threatening infusion-related reactions. (5.7)
- Major adverse cardiovascular events: Optimize management of cardiovascular risk factors. Discontinue BAVENCIO in combination with axitinib for Grade 3-4 events. (5.8)
- Embryo-fetal toxicity: BAVENCIO can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.9, 8.1, 8 3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥ 20%) in patients were:
- MCC: fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema. (6.1)
- UC:
  - Maintenance treatment: fatigue, musculoskeletal pain, urinary tract infection, and rash. (6.1)
  - Previously-treated: fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection. (6.1)
- RCC (with axitinib): diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext. 5563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

APPEARS THIS WAY ON ORIGINAL

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Merkel Cell Carcinoma

BAVENCIO (avelumab) is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC). This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials *[see Clinical Studies (14.1)]*.

1.2 Locally Advanced or Metastatic Urothelial Carcinoma

First-Line Maintenance Treatment of Urothelial Carcinoma

BAVENCIO is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy *[see Clinical Studies (14.2)]*.

Previously-Treated Urothelial Carcinoma

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

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *[see Clinical Studies (14.2)]*.

1.3 Advanced Renal Cell Carcinoma

BAVENCIO in combination with axitinib is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC) *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 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 upon clinical judgment and presence/severity of prior infusion reactions *[see Dosage and Administration (2.5) and Warnings and Precautions (5.7)]*.

2.2 Recommended Dosage for MCC

The recommended dose of BAVENCIO is 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.3 Recommended Dosage for UC

The recommended dose of BAVENCIO is 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.4 Recommended Dosage for RCC

The recommended dose of BAVENCIO 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 BAVENCIO, 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.

2.5 Dose Modifications

Recommended dose modifications of BAVENCIO for adverse reactions are provided in Table 1. Detailed information regarding clinical and laboratory monitoring guidelines for early detection of adverse reactions of BAVENCIO and recommended management (immunosuppressant treatment guidelines) are described in Warnings and Precautions (5).

Table 1: Recommended Dose Modifications of BAVENCIO for Adverse Reactions

Treatment-Related Adverse Reaction	Severity of Adverse Reactions	Dose Modification
Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 2 pneumonitis	Withhold BAVENCIO. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of pneumonitis after corticosteroid taper.
	Grade 3 or 4 pneumonitis or recurrent Grade 2 pneumonitis	Permanently discontinue.
Hepatitis *[see Warnings and Precautions (5.2)]* For BAVENCIO in combination with axitinib, see below.	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold BAVENCIO. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of hepatitis after corticosteroid taper.
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue.
Colitis *[see Warnings and Precautions (5.3)]*	Grade 2 or 3 diarrhea or colitis	Withhold BAVENCIO. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of colitis or diarrhea after corticosteroid taper.

Treatment-Related Adverse Reaction	Severity of Adverse Reactions	Dose Modification
	Grade 4 diarrhea or colitis or recurrent Grade 3 diarrhea or colitis	Permanently discontinue.
Endocrinopathies (including but not limited to hypothyroidism, hyperthyroidism, adrenal insufficiency, hyperglycemia) *[see Warnings and Precautions (5.4)]*	Grade 3 or 4	Withhold BAVENCIO. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of endocrinopathies after corticosteroid taper.
Nephritis and Renal Dysfunction *[see Warnings and Precautions (5.5)]*	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold BAVENCIO. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of nephritis and renal dysfunction after corticosteroid taper.
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue.
Other immune-mediated adverse reactions (including but not limited to myocarditis, pancreatitis, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, bullous dermatitis,	For any of the following: • Moderate or severe clinical signs or symptoms of an immune-mediated adverse reaction not described above • Grade 3 or 4 endocrinopathies	Withhold BAVENCIO pending clinical evaluation. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of other immune-mediated adverse reactions after corticosteroid taper.

Treatment-Related Adverse Reaction	Severity of Adverse Reactions	Dose Modification
Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, hypophysitis, iritis, and encephalitis)* *[see Warnings and Precautions (5.6)]*	For any of the following: • Life-threatening adverse reaction (excluding endocrinopathies) • Recurrent severe immune-mediated adverse reaction • Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks • Persistent Grade 2 or 3 immune-mediated adverse reactions lasting 12 weeks or longer	Permanently discontinue.
Infusion-related reaction *[see Warnings and Precautions (5.7)]*	Grade 1 or 2	Interrupt or slow the rate of infusion.
	Grade 3 or 4	Permanently discontinue.

* Observed with BAVENCIO or with other anti-PD-1/PD-L1 monoclonal antibodies.

In patients with RCC being treated with BAVENCIO in combination with axitinib:

- If ALT or AST ≥ 3 times ULN but < 5 times ULN or total bilirubin ≥ 1.5 times ULN but < 3 times ULN, withhold both BAVENCIO and axitinib until these adverse reactions recover to Grades 0-1. If persistent (greater than 5 days), consider corticosteroid therapy [initial dose of 0.5 to 1 mg/kg/day] prednisone or equivalent followed by a taper. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. Dose reduce per the axitinib Full Prescribing Information if rechallenging with axitinib.
- If ALT or AST ≥ 5 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN or total bilirubin ≥ 3 times ULN, permanently discontinue both BAVENCIO and axitinib and consider corticosteroid therapy [initial dose 1 to 2 mg/kg/day prednisone or equivalent followed by a taper].

When BAVENCIO is administered in combination with axitinib, review the axitinib Full Prescribing Information for recommended dose modifications for axitinib.

2.6 Preparation and Administration

Preparation

- Visually inspect vial for particulate matter and discoloration. BAVENCIO is a clear, colorless to slightly yellow solution. Discard vial if the solution is cloudy, discolored, or contains particulate matter.
- Withdraw the required volume of BAVENCIO from the vial(s) and inject it into a 250 mL infusion bag containing either 0.9% Sodium Chloride Injection or 0.45% Sodium Chloride Injection.
- Gently invert the bag to mix the diluted solution and avoid foaming or excessive shearing.
- Inspect the solution to ensure it is clear, colorless, and free of visible particles.
- Discard any partially used or empty vials.

Storage of diluted BAVENCIO solution

Protect from light.

Store diluted BAVENCIO solution:

- At room temperature up to 77°F (25°C) for no more than 4 hours from the time of dilution.

Or

- Under refrigeration at 36°F to 46°F (2°C to 8°C) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze or shake diluted solution.

Administration

- Administer the diluted solution over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron).
- Do not co-administer other drugs through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

Injection: 200 mg/10 mL (20 mg/mL), clear, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

BAVENCIO can cause immune-mediated pneumonitis, including fatal cases *[see Adverse Reactions (6.1)]*. Monitor patients for signs and symptoms of pneumonitis and evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper) for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) pneumonitis, and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.5)]*.

Pneumonitis occurred in 1.2% of patients receiving BAVENCIO including one (0.1%) patient with fatal, one (0.1%) with Grade 4, and five (0.3%) with Grade 3 pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% of patients. Among the 21 patients with immune-mediated pneumonitis, the median time to onset was 2.5 months (range: 3 days to 11 months) and the median duration of pneumonitis was 7 weeks (range: 4 days to 4+ months). All 21 patients were treated with systemic corticosteroids; 17 (81%) of the 21 patients received high-dose corticosteroids for a median of 8 days (range: 1 day to 2.3 months). Resolution of pneumonitis occurred in 12 (57%) of the 21 patients at the time of data cut-off.

5.2 Hepatotoxicity and Immune-Mediated Hepatitis

BAVENCIO can cause immune-mediated hepatitis including fatal cases *[see Adverse Reactions (6.1)]*. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper) for Grade 2 or greater hepatitis. Withhold BAVENCIO for moderate (Grade 2) immune-mediated hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.5)]*.

BAVENCIO as a Single Agent

Immune-mediated hepatitis occurred in 0.9% of patients receiving BAVENCIO including two (0.1%) patients with fatal and 11 (0.6 %) patients with Grade 3 immune-mediated hepatitis. Immune-mediated hepatitis led to permanent discontinuation of BAVENCIO in 0.5% of patients. Among the 16 patients with immune-mediated hepatitis, the median time to onset was 3.2 months (range: 1 week to 15 months), and the median duration of hepatitis was 2.5 months (range: 1 day to 7.4+ months). All 16 patients were treated with corticosteroids; 15 (94%) of the 16 patients received high-dose corticosteroids for a median of 14 days (range: 1 day to 2.5 months). Resolution of hepatitis occurred in nine (56%) of the 16 patients at the time of data cut-off.

BAVENCIO with Axitinib

BAVENCIO in combination with axitinib can cause hepatotoxicity with higher than expected frequencies of Grade 3 and 4 ALT and AST elevation. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy. Withhold BAVENCIO and axitinib for moderate (Grade 2) hepatotoxicity and permanently discontinue the combination

for severe or life-threatening (Grade 3 or 4) hepatotoxicity. Administer corticosteroids as needed *[see Dosage and Administration (2.5)]*.

In patients treated with BAVENCIO in combination with axitinib in the advanced RCC trials, Grades 3 and 4 increased ALT and increased AST were reported in 9% and 7% of patients, respectively. In patients with ALT ≥ 3 times ULN (Grades 2-4, n=82), ALT resolved to Grades 0-1 in 92%. Among the 73 patients who were rechallenged with either BAVENCIO (59%) or axitinib (85%) monotherapy or with both (55%), 66% had no recurrence of ALT ≥ 3 times ULN. Immune-mediated hepatitis was reported in 7% of patients including 4.9% with Grade 3 or 4 immune-mediated hepatitis. Hepatotoxicity led to permanent discontinuation in 6.5% and immune-mediated hepatitis led to permanent discontinuation of either BAVENCIO or axitinib in 5.3% of patients. Among the 35 patients with immune-mediated hepatitis, the median time to onset was 2.8 months (range: 2.1 weeks to 14.5 months) and the median duration of hepatitis was 15 days (range: 2 days to 9 months). Thirty-four patients were treated with corticosteroids and one patient was treated with a non-steroidal immunosuppressant; 33 patients received high-dose corticosteroids for a median of 21 days (range: 4 days to 3 months). Resolution of hepatitis occurred in 31 of the 35 patients at the time of data cut-off.

5.3 Immune-Mediated Colitis

BAVENCIO can cause immune-mediated colitis *[see Adverse Reactions (6.1)]*. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) for Grade 2 or greater colitis. Withhold BAVENCIO for moderate or severe (Grade 2 or 3) colitis until resolution. Permanently discontinue BAVENCIO for life-threatening (Grade 4) or for recurrent (Grade 3) colitis upon re-initiation of BAVENCIO *[see Dosage and Administration (2.5)]*.

Immune-mediated colitis occurred in 1.5% of patients receiving BAVENCIO including seven (0.4%) patients with Grade 3 colitis. Immune-mediated colitis led to permanent discontinuation of BAVENCIO in 0.5% of patients. Among the 26 patients with immune-mediated colitis, the median time to onset was 2.1 months (range: 2 days to 11 months) and the median duration of colitis was 6 weeks (range: 1 day to 14+ months). All 26 patients were treated with corticosteroids; 15 (58%) of the 26 patients received high-dose corticosteroids for a median of 19 days (range: 1 day to 2.3 months). Resolution of colitis occurred in 18 (70%) of the patients at the time of data cut-off.

5.4 Immune-Mediated Endocrinopathies

BAVENCIO can cause immune-mediated endocrinopathies *[see Adverse Reactions (6.1)]*.

Adrenal Insufficiency

Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment. Administer corticosteroids as appropriate for adrenal insufficiency. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency *[see Dosage and Administration (2.5)]*.

Adrenal insufficiency occurred in 0.5% of patients receiving BAVENCIO including one patient (0.1%) with Grade 3 adrenal insufficiency. Immune-mediated adrenal insufficiency led to

permanent discontinuation of BAVENCIO in 0.1% of patients. Among the 8 patients with immune-mediated adrenal insufficiency, the median time to onset was 2.5 months (range: 1 day to 8 months). All eight patients were treated with corticosteroids; four (50%) of the eight patients received high-dose corticosteroids for a median of 1 day (range: 1 day to 24 days).

Thyroid Disorders (Hypothyroidism/Hyperthyroidism)

BAVENCIO can cause immune-mediated thyroid disorders. Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage hypothyroidism with hormone-replacement therapy. Initiate medical management for control of hyperthyroidism. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders *[see Dosage and Administration (2.5)]*.

Immune-mediated thyroid disorders occurred in 6% of patients receiving BAVENCIO including 3 (0.2%) Grade 3 immune-mediated thyroid disorders. Immune-mediated thyroid disorders led to discontinuation of BAVENCIO in 0.1% of patients. Hypothyroidism occurred in 90 (5%) patients; hyperthyroidism in seven (0.4%) patients; and thyroiditis in four (0.2%) patients treated with BAVENCIO. Among the 98 patients with immune-mediated thyroid disorders, the median time to onset was 2.8 months (range: 2 weeks to 13 months) and the median duration was not estimable (range: 6 days to more than 26 months). Immune-mediated thyroid disorders resolved in seven (7%) of the 98 patients.

Type 1 Diabetes Mellitus

BAVENCIO can cause type 1 diabetes mellitus, including diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold BAVENCIO and administer anti-hyperglycemics or insulin in patients with severe or life-threatening (Grade ≥ 3) hyperglycemia. Resume treatment with BAVENCIO when metabolic control is achieved on insulin replacement or anti-hyperglycemics *[see Dosage and Administration (2.5)]*.

Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% of patients including two cases of Grade 3 hyperglycemia that led to permanent discontinuation of BAVENCIO.

5.5 Immune-Mediated Nephritis and Renal Dysfunction

BAVENCIO can cause immune-mediated nephritis *[see Adverse Reactions (6.1)]*. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to ≤ Grade 1. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis *[see Dosage and Administration (2.5)]*.

Immune-mediated nephritis occurred in 0.1% of patients receiving BAVENCIO; BAVENCIO was permanently discontinued in this patient.

5.6 Other Immune-Mediated Adverse Reactions

BAVENCIO can result in severe and fatal immune-mediated adverse reactions *[see Adverse Reactions (6.1)]*. These immune-mediated reactions may involve any organ system. Most immune-mediated reactions initially manifest during treatment with BAVENCIO; however, immune-mediated adverse reactions can occur after discontinuation of BAVENCIO.

For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending upon the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high dose corticosteroids, and if appropriate, initiate hormone replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper. Resume BAVENCIO when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction *[see Dosage and Administration (2.5)]*.

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% of patients who received BAVENCIO as a single agent or in 489 patients who received BAVENCIO in combination with axitinib: immune-mediated myocarditis including fatal cases, pancreatitis including fatal cases, immune-mediated myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response. The following clinically significant, immune-mediated adverse reactions have been reported with other products in this class: bullous dermatitis, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, hypophysitis, iritis, and encephalitis.

5.7 Infusion-Related Reactions

BAVENCIO can cause severe or life-threatening infusion-related reactions *[see Adverse Reactions (6.1)]*. Premedicate with antihistamine and acetaminophen prior to the first 4 infusions. 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 mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions *[see Dosage and Administration (2.5) and Adverse Reactions (6.1)]*.

Infusion-related reactions occurred in 25% of patients treated with BAVENCIO including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Ninety-three percent of patients received premedication with antihistamine and acetaminophen. Eleven (92%) of the 12 patients with Grade ≥ 3 reactions were treated with intravenous corticosteroids. Fourteen percent of patients had infusion-related reactions that occurred after the BAVENCIO infusion was completed.

5.8 Major Adverse Cardiovascular Events (MACE)

BAVENCIO in combination with axitinib can cause severe and fatal cardiovascular 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. Discontinue BAVENCIO and axitinib for Grade 3-4 cardiovascular events.

MACE occurred in 7% of patients with advanced RCC treated with BAVENCIO in combination with axitinib compared to 3.4% treated with sunitinib in a randomized trial, JAVELIN Renal 101. These events included death due to cardiac events (1.4%), Grade 3-4 myocardial infarction (2.8%), and Grade 3-4 congestive heart failure (1.8%). Median time to onset of MACE was 4.2 months (range: 2 days to 24.5 months).

5.9 Embryo-Fetal Toxicity

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking BAVENCIO, inform the patient of the potential risk to a fetus. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least one month after the last dose of BAVENCIO *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the label:

- Immune-mediated pneumonitis *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity and immune-mediated hepatitis *[see Warnings and Precautions (5.2)]*
- Immune-mediated colitis *[see Warnings and Precautions (5.3)]*
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.4)]*
- Immune-mediated nephritis and renal dysfunction *[see Warnings and Precautions (5.5)]*
- Other immune-mediated adverse reactions *[see Warnings and Precautions (5.6)]*
- Infusion-related reactions *[see Warnings and Precautions (5.7)]*
- Major adverse cardiovascular events *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to BAVENCIO 10 mg/kg intravenously every 2 weeks as a single agent in 1738 patients enrolled in the JAVELIN Merkel 200 and JAVELIN Solid Tumor trials and to BAVENCIO 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. In the BAVENCIO monotherapy population, 24% of patients were exposed for ≥ 6 months and 7% were exposed for ≥ 12 months. The population characteristics of BAVENCIO in combination with axitinib are

shown below. When BAVENCIO was used in combination with axitinib, 70% of patients were exposed for ≥ 6 months and 31% were exposed for ≥ 12 months. The following criteria were used to classify an adverse reaction as immune-mediated: onset within 90 days after last dose of BAVENCIO, no spontaneous resolution within 7 days of onset, treatment with corticosteroids or other immunosuppressant or hormone replacement therapy, biopsy consistent with immune-mediated reaction, and no other clear etiology.

Metastatic Merkel Cell Carcinoma

The data described below reflect exposure to BAVENCIO 10 mg/kg intravenously every 2 weeks in 88 patients with metastatic MCC enrolled in the JAVELIN Merkel 200 trial. Patients with any of the following were excluded: autoimmune disease; medical conditions requiring systemic immunosuppression; prior organ or allogeneic stem cell transplantation; prior treatment with anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies; central nervous system (CNS) metastases; infection with HIV, hepatitis B, or hepatitis C; or ECOG performance score ≥ 2.

The median duration of exposure to BAVENCIO was 4 months (range: 2 weeks to 21 months). Forty percent of patients received BAVENCIO for more than 6 months and 14% were treated for more than one year *[see Clinical Studies (14.1)]*. The study population characteristics were: median age of 73 years (range: 33 to 88), 74% male, 92% White, ECOG performance score of 0 (56%) or 1 (44%), and 65% of patients had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies.

BAVENCIO was permanently discontinued for adverse reactions in six (7%) patients; adverse reactions resulting in permanent discontinuation were ileus, Grade 3 transaminitis, Grade 3 creatine kinase elevation, tubulointerstitial nephritis, and Grade 3 pericardial effusion. BAVENCIO was temporarily discontinued in 21 (24%) patients for adverse events, excluding temporary dose interruption for infusion-related reactions where infusion was restarted the same day. The most common adverse reaction requiring dose interruption was anemia. Serious adverse reactions that occurred in more than one patient were acute kidney injury, anemia, abdominal pain, ileus, asthenia, and cellulitis. The most common adverse reactions (≥ 20%) were fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema.

Table 2 and Table 3 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, that occurred in patients receiving BAVENCIO.

Table 2: Adverse Reactions in ≥ 10% of Patients Receiving BAVENCIO in the JAVELIN Merkel 200 Trial

Adverse Reactions	BAVENCIO (N=88)	
	All Grades %	Grade 3-4 %
General Disorders		
Fatigue[a]	50	2
Infusion-related reaction[b]	22	0
Peripheral edema[c]	20	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	32	2
Arthralgia	16	1
Gastrointestinal Disorders		
Diarrhea	23	0
Nausea	22	0
Constipation	17	1
Abdominal pain[e]	16	2
Vomiting	13	0
Skin and Subcutaneous Tissue Disorders		
Rash[f]	22	0
Pruritus[g]	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	20	2
Decreased weight	15	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	18	0
Dyspnea[h]	11	1
Nervous System Disorders		
Dizziness	14	0
Headache	10	0
Vascular Disorders		
Hypertension	13	6

[a] Fatigue is a composite term that includes fatigue and asthenia.
[b] Infusion-related reaction is a composite term that includes drug hypersensitivity, hypersensitivity, chills, pyrexia, back pain, and hypotension.
[c] Peripheral edema is a composite term that includes peripheral edema and peripheral swelling.
[d] Musculoskeletal pain is a composite term that includes back pain, myalgia, neck pain, pain in extremity.
[e] Abdominal pain is a composite term that includes abdominal pain and abdominal pain upper.
[f] Rash is a composite term that includes rash maculo-papular, erythema, and dermatitis bullous.
[g] Pruritus is a composite term that includes pruritus and pruritus generalized.
[h] Dyspnea is a composite term that includes dyspnea and dyspnea exertional.

Table 3: Selected Treatment-Emergent* Laboratory Abnormalities in Patients Receiving BAVENCIO in the JAVELIN Merkel 200 Trial

Laboratory Tests	Any Grade (N=88) %	Grade 3-4 (N=88) %
Chemistry		
Increased aspartate aminotransferase (AST)	34	1
Increased alanine aminotransferase (ALT)	20	5
Increased lipase	14	4
Increased amylase	8	1
Increased bilirubin	6	1
Hyperglycemia**	-	7
Hematology		
Anemia	35	9
Lymphopenia	49	19
Thrombocytopenia	27	1
Neutropenia	6	1

* Treatment emergent consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.
** Hyperglycemia limited to Grade ≥ 3 events since fasting measurements were not obtained routinely.

Locally Advanced or Metastatic Urothelial Carcinoma

First-Line Maintenance Treatment of Urothelial Carcinoma

The safety of BAVENCIO was evaluated in the JAVELIN Bladder 100 trial where patients received BAVENCIO 10 mg/kg every 2 weeks plus best supportive care (BSC) (N=344) or BSC alone (N=345). Patients with autoimmune diseases or conditions requiring systemic immunosuppression were excluded.

In the BAVENCIO plus BSC arm, 47% were exposed to BAVENCIO for > 6 months and 28% were exposed for > 1 year *[see Clinical Studies (14.2)]*.

The median age of patients treated with BAVENCIO plus BSC was 69 years (range: 37 to 90), 63% of patients were 65 years or older, 76% were male, 67% were White, and the ECOG performance score was 0 (61%) or 1 (39%).

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

Serious adverse reactions occurred in 28% of patients receiving BAVENCIO plus 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%).

Permanent discontinuation due to an adverse reaction of BAVENCIO plus BSC 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, excluding temporary interruptions of BAVENCIO infusions due to infusion-related reactions, occurred in 41% of patients receiving BAVENCIO plus BSC. 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%).

The most common adverse reactions (≥ 20%) in patients receiving BAVENCIO plus BSC were fatigue, musculoskeletal pain, urinary tract infection, and rash.

Thirty-one (9%) patients treated with BAVENCIO plus BSC received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5)]*.

Table 4 summarizes adverse reactions that occurred in ≥ 10% of patients treated with BAVENCIO plus BSC.

Table 4: Adverse Reactions (≥ 10%) of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

Adverse Reactions	BAVENCIO plus BSC (N=344)		BSC (N=345)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 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

[a] Fatigue is a composite term that includes fatigue, asthenia and malaise.
[b] Musculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain.
[c] 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.
[d] 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.
[e] Cough is a composite term that includes cough and productive cough.

Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Infusion-related reactions occurred in 10% (Grade 3: 0.9%) of patients treated with BAVENCIO plus BSC.

Table 5: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 10% of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

Laboratory Abnormality	BAVENCIO plus BSC*		BSC*	
	Any Grade %	Grade 3-4 %	Any Grade %	Grade 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 plus BSC group (range: 339 to 344 patients) and BSC group (range: 329 to 341 patients).

Previously-Treated Urothelial Carcinoma

The safety of BAVENCIO was evaluated in 242 patients with locally advanced or metastatic UC receiving BAVENCIO at 10 mg/kg every 2 weeks in the UC cohorts of the JAVELIN Solid Tumor trial. Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. The median duration of exposure to BAVENCIO was 12 weeks (range: 2 weeks to 92 weeks) *[see Clinical Studies (14.2)]*.

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.

Grade 1-4 serious adverse reactions were reported in 41% of patients. The most frequent serious adverse reactions reported in ≥ 2% of patients were urinary tract infection/urosepsis, abdominal pain, musculoskeletal pain, creatinine increased/renal failure, dehydration, hematuria/urinary tract hemorrhage, intestinal obstruction/small intestine obstruction, and pyrexia.

Permanent discontinuation due to an adverse reaction for BAVENCIO occurred in 12% of patients. The adverse reaction that resulted in permanent discontinuation in > 1% of patients was fatigue.

Dose interruptions due to an adverse reaction, excluding temporary interruptions due to infusion-related reactions, occurred in 29% of patients receiving BAVENCIO. Adverse reactions leading to interruption of BAVENCIO in > 1% of patients were diarrhea, fatigue, dyspnea, urinary tract infection, and rash.

The most common Grade 3 and 4 adverse reactions (≥ 3%) were anemia, fatigue, hyponatremia, hypertension, urinary tract infection, and musculoskeletal pain.

The most common adverse reactions (≥ 20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

Eleven (4.5%) patients received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5)]*.

Advanced Renal Cell Carcinoma

The safety of BAVENCIO was evaluated in JAVELIN Renal 101. Patients with autoimmune disease other than type I diabetes mellitus, vitiligo, psoriasis, or thyroid disorders not requiring immunosuppressive treatment were excluded. Patients received BAVENCIO 10 mg/kg every 2 weeks administered in combination with axitinib 5 mg twice daily (N=434) or sunitinib 50 mg once daily for 4 weeks followed by 2 weeks off (N=439).

In the BAVENCIO plus axitinib arm, 70% were exposed to BAVENCIO for ≥ 6 months and 29% were exposed for ≥ 1 year in JAVELIN Renal 101 *[see Clinical Studies (14.3)]*.

The median age of patients treated with BAVENCIO in combination with axitinib was 62 years (range: 29 to 83), 38% of patients were 65 years or older, 71% were male, 75% were White, and the ECOG performance score was 0 (64%) or 1 (36%).

Fatal adverse reactions occurred in 1.8% of patients receiving BAVENCIO 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 BAVENCIO in combination with axitinib. Serious adverse reactions in ≥ 1% of patients included diarrhea (2.5%), dyspnea (1.8%), hepatotoxicity (1.8%), venous thromboembolic disease (1.6%), acute kidney injury (1.4%), and pneumonia (1.2%).

Permanent discontinuation due to an adverse reaction of either BAVENCIO or axitinib occurred in 22% of patients: 19% BAVENCIO only, 13% axitinib only, and 8% both drugs. The most common adverse reactions (> 1%) resulting in permanent discontinuation of BAVENCIO or the combination were hepatotoxicity (6%) and infusion-related reaction (1.8%).

Dose interruptions or reductions due to an adverse reaction, excluding temporary interruptions of BAVENCIO infusions due to infusion-related reactions, occurred in 76% of patients receiving BAVENCIO in combination with axitinib. This includes interruption of BAVENCIO in 50% of patients. Axitinib was interrupted in 66% and dose reduced in 19% of patients. The most common adverse reaction (> 10%) resulting in interruption of BAVENCIO was diarrhea (10%) and the most common adverse reactions resulting in either interruption or dose reduction of axitinib were diarrhea (19%), hypertension (18%), palmar-plantar erythrodysesthesia (18%), and hepatotoxicity (10%).

The most common adverse reactions (≥ 20%) in patients receiving BAVENCIO in combination with axitinib were diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain, and headache.

Forty-eight (11%) patients treated with BAVENCIO in combination with axitinib received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5)]*.

Table 6 summarizes adverse reactions that occurred in ≥ 20% of BAVENCIO in combination with axitinib-treated patients.

Table 6: Adverse Reactions (≥ 20%) of Patients Receiving BAVENCIO in Combination with Axitinib (JAVELIN Renal 101 Trial)

Adverse Reactions	BAVENCIO plus Axitinib (N=434)		Sunitinib (N=439)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal Disorders				
Diarrhea[a]	62	8	48	2.7
Nausea	34	1.4	39	1.6
Mucositis[b]	34	2.8	35	2.1
Hepatotoxicity[c]	24	9	18	3.6
Abdominal pain[d]	22	1.4	19	2.1
General Disorders and Administration Site Conditions				
Fatigue[e]	53	6	54	6
Vascular Disorders				
Hypertension[f]	50	26	36	17
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[g]	40	3.2	33	2.7
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	33	6	34	4
Rash[h]	25	0.9	16	0.5
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	31	0.5	3.2	0
Dyspnea[i]	23	3	16	1.8
Cough	23	0.2	19	0
Metabolism and Nutrition Disorders				
Decreased appetite	26	2.1	29	0.9
Endocrine Disorders				
Hypothyroidism	25	0.2	14	0.2
Nervous System Disorders				
Headache	21	0.2	16	0.2

[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, and 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.

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

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 BAVENCIO in combination with axitinib.

Table 7 summarizes selected laboratory abnormalities that occurred in ≥ 20% of BAVENCIO in combination with axitinib-treated patients.

Table 7: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients Receiving BAVENCIO in Combination with Axitinib (JAVELIN Renal 101 Trial)

Laboratory Abnormality	BAVENCIO plus Axitinib*		Sunitinib*	
	Any Grade %	Grade 3-4 %	Any Grade %	Grade 3-4 %
Chemistry				
Blood triglycerides increased	71	13	48	5
Blood creatinine increased	62	2.3	68	1.4
Blood cholesterol increased	57	1.9	22	0.7
Alanine aminotransferase increased (ALT)	50	9	46	3.2
Aspartate aminotransferase increased (AST)	47	7	57	3.2
Blood sodium decreased	38	9	37	10
Lipase increased	37	14	25	7
Blood potassium increased	35	3	28	3.9
Blood bilirubin increased	21	1.4	23	1.4
Hematology				
Platelet count decreased	27	0.7	80	15
Hemoglobin decreased	21	2.1	65	8

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: BAVENCIO in combination with axitinib group (range: 413 to 428 patients) and sunitinib group (range: 405 to 433 patients).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to avelumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Of the 344 patients treated with BAVENCIO 10 mg/kg as an intravenous infusion every 2 weeks plus BSC, 325 were evaluable for treatment-emergent anti-drug antibodies (ADA) and 62 (19.1%) tested positive in the JAVELIN Bladder 100 trial.

Of the 480 patients treated with BAVENCIO 10 mg/kg as an intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily, 453 were evaluable for treatment-emergent ADA and 66 (15%) tested positive in the JAVELIN Renal 100 and JAVELIN Renal 101 trials.

Patients who tested positive for treatment-emergent ADA had decreased systemic BAVENCIO exposure *[see Clinical Pharmacology (12.3)]*. In exploratory analyses, the effect of ADA on the efficacy or safety could not be determined due to insufficient numbers of patients in the ADA-positive subgroup and confounding variables.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of BAVENCIO in pregnant women *[see Clinical Pharmacology (12.1)]*. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death *[see Data]*. Human IgG1 immunoglobulins (IgG1) are known to cross the placenta. Therefore, BAVENCIO has the potential to be transmitted from the mother to the developing fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with BAVENCIO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering BAVENCIO during

pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to BAVENCIO may increase the risk of developing immune-related disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of avelumab in human milk, the effects on the breastfed infant, or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise a lactating woman not to breastfeed during treatment and for at least one month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO.

8.4 Pediatric Use

The safety and effectiveness of BAVENCIO have been established in pediatric patients aged 12 years and older for metastatic MCC. Use of BAVENCIO in this age group is supported by evidence from adequate and well-controlled studies of BAVENCIO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of avelumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MCC is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients 12 years of age or greater is the same as that in adults *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

Safety and effectiveness of BAVENCIO have not been established in pediatric patients less than 12 years of age.

8.5 Geriatric Use

Metastatic Merkel Cell Carcinoma

Clinical studies of BAVENCIO in MCC did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Locally Advanced or Metastatic Urothelial Carcinoma

Of the 344 patients randomized to BAVENCIO 10 mg/kg plus BSC in the JAVELIN Bladder 100 trial, 63% were 65 years or older and 24% were 75 years or older. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

Advanced Renal Cell Carcinoma

Of the 434 patients randomized to BAVENCIO 10 mg/kg administered in combination with axitinib 5 mg twice daily in the JAVELIN Renal 101 trial, 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety or efficacy were reported between elderly patients and younger patients.

11 DESCRIPTION

Avelumab is a programmed death ligand1 (PD-L1) blocking antibody. Avelumab- is a human IgG1 lambda monoclonal antibody produced in Chinese hamster ovary cells and has a molecular weight of approximately 147 kDa.

BAVENCIO (avelumab) Injection for intravenous use is a sterile, preservative-free, non-pyrogenic, clear, colorless to slightly yellow solution. Each single-dose vial contains 200 mg avelumab in 10 mL (20 mg/mL). Each mL contains 20 mg avelumab, D-mannitol (51 mg), glacial acetic acid (0.6 mg), polysorbate 20 (0.5 mg), sodium hydroxide (0.3 mg), and Water for Injection. The pH range of the solution is 5.0 – 5.6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PD-L1 may be expressed on tumor cells and tumor-infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation, and cytokine production. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This interaction releases the inhibitory effects of PD-L1 on the immune response resulting in the restoration of immune responses, including anti-tumor immune responses. Avelumab has also been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

12.2 Pharmacodynamics

Based on exposure efficacy and exposure safety relationships, there are no expected clinically meaningful differences in the safety or efficacy of BAVENCIO administered every 2 weeks at 800 mg or 10 mg/kg in patients with metastatic Merkel cell carcinoma, in patients with urothelial carcinoma and in patients with advanced renal cell carcinoma.

12.3 Pharmacokinetics

Avelumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent BAVENCIO and BAVENCIO in combination with axitinib. There are no expected clinically meaningful differences in exposure of avelumab administered every 2 weeks at 800 mg or 10 mg/kg in both settings.

BAVENCIO as a single agent

The pharmacokinetics of avelumab as a single agent was studied in 1629 patients who received doses ranging from 1 to 20 mg/kg every 2 weeks. The data showed that the exposure of

avelumab increased dose-proportionally in the dose range of 10 to 20 mg/kg every 2 weeks. Steady-state concentrations of avelumab were reached after approximately 4 to 6 weeks (2 to 3 cycles) of repeated dosing, and the systemic accumulation was approximately 1.25-fold. The geometric mean volume of distribution at steady state for a subject receiving 10 mg/kg was 4.72 L. The primary elimination mechanism of avelumab is proteolytic degradation. Based on population pharmacokinetic analyses in patients with solid tumors, the total systemic clearance was 0.59 L/day and the terminal half-life was 6.1 days in patients receiving 10 mg/kg. In a post hoc analysis, avelumab clearance was found to decrease over time in patients with MCC, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline value of approximately 32.1% (36.2%), which is not considered clinically important. There was no evidence to suggest a change of avelumab clearance over time in patients with UC.

BAVENCIO with axitinib
When BAVENCIO 10 mg/kg was administered in combination with axitinib 5 mg, the respective exposures of avelumab and axitinib were comparable to the single agents. There was no evidence to suggest a clinically relevant change of avelumab clearance over time in patients with advanced RCC.

Specific Populations
Body weight was positively correlated with total systemic clearance in population pharmacokinetic analyses. No clinically meaningful differences in pharmacokinetics were observed in the clearance of avelumab based on age; sex; race; PD-L1 status; tumor burden; mild [calculated creatinine clearance (CLcr) 60 to 89 mL/min, n=623 as estimated by the Cockcroft-Gault formula], moderate [CLcr 30 to 59 mL/min, n=320], or severe [CLcr 15 to 29 mL/min, n=4] renal impairment; and mild [bilirubin less than or equal to ULN and AST greater than ULN or bilirubin between 1 and 1.5 times ULN, n=217] or moderate [bilirubin between 1.5 and 3 times ULN, n=4] hepatic impairment. There are limited data from patients with severe hepatic impairment [bilirubin greater than 3 times ULN, n=1], and the effect of severe hepatic impairment on the pharmacokinetics of avelumab is unknown. In patients with advanced UC or advanced RCC, BAVENCIO clearance in patients who tested positive for treatment-emergent ADA was approximately 15% higher as compared to clearance in patients who tested negative for treatment-emergent ADA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess the potential of avelumab for genotoxicity or carcinogenicity.

Fertility studies have not been conducted with avelumab; however, an assessment of male and female reproductive organs was included in 3-month repeat-dose toxicity study in Cynomolgus monkeys. Weekly administration of avelumab did not result in any notable effects in the male and female reproductive organs.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Metastatic Merkel Cell Carcinoma

The efficacy and safety of BAVENCIO was demonstrated in the JAVELIN Merkel 200 trial (NCT02155647), an open-label, single-arm, multi-center study conducted in patients with histologically confirmed metastatic MCC whose disease had progressed on or after chemotherapy administered for distant metastatic disease. The trial excluded patients with autoimmune disease; medical conditions requiring systemic immunosuppression; prior organ or allogeneic stem cell transplantation; prior treatment with anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies; CNS metastases; infection with HIV, hepatitis B, or hepatitis C; or ECOG performance score ≥ 2.

Patients received BAVENCIO 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms, no change in performance status for greater than 2 weeks, and no need for salvage therapy, could continue treatment. Tumor response assessments were performed every 6 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by a blinded independent central review committee (IRC) and IRC-assessed duration of response. The efficacy analysis was conducted when the last patient enrolled had completed 12 months of follow-up.

A total of 88 patients were enrolled. Baseline patient characteristics were a median age of 73 years (range: 33 to 88), 74% of patients were male, 92% were White, and the ECOG performance score was 0 (56%) or 1 (44%). Seventy-five percent of patients were 65 years or older, 35% were 75 or older, and 3% were 85 or older. Sixty-five percent of patients were reported to have had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies. Fifty-three percent of patients had visceral metastases. All patients had tumor samples evaluated for PD-L1 expression; of these, 66% were PD-L1-positive (≥ 1% of tumor cells), 18% were PD-L1 negative, and 16% had non-evaluable results by an investigational immunohistochemistry assay. Archival tumor samples were evaluated for Merkel cell polyomavirus (MCV) using an investigational assay; of the 77 patients with evaluable results, 52% had evidence of MCV.

Efficacy results are presented in Table 8. Responses were observed in patients regardless of tumor PD-L1 expression or presence of MCV.

Table 8: Efficacy Results of the JAVELIN Merkel 200 Trial

Efficacy Endpoints	Results (N=88)
Overall Response Rate (ORR)	
Overall response rate, (95% CI)	33.0% (23.3%, 43.8%)
Complete response (CR) rate, (95% CI)	11.4% (6.6%, 19.9%)
Partial response (PR) rate, (95% CI)	21.6% (13.5%, 31.7%)
Duration of Response (DOR)	N=29
Range in months	2.8 to 23.3+
Patients with DOR ≥ 6 months, n (%)	25 (86%)
Patients with DOR ≥ 12 months, n (%)	13 (45%)

CI: Confidence interval.

14.2 Locally Advanced or Metastatic Urothelial Carcinoma

First-Line Maintenance Treatment of Urothelial Carcinoma

The efficacy and safety of BAVENCIO was demonstrated in the JAVELIN Bladder 100 trial (NCT02603432), a randomized, multi-center, open-label study conducted in 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing chemotherapy. Patients with autoimmune disease or a medical condition that required immunosuppression were excluded.

Randomization was stratified by best response to chemotherapy (CR/PR vs. stable disease [SD]) and site of metastasis (visceral vs. non-visceral) at the time of initiating first-line chemotherapy. Patients were randomized (1:1) to receive either BAVENCIO 10 mg/kg intravenous infusion every 2 weeks plus best supportive care (BSC) or BSC alone. Treatment was initiated within 4-10 weeks after the last dose of chemotherapy.

Treatment with BAVENCIO continued until RECIST v1.1-defined progression of disease by Blinded Independent Central Review (BICR) assessment or unacceptable toxicity. Administration of BAVENCIO was permitted beyond RECIST-defined disease progression if the patient was clinically stable and was 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.

Baseline characteristics were well-balanced between arms. Overall, the median age was 69 years (range: 32 to 90), with 66% of patients ≥ 65 years of age and 24% of patients ≥ 75 years of age. Most patients were male (77%). The majority of patients were White (67%) and 22% were Asian. Baseline ECOG PS was 0 (61%) or 1 (39%).

Fifty-six percent (56%) of patients received prior gemcitabine plus cisplatin, 38% of patients received prior gemcitabine plus carboplatin, and 6% of patients received prior gemcitabine plus cisplatin and gemcitabine plus carboplatin. Best response to first-line chemotherapy was CR or PR (72%) or SD (28%). Sites of metastasis prior to chemotherapy were visceral (55%) or non-visceral (45%). Fifty-one (51%) of patients had PD-L1-positive-tumors, 39% of patients had

PD-L1-negative tumors, and 10% of patients had unknown PD-L1 tumor status. Six percent (6%) of patients received another PD-1/PD-L1 checkpoint inhibitor after discontinuation of treatment in the BAVENCIO plus BSC arm and 44% of patients in the BSC arm.

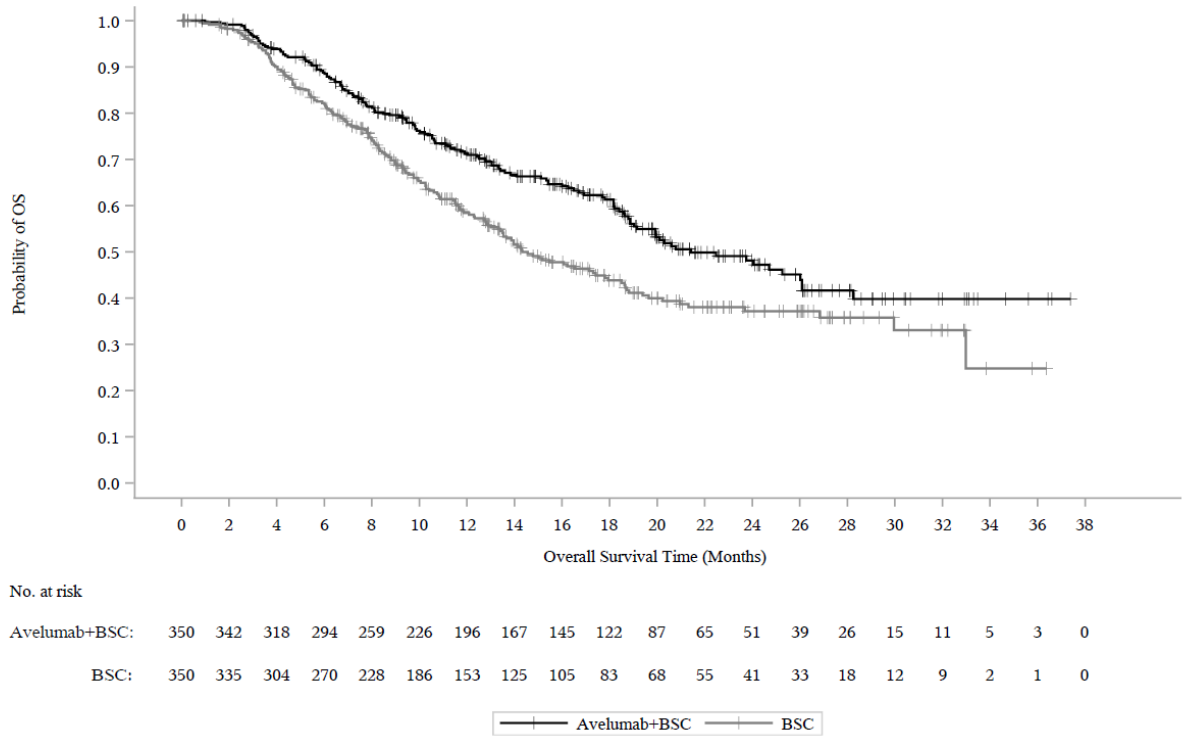
The major efficacy outcome measure was overall survival (OS) in all randomized patients and patients with PD-L1-positive tumors. The trial demonstrated a statistically significant improvement in OS for patients randomized to BAVENCIO plus BSC as compared with BSC alone (Table 9 and Figure 1). Consistent results were observed across the pre-specified subgroup of CR/PR versus SD to first-line chemotherapy.

Table 9: Efficacy Results from the JAVELIN Bladder 100 Trial

Efficacy Endpoints	**BAVENCIO plus BSC** (N=350)	**BSC** (N=350)
Overall Survival (OS)		
Events (%)	145 (41.4)	179 (51.1)
Median in months (95% CI)	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)
Hazard ratio (95% CI)	0.69 (0.56, 0.86)	
2-sided p-value*	0.001	

BSC: Best supportive care; CI: Confidence interval.
* p-value based on stratified log-rank.

Figure 1: K-M Estimates for OS from the JAVELIN Bladder 100 Trial



In the prespecified endpoint of OS among patients with PD-L1-positive tumors (n=358, 51%), the hazard ratio was 0.56 (95% CI: 0.40, 0.79; 2-sided p-value <0.001) for patients randomized to BAVENCIO plus BSC versus BSC alone. In an exploratory analysis of patients with PD-L1-negative tumors (n=271, 39%), the OS hazard ratio was 0.85 (95% CI: 0.62, 1.18).

Previously-Treated Urothelial Carcinoma

The efficacy and safety of BAVENCIO was demonstrated in the UC cohorts of the JAVELIN Solid Tumor trial, an open-label, single-arm, multi-center study that included 242 patients with locally advanced or metastatic urothelial carcinoma (UC) with disease progression on or after platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Patients with active or history of central nervous system metastasis; other malignancies within the last 5 years; organ transplant; conditions requiring therapeutic immune suppression; or active infection with HIV, hepatitis B, or hepatitis C were excluded. Patients with autoimmune disease, other than type 1 diabetes, vitiligo, psoriasis, or thyroid disease that did not require immunosuppressive treatment, were excluded. Patients were included regardless of their PD-L1 status.

Patients received BAVENCIO at a dose of 10 mg/kg intravenously every 2 weeks until radiographic or clinical progression or unacceptable toxicity. Tumor response assessments were performed every 6 weeks. Efficacy outcome measures included confirmed overall response rate (ORR), as assessed by an Independent Endpoint Review Committee (IERC) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and duration of response (DOR). Efficacy

was evaluated in patients who were followed for a minimum of both 13 weeks and 6 months at the time of data cut-off.

Baseline demographic and disease characteristics for the 226 patients with a minimum of 13 weeks of follow-up were median age 68 years (range: 30 to 89), 72% male, 80% White, and 34% and 66% of patients had an ECOG performance status 0 and 1, respectively. Forty-four percent of patients had non-bladder urothelial carcinoma including 23% of patients with upper tract disease, and 83% of patients had visceral metastases (baseline target and/or non-target lesions present outside of the lymph nodes). Nine (4%) patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy only. Forty-seven percent of patients only received prior cisplatin-based regimens, 32% received only prior carboplatin-based regimens, and 20% received both cisplatin and carboplatin-based regimens. At baseline, 17% of patients had a hemoglobin < 10 g/dL and 34% of patients had liver metastases.

Efficacy results are presented in Table 10. The median time to response was 2.0 months (range: 1.3 to 11.0) among patients followed for either ≥ 13 weeks or ≥ 6 months. Using a clinical trial assay to assess PD-L1 staining, with 16% of patients not evaluable, there were no clear differences in response rates based on PD-L1 tumor expression. Among the total 30 responding patients followed for ≥ 13 weeks, 22 patients (73%) had an ongoing response of 6 months or longer and 4 patients (13%) had ongoing responses of 12 months or longer. Among the total 26 responding patients followed for ≥ 6 months, 22 patients (85%) had ongoing responses of 6 months or longer and 4 patients (15%) had ongoing responses of 12 months or longer.

Table 10: Efficacy Results of the UC Cohorts in the JAVELIN Solid Tumor Trial

Efficacy Endpoints	**≥ 13 Weeks Follow-Up (N=226)**	**≥ 6 Months Follow-Up (N=161)**
Confirmed Overall Response Rate (ORR)		
Overall Response Rate n (%)	30 (13.3%)	26 (16.1%)
(95% CI)	(9.1, 18.4)	(10.8, 22.8)
Complete Response (CR) n (%)	9 (4.0%)	9 (5.6%)
Partial Response (PR) n (%)	21 (9.3%)	17 (10.6%)
Duration of Response (DOR)		
Median, months (range)	NE (1.4+ to 17.4+)	NE (1.4+ to 17.4+)

CI: Confidence interval; NE: Not estimable; + denotes a censored value.

14.3 Advanced Renal Cell Carcinoma

The efficacy and safety of BAVENCIO in combination with axitinib was demonstrated in the JAVELIN Renal 101 trial (NCT02684006), a randomized, multicenter, open-label, study of BAVENCIO in combination with axitinib in 886 patients with untreated advanced RCC regardless of tumor PD-L1 expression [intent-to-treat (ITT) population]. Patients with autoimmune disease or conditions requiring systemic immunosuppression were excluded.

Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0 vs. 1) and region (United States vs. Canada/Western Europe vs. the rest of the world). Patients were randomized (1:1) to one of the following treatment arms:

- BAVENCIO 10 mg/kg intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily orally (N=442). Patients who tolerated axitinib 5 mg twice daily without Grade 2 or greater axitinib-related adverse events for 2 consecutive weeks could increase to 7 mg and then subsequently to 10 mg twice daily. Axitinib could be interrupted or reduced to 3 mg twice daily and subsequently to 2 mg twice daily to manage toxicity.
- Sunitinib 50 mg once daily orally for 4 weeks followed by 2 weeks off (N=444) until radiographic or clinical progression or unacceptable toxicity.

Treatment with BAVENCIO and axitinib continued until RECIST v1.1-defined progression of disease by Blinded Independent Central Review (BICR) assessment or unacceptable toxicity. Administration BAVENCIO 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. 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.

Baseline characteristics were a median age of 61 years (range: 27 to 88), 38% of patients were 65 years or older, 75% were male, 75% were White, and the ECOG PS was 0 (63%) or 1 (37%), respectively. Patient distribution by International Metastatic Renal Cell Carcinoma Database (IMDC) risk groups was 21% favorable, 62% intermediate, and 16% poor.

The major efficacy outcome measures were progression-free survival (PFS), as assessed by an BICR using RECIST v1.1 and overall survival (OS) in patients with PD-L1-positive tumors using a clinical trial assay (PD-L1 expression level ≥ 1%). 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.

With a median overall survival follow-up of 19 months, overall survival data were immature with 27% deaths in the ITT population.

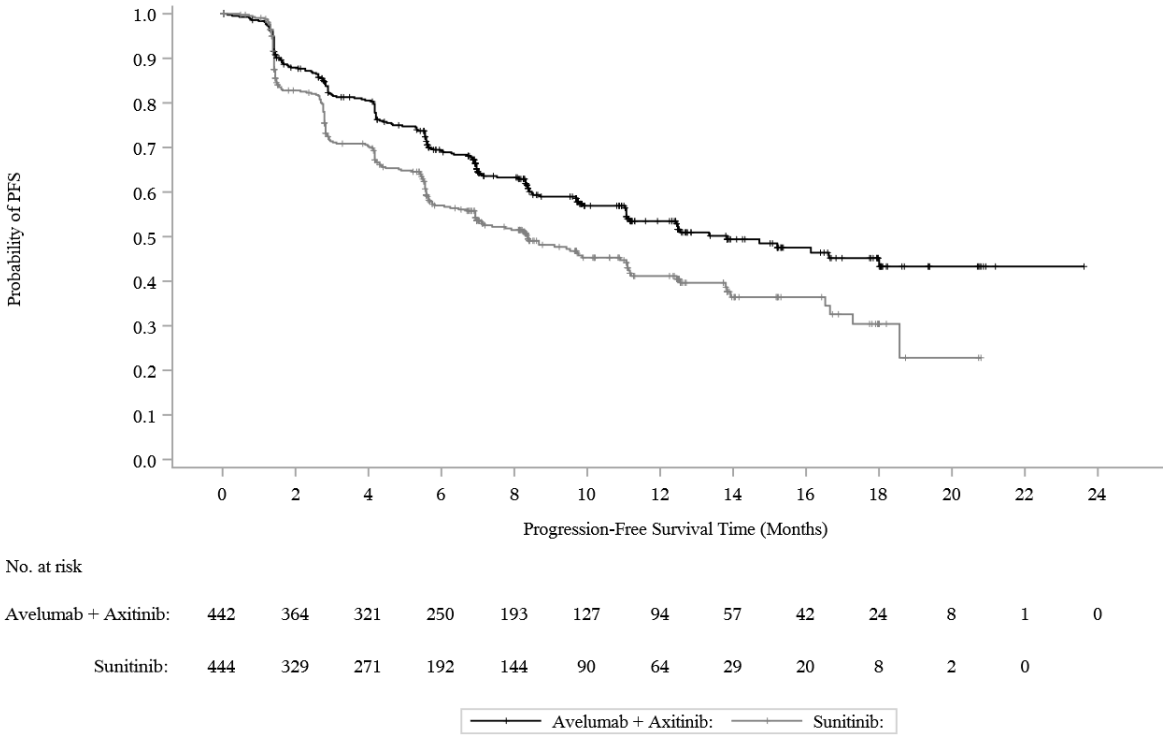
Efficacy results are presented in Table 11 and Figure 2.

Table 11: Efficacy Results from JAVELIN Renal 101 Trial - ITT

Efficacy Endpoints (Based on BICR Assessment)	BAVENCIO plus 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*	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 (CR) n (%)	15 (3.4)	8 (1.8)
Partial Response (PR) n (%)	212 (48)	106 (24)

BICR: Blinded Independent Central Review; CI: Confidence interval; NE: Not estimable.
* p-value based on stratified log-rank.

Figure 2: K-M Estimates for PFS based on BICR Assessment – ITT



16 HOW SUPPLIED/STORAGE AND HANDLING

BAVENCIO (avelumab) Injection is a sterile, preservative-free, and clear, colorless to slightly yellow solution for intravenous infusion supplied as a single-dose vial of 200 mg/10 mL (20 mg/mL), individually packed into a carton (NDC 44087-3535-1).

Store refrigerated at 36°F to 46°F (2°C to 8°C) in original package to protect from light.

Do not freeze or shake the vial.

The vial stopper is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions requiring corticosteroids or hormone replacement therapy, including, but not limited to:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.2)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.3)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions (5.4)]*.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.5)]*.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions *[see Warnings and Precautions (5.7)]*.

Major Adverse Cardiovascular Events

Advise patients receiving BAVENCIO in combination with axitinib to contact their healthcare provider immediately for signs or symptoms of cardiovascular events including but not limited to new or worsening chest discomfort, dyspnea, or peripheral edema *[see Warnings and Precautions (5.8)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential that BAVENCIO can cause fetal harm. Instruct females of reproductive potential to use effective contraception during and for at least one month after the last dose of BAVENCIO *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise nursing mothers not to breastfeed while taking BAVENCIO and for at least one month after the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
EMD Serono, Inc.
Rockland, MA 02370
U.S.A.

US License No: 1773

Product of Switzerland

Marketed by:
EMD Serono, Inc. and Pfizer Inc., NY, NY 10017

BAVENCIO is a trademark of Merck KGaA, Darmstadt, Germany

MEDICATION GUIDE

BAVENCIO® (buh-VEN-see-oh)
(avelumab)
injection

What is the most important information I should know about BAVENCIO?

BAVENCIO is a medicine that may treat certain cancers by working with your immune system. BAVENCIO can cause your immune system to attack normal organs and tissues and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death**.**

Call or see your healthcare provider right away if you get any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Signs and symptoms of pneumonitis may include:

- new or worsening cough
- shortness of breath
- chest pain

Liver problems, including hepatitis. Signs and symptoms of liver problems may include:

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Intestinal problems (colitis). Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood in your stools or dark, tarry, sticky stools
- severe stomach area (abdomen) pain or tenderness

Hormone gland problems (especially the adrenal glands, thyroid, and pancreas). Signs and symptoms that your hormone glands are not working properly may include:

- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- hair loss
- changes in mood or behavior, such as irritability or forgetfulness
- constipation
- your voice gets deeper
- very low blood pressure
- urinating more often than usual
- dizziness or fainting
- nausea or vomiting
- stomach area (abdomen) pain
- feeling cold

Kidney problems, including nephritis. Signs and symptoms of kidney problems may include:

- decrease in your amount of urine
- blood in your urine
- swelling in your ankles
- loss of appetite

Problems in other organs. Signs and symptoms may include:

- severe muscle weakness
- severe or persistent muscle or joint pains
- chest pain and tightness
- trouble breathing
- skin rash, blisters, or peeling
- tiredness, sleepiness
- swelling of the feet and legs
- dizziness or fainting
- fever, flu-like symptoms
- changes in eyesight
- changes in heartbeat, such as beating fast, or seeming to skip a beat, or pounding sensation

Severe infusion reactions. Signs and symptoms of severe infusion reactions may include:

- chills or shaking
- hives
- flushing
- shortness of breath or wheezing
- low blood pressure
- fever
- back pain
- stomach area (abdomen) pain

Heart problems. When BAVENCIO is used with the medicine axitinib, severe heart problems can happen and can lead to death. Signs and symptoms of heart problems may include:

- swelling of your stomach area (abdomen), legs, hands, feet, or ankles
- shortness of breath
- nausea or vomiting
- chest discomfort, including pain or pressure
- weight gain
- pain or discomfort in your arms, back, neck, or jaw
- breaking out in a cold sweat
- feeling lightheaded or dizzy

Getting medical treatment right away may help keep these problems from becoming more serious.

Your healthcare provider will check you for these problems during your treatment with BAVENCIO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may delay or completely stop treatment with BAVENCIO if you have severe side effects.

What is BAVENCIO?

BAVENCIO is a prescription medicine used to treat:

- a type of skin cancer called Merkel cell carcinoma (MCC) in adults and children 12 years of age and older. BAVENCIO may be used when your skin cancer has spread.
- a type of cancer in the bladder or urinary tract called urothelial carcinoma (UC) when it has spread or cannot be removed by surgery (advanced UC). BAVENCIO may be used:
  - as maintenance treatment when your cancer has responded or stabilized after you have received platinum-containing chemotherapy as your first treatment.
  - when you have received platinum-containing chemotherapy, and it did not work or is no longer working.
- a type of kidney cancer called renal cell carcinoma (RCC). BAVENCIO may be used with the medicine axitinib as your first treatment when your kidney cancer has spread or cannot be removed by surgery (advanced RCC).

It is not known if BAVENCIO is safe and effective in children under the age of 12.

Before you receive BAVENCIO, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease or ulcerative colitis
- have had an organ transplant
- have lung or breathing problems
- have liver or kidney problems
- have diabetes
- have heart problems or high blood pressure
- have a high cholesterol level in your blood
- are pregnant or plan to become pregnant. BAVENCIO can harm your unborn baby. If you are able to become pregnant, you should use an effective method of birth control during your treatment and for at least 1 month after the last dose of BAVENCIO.
- are breastfeeding or plan to breastfeed. It is not known if BAVENCIO passes into your breast milk. Do not breastfeed during treatment and for at least 1 month after the final dose of BAVENCIO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive BAVENCIO?

- Your healthcare provider will give you BAVENCIO into your vein through an intravenous (IV) line over 60 minutes.
- BAVENCIO is usually given every 2 weeks.
- Your healthcare provider will give you medicines before the first 4 infusions and then as needed to help reduce infusion reactions.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for certain side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of BAVENCIO?

BAVENCIO can cause serious side effects, including:

- **See "What is the most important information I should know about BAVENCIO?"**

The most common side effects of BAVENCIO in people with MCC include:

- feeling tired
- muscle and bone pain
- diarrhea
- nausea
- infusion-related reaction including chills, fever, and back pain
- rash
- decreased appetite
- swelling in your hands, feet, or ankles

The most common side effects of BAVENCIO as maintenance treatment in people with UC whose cancer responded or stabilized after platinum-containing chemotherapy as first treatment include:

- feeling tired
- muscle and bone pain
- urinary tract infection
- rash

The most common side effects of BAVENCIO in people with UC after platinum-containing chemotherapy that did not work, or is no longer working, include:

- feeling tired
- infusion-related reaction including chills, fever, back pain, redness, and shortness of breath
- muscle and bone pain
- nausea
- decreased appetite
- urinary tract infection

The most common side effects of BAVENCIO when given with axitinib in people with RCC include:

- diarrhea
- feeling tired
- high blood pressure
- muscle and bone pain
- nausea
- mouth sores
- liver problems
- blisters or rash on the palms of your hands and soles of your feet
- hoarseness
- decreased appetite
- low levels of thyroid hormone
- rash
- shortness of breath
- cough
- stomach area (abdomen) pain
- headache

These are not all the possible side effects of BAVENCIO. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of BAVENCIO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about BAVENCIO, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about BAVENCIO that is written for health professionals.

What are the ingredients in BAVENCIO?

Active ingredient: avelumab

Inactive ingredients: D-mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, and Water for Injection

Manufactured by: EMD Serono, Inc. One Technology Place, Rockland, MA 02370 USA, U.S. License No. 1773.
Marketed by: EMD Serono, Inc. and Pfizer Inc., NY, NY 10017 USA.

For more information, call toll-free 1-844-826-8371 or go to www.bavencio.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: June/2020

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMNA IBRAHIM
06/30/2020 04:13:51 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761049Orig1s009

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	BLA
Application Number(s)	761049/S-009
Priority or Standard	Priority
Submit Date(s)	April 7, 2020
Received Date(s)	April 7, 2020
PDUFA Goal Date	October 7, 2020
Division/Office	DO1/OOD
Review Completion Date	June 30, 2020
Established Name	Avelumab
(Proposed) Trade Name	Bavencio®
Pharmacologic Class	PD-L1 blocking monoclonal antibody
Code name	MSB0010718C
Applicant	EMD Serono, Inc.
Formulation	200 mg /10 mL in single dose vial
Dosing Regimen	Injection, solution, concentrate
Applicant Proposed Indication/Population	BAVENCIO is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy BAVENCIO is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who: • Have disease progression during or following platinum-containing chemotherapy • Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	*First-Line Maintenance Treatment of Urothelial Carcinoma* BAVENCIO is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy. *Previously-Treated Urothelial Carcinoma*

	BAVENCIO is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who: • Have disease progression during or following platinum-containing chemotherapy • Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

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REVIEWERS OF MULTI-DISCIPLINARY REVIEW AND EVALUATION

ADDITIONAL REVIEWERS OF APPLICATION

Regulatory Project Manager	Rajesh Venugopal, MPH, MBA
Pharmacology/Toxicology Reviewer(s)	N/A
Pharmacology/Toxicology Team Leader(s)	N/A
Office of Clinical Pharmacology Reviewers	Wentao Fu, PhD; Yuan Xu, PhD
Office of Clinical Pharmacology Team Leaders	Pengfei Song, PhD; Jiang Liu, PhD
Clinical Reviewer	Elaine Chang, MD (Efficacy) Michael Brave, MD (Safety)
Clinical Team Leader	Chana Weinstock, MD
Safety Analyst (if applicable)	Shaily Arora, PharmD
Statistical Reviewer	Erik Bloomquist, PhD
Cross-Disciplinary Team Leader	Chana Weinstock, MD
Associate Director for Labeling (ADL)	William Pierce
Division Director (DHOT)	N/A
Division Director (OCP)	Nam Atiqur Rahman, PhD
Division Director (OB)	Shenghui Tang, PhD
Deputy Division Director (OOD)	Amna Ibrahim, MD
Office Director (or designated signatory authority)	Amna Ibrahim, MD
OBP	Arulvathani Arudchandran, PhD; Patrick Lynch, PhD (TL)
Microbiology	N/A
OPDP	Lynn Panholzer, PhD
OSI	Yang-Min (Max) Ning, MD
OSE/DEPI	N/A
OSE/DMEPA	Tinting Gao (PharmD), Alice Tu, PharmD (TL)
OSE/DRISK	N/A
Other – PT. Labeling	Ruth Mayrosh, PharmD; Barbara Fuller, PHD (TL)

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

GLOSSARY

2L UC	second-line urothelial cancer
AC	advisory committee
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
+ BSC	in combination with best supportive care
ALT	alanine aminotransferase
aPT	activated partial thromboplastin time
aRCC	advanced renal cell carcinoma
AST	aspartate aminotransferase,
aUC	locally advanced or metastatic urothelial carcinoma
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSC	best supportive care
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
cTnI	cardiac troponin subunit I
cTnT	cardiac troponin subunit T
C_{trough}	predose concentration during multiple dosing
DLP	data lock point
DMC	data monitoring committee
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAA	FDA Assessment Aid
FAERS	FDA Adverse Event Reporting System

FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FFPE	formalin-fixed and paraffin-embedded
GCP	good clinical practice
GGT	gamma glutamyltransferase
GLP	good laboratory practice
GRMP	good review management practice
HBV	hepatitis B virus (eg, HBsAg, Hepatitis B core antibody)
HCV	hepatitis C virus (eg, Hep C antibody),
HIV	human immunodeficiency virus
HLT	high level term
ICH	International Conference on Harmonization
IND	Investigational New Drug
INR	international normalized ratio
IR	Information Request
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LDH	lactate dehydrogenase
MCC	merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mMCC	metastatic merkel cell carcinoma
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PADER	Periodic Adverse Drug Experience Report
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PD-1	programmed death protein 1
PD-L1	programmed death-ligand 1
PI	prescribing information
PIPD	Potentially Important Protocol Deviations
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
popPK	population pharmacokinetics
PP	per protocol
PPI	patient package insert

PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	prothrombin time
pts	patients
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q12W	every 12 weeks
REMS	risk evaluation and mitigation strategy
RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental Biologics License Application
SD	stable disease
SGE	special government employee
SOC	standard of care
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
TTR	time to response
UC	urothelial carcinoma
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell

1 EXECUTIVE SUMMARY

1.1. Product Introduction

Avelumab is a programmed death ligand1 (PD-L1)-blocking monoclonal antibody. Avelumab binds PD L1 and blocks the interaction between PD L1 and its receptors PD 1 and B7.1. Avelumab has also been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.

Avelumab is currently approved as a single agent for the treatment of metastatic Merkel cell carcinoma and for the treatment advanced urothelial carcinoma in patients who have progressed after initial platinum-containing chemotherapy. Both of these indications are approved under the accelerated approval pathway. Avelumab is also approved for the first-line treatment of advanced renal cell carcinoma in combination with axitinib. There is no companion diagnostic device currently approved for avelumab for any indication.

The applicant proposed the following additional indication for avelumab: first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy.

The applicant proposed the following dosing regimen in the labeling for approval: 800 mg every 2 weeks. Premedicate for the first 4 infusions and subsequently as needed. Administer as an intravenous infusion over 60 minutes.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for this application is obtained from the randomized, multi-center, open-label study JAVELIN Bladder 100 conducted in 700 patients with locally advanced or metastatic urothelial carcinoma (UC) that had not progressed with first-line platinum-containing chemotherapy. Randomization was stratified by best response to chemotherapy (CR/PR vs. SD) and site of metastasis (visceral vs. non-visceral) at the time of initiating first-line induction chemotherapy. Patients were randomized (1:1) to receive either avelumab 10 mg/kg intravenous infusion every 2 weeks plus best supportive care (BSC) or BSC alone. Per protocol, BSC could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy, received by 4.4% of patients), etc. BSC did not include any active anti-tumor therapy, however local radiotherapy of isolated lesions will palliative intent was acceptable. Treatment was initiated within 4-10 weeks after last dose of chemotherapy and continued until RECIST v1.1-defined progression of disease by BICR) assessment or unacceptable toxicity, although treatment beyond progression was allowed on the avelumab arm for clinically stable patients.

Baseline characteristics were well-balanced between arms. Fifty-two percent (52%) of patients received prior gemcitabine plus cisplatin, 42% of patients received prior gemcitabine plus carboplatin, and 6% of patients received prior gemcitabine plus cisplatin and gemcitabine plus carboplatin. Best response to first-line induction chemotherapy was CR or PR (72%) or SD

(28%). Fifty-one of patients had PD-L1-positive-tumors, 39% of patients had PD-L1-negative tumors, and 10% of patients had unknown PD-L1 tumor status.

The major efficacy outcome measure was overall survival (OS) in all randomized patients and in patients with PD-L1-positive tumors. An improvement in OS was observed for patients randomized to avelumab plus BSC (n=350) vs. BSC alone (n=350). The hazard ratio for OS was 0.69 (95% CI:0.56, 0.86; 2-sided p-value 0.0005). Median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab plus BSC arm vs. 14.3 months (95% CI: 12.9, 17.9) in the BSC alone arm. Consistent results were observed across the pre-specified subgroups of CR/PR versus SD to first-line induction chemotherapy. In the prespecified endpoint of OS among patients with PD-L1-positive tumors (n=358), the hazard ratio was 0.56 (95% CI: 0.40, 0.79; 2-sided p-value <0.001) for patients randomized to avelumab plus BSC versus BSC alone. Median OS in this subgroup was not reached for patients on the avelumab plus BSC arm (95% CI: 20.3, NE) vs. 17.1 months on the BSC alone arm (95% CI: 13.5, 23.7). PFS results in all randomized patients were supportive; (HR 0.62; 95% CI: 0.519, 0.751), although median PFS was relatively short on both arms; 3.7 month for patients on the avelumab + BSC arm (95% CI: 3.5, 5.5) vs. 2.0 months (95% CI: 1.9, 2.7) for patients on the BSC alone arm. We note that absolute improvement in median PFS for patients on the avelumab + BSC arm (1.7 months) was slightly less than the scanning interval of 8 weeks.

Patients with mUC that has not progressed after initial platinum-containing chemotherapy are managed with routine clinical visits and scheduled imaging to detect progression of disease. Several PD-1/PD-L1 directed agents are approved in the second-line setting, including avelumab, although to be eligible for treatment patients are required to have confirmed progression and presumably need to have a performance status that is sufficiently high at the time of progression to allow for further treatment. Therefore the strategy of managing all patients in whom the cancer has not progressed with switch maintenance therapy with avelumab offers the advantage of treating all patients at the point when they are still well enough to receive treatment, although this might mean an extra few months on avelumab in patients who otherwise would have had a 'treatment holiday' in the interval between the end of initial therapy and the time of progression. Thus the fact that Javelin Bladder 100 demonstrated a large and clinically meaningful OS benefit is important in this context.

Crossover was not allowed on this study for patients on the BSC arm at the time of progression. However, as multiple PD-1/PD-L1 directed therapies are approved in the second-line setting, many patients who progressed did in fact receive such therapy at the time of progression. An exploratory analysis appeared to show that those patients who received pembrolizumab on progression, which is the only PD-1/PD-L1 directed therapy with a demonstrated OS advantage in the second-line setting, did equally well to those who received avelumab immediately after finishing initial chemotherapy. Additionally, an exploratory analysis appeared to demonstrate a lesser degree of OS benefit to those patients with PD-L1-negative tumors, in whom the OS hazard ratio was 0.85 (95% CI: 0.62, 1.18). Results from this latter subgroup, the flip side analysis of the pre-planned PD-L1 positive subgroup, were included in labeling to fully inform clinicans' discussions with their patients about the relative benefits of up-front avelumab therapy vs. a treatment holiday followed by treatment at the time of progression. However, no diagnostic

device was approved together with this application as OS benefit was seen in the prespecified ITT analysis and regardless of PD-L1 status.

Although patients on Javelin Bladder 100 were treated with the 10 mg/kg Q2W dosing regimen of avelumab, modeling and simulation suggests that there is no clinically relevant exposure difference between the 800 mg Q2W and 10 mg/kg Q2W dosing regimens. Thus the Applicant's proposal of converison from the weight-based dose regimen of 10 mg/kg IV Q2W to a flat-dose regimen of 800 mg IV Q2W for avelumab in labeling is acceptable.

Safety and tolerability results are important in this setting, as these patients would previously not have received any active therapy until time of progression. Safety results were consistent with the known toxicity profile of avelumab, with 1 treatment-related death. Although the applicant states that there was no decrement in patient-reported quality of life indices for patients on the avelumab plus BSC arm, FDA disagrees with this assertion as the analysis was neither preplanned nor adequately powered to support a non-inferiority conclusion.

The final agreed upon indication for avelumab in this application is for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy. Regular approval of avelumab for this indication is recommended. This application will also convert the previous accelerated approval in previously-treated UC to regular approval as fulfillment of PMR 3201-1. Submission of the analysis and datasets with the final report from Javelin Bladder 100 will be a post-marketing commitment. Submission of a reanalysis of anti-drug antibodies (ADA) in stored samples from avelumab-treated patients with urothelial cancer and Merkel cell carcinoma with a new ADA method.to inform safety analyses will be a postmarketing requirement as a condition of approval for avelumab.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Patients with metastatic urothelial cancer that has not progressed on treatment with prior platinum-containing chemotherapy are currently maintained on BSC alone, with clinical and radiographic follow-up until disease progression, at which point they become eligible for treatment with one of several approved PD-1/PD-L1 directed therapies. However, many patients may no longer be well enough clinically at the time of progression to be able to actually receive second-line therapy. Thus the strategy of randomizing non-progressing patients to immediate switch maintenance with avelumab plus BSC vs. BSC alone was evaluated in JAVELIN Bladder 100, which was powered for OS in both all-comers and in the PD-L1 positive patients. Although the study did not allower crossover to avelumab on progression, patients were able to access approved therapies off-study when they progressed.

The primary efficacy analysis demonstrated an OS benfit to treatment with avelumab plus BSC (n=350) vs. BSC alone (n=350), The hazard ratio for OS was 0.69 (95% CI:0.56, 0.86; 2-sided p-value 0.0005). Median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab plus BSC arm vs. 14.3 months (95% CI: 12.9, 17.9) in the BSC alone arm. In the prespecified endpoint of OS among patients with PD-L1-positive tumors (n=358), the hazard ratio was 0.56 (95% CI: 0.40, 0.79; 2-sided p-value <0.001) for patients randomized to avelumab plus BSC versus BSC alone. Median OS in this subgroup was not reached for patients on the avelumab plus BSC arm (95% CI: 20.3, NE) vs. 17.1 months on the BSC alone arm (95% CI: 13.5, 23.7). PFS results were supportive; (HR 0.62; 95% CI: 0.519, 0.751).

The safety of avelumab is acceptable in this setting. One death due to an adverse event (sepsis) occurred in a patient on the avelumab plus BCS arm, while permanent treatment discontinuation occurred in 12%. Grade 3-4 adverse events occurred in 47% of patients and the most common (>20%) all grade adverse events were fatigue, musculoskeletal pain, urinary tract infection, and rash. The immune-mediated toxicities of pneumonitis, hepatitis, colitis, endocrinopathies, and nephritis are previously labeled as warnings and precautions for avelumab in addition to infusion related reactions, major adverse cardiovascular events, and embryo-fetal toxicity. No changes were made to these warnings and precautions based on this review. Analysis of patient-reported outcomes were inconclusive, and thus no definitive claims can be made regarding tolerability of avelumab treatment in terms of patient reporting.

Regular approval of avelumab for mUCis recommended by all disciplines. The Applicant will be asked to submit the results of the final overall survival analysis from JAVELIN Bladder 100 as a post-marketing commitment. Updated analyses from the previous urothelial cancer and Merkle cell carcinoma studies using new ADA analysis methods to inform safety analyses will be a post-marketing requirement.
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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with metastatic urothelial cancer that has not progressed on treatment with prior platinum-containing chemotherapy are currently maintained on BSC alone until disease progression, at which point they become eligible for treatment with second-line therapy. However, prognosis for these patients overall is poor and their disease is considered incurable.	Patients with metastatic urothelial cancer that has not progressed on treatment with prior platinum-containing chemotherapy have a serious and life-threatening condition.
Current Treatment Options	• No therapies are approved for the maintenance treatment of patients with metastatic urothelial cancer that has not progressed on treatment with prior platinum-containing chemotherapy. • Several PD-1/PD-L1 directed therapies are FDA-approved for patients with disease progression on or after first-line platinum-containing chemotherapy, including avelumab, durvalumab, atezolizumab, nivolumab, and pembrolizumab, although pembrolizumab is the only therapy with a demonstrated OS advantage in this setting. Erdafitinib is approved for second-line treatment of patients with FGFR-altered tumors, and Enfortumab vedotin is approved in the third-line setting.	There are no current approved options for patients with mUC in the maintenance setting after first-line platinum-containing chemotherapy.
Benefit	• In the analysis of JAVELIN Bladder 100, the HR for overall survival of patients on the avleumab plus BSC arm vs. BSC alone was 0.69 (95% CI:0.56, 0.86). Median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab plus BSC arm vs. 14.3 months (95% CI: 12.9, 17.9) in the BSC alone arm. • In the prespecified endpoint of OS among patients with PD-L1-positive tumors (n=358), the hazard ratio was 0.56 (95% CI: 0.40, 0.79) in the avelumab plus BSC arm vs. the BSC alone arm. • PFS results for all enrolled patients were supportive; (HR 0.62; 95% CI: 0.519, 0.751),	Avelumab plus BSC has demonstrated an OS improvement vs. BSC in the maintenance setting after first-line platinum-containing chemotherapy, with an acceptable safety profile.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Avelumab was well-tolerated in most study patients with a low rate of discontinuations due to adverse events. • Important risks include fatigue, musculoskeletal pain, urinary tract infection, and rash. • No changes were made to the labled warnings and precautions for avelumab and no REMS will be required for this application.	The risk-benefit profile of avelumab is acceptable in the approved patient population.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

					Section where discussed, if applicable
□	The patient experience data that was submitted as part of the application, include:				
	X	Clinical outcome assessment (COA) data, such as			Section 8.1.2. Efficacy Results – Secondary or exploratory COA (PRO) endpoints; Section 8.1.3 (Integrated Review of Effectiveness) Additional Efficacy Considerations Section 19.5 Appendix
			X	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			

	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.		

X

Cross-Disciplinary Team Leader

2. THERAPEUTIC CONTEXT

2.1. Analysis of Condition

The Applicant's Position:

Disease Background

Urothelial carcinoma includes tumors originating from the urothelial cells lining the bladder, renal pelvis, ureter, and urethra (NCCN Clinical Practice Guidelines Version 1.2020). Bladder cancer alone accounts for 90% of UC, with approximately 550,000 new cases diagnosed and 200,000 deaths attributed to bladder cancer worldwide each year (Bray et al 2018). Urothelial cancers are the most common type of bladder cancer in North America (Sanli et al. 2017). Urinary bladder cancer is more common in men, with a 2:1 male-to-female incidence ratio for upper tract urothelial carcinoma (Miyazaki et al. 2017).

Approximately 30% of patients with newly diagnosed urothelial cancer present with muscle-invasive urothelial cancer of the bladder, a high-grade, typically aggressive disease requiring multimodal therapy including radical cystectomy in combination with chemotherapy/biological therapy and/or radiation (Rosenberg 2005, Stein 2001, Vishnu 2011).

The FDA's Assessment:

The FDA agrees with the Applicant's position as stated above.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Platinum-based regimens are the standard of care first-line treatment for patients with aUC and result in median OS ranging from 9-14 months (De Santis et al 2011 and Calabro 2009). Despite initial high response rates, durable responses following first-line chemotherapy are uncommon. Following successful first-line treatment, patients are typically managed with BSC until disease progression. Most patients will experience disease progression within 9 months after the initiation of treatment (von der Maase et al 2005). No treatments have demonstrated an improvement in OS at completion of first-line treatment for aUC.

The current standard of care for patients who are able to receive second-line treatment of aUC is a PD-1 or PD-L1 inhibitor, including avelumab in some countries, including the United States (NCCN Clinical Practice Guidelines Version 1.2020). Despite the use of these agents, the median OS for patients with aUC in the second-line setting is approximately 10-11 months (Bellmunt et al 2017; Powles et al 2018).

Given the activity of PD-1/PD-L1 therapy in patients with UC and the growing evidence that maintenance treatment after first-line chemotherapy could be an effective treatment strategy (Grivas et al 2014; Powles et al 2017; Galsky et al 2019), avelumab plus BSC versus BSC was evaluated in the current Phase 3 study (Study B9991001) to determine if OS can be prolonged in patients with aUC whose disease has not progressed with first-line platinum-based induction chemotherapy.

The FDA's Assessment:
The FDA agrees with the Applicant's position above, but would clarify that, based on the references listed, "the median OS for patients with aUC in the second-line setting is approximately 10-11 months" from the time of initiation of second-line therapy.

As the Applicant stated, patients are typically managed with BSC following successful first-line treatment, until disease progression. In the U.S., standard-of-care management in addition to BSC includes routine scans to evaluate for progression, often with a low threshold for as-needed scans for new symptoms. Maintenance therapy has not been approved by any global regulatory agency for aUC and is not standard-of-care; thus patients essentially have a "treatment holiday" between cessation of first-line treatment and evidence of clinical and/or radiographic progression.

Pembrolizumab has regular approval, with a demonstrated OS benefit, in the second-line setting. Other PD-1/PD-L1 inhibitors (avelumab, atezolizumab, durvalumab, and nivolumab) were granted accelerated approval based on ORR, DoR, and favorable toxicity profiles.

There is some evidence to suggest that not all patients who complete their first line therapy and subsequently progress remain eligible for treatment of any sort at the time when they ultimately progress, as many may be too sick at that point to receive subsequent therapy. This is true even in the clinical trial setting, where crossover after maintenance chemotherapy was preplanned in a similar patient population and only 68% (27/40) of progressing patients received planned therapy at time of progression.[1]

In terms of the treatment landscape for initial therapy as it applies to patient eligibility for JAVELIN Bladder 100, cisplatin is the standard first-line therapy in this setting. However, a substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities. The preferred regimens for patients who are not eligible for cisplatin are

- gemcitabine and carboplatin
- atezolizumab or pembrolizumab for patients who either are not eligible for any platinum-containing chemotherapy *or* have PD-L1 expressing tumors

Thus patients were eligible for enrolment for JAVELIN Bladder 100 if they had received prior treatment with either cisplatin or carboplatin containing regimens in the up-front setting, reflective of the commonly-used up-front, non-immunitherapy regimens in this setting.

3. REGULATORY BACKGROUND

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Avelumab received accelerated approval in the US (in 2017), conditional approval in Canada, and approval in Israel, for the treatment of adult patients with aUC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12

months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Avelumab also received accelerated approval from the US FDA in March 2017 for the treatment of adult and pediatric patients 12 years and older with metastatic MCC and received marketing authorization for metastatic MCC in the EU, Switzerland, Japan, Canada, Israel, Australia, and multiple other countries. In October 2018, FDA approved a change from weight-based dosing to a flat 800 mg dose for BAVENCIO. In May 2019, avelumab received approval in the US for the treatment of adult patients with aRCC in combination with axitinib (VEGFR TKI); the same indication was approved in the EU in October 2019 and is approved in multiple other countries. Avelumab is marketed in countries where it is approved.

The FDA's Assessment:
The FDA agrees with the Applicant's position above.
The accelerated approval in 2017 for avelumab in the second line for aUC was granted with a PMR to submit the final overall survival reports for JAVELIN Bladder 100, the phase 3 trial forming the basis of this current sBLA.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
A Type B Pre-Phase 3 meeting with the FDA was held 30 September 2015 to discuss the proposed registrational study of avelumab as a maintenance treatment for patients with urothelial carcinoma, Study B9991001. Key design elements of Study B9991001 were discussed, including overall study design, eligibility criteria, choice of comparator, primary and secondary endpoints, stratification factors, registration strategy, biomarker sub-group analysis, and safety monitoring. Changes to the protocol that were discussed and incorporated into the final protocol included making OS the primary endpoint of the study and removing a crossover following disease progression for patients receiving BSC alone.

On 12 June 2019, pre-sBLA format and content Type C written responses were received from the FDA on specific proposals from the Applicant's clinical studies to be included in a proposed sBLA, clinical pharmacology analysis, diagnostic analysis, subgroups for safety analysis, SAE reports to be included in the submission beyond the Study B9991001 CSR data cutoff date, safety narratives, integrated summary of safety and efficacy, datasets and case report tabulations, clinical site listing, table of contents, RTOR, assessment aid, and the study data standardization plan.

The topline results from Study B9991001 were provided to the FDA on 8 January 2020. On 16 January 2020, a teleconference was held with the FDA to discuss RTOR and BTD requests. The request to participate in the RTOR pilot was submitted to the IND on 21 January 2020; FDA granted participation on 23 January 2020. A request for BTD was submitted to the IND on 27 January 2020.

The FDA's Assessment:
The FDA generally agrees with the Applicant's position above.

Specifically, FDA recommended OS be the primary endpoint and referenced the Oncologic Drugs Advisory Committee (ODAC) meeting on June 25, 2014, where many committee members described a strong preference for a demonstrated improvement in overall survival to support approval in the setting of maintenance therapy.

The Applicant chose not to allow crossover following the pre-IND meeting September 30, 2015. The Applicant asked if the FDA agreed with the original proposal allowing crossover. FDA responded: "The use of a crossover design is at the discretion of the Sponsor. However… your OS analysis may be confounded by the crossover aspect, making a difference in OS difficult to detect. In a circumstance with a small PFS effect and no OS effect, it would be difficult to assess the benefits of your therapy in this population. We recommend you consider these points when weighing the risks of a crossover design vs. its benefits… The FDA advises against a single sided crossover if overall survival will be a primary endpoint."

Additional information to update the regulatory history provided above include: a) The BTD request was granted on March 26, 2020; and b) FDA received the final component of the sBLA RTOR submission on April 7, 2020.

4. SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1. Office of Scientific Investigations (OSI)

The clinical site inspections for this efficacy supplement were waived; the FDA believes the study data are reliable in support of the proposed indication. This drug product has been reviewed and approved in several indications. Since inspections have been completed in other indications and there was no indication of misconduct for this application. COVID-19 had also become a global pandemic by the time this application was submitted and both international and national travel were impractical and unsafe for inspectors.

4.2. Product Quality

[FDA will complete this section.]

4.3. Clinical Microbiology

[FDA will complete this section.]

4.4. Devices and Companion Diagnostic Issues

The applicant did not submit an application for an *in vitro* diagnostic device (IVD). FDA agrees that the use of an IVD is not essential to the safe and effective use of avelumab in the proposed setting as efficacy was observed in patients who were both PD-L1 positive and negative. See efficacy review for further discussion.

5. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5.1. Executive Summary

No data was submitted for review.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
No new information is provided in the current submission.

5.3. Pharmacology

Primary pharmacology

N/A

Secondary Pharmacology

Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
N/A

Safety Pharmacology

Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
N/A

5.4. ADME/PK

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
N/A

5.5. Toxicology

The Applicant's Position:
No new toxicology information is provided in the current submission.

The FDA's Assessment:
N/A

X	X
Primary Reviewer	Supervisor

6. CLINICAL PHARMACOLOGY

6.1. Executive Summary

The FDA's Assessment:
In this supplemental BLA submission, the applicant seeks to gain approval for first-line maintenance treatment of patients with locally advanced or metastatic urothelial cancer. The proposed recommended dosing regimen is acceptable from a clnical pharmacology perspective. The efficacy and safety of body weight-based avelumab dosing regimen of 10 mg/kg intravenous (IV) infusion every 2 weeks (Q2W) plus Best Supportive Care (BSC) were evaluated in a randomized, open-label, parallel 2-arm, Phase 3 registration Study B9991001 in patients with locally advanced or metastatic urothelial cancer (UC) that did not progress after completion of first-line platinum-containing chemotherapy. An open-label, dose-finding, phase 1 supportive Study EMR 100070-001 provided additional pharmacokinetics data in patients with UC. The proposed dose regimen is a flat avelumab 800 mg administered as an IV infusion over 60 minutes Q2W. Modeling and simulation suggested that there is no clinically relevant exposure difference between the 800 mg Q2W and 10 mg/kg Q2W dosing regimens. The converison from the weight-based dose regimen of 10 mg/kg IV Q2W to a flat-dose regimen of 800 mg IV Q2W is acceptable.

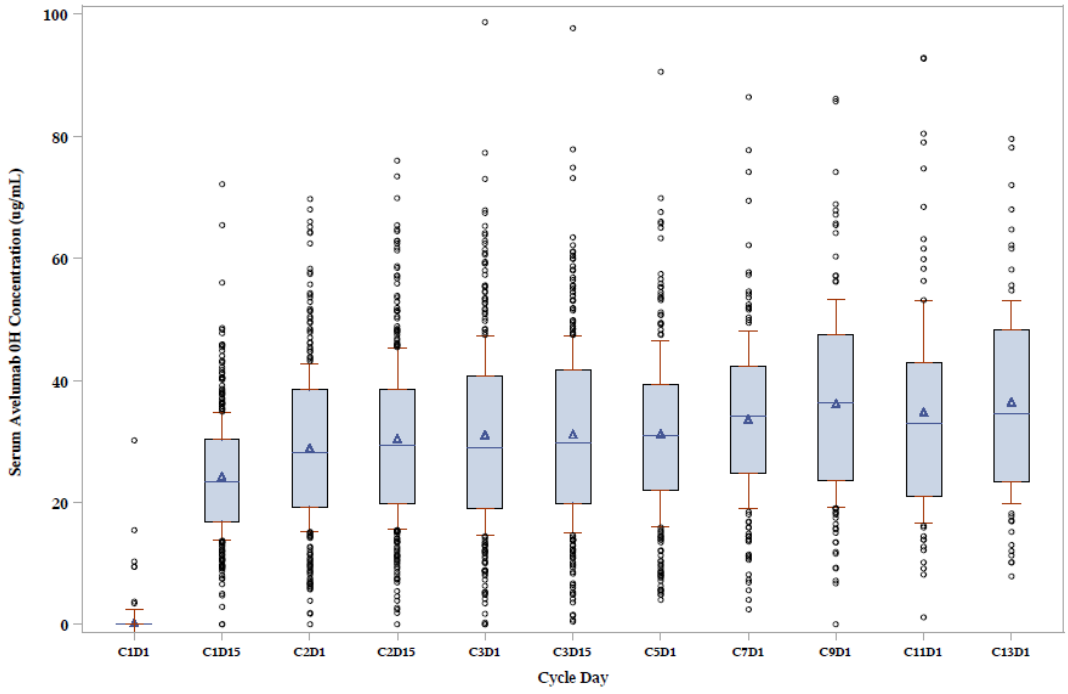
6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:
The pharmacology and clinical PK characteristics of avelumab as a single agent were summarized in prior submissions for MCC (BLA 761049) and UC (BLA 761078), and in combination therapy with axitinib for RCC (BLA 761049/S-006). Updated PK data for avelumab as a single agent are available from 344 patients treated with avelumab in Study B9991001. Figure 1 presents avelumab C_{trough} concentrations by Cycle and Day. Avelumab concentrations appeared to reach steady state at Cycle 2 and did not appear to increase over time, consistent with previous data in the UC population of EMR 100070-001 study. A popPK model using previously submitted PK data from 1827 patients (with 14 different tumor types) treated with single-agent avelumab was used in conjunction with the PK data available in Study B9991001 to generate avelumab exposure metrics (PMAR-EQDD-B999f-sNDA-960). The exposure metrics of steady-state AUC and C_{trough} were used to compare with those of the 800 mg Q2W flat dosing regimen to support the flat dose in patients with UC.

Of the 344 patients with UC treated with avelumab from Study B9991001, 325 were evaluable for treatment-induced ADA and 62 (19.1%) tested positive. For the 62 patients with treatment-induced ADA, the median time to ADA response was 10.2 weeks (range: 2.1, 35.7; Table 1) and the Kaplan-Meier estimate of median duration of ADA response was 2.4 weeks (95% CI: 0.1, 7.7; Figure 2). For the patients with a treatment-induced ADA response, persistent ADA response was observed in 43 (13.2%) patients and the remaining 19 (5.8%) patients experienced a transient response. A positive ADA response was observed at baseline in 4 (1.2%) patients and none experienced treatment-boosted ADA.

Figure 1. Box Plots of Serum Avelumab 0H Concentration by Visit – Avelumab PK Concentration Analysis Set



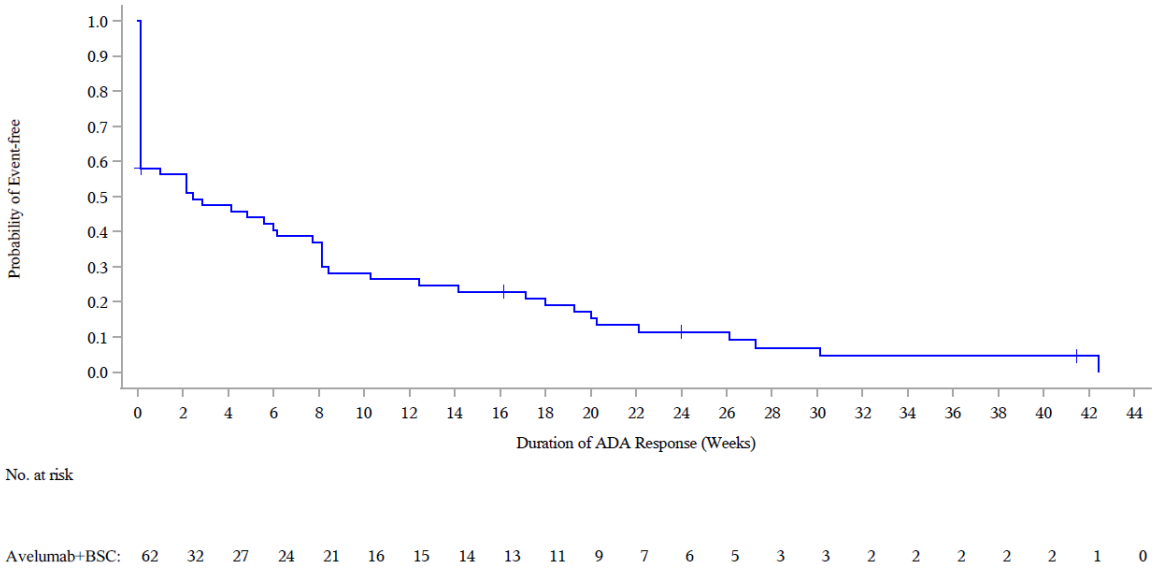
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
The lower limit of quantification is 0.20 ug/mL.
Values included are from samples collected on day of infusion on or prior to infusion start time and following a prior dose that was within ±10% of 10 mg/kg and was administered within 14 ± 3 days of the sample in case of cycles 1 to 3.
Values from anomalous sample which are 3 SD above or below the mean concentration for the same visit and nominal time have been excluded from the presentation.
Symbol in the box interior = Mean. The horizontal line in the box interior = Median. Upper and lower box lines = 1st quantiles and 3rd quantiles, respectively.
End of vertical lines = 1 SD above and below the mean.
Symbols outside the box = measurements outside 1 SD from the mean.
PFIZER CONFIDENTIAL SDTM Creation: 29DEC2019 (22:00) Source Data: ADPC Output File: ./B9991001_restricted/B9991001/pk_plot Date of Generation: 14JAN2020 (09:44)
Cutoff Date: 30JUN2019 Snapshot Date: 21NOV2019

Table 1. Summary of Time to ADA Response - Subjects with Treatment-induced ADA in the Immmugenicity Analysis Set

Time to ADA response (weeks)	Avelumab+BSC (N=62)
Mean (SD)	13.0 (7.52)
Q1	7.7
Median	10.2
Q3	16.1
Range (min, max)	(2.1, 35.7)

The descriptive summary statistics are calculated based on N, the number of subjects in the immunogenicity analysis set with treatment-induced ADA.
Time (weeks) to ADA response is defined as: (date of first positive ADA result - date of first dose of avelumab + 1)/7.
PFIZER CONFIDENTIAL SDTM Creation: 29DEC2019 (22:00) Source Data: ADIS Output File: ./B9991001_restricted/B9991001/adis_s002 Date of Generation: 14JAN2020 (09:19) Cutoff Date: 30JUN2019 Snapshot Date: 24DEC2019

Figure 2. KM Plot of Duration of ADA Response



Source: figure 14.4.9.1.1 of interim report body.

The Applicant's Position:

The clinical pharmacology package for this sBLA includes descriptive summaries of avelumab concentrations, population PK assessments, and characterization of ADA for avelumab from data collected in patients with UC in Study B9991001. The avelumab PK parameter estimates from the popPK analysis were similar to those obtained in the single-agent setting in various solid

tumor types.

This study used a more sensitive and drug-tolerant ADA assay than the assay used in previous studies for single-agent avelumab in various solid tumor types. Treatment-induced ADA incidence (19.1%) in Study B9991001 was similar to the incidence reported in the aRCC population (14.6%), which used the same assay.

The FDA's Assessment:
FDA agrees with the Applicant's description of avelumab concentrations, population PK assessments, and characterization of ADA for avelumab from data collected in patients with UC in Study B9991001.
In the applicant provided Data section above, the referred Tables and Figure (Table 14.1.1.1, Table 14.4.9.1.2 and Figure 14.4.9.1.1) are from Interim Clinical Study Report Protocol JAVELIN BLADDER 100/B9991001 (Final Sign-off Date: 24 February 2020).

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
Administration of 10 mg/kg IV Q2W of avelumab to patients with aUC in Study B9991001 yielded PK exposures similar to those of the simulated 800 mg IV Q2W regimen previously reported from solid tumor patients. Predicted exposure metrics, including C_{trough} and AUC at steady state showed overlapping distribution with simulated exposures in the avelumab monotherapy clinical database for the 10 mg/kg IV Q2W dosing regimen, and simulated exposures for the 800 mg IV Q2W dosing regimen.

The Applicant's Position:
The proposed dosing regimen for avelumab for patients with locally advanced or metastatic UC is 800 mg IV Q2W, in line with the current USPI. Although Study B9991001 employed the weight-based avelumab regimen of 10 mg/kg IV Q2W, the avelumab exposures observed in the study are similar to the simulated exposures for the 800 mg IV Q2W dosing regimen, thus the 800 mg IV Q2W dosing regimen is proposed for the indication. **[[SCP shell, Sect 2.7.2.1.3]]**

The FDA's Assessment:
The converison from the weight-based dose regimen of 10 mg/kg IV Q2W to a flat-dose regimen of 800 mg IV Q2W is acceptable. The same conversion was accepted based on modeling and simulation approach under BLA 761049 Supplement-3 for pateints with locally advanced or metastatic UC. Modeling and simulation suggested that there is no clinically relevant exposure difference between the 800 mg Q2W and 10 mg/kg Q2W dosing regimens. Refer to ClinPharm review dated 9/21/2018 in DARRTs for more details.

6.2.2.2. Therapeutic Individualization

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant's position above.

6.2.2.3. Outstanding Issues

Data:
Not Applicable.

The Applicant's Position:
PMC Study 3201-2 associated with the accelerated approval of 2L UC, is underway to evaluate safety, efficacy and exposure-response relationships of avelumab with more frequent dosing. The assessment is ongoing under clinical trial EMR100070-005 entitled "A Phase 3, Open-Label, Multicenter Trial of Avelumab (MSB0010718C) Versus Platinum-Based Doublet as a First-Line Treatment of Recurrent or Stage IV PD-L1+ Non-Small Cell Lung Cancer". The final report for this PMC is to be submitted in October 2020.

Per the previous sBLA approval for RCC, a PMC (3588-3) is underway to reanalyze ADA in stored samples from the 249 avelumab-treated patients with UC (Study EMR 100070-001) and 88 patients with MCC (Study EMR 100070-003) using the new ADA assay method. In Study B9991001, ADA have been assessed using the new ADA assay method. The final, comprehensive report on immunogenicity is to be submitted in March 2021.

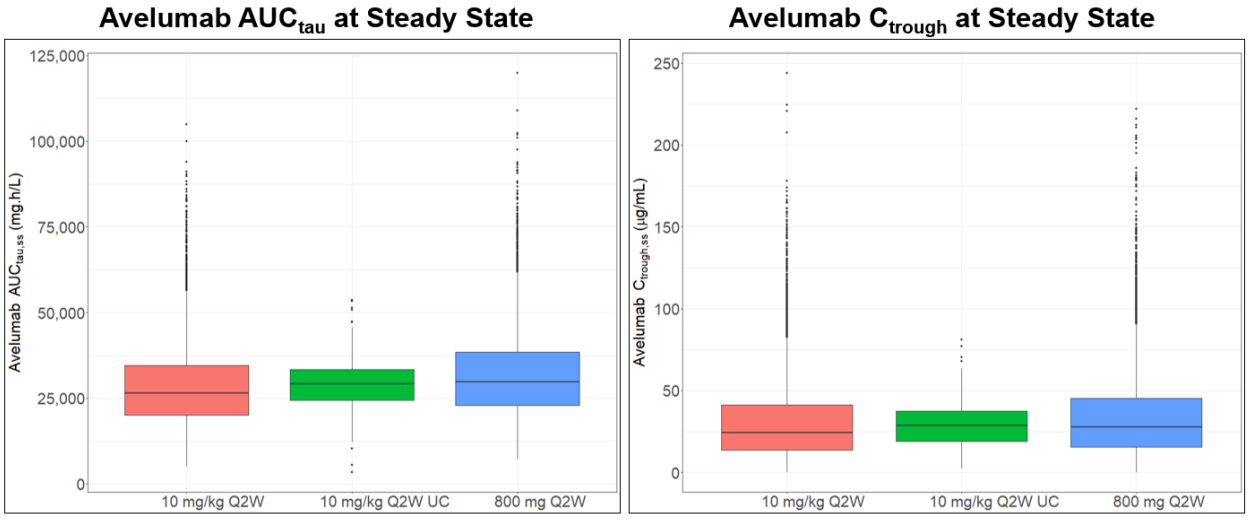
The FDA's Assessment:
FDA agrees with the Applicant's position above.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
The avelumab Summary of Clinical Pharmacology Studies (Module 2.7.2) included in the current sBLA [add current supplement number when assigned] provides a comprehensive summary of avelumab PK, popPK, and ADA. Avelumab exposures with the weight-based regimen of 10 mg/kg IV Q2W used in Study B9991001 are similar to the simulated exposures for the 800 mg IV Q2W flat-dosing regimen (Figure 3).

Figure 3. Boxplots for Predicted Avelumab Exposure in aUC and Simulated Reference Exposure Following Weight Based and Flat Dosing Regimens for AUCtau,ss (Left Plot) and Ctrough,ss (Right Plot)



Source: PMAR-EQDD-B999f-sNDA-960: Figure 16 and Figure 17.
Footnote: Green boxplots are observed (predicted from individual parameter estimates) exposures in aUC population of 344 patients receiving avelumab 10 mg/kg Q2W plus BSC using the current popPK model; red boxplot and blue boxplot are previously-simulated exposures following 10 mg/kg Q2W and 800 mg Q2W, respectively, using popPK model results in solid tumor monotherapy population as performed in flat-dosing report (Modeling and Simulation Population Analysis Report for Weight Based vs Flat Dosing, December 2017, BLA 761049/S-003).

A new ADA assay method with improved sensitivity was used in the UC population from B9991001 and in the previous RCC population. In the RCC population, 453 patients treated with avelumab 10 mg/kg Q2W in combination with axitinib 5 mg twice daily were evaluable for ADA and 66 (14.6%) patients tested positive. Similarly, in the UC population, treatment-induced ADA incidence was 19.1% (62 patients). Patients who tested positive for treatment-induced ADA had approximately 15% increase in avelumab clearance. The development of treatment-induced ADA against avelumab did not appear to alter the risk of infusion-related reactions.

The Applicant's Position:
The PK of avelumab as a single agent is well characterized in UC BLA 761049 (MCC and 2L UC). This sBLA includes PK data from Study B9991001. Avelumab exposures from Study B9991001 are similar to those of previously submitted simulated exposures from various solid tumors at the dose regimen of 800 mg IV Q2W. In alignment with the current avelumab label, the dosing justification of the 800 mg IV Q2W regimen for aUC is supplied as part of the clinical pharmacology package and described in Section 6.2.2.1.

The observed incidence of treatment-induced ADA for patients treated with avelumab single agent in Study B9991001 (19.1%) is similar to the incidence (14.6%) reported in patients with

RCC using the same new ADA assay method. No clinically meaningful impact of ADA on safety of avelumab was observed.

The FDA's Assessment:
FDA agrees with the Applicant's position above on the PK of avelumab.
The effect of ADA on the safety could not be determined due to insufficient numbers of patients in the ADA positive subgroup and confounding variables.
Landmark analyses were conducted for overall survival (OS) and progression-free survival (PFS) in ADA week 9 positive patients. With 18 ADA week 9 positive patients in OS landmark analysis and 13 ADA week 9 patient in PFS landmark analysis, the impact of immunogenicity on efficacy was inclusive due to the insufficient numbers of patients. However, the point estimation suggested there is no strong association between immunogenicity with worse efficacy endpoint of OS or PFS. Refer to Section 19.4 for more details.

6.3.1.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:
No exposure-response analyses for avelumab in locally advanced or metastatic UC were performed.

The Applicant's Position:
PopPK and PK/PD analyses for efficacy and safety for patients with aUC were submitted with the prior submissions (BLA 761078 (now closed and administratively merged with 761049) and BLA 761049/S003)). The results of the updated PK analyses from Study B9991001 demonstrated that avelumab exposures were similar to those from previous analyses in patients treated with single-agent avelumab, including patients with UC. Therefore, the proposed 800 mg IV Q2W flat-dosing regimen is expected to provide the same positive benefit-risk ratio for avelumab in aUC as the weight-based regimen.

The FDA's Assessment:
FDA agrees with the Applicant's position above.

6.3.1.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

APPEARS THIS WAY ON ORIGINAL

Data:
PK data from the UC population in Study B9991001 are presented in Section 6.2.1 and **Error! Reference source not found.**. The results from the popPK analysis confirmed the exposures observed in patients treated with avelumab 10 mg /kg IV Q2W in Study B9991001 overlap with those from reference simulations previously presented for the 800 mg Q2W flat-dosing regimen. [[SCP Shell, Sect 2.7.2.2.2]]

The Applicant's Position:
Avelumab exposures from patients with UC in Study B9991001 were consistent with the 800 mg Q2W flat-dosing regimen that is described in the approved avelumab prescribing information

(Bavencio USPI 2019). The data support the proposed dosing regimen of avelumab 800 mg IV Q2W for the general patient population. [[SCP Shell, Sect 2.7.2.3.2.3]]

The FDA's Assessment:
FDA agrees with the Applicant's position above.

6.3.1.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:
No new information is provided in the current submission.

The Applicant's Position:
No dose adjustments are recommended for other intrinsic or extrinsic factors.

The FDA's Assessment:
FDA agrees with the Applicant's position above

6.3.1.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:
No new information is provided in the current submission.

The Applicant's Position:
Avelumab is administered IV and eliminated by intracellular lysosomal proteolytic degradation throughout the entire body and therefore is not expected to be affected by food or small molecule drugs that are CYP450 enzyme modulators or by transporter modulators.

The FDA's Assessment:
FDA agrees with the Applicant's position above.

X	X
Wentao Fu Primary Reviewer	Pengfei Song Team Leader
X	X
Yuan Xu Pharmacometric Primary Reviewer	Jiang Liu Pharmacometric Team Leader

7. SOURCES OF CLINICAL DATA

7.1. Table of Clinical Studies

Data:

Table 2. Listing of Clinical Trials Relevant to Urothelial Carcinoma Submission B9991001

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Primary Study Endpoints	Treatment Duration/ Follow Up	No. of patients	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
B9991001 (IND 126,217) Sponsor: Pfizer	NCT02603432	Phase 3, multinational randomized, open-label parallel arm- study of avelumab (MSB0010718C) plus best supportive care versus best supportive care alone as a maintenance treatment in patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-based chemotherapy	Avelumab 10 mg/kg every 2 weeks IV plus best supportive care, or best supportive care alone	OS	Treatment until confirmed disease progression or unacceptable toxicity; follow-up for survival until death or end of study	1:1 Randomized patients= 700 avelumab + BSC=350 BSC alone=350 Treated patients: Arm A: avelumab + BSC= 344 Arm B: BSC alone=345	Patients with unresectable locally advanced or metastatic UC whose disease did not progress on or following completion of first-line platinum-based chemotherapy	Multicenter: 231 sites in 30 Countries including: North America, Central/South America, Asia-Pacific (including Japan), and Europe
		Prior Studies in aUC						
EMR100070-001	NCT01772004	Phase 1, open-label, multiple ascending dose trial to	Dose escalation phase:	Dose-escalation part: DLTs	Treatment until confirmed PD, unacceptable	Dose-escalation phase: 61	Total patient population: patients with	Multicenter: 89 sites in Belgium,

(IND 115,747) Sponsor: EMD Serono		investigate the safety, tolerability, PK, biological and clinical activity of avelumab and expansion to selected indications in patients with metastatic or locally advanced solid tumors	1, 3, 10, and 20 mg/kg every 2 weeks Expansion phase: Avelumab 10 mg/kg every 2 weeks IV	during the first 3 weeks of treatment Efficacy Expansion cohorts: Confirmed best overall response, per RECIST 1.1, as adjudicated by an Independent Endpoint Review Committee	toxicity, or if any criterion for withdrawal from the trial or investigational medicinal product occurred; follow-up for survival until death or end of study	•1 mg/kg Q2W - 4 •3 mg/kg Q2W - 13 •10 mg/kg Q2W - 15 •10 mg/kg weekly - 8 •20 mg/kg Q2W - 21 Expansion phase: 1697 •aUC secondary expansion: 44 •aUC efficacy expansion: 205 • 10 mg/kg Q2W	metastatic or locally advanced solid tumors UC expansion cohorts: patients with metastatic or locally advanced UC whose disease progressed after treatment with at least 1 platinum-containing regimen or were platinum ineligible.	Czech Republic, France, Germany, Republic of China, Republic of Korea, United Kingdom, and the United States enrolled 249 patients with aUC.

The Applicant's Position:

Table 2 provides a listing of clinical studies relevant to this sBLA.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the clinical trials relevant to this submission.

8. STATISTICAL AND CLINICAL EVALUATION

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study B9991001

Trial Design

The Applicant's Description:
This Phase 3, multicenter, multinational, randomized, open label, parallel-arm efficacy and safety study was designed to compare avelumab plus BSC to BSC alone as a maintenance treatment in adult patients with locally advanced or metastatic UC whose disease has not progressed with first-line platinum-based induction chemotherapy (gemcitabine + cisplatin or gemcitabine + carboplatin) (Table 4).

The primary objective of Study B9991001 was to demonstrate the benefit of maintenance treatment with avelumab plus BSC versus BSC alone in prolonging OS in patients with aUC who are in complete or partial response or have stable disease with first-line platinum-based chemotherapy in each co-primary patient population: 1) patients determined to have PD-L1-positive tumors and 2) all randomized patients.

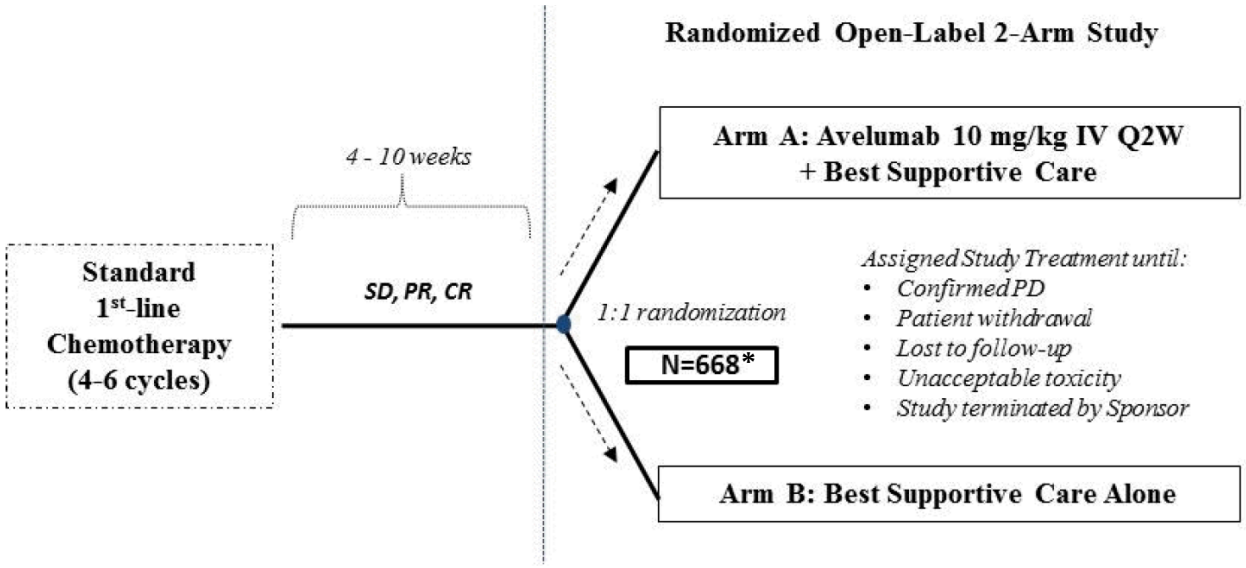
- Patients must have received at least 4 cycles, but not more than 6 cycles, of a first-line chemotherapy regimen consisting of either gemcitabine + cisplatin or gemcitabine + carboplatin before randomization into this study.

- Only patients without PD as per RECIST v1.1 (i.e., with ongoing CR, PR, or SD) after 4-6 cycles of chemotherapy were allowed to be randomized in this study. Randomization should have occurred at least 4 but not more than 10 weeks after the date of administration of the last dose of chemotherapy.

- Patients were randomized in a 1:1 ratio to receive avelumab plus BSC or BSC alone. Randomization was stratified by best response to first-line chemotherapy (CR/PR vs SD), and metastatic disease site (visceral vs non-visceral) at the time of initiating first-line chemotherapy.

Figure 4. Study Design (Study B9991001)

*



* Planned. Actual number of patients randomized, N=700.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the design features, except that patients were allowed to be treated beyond RECIST-defined progression. This was stated in the USPI, i.e. "Administration of BAVENCIO was permitted beyond RECIST-defined disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator."

To identify patients for the first co-primary endpoint, those with PD-L1-positive tumors, the Applicant used the Ventana SP263 assay. Tumors that met one of the following criteria were considered positive:

- ≥25% of tumor cells exhibit membrane staining; or,
- Immune cells present (ICP) > 1% and immune cells with PD-L1 staining (IC+) ≥25%; or,
- ICP = 1% and IC+ = 100%.

Patients enrolled could have up to 10 weeks elapsed from their last dose of chemotherapy prior to study enrollment, although baseline imaging was performed within 4 weeks of the date of initiation of treatment on study drug or BSC arm per protocol. This helped ensure that those who might have had early progression in the slight lapse of time between last dose of chemotherapy and initiation of study treatment were identified, as those with PD as best response to prior chemotherapy were not eligible for enrollment.

Additionally, the fact that this slight lapse in time between chemotherapy ending and initiation of study treatment was allowed was clarified in the USPI, where the following language was added to section 14, "Treatment was initiated within 4-10 weeks after last dose of chemotherapy."

Study Endpoints

The Applicant's Description:
Primary and secondary endpoints were agreed upon following consultation with the FDA (See Section 3.1).

Primary Endpoint:
- Overall Survival (OS)

Secondary Endpoints:
- Progression-free survival (PFS) based on BICR assessment per RECIST v1.1.
- Investigator-assessed PFS per RECIST v1.1.
- Objective Response (OR), Time to Tumor Response (TTR), Duration of Response (DR), and Disease Control (DC), as assessed per RECIST v1.1 by BICR and investigator
- Safety: AEs and laboratory abnormalities as graded by NCI CTCAE v4.03; vital signs (blood pressure, pulse rate)
- PK: C_{max} and C_{trough} concentrations for avelumab
- Immunogenicity: Incidence of anti-drug antibodies (ADA; neutralizing antibody [nAb]) against avelumab.
- Biomarkers: Tumor tissue biomarkers including, but not limited to, PD-L1 expression and tumor-infiltrating CD8+ T lymphocytes.
- Patient-Reported Outcomes: patient-reported bladder cancer symptom, functioning, global quality of life (QOL), and Time to Deterioration (TTD) using the NCCNFACT FBlSI-18; and health status using the EQ-5D-5L.

The FDA's Assessment:
The FDA generally agrees with the Applicant's description of the endpoints.

Statistical Analysis Plan and Amendments

The Applicant's Description:
The original SAP (Version 1), dated 23 December 2015, described all of the planned analyses for Study B9991001 and was updated once after protocol amendment 4. Version 2 of the SAP was dated 02 April 2019. [[B9991001 SAP Table 1]]

The study was designed to test, in parallel, the following hypotheses:

$H_{0\ \text{All patients}}$: $HR_{OS\ (\text{Arm A/Arm B})} \geq 1$, versus $H_{a\ \text{All patients}}$: $HR_{OS\ (\text{Arm A/Arm B})} < 1$

$H_{0\ \text{PD-L1+}}$: $HR_{OS\ (\text{Arm A/Arm B})} \geq 1$, versus $H_{a\ \text{PD-L1+}}$: $HR_{OS\ (\text{Arm A/Arm B})} < 1$

To maintain the overall significance level in the study at or below 1-sided 0.025, α=0.015 was allocated to the OS comparison in all randomized patients and α= 0.010 to the OS comparison in

patients with PD-L1-positive tumors. The significance levels for each test also took into account the group sequential nature of the design.

For all patients, 425 OS events were required to have at least 93% power to detect a hazard ratio of 0.7 using a 1-sided log-rank test at a significance level of 0.015, and a 2-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-8) β-spending function to determine the non-binding futility boundary.

For patients with PD-L1-positive tumors, 219 OS events would provide 80% power to detect a hazard ratio of 0.65 using a 1-sided log-rank test at a significance level of 0.01, and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-8) β-spending function to determine the non-binding futility boundary.

A maximum of 2 distinct analyses cutoffs were planned in the study:

- IA after all patients had been randomized in the study and with a cutoff corresponding to the latest of approximately 315 deaths in all randomized patients and 146 deaths in patients with PD-L1-positive tumors;
- the final analysis after all patients randomized in the study had been followed for a minimum of 12 months and with a cutoff corresponding to the latest of 425 deaths in all randomized patients and 219 deaths in patients with PD-L1-positive tumors

Since the observed number of events at the IA was not exactly equal to the planned number of events, the efficacy and futility boundaries were determined based on the actual number of observed events using the pre-specified α-and β-spending functions (Table 3). The efficacy boundaries were crossed for both the all randomized population and the PD-L1-positive population at the time of the IA.

Table 3. Efficacy and Futility Boundaries at Interim Analysis- Randomized Patients

	Population	
	All patients	**Patients with PD-L1-positive tumors**
Observed number of events (IF)	324 (76.2%)	143 (65.3%)
p-value (z-value) for efficacy	<0.0053 (<-2.553)	<0.0014 (<-2.981)
p-value (z-value) for futility [a]	>0.1849 (>-0.897)	>0.3718 (>-0.327)

[a] Non-binding.

The FDA's Assessment:
FDA generally agrees with Applicant's description of the Statistical Analysis Plan. As noted in the last sentence above, the efficacy boundaries were crossed for both the all randomized population and the PD-L1-positive population at the time of the Interim Analysis (IA). At the

Applicant Orientation Meeting on May 5, 2020, the Applicant stated that the final analysis was "no longer planned since efficacy boundaries at IA were crossed." During PMC discussions, the Applicant agreed to submit the final survival results, analyses, and datasets. The final report is expected in 2021. See Section 13.

Protocol Amendments

The Applicant's Description:
The final Study B9991001 protocol was dated 29 October 2015. During the study, there were 4 protocol amendments (17 December 2015, 24 March 2016, 19 December 2016, 28 March 2019). Some of the amendment changes modified the conduct of the study, including:

- Clarified that first-line chemotherapy must have been completed no less than 4 weeks and no more than 10 weeks prior to randomization.
- An expedited blinded independent central review (BICR) for investigator-assessed disease progression was added.
- The requirement for central eligibility review of first-line chemotherapy response was removed.
- Mandatory measurement of cardiac troponin levels was added.
- Management guidelines for myocarditis were added.
- Premedications to mitigate avelumab infusion-related reactions were revised to only be required for the first 4 infusions.

The FDA's Assessment:
FDA generally agrees with the Applicant's description of the Protocol Amendments above. None of the implemented changes significantly impacted the integrity of the trial or the interpretation of the results.

However, subsequent to the Applicant's submission of this Assessment Aid, an additional Protocol Amendment was submitted February 13, 2020. In Protocol Amendment 5, an important change was made:

- Based on the result of the interim analysis, the External-Data Monitoring Committee (E-DMC) recommended that remaining patients on Arm B who are progression-free be offered crossover to avelumab. The sponsor thus added a supplement with eligibility criteria for patients randomized to BSC to cross over to the avelumab arm. Crossover is offered to patients who have not progressed while on study.

FDA notes that 7% of patients randomized to the BSC alone arm remain on protocol therapy as of data cutoff (October 21, 2019). The protocol amendment that allows crossover will therefore

have only minor impact on the final analysis for OS.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:
Study B9991001 was conducted in accordance with the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

The Applicant's Position:
Study B9991001 was GCP compliant.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Financial Disclosure

Data:
Study B9991001 financial interests/arrangements with clinical investigators were tracked and disclosed.

The Applicant's Position:
The integrity of Study B9991001 data was not affected by the financial interest of the investigators.

The FDA's Assessment:
FDA agrees with the Applicant's assessment above. No concerns with regards to conflict of interest or financial disclosures were raised.

Patient Disposition

Data:
In this study, 'study treatment' (or 'treatment arm') refers to the avelumab plus BSC (Arm A) or BSC alone (Arm B).

Subject disposition at the time of the IA cutoff is summarized in Table 4.

Table 4. Subject Disposition for Study Drugs at End of Treatment - All Subjects and Subjects with PD-L1-Positive Tumors in the Full Analysis Set (Protocol B9991001)

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
	n (%)	n (%)	n (%)	n (%)
Disposition phase: end of treatment				
Discontinued	**265 (75.7)**	**324 (92.6)**	**131 (69.3)**	**156 (92.3)**
Reason for discontinuation				
Death	**5 (1.4)**	**14 (4.0)**	**3 (1.6)**	**8 (4.7)**
Progressive disease	**189 (54.0)**	**263 (75.1)**	**84 (44.4)**	**126 (74.6)**
Adverse event	**39 (11.1)**	**2 (0.6)**	**26 (13.8)**	**1 (0.6)**
Non-Compliance with study drug	**1 (0.3)**	**0**	**1 (0.5)**	**0**
Physician's decision	**5 (1.4)**	**7 (2.0)**	**4 (2.1)**	**6 (3.6)**
No longer meets eligibility criteria	**3 (0.9)**	**0**	**1 (0.5)**	**0**
Global deterioration of health status	**4 (1.1)**	**6 (1.7)**	**2 (1.1)**	**1 (0.6)**
Withdrawal by subject	**16 (4.6)**	**29 (8.3)**	**7 (3.7)**	**12 (7.1)**
Lost to follow-up	**2 (0.6)**	**2 (0.6)**	**2 (1.1)**	**1 (0.6)**
Other	**1 (0.3)**	**1 (0.3)**	**1 (0.5)**	**1 (0.6)**
Ongoing	**85 (24.3)**	**26 (7.4)**	**58 (30.7)**	**13 (7.7)**

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 14JAN2020 (07:59) Source Data: ADDS Output File: ./B9991001/B9991001_CSR/adds_s002_pdl1c Date of Generation: 14JAN2020 (22:41) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.1.1.2.4 is for Pfizer internal use.

The Applicant's Position:
The causes of study treatment discontinuation were consistent with the disease under study.

The FDA's Assessment:
FDA generally agrees with the Applicant's assessment. As expected in a randomized trial of an active neoplastic agent against BSC alone, reasons for discontinuation were not balanced between the arms. More patients randomized to avelumab+BSC discontinued due to adverse event. However, the excess number of patients who discontinued in the avelumab+BSC arm compared to BSC alone (n=37, 11%) was still less than the cumulative excess number of patients who discontinued due to death or progressive disease in the BSC alone compared to avelumab+BSC (n=83, 24%). Ultimately, a greater number of patients continued on therapy by the data cutoff in the avelumab+BSC arm compared to the BSC alone arm.

FDA notes that almost twice as many patients randomized to BSC as compared to avelumab+BSC withdrew prior to progression or other clear explanation such as adverse event ("Withdrawal by subject": n=29 in the BSC arm vs. n=16 in the avelumab+BSC arm). FDA's

analysis of the association between geography and reason for discontinuation identified higher rates of "Withdrawal by subject" in the BSC alone arm in countries such as U.S., Australia, and Japan where newer therapies may be available in the second-line setting. Subgroup analyses in these regions for PFS and OS are in Figures 6 and 7 of this review. It is possible that patients who withdrew early from BSC alone had improved survival outcomes due to early treatment with other anticancer drugs. However, this represents a minority of the BSC arm. Fifteen (4%) of patients randomized to BSC alone withdrew within the first 60 days for "Withdrawal by subject," of which 10 patients were treated in the U.S., Australia, or Japan.

Protocol Violations/Deviations

Data:
All protocol deviations were systematically reviewed by study management and the study team to identify PIPD.

At least 1 PIPD was reported for 38.9% of patients (**Table 5**). The number of patients with a PIPD was similar in both treatment arms.

Table 5. Potentially Important Protocol Deviations - Full Analysis Set (Protocol B9991001)

	Avelumab+BSC (N=350) n (%)	BSC (N=350) n (%)	Total (N=700) n (%)
Subjects with any potentially important deviations	145 (41.4)	127 (36.3)	272 (38.9)
CCMEDS	39 (11.1)	2 (0.6)	41 (5.9)
Patient did not take protocol-required concomitant medication/ pre-medication.	9 (2.6)	0	9 (1.3)
Took prohibited Concomitant Medication / Vaccine as defined per protocol.	31 (8.9)	2 (0.6)	33 (4.7)
INCLUSION/EXCLUSION	42 (12.0)	70 (20.0)	112 (16.0)
Did not meet Inclusion Criterion 01.a. Histologically confirmed, unresectable locally advanced or metastatic transitional cell carcinoma of the urothelium.	0	1 (0.3)	1 (0.1)
Did not meet Inclusion Criterion 01.b. Documented stage IV disease at the start of first-line chemotherapy.	0	1 (0.3)	1 (0.1)
Did not meet Inclusion Criterion 01.c. Measurable disease prior to the start of first-line chemotherapy by RECIST v1.1.	7 (2.0)	8 (2.3)	15 (2.1)
Did not meet Inclusion Criterion 02. Prior first-line chemotherapy of at least 4 cycles and no more than 6 cycles of gemcitabine plus cisplatin and/or gemcitabine plus carboplatin	0	5 (1.4)	5 (0.7)
Did not meet Inclusion Criterion 02.a. (PA3 and later) The last dose of first-line chemotherapy must have been received no less than 4 weeks, and no more than 10 weeks, prior to randomization in the present study.	8 (2.3)	7 (2.0)	15 (2.1)

	Avelumab+BSC (N=350) n (%)	BSC (N=350) n (%)	Total (N=700) n (%)
Did not meet Inclusion Criterion 03. (PA2 and earlier) Patients without progressive disease as per RECIST v1.1 guidelines following completion of first line chemotherapy as determined by independent central review.	1 (0.3)	0	1 (0.1)
Did not meet Inclusion Criterion 03. (PA3 and later) Patients without progressive disease as per RECIST v1.1 guidelines following completion of first line chemotherapy as determined by investigator review.	10 (2.9)	17 (4.9)	27 (3.9)
Did not meet Inclusion Criterion 04. (PA2 and earlier) Provision of recent FFPE tumor tissue block or slides obtained within one year prior to randomization with no intervening chemotherapy.	1 (0.3)	2 (0.6)	3 (0.4)
Did not meet Inclusion Criterion 04. (PA3 and later) Provision of recent FFPE tumor tissue block or slides obtained within 24 months prior to randomization with no intervening chemotherapy.	2 (0.6)	8 (2.3)	10 (1.4)
Did not meet Inclusion Criterion 04.a. (PA2 and earlier) Provision of an archival FFPE tumor tissue block or slides from primary tumor resection specimen.	1 (0.3)	0	1 (0.1)
Did not meet Inclusion Criterion 10. Adequate bone marrow function as per protocol.	1 (0.3)	3 (0.9)	4 (0.6)
Did not meet Inclusion Criterion 11. Adequate renal function, defined as estimated creatinine clearance greater or equal to 30 mL/min.	1 (0.3)	0	1 (0.1)
Did not meet Inclusion Criterion 12. Adequate liver function as per protocol.	0	1 (0.3)	1 (0.1)
Met Exclusion Criterion 01. Patients whose disease progressed by RECIST v1.1 on or after first-line chemotherapy for urothelial cancer.	8 (2.3)	7 (2.0)	15 (2.1)
Met Exclusion Criterion 02. Prior adjuvant or neoadjuvant systemic therapy within 12 months of randomization.	0	2 (0.6)	2 (0.3)
Met Exclusion Criterion 07. Diagnosis of any other malignancy within 5 years prior to randomization, with exceptions noted in protocol.	1 (0.3)	1 (0.3)	2 (0.3)
Met Exclusion Criterion 10. Clinically significant (ie, active) cardiovascular disease as defined in the protocol.	2 (0.6)	0	2 (0.3)
Met Exclusion Criterion 11. Active infection requiring systemic therapy.	2 (0.6)	0	2 (0.3)
Met Exclusion Criterion 14. Current or prior use of immunosuppressive medication within 7 days prior to randomization, with exceptions as noted in protocol	0	1 (0.3)	1 (0.1)
Met Exclusion Criterion 17. (PA3 and later) Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).	0	2 (0.6)	2 (0.3)
Patient dosed even though a procedure/lab/assessment required for eligibility determination was not done or results were not available.	4 (1.1)	11 (3.1)	15 (2.1)
Patient dosed even though a procedure/lab/assessment required for eligibility determination was not done.	1 (0.3)	8 (2.3)	9 (1.3)
INFORMED CONSENT	52 (14.9)	38 (10.9)	90 (12.9)
Original or subsequent ICD not translated to patient?s native language.	1 (0.3)	0	1 (0.1)
Original or subsequent signed ICD had not undergone the proper Pfizer/CRO approval process or IRB/IEC approval.	1 (0.3)	0	1 (0.1)
Patient signed a superseded/outdated version of the ICD.	11 (3.1)	10 (2.9)	21 (3.0)
Patient signed main ICD after screen/enroll date or after study procedures had been performed.	0	3 (0.9)	3 (0.4)
Subsequent (revised, updated) ICD not signed at the first patient visit after the revised/approved ICD was available at site.	41 (11.7)	27 (7.7)	68 (9.7)

	Avelumab+BSC (N=350) n (%)	BSC (N=350) n (%)	Total (N=700) n (%)
INVESTIGATIONAL PRODUCT	14 (4.0)	0	14 (2.0)
Dose modifications (omission or infusion rate change, dose reduction, dose interruption) not done in response to toxicity as specified in protocol.	4 (1.1)	0	4 (0.6)
Dosing Error such as wrong drug, incorrect dose (equal to or greater than protocol-specified overdose or under dose equivalent) and/or medication error.	6 (1.7)	0	6 (0.9)
Patient received drug that had undergone a temperature excursion without Pfizer?s approval of drug administration.	4 (1.1)	0	4 (0.6)
PROCEDURES/TESTS	9 (2.6)	9 (2.6)	18 (2.6)
Baseline tumor scans were performed >28 days from randomization.	7 (2.0)	6 (1.7)	13 (1.9)
Clinically significant Abnormal Procedure / Test Result not followed up appropriately per protocol.	1 (0.3)	0	1 (0.1)
Patient underwent protocol prohibited intervention (e.g. Radiation for curative intent, surgery).	1 (0.3)	2 (0.6)	3 (0.4)
Procedure / Test not performed per protocol.	0	1 (0.3)	1 (0.1)
PROTOCOL SPECIFIC DISCONTINUATION CRITERIA	0	3 (0.9)	3 (0.4)
Inappropriately discontinued due to site error.	0	2 (0.6)	2 (0.3)
Patient met any of the protocol-specified study treatment discontinuation criteria, but was not discontinued from study treatment appropriately.	0	1 (0.3)	1 (0.1)
RANDOMIZATION	32 (9.1)	35 (10.0)	67 (9.6)
Randomized under wrong stratification of CR/PR vs SD AND visceral vs non-visceral.	1 (0.3)	2 (0.6)	3 (0.4)
Randomized under wrong stratification of CR/PR vs SD.	23 (6.6)	22 (6.3)	45 (6.4)
Randomized under wrong stratification of visceral vs. non-visceral.	8 (2.3)	11 (3.1)	19 (2.7)

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: DV Output File: ./B9991001/B9991001 CSR/addv s001 Date of Generation: 14JAN2020 (08:13) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.1.2.5 is for Pfizer internal use.

The Applicant's Position:

There were 9.6% patients with a PIPD associated with randomization in the IRT system under the wrong stratification value. To assess the impact of these errors, a sensitivity analysis for OS was done based on actual CRF-derived strata data; the results (stratified HR = 0.70, 1-sided p-value = 0.0006 for all randomized patients, stratified HR = 0.56, 1-sided p-value = 0.0003 for patients with PD-L1-positive tumors) were similar to the results based on the IRT-entered randomization stratification factors (stratified HR = 0.69, 1-sided p-value = 0.0005 for all randomized patients, stratified HR = 0.56, 1-sided p-value = 0.0003 for patients with PD-L1-positive tumors;). Other PIPD categories were also deemed to not have an impact on the study results and conclusions drawn and were deemed to not undermine or affect the data integrity of this study. [[CSR Table 14.2.5.2.1]]

The FDA's Assessment:
FDA agrees with the Applicant's assessment that the overall pattern and nature of protocol deviations would not alter the conclusion of a net favorable benefit-risk relationship for use of avelumab in the indicated population.

Table of Demographic Characteristics

Data:
In the avelumab plus BSC arm, at baseline median age was 68.00 years (range: 37.0 to 90.0), 63.1% of patients were 65 years or older, 76.0% were male, 66.3% were White, and the ECOG PS was 0 (60.6%) or 1 (39.2%).

In the avelumab plus BSC arm 52.3% of patients received gemcitabine plus cisplatin, 42.0% of patients gemcitabine plus carboplatin, and 5.7 % of patients a combination of gemcitabine plus carboplatin and gemcitabine plus cisplatin as first-line induction chemotherapy. Best response to first-line chemotherapy was CR or PR (72.3%) or SD (27.7%). Sites of metastasis prior to chemotherapy were visceral (54.6%) or non-visceral (45.4%). The most common site of primary tumor was the bladder for patients in both treatment arms. [[CSR Table 14.1.2.2]]

Table 6. Demographic, Baseline and Disease Characteristics - All Subjects and Subjects with PD-L1-Positive Tumors in the Full Analysis Set (Protocol B9991001)

	All Subjects			Subjects with PD-L1-Positive Tumors		
	Avelumab+BSC (N=350)	BSC (N=350)	Total (N=700)	Avelumab+BSC (N=189)	BSC (N=169)	Total (N=358)
Age (years), n (%)						
<65 years	129 (36.9)	107 (30.6)	236 (33.7)	62 (32.8)	49 (29.0)	111 (31.0)
≥65 years	221 (63.1)	243 (69.4)	464 (66.3)	127 (67.2)	120 (71.0)	247 (69.0)
65-<75 years	136 (38.9)	163 (46.6)	299 (42.7)	72 (38.1)	73 (43.2)	145 (40.5)
75-<85 years	80 (22.9)	78 (22.3)	158 (22.6)	51 (27.0)	47 (27.8)	98 (27.4)
≥85 years	5 (1.4)	2 (0.6)	7 (1.0)	4 (2.1)	0	4 (1.1)
n [1]	350	350	700	189	169	358
Mean (SD)	67.2 (9.52)	67.7 (9.20)	67.5 (9.36)	68.2 (9.87)	68.0 (9.71)	68.1 (9.78)
Q1	61.00	62.00	62.00	62.00	62.00	62.00
Median	68.00	69.00	69.00	70.00	70.00	70.00
Q3	74.00	74.00	74.00	75.00	75.00	75.00
Range (min, max)	(37.0, 90.0)	(32.0, 89.0)	(32.0, 90.0)	(37.0, 90.0)	(32.0, 84.0)	(32.0, 90.0)
Race, n (%)						
Black or African American	2 (0.6)	0	2 (0.3)	1 (0.5)	0	1 (0.3)
American Indian or Alaska Native	0	0	0	0	0	0

	All Subjects			Subjects with PD-L1-Positive Tumors		
	Avelumab+BSC (N=350)	BSC (N=350)	Total (N=700)	Avelumab+BSC (N=189)	BSC (N=169)	Total (N=358)
Asian	75 (21.4)	81 (23.1)	156 (22.3)	42 (22.2)	33 (19.5)	75 (20.9)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
White	232 (66.3)	238 (68.0)	470 (67.1)	121 (64.0)	119 (70.4)	240 (67.0)
Other	21 (6.0)	15 (4.3)	36 (5.1)	12 (6.3)	7 (4.1)	19 (5.3)
Unknown	20 (5.7)	16 (4.6)	36 (5.1)	13 (6.9)	10 (5.9)	23 (6.4)
Gender, n (%)						
Male	266 (76.0)	275 (78.6)	541 (77.3)	145 (76.7)	129 (76.3)	274 (76.5)
Female	84 (24.0)	75 (21.4)	159 (22.7)	44 (23.3)	40 (23.7)	84 (23.5)
Ethnicity, n (%)						
Hispanic or Latino	18 (5.1)	12 (3.4)	30 (4.3)	9 (4.8)	3 (1.8)	12 (3.4)
Not Hispanic or Latino	286 (81.7)	298 (85.1)	584 (83.4)	152 (80.4)	146 (86.4)	298 (83.2)
Not reported	42 (12.0)	36 (10.3)	78 (11.1)	24 (12.7)	18 (10.7)	42 (11.7)
Unknown	4 (1.1)	4 (1.1)	8 (1.1)	4 (2.1)	2 (1.2)	6 (1.7)
Pooled Geographic Region, n (%)						
North America	12 (3.4)	22 (6.3)	34 (4.9)	8 (4.2)	8 (4.7)	16 (4.5)
Europe	214 (61.1)	203 (58.0)	417 (59.6)	110 (58.2)	102 (60.4)	212 (59.2)
Asia	73 (20.9)	74 (21.1)	147 (21.0)	40 (21.2)	31 (18.3)	71 (19.8)
Australasia	34 (9.7)	37 (10.6)	71 (10.1)	20 (10.6)	24 (14.2)	44 (12.3)
Rest of the World	17 (4.9)	14 (4.0)	31 (4.4)	11 (5.8)	4 (2.4)	15 (4.2)
Best response to first-line chemotherapy (IRT)						
CR or PR	253 (72.3)	252 (72.0)	505 (72.1)	139 (73.5)	128 (75.7)	267 (74.6)
SD	97 (27.7)	98 (28.0)	195 (27.9)	50 (26.5)	41 (24.3)	91 (25.4)
Site of metastasis (IRT)						
Visceral	191 (54.6)	191 (54.6)	382 (54.6)	88 (46.6)	79 (46.7)	167 (46.6)
Non-Visceral	159 (45.4)	159 (45.4)	318 (45.4)	101 (53.4)	90 (53.3)	191 (53.4)
Histopathological classification						
Carcinoma	306 (87.4)	292 (83.4)	598 (85.4)	163 (86.2)	137 (81.1)	300 (83.8)
Carcinoma with Squamous	16 (4.6)	26 (7.4)	42 (6.0)	8 (4.2)	13 (7.7)	21 (5.9)
Carcinoma with Glandular	6 (1.7)	9 (2.6)	15 (2.1)	3 (1.6)	6 (3.6)	9 (2.5)
Carcinoma with Variant	22 (6.3)	22 (6.3)	44 (6.3)	15 (7.9)	13 (7.7)	28 (7.8)
Other	0	1 (0.3)	1 (0.1)	0	0	0
ECOG performance status						
0	213 (60.9)	211 (60.3)	424 (60.6)	114 (60.3)	107 (63.3)	221 (61.7)
1	136 (38.9)	136 (38.9)	272 (38.9)	74 (39.2)	61 (36.1)	135 (37.7)
2	1 (0.3)	0	1 (0.1)	1 (0.5)	0	1 (0.3)

	All Subjects			Subjects with PD-L1-Positive Tumors		
	Avelumab+BSC (N=350)	BSC (N=350)	Total (N=700)	Avelumab+BSC (N=189)	BSC (N=169)	Total (N=358)
3	0	3 (0.9)	3 (0.4)	0	1 (0.6)	1 (0.3)
4	0	0	0	0	0	0
Not reported	0	0	0	0	0	0
PD-L1 Status						
Positive	189 (54.0)	169 (48.3)	358 (51.1)	189 (100.0)	169 (100.0)	358 (100.0)
Negative	139 (39.7)	132 (37.7)	271 (38.7)	0	0	0
Unknown	22 (6.3)	49 (14.0)	71 (10.1)	0	0	0

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group. Baseline is defined as the last assessment on or prior to randomization for subjects randomized but not dosed, and the last assessment on or prior to first dose of
study treatment for subjects randomized and dosed.
[1] n is the number of subjects with non-missing age. Age at Screening (years) = (date of given informed consent - date of birth + 1)/365.25.
PFIZER CONFIDENTIAL SDTM Creation: 21DEC2019 (12:42) Source Data: ADSL Output File: ./B9991001/B9991001 CSR/adsl s002 fas pdl1 Date of Generation: 21JAN2020 (14:36) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.1.2.1.1.1 is for Pfizer internal use.

The Applicant's Position:

The distribution of baseline demographic and disease characteristics was similar between treatment arms and was similar between the overall and PD-L1-positive populations. Disease characteristics were consistent with what is expected in the aUC population in this setting.

The FDA's Assessment:

The FDA generally agrees with the Applicant. Overall, the median age was 69 years (range: 32 to 90). White patients represented 67% and Asian patients represented 22% of the overall population. Black or African American patients comprised less than 1%, and other races (including "Other" and "Unknown") comprised 10%. This distribution is not representative of the U.S. population, but the pharmacokinetic and pharmacodynamic properties of avelumab are not known to be significantly impacted by race. The clinical data from JAVELIN Bladder 100 is acceptable for regulatory purposes, as per ICH E5 (R1).

As noted in Table 6, a higher proportion of patients in the avelumab+BSC arm had PD-L1 positive tumors. However, a greater proportion of patients in the BSC alone arm had tumors with PD-L1 status unknown. The "true" PD-L1 positive proportions may therefore be balanced between the arms.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:
See Table 6 for all baseline characteristics.

The Applicant's Position:
See the previous Applicant's position in "Table of Demographic Characteristics" subsection.

The FDA's Assessment:
See above.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:
In the avelumab plus BSC arm, the median relative dose intensity for avelumab was 88.2%, which takes into account dose modifications. [[CSR Table 14.4.1.2]] A similar proportion of patients reported concomitant medications in both treatment arms: 97.7% in the avelumab plus BSC arm and 91.6% in the BSC arm. [[CSR Table 14.4.2.6.1]]

There were 148 (42.3%) patients (including 68 [36.0%] with PD-L1-positive tumors) in the avelumab plus BSC arm, and 216 (61.7%) patients (including 109 [64.5%] with PD-L1-positive tumors) in the BSC arm who started subsequent anti-cancer drug therapies (Table 7). Among all randomized patients, 22 (6.3%) patients in the avelumab plus BSC arm, and 153 (43.7%) patients in the BSC alone arm, received subsequent therapy with a PD-1 or PD-L1 inhibitor.

Table 7. Follow-up Anti-Cancer Drug Therapies by Category - All Subjects and Subjects with PD-L1-Positive Tumors in the Full Analysis Set (Protocol B9991001)

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
Category	n (%)	n (%)	n (%)	n (%)
Subjects with any follow-up anti-cancer drug therapies	148 (42.3)	216 (61.7)	68 (36.0)	109 (64.5)
Any PD-1 or PD-L1 inhibitor	22 (6.3)	153 (43.7)	10 (5.3)	81 (47.9)
FGFR inhibitor	9 (2.6)	8 (2.3)	3 (1.6)	4 (2.4)
Any other drug therapy	140 (40.0)	119 (34.0)	67 (35.4)	57 (33.7)

Subjects are counted only once within a given category but may be counted in more than one category.
The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADCM Output File: ./B9991001/B9991001_CSR/adcm_s009b_pdl1c Date of Generation: 14JAN2020 (21:38) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.4.2.7.1.4 is for Pfizer internal use.

The Applicant's Position:
A higher number of patients in the BSC alone treatment arm received follow-up anti-cancer therapy. A statistically significant and clinically meaningful improvement in OS was demonstrated for avelumab plus BSC in spite of the large (43.7%) use of PD-1/PD-L1 inhibitors in patients from the BSC alone arm.

The FDA's Assessment:
FDA agrees that a clinically meaningful improvement in OS was demonstrated for avelumab+BSC in spite of the fact that only approximately half of patients randomized to BSC eventually received PD-1/PD-L1 inhibitors. The Applicant's assessment above is that this represents a large proportion of patients overall who used PD-1/PD-L1 inhibitors as subsequent therapy in the BSC alone arm, but this is still far from complete crossover. FDA considers the issue of subsequent anticancer therapy an important issue in the contextualization of the overall study results and therefore conducted further analyses on this topic.

In the U.S., there are 5 PD-1/PD-L1 inhibitors that have received FDA approval for second-line treatment of patients who have proressed on or during treatment with initial platinum-based chemotherapy. The standard of care in the US and in much of the world for unselected patients with aUC following platinum is thus treatment with a PD-1/PD-L1 inhibitor. Therefore, approval of avelumab based on JAVELIN Bladder 100 results would presumably result in a discussion between clinicians and patients in the U.S. on the benefits and risks of earlier use of a PD-L1 inhibitor immediately following response to platinum-based combination chemotherapy vs. after a treatment holiday and subsequent treatment with a PD-1/PD-L1 inhibitor in the second-line setting. Clinicians and patients would presumably use the JAVELIN Bladder 100 data to make this decision, but it is not clear that the BSC alone data fully represents expected outcomes in the U.S., where PD-1/PD-L1 inhibitors are widely available even for most patients who delay resuming treatment until progression.

We note that the JAVELIN Bladder patients represent a selected patient population; i.e. those with at least stable disease and ECOG PS of 0-1 after completion of first-line therapy, and thus a substantial proportion of progressors on the BSC arm would be expected to be doing well enough clinically to receive therapy at the time of progression, which was generally a short period of time after randomization for many of these patients. Yet, of the 350 patients randomized to BSC alone, 324 had discontinued treatment by data cutoff, of which 263 had discontinued due to progressive disease. Among the 263 patients, 216 received any second-line therapy, of which 153 (44% of 350, or 58% of the 263 progressors) received a PD-1/PD-L1 inhibitor.

FDA sent an Information Request to elucidate possible reasons for apparent undertreatment of patients on the BSC arm upon their progression. The sponsor did not capture this data; i.e. no reason for non-initiation of second line therapy was captured on the patients' CRF. There are other therapies that can be used for recurrent aUC other than immunotherapies, including cytotoxic chemotherapy, erdafitinib, and/or enfortumab vedotin. Patients who received second-

line therapy other than PD-1/PD-L1 inhibitor most commonly received cytotoxic chemotherapy, and some received FGFR inhibitors or enfortumab vedotin.. The sponsor noted that this was a global study which involved sites for which certain subsequent therapies may not have been available. However, in FDA's review of subsequent therapy according to geographic region, significant differences were not apparent between the major geographic regions.

Besides region of the world, other nonclinical factors may impact access to standard of care therapy, including proximity to large medical centers. To further evaluate the benefit of avelumab maintenance therapy, FDA conducted exploratory analyses in patients who received BSC alone followed by standard of care second-line therapy (see Additional Analyses Conducted on the Individual Trial towards the end of Section 8.1.2). However, the question of whether there may be individual patients for whom a treatment holiday rather than maintenance treatment is the most appropriate management strategy is likely not fully answered due to lack of planned crossover in the design of JAVELIN Bladder 100. See also analysis of efficacy in patients with PD-L1–negative tumors discussed below.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:
The study met its primary objective and demonstrated that avelumab plus BSC significantly prolongs OS compared to BSC alone, in all randomized patients and in patients with PD-L1-positive tumors.

- Clinically meaningful and statistically significant improvement in OS was demonstrated for all patients assigned to the avelumab plus BSC arm (1-sided p<0.0005; **Table 8**), with a 31% reduction in the risk of death compared with patients assigned to the BSC alone arm (stratified HR 0.69; 95% RCI: 0.536, 0.923). Median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab plus BSC arm and 14.3 months (95% CI: 12.9, 17.9) in the BSC alone arm (Figure 5 and **Table 8**).

- In patients with PD-L1-positive tumors, a clinically meaningful and statistically significant improvement in OS was also demonstrated for patients assigned to the avelumab plus BSC arm (1-sided p=0.0003; Figure 6), with a 44% reduction in the risk of death compared with patients assigned to the BSC alone arm (stratified HR 0.56; RCI: 0.388, 0.937). Median OS was not reached (95% CI: 20.3 months, not reached) in the avelumab plus BSC arm and was 17.1 months (95% CI: 13.5, 23.7) in the BSC alone arm (Figure 6).

The OS benefit in the all randomized population was not solely driven by patients with PD-L1-positive tumors: since the observed OS was longer in the avelumab plus BSC arm than in the BSC alone arm for patients with PD-L1-negative tumors (stratified HR 0.85; 95% CI: 0.616, 1.181) and for patients with PD-L1 unknown tumors (stratified HR 0.71; 95% CI: 0.311, 1.599) (

Table 9).

- The observed OS was longer for avelumab plus BSC compared with BSC alone across all prespecified subgroups for all randomized patients (Figure 7), and for patients with PD-L1-positive tumors (Figure 8) with the exception of the small subgroups of patients with PD-L1-positive tumors randomized in ' Rest of the World' and the small subgroup of patients with PD-L1-positive tumors with a race other than White or Asian (but with no significant treatment by subgroup interaction).

Table 8. Summary of Efficacy Endpoints for All Subjects and Subjects with PD-L1-Positive Tumors in the Full Analysis Set (Protocol B9991001)

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=350)	**BSC (N=350)**	**Avelumab+BSC (N=189)**	**BSC (N=169)**
Overall Survival				
Subjects with event, n (%)	145 (41.4)	179 (51.1)	61 (32.3)	82 (48.5)
Kaplan-Meier estimates of Time to Event (months) Median (95% CI) [1]	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)	NE (20.3, NE)	17.1 (13.5, 23.7)
Probability of being event-free (95% CI) [2] at 24 months	0.481 (0.413, 0.547)	0.372 (0.309, 0.434)	0.577 (0.481, 0.662)	0.405 (0.314, 0.494)
Stratified analysis [3] Comparison vs BSC				
Hazard Ratio [4]	0.69		0.56	
95% CI [4]	0.556, 0.863		0.404, 0.787	
1-sided p-value [5]	0.0005		0.0003	
Progression-Free Survival [6]				
Subjects with event, n (%)	225 (64.3)	260 (74.3)	109 (57.7)	130 (76.9)
Kaplan-Meier estimates of Time to Event (months) Median (95% CI) [1]	3.7 (3.5, 5.5)	2.0 (1.9, 2.7)	5.7 (3.7, 7.4)	2.1 (1.9, 3.5)
Probability of being event-free (95% CI) [2] at 6 months	0.407 (0.352, 0.461)	0.218 (0.172, 0.267)	0.481 (0.403, 0.555)	0.229 (0.165, 0.300)
Stratified analysis [3] Comparison vs BSC				
Hazard Ratio [4]	0.62		0.56	
95% CI [4]	0.519, 0.751		0.431, 0.728	
1-sided p-value [5]	<.0001		<.0001	
Confirmed Best Overall Response, n (%) [6]				
Complete response (CR)	21 (6.0)	3 (0.9)	18 (9.5)	1 (0.6)
Partial response (PR)	13 (3.7)	2 (0.6)	8 (4.2)	1 (0.6)

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
Stable disease (SD)	44 (12.6)	46 (13.1)	19 (10.1)	23 (13.6)
Non-CR/Non-PD	66 (18.9)	45 (12.9)	38 (20.1)	22 (13.0)
Progressive disease (PD)	130 (37.1)	169 (48.3)	59 (31.2)	82 (48.5)
Not evaluable (NE)	76 (21.7)	85 (24.3)	47 (24.9)	40 (23.7)
Objective Response (CR+PR), n (%) [6]	34 (9.7)	5 (1.4)	26 (13.8)	2 (1.2)
95% CI [7]	6.8, 13.3	0.5, 3.3	9.2, 19.5	0.1, 4.2

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] CIs are calculated using Brookmeyer and Crowley method.
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
[4] Cox proportional hazard model used.
[5] Log-rank test is used.
[6] Based on BICR assessment.
[7] Clopper-Pearson method used.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADTTEB Output File: ./B9991001/B9991001 CSR/eff condensed Date of Generation: 14JAN2020 (17:04) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.2.1 is for Pfizer internal use.

Table 9. Summary of Efficacy Endpoints for Subjects with PD-L1-Negative and PD-L1-Unknown Tumors in the Full Analysis Set (Protocol B9991001)

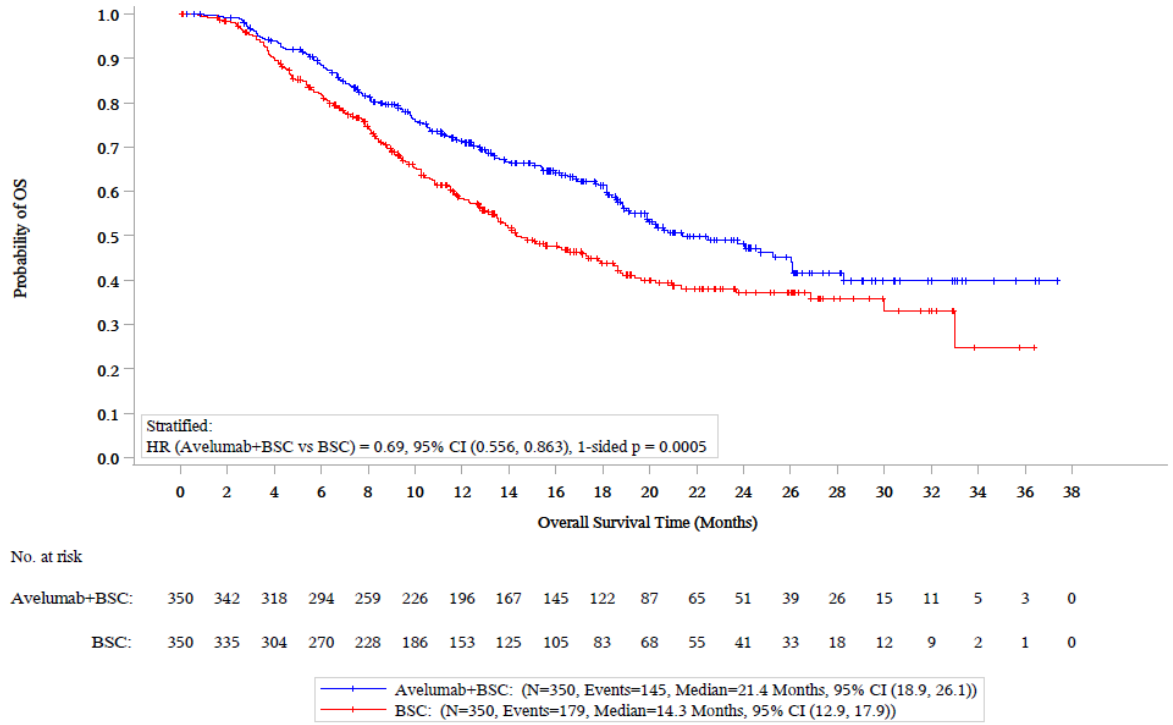
	Subjects with PD-L1-Negative Tumors		Subjects with PD-L1-Unknown Tumors	
	Avelumab+BSC (N=139)	BSC (N=132)	Avelumab+BSC (N=22)	BSC (N=49)
Overall Survival				
Subjects with event, n (%)	76 (54.7)	72 (54.5)	8 (36.4)	25 (51.0)
Kaplan-Meier estimates of Time to Event (months) Median (95% CI) [1]	18.8 (13.3, 22.5)	13.7 (10.8, 17.8)	20.1 (10.6, NE)	12.8 (9.6, NE)
Probability of being event-free (95% CI) [2] at 24 months	0.371 (0.271, 0.471)	0.315 (0.218, 0.417)	0.415 (0.150, 0.665)	0.408 (0.254, 0.557)

	Subjects with PD-L1-Negative Tumors		Subjects with PD-L1-Unknown Tumors	
	Avelumab+BSC (N=139)	**BSC (N=132)**	**Avelumab+BSC (N=22)**	**BSC (N=49)**
Stratified analysis [3] Comparison vs BSC				
Hazard Ratio [4]	0.85		0.71	
95% CI [4]	0.616, 1.181		0.311, 1.599	
1-sided p-value [5]	0.1690		0.2005	
Progression-Free Survival [6]				
Subjects with event, n (%)	103 (74.1)	100 (75.8)	13 (59.1)	30 (61.2)
Kaplan-Meier estimates of Time to Event (months) Median (95% CI) [1]	3.0 (2.0, 3.7)	1.9 (1.9, 2.0)	3.6 (1.9, 16.7)	2.1 (1.9, 9.2)
Probability of being event-free (95% CI) [2] at 6 months	0.311 (0.233, 0.393)	0.145 (0.085, 0.222)	0.402 (0.184, 0.612)	0.382 (0.230, 0.533)
Stratified analysis [3] Comparison vs BSC				
Hazard Ratio [4]	0.63		1.00	
95% CI [4]	0.470, 0.839		0.502, 1.988	
1-sided p-value [5]	0.0008		0.4987	
Confirmed Best Overall Response, n (%)[6]				
Complete response (CR)	3 (2.2)	1 (0.8)	0	1 (2.0)
Partial response (PR)	5 (3.6)	0	0	1 (2.0)
Stable disease (SD)	24 (17.3)	14 (10.6)	1 (4.5)	9 (18.4)
Non-CR/Non-PD	24 (17.3)	19 (14.4)	4 (18.2)	4 (8.2)
Progressive disease (PD)	62 (44.6)	67 (50.8)	9 (40.9)	20 (40.8)
Not evaluable (NE)	21 (15.1)	31 (23.5)	8 (36.4)	14 (28.6)
Objective Response (CR+PR), n (%)[6]	8 (5.8)	1 (0.8)	0	2 (4.1)
95% CI [7]	2.5, 11.0	0.0, 4.1	0.0, 15.4	0.5, 14.0

	Subjects with PD-L1-Negative Tumors		Subjects with PD-L1-Unknown Tumors	
	Avelumab+BSC (N=139)	**BSC (N=132)**	**Avelumab+BSC (N=22)**	**BSC (N=49)**

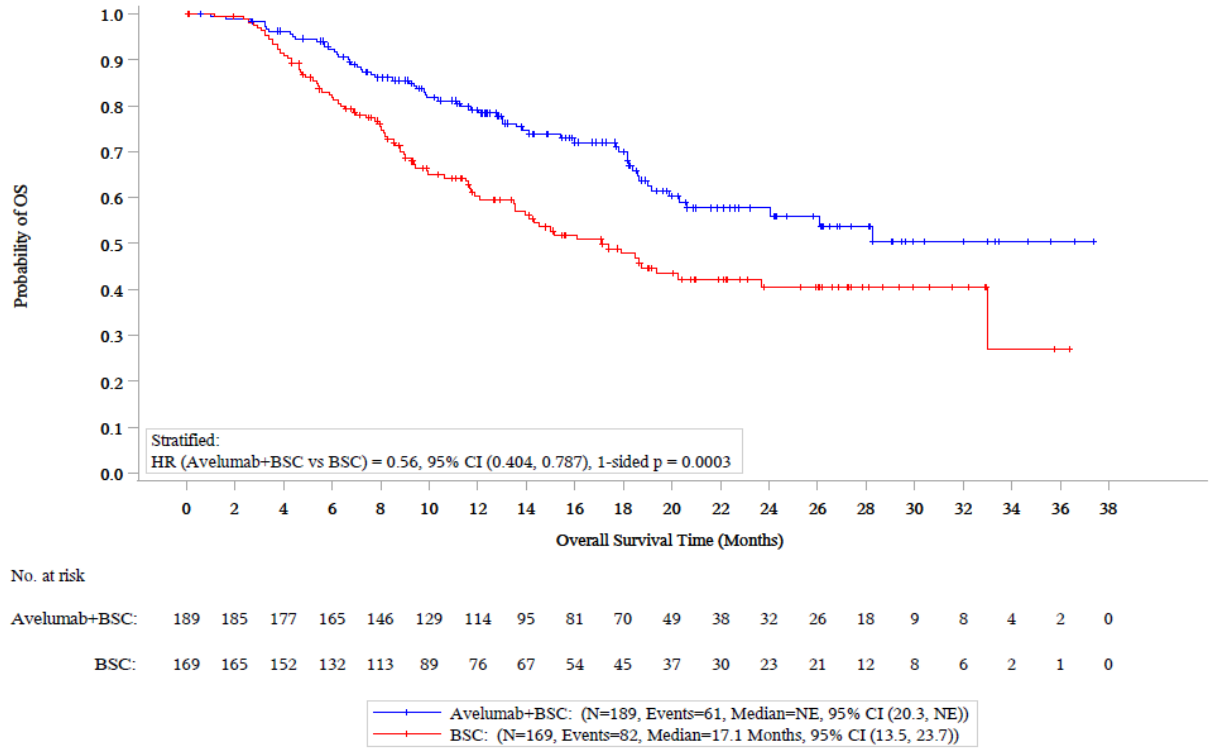
The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] CIs are calculated using Brookmeyer and Crowley method.
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
[4] Cox proportional hazard model used.
[5] Log-rank test is used.
[6] Based on BICR assessment.
[7] Clopper-Pearson method used.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADTTEB Output File: ./B9991001/B9991001 CSR/eff condensed pdl1 neg unk Date of Generation: 14JAN2020 (17:14) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.2.1.0.3 is for Pfizer internal use.

Figure 5. Kaplan-Meier Plot of Overall Survival (Full Analysis Set)



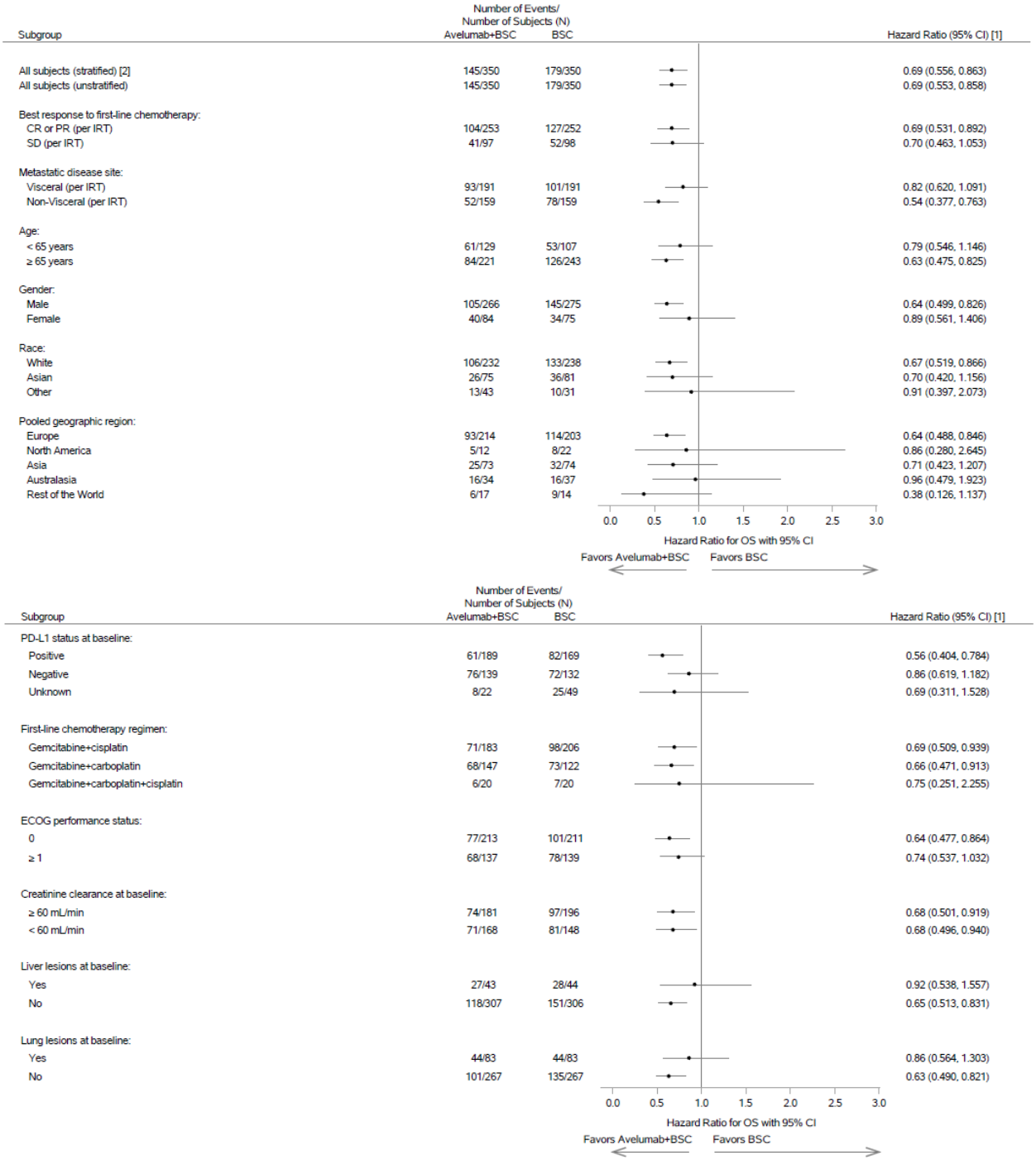
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADTTE Output File: ./B9991001/B9991001_CSR/adtte_os_f001 Date of Generation: 14JAN2020 (13:30) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Figure 6. Kaplan-Meier Plot of Overall Survival (Patients with PD-L1-Positive Tumors in the Full Analysis Set)



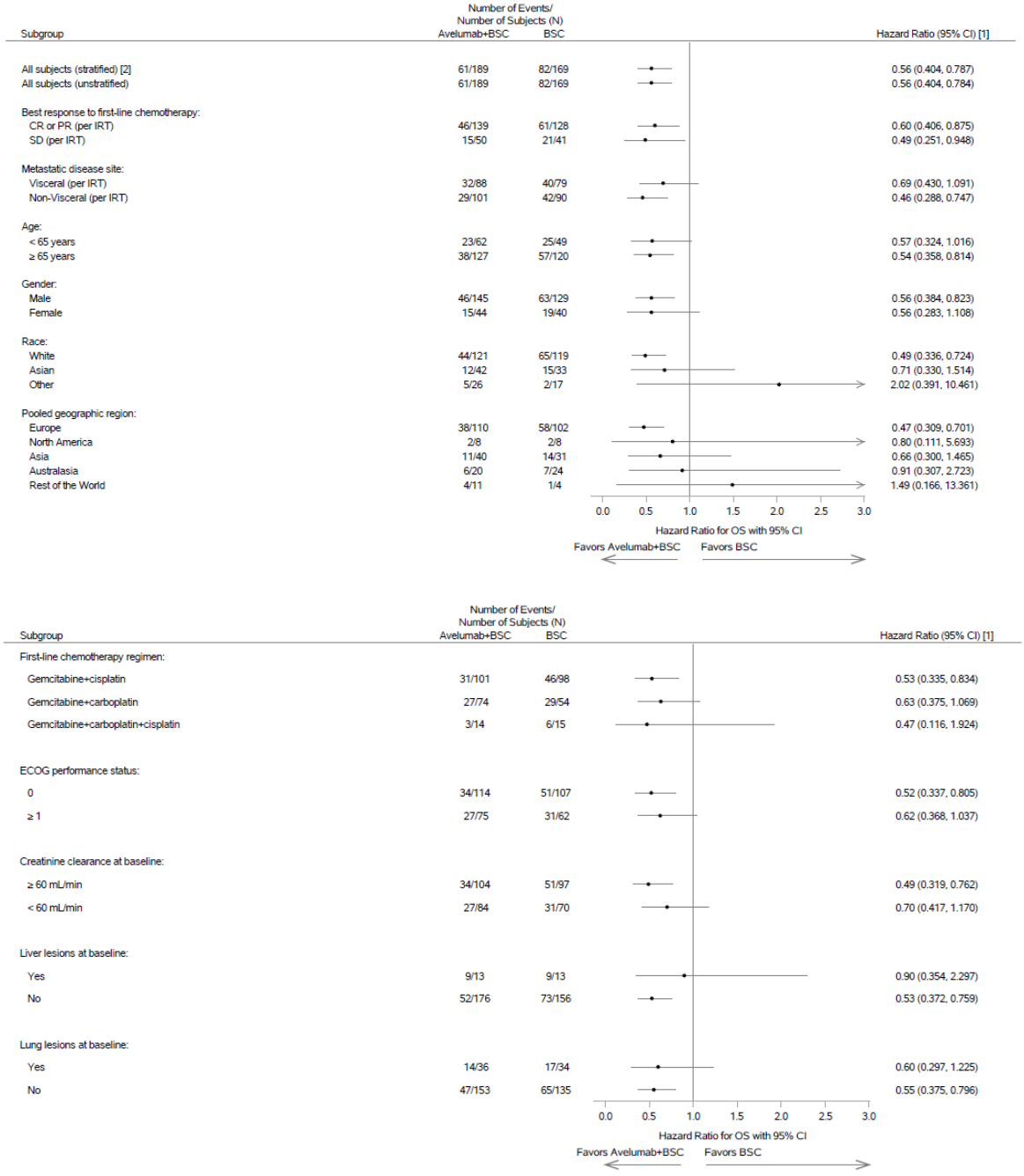
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADTTE Output File: ./B9991001/B9991001_CSR/adtte_os_f001_pdl1 Date of Generation: 14JAN2020 (13:32) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Figure 7. Forest Plot of Overall Survival by Subgroups (Full Analysis Set)



N is the number of subjects in the full analysis set within each subgroup and treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.
Subgroups with <5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is <5% of the patient population).
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Output File: ./B9991001/B9991001_CSR/adtte_os_f003 Date of Generation: 14JAN2020 (13:45) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Figure 8. Forest Plot of Overall Survival by Subgroups (Patients with PD-L1-Positive Tumors in the Full Analysis Set)



N is the number of subjects with PD-L1-positive tumors in the full analysis set in each treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.
Subgroups with <5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is <5% of the patient population).
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Output File: ./B9991001/B9991001_CSR/adtte_os_f003_pdlpop Date of Generation: 14JAN2020 (13:49) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Sensitivity analyses were performed to explore the robustness of the primary analysis results; the results of the analyses were similar to those of the primary analysis, with the modifications listed below:

- OS of the Per Protocol Analysis Set: stratified HR 0.70 (95% CI: 0.550, 0.880; 1 sided p-value 0.0012) for the all randomized patient population and stratified HR 0.56 (95% CI: 0.379, 0.775; 1-sided p-value 0.0003) for the PD-L1-positive patient population. [[CSR Table 14.2.5.1.1.1]]

- OS using an unstratified analysis: unstratified HR 0.69 (95% CI: 0.553, 0.858; 1 sided p-value 0.0004) for the all randomized patient population and unstratified HR 0.54 (95% CI: 0.404, 0.784; 1-sided p-value 0.0003) for the PD-L1-positive patient population. [[CSR Table 14.2.5.2]]

- OS considering actual strata: stratified HR 0.70 (95% CI: 0.560, 0.870; 1 sided p-value 0.0006) for the all randomized patient population and stratified HR 0.56 (95% CI: 0.403, 0.786; 1-sided p-value 0.0003) for the PD-L1-positive patient population. [[CSR Table 14.2.5.2.1]]

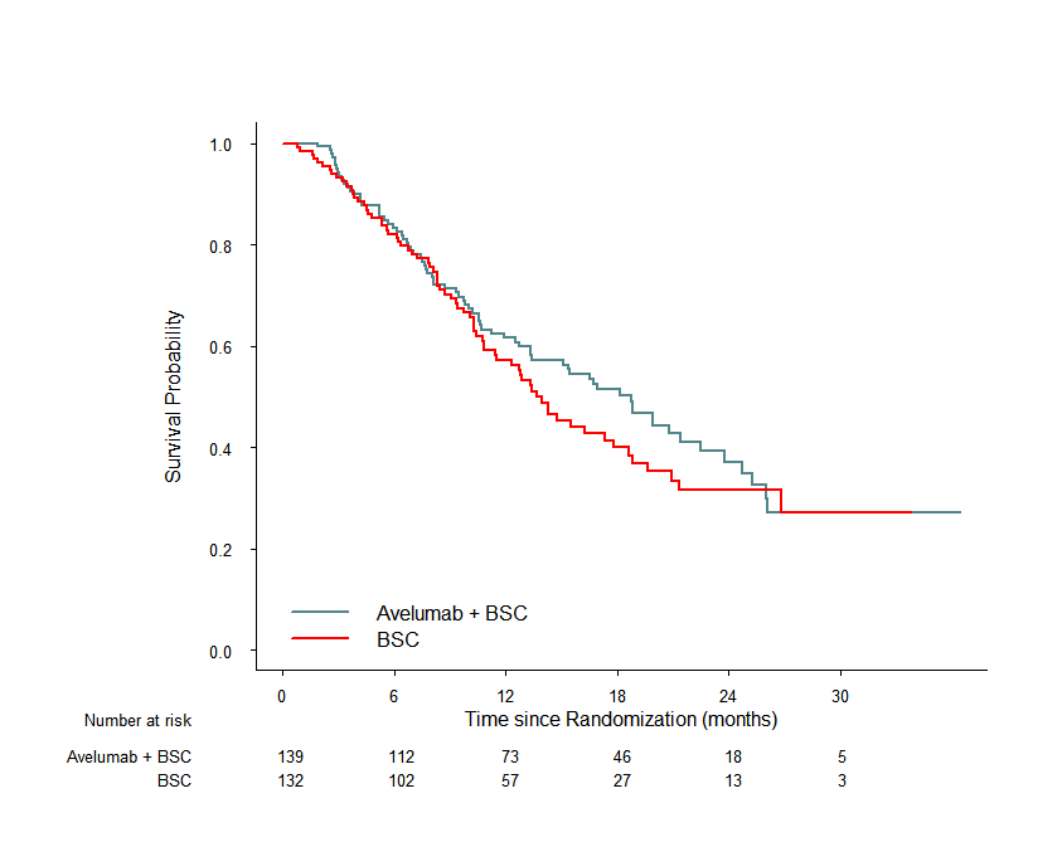
The Applicant's Position:
A clinically meaningful and statistically significant improvement in OS was demonstrated for patients assigned to avelumab plus BSC compared with BSC alone, both in all randomized patients and in patients with PD-L1-positive tumors. The results observed for OS in all randomized patients were not driven solely by the benefit observed in patients with PD-L1-positive tumors since the observed OS was longer in the avelumab plus BSC arm than in the BSC alone arm for patients with PD-L1-negative tumors. An OS benefit for avelumab plus BSC compared with BSC alone was observed across all prespecified subgroups in the all randomized patient population (Figure 7 and Figure 8).

The FDA's Assessment:
FDA agrees that a clinically meaningful improvement in OS was demonstrated for avelumab+BSC compared to BSC alone in both pre-specified analyses, all randomized patients and patients with PD-L1-positive tumors. However, p values for the sensitivity analyses as presented above by the Applicant are not interpretable because they were not adjusted for multiplicity. Additionally, FDA disagrees, that an OS benefit for avelumab plus BSC compared with BSC alone was consistently observed across all prespecified subgroups. A differential effect is possible in a) patients with PD-L1–negative tumors, b) baseline liver lesions, c) female patients, and d) patients treated in North America and Australasia.

Patients with PD-L1-negative tumors had an OS HR of 0.86 (95% CI 0.62, 1.18). FDA acknowledges that the analysis in the PD-L1-negative population was not part of the multiple testing hierarchy. However, the OS HR for patients with PD-L1-negative tumors was included in the USPI because it is likely clinically relevant, given that a) the PD-L1-negative population was a large subgroup (n=271), and b) OS in the PD-L1-positive population was a prespecified

analysis, and the number of patients with PD-L1 status unknown was low. As these data might inform the decision to offer a patient a treatment holiday until time of progression rather than maintenance treatment with avelumab, OS results in the PD-L1 negative patients were included in section 14 of product labeling. A Kaplan-Meier curve of OS for patients with PD-L1–negative tumors is shown below.

Figure 9. Overall Survival in Patients with PD-L1–Negative Tumors



As noted in Figure 6, patients with liver lesions at baseline (n=77) had an OS HR of 0.92 (95% CI (0.54, 1.56). Patients with PD-L1-negative tumors had an OS HR of 0.86 (95% CI 0.62, 1.18). The predictive and prognostic role of liver as well as lung lesions are discussed in the "Efficacy Results – Secondary and other relevant endpoints" section. The HRs in Figure 6 also suggest a differential effect by gender and geographic region. Female patients comprised 24% of the patient population. The OS HR in female patients was 0.89 (95% CI: 0.56, 1.41) , compared to 0.64 (95% CI: 0.38, 0.82) in male patients. Female sex was not noted to be associated with attenuated treatment effect on OS or PFS in a recent meta-analysis of PD-1/PD-L1 inhibitors across tumor types,[2] nor on ORR in the original second-line indication.[3] In the pooled geographic region variable, the magnitude of benefit of avelumab maintenance therapy in patients in Australasia (HR 0.96, 95% CI: 0.48, 1.92) and North America (HR 0.86, 95% CI: 0.28, 2.65) was smaller than the benefit seen in patients in other regions of the world. These subgroup

results should be interpreted with caution because of the limited size of these groups (n=71 and n=34, respectively). FDA's review of subsequent therapy use in patients in the control arm of these regions were similar to the distribution of subsequent therapy use in patients in other regions of the world. However, many of these countries had high rates of early "withdrawal by subject" in the control arm, as discussed in FDA's assessment of Table 4.

Figure 6 indicates that the treatment effect was similar across two important baseline variables: patients with prior cisplatin versus without cisplatin induction chemotherapy as well as patients with best response of PR/CR versus SD. FDA conducted an exploratory analysis to evaluate if any interaction between best response to platinum and choice of platinum could demonstrate a differential treatment effect. Review of these results (Table 10 below) does not indicate that cisplatin (± carboplatin) with PR/CR versus carboplatin with PR/CR versus cisplatin (± carboplatin) with SD versus carboplatin with SD was strongly correlated with uniquely better or worse treatment effect. Additionally, the duration of therapy was only slightly higher in the prior cisplatin compared to the no cisplatin recipients in the avelumab + BSC arm: of the 85 patients still with ongoing avelumab therapy as of data cutoff, 66% had received prior cisplatin; of those who discontinued therapy, the median duration of therapy was 161 days among the cisplatin recipients and 142 days among the no-cisplatin recipients.

Table 10. Efficacy Results According to Prior Cisplatin Use And Best Response to Chemotherapy

	Avelumab (n=350)		**BSC (n=350)**	
	n	**%**	**n**	**%**
Prior cisplatin use*				
Best response of PR/CR	150	42.9	169	48.3
OS HR (95% CI)	0.66 (0.47, 0.93)			
PFS HR (95% CI)	0.55 (0.42, 0.71)			
Best response of SD	53	15.1	57	16.3
OS HR (95% CI)	0.78 (0.44, 1.38)			
PFS HR (95% CI)	0.50 (0.31, 0.80)			
No prior cisplatin use (carboplatin + gemcitabine)				
Best response of PR/CR	107	30.6	85	24.3
OS HR (95% CI)	0.68 (0.46, 1.01)			
PFS HR (95% CI)	0.48 (0.35, 0.67)			
Best response of SD	40	11.4	37	10.6
OS HR (95% CI)	0.63 (0.34, 1.15)			
PFS HR (95% CI)	0.57 (0.34, 0.97)			

*Approximately 90% of cisplatin recipients received cisplatin in combination with gemcitabine throughout their induction chemotherapy; the other 10% received cisplatin in combination with gemcitabine as well as carboplatin in combination with gemcitabine.

Given that cisplatin is the preferred frontline standard of care in aUC due to high overall response rates and the potential for conferring durable, long-term survival, and the observation across tumor types that depth of response generally correlates with time-to-event endpoints, the relatively similar results between cisplatin and no-cisplatin recipients, as well as the similarity in outcomes between patients with CR/PR versus SD, is not entirely expected.

Data Quality and Integrity

Data:
No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data and change the conclusions drawn.

The Applicant's Position:
All study sites had a site initiation visit conducted by the sponsor or designated representative. Each site was provided with instructional manuals to ensure the collection of accurate, consistent, complete, and reliable data.

The sponsor, either directly or through delegated CROs, monitored the study through routine center visits. At these visits, study procedures were reviewed, CRF/DCT data compared to original clinical records, data queries resolved, and protocol deviations discussed with the investigator. Telephone and e-mail contact were maintained with the investigators between center visits. In addition, the overall study conduct was subject to internal quality review by the sponsor.

The sponsor (b) (4) or equivalent role provided study and site level oversight to ensure that the trial was delivered to high quality standards (b) (4) performed on-site and remote oversight to assess monitoring effectiveness and ensure compliance with the study protocol by investigational sites according to ICH/GCP, applicable SOPs, and local regulation.

The FDA's Assessment:
There were no concerns regarding data quality or integrity raised during review of this study.

Efficacy Results – Secondary and other relevant endpoints

Data:
Progression-free Survival Based on BICR Assessment

Patients assigned to avelumab plus BSC had a clinically meaningful improvement in PFS compared with patients assigned to the BSC alone arm (Table 8).

Patients assigned to avelumab plus BSC had a 38% reduction of the risk of progression (based on BICR assessment per RECIST v1.1) or death compared with patients assigned to BSC alone

(stratified HR 0.62; 95% CI: 0.519, 0.751). [[CSR Table 14.2.4.2]] The median PFS for the avelumab plus BSC arm was 3.7 months (95% CI: 3.5, 5.5) and was 2.0 months (95% CI: 1.9, 2.7) for the BSC alone arm.

Similar clinically meaningful improvements in PFS were observed in patients with PD-L1-negative tumors, and patients with unknown PD-L1 expression status (
Table 9). A PFS benefit of avelumab plus BSC compared with BSC alone was observed across all prespecified subgroups. [[CSR Figure 14.2.4.2.3]].

Best Overall Response and Objective Response

The ORR (by BICR Assessment) in the avelumab plus BSC arm was higher than for the BSC alone arm in all randomized patients (9.7% [95% CI: 6.8, 13.3] vs 1.4% [95% CI: 0.5, 3.3]; stratified odds ratio 7.464 (95% CI: 2.824, 24.445) and in patients with PD-L1-positive tumors (13.8% [95% CI: 9.2,19.5] vs 1.2% [95% CI: 0.1,4.2] with a stratified odds ratio of 12.699 (95% CI: 3.160, 114.115) . [[CSR Table 14.2.1.2]]

For subgroups with at least one responder (BOR of CR or PR) in both treatment arms, the ORR based on BICR assessment was higher for avelumab plus BSC compared with BSC alone across all prespecified subgroups including patients with PD-L1-negative tumors.

The Applicant's Position:
The results of the secondary efficacy analysis of PFS and ORR (by BICR assessment) support the primary analysis of OS in both coprimary populations. The ORR was calculated for all randomized patients, on each arm, and in each population. Patients were considered NE for response at baseline if they were assessed to have a CR by BICR following first-line chemotherapy. However, if in these patients a BOR of progression was observed during maintenance treatment, those patients were included in the PD category.

The FDA's Assessment:
FDA agrees with the Applicant's above assessment that the efficacy analysis of PFS support the primary analysis of OS in both coprimary populations, but the PFS results also clearly show short PFS for most patients, regardless of treatment arm (Figures 9, 10, and 11 below). Approximately half of patients in the BSC arm had progressed by the first assessment, and approximately half of patients in the avelumab + BSC arm had progressed by the second assessment. The precision of PFS measurement is also limited by the frequency of radiological efficacy assessments. In JAVELIN Bladder 100, radiological assessments were repeated every 8 weeks, a time period which is slightly longer in duration than the absolute difference in median PFS between the two arms. Although it is expected that a minority of patients with aUC respond to PD-1/PD-L1 inhibitors, the rapid progression in this patient population overall suggests a short duration of response to standard-of-care platinum combination chemotherapy.

It is unclear if this short PFS following standard-of-care platinum combination chemotherapy is consistent with previous data. The literature suggests that the expected PFS for platinum/gemcitabine induction chemotherapy is approximately 6-9 months.[2-4] Assuming that

patients enrolled in JAVELIN Bladder 100 would have had an initial scan halfway through their induction chemotherapy, time "0" would begin 1.5-2 months before last dose of chemotherapy, and screening would take another 1-2.5 months. This would mean that the median PFS based on purely the effect of the initial chemotherapy should be about 1.5-5.5 months, from time of initiation of maintenance/BSC. The precision of these estimates are also limited by frequency of imaging, but the actual median PFS (3.7 and 2.0 months in the avelumab + BSC arm and BSC arm, respectively) results in JAVELIN Bladder 100 fell within this range.

Using the sponsor's predefined subgroups based on demographic or clinical characteristics, FDA did not identify strong prognostic factors for early progression by the first radiographic assessment. The predicted prognostic factors of best response to chemotherapy of CR/PR vs. SD, having baseline lung lesions, or having baseline liver lesions are addressed in Table 11 below. Overall, about 2.5x as many patients withdrew from the trial due to progression of disease (PD) in the BSC arm compared to the avelumab+BSC arm (39% vs. 16%) by day 90. This ratio is similar regardless of whether patients had CR/PR vs. SD upon enrollment. It was also similar whether patients had lung lesions or not upon enrollment. However, having liver lesions upon enrollment was not only a prognostic factor for early progression (patients with baseline liver lesions comprise 16% of the early progressors but only 12% of the all randomized population) but also predictive for a lesser degree of benefit from avelumab + BSC over BSC alone (the number of patients who early progressors in each treatment arm were relatively similar). This suggests that the treatment effect was not similar across subgroups. FDA did not agree with the Applicant's proposed (b) (4) (b) (4). See also FDA's Assessment following Figures 6 and 7.

Table 11. Characteristics of Early Progressors*

	avelumab		BSC	
	n	**%**	**n**	**%**
Liver lesions at baseline/total enrolled in arm	43/350	12.3%	44/350	12.6%
Of pts with liver lesions, % who were early progressors	13/43	30.2%	18/44	40.9%
Lung lesions at baseline/total enrolled in arm	83/350	23.7%	83/350	23.7%
Of pts with lung lesions, % who were early progressors	16/83	19.3%	43/83	51.8%
Patients with CR/PR on enrollment	253/350	72.3%	252/350	72.0%
Of pts with CR/PR on enrollment, % who were early progressors	38/253	15.0%	95/252	37.7%
Patients with SD on enrollment	97/350	27.7%	98/350	28.0%
Of pts with SD on enrollment, % who were early progressors	17/97	17.5%	41/98	41.8%
Number of early progressors	**55/350**	**15.7%**	**136/350**	**38.9%**

*For the purposes of this analysis, "early progressors" is defined as patients who withdrew due to progression of disease within 90 days

Figure 10. Progression-Free Survival in All Randomized Patients

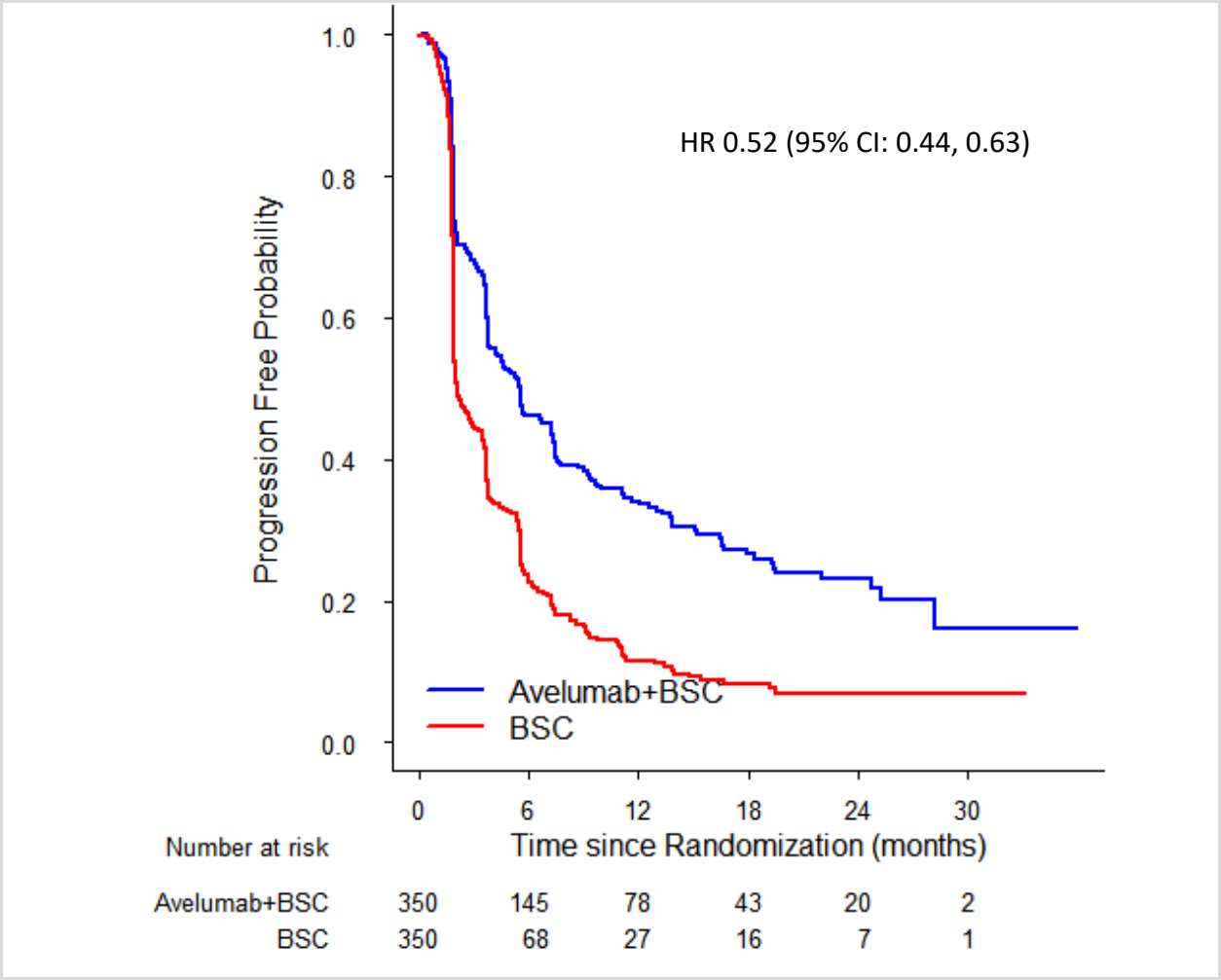
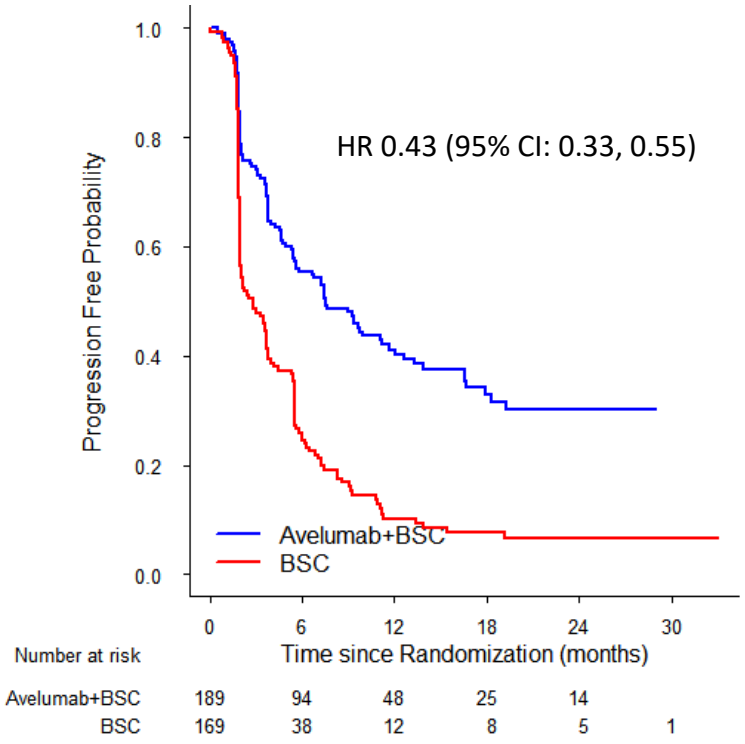
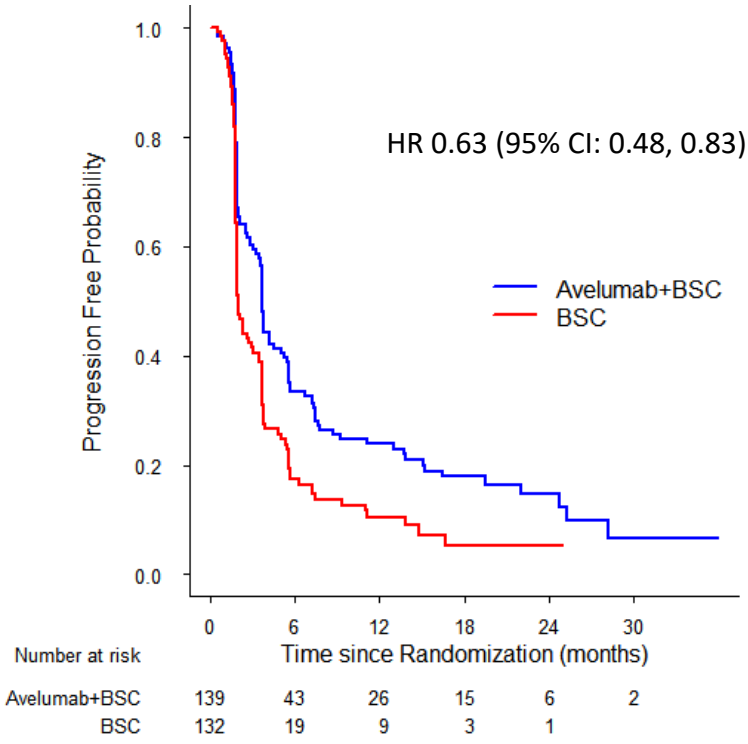


Figure 11. Progression-Free Survival in Patients with PD-L1–Positive Tumors



A comparison of Figures 10 and 11 demonstrates that patients with PD-L1-positive tumors had a slightly better prognosis in both arms, compared to patients with patients with PD-L1–negative tumors. The prognostic value of PD-L1 in this treatment setting has not been well-defined previously. A meta-analysis of 2755 patients with aUC who received PD-1/PD-L1 inhibitors in first- or second-line trials reported that PD-L1 expression predicted higher ORR but not OS.[7] However, interpretation of this meta-analysis is limited by the lack of consistency in PD-L1 assay and cutpoint used in trials.

Figure 12. Progression-Free Survival in Patients with PD-L1–Negative Tumors



Patients in both treatment arms experienced tumor responses (Table 8): n=34 (9.7%) of the avelumab + BSC arm and n=5 (1.4%) of the BSC arm alone. In the case of the patients who achieved tumor responses on the BSC arm, this may represent delayed response to initial chemotherapy. The 9.7% ORR for avelumab + BSC is lower than the response rates seen in the second-line data which led to the approval of avelumab in 2017 (ORR 13.3%),[3] which is not unexpected because patients enrolled in JAVELIN Bladder 100 were already in deep response following induction chemotherapy. The role of maintenance therapy is typically not to induce deep response, and ORR may therefore not be as meaningful of an endpoint as it would be in the second-line setting. Additionally, patients were only eligible for evaluation of ORR if their initial tumor response upon enrollment was PR or SD and not CR which likely further lowered the observed ORR to avelumab + BSC in the maintenance setting.

For the subgroups analyses of ORR mentioned by the applicant, the only pre-specified subgroup that had 0 responses in the Avelumab+BSC arm and that trended opposite of the BSC arm was PDL1 unknown (0% vs 4.0%). In the PD-L1 positive arm, the ORR for Avelumab+BSC vs. BSC was 13.8% vs. 1.2% and in the PD-L1 negative arm, the ORR for Avelumab+BSC vs. BSC was 5.8% vs. 0.8%. Thus, the differences in the unknown arm are likely just a chance finding and do indicate a harmful effect.

The remainder of subgroups exaimed for ORR differeces numerically favored the Avelumab+BSC arm over the BSC arm. These subgroups results however should be considered exploratory withtout type I error control.

Dose/Dose Response

Data:
No new information is provided in the current submission.

The Applicant's Position:
All patients were dosed at 10 mg/kg; therefore, this is not applicable for this submission.

The FDA's Assessment:
See Section 6, Clinical Pharmacology.

Durability of Response

Data:
The median DoR for patients who responded was not reached for both treatment arms.

The Applicant's Position:
Response was durable among responders in the avelumab plus BSC arm.

The FDA's Assessment:
FDA agrees that the median duration of response for patients who responded was not reached for both arms. However, durability of response is a metric that is applicable for only a small subset of patients since there are so few responders (Table 12 below).

Table 12. Duration of Response

	All Randomized Patients		Patients with PD-L1–Positive Tumors	
	Avelumab + BSC (N=34)	BSC (N=5)	Avelumab + BSC (N=26)	BSC (N=2)
Duration of response (95% CI)	NE (15.6, NE)	NE (NE, NE)	NE (10, NE)	NE (NE, NE)

The long duration of response in the control arm also recapitulates the fact that there is a "tail" on the curve for cisplatin recipients; i.e., cisplatin-containing combination chemotherapy induces a long-term response for a subset of patients, and those patients would not benefit from (and may be harmed by) maintenance therapy. Of note, 4 of the 5 responders in the BSC arm received prior cisplatin, and 1 received prior carboplatin. In contrast, the baseline characteristics of the responders in the avelumab arm more closely reflect the overall population (19 [56%] received prior cisplatin+gemcitabine, 13 [38%] received prior carboplatin+gemcitabine, and 2 [6%] received prior gemcitabine plus cisplatin and gemcitabine plus carboplatin). How to identify the patients who retain long-term responses to first-line platinum chemotherapy without maintenance

therapy is an unanswered question, although we note the overall relative rarity of these responses (5 of 350 patients on the BSC arm, or 1.4%).

Persistence of Effect

Data:
There was a clinically meaningful improvement in OS for all patients randomized to the avelumab plus BSC arm, with a 31% reduction in the risk of death, compared with patients assigned to BSC alone (See Figure 5 above). OS is a reflection of patient benefit both during and after treatment discontinuation.

The Applicant's Position:
OS is the gold standard to demonstrate persistent long-term treatment benefit. The study has demonstrated persistence of effect over time.

The FDA's Assessment:
FDA agrees that OS is generally the best endpoint to demonstrate persistent long-term treatment benefit. At the time of data cutoff, fewer than 50% of the patients with PD-L1–positive tumors had died. Given the relative immaturity of the data, a PMC will require the sponsor to submit the final OS analysis results as originally planned per SAP.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:
Patient-reported outcomes of HRQoL were evaluated using NCCN-FACT Bladder Symptom Index (FBlSI-18), and the EQ-5D-5L. The FBlSI-18 was developed by asking patients to rank a list of symptoms in importance to them, then the questionnaire was developed based on patient and physician input. Thus, the instrument measures disease-related symptoms found to be most important to patients with aUC.

The overall completion rates of the FB lSI-18 were >90% for both the avelumab plus BSC arm and the BSC alone arm for the majority of the treatment period. [[CSR Table 14.5.2.3.1.1]] Completion rates for patients with PD-L1-positive tumors were similar to those of the all randomized population [[CSR Table 14.5.2.3.1.1.1]].

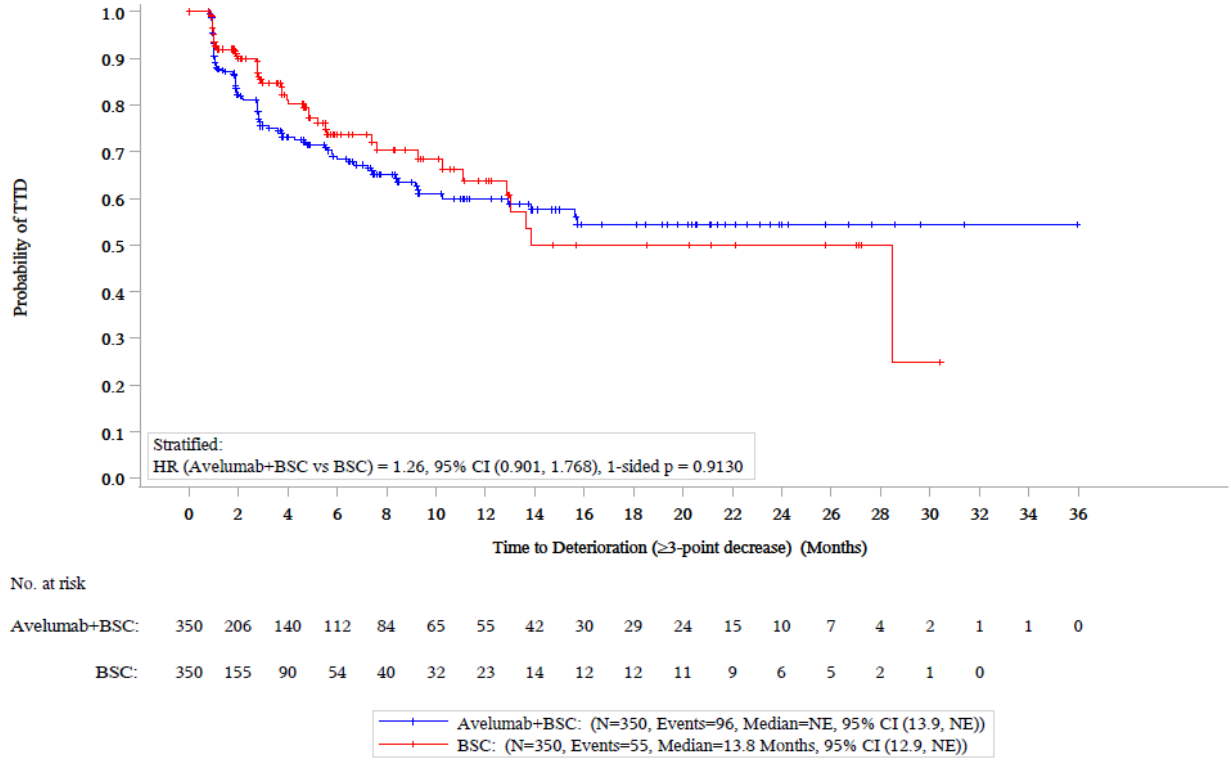
Overall, health status and quality of life in the avelumab plus BSC arm were similar compared with the BSC arm based on the EQ-5D-5L and FBlSI-18. [[CSR Section 11.1.2.1.2.5]]

For disease-related symptoms most important to patients with UC, the HR for time to deterioration (TTD) was 1.26 (95% CI: 0.901, 1.768). Median TTD was not reached in the avelumab plus BSC arm (95% CI: 13.9 months, not reached) and 13.8 months in the BSC arm (95% CI: 12.9 months, not reached) (Figure 13). TTD is based on a ≥3-point decrease from baseline in FBlSI-18DRS-P scores for 2 consecutive assessments, and death and progression were not considered as deterioration events. As a result, the KM method for TTD may be biased favoring the BSC arm due to 1) informative censoring as a substantial lower number of patients

were at risk in the BSC arm compared to the avelumab plus BSC arm starting from Cycle 2 [[CSR Table 14.5.2.3.2.1]], and 2) competing risks of death and progression. Sensitivity analyses based on a ≥2-point or ≥4-point decrease from baseline showed similar results. [[CSR Section 11.1.2.1.3]]

Similar results for time to deterioration and total scores from the EQ-5D-5L and FB1SI-18 were seen in patients with PD-L1-positive tumors as all randomized patients. [[CSR Section 11.1.2.1.3 [time to deterioration] and CSR Section 11.1.2.1.2.5 [total score]]

Figure 13. Kaplan-Meier Plot of Time to Deterioration (≥ 3 Points Decrease Prior to End of Treatment) in FBlSI-18 DRS-P Scores - Full Analysis Set



PFIZER CONFIDENTIAL SDTM Creation: 14JAN2020 (16:21) Source Data: ADTTECA Output File: ./B9991001/B9991001_CSR/adtteca_ttdt3_f001 Date of Generation: 14JAN2020 (16:41) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

The Applicant's Position:

There was no worsening of health status or quality of life in the avelumab plus BSC arm compared with the BSC arm based on total scores and mixed model results after adjusting for covariates from the EQ-5D-5L and FBlSI-18.

The FDA's Assessment:

FDA disagrees with the applicant's conclusions regarding COA (PRO) endpoints.
The PRO analyses were not controlled for multiple comparisons, and therefore all of these analyses are considered exploratory. The analysis of COA endpoints was not adequately powered to support a non-inferiority conclusion (i.e., a finding of no difference between the two arms). It is not possible to exclude a detriment in global health status or quality of life for patients in the avelumab+BSC arm.

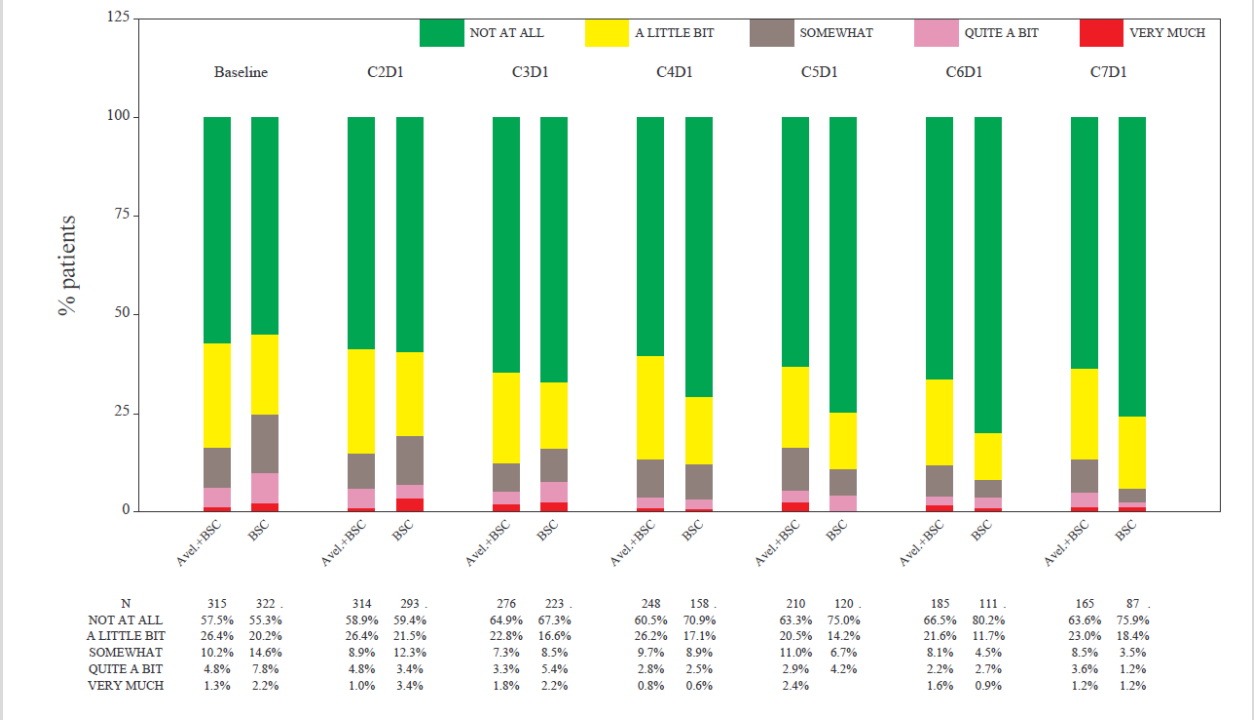
FDA agrees with the Applicant's assessment of completion rates. The FDA obtained and analyzed additional information from the applicant regarding descriptive PRO data for healthcare utilization and item level analyses for "I feel weak all over" and "I am bothered by side effects of treatment" from the FBlSI-18 questionnaire.

For an assessment of the responses to "I feel weak all over," see Appendix, Section 19.5, for Additional Safety Analyses Conducted by FDA.

FDA focused on side effect bother because this randomized trial compares outcomes of patients receiving an active antineoplastic agent against patients receiving a treatment holiday. Prolonged survival at the expense of side effect bother is an important potential consideration in the risk-benefit calculation for this population with an incurable disease with 5-year survival about 6%. For the time frame of COA to evaluate, FDA focused on the first 6 months of treatment because of high attrition after 6 months.

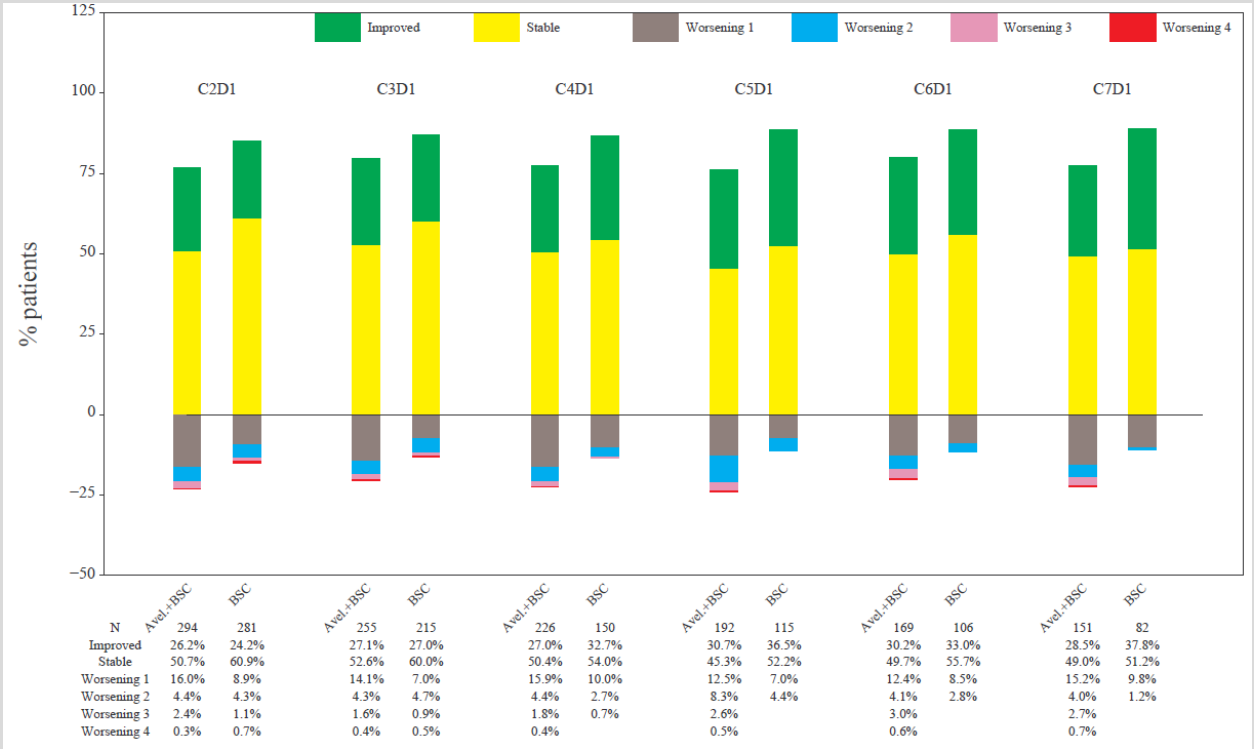
The results show that the proportion of patients randomized to avelumab+BSC who were bothered by side effects was about 10-14% more than the proportion of the control arm who were bothered during assessments every cycle for during months 3-6 of treatment (Figure 13 below). Additionally, an analysis of patient-level change-from-baseline responses to this item showed that about 20% of the avelumab+BSC arm worsened by at least 1 category at each assessment compared to about 10% of the BSC alone arm at each assessment (Figure 14). However, it is unclear if this difference is clinically meaningful.

Figure 14. Distribution of Responses to "I am bothered by side effects of treatment"



	Baseline		C2D1		C3D1		C4D1		C5D1		C6D1		C7D1	
	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC
N	315	322	314	293	276	223	248	158	210	120	185	111	165	87
NOT AT ALL	57.5%	55.3%	58.9%	59.4%	64.9%	67.3%	60.5%	70.9%	63.3%	75.0%	66.5%	80.2%	63.6%	75.9%
A LITTLE BIT	26.4%	20.2%	26.4%	21.5%	22.8%	16.6%	26.2%	17.1%	20.5%	14.2%	21.6%	11.7%	23.0%	18.4%
SOMEWHAT	10.2%	14.6%	8.9%	12.3%	7.3%	8.5%	9.7%	8.9%	11.0%	6.7%	8.1%	4.5%	8.5%	3.5%
QUITE A BIT	4.8%	7.8%	4.8%	3.4%	3.3%	5.4%	2.8%	2.5%	2.9%	4.2%	2.2%	2.7%	3.6%	1.2%
VERY MUCH	1.3%	2.2%	1.0%	3.4%	1.8%	2.2%	0.8%	0.6%	2.4%		1.6%	0.9%	1.2%	1.2%

Figure 15. Change from Baseline Response to "I am bothered by side effects of treatment"



	C2D1		C3D1		C4D1		C5D1		C6D1		C7D1	
	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC
N	294	281	255	215	226	150	192	115	169	106	151	82
Improved	26.2%	24.2%	27.1%	27.0%	27.0%	32.7%	30.7%	36.5%	30.2%	33.0%	28.5%	37.8%
Stable	50.7%	60.9%	52.6%	60.0%	50.4%	54.0%	45.3%	52.2%	49.7%	55.7%	49.0%	51.2%
Worsening 1	16.0%	8.9%	14.1%	7.0%	15.9%	10.0%	12.5%	7.0%	12.4%	8.5%	15.2%	9.8%
Worsening 2	4.4%	4.3%	4.3%	4.7%	4.4%	2.7%	8.3%	4.4%	4.1%	2.8%	4.0%	1.2%
Worsening 3	2.4%	1.1%	1.6%	0.9%	1.8%	0.7%	2.6%		3.0%		2.7%	
Worsening 4	0.3%	0.7%	0.4%	0.5%	0.4%		0.5%		0.6%		0.7%	

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

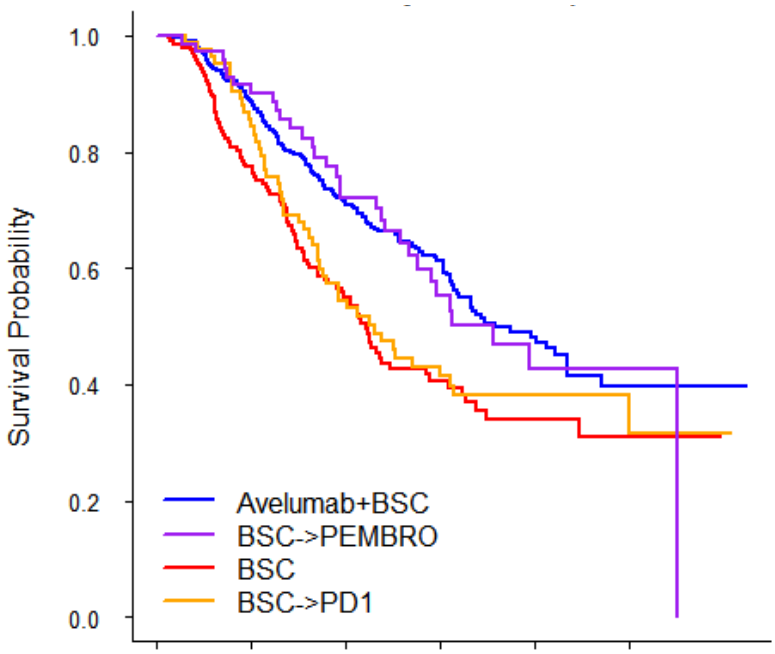
Additional Analyses Conducted on the Individual Trial

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
An exploratory analysis of OS by type of subsequent therapy was conducted. Results are shown in Figure 15 below. The Kaplan-Meier curve representing patients who received BSC per protocol followed by pembrolizumab upon progression (n=70) closely approximates the Kaplan-Meier curve for patients who received avelumab+BSC maintenance therapy (n=350). FDA acknowledges, however, that choice of subsequent therapy is a non-randomized comparison and thus results should be interpreted cautiously.

Figure 16. Overall Survival According to Subsequent Therapies



Number at risk						
Avelumab+BSC	350	294	196	122	51	15
BSC->PEMBRO	70	62	41	22	10	3
BSC	197	138	73	35	14	4
BSC->PD1	83	70	39	26	17	5

Abbreviations
BSC: best supportive care;
PD1: PD-1/PD-L1 inhibitors other than pembrolizumab
Pembro: pembrolizumab

These results suggest that for patients who have guaranteed access to pembrolizumab (the only PD-1/PD-L1 inhibitor that has demonstrated survival benefit in the second-line setting) upon progression, foregoing maintenance avelumab in favor of a treatment holiday, as per preexisting standard-of-care, may not necessarily negatively impact survival. This is relevant, considering that

- Survival in the patients with PD-L1–negative tumors in JAVELIN Bladder 100 was not clearly superior in patients randomized to avelumab + BSC over BSC alone (OS HR 95% CI was 0.62, 1.18)
- Patients receiving BSC alone in the real world will have lower treatment burden, including the possibility of adverse reactions and inconvenience of Q2W infusions
- In the exploratory analysis of patient-reported outcomes, patients receiving avelumab + BSC reported slightly more side effect "bother" compared to patients receiving BSC alone (Figures 13 and 14).

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
Although this efficacy evaluation is based on JAVELIN Bladder 100 only, FDA also reviewed

the literature which included a trial with similar design, HCRN GU14-182.[1] In this phase II trial, patients with CR/PR/SD following 1-8 cycles of platinum-containing chemotherapy were randomized to pembrolizumab 200 mg IV q3 weeks versus placebo. The key differences in trial design were that patients did not have to receive a minimum of 4 cycles of platinum chemotherapy in order to be eligible for enrollment; crossover to pembrolizumab was provided for patients who progressed in the control arm; and the trial was double-blinded because the control arm received placebo infusions. Additionally, JAVELIN 100 was an international trial while HCRN GU14-182 was a U.S.-only trial. As such, it is possible that the results of HCRN GU14-182 will correlate with real-world effectiveness of maintenance PD-1/PD-L1 inhibitor in the U.S. treatment setting.

The data for HCRN GU14-182 was not submitted to FDA for review. However, based on the published results, 108 patients were randomized, and PFS was prolonged in the pembrolizumab arm (median 5.4 versus 3.0 months). This appears to be a similar magnitude of PFS benefit (median extended by ~80% with PD-1/PD-L1 inhibitor maintenance therapy) as compared to JAVELIN Bladder 100, yet the OS curves of the 2 treatment arms in JAVELIN Bladder 100 separate (with a HR of 0.69), while they significantly overlap in HCRN GU14-182 (HR 0.91; 95% CI, 0.52 to 1.59, after a median follow-up of 13 months, at which point 47% of patients had died). Crossover data from JAVELIN Bladder 100 may be less accurate than that of HCRN GU14-182, because post-protocol therapy is often not thoroughly captured, but the data presented suggest that the proportion of patients who crossed over in HCRN GU14-182 exceeds the proportion of eligible patients (progressors) who crossed over to second-line PD-1/PD-L1 inhibitor in JAVELIN Bladder 100 by 10% (68% versus 58%), with 80% of patients receving therapy of any sort at the time of progression. This underscores the impact of small differences in trial design, including crossover, on survival outcomes and may further inform the literature available to physicians and patients when deciding to adopt a maintenance vs. a treatment holiday approach for individual patients.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:
This is a single study submission and this section is not applicable to this review.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
The FDA agrees with the Applicant's position above.

Secondary and Other Endpoints

Data:
This is a single study submission and this section is not applicable to this review.

The Applicant's Position:
Not Applicable.

The FDA's Assessment:
The FDA agrees with the Applicant's position above.

Subpopulations

Data:
This is a single study submission and this section is not applicable to this review.

The Applicant's Position:
Not Applicable.

The FDA's Assessment:
See Figures 6 and 7.

Additional Efficacy Considerations

The FDA's Assessment:
The impact of ADAs on efficacy is not clear in this application. Among the 18 patients in the avelumab + BSC arm who deveLed ADAs by week 9, the magnitude of effect of maintenance avelumab on PFS and OS is similar to that of the patients who did not develop ADAs. See Table 40 and Figures 18-20 in the Appendix.

Healthcare utilization is a metric that may characterize risk-benefit ratio of antineoplastic therapy. The Applicant submitted a response to FDA's IR regarding healthcare utilization during the first 6 months of therapy.

- The rate of hospitalizations was higher in the avelumab + BSC arm compared to BSC in the first cycle. Subsequently, hospitalization rates in both arms fluctuated in similar ranges.
- During cycle 1, 6% of patients receiving avelumab required oral or IV steroids. After cycle 1, approximately 2-3% of patients received steroids each cycle.

See Section 8.1.3, Integrated Review of Effectiveness.

8.1.5. Integrated Assessment of Effectiveness

Data:
At the prespecified IA, the study B9991001 met its primary objective and demonstrated that, for patients with unresectable aUC whose disease did not progress on or following completion of first-line chemotherapy, avelumab plus BSC significantly prolongs OS compared to BSC alone in all randomized patients and in patients with PD-L1-positive tumors.

- A clinically meaningful and statistically significant improvements in OS was demonstrated for all patients assigned to avelumab plus BSC, with a 31% reduction in the risk of death compared with patients assigned to BSC alone. In patients with PD-L1-positive tumors, a clinically meaningful and statistically significant improvement in OS was also demonstrated for patients assigned to avelumab plus BSC with a 44% reduction in the risk of death compared with patients assigned to BSC alone.

- Further, the OS benefit for patients in the avelumab plus BSC alone arm was observed despite the large proportion of patients in the BSC alone arm than in the avelumab plus BSC arm who received a follow-up anticancer drug therapy, in general, and anti-PD-1/PD-L1, in particular.

- The results of the sensitivity analyses for OS were similar to the results of the primary analysis.

A clinically meaningful improvement in PFS was also observed in both coprimary populations. In the all randomized patient population, a 38% reduction of the risk of progression (by BICR assessment per RECIST v1.1) or death was observed for patients in the avelumab plus BSC arm compared to the BSC alone, and a 44% reduction of the risk of progression (by BICR assessment per RECIST v1.1) or death was observed in the PD-L1-positive patient population.

- The observed PFS based on BICR assessment was longer for avelumab plus BSC compared with BSC alone across all prespecified subgroups including the subgroup of patients with PD-L1-negative tumors.

The ORR (by BICR assessment) in the avelumab plus BSC arm was higher than the ORR in the BSC alone arm in all randomized patients (9.7% and 1.4%, respectively) and in patients with PD-L1-positive tumor patient population (13.8% and 1.2%, respectively). [[CSR Table 14.2.1.2.1.1]]

- For subgroups with at least 1 responder (BOR of CR or PR) in both treatment arms, the ORR based on BICR assessment was higher for avelumab plus BSC compared with BSC alone across all prespecified subgroups including the subgroup of patients with PD-L1-negative tumors.

The Applicant's Position:

The study met its primary endpoint showing a statistically significant OS benefit of avelumab plus BSC as compared to BSC alone in both coprimary populations. The results observed for OS in all randomized patients were not driven solely by the benefit observed in patients with PD-L1-positive tumors since the observed OS was longer in the avelumab plus BSC arm than in the BSC alone arm for patients with PD-L1-negative tumors and for patients with PD-L1 unknown tumors. Clinically meaningful PFS benefit was also shown for avelumab plus BSC vs BSC

alone. Taken together, these data support the conclusion that avelumab plus BSC is efficacious as a first-line maintenance treatment in patients with aUC whose disease has not progressed with first-line platinum-based induction chemotherapy.

The FDA's Assessment:

FDA agrees that JAVELIN Bladder 100 met its primary endpointsand demonstrated a clinically meaningful OS benefit of avelumab + BSC maintenance therapy as compared to BSC alone in both coprimary populations (overall and in patients with PD-L1 positive tumors), with approximately a 30% risk reduction of death after a median follow-up of 19.5 months.

Limitations in the interpretation of the results of this trial are similar to the limitations in maintenance trials in general. This topic has been extensively discussed in the NSCLC disease area.[8] The basic theory of the advantage of switch-maintenance therapy (i.e., introduction of a second-line therapy earlier) is that initiation of the second-line therapy at a time of lower tumor burden would be beneficial because there would be fewer clones of inherently resistant cells, and that patients would be less likely to clinically deteriorate prior the time of progression and thus be ineligible for second-line therapy at that time. FDA's exploratory analysis showed similar survival outcomes in patients who received BSC followed by pembrolizumab upon progression as patients who received avelumab maintenance therapy. However, 14 patients in the BSC arm died before progression was captured (Table 4), and only 216 of the 263 progressors who were randomized to BSC received any second-line therapy, which suggests that some patients may have no longer been candidates for treatment. Overall, these results may indicate that initiating PD-1/PD-L1 inhibitor in the maintenance (earlier) setting rather than waiting for progression may allow more patients to potentially benefit from therapy.

Another theorized benefit of maintenance therapy is that it is actually early second-line treatment of progression in patients classified as having SD to initial therapy but who might actually have enlargement of lesions that does not yet precisely meet RECIST v1.1-specified size criteria to be considered PD.[8] Thus the argument could be made that vigilance for progression of any sort and timely initiation of treatment in SD patients might acheive a similar survival benefit, especially if the overall benefit of a maintenance strategy were primarily driven by benefit in these particular patients. However, prespecified analysis of patients with BOR to initial therapy of CR or PR vs. SD did not show any overall difference in benefit between the two groups, i.e. both categories of patients seemed to benefit equally from maintenance treatment with avelumab. We note, however, that progression of disease even on the avelumab + BSC arm occurred relatively quickly in patients, regardless of response to initial therapy.

In summary, FDA agrees with the Applicant's assessment that avelumab + BSC was associated with clinical benefit in terms of OS and PFS compared to BSC alone in patients with urothelial cancer following non-progressive disease with platinum combination chemotherapy. This benefit was seen across most pre-specified subgroups, but the benefit in patients with baseline liver lesions or in those who received carboplatin as induction therapy with SD as best response was not clear. Both of these are small subgroups and the confidence intervals are wide; the results are therefore difficult to interpret. The OS benefit in patients who would have reliable access to

pembrolizumab upon progression is also not clear, and this should be a consideration for all patients, particularly those with PD-L1–negative tumors.

8.2. Review of Safety

Data:
Data on Deaths, TEAEs, Serious TEAEs, irAEs, IRRs and ADRs are located in Section 8.2.4.

The Applicant's Position:
Avelumab plus BSC had a manageable and acceptable safety profile in patients with aUC whose disease has not progressed with first-line platinum-based induction chemotherapy. The safety profile of avelumab was consistent with prior experience with avelumab in aUC and other solid tumors.

The FDA's Assessment:
The FDA generally agrees with the Applicant's assessment.

8.2.1. Safety Review Approach

Data:
Safety data were collected at regular intervals and in accordance to best clinical practice for the patient population under study (see Section 8.2.3.). The safety analyses supporting this application were comprehensive and included all grades and Grade ≥3 all-causality and treatment-related AEs, AEs leading to permanent discontinuations, SAEs, and deaths.
A consistent approach for the categorization of an AE as irAE was applied following a pre-specified case definition consisting of both programmatic checks and medical review in both arms of Study B9991001. IRRs were identified based on a pre-specified case definition.

The Applicant's Position:
The safety review approach implemented for Study B9991001 was appropriate for the patient population studied, and consistent with that implemented in previous submissions of avelumab.

The FDA's Assessment:
The FDA generally agrees with the Applicant's assessment. The safety database consists of data from Study B9991001. AEs of interest for avelumab are pneumonitis, colitis, hepatitis, endocrinopathies (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, and pituitary dysfunction), nephritis and renal dysfunction, rash, and other immune-related adverse events.

The FDA review team conducted safety analyses unadjusted for exposure time, since part of the risk-benefit consideration in the maintenance thearpy setting is the added exposure to therapy for patients in whom BSC may be an alternative management strategy.

8.2.2. Review of the Safety Database

In this study, 'study drug' refers to avelumab or BSC and 'study treatment' (or 'treatment arm') refers to avelumab plus BSC (Arm A) or BSC alone (Arm B).

Other than irAEs and IRRs, adverse event data are summarized based on TEAEs, i.e., events with onset dates occurring during the on-treatment period. On-treatment period was defined as follows:

- Avelumab plus BSC arm: time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day)

- BSC alone arm: time from Cycle 1 Day 1 through minimum (30 days + end date of BSC, start day of new anti-cancer drug therapy – 1 day). 'End date of BSC' is the date of completion or discontinuation as collected in the 'Disposition - Treatment Phase' eCRF page.

Overall Exposure

Data:
The median duration of exposure to study drugs was 24.9 weeks (range; 2.0, 159.9) in the avelumab plus BSC arm and 13.1 weeks (range; 0.1, 155.6) in the BSC alone arm. [[CSR Table 14.4.1.1.1]] In the avelumab plus BSC arm, 163 (47.4%) of patients were exposed to avelumab for > 6 months and 97 (28.2%) of patients were exposed for > 1 year. [[SCS Table 14.4.1.1.11]]

The Applicant's Position:
This dataset provided sufficient safety data for assessing the safety profile of avelumab in patients with aUC whose disease has not progressed with first-line platinum-based induction chemotherapy.

The FDA's Assessment:
Overall exposure to avelumab was adequate to support characteriaton of the safety profile in the proposed patient population.

Relevant characteristics of the safety population:

Data:
The median age of patients treated with avelumab plus BSC was 68 years (range: 37 to 90); 63% of patients were 65 years or older, 76% were male, 66% were White, and the ECOG performance score was 0 (61%) or 1 (39%).

Ongoing medical conditions were present in 94.5% and 94.2% of patients in the avelumab plus BSC and BSC alone arms, respectively. The most frequent ongoing medical condition at baseline was hypertension in both study arms (51.7% in the avelumab plus BSC arm and 44.9% in the BSC alone arm). Renal and urinary disorders in 26.5% and 23.2% of patients in the avelumab plus BSC and BSC alone arms, respectively. [[CSR Table 14.4.2.6.1]] The majority of patients in both study arms received concomitant medications (97.7% and 91.6% in the avelumab plus BSC arm and BSC alone arm, respectively). [[CSR Table 14.1.1.2.4]]

The Applicant's Position:
Baseline characteristics and conditions, and use of concomitant medications were consistent with

the patient population under study.

The FDA's Assessment:
The clinial reviewer queried dataset ADAE (variables ACTARM, AAGE, ECOGBL) and confirmed the Applicant's description of baseline characteristics and conditions and use of concomitant medications. The FDA agrees that these were consistent with the patient population under study.

Adequacy of the safety database:

Data:
Study B9991001 included 344 patients treated with avelumab plus BSC and 345 patients treated with BSC only. Median exposure to study drugs was 24.9 weeks in the avelumab plus BSC arm and 13.1 weeks in the BSC alone arm. In the avelumab plus BSC arm, 47.4% of patients were exposed to avelumab for > 6 months and 28.2% of patients were exposed for > 1 year. At the time of data cutoff, 75.7% of patients in the avelumab plus BSC arm and 92.6% of patients in the BSC alone arm had completed the End of Treatment visit. [[SCS Table 14.1.1.2.2]]

The Applicant's Position:
The study design, the number of patients treated in each study arm, the duration of exposure to study treatment , and the proportion of patients who had completed the End of Treatment visit in both study arms by the cutoff date permit an adequate assessment of the safety of avelumab as a single agent in patients with aUC whose disease has not progressed with first-line platinum-based induction chemotherapy.

The FDA's Assessment:
Overall exposure to avelumab was adequate to support characteriaton of the safety profile in the proposed patient population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
No issues were identified regarding the integrity and quality of the safety data included in this sBLA.

The Applicant's Position:
The Applicant has a comprehensive quality management system in place for monitoring safety data quality across the entire clinical trial. Quality management methods include site inspections, safety data review by qualified experts, management of data quality (site collection, site-to-Sponsor data transmission, data analysis and data summarization), and management of regulatory document quality. No issues were identified that could potentially impact data integrity, prevent adequate assessment of the data, and change the conclusions drawn.

The FDA's Assessment:
Based on the Agency's review, the FDA agrees with the Applicant's assement regarding the quality and integrity of the submitted datasets. Refer to Section 4.1 of this review for discussion on rationale for no clinical site inspectons for this supplemental application.

Categorization of Adverse Event

Data:
AEs were coded using the MedDRA Version 22.1 and graded using the NCI CTCAE Version 4.03. TEAEs were defined as any AE with an onset date from the first dose of study treatment through a minimum of 30 days plus last dose of study treatment, start day of new anti-cancer drug therapy minus 1 day. Since irAEs can have onset several weeks after the end of treatment with a checkpoint inhibitor, irAEs were summarized including AEs with onset up to 90 days after the last dose of study drug.

Detailed information collected for each AE included a description of the event, duration, whether the AE was serious, severity, relationship to study drug per the Investigator, action taken with study drug, and clinical outcome. TEAEs leading to discontinuation of study drug, TEAEs leading to dose reduction, TEAEs leading to study drug interruption, and TEAEs leading to both study drug interruption and dose reduction were summarized.

The Applicant's Position:
The overall approach to evaluate the safety data in this study was adequate and consistent with prior submissions for avelumab.

The FDA's Assessment:
The FDA generally agrees with the Applicant's assessment.

Routine Clinical Tests

Data:
Clinical safety tests carried out in Study B9991001 are summarized in Table 13 and Table 14.

Table 13. Safety Assessments for Screening and Study Treatment Periods

Visit Identifiers	Screening	Study Treatment (1 cycle = 4 weeks)			
		Arm A Avelumab + BSC		Arm B BSC	
	Within 28 Days Prior to Randomization	Cycle 1 Day 1 Cycle ≥2 Day 1 (±3 days)	Day 15 (±3 days) All Cycles	Cycle 1 Day 1 Cycle ≥2 Day 1 (±3 days)	Day 15 (±3 days) All Cycles
Clinical Assessments					
Informed Consent	X				
Medical/Oncological History	X				

Table 13. Safety Assessments for Screening and Study Treatment Periods

Visit Identifiers	Screening	Study Treatment (1 cycle = 4 weeks)			
		Arm A Avelumab + BSC		Arm B BSC	
	Within 28 Days Prior to Randomization	Cycle 1 Day 1 Cycle ≥2 Day 1 (±3 days)	Day 15 (±3 days) All Cycles	Cycle 1 Day 1 Cycle ≥2 Day 1 (±3 days)	Day 15 (±3 days) All Cycles
Baseline Signs/Symptoms		X (Cycle 1 only)		X (Cycle 1 only)	
Physical Examination	X	X		X	
ECOG Performance Status	X	X		X	
Vital Signs and Weight	X	X	X	X	
Contraception Check	X	X	X		
Laboratory Studies					
Coagulation	X	X	X	X	
Hematology	X	X	X	X	
Blood Chemistry (full and core)	X	X	X	X	
Thyroid Function and ACTH Tests	X	X (at Cycles 3, 5, 7, etc.)		X (at Cycles 3, 5, 7, etc.)	
Serum/Urine Pregnancy Test	X	X	X		
Troponin	X	X (Cycles 1-4 and as clinically indicated)	X (Cycles 1-3 and as clinically indicated)	X (Cycles 1-4 and as clinically indicated)	
HBV, HCV Tests	X	If clinically indicated		If clinically indicated	
HIV test	X				
Urinalysis	X	If clinically indicated		If clinically indicated	
12-Lead ECG	X	If clinically indicated		If clinically indicated	
Other Clinical Assessments					
Adverse Events		X	X	X	X
Concomitant Medications/Treatments	X	X	X	X	X

Table 14. Safety Assessments for End of Treatment/Withdrawal and Follow-up Periods

Visit Identifiers	End of Treatment/ Withdrawal (±3 days)	Follow-up			
		Short-Term			Long-Term every 3 months ±14 days)
		30 days (±3 days) After Last Dose (Arm A) or EOT/Withdrawal Visit (Arm B)	60 days (±3 days) After Last Dose (Arm A) or EOT/Withdrawal Visit (Arm B)	90 days (±3 days) After Last Dose (Arm A) or EOT/Withdrawal Visit (Arm B)	
Documentation					
Physical Examination	X	X	X	X	
ECOG Performance Status	X	X	X	X	
Vital Signs and Weight	X	X	X	X	
Contraception Check (Arm A ONLY)	X	X			
Laboratory Studies					
Hematology	X	X	X	X	
Blood Chemistry (full panel)	X	X	X	X	
Coagulation	X	X	X	X	
Thyroid Function Tests and ACTH	X	X	X	X	
Serum/Urine Pregnancy Test (Arm A ONLY)	X	X			
Urinalysis	X				
12-lead ECG	If clinically indicated				
Other Clinical Assessments					
Adverse Events	X	X	X	X	
Concomitant Medications/Treatments	X	X	X	X	

Hematology, blood chemistry, and urinalysis consisted of laboratory tests processed at local laboratories.

The Applicant's Position:
The clinical safety tests carried out in Study B9991001 were appropriate for the safety monitoring of the population under study, and for the known safety profile of avelumab. Troponin was included at the request of the FDA to determine if troponin could be used as a biomarker for the early detection of myocarditis in patients exposed to avelumab.

The FDA's Assessment:
The FDA generally agrees with the Applicant's assessment.

8.2.4. Safety Results

Deaths

Data:
Among the patients in the safety analysis set, 144 (41.9%) in the avelumab plus BSC arm and 176 (51.0%) of patients in the BSC alone arm died. Disease progression was the most frequent cause of death in both the avelumab plus BSC arm (133 [38.7%]) and BSC alone arm (157 [45.5%]) (Table 15). In the avelumab plus BSC arm, there were 2 (0.6%) deaths related to study treatment toxicity per investigator, including 1 death due to ischemic stroke (more than 30 days after the last dose of study treatment) and 1 death due to sepsis (within 30 days after the last dose of study treatment). [[CSR Table 14.3.1.2.2 and CSR Table 16.2.7.2]] Both deaths were considered unrelated to study treatment by the Sponsor. There were no fatal irAEs or IRRs in the study.

Table 15. Summary of Deaths - Safety Analysis Set (Protocol B9991001)

	Avelumab+BSC (N=344) n (%)	**BSC (N=345) n (%)**
Deaths	144 (41.9)	176 (51.0)
Cause of death		
Disease progression	133 (38.7)	157 (45.5)
Study treatment toxicity	2 (0.6)	0
Adverse event not related to study treatment	2 (0.6)	10 (2.9)
Other	2 (0.6)	3 (0.9)
Unknown	6 (1.7)	6 (1.7)
Deaths within 30 days after last dose of study treatment	5 (1.5)	33 (9.6)
Cause of death		
Disease progression	4 (1.2)	27 (7.8)
Study treatment toxicity	1 (0.3)	0
Adverse event not related to study treatment	0	6 (1.7)
Other	0	0
Unknown	0	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
A subject can have more than one cause of death.
Last dose of study treatment in BSC arm refers to the date of completion or discontinuation as collected on the End of treatment disposition CRF
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADSL Output File: ./B9991001/B9991001 CSR/adae s500a Date of Generation: 14JAN2020 (04:39) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.2.1.1 is for Pfizer internal use.

AEs Leading to Death:
The most common TEAE leading to death was disease progression in both study arms. The only TEAE other than disease progression leading to death in the avelumab plus BSC arm was sepsis (1 patient, 0.3%).

Table 16. Summary of TEAEs During the On-Treatment Period Leading to Death by SOC and PT - Safety Analysis Set (Protocol B9991001)

System Organ Class and Preferred Term	Avelumab+BSC (N=344) n (%)	BSC (N=345) n (%)
Subjects with events	4 (1.2)	24 (7.0)
General disorders and administration site conditions	3 (0.9)	16 (4.6)
Disease progression	3 (0.9)	16 (4.6)
Infections and infestations	1 (0.3)	2 (0.6)
Sepsis	1 (0.3)	0
Biliary sepsis	0	1 (0.3)
Urosepsis	0	1 (0.3)
Cardiac disorders	0	1 (0.3)
Cardiogenic shock	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (1.2)
Bladder cancer	0	1 (0.3)
Malignant neoplasm progression	0	1 (0.3)
Metastatic carcinoma of the bladder	0	1 (0.3)
Neoplasm progression	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0	1 (0.3)
Chronic obstructive pulmonary disease	0	1 (0.3)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event within a preferred term are counted only once in that preferred term.
Subjects reporting multiple preferred terms within the same system organ class (SOC) are counted only once within each SOC.
Sorted in descending order of the frequency of SOC and PTs in Avelumab + BSC arm.
MedDRA v22.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001/B9991001 CSR/adae s180 dth socpt Date of Generation: 14JAN2020 (04:11) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.1.2.2 is for Pfizer internal use.

The Applicant's Position:

The TEAEs leading to death in Study B9991001 were consistent with the progression or medical complications of the disease under study, the lack of active treatment in the control arm, and prior experience with avelumab as single agent in aUC.

The FDA's Assessment:

The clinical reviewer confirmed the results reported in Applicant's Table 16 by querying dateaset ADAE (variables AETOXGR, USUBJID, ARM and AEDECOD). The clinical reviewer confirmed the results in Applicant's Table 15 by querying dataset ADSL (variables ARM ADTH30FL, and ADTHCAU1).

The Applicant considered one death on the avelumab + BSC arm (Subject (b) (6)) to have been due to a drug-related adverse events. Patient (b) (6) was a 75-year-old Asian male whose medical history included angina pectoris, hyperlipidemia, hypertension, and compression fracture, and prior anticancer therapy included transurethral bladder resection, cisplatin, and gemcitabine. On Study Day 13, the patient developed Grade 3 erythema multiforme. Concomitant medications included aspirin, clopidogrel, candesartan, imidapril, rosuvastatin, and silodosin. Treatment included prednisolone and interruption of avelumab. On Day 72, the erythema multimore resolved and avelumab was resumed. On Day 260, the patient was . hospitalized and treated with antibiotics for Grade 4 sepsis (pyrexia, disturbed consciousness, percussion tenderness on the back, hypotension, disseminated intravascular coagulation, Gram-positive cocci cultured from blood. Avelumab was disconintued. The patient's blood pressure normalized the next day. On Day 272, cranial computed tomography of the head, chest, and abdomen detected no metastases. On Day 276, the patient's level of consciousness decreased to a Japan Coma Scale score of 200. On Day 284, the patient died due to sepsis, the source of which was thought to be a central venous port. This reviewer considered this death possibly but not likely related to avelumab.

The Applicant proposed to remove safety data from the USPI for patients treated in the second-line aUC setting and to replace those data with safety data from JAVELIN Bladder 100, as it included a control (BSC) arm. However, the FDA disagreed with complete removal of the second-line aUC data because while overall safety data appeared concordant between the two settings, the rate of fatal adverse events observed in the second-line setting (6%) was appreciably higher than that observed in the first-line setting (0.3%), possibly due to frailty of patients later in the course of disease. In addition, rates of certain common AEs were higher in the second-line setting, thus these data were retained in labeling as well.

Serious Adverse Events

Data:
A summary of the most common SAEs is presented in **Table 17**. SAEs occurred in 27.9% of patients receiving avelumab plus BSC. Serious adverse events in ≥ 1% of patients included urinary tract infection (4.7%), acute kidney injury (1.7%), haematuria (1.5%), infusion-related reaction (1.2%), pain (1.2%), and sepsis (1.2%).

Table 17. Summary of Most Common Serious TEAEs (≥2 Subjects in Any Treatment Group), by PT During the On-Treatment Period - Safety Analysis Set (Protocol B9991001)

Preferred Term	Avelumab + BSC (N=344) (n %)	BSC (N=345) (n %)
Subjects with events	96 (27.9)	69 (20.0)
Urinary tract infection	16 (4.7)	7 (2.0)

Preferred Term	Avelumab + BSC (N=344) (n %)	BSC (N=345) (n %)
Acute kidney injury	6 (1.7)	6 (1.7)
Haematuria	5 (1.5)	2 (0.6)
Infusion related reaction	4 (1.2)	0
Pain	4 (1.2)	1 (0.3)
Sepsis	4 (1.2)	1 (0.3)
Atrial fibrillation	3 (0.9)	1 (0.3)
Back pain	3 (0.9)	1 (0.3)
Disease progression	3 (0.9)	16 (4.6)
Hydronephrosis	3 (0.9)	1 (0.3)
Ileus	3 (0.9)	1 (0.3)
Pyelonephritis	3 (0.9)	3 (0.9)
Vomiting	3 (0.9)	0
Blood creatine phosphokinase increased	2 (0.6)	0
Colitis	2 (0.6)	0
Constipation	2 (0.6)	0
Dyspnoea	2 (0.6)	1 (0.3)
Kidney infection	2 (0.6)	0
Myocardial infarction	2 (0.6)	0
Pyrexia	2 (0.6)	1 (0.3)
Vascular device infection	2 (0.6)	0
Abdominal pain	1 (0.3)	3 (0.9)
Anaemia	1 (0.3)	2 (0.6)
Basal cell carcinoma	1 (0.3)	2 (0.6)
Urosepsis	1 (0.3)	2 (0.6)
Syncope	0	2 (0.6)
Tumour pain	0	2 (0.6)
Urinary tract obstruction	0	2 (0.6)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
Sorted in descending order of the frequency of PTs in the Avelumab+BSC arm.
MedDRA (v22.1) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001/B9991001 CSR/adae s999 ser Date of Generation: 14JAN2020 (04:41) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.1.2.2.15 is for Pfizer internal use.

The Applicant's Position:

The SAE profile in the avelumab plus BSC arm was mostly consistent with the medical complications of the disease under study and prior experience with avelumab as a single agent in

aUC.

The FDA's Assessment:
The clinical reviewer confirmed the results presented in Applicant's Table 17 above using dataset ADAE (variables TRTEMFL, AESER, USUBJID, AEDECOD, ARM, and AETOXGR). The Applicant reported TEAEs irrespective of attribution, and the 'overall' rate of events reported reflects the number of patients who experienced any serious TEAE, which is consistent with how the FDA presents safety data in product package inserts.

The clinical reviewer pooled certain MedDRA Preferred Terms, where appropriate, into more clinically meaningful composite terms and thus the labled SAEs differ slightly from those numbers presented above. Grouped terms use to calculate SAEs by the clinical reviewer that differ from the applicant's are presented in Table 18 below.

Table 18. Common Serious TEAEs by Composite Preferred Term

Composite Term	**Individual Preferred Terms**		**N**
Preferred Term	**Composite Preferred Term**	**Avelumab + BSC (N = 344)**	**BSC (N = 345)**
Urinary tract infection	Urinary tract infection, Kidney infection, Pyelonephritis, pyelonephritis acute, urosepsis	21 (6.1%)	11 (3.2%)
Pain	Abdominal pain, back pain, bone pain, flank pain, musculoskeletal pain, pain, pain in extremity, pelvic pain, tumor pain	11 (3.2%)	8 (2.3%)
Acute kidney injury	Acute kidney injury, anuria, renal impairment	6 (1.7%)	8 (2.3%)
Sepsis	Sepsis, biliary sepsis, urosepsis	5 (1.5%)	4 (1.2%)
Hydronephrosis	Hydronephrosis, ureteric obstruction, urinary tract obstruction	4 (1.2%)	3 (0.9%)
Disease progression	Disease progression, metastatic carcinoma of the bladder, malignant neoplasm progression	3 (0.9%)	19 (5.5%)

Dropouts and/or Discontinuations Due to Adverse Effects

Data:
A summary of the causes of avelumab discontinuation is available in Table 4. Avelumab was permanently discontinued due to a TEAE in 11.9% of patients (Table 19). The most common TEAE (> 1%) leading to discontinuation of avelumab was infusion-related reaction (1.2%).

Table 19. Summary of TEAEs Leading to Discontinuation of Study Drug by SOC and PT - Safety Analysis Set (Protocol B9991001)

System Organ Class and Preferred Term	Avelumab+BSC (N=344) n (%)	BSC (N=345) n (%)
Subjects with events	41 (11.9)	0
Investigations	10 (2.9)	0
Lipase increased	3 (0.9)	0
Troponin T increased	3 (0.9)	0
Alanine aminotransferase increased	2 (0.6)	0
Amylase increased	2 (0.6)	0
Aspartate aminotransferase increased	1 (0.3)	0
Blood alkaline phosphatase increased	1 (0.3)	0
Gamma-glutamyltransferase increased	1 (0.3)	0
Neutrophil count decreased	1 (0.3)	0
Platelet count decreased	1 (0.3)	0
Gastrointestinal disorders	6 (1.7)	0
Colitis	2 (0.6)	0
Autoimmune pancreatitis	1 (0.3)	0
Gastric ulcer	1 (0.3)	0
Pancreatitis	1 (0.3)	0
Vomiting	1 (0.3)	0
General disorders and administration site conditions	4 (1.2)	0
Disease progression	2 (0.6)	0
Fatigue	1 (0.3)	0
Malaise	1 (0.3)	0
Injury, poisoning and procedural complications	4 (1.2)	0
Infusion related reaction	4 (1.2)	0
Musculoskeletal and connective tissue disorders	3 (0.9)	0
Muscular weakness	1 (0.3)	0
Myositis	1 (0.3)	0
Rheumatoid arthritis	1 (0.3)	0
Renal and urinary disorders	3 (0.9)	0
Nephritis	1 (0.3)	0
Tubulointerstitial nephritis	1 (0.3)	0
Ureteric obstruction	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	3 (0.9)	0
Interstitial lung disease	2 (0.6)	0
Pneumonitis	1 (0.3)	0
Cardiac disorders	2 (0.6)	0
Acute myocardial infarction	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Endocrine disorders	2 (0.6)	0

System Organ Class and Preferred Term	Avelumab+BSC (N=344) n (%)	BSC (N=345) n (%)
Autoimmune thyroiditis	1 (0.3)	0
Hyperthyroidism	1 (0.3)	0
Hepatobiliary disorders	2 (0.6)	0
Autoimmune hepatitis	1 (0.3)	0
Hepatotoxicity	1 (0.3)	0
Infections and infestations	2 (0.6)	0
Sepsis	2 (0.6)	0
Blood and lymphatic system disorders	1 (0.3)	0
Anaemia	1 (0.3)	0
Metabolism and nutrition disorders	1 (0.3)	0
Hypokalaemia	1 (0.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0
Oesophageal squamous cell carcinoma	1 (0.3)	0
Nervous system disorders	1 (0.3)	0
Toxic neuropathy	1 (0.3)	0
Skin and subcutaneous tissue disorders	1 (0.3)	0
Pruritus	1 (0.3)	0
Rash maculo-papular	1 (0.3)	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event within a preferred term are counted only once in that preferred term.
Subjects reporting multiple preferred terms within the same system organ class (SOC) are counted only once within each SOC.
MedDRA v22.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001/B9991001 CSR/adae s180 disc Date of Generation: 14JAN2020 (04:03) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.1.2.3 is for Pfizer internal use.

The Applicant's Position:

The profile of TEAEs leading to avelumab discontinuation was consistent with the known safety profile of avelumab in solid tumors.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. The clinical reviewer confirmed the results presented in Applicant's Table 20 above using dataset ADAE (variables TRTEMFL, AEACN, AEDECOD, ARM, and USUBJID). The most common TEAE leading to discontinuation was infusion related reaction (4 patients), followed by lipase increased, toponin T increased (3 patients each). The clinical reviewer pooled certain MedDRA Preferred Terms, where appropriate, into more clinically meaningful composite terms, and although this did not change the overall percentage of patients discontinuing therapy due to SAEs, this impacts several composite terms as presented in Table 20 below.

Table 20. Common TEAEs Leading to Discontinuation of Avelumab by Composite Preferred Term

Composite Term	Individual Preferred Terms	N
Myocardial infarction	Acute myocardial infarction, myocardial infarction, and troponin increased	5 (1.5%)
Intersitial lung disease	Interstitial lung disease and pneumonitis	2 (0.6%)
Fatigue	Fatigue and malaise	2 (0.6%)
Nephritis	Nephritis and tubulointersitial nephritis	2 (0.6%)

Dose Interruption/Reduction Due to Adverse Effects

Data:
Avelumab was temporarily discontinued for a TEAE in 40.7% of patients, excluding temporary dose interruption for infusion-related reactions where infusion was restarted the same day. The only TEAE that resulted in temporary discontinuation of avelumab in > 2% of patients was urinary tract infection (3.5%). [[CSR Table 14.3.1.2.5]] Modification of the starting dose of avelumab (10 mg/kg) was not permitted by protocol, however the dose was reduced in 1 patient (0.3%) due to asthenia. [[CSR Table 14.3.1.2.6]] TEAEs leading to both dose interruption and dose reduction of avelumab were not reported in any patient. [[CSR Table 14.3.1.2.8]]

The Applicant's Position:
The profile of TEAEs leading to avelumab interruption was consistent with the medical complications of the disease under study.

The FDA's Assessment:
The B9991001 treatment protocol did not permit dose reduction of avelumab, but the next dose could be omitted based on toxicity. Avelumab dose interruptions were therefore for at least two weeks, and could thus be referred to as dose omissions.

AEs were defined as leading to interruption if the action taken with study treatment was 'drug interrupted' excluding 1) IRRs that occurred on the day of infusion with ≥90% of the planned dose given and the subsequent administration of study drug had no delay, and 2) IRRs occurring on the day after infusion and subsequent dose administration had no delay.

The following PTs were considered IRRs if they began the day of avelumab infusion (during or after infusion) and they resolved within 2 days of onset: Pyrexia, Chills, Flushing, Hypotension, Dyspnea, Wheezing, Back pain, Abdominal pain, Urticaria. The following PTs were considered IRRs if they began the day of avelumab infusion (during or after infusion) or the day after the avelumab infusion, irrespective of their resolution date: Infusion related reaction, Drug hypersensitivity, Anaphylactic reaction, Hypersensitivity, and Type 1 hypersensitivity.

The most common TEAEs leading to dose interruption are presented in Table 21 below, including minor differences from the applicant's numbers presented above due to broader grouping of terms. Because B9991001 was an open-label trial, there was no placebo to be discontinued in the BSC arm.

Table 21. Protocol B9991001 TEAEs Leading to Dose Interruption in ≥3 Patients

Composite Term	Avelumab + BSC (N = 344)
Any	**140 (40.7%)**
Urinary tract infection[a]	16 (4.7%)
Blood creatinine increased[b]	13 (3.8%)
Influenza[c]	8 (2.3%)
Hyperthyroidism	7 (1.7%)
Alanine aminotransferase increased	7 (2.0%)
Lipase increased	7 (2.0%)
Amylase increased	6 (1.7%)
Back pain	6 (1.7%)
Diarrhea	6 (1.7%)
Infusion related reaction	6 (1.7%)
Rash[d]	6 (1.7%)
Aspartate aminotransferase increased	5 (1.5%)
Chills	5 (1.5%)
Neutrophil count decreased[e]	5 (1.5%)
Anemia	4 (1.2%)
Arthralgia	4 (1.2%)
Blood creatine phosphokinase increased	4 (1.2%)
Colitis	4 (1.2%)
Fatigue[f]	4 (1.2%)
Gamma-glutamyltransferase increased	4 (1.2%)
Hematuria	4 (1.2%)
Hypothyroidism	4 (1.2%)
Troponin increased	4 (1.2%)
Adrenal insufficiency[g]	3 (0.9%)
Arthritis	3 (0.9%)
Blood alkaline phosphatase increased	3 (0.9%)
Dyspnea	3 (0.9%)
Edema peripheral	3 (0.9%)
Hydronephrosis	3 (0.9%)
Pneumonitis	3 (0.9%)
Vomiting	3 (0.9%)

Source: Dataset ADAE; variables TRTEMFL, AEINT1, USUBJID, AEDECOD, ACTARM
[a] includes urinary tract infection and pyelonephritis
[b] includes blood creatinine increase, acute kidney injury, renal insufficiency, and renal failure
[c] includes influenza and influenza like illness
[d] includes rash, erythema multiforme, rash erythematouys, and rash maculopapular
[e] includes neutropenia and neutrophil count decreased
[f] includes fatigue and asthenia
[g] includes adrenal insufficiency and cortisol decreased

Significant Adverse Events

Data:
irAEs and IRRs are considered adverse events of special interest for avelumab.

irAEs

The most common irAEs (>5%) in the avelumab plus BSC arm by irAE Cluster were Immune-related Endocrinopathies: Thyroid disorders (42 [12.2%] patients, with 37 (10.8%) patients diagnosed with Hypothyroidism, 16 (4.7%) patients with Hyperthyroidism, and 3 (0.9%) with Thyroiditis), and Immune-related Rash (35 [10.2%] patients). In the avelumab plus BSC arm, out of the 101 patients with an irAE, 46 (13.4%) patients received systemic corticosteroids for an irAE and 31 (9.0%) received an oral prednisone dose equivalent ≥40 mg daily. [[SCS Table 14.3.3.3.1.1.10.1]] irAEs led to discontinuation of treatment with avelumab in 19 patients (5.5%), with the most frequent irAE leading to discontinuation being immune-related hepatitis (cluster term) in 4 (1.2%) patients. irAEs in Study B9991001 are summarized by cluster, PT, All Grades, and Grade ≥3 in Table 22. There were no Grade 4 or Grade 5 irAEs.

Table 22. Summary of irAEs by Cluster, PT and Maximum CTCAE Grade - Safety Analysis Set (Protocol B9991001)

	Avelumab+BSC (N=344)		BSC (N=345)	
Cluster and Preferred Term	**All Grades n (%)**	**Grade ≥3 n (%)**	**All Grades n (%)**	**Grade ≥3 n (%)**
Subjects with events	101 (29.4)	24 (7.0)	5 (1.4)	1 (0.3)
IMMUNE-RELATED ENDOCRINOPATHIES: THYROID DISORDERS	42 (12.2)	1 (0.3)	2 (0.6)	0
Hypothyroidism	35 (10.2)	1 (0.3)	1 (0.3)	0
Hyperthyroidism	16 (4.7)	0	1 (0.3)	0
Autoimmune thyroiditis	2 (0.6)	0	0	0
Autoimmune hypothyroidism	1 (0.3)	0	0	0
Blood thyroid stimulating hormone increased	1 (0.3)	0	0	0
Thyroiditis	1 (0.3)	0	0	0
Thyroxine free decreased	1 (0.3)	0	0	0
IMMUNE-RELATED RASH	35 (10.2)	5 (1.5)	1 (0.3)	0
Rash	17 (4.9)	1 (0.3)	0	0
Rash maculo-papular	8 (2.3)	1 (0.3)	0	0
Pruritus	7 (2.0)	0	1 (0.3)	0
Erythema	2 (0.6)	1 (0.3)	0	0
Purpura	2 (0.6)	0	0	0
Rash erythematous	2 (0.6)	0	0	0
Drug eruption	1 (0.3)	1 (0.3)	0	0
Erythema multiforme	1 (0.3)	1 (0.3)	0	0
Lichen planus	1 (0.3)	0	0	0
Rash papular	1 (0.3)	0	0	0
Rash pruritic	1 (0.3)	0	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: OTHER	9 (2.6)	2 (0.6)	0	0
Psoriasis	3 (0.9)	0	0	0
Vitiligo	2 (0.6)	0	0	0

Cluster and Preferred Term	Avelumab+BSC (N=344) All Grades n (%)	Avelumab+BSC (N=344) Grade ≥3 n (%)	BSC (N=345) All Grades n (%)	BSC (N=345) Grade ≥3 n (%)
Arthritis	1 (0.3)	0	0	0
Dermatitis psoriasiform	1 (0.3)	0	0	0
Oligoarthritis	1 (0.3)	1 (0.3)	0	0
Polyarthritis	1 (0.3)	0	0	0
Rheumatoid arthritis	1 (0.3)	1 (0.3)	0	0
IMMUNE-RELATED PNEUMONITIS	7 (2.0)	1 (0.3)	0	0
Pneumonitis	5 (1.5)	1 (0.3)	0	0
Interstitial lung disease	2 (0.6)	0	0	0
IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION	6 (1.7)	1 (0.3)	0	0
Nephritis	3 (0.9)	0	0	0
Renal failure	3 (0.9)	1 (0.3)	0	0
Tubulointerstitial nephritis	1 (0.3)	0	0	0
IMMUNE-RELATED COLITIS	5 (1.5)	3 (0.9)	0	0
Colitis	3 (0.9)	2 (0.6)	0	0
Diarrhoea	2 (0.6)	0	0	0
Enteritis	1 (0.3)	1 (0.3)	0	0
Proctitis	1 (0.3)	0	0	0
IMMUNE-RELATED HEPATITIS	5 (1.5)	5 (1.5)	0	0
Alanine aminotransferase increased	3 (0.9)	3 (0.9)	0	0
Aspartate aminotransferase increased	2 (0.6)	2 (0.6)	0	0
Autoimmune hepatitis	1 (0.3)	1 (0.3)	0	0
Hepatotoxicity	1 (0.3)	1 (0.3)	0	0
IMMUNE-RELATED ENDOCRINOPATHIES: ADRENAL INSUFFICIENCY	3 (0.9)	0	0	0
Adrenal insufficiency	3 (0.9)	0	0	0
IMMUNE-RELATED ENDOCRINOPATHIES: TYPE 1 DIABETES MELLITUS	3 (0.9)	3 (0.9)	1 (0.3)	1 (0.3)
Hyperglycaemia	3 (0.9)	3 (0.9)	0	0
Diabetes mellitus	0	0	1 (0.3)	1 (0.3)
IMMUNE-RELATED PANCREATITIS	2 (0.6)	1 (0.3)	0	0
Autoimmune pancreatitis	1 (0.3)	1 (0.3)	0	0
Pancreatitis	1 (0.3)	0	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: MYOSITIS	2 (0.6)	2 (0.6)	0	0
Myositis	2 (0.6)	2 (0.6)	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: GUILLAIN-BARRE SYNDROME	1 (0.3)	1 (0.3)	0	0
Miller Fisher syndrome	1 (0.3)	1 (0.3)	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: UVEITIS	1 (0.3)	0	1 (0.3)	0
Uveitis	1 (0.3)	0	1 (0.3)	0

Cluster and Preferred Term	Avelumab+BSC (N=344) All Grades n (%)	Avelumab+BSC (N=344) Grade ≥3 n (%)	BSC (N=345) All Grades n (%)	BSC (N=345) Grade ≥3 n (%)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
Subjects reporting multiple preferred terms within the same cluster are counted only once within each cluster.
For subjects reporting more than one AE within a cluster or preferred term, the AE with maximum grade are included in the table.
Sorted in descending order of the frequency of clusters and PTs within cluster for all grades in the Avelumab+BSC arm.
MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAEI Output File: ./B9991001/B9991001 CSR/adae s062 irae2 Date of Generation: 14JAN2020 (03:27) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.1.7.1.11.1 is for Pfizer internal use.

A summary of irAEs by cluster term is provided below.

IMMUNE-RELATED PNEUMONITIS

IMMUNE-RELATED PNEUMONITIS occurred in 7 (2.0%) of patients receiving avelumab including 1 (0.3%) patient with Grade 3 IMMUNE-RELATED PNEUMONITIS. IMMUNE-RELATED PNEUMONITIS led to permanent discontinuation of avelumab in 0.9% of patients. Among the 7 patients with IMMUNE-RELATED PNEUMONITIS, the median time to onset was 3.6 months (range: 1.5 months to 13.8 months) and the median duration was 2.3 months (range: 1 month to 4.9 months). All 7 patients were treated with systemic corticosteroids; 4 (57.1%) of the 7 patients received high-dose corticosteroids for a median of 20.0 days (range: 1 week to 1.6 months). No patients received additional immunosuppressants. Resolution of IMMUNE-RELATED PNEUMONITIS occurred in 6 (85.7%) of the 7 patients at the time of data cutoff. [[SCS Tables 14.3.1.7.3.1.4.8, 14.3.3.3.1.1.3.6, 14.3.3.3.1.1.10 and 14.3.3.3.1.1.11]]

IMMUNE-RELATED HEPATITIS

IMMUNE-RELATED HEPATITIS occurred in 5 (1.5%) of patients receiving avelumab including 5 (1.5%) patients with Grade 3 IMMUNE-RELATED HEPATITIS. IMMUNE-RELATED HEPATITIS led to permanent discontinuation of avelumab in 1.2% of patients. Among the 5 patients with IMMUNE-RELATED HEPATITIS, the median time to onset was 4.2 months (range: 2.8 months to 8.9 months), and the median duration was 2.2 months (range: 1.3 weeks to 3.0+ months). All 5 patients were treated with high dose systemic corticosteroids for a median of 3.3 weeks (range: 1.9 weeks to 4.1 months). Resolution of IMMUNE-RELATED HEPATITIS occurred in 3 (60%) of the 5 patients at the time of data cutoff. [[SCS Tables 14.3.1.7.3.1.4.5, 14.3.3.3.1.1.3.3, 14.3.3.3.1.1.10 and 14.3.3.3.1.1.11]]

IMMUNE-RELATED COLITIS

IMMUNE-RELATED COLITIS occurred in 1.5% of patients receiving avelumab including 3 (0.9%) patients with Grade 3 IMMUNE-RELATED COLITIS. IMMUNE-RELATED

COLITIS led to permanent discontinuation of avelumab in 0.6% of patients. Among the 5 patients with IMMUNE-RELATED COLITIS, the median time to onset was 4.0 months (range: 2.1 weeks to 5.8 months) and the median duration was 3.7 weeks (range: 2 weeks to 5.4+ months). All 5 patients were treated with systemic corticosteroids; 4 (80%) of the 5 patients received high-dose corticosteroids for a median of 2 weeks (range: 1.0 day to 1.1 months). One patient was treated with a non- steroidal immunosuppressant. Resolution of IMMUNE-RELATED COLITIS occurred in 4 (80%) of the 5 patients at the time of data cutoff [[SCS Tables 14.3.1.7.3.1.4.1, 14.3.3.3.1.1.3, 14.3.3.3.1.1.9 and 14.3.3.3.1.1.11]]

IMMUNE-RELATED ENDOCRINOPATHIES: ADRENAL INSUFFICIENCY
IMMUNE-RELATED ADRENAL INSUFFICIENCY occurred in 3 (0.9%) of patients receiving avelumab. IMMUNE-RELATED ADRENAL INSUFFICIENCY led to permanent discontinuation of avelumab in 0 patients. Among the 3 patients with IMMUNE-RELATED ADRENAL INSUFFICIENCY, the median time to onset was 3.7 months (range: 2 weeks to 6.5 months), and the median duration was 2.14 weeks (range: 2.1 weeks to 2.2 months). All 3 patients were treated with systemic corticosteroids; 1 (33.3%) of the 3 patients received high-dose corticosteroids for 2.3 weeks. Resolution of IMMUNE-RELATED ADRENAL INSUFFICIENCY occurred in 3 (100.0%) of the 3 patients at the time of data cutoff. [[SCS Tables 14.3.1.7.3.1.4.2, 14.3.3.3.1.1.3.2, 14.3.3.3.1.1.9 and 14.3.3.3.1.1.11]]

IMMUNE-RELATED ENDOCRINOPATHIES: THYROID DISORDERS (HYPOTHYROIDISM/ HYPERTHYROIDISM)
IMMUNE-RELATED THYROID DISORDERS occurred in 42 (12.2%) of patients receiving avelumab including 1 (0.3%) patient with Grade 3 IMMUNE-RELATED THYROID DISORDERS. Immune-related THYROID DISORDERS led to permanent discontinuation of avelumab in 0.6% of patients. HYPOTHYROIDISM occurred in 37 (10.8%) patients; HYPERTHYROIDISM in 16 (4.7%) patients; and THYROIDITIS in 3 (0.9%) patient treated with avelumab. Among the 42 patients with IMMUNE-RELATED THYROID DISORDERS, the median time to onset was 1.9 months (range: 2.14 weeks to 9.4 months), and the median duration was not estimable (range: 3.0 days to 27.6+ months). Thirty-eight (90.5%) of patients with IMMUNE-RELATED THYROID DISORDERS required thyroid hormonal replacement therapy, with 37 (88.1%) maintaining thyroid hormonal replacement therapy as of the data cutoff date. Five (11.9%) patients with IMMUNE-RELATED THYROID DISORDERS required antithyroid preparations. Seven (16.7%) patients were treated with systemic corticosteroids; 6 (14.3%) of 42 patients received high-dose corticosteroids for a median of 1.9 weeks (range: 1.0 day to 2.2 months). Resolution of THYROID DISORDERS occurred in 7 (16.7%) of the 42 patients at the time of data cutoff. [[SCS Tables, 14.3.1.7.3.1.4.3, 14.3.1.7.3.1.4.3.1, 14.3.3.3.1.1.5, 14.3.3.3.1.1.9 and 14.3.3.3.1.1.11]]

IMMUNE-RELATED ENDOCRINOPATHIES: TYPE 1 DIABETES MELLITUS
IMMUNE-RELATED TYPE 1 DIABETES MELLITUS occurred in 3 (0.9%) of patients receiving avelumab including 3 (0.9%) patients with immune-related Grade 3 TYPE 1 DIABETES MELLITUS. IMMUNE-RELATED TYPE 1 DIABETES MELLITUS led to permanent discontinuation of avelumab in 0 patients. Among the 3 patients with IMMUNE-RELATED TYPE 1 DIABETES MELLITUS, the median time to onset was 2.0 months (range:

0.7 days to 9.2 months) and the median duration was 4.1 weeks (range: 2 weeks to 4.8+ months). Three (100.0%) of patients with IMMUNE-RELATED TYPE 1 DIABETES MELLITUS were treated with insulin. Resolution of TYPE 1 DIABETES MELLITUS occurred in 2 (66.7%) of the 3 patients at the time of data cutoff. [[SCS Tables 14.3.1.7.3.1.4.4, 14.3.3.3.1.1.6, and 14.3.3.3.1.1.11]]

IMMUNE-RELATED NEPHRITIS and RENAL DYSFUNCTION

IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION occurred in 6 (1.7%) of patients receiving avelumab including 1 (0.3%) patient with Grade 3 IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION. IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION led to permanent discontinuation of avelumab in 0.9% of patients. Among the 6 patients with IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION, the median time to onset was 3.0 months (range: 1.6 months to 21.9 months), and the median duration was 3.14 weeks (range: 1.3 weeks to 6.1 months). All 6 patients were treated with systemic corticosteroids; 5 (83.3%) of the 6 patients received high-dose corticosteroids for a median of 2.4 weeks (range: 6.0 days to 2.8 months). Resolution of NEPHRITIS AND RENAL DYSFUNCTION occurred in 4 (66.7%) of the 6 patients at the time of data cutoff. [[SCS Tables 14.3.1.7.3.1.4.6, 14.3.3.3.1.1.3.4, 14.3.3.3.1.1.9 and 14.3.3.3.1.1.11]]

Other Immune-Related Adverse Events

The following clinically significant, immune-related adverse events occurred at an incidence of less than 1%: pancreatitis, immune-related myositis, psoriasis, arthritis, erythema multiforme, uveitis, and Guillain-Barre syndrome.

IRRs

Infusion-related reactions occurred in 74 (21.5%) of patients treated with avelumab including 3 (0.9%) Grade 3 infusion-related reactions. In the avelumab plus BSC arm 100.00% of the patients received premedication. Fifty (50.0%) percent of the patients with an IRR received treatment for the event. [[CSR Table 14.3.1.7.2 and 14.4.2.5, and SCS Table 14.3.3.3.2.9]]

IRRs in Study B9991001 are summarized by PT, and maximum severity grade in **Table 23**.

Table 23. Summary of IRRs by PT and Maximum CTCAE Grade - Safety Analysis Set (Protocol B9991001)

	Avelumab+BSC (N=344)		BSC (N=345)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with events	74 (21.5)	3 (0.9)	0	0
Infusion related reaction	35 (10.2)	3 (0.9)	0	0
Chills	22 (6.4)	0	0	0
Pyrexia	18 (5.2)	0	0	0

	Avelumab+BSC (N=344)		BSC (N=345)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Back pain	4 (1.2)	0	0	0
Hypersensitivity	4 (1.2)	0	0	0
Dyspnoea	1 (0.3)	0	0	0
Hypotension	1 (0.3)	0	0	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For subjects reporting more than one AE within a preferred term, the AE with maximum grade is included in the table.
MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001/B9991001 CSR/adae s062 irr ct allgr Date of Generation: 14JAN2020 (03:34) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.1.7.2.11.1 is for Pfizer internal use.

The Applicant's Position:
The profile of irAEs observed in the avelumab plus BSC arm of Study B9991001 was consistent with prior experience for avelumab as a single agent. Of note, median exposure to avelumab in Study B9991001 (24.9 weeks) was longer than in prior studies with avelumab single agent (median exposure 12.0 weeks), which supports the observed overall higher rate of irAEs. The difference in total irAE rates (29.4% vs 14.2%) was largely driven by an increased frequency of Thyroid disorders in the avelumab plus BSC arm of Study B9991001 (12.2%) compared to prior experience in a variety of solid tumors (6%). The overall profile of IRRs in Study B9991001 was consistent with prior experience with avelumab single agent.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. The reviewer confirmed Applicant's Table 22 above using dataset ADAEI2A (variables TRTEMFL, USUBJID, AEDECOD, AETOXGRN, and ARM). As expected, irAEs were uncommon in the BSC arm. The profile of irAEs observed in the avelumab plus BSC arm was consistent with prior experience and is adequately labeled in Sections 5 and 6 of the Bavencio prescribing information, thus no section 5 updates were made with this review.

Treatment-Emergent Adverse Events and Adverse Reactions

Data:
In the avelumab plus BSC arm, 98.0% of patients experienced any grade TEAEs and 47.4% of patients experienced Grade ≥3 TEAEs. In the BSC alone arm 77.7% patients reported any grade TEAEs, and 25.2% patients reported Grade ≥3 TEAEs. Grade 3 TEAEs were reported in 42.7% and 16.2% of patients in the avelumab plus BSC arm and BSC arm, respectively. Grade 4 TEAEs were reported in 3.5% and 2.0% of patients in the avelumab plus BSC arm and BSC arm, respectively. [[Table 14.3.1.2.1]] TEAEs are summarized in **Table 24**.

Table 24. Summary of Adverse Events - Safety Analysis Set (Protocol B9991001)

Number (%) of Subjects	Avelumab+BSC (N=344) n (%)	BSC (N=345) n (%)
Subjects with TEAEs	337 (98.0)	268 (77.7)
Subjects with grade ≥ 3 TEAEs	163 (47.4)	87 (25.2)
Subjects with treatment-related TEAEs	266 (77.3)	4 (1.2)
Subjects with grade ≥ 3 treatment-related TEAEs	57 (16.6)	0
Subjects with serious TEAEs	96 (27.9)	69 (20.0)
Subjects with serious treatment-related TEAEs	31 (9.0)	0
Subjects with TEAEs leading to dose reduction of Avelumab	1 (0.3)	0
Subjects with TEAEs leading to interruption of Avelumab	140 (40.7)	0
Subjects with TEAEs leading to discontinuation of study drug	41 (11.9)	0
Subjects with treatment-related TEAEs leading to discontinuation of study drug	33 (9.6)	0
Subjects with TEAEs leading to death	4 (1.2)	24 (7.0)
Subjects with treatment-related TEAEs leading to death	1 (0.3)	0
Subjects with immune-related adverse events (irAEs)	101 (29.4)	5 (1.4)
Subjects with infusion-related reactions (IRRs)	74 (21.5)	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001/B9991001_CSR/adae_s012 Date of Generation: 14JAN2020 (02:48) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.1.1.1 is for Pfizer internal use.

In the avelumab plus BSC arm, no TEAE was reported at a frequency ≥20%. See **Table 25** below for the most common TEAEs.

Table 25. Summary of Most Common TEAEs (Any Grade in ≥10% Subjects or Grade ≥3 in ≥5% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period –Safety Analysis Set (Protocol B9991001)

Preferred Term	Avelumab + BSC (N=344)		BSC (N=345)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Subjects with events	337 (98.0)	163 (47.4)	268 (77.7)	87 (25.2)
Fatigue	61 (17.7)	6 (1.7)	24 (7.0)	2 (0.6)

Preferred Term	Avelumab + BSC (N=344)		BSC (N=345)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Pruritus	59 (17.2)	1 (0.3)	6 (1.7)	0
Urinary tract infection	59 (17.2)	15 (4.4)	36 (10.4)	9 (2.6)
Diarrhoea	57 (16.6)	2 (0.6)	17 (4.9)	1 (0.3)
Arthralgia	56 (16.3)	2 (0.6)	19 (5.5)	0
Asthenia	56 (16.3)	0	19 (5.5)	4 (1.2)
Constipation	56 (16.3)	2 (0.6)	31 (9.0)	0
Back pain	55 (16.0)	4 (1.2)	34 (9.9)	8 (2.3)
Nausea	54 (15.7)	1 (0.3)	22 (6.4)	2 (0.6)
Pyrexia	51 (14.8)	1 (0.3)	12 (3.5)	0
Decreased appetite	47 (13.7)	1 (0.3)	23 (6.7)	2 (0.6)
Cough	44 (12.8)	1 (0.3)	16 (4.6)	0
Vomiting	43 (12.5)	4 (1.2)	12 (3.5)	2 (0.6)
Hypothyroidism	40 (11.6)	1 (0.3)	2 (0.6)	0
Rash	40 (11.6)	1 (0.3)	4 (1.2)	0
Anaemia	39 (11.3)	13 (3.8)	23 (6.7)	10 (2.9)
Haematuria	36 (10.5)	6 (1.7)	37 (10.7)	5 (1.4)
Infusion related reaction	35 (10.2)	3 (0.9)	0	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For subjects reporting more than one AE within a preferred term, the AE with maximum grade is included in the table.
Sorted in descending order of the frequency of PTs by all grades in Avelumab + BSC arm.
MedDRA (v22.1) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001/B9991001_CSR/adae_s999a Date of Generation: 14JAN2020 (04:46) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.1.2.15 is for Pfizer internal use.

ADRs that occurred in ≥ 10% of patients in the avelumab plus BSC arm are summarized in **Table 26**. The most frequent (≥20%) ADRs in the avelumab plus BSC arm were fatigue, musculoskeletal pain, rash, and urinary tract infection.

Table 26. Summary of Adverse Drug Reactions by SOC and PT or Clustered PT - Safety Analysis Set (Protocol B9991001)

System Organ Class and Preferred Term/ Clustered Preferred Term	Avelumab+BSC (N=344)		BSC (N=345)	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
General disorders and administration site conditions				
Fatigue[a]	122 (35.5)	6 (1.7)	46 (13.3)	6 (1.7)
Pyrexia	51 (14.8)	1 (0.3)	12 (3.5)	0
Gastrointestinal disorders				
Diarrhoea	57 (16.6)	2 (0.6)	17 (4.9)	1 (0.3)
Constipation	56 (16.3)	2 (0.6)	31 (9.0)	0
Nausea	54 (15.7)	1 (0.3)	22 (6.4)	2 (0.6)
Vomiting	43 (12.5)	4 (1.2)	12 (3.5)	2 (0.6)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[b]	81 (23.5)	4 (1.2)	51 (14.8)	9 (2.6)
Arthralgia	56 (16.3)	2 (0.6)	19 (5.5)	0
Skin and subcutaneous tissue disorders				
Rash[c]	69 (20.1)	4 (1.2)	8 (2.3)	0
Pruritus	59 (17.2)	1 (0.3)	6 (1.7)	0
Infections and infestations				
Urinary tract infection[d]	70 (20.3)	20 (5.8)	38 (11.0)	13 (3.8)
Respiratory, thoracic and mediastinal disorders				
Cough[e]	48 (14.0)	1 (0.3)	16 (4.6)	0
Metabolism and nutrition disorders				
Decreased appetite	47 (13.7)	1 (0.3)	23 (6.7)	2 (0.6)
Endocrine disorders				
Hypothyroidism	40 (11.6)	1 (0.3)	2 (0.6)	0
Injury, poisoning and procedural complications				
Infusion related reaction	35 (10.2)	3 (0.9)	0	0

	Avelumab+BSC (N=344)		BSC (N=345)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
System Organ Class and Preferred Term/ Clustered Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**

[a]Fatigue is a composite term that includes Fatigue, Asthenia and Malaise.
[b]Musculoskeletal pain is a composite term that includes Musculoskeletal pain, Back pain, Myalgia and Neck pain.
[c]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.
[d]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.
[e]Cough is a composite term that includes Cough and Productive cough.
The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event within a preferred term or clustered preferred term are counted only once in that term.
MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 14JAN2020 (02:36) Source Data: ADAEI Output File: ./B9991001/B9991001_SCS/adae_adr Date of Generation: 14JAN2020 (08:09) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.3.3.3.1 is for Pfizer internal use.

The Applicant's Position:

The safety profile in the avelumab plus BSC arm (Table 25 and Table 26) was consistent with the prior experience with avelumab in patients with aUC as well as with the pooled single-agent safety dataset as reflected in the USPI (N=1738 patients from the Phase 1 study EMR100070-001 in patients with solid tumors [including 249 patients from the UC cohorts]).

The FDA's Assessment:

The clinical reviewer confirmed the results presented in Applicant's Tables 25 and 26 above using dataset ADAE (variables TRTEMFL, USUBJID, AEDECOD, AETOXGR, and ARM). The reported incidences of most ADRs are generally consistent with the previously described safety profile of avelumab.

With the exception of TEAEs leading to death, all categories of TEAEs were more common in the avelumab + BSC arm compared to the BSC arm, and the only individual Preferred term reported more commonly in the BSC arm compared to the avelumab + BSC arm was hematuria. These incidences of TEAEs leading to death and hematuria likely reflect disease progression rather than drug toxicity.

The clinical reviewer grouped certain adverse reaction terms into clinically meaningful clusters. The product labeling will therefore reflect incidences that differ from the applicant's for fatigue, musculoskeletal pain, rash, urinary tract infection, and cough.

The Applicant proposed to remove data regarding safety in the second-line aUC setting from the USPI. However, the FDA disagreed with complete removal because while the overall safety data

appeared concordant, the death rate (see discussion above) and the rates of certain common AEs were higher in the second-line setting. i.e. in the maintenance setting, the most common AEs (>20%) were fatigue, musculoskeletal pain, urinary tract infection, and rash, vs. the second-line setting, where the ordered list was slightly different: fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

The data cutoff date for the Summary of Clinical Safety submitted on 18 February 2020 was 21 October 2019. On 21 April 2020, the Applicant submitted a 90-Day Safety Update with a cutoff date of 19 January 2020. The safety profile of avelumab in this 90-Day Safety Update was consistent with that described in the Summary of Clinical Safety (Table 27).

Table 27. Overview of 90-day Safety Update Compared to Original sBLA Safety Data

	Avelumab + BSC (N = 344)		**BSC (N = 345)**	
	Orig. sBLA	**90-DSU**	**Orig. sBLA**	**90-DSU**
Subjects with TEAEs	337 (98.0%)	337 (98.0%)	268 (77.7%)	268 (77.7%)
Subjects with Grade ≥3 TEAEs	163 (47.4%)	171 (49.7%)	87 (25.2%)	89 (25.8%)
Subjects with treatment-related TEAEs	266 (77.3%)	266 (77.3%)	4 (1.2%)	6 (1.7%)
Subjects with Grade ≥3 treatment-related TEAEs	57 (16.6%)	60 (17.4%)	0	0
Subjects with serious TEAEs	96 (27.9%)	97 (28.2%)	69 (20.0%)	70 (20.3%)
Subjects with serious treatment-related TEAEs	31 (9.0%)	31 (9.0%)	0	0
Subjects with TEAEs leading to dose reduction of avelumab	1 (0.3%)	1 (0.3%)	0	0
Subjects with TEAEs leading to interruption of avelumab	140 (40.7%)	143 (41.6%)	0	0
Subjects with TEAEs leading to discontinuation of study drug	41 (11.9%)	41 (12.2%)	0	0
Subjects with treatment-related TEAEs leading to discontinuation of study drug	33 (9.6%)	34 (9.9%)	0	0
Subjects with TEAEs leading to death	4 (1.2%)	5 (1.5%)	24 (7.0%)	24 (7.0%)
Subjects with treatment-related TEAEs leading to death[a]	1 (0.3%)	1 (0.3%)	0	0
Subjects with TEAEs	337 (98.0%)	337 (98.0%)	268 (77.7%)	268 (77.7%)
Subjects with Grade ≥3 TEAEs	163 (47.4%)	171 (49.7%)	87 (25.2%)	89 (25.8%)
Subjects with treatment-related TEAEs	266 (77.3%)	266 (77.3)	4 (1.2%)	6 (1.7%)
Subjects with Grade ≥3 treatment-related TEAEs	57 (16.6%)	60 (17.4%)	0	0

Laboratory Findings

Data:
In the avelumab plus BSC arm, on-treatment laboratory abnormalities worsening from baseline were consistent with those observed in other studies of avelumab as a single agent in patients with solid tumors.

Table 28. Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Treated with Avelumab and at a Higher Incidence than in the BSC Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) - Safety Analysis Set (Protocol B9991001)

Laboratory Abnormality	Avelumab+BSC N	Avelumab+BSC All Grades n (%)	Avelumab+BSC Grade ≥3 n (%)	BSC N	BSC All Grades n (%)	BSC Grade ≥3 n (%)
Chemistry						
Hypertriglyceridemia	339	116 (34.2)	7 (2.1)	334	95 (28.4)	4 (1.2)
Alkaline Phosphatase Increased	344	103 (29.9)	10 (2.9)	341	69 (20.2)	8 (2.3)
Hyponatremia	344	97 (28.2)	19 (5.5)	341	67 (19.6)	9 (2.6)
GGT Increased	343	91 (26.5)	18 (5.2)	340	66 (19.4)	13 (3.8)
Lipase Increased	343	87 (25.4)	27 (7.9)	333	52 (15.6)	19 (5.7)
Aspartate Aminotransferase Increased	344	84 (24.4)	6 (1.7)	340	42 (12.4)	3 (0.9)
Hyperkalemia	344	82 (23.8)	13 (3.8)	341	56 (16.4)	3 (0.9)
Alanine Aminotransferase Increased	344	81 (23.5)	9 (2.6)	341	40 (11.7)	2 (0.6)
Hypoalbuminemia	343	81 (23.6)	1 (0.3)	340	58 (17.1)	1 (0.3)
Cholesterol High	339	75 (22.1)	4 (1.2)	335	53 (15.8)	1 (0.3)
Serum Amylase Increased	339	70 (20.6)	18 (5.3)	329	38 (11.6)	6 (1.8)
CPK Increased	339	65 (19.2)	8 (2.4)	332	40 (12.0)	0
Hypophosphatemia	343	65 (19.0)	11 (3.2)	340	50 (14.7)	4 (1.2)
Hematology						
Lymphocyte Count Decreased	344	136 (39.5)	17 (4.9)	339	91 (26.8)	11 (3.2)
Anemia	344	95 (27.6)	15 (4.4)	339	62 (18.3)	11 (3.2)
White Blood Cell Decreased	344	67 (19.5)	2 (0.6)	339	34 (10.0)	0
Platelet Count Decreased	344	62 (18.0)	2 (0.6)	339	40 (11.8)	1 (0.3)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set who can be evaluated for CTCAE criteria for each parameter in
each treatment group.
NCI-CTCAE criteria version 4.03 is used.
PFIZER CONFIDENTIAL SDTM Creation: 14JAN2020 (09:36) Source Data: ADLB Output File: ./B9991001/B9991001_SCS/adlb_adr Date of Generation: 14JAN2020 (16:39) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.4.1.5.2.1 is for Pfizer internal use.

The Applicant's Position:

The profile of laboratory abnormalities was consistent with the known safety profile of avelumab.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. The clinical reviewer confirmed the results presented in Applicant's Table 28 above using datasets ADLB and ADSL following the steps in

the Applicant's response to an information request which the FDA issued on 14 April 2020. Laboratory abnormalities were commonly observed on the trial. Although the incidence of each laboratory value collected was higher in the avelumab + BSC arm compared to the BSC arm, these incidences were consistent with the previously described safety profile of avelumab.

Vital Signs

Data:
Vital signs were summarized by visit. If investigators identified changes in vital signs that were clinically meaningful, they were to be reported as adverse events. [[CSR Table 14.3.4.2.1]]

The Applicant's Position:
Based on TEAEs reported, there was no evidence of a clinically significant effect of avelumab on vital signs.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Electrocardiograms (ECGs)

Data:
ECGs were performed during the screening process and then repeated during the study only if clinically indicated. TEAEs of ECG abnormalities were reported in 2 patients in the avelumab plus BSC arm (Grade 1 Electrocardiogram Q wave abnormal and Grade 1 Electrocardiogram T wave inversion, each in 1 patient). [[CSR Table 14.3.1.2.1]]

The Applicant's Position:
Based on TEAEs reported, there was no evidence of a clinically significant effect of avelumab on ECG parameters.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

QT

Data
ECGs were performed during the screening process and then repeated during the study only if clinically indicated. TEAEs of QT abnormalities were reported in 1 patient in the avelumab plus BSC arm (Grade 1 Electrocardiogram Q wave abnormal).

The Applicant's Position:
Based on TEAEs reported, there was no evidence of a clinically significant effect of avelumab on QT.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Immunogenicity

Data:
Of the 344 patients treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks, 325 patients were evaluable for treatment-induced ADA and 62 (19.1%) tested positive. [[CSR Table 14.4.9.1.1]] Patients who tested positive for treatment-induced ADA had numerically lower avelumab C_{trough} versus those of ADA never-positive or baseline ADA positive patients; however, variability was high with significant overlap of error bars. The development of treatment-induced ADA against avelumab did not appear to alter the risk of TEAEs including infusion-related reactions.

A summary of AEs by ADA status is presented in **Table 29**.

Table 29. Summary of Adverse Events, by Treatment-Induced ADA versus ADA Never-Positive or Baseline ADA Positive - Immunogenicity Analysis Set (Protocol B9991001)

	Avelumab+BSC		
	Treatment-induced ADA (N=62)	ADA never-positive or baseline ADA positive (N=282)	Total (N=344)
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**
Subjects with TEAEs	61 (98.4)	276 (97.9)	337 (98.0)
Subjects with Grade ≥3 TEAEs	32 (51.6)	131 (46.5)	163 (47.4)
Subjects with Serious TEAEs	22 (35.5)	74 (26.2)	96 (27.9)
Subjects with TEAEs Leading to Dose Reduction of Avelumab	0	1 (0.4)	1 (0.3)
Subjects with TEAEs Leading to Discontinuation of Avelumab	11 (17.7)	30 (10.6)	41 (11.9)
Subjects with Infusion-Related Reactions (IRRs)	17 (27.4)	57 (20.2)	74 (21.5)

The denominator to calculate percentages is N, the number of subjects in the immunogenicity analysis set within each ADA category.
MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001 restricted/B9991001/adae ada s020 1 Date of Generation: 14JAN2020 (10:00) Cutoff Date: 30JUN2019 Snapshot Date: 24DEC2019
Table 14.4.9.9.9 is for Pfizer internal use.

The Applicant's Position:
No clinically meaningful impact of ADA on safety profile was identified.

The FDA's Assessment:
The reviewer reproduced Table 29 above using datasets ADIS (variables USUBJID, PARAM, and AVAL) and ADAE (variables USUBJID, TRTEMFL, ACTARM, AESER, AETOXGR,

AEACN, and IRRFL)

The FDA disagrees with the statement that no clinically meaningful impact of ADA on safety profile was identified. Patients with treatment-induced ADA had numerically higher incidences of Grade 3 TEAEs, serious TEAEs, TEAEs leading to dose reduction of avelumab, TEAEs leading to discontinuation of avelumab, and infusion-related reactions.

TEAEs reported with incidences >10% and ≥5% higher in patients with treatment-induced ADA compared to patients without treatment-induced ADA were anemia, nasopharyngitis, and hyperthyroidism. Grade 3-4 TEAEs reported with incidences ≥2% and ≥3% higher in patients with treatment-induced ADA compared to patients without treatment-induced ADA were amylase increased, lipase increased, and hematuria. Infusion-related reactions with incidences ≥10% and ≥3% higher in patients with treatment-induced ADA compared to patients without treatment-induced ADA were chills, vomiting, anemia, constipation, fatigue, nasopharyngitis, urinary tract infection, and nausea.

Table 30. Protocol B9991001 TEAEs Reported by >10% of Patients by ADA Group

Preferred Term	Treatment-induced ADA (N = 62)	No Treatment-induced ADA (N = 282)
Fatigue	12 (19.4%)	49 (17.3%)
Urinary tract infection	12 (19.4%)	47 (16.7%)
Anemia	11 (17.7%)	28 (9.9%)
Constipation	11 (17.7%)	45 (15.9%)
Pruritus	11 (17.7%)	48 (17.0%)
Arthralgia	7 (11.3%)	49 (17.3%)
Asthenia	8 (12.9%)	48 (17.0%)
Back pain	8 (12.9%)	47 (16.7%)
Diarrhea	10 (16.1%)	47 (16.7%)
Nausea	8 (12.9%)	46 (16.3%)
Nasopharyngitis	10 (16.1%)	16 (5.7%)
Vomiting	10 (16.1%)	33 (11.7%)
Pyrexia	6 (9.6%)	45 (15.9%)
Decreased appetite	7 (11.3%)	40 (14.2%)
Cough	6 (9.7%)	38 (13.5%)
Hematuria	8 (12.9%)	28 (9.9%)
Hyperthyroidism	8 (12.9%)	13 (4.6%)
Rash	8 (12.9%)	32 (11.3%)
Hypothyroidism	7 (11.3%)	33 (11.7%)
Infusion related reaction	7 (11.3%)	28 (9.9%)

Table 31. Protocol B9991001 Grade 3-4 TEAEs Reported by ≥2% of Patients by ADA Group

Preferred Term	Treatment-induced ADA (N = 62)	No Treatment-induced ADA (N = 282)
Amylase increased	4 (6.5%)	8 (2.8%)
Lipase increased	4 (6.5%)	10 (3.5%)
Anemia	3 (4.8%)	10 (3.5%)
Hematuria	3 (4.8%)	3 (1.0%)
Urinary tract infection	3 (4.8%)	12 (4.2%)
Acute kidney injury	2 (3.2%)	3 (1.1%)
Hypertension	2 (3.2%)	4 (1.4%)
Hypophosphatemia	2 (3.2%)	5 (1.7%)
Neutropenia	2 (3.2%)	1 (0.4%)
Gamma-glutamyltransferase increased	0	6 (2.1%)

Table 32. Protocol B9991001 Serious TEAEs Reported by ≥2% of Patients by ADA Group

Preferred Term	Treatment-induced ADA (N = 62)	No Treatment-induced ADA (N = 282)
Urinary tract infection	3 (4.8%)	13 (4.6%)
Acute kidney injury	2 (3.2%)	4 (1.4%)

Table 33. Protocol B9991001 TEAEs Leading to Discontinuation by ≥2% of Patients by ADA Group

Preferred Term	Treatment-induced ADA (N = 62)	No Treatment-induced ADA (N = 282)
Lipase increased	2 (3.2%)	1 (0.3%)
Acute myocardial infarction	1 (1.6%)	0
Amylase increased	1 (1.6%)	1 (0.3%)
Anemia	1 (1.6%)	0
Autoimmune thyroiditis	1 (1.6%)	0
Gastric ulcer	1 (1.6%)	0
Hyperthyroidism	1 (1.6%)	0
Infusion related reaction	1 (1.6%)	3 (0.2%)
Myocardial infarction	1 (1.6%)	0
Esophageal squamous cell carcinoma	1 (1.6%)	0
Platelet count decreased	1 (1.6%)	0
Sepsis	1 (1.6%)	1 (0.3%)
Troponin T increased	1 (1.6%)	2 (0.7%)
Tubulointerstitial nephritis	1 (1.6%)	0

Table 34. Protocol B9991001 Infusion-Related Reactions Reported by ≥10% of Patients

by ADA Group

Preferred Term	Treatment-induced ADA (N = 62)	No Treatment-induced ADA (N = 282)
Infusion related reaction	7 (11.3%)	28 (9.9%)
Chills	6 (9.7%)	18 (0.6%)
Vomiting	6 (9.7%)	5 (1.7%)
Anemia	5 (8.0%)	8 (2.8%)
Constipation	5 (8.0%)	7 (2.5%)
Fatigue	5 (8.0%)	11 (3.9%)
Nasopharyngitis	5 (8.0%)	4 (1.4%)
Urinary tract infection	5 (8.0%)	10 (3.5%)
Decreased appetite	4 (6.4%)	11 (3.9%)
Diarrhea	4 (6.4%)	14 (5.0%)
Nausea	4 (6.4%)	17 (0.6%)

Reviewer's comments:

1. *No particular Preferred Term or cluster of Preferred Terms appeared to explain the observed higher overall incidences of TEAEs, Grade 3-4 TEAEs, TEAEs leading to discontinuation, and infusion-related reactions among patients who developed treatment-induced ADA.*
2. *It is unclear why some of the Preferred Terms which the Applicant included as infusion-related reactions (e.g., constipation, urinary tract infection) were included in this category*.

The other avelumab indication supported by a randomized controlled trial to date was the RCC indication, where Trial B9991003 demonstrated the combination of avelumab plus axitinib to be superior to sunitinib in terms of PFS and confirmed ORR. In the avelumab plus axitinib arm of Trial B9991003, the proportions of patients who developed treatment-induced ADA were comparable to that in JAVELIN Bladder 100 (13.4 % vs. 18.0%), and the overall safety profile in that patient subset was worse to a similar degree (Table).

Table 35. Protocol B9991003 Safety Summary by ADA Group

	Treatment-induced ADA (N = 57)	ADA never-positive or baseline ADA positive (N = 369)
Subjects with TEAEs	56 (98.2%)	368 (99.7%)
Subjects with Grade ≥3 TEAEs	41 (71.9%)	260 (70.5%)
Subjects with Serious TEAEs	23 (40.4%)	122 (33.1%)
Subjects with TEAEs Leading to Dose Reduction of Avelumab	1 (1.8%)	0
Subjects with TEAEs Leading to Discontinuation of Avelumab	16 (28.1%)	65 (17.6%)
Subjects with TEAEs Leading to Discontinuation of Any Study Drug	19 (33.3%)	77 (20.9%)
Subjects with Infusion-Related Reactions (IRRs)	23 (40.4%)	97 (26.3%)

A new ADA method with improved sensitivity was used in the sBLA submission for aRCC. The treatment-emergent ADAs to avelumab in patients with aRCC was reported as 15% (66 out of

453 patients), which is higher than 4.1% (64 out of 1558 patients) as reported in the previous label using an older ADA assay. As part of the aRCC approval, the Applicant agreed to a PMC to reanalyze ADA in stored samples from avelumab-treated patients with UC and with Merkel cell carcinoma with a new ADA assay. This was to include an assessment of the ADA rate; median time to detection of ADA; median duration of ADA positivity, and the effects of ADA on key PK and efficacy endpoints. The final report for PMC 3588-3 is due in 2021, and the final report for 3588-4 is due in 2026.

The FDA considered these findings to constitute a potential new safety signal in patients with treatment-induced ADA. The clinical reviewers therefore recommended that approval of avelumab for the proposed indication be contigent upon a postmarketing commitment to further investigate this potential signal (discussed in Seciton 13 of this Multi-disciplinary Review).

8.2.5. Analysis of Submission-Specific Safety Issues

Data:
There are no safety issues specific to this application.

The Applicant's Position:
Not applicable due to no new information.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:
No COA analyses informing safety/tolerability were performed.

The Applicant's Position:
No COA analyses informing safety/tolerability were performed.

The FDA's Assessment:
See Appendix, Section 19.5, Additional Safety Analyses Conducted by FDA.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Intrinsic Factors
The safety of Study B9991001 was analyzed by the following subgroups: age, gender, race, ethnicity, and randomization stratification factors (best response to first-line chemotherapy, and metastatic disease site at the time of initiating first-line chemotherapy).

Extrinsic Factors
The safety of Study B9991001 was analyzed by pooled geographical region.

The Applicant's Position:
Of the 345 patients randomized to avelumab 10 mg/kg in Study B9991001, 66.3% were 65 years or over and 24.7% were 75 years or over. No overall difference in safety was reported between elderly patients and younger patients. There were also no overall differences in safety among patients based on gender, race, ethnicity, randomization stratification factors, or pooled geographic regions.

The FDA's Assessment:
The FDA generally agrees with the Applicant's assessment.

Table 36. B9991001 Summary of TEAEs by Demographic Subgroup

Adverse Event	Avelumab + BSC		BSC	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Age				
< 65	127/129 (98.4%)	69/129 (53.5%)	82/106 (77.4%)	29/106 (27.4%)
65 to < 75	128/130 (98.5%)	64/130 (49.2%)	130/162 (80.2%)	54/162 (33.3%)
≥ 75	82/85 (96.5%)	45/85 (52.9%)	63/77 (81.8%)	22/77 (28.6%)
Gender				
M	254/260 (97.7%)	125/260 (48.1%)	214/271 (79.0%)	82/271 (30.3%)
F	84/84 (100%)	53/84 (27.4%)	62/74 (83.8%)	23/74 (31.1%)
Race				
White	227/229 (99.1%)	127/229 (55.5%)	193/233 (82.8%)	74/233 (31.8%)
Asian	72/74 (97.3%)	38/74 (51.4%)	58/81 (71.6%)	20/81 (24.7%)
Black	2/2 (100%)	1/2 (50.0%)	N/A	N/A
Other or unknown	37/39 (94.9%)	12/39 (30.8%)	25/31 (80.6%)	11/31 (35.5%)

8.2.8. Specific Safety Studies/Clinical Trials

Data:
No new information is provided in the current submission.

The Applicant's Position:
Not Applicable.

The FDA's Assessment:
Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:
For avelumab, human carcinogenicity or tumor development studies were not conducted per ICH S6, ICH S1, and ICH S9.

The Applicant's Position:

Not applicable.

The FDA's Assessment:
One second neoplasm, a Grade 3 colon adenocarcinoma, was reported in the BSC arm of B991001, and the following two second neoplasms were reported in the avelumab treatment arm.

- Patient (b) (6) was an 84-year-old white Australian man with PD-L1 positive metastatic urothelial carcinoma previously treated with carboplatin and gemcitabine. His medical history included hypertension, hypercholesterolemia, atrial fibrillation, chronic obstructive pulmonary disease, depression, insomnia, cognitive disorder, and gastroesophageal reflux. Serious TRAEs included Grade 3 sinus tachycardia on Day 59, Grade 3 supraventricular tachycardia on day 503, and a Grade 3 fall on Day 613. On Day 444, he developed a Grade 2 squamous cell carcinoma of the left leg. Concomitant medications taken within 2 weeks prior to the onset of the event of squamous cell carcinoma were loratadine and paracetamol as premedications, aspirin for atrial fibrillation, citalopram for depression, hydrochlorothiazide and metoprolol for hypertension, loperamide hydrochloride for diarrhea, omeprazole for gastroesophageal reflux, and simvastatin for hypercholesterolaemia. The patient underwent a complete excision of the squamous cell carcinoma (date of excision not provided). No action was taken with avelumab in response to this event.
- Patient (b) (6) was a 59 year-old man from France previously treated for stage 4 urothelial carcinoma with first-line platinum-containing chemotherapy. He used tobacco and alcohol. He was receiving avelumab 740 mg Q2W as of Study Day 229, when PET-CT showed esophageal hypermetabolism. On Day 242, a biopsy esophageal squamous cell carcinoma, and avelumab was permanently discontinued. The Investigator and Sponsor considered the esophageal cancer to be related to tobacco and alcohol use and not to avelumab, an attribution which this reviewer finds reasonable.

Reviewer's comment: These second neoplasms are not unexpected in this patient population, and were unlikely caused by avelumab.

Human Reproduction and Pregnancy
Data:
Exposure to avelumab during pregnancy was not permitted in Study B9991001. There were no cases of pregnancy or lactation in Study B9991001.

The Applicant's Position:
No changes are proposed to the USPI based on the results of this study.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Pediatrics and Assessment of Effects on Growth
Data:
Only adult patients were randomized in Study B9991001.

The Applicant's Position:
Due to the rarity of aUC in pediatric populations, the Applicant received a Full Waiver from the conduct of Pediatric studies from the FDA on 30 August 2016.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Data:
Overdose
No adverse events related to an overdose of avelumab were reported in Study B9991001. [[SCS Table 16.2.7.1.2]]

Drug Abuse
No adverse events related to abuse of avelumab were reported in Study B9991001. [[SCS Table 16.2.7.1.1.1]]

Withdrawal and Rebound
No formal studies for withdrawal or rebound effects associated with avelumab treatment have been conducted. No adverse events related to withdrawal of avelumab were reported in Study B9991001. [[SCS Table 16.2.7.1.4.1]]

The Applicant's Position:
No adverse events related to overdose, abuse or withdrawal of avelumab were reported. Due to its mechanism of action, the potential for abuse, withdrawal and rebound of avelumab is considered very low.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
Data:
The Applicant submitted 4 quarterly PADERs to the FDA and continues to submit PBRERs every 6 months to the FDA, EMA and other Health Authorities worldwide since first the regulatory approval in the US on 23 March 2017 and in the EU on 18 September 2017. The last submitted PADER and PBRERs included safety data received during the reporting periods 23 December 2017 through 22 March 2018 and 23 March 2019 through 22 September 2019, respectively.

The Applicant's Position:
The overall safety data originating from post-marketing sources was consistent with the known avelumab safety profile with no new safety signals identified from post-marketing sources during these reporting periods.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. All confirmed safety signals described in the last submitted PADER and PBRER are adequately described in the Bavencio package insert.

This reviewer queried the FAERS database for all Preferred terms reported with avelumab. The statistical algorithm that FDA uses to datamine FAERS reports, the multi-item gamma poisson shrinker (MGPS), produces empirical Bayesian geometric mean (EGBM) scores, the lower and upper 90% confidence limits of which are denoted EB_{05} and EB_{95}, respectively. Associations with $EB_{05} \geq 2$ are conventionally considered noteworthy safety signals. Table 37 summarizes all Preferred terms with $EB_{05} \geq 2$ and the sections of the US package insert (USPI) addressing those adverse reactions.

Table 37. FAERS Search and Safety Labeling for Preferred terms with $EB_{05} \geq 2$

MedDRA Preferred Term	N	EB_{05}	Section(s) of USPI
Duodenal perforation	7	36.3	Unlabeled
Infusion related reaction	42	13.7	2, 5, 6, 17
Disease progression	52	6.6	N/A (underlying disease)
Pneumonitis	20	4.7	2, 5, 6, 17
Myocarditis	11	4.4	2, 5, 6
Sjogren's syndrome	7	4.1	Unlabeled
Colitis	17	3.7	2, 5, 6, 17
Chills	29	3.2	5, 6
Neoplasm progression	17	3.1	N/A (underlying disease)
Febrile neutropenia	19	2.9	N/A (likely due to concomitant medications)
General physical health deterioration	24	2.8	N/A (likely due to underlying disease)
Laryngeal oedema	6	2.6	N/A (convered by infusion reaction)
Cytokine release syndrome	7	2.3	N/A (covered by infusion reaction)
Device related infection	7	2.3	N/A (not an adverse drug reaction)
Myositis	6	2.1	2, 5

Duodenal ulcer and Sjogren's syndrome were unlabeled events with high EB_{05} values. This reviewer therefore examined those reports in detail.

All seven reports of duodenal perforation pertained to the same patient (i.e., six were duplicate reports). This patient was a 72-year-old male with a history of bleomycin lung toxicity who enrolled in phase 1 protocol B9991007 for patients with previously treated advanced non-Hodgkin's lymphoma. After 14.5 months of therapy with avelumab 350 mg Q2W, the patient was hospitalized for pneumonitis. He was treated with methylprednisolone, and avelumab was discontinued. Twenty-three days later, the patient experienced a bleeding duodenal ulcer requiring transfusion of 7 units of red cells. The investigator suspected the bleeding to be caused or exacerbated by steroids that were being given to treat pneumonitis and apixaban that was being given to treat a superficial vein clot. Subsequent to this bleed, the subject's respiratory function declined, and despite mechanical ventilation he died of pneumonitis.

Reviewer's comment: Duodenal perforation occurred in one patient, not in seven patients, and this reviewer agrees with the investigator that this patient's duodenal perforation was more

likely due to systemic corticosteroids than to avelumab. This reviewer therefore does not recommend adding duodenal perforation as an adverse reaction to the Bavencio package insert.

Table 38. FAERS Reports of Sjogren's Syndrome Associated with Avelumab

Report ID	Reviewer's Description	Reviewer's Opinion on Cauality
16269936	57 year old male from the United States who was receiving avelumab for metastatic prostate cancer. A concomitant medication was enzalutamide. Thirty days after starting avelumab, the patient experienced dry mouth and dry eye which were diagnosed as autoimmune Sicca syndrome. A Schirmer's test showed 22 mm/5 min, whole unstimulated saliva flow was 0.97 ml/15 min, Tarpley sialadenitis class was 0, Greenspana sialadenitis grade was at 2 and the histology showed mild chronic sialadenitis. Antinuclear antigen, rheumatoid factor and extractable nuclear antigen tests were negative. Avelumab was stopped because of disease progression 8.5 months after the onset of dry mouth.	Probably related
16270042	55 year old male from mthe United States with a history of undifferentiated connective tissue disease, polyarthritis, Sicca, rheumatoid factor and anti-SSA antibodies. Fifty-three days after starting avelumab for metastatic thymic carcinoma, the patient experienced dry mouth (grade 2) and elevated creatine kinase. Schirmer's test showed 7 mm/5 min, whole unstimulated saliva flow was 0.43 ml/15 min, Tarpley sialadenitis class was 3, Greenspana sialadenitis grade was at 4, focus score was 8 and the histology showed severe sialadenitis. Antinuclear antigen and rheumatoid factor were positive. No action was taken with avelumab.	Possibly related, confounded by prior connective tissue disease
16270060	66 year old female from the United States who, 95 days after starting avelumab for metastatic thymic carcinoma, experienced dry mouth and dry eye. Schirmer's test showed 4 mm/5 min, whole unstimulated saliva flow showed 0 mL/15 minutes, Tarpley sialadenitis class was 3, Greenspana sialadenitis grade was 4, and histology showed severe sialadenitis. Antinuclear antigen test was negative, rheumatoid factor was positive, and extractable nuclear antigens showed SSA. The patient was diagnosed as having autoimmune Sicca syndrome, for which she was treated with prednisone, and avelumab was discontinued. Follow-up testing showed improved whole unstimulated salivary flow, and avelumab was resumed.	Probably related
16270068	55 year old female from the United States who, 56 days after starting avelumab for recurrent respiratory papillomatosis (off-label), experienced dry mouth. Schirmer's test showed 10 mm/5 min, whole unstimulated saliva flow was 0.59 ml/15 min, Tarpley sialadenitis class was 0, Greenspana sialadenitis grade was 0, and histology showed mild chronic sialadenitis. Antinuclear antigen, rheumatoid factor, and extractable nuclear antigen tests were negative. The patient was diagnosed as having autoimmune Sicca syndrome. Avelumab was discontinued, as protocol therapy was complted, and the sicca symptoms improved.	Probably related, positive dechallenge
16270084	55 year old male from the United States who, 100 days after starting avelumab for recurrent respiratory papillomatosis, experienced dry mouth. Schirmer's test showed 10 mm/5 min, whole unstimulated saliva flow was 0.48 ml/15 min, Tarpley sialadenitis class was 0, Greenspana sialadenitis grade was at 2, and histology showed mild chronic sialadenitis. Antinuclear antigen), rheumatoid factor and extractable nuclear antigen tests were negative.	Probably related, positive dechallenge

	Avelumab was discontinued, as protocol therapy was complted, and the sicca symptoms improved.	
16271275	56 year old male from the United States who, 62 days after starting avelumab for recurrent respiratory papillomatosis, experienced dry mouth. Schirmer's test showed 17 mm/5 min, whole unstimulated saliva flow was 0 mL/15 minutes, Tarpley sialadenitis class was 3, Greenspana sialadenitis grade was at 3, focus score was 1, and histology showed mild-to-moderate sialadenitis. Antinuclear antigen, rheumatoid factor and extractable nuclear antigen tests were negative.	Possibly related
16271307	26 year old male from the United States who, 30 days after starting avelumab for recurrent respiratory papillomatosis, experienced dry mouth. Schirmer's test showed 20 mm/5 min, whole unstimulated saliva flow was 0.47 ml/15 min, Tarpley sialadenitis class was 1, Greenspana sialadenitis grade was at 3, focus score was 1, and histology showed mild chronic sialadenitis. Antinuclear antigen, rheumatoid factor, and extractable nuclear antigen tests were negative. The patient was diagnosed with autoimmune induced Sicca syndrome.	Possibly related

Reviewer's commenst:

1. *This reviewer finds Sjogren's syndrome in all seven of these case reports to be at least possibly related to avelumab, and one case (Report #16270068) to be probably related, based on a positive dechallenge and the absence of identified confounding factors.*
2. *All seven patients who were reported to develop autoimmune Sicca syndrome while receiving avelumab were initially identified by a search performed by Merck, all were using avelumab for off-label indications (prostate cancer, thymic carcinoma, recurrent respiratory papillomatosis) and were evaluated similarly (Schirmer's test, whole unstimulated saliva flow, etc.). These features suggest that these cases are part of a cluster where detection may have been intensified by active surveillance. This reviewer therefore does not recommend adding Sjogren's syndrome as an adverse reaction to the Bavencio package insert.*

Expectations on Safety in the Postmarket Setting

Data:

Not applicable.

The Applicant's Position:

There is no expectation of an increased risk for patients in the post-marketing setting. Avelumab will be subject to restricted medical prescription and administration will occur at medical sites. The label will include instructions for the management of avelumab-related toxicities and the patients will be informed of the avelumab-associated risks via the medication guide.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.11. Integrated Assessment of Safety

Data:

- The median duration of treatment was 24.9 weeks (range 2.0, 159.9) in the avelumab plus BSC arm and 13.1 weeks (range 0.1, 155.6) in the BSC alone arm.

- As expected, based on a control arm including BSC alone, TEAEs were reported at a higher frequency (98% vs 77.7%) and severity Grade ≥3 (47.4% vs 25.2%) for patients treated with avelumab plus BSC than for patients treated with BSC alone.

- Fatal TEAEs were reported in 1.2% of patients treated with avelumab plus BSC and 7.0% of patients treated with BSC alone. In the avelumab plus BSC arm, one patient (0.3%) had a fatal treatment-related TEAE (Sepsis), and another patient (0.3%) died due to an event (Ischemic stroke) that occurred 100 days after the only dose of avelumab, both were considered related to avelumab by the investigator.

- TEAEs leading to avelumab discontinuation were reported in 11.9% of patients in the avelumab plus BSC arm. The primary reason for study treatment discontinuation was disease progression in both treatment arms.

- Treatment-emergent SAEs occurred in 27.9% of patients in the avelumab plus BSC arm and 20.0% of patients in the BSC alone arm.

- No TEAEs were reported at a frequency > 20% in the avelumab plus BSC arm. In the avelumab plus BSC arm, the most common TEAEs (defined as ≥10% for any grade or ≥5% for ≥Grade 3 in any treatment group, and ordered by decreasing frequency) included Fatigue, Pruritus, Urinary tract infection, Diarrhea, Arthralgia, Asthenia, Constipation, Back pain, Nausea, Pyrexia, Decreased appetite, Cough, Vomiting, Hypothyroidism, Rash, Anemia, Hematuria, and Infusion related reaction.

- IRRs were reported for 21.5% of patients in the avelumab plus BSC alone arm. Grade 3 IRRs were reported in 0.9% of patients. There were no Grade 4 or 5 IRRs in the study.

- irAEs were observed in 29.4% of patients in the avelumab plus BSC alone arm. The most common irAEs in the avelumab plus BSC arm were "Immune-related Endocrinopathies": "Thyroid disorders" in 12.2% of patients. Grade 3 irAEs were observed in 7.0% of patients. There were no Grade 4 or 5 irAEs in the study.

- Laboratory abnormalities reported in the avelumab plus BSC arm were consistent with the known safety profile of avelumab and the population on study. No patients in the avelumab plus BSC arm met the criteria for a potential Hy's Law case.

- The incidence of ADA in this study was consistent with previously reported results using the same ADA assay and ADA did not appear to impact the PK or safety of avelumab treatment.

<u>The Applicant's Position:</u>

The overall safety profile of avelumab as a first-line maintenance treatment in patients with aUC whose disease has not progressed with first-line platinum-based induction chemotherapy was tolerable, manageable, and consistent with that previously described for avelumab as a single agent in the approved label. No new safety concerns were identified.

The FDA's Assessment:
The FDA generally agrees with the Applicant's assessment. One exception is that the FDA identified a potential new safety signal in patients with treatment-induced ADA, as discussed in Seciton 8.2.4 and Section 13 of this Multidisciplinary Review.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:
There are no major statistical issues with this application.

8.4. Conclusions and Recommendations

The FDA's Assessment:
The review team recommends full approval for avelumab for maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy.

This recommendation is based upon the review of the results of the JAVELIN Bladder 100 study, which was a randomized, multi-center, open-label study conduted in 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma whose disease did not progress with first-line platinum-containing induction chemotherapy. Approximately half of patients had PD-L1–positive tumors. The trial met both co-primary endpoints, demonstrating prolonged survival with maintenance avelumab compared to BSC alone in all randomized patients and in patients with PD-L1–positive tumors. The review team recommends regular approval for the all-comers population regardless of PD-L1–expression, and recommends conversion of the BLA 761078 accelerated approval to full approval, as these results fulfill PMR 3201-1.

In JAVELIN Bladder 100, 18% of patients who progressed on BSC alone did not receive any second-line therapy. This is true despite these patients having a performance status of ECOG 0-1 and stable or responding disease to initial therapy, which means that these patients were in relatively good clinical condition at the start of the study. It is possible that these patients were no longer eligible for second-line therapy due to declining organ function or performance status. The large and clinically meaningful OS benefit with maintenance avelumab in this trial may support the theory that the advantage of a switch maintenance strategy is that more patients are well enough to receive the benefits of that therapy immediately after the completion of first-line therapy than upon progression/recurrence.

While cross-trial comparisons are problematic, the results of HCRN GU14-182 may be pertinent for patients and clinicians in the U.S. They suggest that the survival benefit of maintenance PD-1/PD-L1 inhibitor is not as clear when patients have reliable future access to PD-1/PD-L1 inhibitor. In addition, a potential for adverse reactions and treatment-related burden, and attenuated benefit in patients with PD-L1–negative tumors, the OS HR for patients with PD-L1–

negative tumor was included in the USPI to facilitate individualized decision-making for clinicians and their patients.

The review team recommends approval of the proposed flat 800 mg Q2W dosing regimen for this indication, based on clinical pharmacology dosing models and simulation that predicted no clinically relevant exposure differences.

The safety profile of avelumab was consistent with what has been described in previous avelumab studies with the exception of higher risks of TEAEs, serious TEAEs, TEAEs leading to dose reduction of avelumab, TEAEs leading to discontinuation of avelumab, and infusion-related reactions among patients with treatment-induced ADA.

X X

Erik Bloomquist, PhD

Statistical Reviewer

X X

Primary Clinical Reviewer Clinical Team Leader

9. ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

The FDA's Assessment:

This application was not discussed with an Advisory Committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

10. PEDIATRICS

The Applicant's Position:
Due to the rarity of aUC in pediatric populations, the Applicant received a Full Waiver from the conduct of Pediatric studies from the FDA on 30 August 2016.

The FDA's Assessment:
The FDA agrees with the Applicant's position as stated above.

11. LABELING RECOMMENDATIONS

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1 INDICATIONS AND USAGE	1.2 Locally Advanced or Metastatic Urothelial Carcinoma • Add first-line UC indication [redacted] (b) (4)	The Applicant's proposal was [redacted] (b) (4) [redacted] (b) (4) FDA changed this to "…indicated for the maintenance treatment… first-line platinum-**containing** induction chemotherapy." FDA also changed [redacted] (b) (4) to "-containing" throughout the label.
5 WARNINGS AND PRECAUTIONS	The Warnings and Precautions Section will not be updated because the safety profile of avelumab has not changed.	FDA agreed with the Applicant's assessment.
6 ADVERSE REACTIONS	6.1 Clinical Trial Experiences Locally Advanced or Metastatic Urothelial Carcinoma • Replace current text for Locally advanced or Metastatic Urothelial Carcinoma, Table 4 (adverse reactions) and Table 5 (laboratory tests) with data from the randomized JAVELIN Bladder 100 trial 6.2 Immunogenicity • Replace the avelumab single agent immunogenicity data generated with the original assay with the data from the JAVELIN Bladder 100 trial that was generated with the more sensitive assay	FDA generally agreed with the Applicant's assessment. FDA combined certain MedDRA Preferred Terms to form clusters of terms that were more clinically meaningful.
8 USE IN SPECIFIC POPULATIONS	8.5 Geriatric Use • Replace current text on geriatric use in patients with aUC with data from the JAVELIN Bladder 100 trial	FDA agreed with the Applicant's assessment.
14 CLINICAL STUDIES	14.2 Locally Advanced or Metastatic Urothelial Carcinoma • Include efficacy data from the JAVELIN Bladder 100 trial	FDA's additions upon the Applicant's proposed labeling changes were • At the end of the description of the trial design: "Treatment was initiated within 4-10 weeks

		after last dose of chemotherapy." • Proportion of patients who were Asian, in the baseline characteristics paragraph. • After description of proportion of patients with PD-L1–positive tumors: "39% of patients had PD-L1-negative tumors, and 10% of patients had unknown PD-L1 tumor status." • "In an exploratory analysis of patients with PD-L1-negative tumors (n=271, 39%), the OS hazard ratio was 0.85 (95% CI: 0.62, 1.18." FDA's removed the following proposed language/components: (b) (4)

Medication Guide

The current Medication Guide for BAVENCIO is being revised to incorporate information and reference the use of avelumab as a single agent in the treatment of urothelial carcinoma that did not progress with first-line platinum-based induction chemotherapy. Updates are being made to section 'What are the possible side effects of BAVENCIO' of the medication guide to replace the current information on most common side effect in patients with aUC with the information from the Full Prescribing Information.

The Applicant's Position:
All pertinent label sections will be updated as indicated above. The Warnings and Precautions do not need to be updated because the safety profile of avelumab in Study JAVELIN Bladder 100 trial was consistent with that described for avelumab as a single agent in the approved label and neither the toxicity management instructions nor Table 1 (recommended dose modifications) will change.

The FDA's Assessment:
FDA generally agreed with the Applicant's proposed labeling updates, (b) (4)

(b) (4) However, as deaths were higher in the second-line setting, a brief summary of the JAVELIN Solid Tumor trial, which included the cohorts that led to approval in the second-line setting, was included in Section 6. This summary included adverse reactions that led to death in the second-line setting.

In Section 14, the key changes made included removal of (b) (4) and addition of the OS HR for the patients with PD-L1–negative tumors.

12. RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The FDA's Assessment:

Based on the benefit-risk profile of avelumab, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance. REMS are not required by the FDA for this application.

13. POSTMARKETING REQUIREMENTS AND COMMITMENT

The FDA's Assessment:

This sBLA provides sufficient evidence to support regular approval of the product for use in the intended patient population. However, the overall survival results were based on the interim analysis, at which point the median OS in the patients with PD-L1–positive tumors receiving avelumab + BSC was not reached. To generate a more accurate estimate of overall survival in this treatment group and arm, the review team proposed a PMC which is to provide the final analysis for overall survival and relevant datasets. See detailed information in the signed PMC Development Template. The agreed-upon PMC and timelines are as follows:

Submit the final overall survival analysis and datasets from clinical trial JAVELIN Bladder 100 titled; *A Phase 3 Multicenter, Multinational, Randomized, Open Label, Parallel-Arm Study of Avelumab Plus Best Supportive Care Versus Best Supportive Care Alone As a Maintenance Treatment in Patients With Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion of First-Line Platinum-Containing Chemotherapy,* to provide additional efficacy data for avelumab as maintenance treatment in patients with advanced or metastatic urothelial cancer that may inform product labeling.

PMC Schedule Milestones

Trial Completion: 09/2020
Final Report Submission: 03/2021

Avelumab was previously approved in combination with axitinib for the first-line treatment of patients with aRCC. The applicant agreed to 2 PMCs, 3588-3 and 3588-4, during the aRCC approval, to compare PK and efficacy findings between patients with and without treatment-induced ADA. In both aRCC and in JAVELIN Bladder 100, the proportion of patients who developed treatment-induced ADA, the overall safety profile in that patient subset was worse than in patients who remained ADA-negative. Since the existing PMCs only addressed PK and efficacy outcomes, the review team recommended an additional PMR to require safety analyses. The agreed-upon PMR and timelines are as follows:

Reanalyze anti-drug antibodies (ADA) in the stored samples from 249 avelumab-treated patients with urothelial cancer (UC) (Study EMR100070-001) and 88 avelumab-treated patients with Merkel cell carcinoma (MCC) (Study EMR100070-003 Part A) that are evaluable for treatment-emergent ADA with the new ADA method. Using the updated treatment-emergent ADA data from the above two studies and emerging treatment-emergent ADA data from approximately 350 patients with UC in Study B9991001, assess the effect of treatment-emergent ADA on safety endpoints in patients with metastatic MCC or locally advanced or metastatic UC. The final report should include the following analyses and datasets:

(a) Individual trial analyses assessing the effects of ADA on safety as the numbers of treatment-emergent adverse events (TEAEs), Grade 3-4 TEAEs, serious TEAEs, TEAEs leading to discontinuation, and infusion-related reactions (IRRs).
(b) The ADA rate; median time to detection of ADA; median duration of ADA

positivity in months, and the numbers of doses (before/after first detection of ADA and total) received in patients with treatment-emergent ADA.

(c) Effect of "early" ADA (e.g., based on ADA at Week 5 or at another early visit with adequate justification) on safety outcome measures (TEAEs), Grade 3-4 TEAEs, serious TEAEs, TEAEs leading to discontinuation, and IRRs) in individual trials.

PMR Schedule Milestones

Trial Completion: 09/2020
Final Report Submission: 03/2021

14. DIVISION DIRECTOR (DHOT) (NME ONLY)

X

15. DIVISION DIRECTOR (OCP)

X

16. DIVISION DIRECTOR (OB)

X

Shenghui Tang, PhD
Division Director, DB5

17. DIVISION DIRECTOR (CLINICAL)

X

18. OFFICE DIRECTOR (OR DESIGNATED SIGNATORY AUTHORITY)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19. APPENDICES

19.1. References

The Applicant's References:

Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicenter, single-arm, phase 2 study. Lancet Oncol. 2017;18(11):1483-1492.

Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017; 376:1015-1026.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424.

Calabrò F, Lorusso V, Rosati G, et al. Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer 2009;115(12):2652-59.

De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012 Jan 10;30(2):191-9.

Galsky MD, Pal SK, Mortazavi A, et al. Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients (pts) with metastatic urothelial cancer (mUC): HCRN GU14-182. J Clin Oncol 2019;37(suppl; abstr 4504).

García-Donas J, Font A, Pérez-Valderrama B, et al. Maintenance therapy with vinflunine plus best supportive care versus best supportive care alone in patients with advanced urothelial carcinoma with a response after first-line chemotherapy (MAJA; SOGUG 2011/02): a multicentre, randomised, controlled, open-label, phase 2 trial. Lancet Oncol 2017;18: 672–681.

Grivas PD, Daignault S, Tagawa ST, et al. Double-blind, randomized, phase 2 trial of maintenance sunitinib versus placebo after response to chemotherapy in patients with advanced urothelial carcinoma. Cancer 2014;120:692–701.

Miyazaki J, Nishiyama H. Epidemiology of urothelial carcinoma. Int J Urol. 2017;24(10):730-734.

NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer Version 1.2020. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed January 6, 2020.

Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial.Lancet Oncol. 2018: 19(1): 51-64.

Powles T, Huddart RA, Elliott T, et al. Phase III, double-blind, randomized trial that compared maintenance lapatinib versus placebo after first-line chemotherapy in patients with human epidermal growth factor receptor 1/2–positive metastatic bladder cancer. J Clin Oncol 2017;35(1):48-55.

Powles T et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. The Lancet 2018; 391(10122):748-757.

Rosenberg JE, Carroll PR, Small EJ. Update on chemotherapy for advanced bladder cancer. J Urol 2005;174(1):14-20.

Sanli O, Dobruch J, Knowles MA, et al. Bladder cancer. Nat Rev Dis Primers. 2017; 3:17022.

Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017; 18:312-322.

Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001;19(3):666-75.

Vishnu P, Mathew J, Tan WW. Current therapeutic strategies for invasive and metastatic bladder cancer. Onco Targets Ther 2011;4:97-113.

von der Maase H et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23(21):4602-8.

The FDA's References:

1. Galsky MD, Mortazavi A, Milowsky MI, et al. Randomized Double-Blind Phase II Study of Maintenance Pembrolizumab Versus Placebo After First-Line Chemotherapy in Patients With Metastatic Urothelial Cancer. *Journal of Clinical Oncology.* 2020;38(16):1797-1806.
2. Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *European journal of cancer (Oxford, England : 1990).* 2006;42(1):50-54.
3. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC

study 30986. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012;30(2):191-199.
4. Holmsten K, Jensen NV, Mouritsen LS, et al. Vinflunine/gemcitabine versus carboplatin/gemcitabine as first-line treatment in cisplatin-ineligible patients with advanced urothelial carcinoma: A randomised phase II trial (VINGEM). *European journal of cancer (Oxford, England : 1990).* 2020;127:173-182.
5. Ghate K, Amir E, Kuksis M, et al. PD-L1 expression and clinical outcomes in patients with advanced urothelial carcinoma treated with checkpoint inhibitors: A meta-analysis. *Cancer Treatment Reviews.* 2019;76:51-56.
6. Edelman MJ, Le Chevalier T, Soria J-C. Maintenance Therapy and Advanced Non-Small-Cell Lung Cancer: A Skeptic's View. *Journal of Thoracic Oncology.* 2012;7(9):1331-1336.

19.2. Financial Disclosure

The Applicant's Position:
All investigators have been researched for conflicts of interest. None were identified as having financial interests/arrangements with the Sponsor.

The FDA's Assessment:
FDA's review of the financial disclosures revealed 10 investigators of the 206 who enrolled any patients in the safety population had disclosures ≥$25,000. These 10 investigators cumulatively enrolled a total of 38 patients (20 in the avelumab + BSC arm and 18 in the BSC arm). Given that this comprises 5% of the enrolled population and that the primary endpoint was OS, no specific concerns with regards to conflict of interest or financial disclosures were raised.

Covered Clinical Study (Name and/or Number): B9991001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1411[a]		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none[b]		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in study: NA Sponsor of covered study: NA		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 77[c]		

Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant)

aThe total count of investigators shown here may have 'minor' differences with the 16.1.4.1. Our count (which is derived from our Global POS Report and is structured for Financial Disclosure purposes) lists unique investigators and lists only those individuals that participated in the trial. We believe the 16.1.4.1 may show more investigators--e.g. if an investigator held multiple roles (PI/ Sub-I) for instance and may be more lenient/inclusive on the participation criteria, etc.
[b]Financial Disclosure information provided here are derived from the disclosed amounts reported by the clinical investigators as part of their Financial Disclosure Form submission responsibility (via the TransCelerate FD or equivalent FD form) following US Title 21 CFR Part 54. These figures may differ from the amounts reported in the Financial Disclosure Certificates 3454 / 3455 that will be found in Submission module Sec 1.3.4 (Financial Certification and Disclosure) that include Pfizer's internal payment due diligence review of clinical investigators to ensure that all relevant disclosures are submitted for FDA review.
[c]77 confirmed due diligence.

19.3. Nonclinical Pharmacology/Toxicology

Data:
No new information is provided in the current submission.

The FDA's Assessment:
[FDA will complete this section.]

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

Summary of Findings

The clinical pharmacology review is mainly focusing on the assessment of treatment-emergent anti-drug antibodies (ADA) for avelumab on PK and efficacy and dosing regimen conversion from 10 mg/kg Q2W to 800 mg Q2W flat dose:

1. ADA positive rate is 19.1% (62/325 patients) and 5.5% (18/325 patients) at week 9 landmark. Median time to ADA onset among treatment-emergent ADA positive patients was 10.2 weeks with a range from 2 weeks to 36 weeks.
2. Clearance in ADA positive subgroup increased by 15% compared with ADA negative subgroup by post-hoc comparison.
3. Multivariate cox regression model was conducted to adjust imbalanced covariates between ADA positive and ADA negative subgroups. Overall survival hazard ratio with 95% confidence interval (95%CI) compared with best supporting care (BSC) for ADA week 9 positive and ADA week 9 negative group is 0.81 (0.41, 1.58) vs. 0.69 (0.55, 0.87) with best response to first-line chemotherapy (CR/PR vs. SD) and metastatic disease site (non-visceral vs. visceral) adjusted.

With 18 ADA week 9 positive patients in OS landmark analysis and 13 ADA week 9 patient in PFS landmark analysis, the impact of immunogenicity on efficacy is inclusive. However, the point estimation suggested there is no strong association between immunogenicity with worse efficacy endpoint of OS or PFS.

Clearance in UC indication is consistent with other solid tumor indications. Thus, the transfer of body weight based IV dose of 10 mg/kg Q2W to a fixed dose of 800 mg Q2W for avelumab is approvable since it has been approved in other indications.

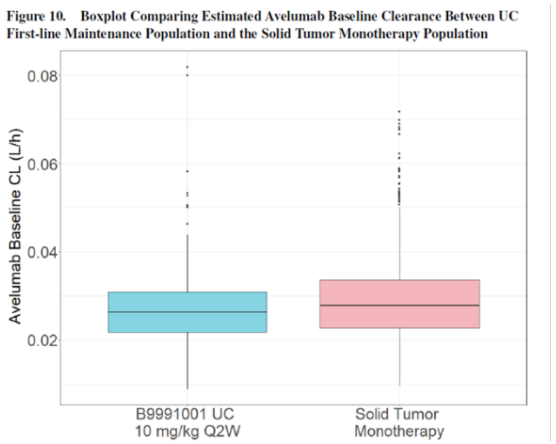
19.4.1. Is avelumab pharmacokinetics in UC patients in B9991001 comparable with previous solid tumor?

The dataset for popPK analysis contains a total of 2171 patients receiving avelumab; 1827 patients are from the avelumab monotherapy solid tumor popPK dataset and 344 patients are from the current study B9991001 in which avelumab is administered as first-line maintenance therapy to patients with UC. In total there are 15,392 PK records with measurable avelumab concentration, 4,566 of which are from the UC first-line maintenance population. Parameter estimates from the current analysis are consistent with those reported previously in the popPK model characterizing monotherapy in patients with solid tumors particularly CL. A comparison of avelumab baseline clearance and percent change of avelumab clearance from baseline are represented in Figure 17.

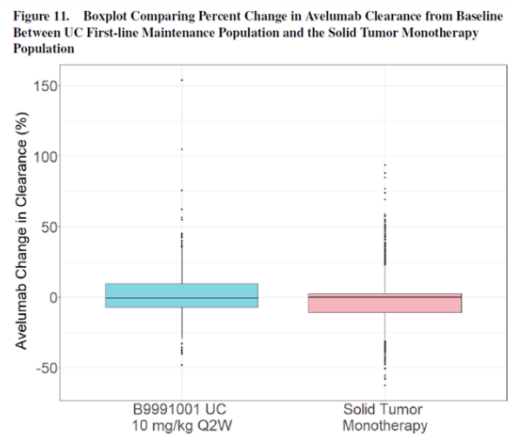
Dose conversion from 10 mg/kg Q2W tested in study B9991001 to the proposed 800 mg Q2W flat dose is acceptable since this transfer has been previously reviewed and approved in other indications. The exposure of avelumab between body weight based dosing and flat dosing are comparable based on modeling and simulation results in previous approved indication.

Figure 17. Comparing Estimated Avelumab Baseline Clearance (Left) and Change in Clearance (Right) between UC First-Line Maintenance Population and the Solid Tumor Monotherapy Population

Baseline Clearance



Change in Clearance



Source: Figure 10 and Figure 11 of POPPK report.

19.4.2. What is the impact of immunogenicity on pharmacokinetics in Study B9991001?

Clearance in ADA positive subgroup increased by 15% (Ratio of ADA+ clearance vs. ADA- clearance: 0.0295/0.0257=1.15) compared with ADA negative subgroup by post-hoc comparison (Table 39).

Table 39. Comparison of Baseline Clearance Estimates from Current PopPK Model by ADA Status and PD-L1 Status for UC First-Line Maintenance Population

Parameter	Population	N	Geometric Mean	Lower 95% CI	Upper 95% CI	Mean (SD)	Median (Range)
$CL_{baseline}$ (L/h)	ADA Ever-Positive	66	0.0295	0.0271	0.0322	0.032 (0.013)	0.030 (0.012-0.082)
	ADA Never-Positive	278	0.0257	0.0249	0.0265	0.027 (0.007)	0.026 (0.009-0.053)
	PD-L1-Negative	137	0.0259	0.0248	0.0271	0.027 (0.008)	0.026 (0.015-0.053)
	PD-L1-Positive	187	0.0267	0.0256	0.0279	0.028 (0.010)	0.026 (0.009-0.082)
	PD-L1 Missing	20	0.0267	0.0245	0.0291	0.027 (0.006)	0.026 (0.019-0.040)

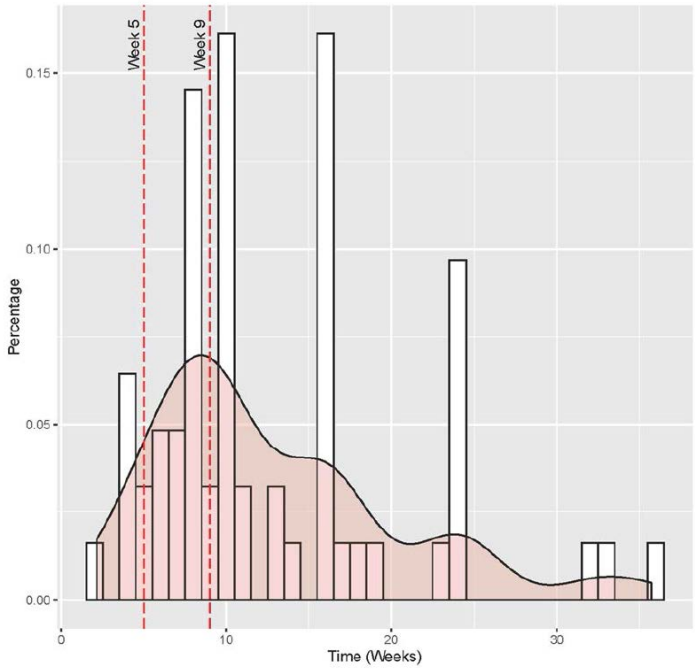
Source: Table 7 of population PK report

19.4.3. What is ADA Onset Rate and Onset Time in Study B9991001?

ADA positive rate is 19.1% (62/325 patients) in study B9991001 for ADA-evaluable patients who had at least one valid post-baseline ADA result and without a positive baseline ADA result.

The median time to onset of ADAs among treatment-emergent ADA-positive patients was 10.2 weeks (range: 2.1, 35.7). The median duration of ADA-positive status estimated by Kaplan-Meier was 2.4 weeks (95% CI: 0.1 – 7.7 weeks). The median total number of avelumab doses administered in patients with treatment-induced ADA was 12 doses (range: 1, 62) with a median of 5 doses (range: 1, 15) prior to first ADA positive value. At week 5, there were 6 patients (1.8% out of 325 evaluable) who were treatment-induced ADA-positive. At week 9, there were 18 patients (5.5% out of 325 evaluable) who were treatment-induced ADA-positive (Figure 18).

Figure 18. Summary of Avelumab ADA Onset Time in Study B9991001



Source: Figure 1 of immunogenicity IR.

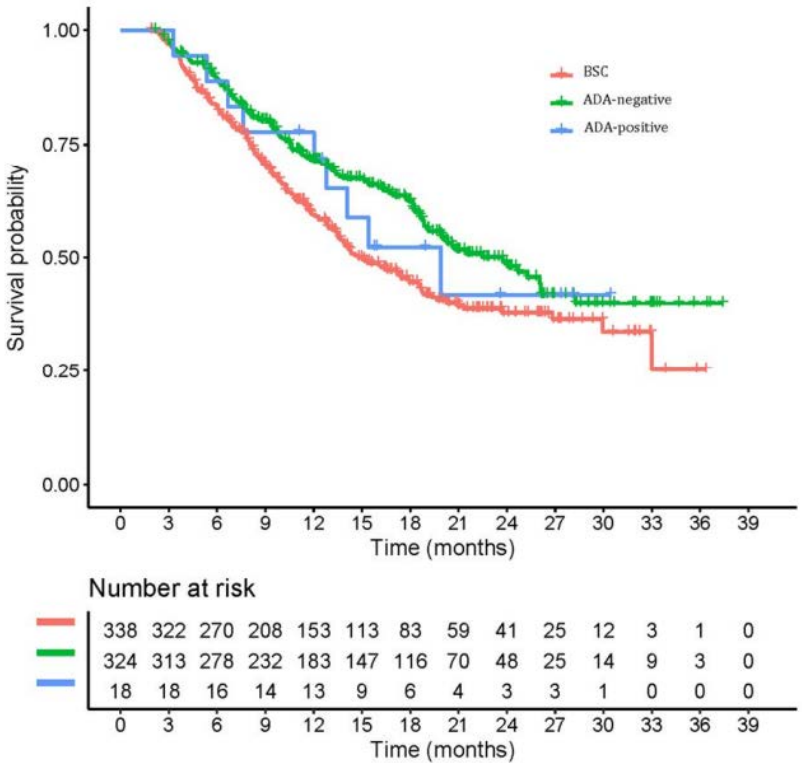
19.4.4. Landmark Analysis of Avelumab ADA on Efficacy

An exploratory landmark analysis based on ADA status at week 9 were conducted. UC patients in both arms who had event or censored before week 9 were removed.

OS results based on ADA status at week 9:

The results of landmark OS analysis were shown in (Figure 19, Table 40, Figure 20). Shown in Table 40, the death rate is 50% in avelumab early ADA positive subgroup, which is higher than the 41% death rate in the ADA negative group. The death rate is 51% in the BSC arm for the landmark analysis. The median OS time in the ADA positive subgroup is 19.9 (95% CI: 12.0, NA) months which is a little shorter than the median OS time for the ADA negative subgroup 22.5 (95% CI: 19 – 26) months. The median survival time is 14.8 (13.4, 18.6) months in the BSC arm. Based on the multivariate Cox regression analysis, the hazard ratio with 95% confidence interval (95%CI) compared with BSC for ADA week 9 positive and ADA week 9 negative group is 0.81 (0.41, 1.58) vs. 0.69 (0.55, 0.87) adjusted for stratification factors including: best response to first-line chemotherapy (CR/PR vs. SD) and metastatic disease site (non-visceral vs. visceral). The forest plot of OS HR for the adjusted with stratification factors was shown in Figure 20. In summary, the overall survival benefit seems to be similar between ADA subgroup arm and the ADA negative subgroup.

Figure 19. Overall Survival in UC Patients in B9991001 by ADA Week 9 Status in Avelumab and BSC Combination Arm



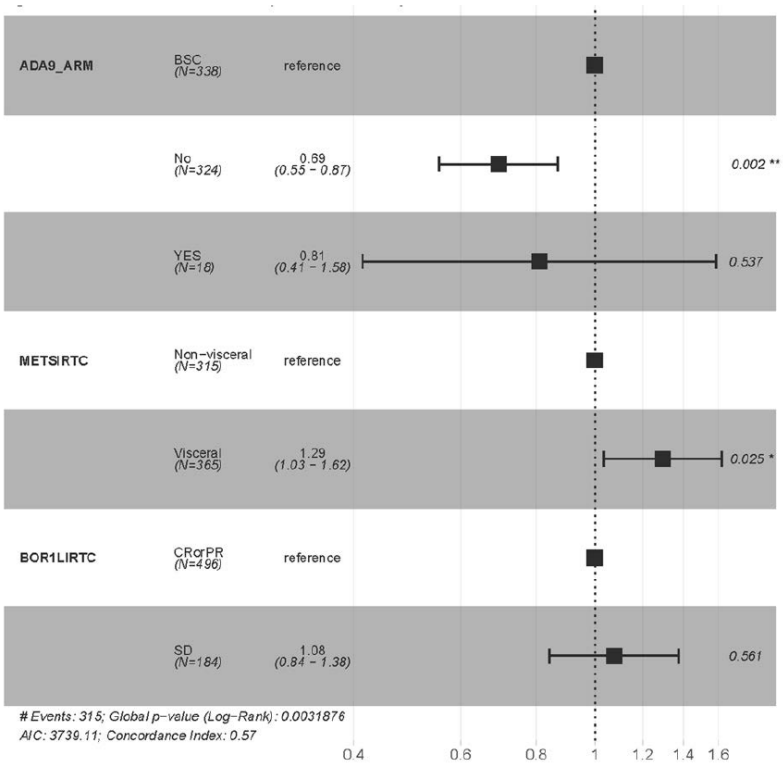
Source: Figure 6 of Sponsor's immunogenicity IR.

Table 40. Overall Survival Result in aUC Patients in B9991001 By ADA Week 9 Status in Avelumab And BSC Combination Arm

ADA Status	N	Events	Median (months)	HR adjusted*
ADA+ 9wks	18	9 (50%)	19.9 (12.0 - NR)	0.81 (0.41 – 1.58)
ADA- 9wks	324	133 (41%)	22.5 (19.0 – 26.1)	0.69 (0.55 – 0.87)
BSC	338	173 (51%)	14.8 (13.4 – 18.6)	-

Source: Sponsor's immunogenicity IR. * HR stratified on best response to first-line chemotherapy (CR/PR vs. SD) and metastatic disease site (non-visceral vs. visceral)

Figure 20. Forest Plot of Overall Survival in UC Patients in B9991001 by ADA Week 9 Status

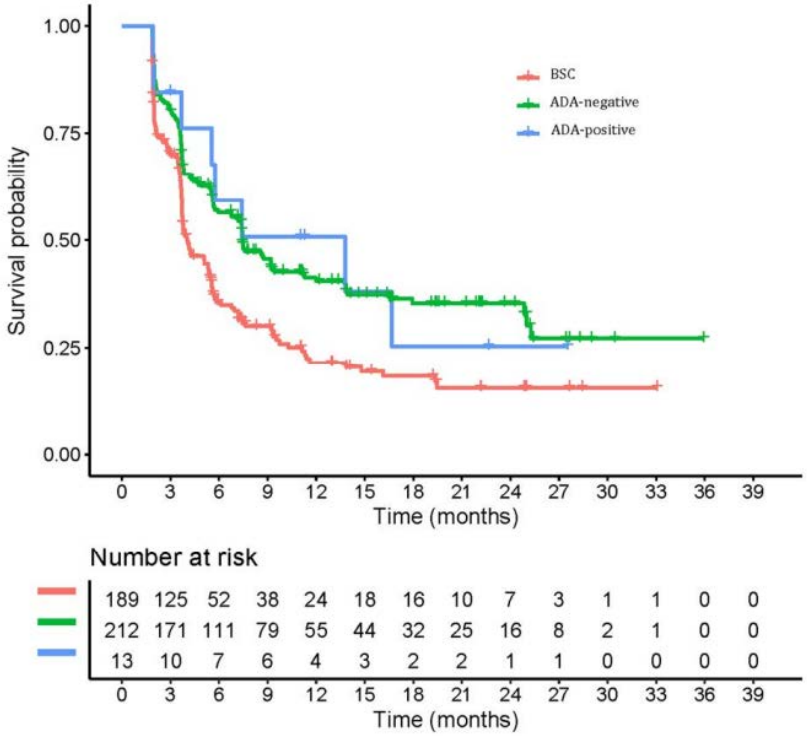


Source: Figure 7 of Sponsor's immunogenicity IR.

PFS results based on ADA status at Week 9:

The results of landmark PFS were shown in (Figure 21, Table 40, Figure 22). Median PFS for the ADA week 9 positive, ADA week 9 negative subgroups in Avelumab + BSC arm and the BSC control arm were 13.8 months (95% CI: 3.7, NR), 7.4 months (95% CI: 5.7, 9.4) and 4 months (95% CI: 3.7, 5.4) respectively (Table 41). Based on the multivariate Cox regression analysis, the hazard ratio with 95% confidence interval (95%CI) compared with BSC for the ADA week 9 positive group and the ADA week 9 negative group is 0.58 (0.28, 1.18) vs. 0.61 (0.48, 0.77) with adjustment for stratification factors: best response to first-line chemotherapy (CR/PR vs. SD) and metastatic disease site (non-visceral vs. visceral). The forest plot for HRs adjusted with stratification factors was shown in Figure 22.

Figure 21. Progression Free Survival in aUC Patients in B9991001 by ADA Week 9 Status in Avelumab plus BSC Arm



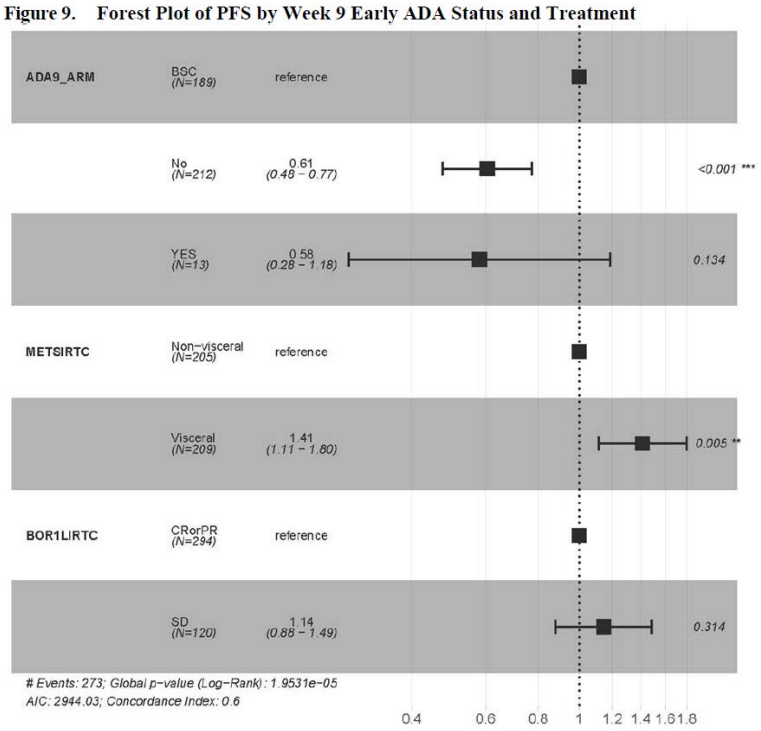
Source: Figure 8 of Sponsor's immunogenicity IR.

Table 41. Progression Free Survival Result in Landmark ADA Subgroups (ADA 9wks)

ADA Status	N	Events	Median	HR adjusted*
ADA+ 9wks	13	8 (62%)	13.8 (3.7, NR)	0.58 (0.28 – 1.18)
ADA- 9wks	212	128 (60%)	7.4 (5.7 -9.4)	0.61 (0.48 – 0.77)
BSC	189	137 (72%)	4.0 (3.7 – 5.4)	-

Source: Sponsor's immunogenicity IR. * HR stratified on best response to first-line chemotherapy (CR/PR vs. SD) and metastatic disease site (non-visceral vs. visceral)

Figure 22. Forest Plot of Progression Free Survival in 1L HCC Patients in B9991001 by ADA Week 6 Status



Source: Figure 9 of Sponsor's immunogenicity IR.

19.4.5. Demographic and Baseline Characteristics Comparison by ADA Status at Landmark (Week 9)

ADA positive patients were associated with a worse baseline characteristic including: higher mean CRP level, higher proportion of patients with ECOG=1 (compared with ECOG=0) and best response after first line therapy of SD (Compared with CR/PR). In addition, higher proportion of ADA positive patients has non-visceral disease status and more patients are PD-L1 positive.

Table 42. Summary of Baseline Characteristics by Week 9 Early ADA Status and Treatment (Continuous Variables)

Baseline Variable		ADA-positive (N=18)	ADA-negative (N=324)	BSC (N=338)
Age (years)	n	18	324	338
	Mean (stdev)	66 (13.3)	67 (9.4)	68 (9.1)
Creatinine Clearance (mL/min)	n	18	322	334
	Mean (stdev)	77.5 (34.2)	65.6 (22.9)	69.3 (27.6)
C-reactive protein (mg/L)	n	18	316	317
	Mean (stdev)	18.1 (21.0)	8.76 (16.2)	8.93 (15.0)
Tumor size (mm)	n	10	215	231
	Mean (stdev)	18.8 (22.2)	27.1 (28.2)	26.8 (29.4)

Baseline Variable n (%)		ADA-positive (N=18)	ADA-negative (N=324)	BSC (N=338)
ECOG performance status	0	9 (50%)	198 (61%)	206 (61%)
	≥ 1	9 (50%)	126 (39%)	132 (39%)
Metastatic disease (by IRT)	Non-visceral	10 (56%)	148 (46%)	157 (46%)
	Visceral	8 (44%)	176 (54%)	181 (54%)
Best response to 1L chemotherapy	CR or PR	12 (67%)	239 (74%)	245 (72%)
	SD	6 (33%)	85 (26%)	93 (28%)
1L chemotherapy regimen	Gemcitabine + cisplatin	8 (44%)	172 (53%)	201 (59%)
	Gemcitabine + carboplatin	10 (56%)	132 (41%)	115 (34%)
	Gemcitabine + cisplatin+ carboplatin	0 (0%)	20 (6%)	20 (6%)
	Missing	0 (0%)	0 (0%)	2 (1%)

Source: Table 6 and Table 7 of Sponsor's immunogenicity IR

19.5. Additional Safety Analyses Conducted by FDA

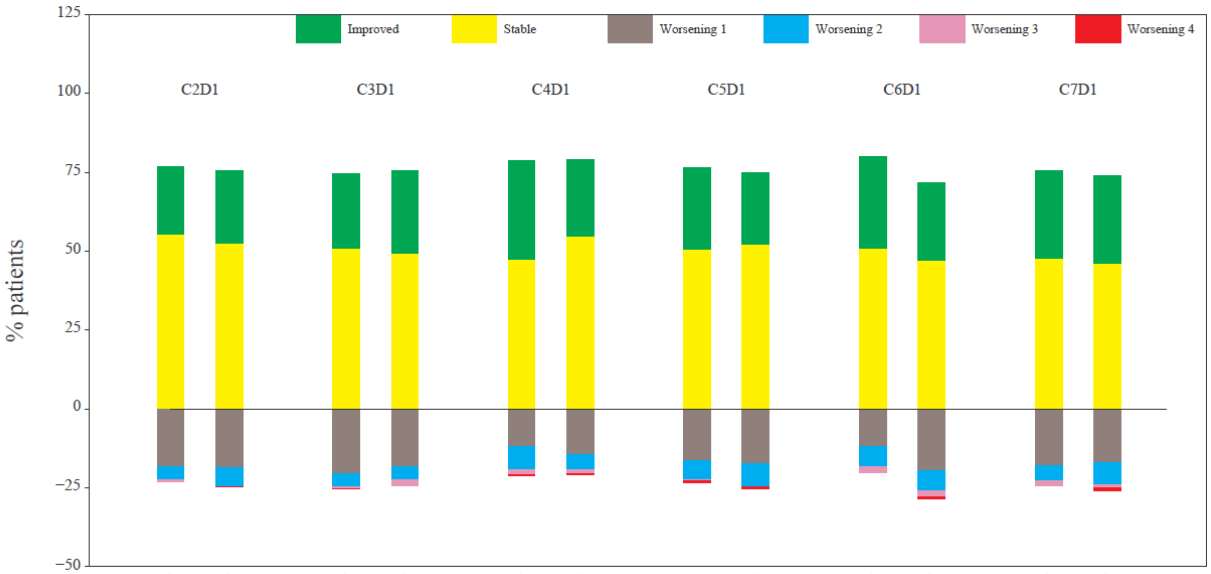
The FDA's Assessment:

FDA sent an IR to the Applicant requesting summary analyses of COA results.

The most common TEAE in patients treated with avelumab is fatigue, occurring in 17.7% of patients. Therefore, FDA's IR asked the Applicant to provide an item level analysis for the first 6 months for the item "I have a lack of energy," to better characterize the patient experience of fatigue.

The proportion of patients who reported worsening "lack of energy" was about the same as the proportion of patients who reported improved "lack of energy" compared to baseline, which was similar in both arms (Figure 22).

Figure 23. Change from Baseline Response to "I have a lack of energy"



	C2D1		C3D1		C4D1		C5D1		C6D1		C7D1	
	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC	Avel.+BSC	BSC
N	308	297	268	222	240	154	201	119	179	109	160	85
Improved	21.8%	23.2%	23.9%	26.6%	31.7%	24.7%	26.4%	22.7%	29.1%	24.8%	28.1%	28.2%
Stable	55.2%	52.2%	50.8%	49.1%	47.1%	54.6%	50.3%	52.1%	50.8%	46.8%	47.5%	45.9%
Worsening 1	17.9%	18.2%	20.2%	18.0%	11.7%	14.3%	15.9%	16.8%	11.7%	19.3%	17.5%	16.5%
Worsening 2	4.2%	6.1%	4.1%	4.1%	7.1%	4.6%	6.0%	7.6%	6.2%	6.4%	5.0%	7.1%
Worsening 3	1.0%		0.8%	2.3%	1.7%	1.3%	0.5%		2.2%	1.8%	1.9%	1.2%
Worsening 4		0.3%	0.4%		0.8%	0.7%	1.0%	0.8%		0.9%		1.2%

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Pharmacometrics Reviewer	Yuan Xu	OCP/DPM	Sections: 6, 19.4	**Select one:** X Authored ___ Approved
	Signature: Yuan Xu -S Digitally signed by Yuan Xu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuan Xu -S, 0.9.2342.19200300.100.1.1=2001686060 Date: 2020.06.24 15:12:06 -04'00'			
Pharmacometrics Team Leader	Jiang Liu	OCP/DPM	Sections: 6, 19.4	**Select one:** X Authored X Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2020.06.27 15:06:40 -04'00'			
Clinical Pharmacology Reviewer	Wentao Fu	OCP/DCPI	Sections: 6	**Select one:** x Authored _____ Approved
	Signature: Wentao Fu -S Digitally signed by Wentao Fu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Wentao Fu -S, 0.9.2342.19200300.100.1.1=2001855706 Date: 2020.06.26 16:25:21 -04'00'			
Clinical Pharmacology Team Leader	Pengfei Song	OCP/DCPII	Sections: 6	**Select one:** X Authored X Approved
	Signature: Pengfei Song -S Digitally signed by Pengfei Song -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Pengfei Song -S, 0.9.2342.19200300.100.1.1=2000464900 Date: 2020.06.26 19:48:15 -04'00'			
Statistical Reviewer/ Team Leader	Erik Bloomquist	OB/DBV	Sections: 1, 8	**Select one:** x Authored X Approved
	Signature: Erik W. Bloomquist -S Digitally signed by Erik W. Bloomquist -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000477083, cn=Erik W. Bloomquist -S Date: 2020.06.26 16:56:48 -04'00'			

BLA 761049/S-009 (Avelumab)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Division Director (OB)	Shenghui Tang	OB/DBV	Sections: 1, 8	**Select one:** ___ Authored X Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2020.06.24 15:13:44 -04'00'			
Clinical Reviewer (Efficacy)	Elaine Chang	OOD/DO1	Sections: 2, 3, 4.1, 4.4, 7, 8.1, 8.4, 11, 12, 13, 19.1, 19.2, 19.5	**Select one:** x Authored __ Approved
	Signature: Elaine Chang -S Digitally signed by Elaine Chang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Elaine Chang -S, 0.9.2342.19200300.100.1.1=2002602609 Date: 2020.06.25 10:58:17 -04'00'			
Clinical Reviewer (Safety)	Michael Brave	OOD/DO1	Sections: 8.2, 8.4, 11	**Select one:** x Authored __ Approved
	Signature: Michael H. Brave -S Digitally signed by Michael H. Brave -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300221205, cn=Michael H. Brave -S Date: 2020.06.25 12:19:59 -04'00'			
Associate Director of Safety	Shaily Arora	OND/OOD	Section: 13	**Select one:** X Reviewed X Approved
	Signature: Shaily Arora -S Digitally signed by Shaily Arora -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shaily Arora -S, 0.9.2342.19200300.100.1.1=2000835215 Date: 2020.06.25 11:09:04 -04'00'			
Associate Director for Labeling	William Pierce	OND/OOD	Sections: 11	**Select one:** ___ Authored x Approved
	Signature: William F. Pierce -S5 Digitally signed by William F. Pierce -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5 Date: 2020.06.24 16:41:42 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Chana Weinstock	OOD/DO1	Sections: Section 1 ALL	**Select one:** x Authored x Approved
	Signature: Chana Weinstock -S Digitally signed by Chana Weinstock -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001659606, cn=Chana Weinstock -S Date: 2020.06.26 16:21:13 -04'00'			

BLA 761049/S-009 (Avelumab)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Deputy Division Director (Clinical)	Amna Ibrahim	OOD/DO1	Sections: ALL	**Select one:** ___ Authored _x_ Approved
	Signature: Amna Ibrahim -S Digitally signed by Amna Ibrahim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amna Ibrahim -S, 0.9.2342.19200300.100.1.1=1300150984 Date: 2020.06.30 13:55:40 -04'00'			

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/s/

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CHANA WEINSTOCK
06/30/2020 03:42:34 PM

AMNA IBRAHIM
06/30/2020 03:44:31 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761049Orig1s009

PRODUCT QUALITY REVIEW(S)

Memorandum of Review:

Submission Tracking Number (STN):	BLA 761049.0158-Supplement 9
Subject:	This efficacy supplement seeks approval for avelumab as first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy. For CMC, the Sponsor submitted the claim for the categorical exclusion from the requirement to submit an environmental assessment.
Stamp Date:	April 7, 2020
Review/Revision Date:	May 18, 2020
Primary Reviewer:	Arulvathani Arudchandran
Secondary Reviewer:	Patrick Lynch
RBPM:	Kelly Ballard
Consults:	N/A
Applicant:	EMD Serono, Inc.
Product:	Bavencio (avelumab)
Indication:	Treatment of patients with locally advanced or metastatic urothelial carcinoma
Dosage/frequency	800 mg/every two weeks
Strength	200 mg/10 mL (20 mg/mL)
Target/ Mode of action:	Blocks the interaction between PD-L1 and its receptors PD-1 and B7.1.
Filing Date:	May 11, 2020
Action Due Date- PDUFA / priority time line :	October 3, 2020/ June 30, 2020

1. Summary Basis of Recommendation:

a. Recommendation: I recommend the approval of this efficacy supplemental Biologics License Application from the product quality perspective.

b. Justification:
This efficacy supplemental Biologics License Application (sBLA) seeks approval for avelumab as first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy.

For CMC, no information is submitted in module 3. The Sponsor submitted the claim for the categorical exclusion from the requirement to submit an environmental assessment. The claim was submitted based on the exclusions allowed by 21 CFR 25.15 (a),(d). The information submitted in this supplement supported that no extraordinary circumstances, as described in 21 CFR 25.31(c), exist that would result in a significant impact to the environment from the discharge of avelumab drug product. In addition, the classes of actions listed for the categorical exclusion per 21 CFR 25.15 (a),(d), are appropriate for this submission. Therefore, this waiver is appropriate and acceptable.
Approved immunogenicity assays that were validated by utilizing the solid tumor patient sera were employed to assess the treatment-emergent anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs). Therefore, these assays are found suitable for the intended purpose.

2. Suggested Language for Action Letter:
Language for the action letter is deferred to the Office of New Drugs.

3. Review:
For this efficacy supplement-9, no CMC information is submitted in module 3. Approved immunogenicity assays previously submitted to the BLA were used in the clinical studies to evaluate the immunogenicity.

The immunogenicity assay used to evaluate the treatment-emergent ADAs was reviewed and approved in BLA 761049-supplement 6. The assay was validated for the detection of ADAs against avelumab in solid patient serum samples, where samples were obtained from the patients with advanced renal cell carcinoma. In addition, the dosage and frequency of avelumab treatment are the same as the ones proposed in this submission. Therefore, the ADA assay is found suitable to detect the treatment-emergent ADAs in the urothelial carcinoma patients.
It was noted that 19.1% and 14.6% treatment -induced ADA-positive incidence was observed in urothelial carcinoma and renal cell carcinoma clinical studies, respectively. These rates are higher than the 4.1% of treatment -induced ADA-positive incidence observed for the Merkle cell carcinoma clinical studies using a different assay. The Sponsor proposed that the higher incidences of immunogenicity observed for the urothelial carcinoma and renal cell carcinoma patient population are likely due to the more sensitive ADA assay compared to the one approved for the initial BLA, for the ADA evaluation in the Merkle cell carcinoma patient population. These results further support a conclusion that the assays are sensitive to detect binding ADA in clinical samples from the urothelial carcinoma study.

The NAb assay is approved in the initial BLA for evaluation of NAb in Merkle cell carcinoma population. Patients with Merkle cell carcinoma are treated with comparable dosage and frequency. Therefore, this assay is also found suitable for

the intended purpose. It was noted that the NAb antibody data will be analyzed upon study # B9991001 (urothelial carcinoma) completion.

A claim for a categorical exclusion is being made under 21 CFR 25.15 (a),(d) for this efficacy supplemental Biologics License Application supplement-9. The Sponsor claims that no extraordinary circumstances as described in 21 CFR 25.15 (a),(d) exist that could require an environmental assessment.
Of note, a waiver for the requirement to submit an environmental assessment was grated for the original BLA 761049 per 21 CFR 25.31(c).

Reviewer comment:
The use of avelumab under this sBLA 761049 is unlikely to impact the environment. Therefore, I recommend granting a waiver for the requirement to submit an environmental assessment. Further, the Sponsor used the approved assays to detect the treatment-emergent immunogenicity outcome. Assays were validated by utilizing solid tumor patient serum samples, suitable for the intended purpose. In addition, correlating the sensitivity of the current assay for the detection of higher treatment-induced ADA in the urothelial carcinoma clinical studies is also reasonable. However, the safety evaluation for the incidence of the higher ADA and the impact on PK is deferred to the Clinical and Clin.Pharm teams.

4. Reviewer conclusions:

A claim for a categorical exclusion is made under 21 CFR 25.15 (a),(d). This sBLA 761049.0158 application is for a biologic product comprised of substances that occur naturally in the environment and approval of this action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment per 21 CFR 25.31(c). In addition, the classes of actions, listed for the categorical exclusion per 21 CFR 25.15 (a),(d) are appropriate for this submission. Therefore, I recommend granting a waiver for the requirement to submit an environmental assessment.
In addition, the immunogenicity assays are found suitable for the intended purpose, the approved assays are validated with the solid tumor patient serum samples, same as the indication of this sBLA.

5. Future Inspection Items:

N/A

Arulvathani Arudchandran

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Patrick Lynch

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761049Orig1s009

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 18, 2020

To: Rajesh Venugopal, Regulatory Project Manager, Division of Oncology 1 (DO1)

William Pierce, PharmD, Associate Director for Labeling

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for Bavencio (avelumab) injection, for intravenous use

BLA: 761049/Supplement 009

In response to DO1's consult request dated February 19, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for Bavencio (avelumab) injection, for intravenous use. This supplement (S-009) proposes a new indication for the first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy.

OPDP's comments on the proposed PI are based on the draft PI received by electronic mail from DO1 on June 12, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the proposed Medication Guide was completed, and comments on the proposed Medication Guide were sent under separate cover on June 18, 2020.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 18, 2020
To:	Rajesh Venugopal, MPH, MBA Senior Regulatory Project Manager **Division of Oncology 1 (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	BAVENCIO (avelumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761049
Supplement Number:	S-009
Applicant:	EMD Serono, Inc.

1 INTRODUCTION

On February 18, 2020, EMD Serono, Inc. submitted presubmission material as agreed to with the Agency as a part of the Real-Time Oncology Review (RTOR) Pilot for a Prior Approval Supplement (PAS) – Efficacy to their approved Biologics License Application (BLA) 761049/S-009 for BAVENCIO (avelumab) injection. On April 7, 2020, the Applicant submitted the final submission material for the proposed indication for the first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 1 (DO1) on February 19, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BAVENCIO (avelumab) injection.

2 MATERIAL REVIEWED

- Draft BAVENCIO (avelumab) injection MG received on April 7, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 12, 2020.
- Draft BAVENCIO (avelumab) injection Prescribing Information (PI) received on April 7, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 12, 2020.

3 REVIEW METHODS

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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BARBARA A FULLER
06/18/2020 11:17:53 AM

LASHAWN M GRIFFITHS
06/18/2020 01:36:57 PM

LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 12, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761049/S-009
Product Name, Dosage Form, and Strength:	Bavencio (avelumab) Injection, 200 mg/10 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	EMD Serono, Inc
FDA Received Date:	April 7, 2020
OSE RCM #:	2020-431
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

EMD Serono, Inc submitted an Efficacy Supplement for Bavencio (avelumab) Injection to revise the indication to include first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (1L UC) whose disease has not progressed with first-line platinum-based induction chemotherapy. Subsequently, the Division of Oncology 1 (DO1) requested that we review the proposed Bavencio prescribing information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Bavencio PI and noted that there are no changes to Section 2 Dosage and Administration, Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information. The proposed changes in the MG are also acceptable from a medication error perspective. Additionally, our routine postmarket safety surveillance did not identify any medication error related to label and labeling that is relevant for this review. Therefore, we have no recommendations for the proposed Bavencio PI from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Bavencio PI and MG are acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bavencio received on April 7, 2020 from EMD Serono, Inc.

Table 2. Relevant Product Information for Bavencio	
Initial Approval Date	March 23, 2017
Proper Name	avelumab
Indication	Merkel Cell Carcinoma Urothelial Carcinoma Renal Cell Carcinoma
Route of Administration	Intravenous
Dosage Form	Injection
Strength	200 mg/10 mL (20 mg/mL)
Dose and Frequency	Merkel Cell Carcinoma: 800 mg every 2 weeks. Urothelial Carcinoma; 800 mg every 2 weeks. Renal Cell Carcinoma: 800 mg every 2 weeks in combination with axitinib 5 mg orally twice daily.
How Supplied	Carton of one single-dose vial
Storage	Store refrigerated at 36°F to 46°F (2°C to 8°C) in original package to protect from light.
Container Closure	16 mL nominal capacity colorless type I (b) (4) glass vial with grey rubber stopper and aluminum seal with a removable plastic cap.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 5, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Bavencio. Our search identified 1 previous review[a] since January 29, 2018, and we confirmed that our previous recommendations were implemented.

[a] Straka, M. Label and Labeling Review for Bavencio (BLA 761049/S-003). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Feb 14. RCM No.: 2017-2617.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Bavencio labels and labeling submitted by EMD Serono, Inc.

- Prescribing Information (Image not shown) received on April 7, 2020, available from \\cdsesub1\evsprod\bla761049\0158\m1\us\114-labeling\1141-draft-label\us-pi-avelumab-2020-04-07-uc-1l-tc-annotated.docx
- Medication Guide (Image not shown) received on April 7, 2020, available from \\cdsesub1\evsprod\bla761049\0158\m1\us\114-labeling\1141-draft-label\us-medguide-avelumab-2020-04-07-uc-1l-tc-annotated.docx

G.2 Label and Labeling Images

N/A

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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