CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761078Orig1s000

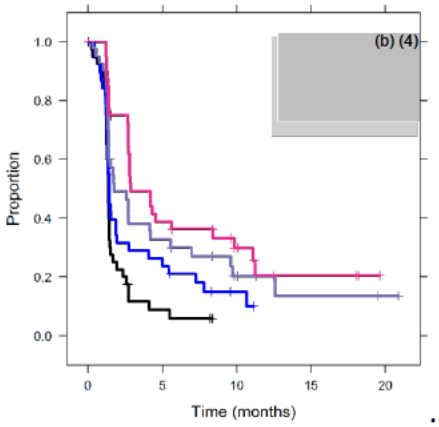
MULTI-DISCIPLINE REVIEW

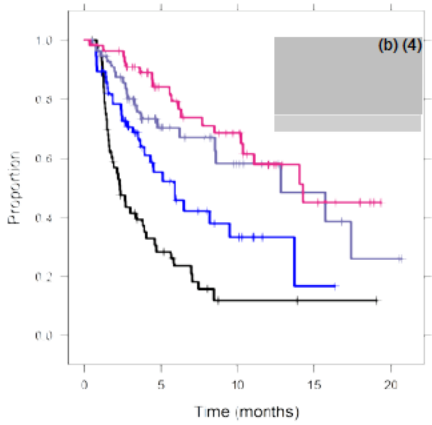
Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761078
Priority or Standard	Priority
Submit Date(s)	12/23/2016
Received Date(s)	12/27/2016
PDUFA Goal Date	August 27, 2017
Division/Office	DOP1/OHOP
Review Completion Date	
Established Name	Avelumab
(Proposed) Trade Name	BAVENCIO
Pharmacologic Class	PD-L1 Blocking Antibody
Code name	MSB0010718C
Applicant	EMD Serono Inc.
Formulation(s)	20 mg/mL Sterile solution in a single-dose glass vial
Dosing Regimen	10 mg/kg given as an intravenous infusion every 2 weeks (Q2W)
Applicant Proposed Indication(s)/Population(s)	Bavencio is indicated for the treatment of patients with locally advanced or metastatic urothelial cancer with disease progression on or after platinum-based therapy.
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s) (if applicable)	Bavencio (avelumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial cancer who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Table of Contents





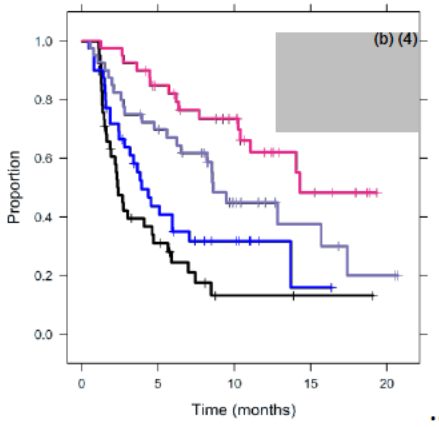


Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Kim J. Robertson
Nonclinical Reviewer	Wei Chen, PhD
Nonclinical Team Leader	Todd Palmby, PhD
Office of Clinical Pharmacology Reviewer(s)	Nan Zheng, PhD
Office of Clinical Pharmacology Team Leader(s)	Pengfei Song, PhD; Jingyu Yu, PhD
Associate Director for Labeling	Capt. William Pierce, PharmD
Clinical Reviewer	Chana Weinstock, MD
Clinical Team Leader	Virginia Ellen Maher, MD
Statistical Reviewer	Joyce Cheng, PhD
Statistical Team Leader	Shenghui Tang, PhD
Cross-Disciplinary Team Leader	Virginia Ellen Maher, MD
Division Director (DHOT)	N/A
Division Director (OCP)	Nam Atiqur Rahman, PhD
Division Director (OB)	Rajeshwari Sridhara, PhD
Division Director (OHOP)	Julia Beaver, MD
Office Director (or designated signatory authority)	N/A

Additional Reviewers of Application

OPQ	N/A
Microbiology	Maria Reyes Candau-Chacon, PhD/ Lakshmi Narasimhan, PhD
OPDP	Nicholas J. Senior, PharmD, JD
OSI	Lauren C. Iacono-Connors, PhD
OSE/DEPI	N/A
OSE/DMEPA	Tingting Gao, PharmD
OSE/DRISK	Elizabeth Everhart, MSN
Other	Arulvathani Arudchandran, PhD, OBP; Patrick Lynch, PhD, OBP

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

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AKP	alkaline phosphatase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
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
CK	creatine kinase
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
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram

eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GRMP	good review management practice
ICH	International Conference on Harmonization
IERC	Independent Endpoint Review Committee
IND	Investigational New Drug
IRR	Independent Radiology Review
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
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
OSE	Office of Surveillance and Epidemiology
OS	overall survival
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PD-1	Programmed Death 1 protein
PD-L1	Programmed Death Ligand 1
PFS	progression-free survival
PI	prescribing information

PK	pharmacokinetics
PMA	Pre-marketing Application
PMC	postmarketing commitment
PMR	postmarketing requirement
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	patient
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Avelumab is a fully human monoclonal antibody directed against programmed death-ligand 1 (PD-L1). PD-L1 is expressed on resting T cells, B cells, dendritic cells, and macrophages. Binding of PD-L1 to its receptor, PD-1, acts as part of a feedback loop, inhibiting the immune response. Tumor cells are able to express PD-L1, bind to PD-1, and to use this to inhibit the immune response. Avelumab is thought to bind to PD-L1 on tumor cells, preventing suppression of the immune response and allowing the immune system to attack the tumor cells.

Compared to other monoclonal antibodies directed against PD-1/L-1, avelumab is unique in that the Fc portion of the molecule is intact. That is, avelumab is able to lyse target cells by antibody-dependent cell-mediated cytotoxicity and to fix complement. This may improve the activity of avelumab against tumor cells, but it is possible that the bindings of avelumab will result in lysis of immune effector cells that express PD-L1. Another unique aspect of avelumab is that its half-life is only 6.1 days. Studies of target occupancy in patients receiving 10 mg/kg of avelumab every 2 weeks found a mean target occupancy > 90% by flow cytometry on peripheral blood mononuclear cells throughout the dosing interval. However, exposure-response analyses suggest that increased avelumab exposure was associated with an increase in response when corrected for prognostic variables. (b) (4)

Avelumab received accelerated approval on March 23, 2017 for the treatment of metastatic Merkel cell carcinoma. The current application was submitted on December 27, 2016 with the proposed indication: treatment of patients with locally advanced or metastatic urothelial cancer with disease progression on or after platinum-based therapy. Atezolizumab, nivolumab, and durvalumab (all PD-1/L1 inhibitors) have received accelerated approval for a similar indication.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant conducted a Phase 1 dose escalation study followed by examination of the activity of avelumab in a variety of cancer types. This included a secondary expansion cohort (N = 44) and an efficacy expansion cohort (N = 205) in patients with urothelial cancer. The primary endpoint for these cohorts was the confirmed response rate as determined by Independent Endpoint Review

Committee. Patients received avelumab 10 mg/kg every 2 weeks. Among these 249 pts, 242 pts who had received prior platinum-based therapy are included in the safety population. The study is ongoing and efficacy analyses of the confirmed response rate have been conducted on 2 groups of patients; those followed for at least 13 weeks (N = 226) and for at least 6 months (N = 161). Patients should have completed two tumor assessments by 13 weeks and it is the earliest time point (and the largest number of patients) at which a confirmed response can be determined. The 6 month time point was chosen because some responses occurred late in the treatment period. This allowed late response to be included in the confirmed response rate. The median time to response was 2.0 months in both groups, but ranged from 1.3 to 11.0 months. The table below provides information on the response rates in these 2 groups of patients. These response rates are consistent with those seen with other PD-1/PD-L1 inhibitors that have received accelerated approval for this indication. For example, the response rate of atezolizumab is 14.8%.

Table 1: Primary Analysis by IRR

	≥ 13 Weeks of Follow Up	≥ 6 Months of Follow Up
	N = 226	N = 161
Confirmed Response Rate (95% CI)	30 (13.3%) (9.1, 18.4)	26 (16.1%) (10.8, 22.8)
Complete Response	9	9
Partial Response	21	17
Median Duration of Response (weeks) (range)	NR (6.1+, 75.4+)	NR (6.1+, 75.4+)

Data Cutoff: 6-9-16

The same indication statement is recommended for avelumab as for the other PD-1/PD-L1 inhibitors approved in this setting. However, few patients (N = 9) in the avelumab trial received only neoadjuvant or adjuvant platinum-based therapy prior to study entry. This may have had an effect on the response rate.

Avelumab will not be approved with a complementary diagnostic. A complementary diagnostic was been approved with both atezolizumab and durvalumab while nivolumab was approved with a postmarketing commitment to develop a complementary diagnostic. Among the 226 pts with ≥ 13 weeks of follow up, tumor samples were tested for PD-L1 staining with an initial research use only assay in 44 pts and with a good manufacturing use assay in 182 pts. Both assays used the same anti-PD-L1 antibody. In the initial 44 patients in the secondary expansion cohort, 5/13 (38%) pts with PD-L1 high and 1/24 (4%) pts with PD-L1 low/negative

tumor staining responded to avelumab. In the 182 pts in the efficacy expansion cohort, 10/68 (15%) pts with PD-L1 high, 12/87 (14%) pts with PD-L1 low/negative, and 2/27 (7%) pts with unevaluable tumor staining responded to avelumab. Note that these response rates are based on FDA review of response. In both groups of patients, N = 44 and N = 182, PD-L1 high was defined as $\geq$ 5% tumor cell staining. Although a statistical plan specifying a single cutoff for PD-L1 staining was not finalized, it seems, based on the pathologist's case report forms, that the 5% cutoff was specified prior to the analysis of the efficacy cohort. The response rates in patients with high and low/negative PD-L1 tumor staining in the efficacy cohort were similar. Based on the lack of difference in the response rate by PD-L1 status in this cohort, the Applicant chose not to submit an application for a complementary diagnostic. Note that a substantial number of patients were unevaluable (34/226, 15%) in this assessment of response rate and PD-L1 status.

The Applicant submitted a preliminary request for breakthrough designation in December 2015 based on the 44 patients with PD-L1 high tumor staining in the secondary expansion cohort discussed above. The Applicant was asked to provide data on additional patients prior to breakthrough determination. This data was provided in June 2016. At that time, the Applicant asked whether this data would support a BLA and was asked to request a pre-BLA meeting.

The safety profile of avelumab is similar to other PD-1/L1 inhibitors. However, the incidence of infusion-related reactions is higher than other PD-1/L1 inhibitors. Despite pre-medication with an anti-histamine and acetaminophen with each infusion, the incidence of infusion-related reactions in the urothelial cohort was 31%, 0.4% grade 3-4. In the safety database, the incidence of infusion-related reactions was 25%, with 14% occurring after completion of the infusion. The most common ($\geq$ 20%) all grade adverse events were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection. The table below provides a summary of the safety profile of avelumab.

Table 2: Safety Summary

	Prior Platinum-based Therapy N = 242 (%)
Deaths due to an Adverse event	14 (6)
Permanent Treatment Discontinuation	30 (12)
Serious Adverse Events	100 (41)
Grade 3-4 Adverse Events	143 (59)
Immune-related Adverse Events Requiring High-dose Steroids[1]	11 (5)

[1]High-dose is defined as the equivalent of > 40 mg prednisone/d Data Cutoff: 6-9-16

The incidence of these categories of events is higher or similar to those reported with atezolizumab and lower or similar to those reported with nivolumab. Again, the distinguishing feature is the incidence of, primarily grade 1-2, infusion-related reactions. In examining the relationship between exposure and safety, a weak relationship was found between the incidence of immune-related adverse events and increased exposure to avelumab.

Two formulations of avelumab were used during the trial. The formulations were considered comparable by the chemistry, manufacturing and control reviewers and the examination of safety and efficacy based on formulation by the clinical pharmacology group showed no differences.

In conclusion, the safety and efficacy of avelumab is similar to that of other products in this class that have been approved for the treatment of patients with locally advanced or metastatic urothelial cancer 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.

- Accelerated approval of avelumab is recommended by all disciplines.

The Applicant will be asked to conduct a confirmatory trial to determine the clinical benefit of avelumab. A randomized trial of avelumab compared to placebo in patients with urothelial cancer who have stable disease or better on conventional chemotherapy is ongoing. The primary endpoint is overall survival.

Patients with locally advanced or metastatic urothelial cancer have a poor prognosis despite the high response rate seen with standard platinum/gemcitabine chemotherapy. Second-line taxane-based chemotherapy has a low response rate and patients have a short overall survival. Further, conventional cytotoxic chemotherapy is associated with an unfavorable adverse event profile. Recently, PD-1/L1 inhibitors have received accelerated approval for the treatment of patients with urothelial cancer who have received prior platinum-based therapy. Response rates with these agents have been modest, but the duration of response has been substantial.

Avelumab is a PD-L1 inhibitor that is seeking accelerated approved based on a single-arm study which assessed independently-determined confirmed response rate and safety in a group of patients with locally advanced or metastatic urothelial cancer who received prior platinum-based therapy. The study is ongoing and efficacy analyses have been conducted on 2 groups of patients; those followed for at least 13 weeks (N = 226) and for at least 6 months (N = 161). The response rate in patients followed for at least 13 weeks was 13.3%. This increased to 16.1% in patients who had been followed for at least 6 months. The median duration of response was not reached in either group, but patients had ongoing response at 6.1 to 75.4 weeks.

A complementary diagnostic will not be approved with avelumab. Based on the response rates in the patients with high and low PD-L1 tumor staining in a cohort of 182 patients, 15% and 14%, respectively, the Applicant or their partner chose not to submit an application for a complementary diagnostic.

The safety profile of avelumab is similar to other PD-1/L1 inhibitors. However, the incidence of infusion-related reactions with avelumab is higher than with other agents. Despite pre-medication with acetaminophen and an anti-histamine, the incidence of infusion-related reactions in the urothelial cancer cohort was 31%, 0.4% grade 3-4. Deaths due to an adverse event occurred in 6% of patients while permanent treatment discontinuation occurred in 12%. Grade 3-4 adverse events occurred in 59% of patients and the most common ($\geq$ 20%) all grade adverse events were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection. Five percent (5%) of patients required high-dose steroids for treatment of an immune-mediated adverse event.

In conclusion, the safety and efficacy of avelumab is similar to that of other products in this class that have been approved for the treatment of patients with locally advanced or metastatic urothelial cancer 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. Accelerated approval of avelumab is recommended. The Applicant will be asked to conduct a confirmatory trial to determine the clinical benefit of avelumab.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Patients with locally advanced or metastatic urothelial cancer have a poor prognosis despite the high response rate seen with standard platinum/gemcitabine chemotherapy. Second-line taxane-based chemotherapy has a low response rate and an unfavorable adverse event profile.	Patients with locally advanced or metastatic urothelial cancer who have received prior platinum-based therapy have a serious and life-threatening condition.
Current Treatment Options	Treatment options include taxane-based (single agent or combination therapy) and PD-1/L1 inhibitors. Recently, atezolizumab, nivolumab, and durvalumab have received accelerated approval for the treatment of patients with urothelial cancer who have received prior platinum-based therapy.	Taxanes and PD-1/L1 inhibitors have shown activity in patients with locally advanced or metastatic urothelial cancer who have received prior platinum-based therapy. Avelumab in a PD-L1 inhibitor
Benefit	In a single-arm trial, the confirmed response rate by Independent Radiology Review for avelumab was 13.3% in patients followed for ≥ 13 Weeks and 16.1% in patients followed for ≥ 6 months. The median duration of response has not reached in either group, but patients had ongoing response at 6.1 to 75.4 weeks.	Avelumab has demonstrated a modest response rate with a substantial duration of response. This response rate is consistent with the response rates of previously approved PD-1/L1 inhibitors.
Risk	The incidence of infusion-related reactions is higher with avelumab than with other PD-1/L1 inhibitors. Despite pre-medication with acetaminophen and an anti-histamine, the incidence of infusion-related reactions in the urothelial cancer cohort was 31%, 0.4% grade 3-4. Deaths due to an adverse event occurred in 6% of patients while permanent treatment discontinuation occurred in 12%. Grade 3-4 adverse events occurred in 59% of patients and the most common (≥ 20%) all grade adverse events were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection. Five percent (5%) of patients required high-dose steroids for treatment of immune-mediated adverse events.	The safety profile of avelumab is similar to other PD-1/L1 inhibitors. However, the incidence of infusion-related reactions, mostly grade 1-2, is higher with avelumab.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	No REMS will be required. The package insert already contains a Warning concerning the risk of infusion-related reactions. The Applicant will be required to conduct a confirmatory study to definitively determine clinical benefit. The Applicant has agreed to conduct a study, in patients with non-small cell lung cancer, to optimize the dose of avelumab.	The risk-benefit profile of avelumab is acceptable. Risk can be mitigated by careful observation of patients during and after the infusion of avelumab as well as careful observation for the development of immune-mediated events.

Virginia E. Maher, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Urothelial carcinoma is the most common malignancy in the urinary tract system and accounts for approximately 16,000 deaths yearly in the USA[1,2]. Although most urothelial carcinomas are non-muscle invasive at diagnosis and can be managed effectively with surgical resection and/or intravesical therapies, approximately 10-15% of patients may develop invasive, locally advanced, and metastatic urothelial carcinoma[3]. In addition, approximately 10% of patients have regionally advanced or metastatic disease at diagnosis[1].

Standard of care for patients with advanced disease is/has been platinum-containing therapy, such as gemcitabine and cisplatin (GC) or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). However, almost all patients experience disease progression or intolerance to treatment during or after platinum-containing chemotherapy. Atezolizumab, an anti-PD-L1 antibody, was approved for the second-line treatment of bladder cancer on June 7, 2016 on the basis of increased response rate and duration of response compared to available therapy. Subsequently, nivolumab, an anti-PD-1 antibody, was approved for the same indication on February 2, 2017. However, as atezolizumab and nivolumab were approved under the Accelerated Approval pathway, they do not constitute available therapy with regards to the current application. There is no efficacious or standard second-line available therapy after disease progression (See Section 2.2). The reported median survival of patients after platinum containing therapy ranges from 5 to 10 months. Clearly, there is an unmet need for effective therapy to treat patients with this serious and life-threatening disease.

2.2. Analysis of Current Treatment Options

In the USA, atezolizumab and nivolumab are the only FDA-approved second-line therapies for locally advanced or metastatic urothelial carcinoma, although both are currently approved under the Accelerated Approval pathway as described above.

Outside the USA, vinflunine is approved as a second-line treatment in this setting. Table 3 summarizes key efficacy and safety information about vinflunine and other second-line chemotherapies studied or used off-label after platinum-containing chemotherapy. As shown in Table 3, these chemotherapeutics are associated with a low response rate but considerable toxicities. Except for vinflunine, response durations remain unknown or unreported. Nab-paclitaxel monotherapy was associated with a response rate of 28% and a longer survival time relatively to other agents. However, the results may not be reliable given the small sample size of a single-arm study. In addition, the heterogeneity of study patient populations is an issue among these studies, which may contribute to the varying response rates and survival times.

There is no standard of care in the second-line setting for treatment of (b) (4) advanced urothelial carcinoma. Aside from atezolizumab and nivolumab, preferred off-label treatments of advanced urothelial carcinoma after platinum-containing chemotherapy may include monotherapy with a taxane, gemcitabine, or pemetrexed. Given the modest activity of a taxane or other optional chemotherapeutics in the disease setting and the preliminary nature of the data for the activity of atezolizumab and nivolumab, participation in clinical trials is currently recommended in this setting[2].

Table 3: Activity and Safety of Second-Line Chemotherapeutics Studied in Advanced Urothelial Carcinoma

	Vinflunine +BSC[a]	Gemcitabine + Paclitaxel[b]	Docetaxel[c]	Nab-Paclitaxel[d]	Atezolizumab[e]	Nivolumab[f]
Trial Phase	III	III	II	II	II	II
Patient Population Regarding Prior Platinum Use Requirement	After first line platinum containing chemotherapy ; no time interval specified	During or after cisplatin based first line chemotherapy ; no time interval specified	After platinum containing chemotherapy ; no time interval specified	Progression on or within 12 months of treatment with one prior platinum containing regimen	Progression on prior platinum containing regimen; prior neoadjuvant/ adjuvant platinum ≤ 12 mos of recurrence	Progression on prior platinum containing regimen; prior neoadjuvant/ adjuvant platinum ≤ 12 mos of recurrence
# evaluable patients	N= 185	N = 40	N = 70	N = 47	N = 310	N = 270
Overall Response Rate N (%)	16 (9%)	15 (38%)	5 (11%)	13 (28%)	46 (15%)	53 (20%)
Response Duration (mos), median	7.4	NR	NR	NR	NR	10.3
Overall Survival*, median	6.9 months (vs 4.6 mos with BSC, HR 0.88 p=0.287)	7.8 months	7.0 months	10.8 months	7.9 months	8.6 months
Key Safety Issues (Grade 3 or 4 Toxicity)** (%)	Neutropenia (50%); Febrile neutropenia (6%); Anemia (19%); Fatigue (19%); Constipation	Anemia (7%)	Neutropenia (14%); Anemia (1%); Fatigue (6%); Infection (6%) Electrolyte abnormalities (6%)	Fatigue (10%); Weakness (8); Neuropathy (6%) Dyspnea (6%) Hypertensi	Urinary tract infection (9%); Fatigue (6%); Abdominal pain (4%); Dyspnea (4%); Hematuria (3%)	Fatigue (7%); Urinary tract infection (7%) Dyspnea (3.3%); Diarrhea (2.6%); Musculoskeletal pain

	Vinflunine +BSC[a]	Gemcitabine + Paclitaxel[b]	Docetaxel[c]	Nab-Paclitaxel[d]	Atezolizumab[e]	Nivolumab[f]
	(16%)			on (6%)		(2.6%)

NR: not reported;

**In the relevant treatment arm or study of the enrolled patients.*

*** As reported from each study, which may not represent the comprehensive safety profile of each treatment based on the approved product label.*

a) Bellmunt J. et al. (2009) J Clin Oncol 27:4454-4461. An improvement in OS (not statistically significant) was seen. This trial led to the EMA approval of vinflunine for its use as a second-line treatment.
b) Albers P et al. (2011) Annals of Oncology 22: 288–294. Results from the short-treatment arm (6 cycles) are shown for its tolerability. The prolonged treatment arm was intolerable due to safety concerns and the results are not listed.
c) Choueiri TK et al (2011) J Clin Oncol 30:507-512. The results as shown were from the docetaxel + placebo arm alone.
d) Ko YJ et al (2013) Lancet Oncol 2013; 14: 769–76. The preliminary results from this trial were reported in an abstract in the 2010 GUASCO meeting. The ORR at that time was 33% in 40 study patients.
e) Per FDA review of BLA 761034
f) Per FDA review of BLA 125554, Supplement 24

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BLA 761049 was approved for the use of avelumab in pts with Merkel cell carcinoma on March 23, 2017. Given the short time interval between the prior approval for Merkel cell and the current review, a PSUR has not been generated.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Phase 1 study EMR100070-001, which was an open-label, dose-escalation study with expansion phase consisting of several disease-specific cohorts evaluating avelumab in locally advanced or metastatic solid tumors with no available curative options was initiated under IND 115,747 in November 2012. Two of these expansion cohorts were in urothelial carcinoma (UC).

(b) (4)

On December 23, 2015 the Sponsor (EMD Serono) submitted a Preliminary Breakthrough Therapy Designation (BTD) Advice Request describing preliminary results from one of the UC cohorts of study EMR100070-001, the secondary expansion cohort (N=44 UC subjects). The BTD was to be primarily based on the ORR in the 12 subjects with positive PD-L1 expression. Based on a primary PDL1 expression level cutoff, defined as ≥ 5% positive tumor cells with staining of any intensity, in 35 evaluable patients, the Applicant reported an ORR of 50.0% [6/12; 95% CI (21.1, 78.9)] in the PD-L1-positive population.

On January 27, 2016 the Sponsor had a BTD advice teleconference wherein the Agency requested that the Sponsor submit data from an additional 25 to 35 subjects with metastatic or locally advanced UC with positive PD-L1 expression. The Sponsor did not subsequently elect to submit a formal Breakthrough Therapy Designation Request.

On June 9, 2016, the FDA was provided with an update on the secondary expansion cohort of 44 subjects as well as data on the efficacy cohort of UC subjects according to a planned interim analysis (N=109 with 6 months of follow-up including 42 subjects with PD-L1+ tumors, and N=197 in the safety analysis set); the Sponsor was asked to submit a formal request for a pre-BLA meeting.

On November 17, 2016, a pre-BLA meeting was held between the Sponsor and the FDA to discuss format and content of a planned BLA submission for avelumab used in the treatment of patients with locally advanced or metastatic UC with disease progression on or during prior platinum-based chemotherapy. The Sponsor requested to cross-reference the following

sections of BLA 761049, for avelumab for the treatment of metastatic Merkel cell carcinoma, (originally submitted for review on July 2016):

1. The CMC sections (Modules 2.3 and 3), and
2. The nonclinical pharmacology and toxicology sections (Modules 2.4, 2.6, and Module 4), with the addition of UC-specific safety data within the exposure/safety analyses.

FDA preliminarily agreed to this approach. It was decided that the Applicant would provide efficacy data with a cutoff of June 9, 2016 on all 249 UC patients within 30 days of submission of the BLA. Safety data was to be provided with the initial BLA and with a data cutoff of June 9, 2016.

The Applicant chose not to submit a pre-marketing application based on similar response rates in patients with high and low/negative PD-L1 tumor staining in the efficacy expansion cohort (patients enrolled after the initial 44 patients).

On December 27, 2016, BLA 761078 for avelumab in urothelial carcinoma was submitted. Updated efficacy data with a data cutoff date of June 9, 2016 was submitted on January 23, 2017. The Safety Update was submitted on March 24, 2017 with a data cutoff of September 30, 2016 and contained additional safety information only on patients with urothelial carcinoma.

On March 23, 2017, the FDA issued an Accelerated Approval letter for BLA761049, for new molecular entity avelumab for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The data from Study EMR100070-001 were submitted to the Agency in support of BLA 761078. Three clinical sites, Dr. Hendrik-Tobias Arkenau (Site 805), Dr. Manish Patel (Site 141), and Dr. Julio Peguero (Site 171), were selected for audit. The study sponsor, EMD Serono, Inc., inspection was cancelled due to FDA field investigator resource constraints.

The primary efficacy endpoint, best overall response (BOR) per RECIST 1.1 as determined by an Independent Endpoint Review Committee (IERC), was corroborated with the source records generated at the inspected clinical sites. There were no significant inspectional findings for clinical investigators Dr. Hendrik-Tobias Arkenau, Dr. Manish Patel, and Dr. Julio Peguero. The data from Study EMR100070-001 submitted to the Agency in support of BLA 761078, appear reliable based on available information.

Please see the Office of Scientific Investigations' Clinical Inspection Summary for full details.

4.2. Product Quality

No significant issues were identified regarding the CMC part of the application.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

No companion or complementary diagnostic assays or devices were submitted to CDRH for review in conjunction with this BLA submission to CDER. See section 7.2.2 for a complete discussion on exploratory use of PD-L1 staining in this application, including the use of both the Dako 73-10 PD-L1 IHC Research Use Only kit initially used to assess PD-L1 staining as well as the Dako 73-10 PD-L1 IHC Good Manufacturing Practice kit used for re-testing specimens.

Table 16 presents the efficacy results in various PD-L1 subgroups; ultimately the Applicant decided not to submit a device application based on these data.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Avelumab is an IgG1 monoclonal antibody directed against programed death ligand 1 (PD-L1). Interactions between programmed death receptor-1 (PD-1), expressed primarily on activated T cells, and its ligands, PD-L1 and PD-L2, result in inhibition of T cell activity. PD-L1 is upregulated on the surface of many tumor cells and is postulated to be a means of evasion from the immune response. Blocking the interaction between PD-L1 and its receptors, PD-1 and B7.1, can release the inhibitory effects of this pathway on the immune response, including the restoration of anti-tumor immune responses. In vitro studies have confirmed the ability of avelumab to inhibit the interaction between PD-L1 and PD-1. Additionally, unlike other similar IgG1 monoclonal antibodies directed against PD-L1, avelumab was engineered with an intact Fc region. This enables avelumab to mediate antibody-dependent cell-mediated cytotoxicity (ADCC).

For full details of the non-clinical pharmacology and toxicology studies done in support of avelumab, please refer to the relevant potions of the review of BLA 761049.

5.2. Referenced NDAs, BLAs, DMFs

BLA 761049; avelumab 10 mg/kg given as an intravenous infusion every 2 weeks (Q2W) for the treatment of patients with metastatic Merkel cell carcinoma, was cross-referenced in this BLA.

5.3. Pharmacology

Not applicable for this BLA.

5.4. ADME/PK

Not applicable for this BLA.

5.5. Toxicology

Not applicable for this BLA.

Wei Chen, PhD
Primary Reviewer

Todd Palmby, PhD
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Clinical Pharmacology section of BLA 761078 is supported by population pharmacokinetics (popPK) analysis, exposure-response (E-R) analysis, immunogenicity assessment, and assessment of the QT/QTc prolongation potential. The content regarding popPK analysis, immunogenicity, and assessment of the QT/QTc prolongation potential cross-referenced corresponding evaluations under BLA 761049.

E-R analysis was conducted with efficacy data from patients with locally advanced or metastatic UC in EMR100070-001 (Study 001) at 10 mg/kg Q2W dose level. Positive E-R relationships were observed between avelumab steady state exposure metrics and best objective response (BOR), progression-free survival (PFS), and overall survival (OS). Given the short elimination half-life of avelumab relative to the proposed dosing interval, the low trough concentration at steady state, and the observed exposure-efficacy relationship, it is possible that a higher dose or more frequent dosing of avelumab may be more efficacious. E-R analysis with safety data from 1712 subjects from Studies 001, 002, and 003 at doses of 1 mg/kg to 20 mg/kg Q2W suggested no substantial E-R relationships between avelumab exposure metrics and safety endpoints.

The proposed dosing regimen is acceptable for the accelerated approval from a Clinical Pharmacology perspective. However, a Post-Marketing Commitment is recommended to obtain efficacy and safety data and to evaluate avelumab E-R relationships with a wider exposure range in patients with non-small-cell lung cancer (NSCLC) (Study EMR100070-005). Depending on results of the PMC analyses, a clinical trial may be necessary to optimize the dose for efficacy in patients with UC.

6.1.1. Recommendations

The Office of Clinical Pharmacology recommends the approval of BLA 761049 from a Clinical Pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Sufficiently Supported?	Recommendations and Comments
Dose Selection	☐ Yes ☒ No	The proposed dose of 10 mg/kg administered as an IV infusion over 60 minutes every 2 weeks is acceptable for the accelerated approval based on clinical efficacy and safety demonstrated in two UC expansion cohorts in Study 001. However, this dose may not be optimal considering the short half-life relative to the dosing interval, low steady state exposure, positive E-R relationship for efficacy, a lack of substantial E-R relationship for safety, as well as the fact that MTD was not reached at the 20 mg/kg dose level in the dose escalation phase of Study 001. Therefore, a PMC is recommended to obtain efficacy and safety data and to conduct E-R analysis in patients with higher avelumab

		exposure (Study EMR100070-005). See Section 6.1.2 for more information.
Dosing in patient subgroups (intrinsic and extrinsic factors)	☒ **Yes** ☐ **No**	Dose modifications are not recommended based on intrinsic and extrinsic factors. Refer to Section 6 of the Multidisciplinary Review of BLA 761049.
Bridge between the to-be-marketed and clinical trial formulations	☒ **Yes** ☐ **No**	Two formulations, including the to-be-marketed formulation, were used in the 3 clinical trials. PopPK analysis suggests that the formulation process does not have a significant effect on avelumab exposure in the studied population. Refer to Section 6 of the Multidisciplinary Review of BLA 761049.
Labeling	☒ **Yes** ☐ **No**	Acceptable.

6.1.2. Post-Marketing Requirement (PMR) and Commitment (PMC)

The proposed dose of avelumab (10 mg/kg IV Q2W) may not be optimized for efficacy and a higher dose or more frequent dosing may lead to improved efficacy. (b) (4) Study EMR100070-005 (Study 005), a Phase 3 study in the first-line non-small cell lung cancer (NSCLC) (b) (4)

Therefore, a PMC is recommended to obtain efficacy and safety data from Study 005 and to conduct exposure-response analyses for efficacy and safety based on data from Study 005. Depending on results of these analyses, a clinical trial may be necessary to evaluate a higher dose or more frequent dosing in patients with UC.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacology and Clinical Pharmacokinetics characteristics of avelumab are summarized in Section 6.2.1 of the Multidisciplinary Review of BLA 761049. In brief, popPK analysis suggests a geometric mean (%CV) volume of distribution at steady state (V_{SS}), total clearance (CL), and elimination half-life ($t_{1/2}$) of 4.72 L (44.5%), 0.0267 L/h (29.9%), and 6.1 days (91.5%), respectively, in patients taking the 10 mg/kg Q2W dose.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant proposes a dosing regimen of 10 mg/kg administered as an IV infusion over 60 minutes once every two weeks. The two UC expansion cohorts in Study 001 evaluated the efficacy and safety of avelumab at this dosing regimen in 242 patients with locally advanced or metastatic UC with disease progression during or after platinum-based therapy. The proposed dose is acceptable from a clinical pharmacology perspective.

Therapeutic Individualization

Therapeutic individualization is not recommended based on intrinsic and extrinsic factors (refer to Section 6 of the Multidisciplinary Review of BLA 761049).

Outstanding Issues

The proposed dosing regimen may not be optimal. A PMC was issued to evaluate the efficacy, safety, and E-R relationships of BAVENCIO at a higher exposure in patients with NSCLC. Depending on results of the PMC analyses, a clinical trial may be necessary to evaluate the efficacy and safety at higher dose or more frequent dosing in patients with UC.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General Pharmacology and Clinical Pharmacokinetics Characteristics of avelumab are summarized in Section 6.3.1 of the Multidisciplinary Review of BLA 761049. BLA 761078 does not include new pharmacology or PK data as compared to BLA 761049.

6.3.2. Clinical Pharmacology Questions

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

Yes, the proposed dosing regimen is acceptable for the general patient population for which the indication is being sought. However, the proposed dosing regimen may not be optimal considering the short half-life relative to the dosing interval, low steady state exposure, a positive E-R relationship for efficacy, a lack of a substantial E-R relationship for safety, as well as the fact that the MTD was not reached at the 20 mg/kg dose level in the dose escalation phase of Study 001.

Dose Selection

The proposed avelumab dosing regimen was used in the two UC expansion cohorts in Study 001. This dose was selected based on safety and tolerability outcome in the dose escalation

phase of Study 001 where MTD was not reached at the 20 mg/kg Q2W dose level. In addition, ex vivo PD-L1 target occupancy (TO) was measured in peripheral blood mononuclear cells (PBMCs) by flow cytometry on serum samples from subjects who participated in the dose escalation phase of Study 001. TO in PBMC appears to be saturated at dose levels above 3 mg/kg and a mean TO of greater than 90% was reached at the 10 mg/kg Q2W dose level throughout the dosing interval. Even though the selection of the 10 mg/kg Q2W dose for use in Study 001 expansion cohorts appears reasonable, it is unknown whether 20 mg/kg Q2W dose will have improved efficacy in the proposed patient population.

Exposure-Efficacy Analysis

Clinical efficacy data was obtained from the two UC expansion cohorts in Study 001 in 242 patients with UC whose disease progressed on or after platinum-based therapy. By Data Cut-off date of June 9, 2016, the ORR was 13.3% (95% CI: 9.1% – 18.4%) in patients with at least 13-week follow-up and 16.1% (95% CI: 10.8% – 22.8%) in patients with at least 6 month follow-up.

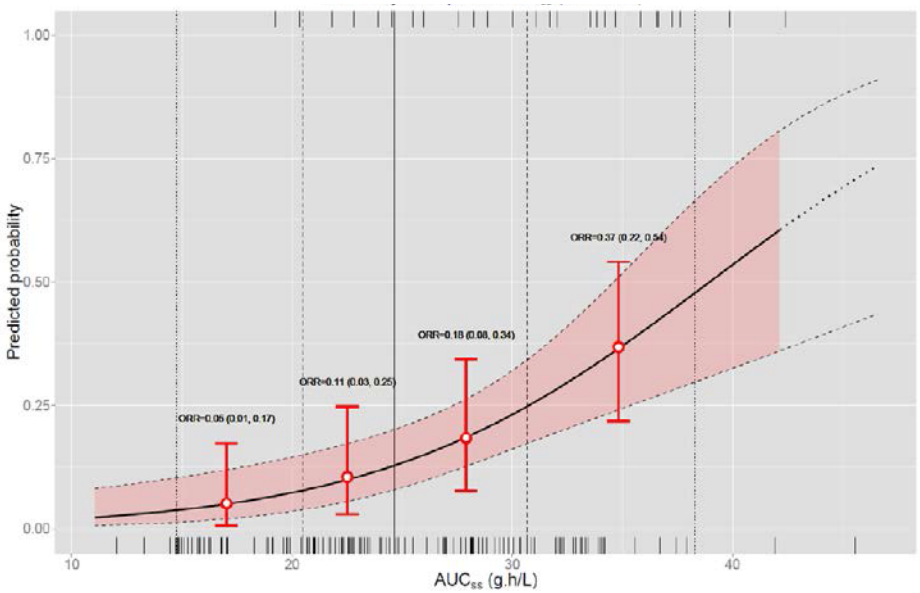
Applicant's E-R analysis for efficacy was conducted with data from 153 patients with UC and with at least 6 month follow-up as of March 19, 2016. E-R relationships were observed between BOR and avelumab exposure metrics including predicted AUC_{ss}, predicted $C_{trough,first}$, and predicted $C_{trough,ss}$ using univariate analysis (Table 4, Figure 1). According to multivariate analysis, avelumab exposure was positively associated with response when adjusting for a number of prognostic covariates (Table 5). The linear assumption between exposure and logit appears appropriate within the current exposure range.

Table 4. Univariate Logistic Regression on Exposure Metrics

Exposure metric	single dose C_{trough} ($C_{trough,first}$, µg/mL)	steady-state C_{trough} ($C_{trough,ss}$, µg/mL)	steady- state AUC (AUC_{ss}, g·h/L)
P value	0.0003	0.0012	0.0001
Odds ratio (95% CI)	1.094 (1.0437– 1.1523)	1.0473 (1.0194– 1.0786)	1.1433 (1.0709 - 1.2304)
AIC	131.9	135.2	129.3
ROC_{AUC}	0.904	0.893	0.917

[Source: Adapted from BLA 761078/SDN 1, M&S Exposure-Efficacy Analysis Report, Table 8]

Figure 1. Observed Objective Response Rate and Predicted Probability of Being a Responder versus AUC at Steady State (AUCss)



[Source: BLA 761078/SDN 1, M&S Exposure-Efficacy Analysis Report, Figure 5]

Table 5. Parameter Estimates for Final Model of Multivariable Analysis of BOR

Variable	Coefficient	Odds ratio	95% CI for Odds ratio
(Intercept)	-6.4890	0.0015	(0.0000 – 0.3446)
AUCss (g·h/L) *	0.1833	1.2010	(1.0890 – 1.3420)
TS_BL (mm)	-0.0139	0.9862	(0.9657 – 1.0030)
PD-L1 ≥ 1% *	1.8850	6.5830	(1.9960 – 25.3600)
RACE = non white *	-3.4570	0.0315	(0.0010 – 0.4057)
BLWEIGHT (kg)	-0.0321	0.9684	(0.9327 – 1.0020)
HGB (g/L) *	0.0462	1.0470	(1.0060 – 1.0960)
ALT (IU/L) *	-0.0691	0.9332	(0.8608 – 0.9952)
VMET = present	-1.0560	0.3478	(0.0809 – 1.4320)
PARTRACT = upper	-1.5150	0.2199	(0.0270 – 1.1550)
NACT > 1	-1.0890	0.3367	(0.0927 – 1.1420)

* Covariates with * indicate that 95% CI of the associated Odds ratio excludes 1.
TS_BL: tumor burden at baseline (mm); BLWEIGHT: body weight at baseline; NACT: number of prior anti-cancer drug therapies; VMET: visceral metastasis status; PARTRACT: tumor sub-site, upper or lower

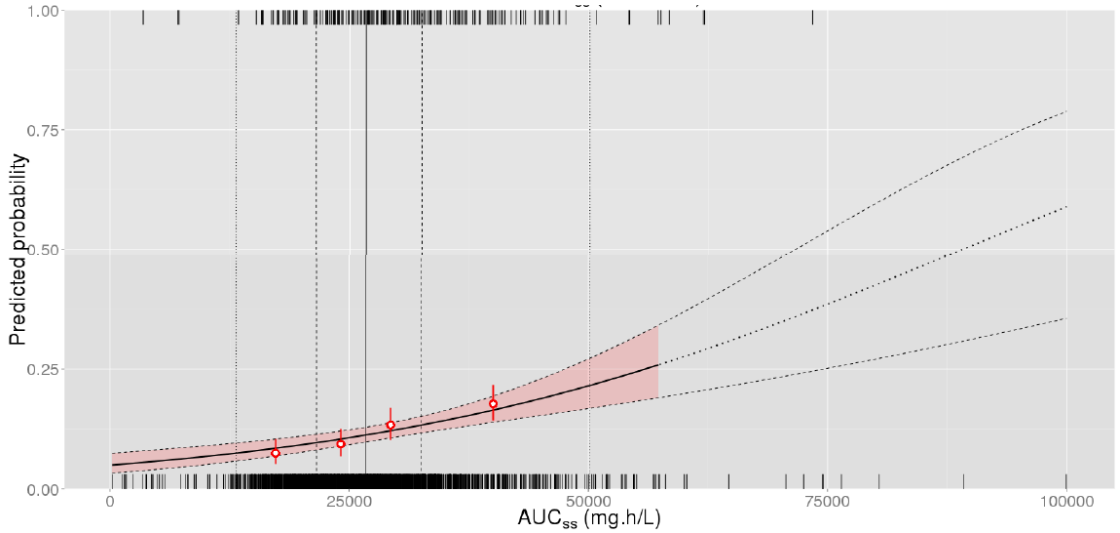
[Source: BLA 761078/SDN 1, M&S Exposure-Efficacy Analysis Report, Table 10]

Survival analysis for PFS and OS indicated, for all examined exposure metrics, that a higher exposure was associated with a lower hazard in univariate models as well as when adjusting for potential prognostic factors in the multivariable Cox regression models (Appendix 13.4.2).
In addition, an E-R analysis was conducted by the FDA reviewer in 226 patients with ≥13 weeks of follow-up or in 161 patients with ≥6 months of follow-up as of Data Cut-off date June 9, 2016 (Appendix 13.4.3). Positive E-R relationships were also observed in these populations where higher avelumab exposure metrics are generally associated with better efficacy in terms of BOR, PFS, and OS.

Exposure-Safety Analysis

E-R analysis for safety was performed on the pooled data from Studies 001, 002, and 003 in a total of 1712 subjects. The adverse event (AE) categories analyzed in the E-R safety analysis included immune-related (irAE), infusion-related reactions (IRR), and treatment-emergent AE (TEAE). Avelumab exposure metrics were generally weak predictors of AEs. For example, univariate logistic regression analysis suggested a 3.4% increase in the odds of irAE (grade ≥1) for every unit increase (1 mg/mL·h) in AUC_{ss} (Figure 2), however, the model's ability to discriminate between subjects having at least one irAE versus having no irAE was assessed as poor by the receiver operating characteristic (ROC). Avelumab exposure was not associated with an increased incidence of IRR or TEAEs of any grade. For multivariate models, only the incidence of irAEs was associated with increasing avelumab exposures, and relatively weakly.

Figure 2. Relationship between Probability of irAE (grade ≥1) and AUC_{ss}



[Source: BLA 761078/SDN 1, M&S Exposure-Safety Analysis Report, Figure 51]

Conclusion

From the clinical pharmacology standpoint, the proposed dosing regimen is acceptable for the general patient population for which the indication is being sought. However, the proposed dosing regimen may not be optimal.

Avelumab has a short elimination half-life (6.1 days) relative to the once every 2 weeks dosing interval, resulting in low accumulation ratio (1.25) and low steady state exposure (the average observed trough concentration at steady state is 25.9 ug/mL in the exposure-efficacy analysis dataset). In contrast, atezolizumab, the other FDA approved anti-PD-L1 mAb for treating patients with UC, shows an accumulation ratio of above 2 on Cmin and a steady state trough concentration approximately 125 ug/mL at the therapeutic dose level.[1] E-R analyses for efficacy suggest positive relationships between avelumab exposure and efficacy endpoints after

[1] Clinical Pharmacology and Biopharmaceutics Reviews of BLA 761034, Table 3 and Table 5: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761034Orig1s000ClinPharmR.pdf

accounting for a number of prognostic factors. The linear assumptions between exposure and response for the E-R analyses appear appropriate within the current exposure range. Even though the E-R analysis for efficacy is often limited for a single arm monoclonal antibody trial in patients with cancer due to potential interaction between response status and late-exposure metrics, such an interaction was not significant in patients with UC based on popPK analysis (Appendix 13.4.4). Overall, it is possible that a higher exposure of avelumab due to higher dose or more frequent dosing may be more efficacious.

Given that MTD was not reached at the 20 mg/kg Q2W dose level in the dose escalation phase of Study 001 and that there is no strong correlation between avelumab exposure and AEs of special interests (i.e. IRR and irAE), a higher dose of avelumab is likely tolerable at the 20 mg/kg Q2W dose level or 10 mg/kg QW level. A PMC is recommended to evaluate the efficacy, safety, and E-R relationships of BAVENCIO based on data from an ongoing trial in patients with NSCLC (Study EMR 100070-005). Depending on the results of these analyses, a clinical trial may be necessary to evaluate the efficacy and safety of BAVENCIO at a higher dose or with more frequent dosing in patients with UC.

Nan Zheng, PhD
Primary Reviewer

Pengfei Song, PhD
Team Leader

7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

The primary evidence to support the efficacy and safety reviews of this application is derived from the data from study EMR 100070-001.

Table 6: Table of Clinical Studies

Trial Identity	Trial Design	Regimen/ Schedule/ route	Study Endpoints	No. of patients treated	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety						

Trial Identity	Trial Design	Regimen/ Schedule/ route	Study Endpoints	No. of patients treated	Study Population	No. of Centers and Countries
EMR 100070-001, Urothelial Cohorts	Single arm, Efficacy study	Avelumab 10mg/kg IV every two weeks	Confirmed BOR, per RECIST 1.1, as adjudicated by an IERC.	N = 242[a] Including: Secondary expansion cohort (N = 44) Efficacy expansion cohort (N = 205)	Patients with metastatic or unresectable urothelial cancer who have progressed or recurred following treatment with a platinum agent	89 sites across 8 countries
Additional Studies Referenced to Support Safety						
EMR100070-001, All Cohorts	Open-label, dose-escalation with expansion phase consisting of several disease-specific cohorts	Dose-escalation: Avelumab 1, 3, 10 or 20 mg/kg IV every two weeks[b] Expansion: 10 mg/kg IV every two weeks	-Safety -PK -Determine MTD -BOR according to RECIST 1.1	N= 1650 Patients treated at a dose of 10 mg/kg every 2 weeks[b]	Patients with metastatic or locally advanced solid tumors with no available curative therapy. Expansion cohorts include ovarian cancer, urothelial carcinoma, gastric and gastroesophageal junction [GEJ] cancer, head and neck squamous cell carcinoma [HNSCC]	134 sites across 11 countries
EMR100070-003 (Part A)	Single arm, open label, multicenter study to assess efficacy, safety and PK	Avelumab 10 mg/kg IV every two weeks	-Confirmed BOR by central review according to -RECIST 1.1 -DOR -PFS -OS -6 month DRR	N= 88	Patients with metastatic MCC with progressive disease following at least one line of prior chemotherapy	38 sites across 8 countries

[a]As of Data Cut-off date June 9, 2016. An additional 7 patients were treated in the first-line locally advanced or metastatic setting who were platinum-ineligible.
[b]An additional 38 patients were treated at doses other than 10 mg/kg every 2 weeks; these patients were excluded from safety analyses.

7.1.1. Review Strategy

Data Sources

The clinical review included the following:

1. Review of the current literature on urothelial carcinoma epidemiology, and treatment, including other immune-mediated therapies
2. Review of Applicant submitted Trial EMR 100070-001 including CSR, protocols, protocol amendments and selected datasets
3. Review and assessment of Applicant analysis of avelumab efficacy and safety, for evaluation of Applicant's claims
4. Review of datasets and SAS programming algorithm submitted by the Sponsor
5. Use of the datasets to determine the baseline patient characteristics, response rate, and adverse event profile
6. Review of patient narratives of serious adverse events, deaths, and immune-mediated AEs
7. Review of meeting minutes conducted during drug development
8. Assessment of the Module 2 summaries including the Summary of Clinical Safety
9. Evaluation of reviews conducted by other FDA disciplines
10. Review of consultation reports from the Office of Scientific Investigations
11. Requests for additional information from the Applicant and review of Applicant responses
12. Formulation of the benefit-risk analysis and recommendations
13. Review and evaluation of proposed labeling

Data and Analysis Quality

Data quality and integrity for this study were acceptable. Case report forms (CRFs) for patients who died were reviewed and compared to the datasets and the patient narratives. Information was found to be consistent.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. EMR10070-001

Trial Design and Endpoints

This sBLA contains data from study EMR 100070-001, entitled "A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumors and expansion to selected indications".

EMR 100070-001 included a dose escalation phase followed by expansion cohorts in patients with a variety of solid tumors. Patients with metastatic or unresectable urothelial cancer were

included in a secondary expansion cohort (N = 44) and an efficacy expansion cohort (N = 205). The data cutoff for this submission was March 19, 2016. As agreed upon between the FDA and the Applicant, an efficacy update was submitted within 30 days of the initial submission with a data cutoff of June 9, 2016. The 90-day safety update was submitted on March 24, 2017 with a data cutoff of September 30, 2017.

Eligibility Criteria:

1. Locally advanced or metastatic transitional cell carcinoma of the urothelium
2. Prior Therapy
    a. Amendment 7: Progressive disease on first line platinum-based chemotherapy; Patients may have received any number of prior regimens
    b. Amendment 8:
        i. Ineligible for cisplatin-based chemotherapy due to impaired renal function, hearing loss, or $\geq$ grade 2 peripheral neuropathy
        ii. Progressed after treatment with at least 1 platinum-containing regimen for locally advanced or metastatic UC or disease recurrence
        iii. Patients may have received any number of prior regimens.
3. Measurable disease
4. Available tumor sample
5. ECOG performance status 0 or 1
6. Laboratories
    a. WBC $\geq$ 3 x 10^9/L, ANC $\geq$ 1.5 x 10^9/L, Lymphocytes $\geq$ 0.5 x 10^9/L , Platelets $\geq$ 100 x 10^9/L, Hemoglobin $\geq$ 9 g/dL
    b. Bilirubin $\leq$ 1.5xULN, AST/ALT $\leq$ 2.5xULN, Creatinine clearance > 30 mL/min
7. Effective contraception from 30 days prior to the first dose until 60 days after the last dose of study drug; A negative pregnancy test was required for women of childbearing potential
8. Inhaled or topical steroids were permitted. Patients with adrenal insufficiency on physiologic replacement doses of steroids could enter the study.
9. Patients with autoimmune disease, other than Type 1 diabetes, vitiligo, psoriasis, or thyroid disease, were excluded from study entry. Patients on immunosuppressive regimens or with immunodeficiency were excluded from study entry.
10. Patients with a cerebrovascular accident or myocardial infarction < 6 months prior to study entry were excluded. Patients with unstable angina, NYHA Class II-IV heart failure, or serious cardiac arrhythmias were excluded.

Treatment:
Avelumab 10 mg/kg IV over 1 hour every two weeks until progression or unacceptable toxicity

- Amendment 7: Pre-medication with an anti-histamine and acetaminophen was required

Dose Modification criteria were provided for immune-related adverse events and are consistent with the current package insert.

Study Monitoring:

- Routine Laboratories:
  - CBC, INR, PTT, electrolytes (including Mg, P, Ca), and liver function tests at baseline, every 2 weeks, then 28 days and 10 weeks after the last dose
  - Additional electrolytes (including Mg, P, Ca) and liver function tests at Weeks 2, 4, and 6 in patients with liver metastases
  - Amylase, lipase, creatine kinase, GGT, cholesterol, triglycerides, CRP, LDH, uric acid, and albumin/total protein at baseline, Weeks 7 and 13, every 6 weeks, then 28 days and 10 weeks after the last dose
  - Urinalysis at baseline and end of study; urine protein every 2 weeks
- Additional Laboratories:
  - Hepatitis B and C and HIV testing at baseline
  - Beta-HCG at baseline then every 4 weeks
  - TSH and free T4 at baseline, Week 13, Week 25, and 28 days and 10 weeks after the last dose
  - Anti-drug antibodies at baseline, every 2 weeks until Week 13, then every 6 weeks until Week 25, then at 28 days after the last dose.
- EKG: Baseline, every 2 weeks until Week 13, then every 6 weeks; EKGs were done prior to infusion and 2 hours after infusion
- Adverse Events:
  - Baseline, with each dose, and 28 days after the last dose of study drug
  - Adverse events were not collected during visits (visits only for patients with liver metastases) at Weeks 2, 4, or 6.
  - AEs thought to be related to study drug were collected at 10 weeks after the last dose
  - SAEs thought to be related to study drug were collected during the every 3 month survival follow up

Tumor imaging was obtained at baseline, every 6 weeks for 12 months, then every 12 weeks. A head CT was only obtained at baseline if clinically indicated. A bone scan was obtained at baseline. Patients with bone metastases were to have follow up scans.

Radiology Charter

(b) (4) provided the radiology review. The radiology charter is atypical of those used in other central radiology reviews. A single radiologist selected target and non-target lesions, provided tumor measurements/assessments, and determined response. In selecting the target lesions, the radiologist is not provided with information concerning prior sites of surgery or radiotherapy. Two oncologists then reviewed the radiologist's findings and information from the patient's CRF and determined the response. Information from the CRFs was not limited to prior sites of surgery or radiotherapy, but also included the date of clinical progression.

Several aspects of the criteria used to determine response were also atypical. The charter stated that clinical data that is trending in the opposite direction of the radiological data could be used to change the response, but that subjective clinical assessments could not be used to change the response. The example provided was an enlarged node that had been biopsied and found to be benign. As in other radiology charters, new lesions must be unequivocal. Patients with regions that are not imaged at baseline and found, when scanned, to contain disease will be considered to have PD. However, the charter also stated that if a convincing argument can be made that the new lesions were "most likely present," the patient will not be considered to have PD. The charter also provided criteria for lesions that become "entirely necrotic." These patients could be considered to have a complete response while the mass (presumably necrotic) was present.

Statistical Analysis Plan

The primary endpoint in the efficacy expansion cohort was the confirmed best overall response (BOR) by RECIST 1.1 as assessed by Independent Endpoint Review Committee (IERC), defined as the best response obtained among all tumor assessment visits after the start of study treatment until documented disease progression, taking into account the requirement for confirmation. For subjects enrolled in the secondary expansion cohort, this was a secondary endpoint. The confirmed objective response rate (ORR) is the proportion of subjects with a confirmed BOR of CR or PR.

Per the Applicant, the planned primary analysis populations included subjects with PD-L1+ tumors, followed by all treated subjects (all-comers). Subjects from both cohorts were pooled since, according to the Applicant, they were considered sufficiently homogenous in terms of the study population and their efficacy outcomes, regardless of PD-L1 expression.

Reviewer's Comment: The primary analysis presented is a pooled analysis of confirmed ORR by RECIST 1.1 as assessed by IERC in both cohorts.

Secondary endpoints also included the following assessed by IERC:

- Duration of Response (DOR): DOR was measured from the time measurement criteria were first met for CR or PR until the first date of PD was objectively documented or death within 84 days following the last tumor assessment. Subjects who had a response and had neither documented PD nor death within 84 days after the last tumor assessment, were censored at the date of last evaluable tumor assessment.
- Progression-free Survival (PFS) was defined as the time from the first administration of study treatment until the date of first documentation of PD or death from any cause (whichever occurred first), when death occurred within 84 days of last tumor assessment or first administration of study treatment (whichever was later)
- Overall Survival (OS) was defined as the time from first dose to death due to any cause. OS was censored at the date of last contact for subjects still alive at time of data analysis or those lost to follow-up.

Investigator-assessed BOR/irBOR, DOR, PFS/irPFS, and time to response by either modified irRC or RECIST 1.1 were all secondary endpoints.

Reviewer's Comment: Note that time-to-event endpoints are not interpretable in single-arm studies.

Calculations of the sample size assumed an ORR of 27% in subjects with PD-L1 high tumors. This sample size of 50-60 patients was expected to provide at least 90% power to reject the null hypothesis of ORR≤10% at a one-sided 0.025 significance level. .

The Applicant planned an interim analysis after the 109th treated subject from the efficacy expansion cohort reached 6 months of follow-up, and these results were included in the initial submission for 153 subjects with at least 6 months of follow-up data based on a March 19, 2016 data cutoff date. At the pre-BLA meeting in October 2016, it was agreed that the Applicant would submit an efficacy update with data from all 249 subjects based on a later cutoff date of June 9, 2016.

For the primary endpoint of confirmed BOR according to RECIST 1.1 as adjudicated by IERC, the number and proportion of BOR were tabulated and confirmed ORR was calculated. The null hypothesis of an ORR≤10% was tested using an exact binomial test in the PD-L1-positive full analysis set (FAS) and the total FAS at a level of 0.025 one-sided. The Applicant stated that results of the analyses would be considered positive if the lower limit of the 95% CI of the confirmed BOR constructed using the Clopper-Pearson method exceeded 10%.

Reviewer Comment: In a single arm trial, FDA does not use inferential procedures to evaluate trial results. Instead the efficacy evaluation is based on the magnitude of response rate and adequate duration of response.

The study report presented the confirmed ORR with corresponding two-sided 95% Clopper-Pearson confidence intervals. For the secondary time to event endpoints, including duration of response, PFS, and OS, Kaplan-Meier estimates and corresponding confidence intervals were presented. All the secondary endpoint analyses and hypotheses testing were considered exploratory.

Safety Monitoring Committee

The Applicant, (b) (4), and external experts were members of the Safety Monitoring Committee. The committee met once to determine dose-limiting toxicity and met again after a given number of patients had been enrolled and treated for 4 weeks on the expansion cohorts.

Protocol Amendments

The original protocol for EMR 100070-001, version 1.0, was dated 25 October 2012. Overall, the protocol was amended 13 times at the time of BLA submission of December 27, 2016. The table below summarizes the protocol amendments with relevance to the urothelial cohorts. (Sources: Section 5.3.5.2 EMR 100070-001 CSR, protocol amendments.)

Table 7: Major Protocol Amendments Relevant to Urothelial Cohorts, EMR 10070-001

Amendment number	Amendment Date	Major changes introduced into the protocol
7	July 30, 2014	• The protocol was amended to add 3 new secondary cohorts including a urothelial cohort. • Patients in the urothelial cohort were required to have progressive disease on first line platinum-based chemotherapy; Patients may have received any number of prior regimens • Interim analyses were added for the new secondary cohorts • Pre-medication with an anti-histamine and acetaminophen was required prior to treatment of patients on-study.
8	November 19, 2014	• Clarified inclusion criteria for subjects with urothelial carcinoma; patients were allowed to be treated if ineligible for cisplatin-based chemotherapy due to impaired renal function, hearing loss, or > grade 2 peripheral neuropathy • Otherwise, patients should have progressed after treatment with at least 1 platinum-containing regimen for locally advanced or metastatic UC or disease recurrence • Patients may have received any number of prior regimens
9	December 22, 2014	• Added new safety visits at Weeks 2, 4, and 6 for blood draws for the analysis of liver enzymes for subjects with liver metastases • Modified Inclusion Criterion 7 regarding hepatic function so that all subjects enrolled in the expansion cohorts must have had ALT and AST ≤ 2.5 × ULN • Added weekly clinical monitoring x 7 weeks for subjects with liver metastases at baseline, as well as laboratory samples for ALT, AST, total bilirubin, and alkaline phosphatase at Weeks 2, 4, and 6.
10	March 4, 2015	• Added 4 new efficacy expansion cohorts including urothelial carcinoma
11	April 16, 2015	• Modified the timing of and added an interim analysis for the urothelial cohorts (13 weeks after the start of treatment of the 30th and 60th subject)
13	October 5, 2015	• Increased the number of subjects in the urothelial

		carcinoma cohort from 100 to 200 • Updated interim analyses • Specified a null hypothesis for the urothelial carcinoma efficacy expansion cohort

7.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated the following: "All avelumab clinical studies were conducted according to the respective protocols, the World Medical Association Declaration of Helsinki, Good Clinical Practice guidelines, and in accordance with the International Conference on Harmonization E6, as well as local regulatory requirements." (Module 2.5, Clinical Overview).

DOP1 consulted the OSI on January 18, 2017 to perform an audit of select clinical sites. Sites were selected based on the high number of patients enrolled and the low overall reporting of safety data such as adverse events and serious adverse events. Two domestic sites were chosen for inspection: Sites 141 and 171. One international site was chosen: Site 805 in Great Britain. Additionally, EMD Serono, Inc. was selected for inspection.

Three clinical sites, Dr. Hendrik-Tobias Arkenau (Site 805), Dr. Manish Patel (Site 141), and Dr. Julio Peguero (Site 171), were selected for audit. The study sponsor, EMD Serono, Inc., inspection was cancelled due to FDA field investigator resource constraints. The inspections conducted by OSI identified the following items:

1. **Dr. Hendrik-Tobias Arkenau, M.D. (Site 805**). The site screened 6 UC cohort subjects and enrolled 4 subjects. There was one minor instance where pleural effusion and ascites were not listed in the data listings or eCRF for one subject. The eCRF has since been updated to include these AEs.

2. **Dr. Manish Patel, M.D. (Site 141).** The site screened 18 UC cohort subjects and enrolled 13 subjects. Source documents at the site corroborated primary efficacy endpoint data reported by the IERC. There was no evidence of under-reporting of AEs.

3. **Dr. Julio Peguero, M.D. (Site 171).** The site screened and enrolled 5 subjects into the UC cohort. There was evidence of underreporting of AEs to the sponsor. Briefly, electronic Case Report Forms (eCRFs) for subject AEs were not completed and submitted to the Sponsor in a timely manner. This resulted in nine non-serious AEs (NSAEs) not being included in the data listings submitted to the application. For example, Subject (b) (6) experienced five AE's during the study; however two AE's (intermittent cough in May 2015 and fatigue in July 2015) were not entered into the eCRFs until April 1, 2017. Overall, the site documented 24 NSAEs for four subjects but had only entered 15 AEs

into the eCRFs until April 2017 when the remaining nine AEs were entered into each Subject's eCRF.

Reviewer's comment: Although the number of missing NSAEs from Site 171, 9 out of 24 (38%), is substantial for the site, this represents a small proportion of the 2,406 non-serious, treatment emergent AEs reported for subjects enrolled in this study. Overall, these findings do not substantially affect the quality or ability to interpret the data submitted in the application. See the FDA Clinical Inspection review for details.

Financial Disclosure

In accordance with 21 CFR 54, the Applicant submitted a financial disclosure certification document in module 1.3.4. The document includes a table listing all investigators who participated in the three covered studies supporting BLA 761078; the table indicates for each investigator whether the investigator has provided a Disclosure Statement (FORM 3455) or if the financial disclosure information is missing. On request, the Applicant provided a table listing any investigators for whom financial disclosure information was missing and the reason why it was not obtained.

A total of one investigator (from Study EMR 100070-001) who participated in the conduct of clinical studies of avelumab supporting this application disclosed financial arrangements. This investigator (b) (6) was the site PI at site (b) (6), which enrolled 3 patients into the UC cohorts, only 2 of whom were included in the efficacy analysis population.

Although subinvestigators who had missing financial disclosure information were identified at 6 sites that enrolled UC patients, none of the subinvestigators with missing disclosures enrolled any UC patients into the trial. Overall, of the 27 investigators for Study EMR 100070-001 (all cohorts) who initially had missing disclosure information, five were actually on file (due to a name change), and nine did not participate in the trial at all. The most common reason for missing information for the other 13 investigators was that the investigator had departed the clinical site at the time of the request.

Patient Disposition

Overall, 341 patients were screened for trial enrollment for both UC cohorts. There were 91 screen failures (Source: Section 5.3.5.1 Dataset IE, DCO June 9, 2016). There was also one patient on the expansion cohort who was enrolled but withdrew prior to treatment. Ultimately, 249 patients were treated with avelumab in both UC cohorts, although the 7 patients who were platinum ineligible were excluded from all analyses of efficacy and safety in this review.

Below are the most common trial inclusion and exclusion criteria not met by the 91 patients screened for trial enrollment in the UC cohorts but not enrolled in the trial.

Table 8: Inclusion/Exclusion Criteria Not Met

Inclusion/Exclusion Criteria not met by ≥5 patients screened for trial enrolment	N
WBC count ≥ 3 x 10^9/L with ANC ≥ 1.5 x 10^9/L , lymph ≥ 0.5 x 10^9/L, platelet ≥ 100 x 10^9/L, and HGB ≥ 9 g/dL	13
Progressive disease following last line of treatment.	12
ECOG performance status of 0 to 1 at trial entry and an estimated life expectancy of at least 3 months.	11
Active or history of CNS metastases	10
Adequate hepatic function defined by BILI level ≤ 1.5 x ULN, AST level ≤ 2.5 x ULN, ALT level ≤ 2.5 x ULN or, for subjects with metastatic disease to liver, AST and ALT levels ≤ 5 x ULN.	9
Disease measurable with at least 1 unidimensional measurable lesion by RECIST 1.1	7
Signed written informed consent	6
Adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula.	5
Previous malignant disease other than the target malignancy to investigated in this trial within the last 5 years with exception of basal, squamous cell carcinoma of skin, cervical carcinoma in situ.	5

(Source: Section 5.3.5.1 Dataset IE)

The following is the disposition data for the 242 post-platinum patients, as well as the 226 patients in the efficacy analysis population dosed with avelumab in the two UC cohorts:

Table 9: Disposition, Safety and Efficacy Populations

Disposition	Safety Population Avelumab n=242 (%)	Efficacy Population Avelumab n=226 (%)
Treatment ongoing at DCO	55 (23)	47 (21)
Off treatment	187 (77)	179 (79)
Progressive Disease	126 (52)	119 (53)
Adverse Event	30 (12)	30 (13)
Death	11 (5)	11 (5)
Withdrawal by Subject	10 (4)	10 (4)
Other	9 (4)	8 (4)
Protocol Violation	1 (0.4)	1 (0.4)[1]

[1]Received radiation therapy

(Source: Dataset ADSL)

Among the 126 patients who discontinued due to progressive disease, 18 did not have radiographic progression prior to discontinuation.

There were 30 patients who discontinued therapy due to adverse events in the disposition dataset. In the adverse event dataset, there were 37 patients who discontinued due to an adverse event. Twenty-five patients overlap in these two groups. One patient (b) (6) who

discontinued therapy due to an AE in the disposition dataset had no corresponding AE on review of the ADAE dataset. However, there were multiple AEs reported between the reported date of treatment discontinuation/final dose date (3/3/15) and death date (3/21/15).

Among the 11 deaths, eight were reported to be due to disease progression and 3 were reported to be due to AE. Seven of the eight patients whose deaths were reported to be due to disease progression had AEs shortly before their death, including three patients with infection and one with diarrhea.

In 10 and nine cases overall, the reason for treatment discontinuation was "withdrawal by subject" and "other," respectively. In five of these cases (n=4 withdrawal by subject and n=1 other), the patients died of their disease within the two months following treatment discontinuation. In the other 14 cases, many of the subjects had multiple AEs around the time of treatment discontinuation which did not appear to be treatment related. However, it was not always readily apparent what the reason for treatment discontinuation was in all of these cases.

Protocol Violations/Deviations

Major protocol deviations were pre-specified in the SAP for Study EMR 100070-001 (Section 12.2.2) and included:

- patients who are treated on the study despite not satisfying the inclusion criteria
- patients who develop withdrawal criteria while on the study but are not withdrawn
- patients who receive the wrong treatment or an incorrect dose
- patients who receive an excluded concomitant medication

Protocol deviations were categorized as: "Study Procedures Criteria," or "Concomitant Medication Criteria" or "Eligibility and Entry Criteria."

There were 283 major protocol deviations in 93 patients. The following are select major protocol deviations reported by the Applicant in the categories of "Eligibility and Entry Criteria" and "Study Procedures Criteria".

Table 10: Major Protocol Deviations

Patient Number	Protocol Deviation	Category
(b) (6)	The site did not perform a brain scan during the screening period to rule out brain metastases.	Eligibility And Entry Criteria
	Screen creatinine clearance did not meet eligibility requirement because it was not calculated using the cockcroft-gault calculation. The creatinine clearance was < 50 ml/min.	Eligibility And Entry Criteria
	Subject (b) (6) was enrolled in the study with decreased renal function.	Eligibility And Entry Criteria
	Subject did not receive platinum containing	Eligibility And

(b) (6)	chemotherapy in metastatic setting in order to meet eligibility criteria #3 specific to the urothelial cohort.	Entry Criteria
	The subject was given corticosteroid injections (depo-medrol and dexamethasone) for treatment of an AE (not an AESI).	Concomitant Medication Criteria
	Subject (b) (6) was given prohibited medication (solumedrol) for treatment of small bowel obstruction during hospital admission.	Concomitant Medication Criteria
	(b) (6), 2014-present took ultra-reishi (Chinese herb) herbal remedy with immunostimulating properties. Concomitant medications with immunostimulating properties are not permitted per 6.5.2 section of protocol.	Concomitant Medication Criteria

*Note that some patients had >1 violations and/or deviations. (Source: ADSL and ADDV datasets)

Reviewer's comment: These protocol deviations were clearly described in the dataset and do not substantially impact the integrity of the study or the reliability of the study results for conducting the safety and efficacy reviews. Patient (b) (6) was reported to have an elevated creatinine at study entry, but screening creatinine is 1.1 mg/dL.

Demographic Characteristics

The baseline demographic data for all 242 platinum-exposed patients are presented below. Additionally, these data are presented for the efficacy populations of the 226 patients with ≥13 weeks of follow-up (n=226) as well as for those with ≥6 months of follow up (n=161). Among the 242 pts, 169 (70%) were from the US. The percentages are similar in the two efficacy populations.

Table 11: Baseline Demographics

	≥13 Weeks Follow Up N=226 (%)	≥ 6 Months Follow Up N = 161 (%)	All Treated N=242 (%)
Sex			
Male	162 (72)	117 (73)	67 (28)
Female	64 (28)	44 (27)	175 (72)
Age			
Mean (years) (SD)	67.6 (11.0)	67.9 (11.3)	67.6 (10.6)
Median (years)	68	68	68
Min, max (years)	30-89	30-89	30-89
Age Group			
< 65 years	73 (32)	50 (31)	78 (32)
65-74 years	87 (38)	63 (39)	96 (40)
75-84 years	60 (27)	42 (26)	62 (26)
≥ 85 years	6 (3)	6 (4)	6 (2)
Race			

	≥13 Weeks Follow Up N=226 (%)	≥ 6 Months Follow Up N = 161 (%)	All Treated N=242 (%)
White	181 (80)	130 (81)	188 (78)
Asian	16 (7)	10 (6)	17 (7)
Black	11 (5)	10 (6)	11 (5)
Other	18 (7)	11 (7)	26 (10)
Region			
United States	167 (74)	131 (81)	169 (70)
Western Europe	42 (19)	21 (13)	54 (22)
Eastern Europe	6 (3)	3 (2)	7 (3)
Asia	11(5)	6 (4)	12 (5)
ECOG PS			
0	77 (34)	56 (35)	84 (35)
1	149 (66)	105 (65)	158 (65)

(Source: ADSL Dataset)

Reviewer Comment: The median age of patients enrolled was 68, which is lower than the median age at diagnosis of patients with bladder cancer, which is 73 years old. The vast majority of patients enrolled overall were White (78%), and were enrolled in the US (70%). Results from this clinical trial population may be less generalizable to an older or non-White patient population.

Other Baseline Characteristics

Table 12 below provides information on the baseline disease characteristics of the patients enrolled. Note that the primary site of disease occurred in the bladder in only ~ 50% of patients and that the majority of patients had metastatic disease. The results of PD-L1 staining are also included in the table below.

The Applicant initially used the Dako 73-10 PD-L1 IHC Research Use Only kit to assess PD-L1 staining in tumor cells and immune cell hotspots in the 44 patients in the secondary expansion cohort and some of the patients in the efficacy expansion cohort. This version of the assay required 50 viable tumor cells. Tumor specimens were considered PD-L1 high if ≥ 5% of tumor cells had ≥ 1+ staining by IHC, ≥ 25% of tumors cells had ≥ 2% staining by IHC, or immune cell hotspots that had ≥ 10% immune cell staining.

The Applicant then used the Dako 73-10 PD-L1 IHC Good Manufacturing Practice kit to assess PD-L1 staining in tumor cells and tumor-associated immune cells in all patients in the efficacy expansion cohort. This version of the assay required 100 viable tumor cells. Tumor specimens were considered PD-L1 high if: ≥ 5% of tumor cells had ≥ 1+ staining by IHC, tumor-associated immune cells expressed PD-L1, or immune cells at the tumor interface expressed PD-L1. Tumor-associated immune cells were defined as a dense infiltrate comprising ≥ 50% of a 40x field and

adjacent to tumor cells. Immune cells at the tumor interface were defined as immune cells and macrophages surrounding tumor nests at the outermost edge of the tumor. Of the 226 patients followed for ≥ 13 weeks, 102 patients in the efficacy expansion cohort had tumor specimens scored using both methods. Agreement was acceptable using these 2 methods of scoring. The 44 patients in the secondary expansion cohort were not rescored using this second method.

A substantial number of patients, 34 (15%) of 226 patients followed for ≥ 13 weeks and 22 (14%) of 161 patients followed for ≥ 6 months, were considered unevaluable. Among the 34 patients, the reason for an unevaluable result was no sample or an inadequate sample received by the data cutoff in 31 patients and technical reasons in 3 patients. The absence of information in 34 patients as well as the lack of retesting in the initial 44 patients could invalidate any conclusions concerning the association between PD-L1 staining and response. Therefore, in the table below, the results of PD-L1 staining are provided separately for the secondary expansion and efficacy cohorts.

Table 12: Baseline Disease Characteristics

	≥ 13 Weeks Follow Up	≥ 6 Months Follow Up
Primary Site n (%)		
Bladder	127 (56)	92 (57)
Renal Pelvis/Ureter	52 (23)	36 (22)
Urethra	47 (21)	33 (20)
Extent of Disease at Entry (%)		
Locally Advanced (%)	8 (4)	4 (2)
Metastatic (%)	218 (96)	157 (98)
PD-L1 Status	N = 44	N = 44
Tumor Cells		
High: ≥ 5% Cells with ≥ 1+ PD-L1 Staining	13 (30)	13 (30)
Low/Negative	24 (55)	24 (55)
Not Evaluable	7 (16)	7 (16)
Immune Cells		
≥ 10% Cells in Hotspots with ≥ 1+ PD-L1	2 (5)	2 (5)
Low/Negative	35 (80)	35 (80)
Not Done/No Results	7 (16)	7 (16)
PD-L1 Status	N = 182	N = 117
Tumor Cells		
High: ≥ 5% Cells with ≥ 1+ PD-L1 Staining	68 (37)	50 (43)
Low/Negative		52 (44)
Not Evaluable	27 (15)	15 (13)
Tumor-Associated Immune Cells		
PD-L1 Expression	15 (8)	9 (8)

	≥ 13 Weeks Follow Up	≥ 6 Months Follow Up
No PD-L1 Expression	3 (2)	1 (1)
Not Present	136 (75)	92 (79)
Not Done/No Results	28 (15)	15 (13)
Tumor Interface Immune Cells		
Positive	51 (28)	34 (29)
Not Present	97 (53)	66 (56)
Not Done/No Results	34 (19)	17 (15)

(Source: ADSL, MI, and TU datasets)

Table 13 provides information on the extent of disease at baseline in the enrolled patients. Two scoring systems have been used in the literature to assess prognostic factors in patients with urothelial cancer, the Bellmunt and MSKCC scoring systems. These have been used in urothelial cancer and have prognostic value in determination of OS. The Bellmunt scoring system uses performance status, hemoglobin, and the presence of liver metastases[4]. The MSKCC system uses performance status and the presence of visceral (bone, liver, and lung) metastases[5].

Table 13: Extent of Disease

	≥ 13 Weeks Follow Up N = 226 (%)		≥ 6 Months Follow Up N = 161 (%)	
	Radiology Committee	Investigator	Radiology Committee	Investigator
Sites of Disease				
Liver	77 (34)	71 (31)	53 (33)	50 (31)
Lung	116 (51)	107 (47)	83 (52)	74 (46)
Bone	34 (15)	40 (18)	23 (14)	29 (18)
Lymph Node Only[1]	39 (17)	9 (4)	25 (16)	5 (3)
Missing	1 (0.4)	0	1 (0.6)	0
Median Sum of Diameter (range)	5.7 cm (1.2, 28.3)	6.0 cm (1.1, 34.3)	5.6 cm (1.3, 28.3)	6.4 cm (1.2, 34.3)
≤ 2 cm	29 (13)	25 (11)	22 (14)	18 (11)
≤ 5 cm	95 (42)	88 (39)	66 (41)	55 (34)
Missing	3 (1)	1 (0.4)	3 (2)	0
Number of Target Lesions				
0	3 (1)	0	3 (2)	0
1-2	129 (57)	138 (61)	88 (55)	94 (58)
≥ 3	94 (42)	88 (39)	70 (43)	67 (42)
Number of Non-target Lesions				
0	32 (14)	46 (20)	14 (9)	33 (20)

	≥ 13 Weeks Follow Up N = 226 (%)		≥ 6 Months Follow Up N = 161 (%)	
	Radiology Committee	Investigator	Radiology Committee	Investigator
1-2	106 (47)	115 (51)	77 (48)	81 (50)
≥ 3	88 (39)	65 (29)	70 (43)	47 (29)
Bellmunt Score				
0	51 (23)	51 (23)	40 (25)	40 (25)
1	101 (45)	103 (46)	70 (43)	69 (43)
2	58 (26)	60 (27)	38 (24)	43 (27)
3	16 (7)	12 (5)	13 (8)	9 (6)
MSKCC Score				
0	69 (31)	76 (34)	49 (30)	57 (35)
1	157 (69)	150 (66)	112 (70)	104 (65)

[1]Including spleen (Source: ADSL, TU, datasets)

Reviewer Comment: Most patients had visceral metastases. The percentage of patients with lymph-node only disease is low overall, although it is higher when looking at review committee vs investigator assessment (16-17% vs. 3-4%). We also note that there were 3 patients who did not have evaluable target lesions at baseline by radiology committee and thus did not have RECIST-defined measurable disease for purposes of subsequent response assessments. All 3 patients did have investigator-assessed measurable disease, and thus their inclusion in the trial was not considered a protocol deviation. They have been included in the denominator of all analyses of response that appear below.

The data on prior therapy is presented below. The number of patients receiving prior cisplatin, carboplatin, or both was derived from the concurrent medication dataset. In several instances, there were patients whose prior therapy was listed as "antineoplastic agents," but one of the components of the regimen when reviewed further was platinum. Additionally, the prior therapies of BCG, interferon, mannitol, mitomycin, thiotepa, valrubicin, and zoledronic acid were excluded from the analysis below, although the route of administration (intravesical vs. other) was not specified, which is especially relevant for the interferon, mitomycin, and thiotepa.

Of note, information on the number of lines of systemic therapy in the metastatic setting is not included below. This is because the number of patients who received at least 2 prior systemic regimens for metastatic disease could not be readily determined from the datasets provided since the regimen number provided (e.g., #1, #2, etc.) included systemic therapy as well as BCG or other intravesical treatments. There were also several patients who were reported to have received previous interferon or mitomycin for treatment of metastatic disease. This seems unlikely. The route of administration was not captured. Thus, the calculation of prior lines of systemic therapy in the metastatic setting could not be accurately performed given the

submitted data.

Table 14: Prior therapy

	≥13 Weeks Follow Up N=226 (%)	≥ 6 Months Follow Up N = 161 (%)
Disease Setting of Prior Therapy		
Neoadjuvant/Adjuvant Only	9 (4)	5 (3)
Locally Advanced Only	11 (5)	7 (4)
Metastatic Only	149 (66)	110 (68)
> 1 Disease Setting[1]	57 (25)	39 (24)
Prior Platinum-based Therapy		
Any	226 (100)	161 (100)
Cisplatin Only	107 (47)	77 (48)
Carboplatin Only	73 (32)	49 (30)
Both Cisplatin and Carboplatin	45 (20)	34 (21)
Platinum NOS	1 (0.4)	1 (0.6)
Progression on Prior Therapy to Study Entry		
> 90 Days	24 (11)	17 (11)
Missing	17 (8)	15 (9)

[1]This includes combinations of the 3 disease settings, neoadjuvant/adjuvant, locally advanced, and metastatic; e.g. treatment in the neoadjuvant/adjuvant setting followed by treatment of metastatic disease. (Source: ADSL, CM datasets)

Reviewer's Comment: The extremely low percentage of patients who received therapy in the neoadjuvant or adjuvant setting only is noted (4% and 3% among patients followed for ≥13 and ≥ 6 Months, respectively). Although these patients are included in the labelled indication since they were included in the enrolled patient population, the low number of actual patients enrolled who met these criteria may affect generalizability of these results to similar patients not in a clinical trial setting.

We also note that there was a relatively low percentage of patients with disease progression >90 days prior to study entry despite overall evidence of good data collection in this regard; this fact is thought to reflect favorably on the trial conduct.

Efficacy Results – Primary Endpoint

Table 15 below shows results from the primary analysis. The confirmed response rate by RECIST 1.1 assessed by IERC was 13.3%% (95% CI: 9.1, 18.4; 9 CRs, 21 PRs) in patients with ≥13 weeks of follow-up (n=226) and 16.1% (95% CI: 10.8, 22.8; 9 CRs and 17 PRs) in patients with ≥6 Months of follow-up (n=161). In both groups, the median duration of response (in months) was not reached (range: 1.4+ to 17.4+ months).

Table 15: Primary Analysis by Independent Review

	≥ 13 Weeks of Follow Up	≥ 6 Months of Follow Up
	All Patients N = 226	All Patients N = 161
Confirmed Response Rate (95% CI)	30 (13.3%) (9.1, 18.4)	26 (16.1%) (10.8, 22.8)
Complete Response	9 (4.0%)	9 (5.6%)
Partial Response	21 (9.3%)	17 (10.6%)
Median Duration of Response (months) (range)	NE (1.4+, 17.4+)	NE (1.4+, 17.4+)
Median Time to Response (months) (range)	2.0 (1.3, 11.0)	2.0 (1.3, 11.0)

NE: Not Estimable; (Source: TR dataset) (Source: TU dataset; Data Cutoff: 6-9-16)

Reviewer Comment: The review team identified 3 patients whose responses were confirmed after the data cutoff ((b) (6)) and 2 patients ((b) (6)) we do not consider as having met RECIST 1.1 criteria for confirmed response. One of these patients had no target lesions at baseline by radiology committee analysis and a second had progression in a non-target lesion at the time of decrease in the target lesion. All 5 patients were not considered confirmed responders in the FDA primary analysis. This affected 5 of the applicant's responders in patients with ≥13 weeks of follow-up and 2 in patients with ≥6 Months of follow-up.

The time to response was longer relative to other PD-1/L-1 inhibitors. Median time to response was 2.0 months (range: 1.3 to 11.0 months) among patients followed for either ≥ 13 weeks or ≥ 6 months. Among the 30 responders in patients followed for ≥13 weeks, 15 responded at their 1st assessment and 8 patients had their first response at their 2nd scan. Among the remaining patients, responses were seen as late as Day 334. The patient who responded at Day 334 had a very small disease burden (1.6 cm at baseline with 3 non-target nodes by IRR) which only gradually decreased by ≥ 0.5 cm. In general, the baseline disease burden was very small in all patients in this trial. Among the 226 patients followed for ≥ 13 weeks, the median SOD at baseline by IRR was 5.7 cm (range: 1.2 to 28.3 cm) with 13% having a tumor burden ≤ 2 cm and 17% with lymph node only disease. Among the 9 patients with a CR, the median SOD was 3.1 cm with lymph nodes ranging from 1.5-1.9 cm as the measurable target lesions in 7 of 9 pts (Table 16). In 6 of these 9 patients, non-target disease was limited to lymph nodes or no non-target disease was identified. One patient with a CR had a baseline SOD of 10.5 cm, achieved a PR at Day 80, and had a gradual decrease in tumor burden to achieve a CR at Day 291.

PD-L1 Subgroups

The table below provides information on the response rate by the extent of PD-L1 staining in tumor samples. These subgroups, using a variety of cutoffs for PD-L1 staining in tumor cells . All show little relationship between response rate and PD-L1 tumor staining. The difference appears to be less with a 25% cutoff than with a 1% cutoff. This is counter intuitive since increased PD-L1 staining would be expected to correlate with an increase in response.

The Applicant also chose to define PD-L1 staining in immune cells. Since immune cells express PD-L1 and avelumab is capable of antibody-dependent cell-mediated cytotoxicity (ADCC), the use of avelumab could theoretically result in immune cell death through ADCC. This, in turn, could theoretically result in a decrease in response rate. When this was tested, a response was seen in 6/17 (35%, 95% CI: 14.2%, 61.7%) of patients with PD-L1 staining within immune cells who were followed for at least 13 Weeks. The number of patients is small and this result should be interpreted with caution, but this result suggests that avelumab may not have a detrimental effect on the immune system.

Table 16: Confirmed Response Rate by PD-L1 Status in Patients Followed for > 13 Weeks

	≥ 13 Weeks of Follow Up N = 226 (%)		
	TC[1] ≥ 5% N = 83	TC < 5% N = 109	Not Evaluable N = 34
Confirmed Response Rate	15 (18)	13 (12)	2 (6)
	TC ≥ 25% N = 52	TC < 25% N = 140	Not Evaluable N = 34
Confirmed Response Rate	8 (15)	20 (14)	2 (6)
	TC ≥ 1% N = 92	TC < 1% N = 100	Not Evaluable N = 34
Confirmed Response Rate	17 (18)	11 (11)	2 (6)

[1]TC-tumor cell; IC-immune cell (Source: TR, MI datasets; Data Cutoff: 6-9-16)

Reviewer's Comment: When the data on the initial 44 patient cohort was presented to the FDA in the December 23, 2015, Preliminary Breakthrough Therapy Designation (BTD) Advice Request submission, it appeared as if the use of PD-L1 as a biomarker in this population was predictive of response to avelumab. At that time, in 35 evaluable patients from the 44-patient secondary expansion cohort of study EMR100070-001 and using a cutoff of ≥ 5% positive tumor cells with staining of any intensity, the Applicant reported an ORR of 50.0% (6/12; 95% CI: 21.1, 78.9) in the PD-L1-positive population. This was compared to an ORR of 4.3% (1/23; 95% CI: 0.1, 21.9) in the PD-L1 negative population (p=0.003, Fisher's exact test for association between PD-L1 status and response). Note that these response rates are similar, but not identical to the response rate in these groups of patients following FDA review of response and used in the summary above.

As is evidenced in Table 16 above, this original strong observed association between PD-L1 status and response to avelumab was not upheld in subsequent analyses, especially in the validation set which was comprised of the patients in the efficacy expansion cohort.

In an information request, the Applicant was asked to account for the discrepancy between the initial and subsequent results. The Applicant submitted detailed descriptions of their investigation of pre-analytical, analytical, and post-analytical variables in an effort to account for the differences in overall response rate for PD-L1 positive patients between the secondary and efficacy expansion cohorts. These variables included baseline characteristics, specimen-related characteristics, sample processing, analytical testing, pathologist scoring, and quality control. Although a few correlations were noted, none of the factors investigated were found to satisfactorily explain the difference between the two cohorts at either the primary cut-off (5% tumor cell plasma membrane staining) or tertiary cut-off (1% tumor cell plasma membrane staining). Verification of individual patient-related factors and a further study to understand potential biological factors in the tumor microenvironment are ongoing as per the Applicant.

Investigator-Assessed Confirmed ORR by RECIST 1.1

The Investigator-determined response rate was 15.5% (35/226). This included five complete and 30 partial responses. Examining the correlation between the Investigator response and response as determined by the IRR, 21 (60%) of the 35 patients considered to have a response by the IRR were also identified by the Investigator (Table 17). Among these 21 patients, the timing of first response differed between Investigator- and IRR-assessment in eight patients.

Reviewer's comment: For purposes of the analysis below, all 35 patients considered to have confirmed responses (CR or PR) by IRR were considered. In the overall FDA analysis of efficacy, 5 of these were excluded as is described earlier (two for not meeting RECIST 1.1 response criteria and three for having responses confirmed after data cutoff date).

Table 16: Correlation between Investigator and Independent Review Response Assessment

	Independent Review					
Investigator	CR	PR	SD	PD	Non-CR/Non-PD or NE	Total
Complete Response (CR)	5	0	0	0	0	5
Partial Response (PR)	5	16	7	1	1	30
Stable Disease (SD)	1	7	43	12	0	64
Progressive Disease (PD)	0	1	12	70	4	87
Not Evaluable (NE)	0	0	0	3	37	40
Total	11	24	62	86	43	226

NE: Not Evaluable (Source: ADTUMOR dataset; Data cutoff 6-9-2016)

Table 17: Agreement on Best Responses and Timing between Investigator and Independent Review

	Agreed on Best Response and Timing	Disagreed on Best Response and Timing
CR	2	3
PR	11	5
SD	43	0
PD	68	2

(Source: ADTUMOR dataset; Data cutoff 6-9-2016)

The following patients with a two-step non-concordance between investigator and central review BOR were reviewed further:

Patient (b) (6) was assessed as having a best confirmed overall response of CR by central review but SD by investigator. This patient had an adrenal lesion that was considered a non-target by the central reviewer but was a target by investigator at 9.9 cm at baseline. This remained stable throughout the course of 16 scans as per investigator. By central review, the non-target adrenal lesion had disappeared by the 5th scan.

Patient (b) (6) had a confirmed BOR of PR by investigator and PD by independent review. The investigator assessed two target lesions in the lung and four non-target lesions- three in the lung and one in the liver. Central review assessed two target lesions and two non-target lesions, all in the lung. SOD per central review was 4.8 cm at baseline, which increased to 6.1 cm on day 43/week 7. This was assessed as PD on day 43. The patient did go on to have an eventual confirmed PR beyond progression by central review.

Patient (b) (6) had a confirmed BOR of PR by investigator and PD by independent review. The investigator assessed one target lesion in the lung and one non-target lesion in the peritoneum. Central review assessed one target lesion in the lung and one non-target lesion in a para-aortic lymph node. SOD at baseline was 1.4 cm per central review and 1.2 cm per investigator. Both central review and investigator had the lesion increasing to 1.8 cm by the week 7/ day 38 visit; per central review that met criteria for SD but per investigator that represented PD.

Efficacy Results – Secondary and other relevant endpoints

PFS and OS by RECIST 1.1 as assessed by IERC were among the secondary endpoints; however, analyses of these time-to-event endpoints are considered exploratory for this single-arm study.

Progression-free Survival

PFS results are shown in Table 19. The median PFS was 6.57 weeks (95% CI: 6.14, 11.57) in the ITT population, 6.57 weeks (95% CI: 6.14, 11.57) in subjects with ≥13 weeks follow-up, and 6.29 weeks (95% CI: 6.00, 10.14) in subjects with ≥6 months follow-up. There were a total of 163 (67.4%) subjects with PFS events in the ITT population. Note that patients with ≥6 months of follow-up had a higher percentage of events (76.4%) than patients with ≥13 weeks of follow-up (68.6%). This is because longer follow-up provides more information as there is more opportunity to detect later events.

Table 18: Progression-free Survival

	ITT (N=242)	≥13 weeks follow-up (N=226)	≥6 Months follow-up (N=161)
Number of Events (%)	163 (67.4)	155 (68.6)	123 (76.4)
Median, weeks (95% CI)	6.57 (6.14, 11.57)	6.57 (6.14, 11.57)	6.29 (6.00, 10.14)

(Source: TR dataset; Data Cutoff: 6-9-16)

Among the 226 patients, 26 died prior to the planned day of the first assessment, Day 42. Among the patients who had scans after the first dose of durvalumab (scan closest to Day 42), 81 had disease progression. Therefore, 107/226 (47%) pts died or had disease progression at the first assessment.

Overall Survival

OS results are shown in Table 20. The median OS was 7.43 months (95% CI: 5.68, 10.25) in the ITT population, 7.43 months (95% CI: 5.68, 10.25) in subjects with ≥13 weeks follow-up, and 6.51 months (95% CI: 4.76, 9.46) in subjects with ≥ 6 months follow-up. There were a total of 116 (47.9%) OS events in the ITT population with 113 events in subjects with ≥13 weeks follow-up and 96 events in subjects with ≥6 months follow-up.

Table 19: Overall Survival

	ITT (N=242)	≥13 weeks follow-up (N=226)	≥6 Months follow-up (N=161)
Number of Events (%)	116 (47.9)	113 (50.0)	96 (59.6)
Median, months (95% CI)	7.43 (5.68, 10.25)	7.43 (5.68, 10.25)	6.51 (4.76, 9.46)

(Source: DS dataset; Data cutoff: 6-9-16)

Additional Exploratory Subgroup Analyses

Further exploratory subgroup analyses of confirmed ORR were also assessed by gender, age group, country, Bellmunt score, MSKCC score, presence of liver lesions at baseline, and number of previous therapies. Results are shown in the table below. In patients followed for at least 13

weeks, the response rate in US patients was 12.6% (21/167).

Table 20: Subgroup Analyses

	≥13 Weeks Follow Up (N=226)			≥ 6 Months Follow Up (N = 161)		
	N	#Responders	ORR (95%CI)	N	#Responders	ORR (95%CI)
Gender						
Male	162	22	13.6 (8.7, 19.8)	117	18	15.4 (9.4, 23.2)
Female	64	8	12.5 (5.6, 23.2)	44	8	18.2 (8.2, 32.7)
Age Group						
<65	73	7	9.6 (3.9, 18.8)	50	7	14.0 (5.8, 26.7)
65-74	87	8	9.2 (4.1, 17.3)	63	7	11.1 (4.6, 21.6)
75-84	60	15	25.0 (14.7, 37.9)	42	12	28.6 (15.7, 44.6)
≥85	6	0		6	0	
Country						
USA	167	21	12.6 (8.0, 18.6)	131	19	14.5 (9.0, 21.7)
All others	59	9	15.3 (7.2, 27.0)	30	7	23.3 (9.9, 42.3)
Bellmunt Score						
0	51	9	17.6 (8.4, 30.9)	40	9	22.5 (10.8, 38.5)
1	101	19	18.8 (11.7, 27.8)	70	15	21.4 (12.5, 32.9)
2	58	2	3.4 (0.4, 11.9)	38	2	5.3 (0.6, 17.7)
3	16	0		13	0	
MSKCC Score						
0	69	14	20.3 (11.6, 31.7)	49	12	24.5 (13.3, 38.9)
1	157	16	10.2 (5.9, 16.0)	112	14	12.5 (7.0, 20.1)
Liver Baseline						
Y	77	5	6.5 (2.1, 14.5)	53	4	7.5 (2.1, 18.2)
N	149	25	16.8 (11.1, 23.8)	108	22	20.4 (13.2, 29.2)
Previous Therapies						
≤1	109	16	14.7 (8.6, 22.7)	68	13	19.1 (10.6, 30.5)
2	67	9	13.4 (6.3, 24.0)	55	9	16.4 (7.8, 28.8)
≥3	50	5	10.0 (3.3, 21.8)	38	4	10.5 (2.9, 24.8)
Received steroids for imAEs						
Yes	27	12	44.4 (25.5, 64.7)	23	11	47.8 (26.8, 69.4)
No	199	18	9.0 (5.4, 13.9)	138	15	10.9 (6.2, 17.3)

(Source: various datasets; Data Cutoff: 6-9-16)

Reviewer's comment: Although the estimates in the smaller subgroups are subject to large sampling variation, the overall results are supportive of primary findings and provide evidence of clinical activity of avelumab in the study population. The response rates tended to be higher in those patients without liver metastases and with lower Bellmunt and MSKCC risk

scores at baseline. It is also important to note that responses were observed in those patients above age 75 at a rate that compares favorably to response rates in younger patients. The fact that response rates were so high in the subgroup of patients who received steroids (topical and/or systemic) for imAEs is notable and is potentially hypothesis-generating.

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

There were no other trials evaluating patients with urothelial cancer that were submitted for review with this BLA.

7.3.2. Integrated Assessment of Effectiveness

The Applicant is seeking approval of avelumab for patients with metastatic, (b) (4) urothelial carcinoma under the Accelerated Approval regulations. Durable objective response rate of sufficient magnitude is an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit (i.e., improved survival) in patients with metastatic (b) (4) urothelial carcinoma. The effect size of avelumab on ORR and DOR demonstrated in the urothelial cohorts of study EMR 100070-001 represents substantial evidence of effectiveness and clinical benefit over off-label use of chemotherapy which produces nondurable response rates and no apparent improvement in overall survival. A randomized trial being conducted under (b) (4)

7.4. Review of Safety

7.4.1. Safety Review Approach

The primary source of the safety data in this review is the 242 platinum-naive patients who received avelumab on the Phase 1, single arm study EMR 100070-001. All patients received at least one dose of single-agent avelumab 10 mg/kg, and the safety monitoring period was from the time the patient signed informed consent through the End of Treatment visit scheduled 28 days following the last dose of study drug. After the End-of-Treatment visit, treatment-related AEs were collected through the post-treatment safety follow-up period which the protocol defined as 10 weeks after the last study drug administration. Additionally, all SAEs suspected to be related to avelumab were required to be reported irrespective of the time elapsed since the last study drug administration.

Hematology tests were assessed prior to trial treatment and every 2 weeks thereafter. Core chemistry was assessed prior to trial treatment, weekly from Weeks 2 – Week 6, and every 2 weeks thereafter. Full serum chemistry was assessed prior to trial treatment, at Week 7 and Week 13 and then every 6 weeks thereafter. In addition, for subjects with liver metastases at baseline, samples for ALT, AST, total bilirubin, and alkaline phosphatase determination were collected at Weeks 2, 4, and 6.

7.4.2. Review of the Safety Database

Overall Exposure

All 242 patients in the two urothelial cohorts of Study EMR 100070-001 received at least one dose of avelumab 10 mg/kg intravenously over 60 minutes. The treatment plan called for study drug administration in clinic every two weeks. At the primary analysis data cut-off date, the median duration of treatment was 12 weeks, and patients received between 1 and 46 infusions. Table 21 summarizes avelumab exposure for the 242 platinum-exposed patients who received avelumab in study EMR 100070-001.

Patients should have received 12-13 doses of avelumab over a 24 week period and 26-27 doses over a 52 week period. Forty-eight (48/242 [20%]) patients received $\geq$ 12 doses and 10 patients (10/242 [4%]) received $\geq$ 26 doses of avelumab. Thus, experience with the long-term safety profile of avelumab in patients with urothelial cancer is very limited. In the safety database, 411/1738 (24%) patients had received > 6 months and 123/1738 (7%) had received > 12 months of avelumab. While the percentage of patients receiving > 12 months of avelumab remains small, the total number of patients is substantial. Thus, the safety database is able to provide adequate information concerning the long-term safety of avelumab.

Table 21: Overall Exposure

	Prior Platinum Therapy N=242
Duration of treatment in weeks	
Median	12
Mean	17
Range	2-92
Number of infusions	
Median	6
Mean	8
Range	1-46
Cumulative dose (mg/kg)	
Median	60
Mean	82
Range	10-461
Dose intensity (mg/kg/cycle)	
Median	10
Mean	10
Range	6-11

(Source: ADEX dataset, DCO: 6-9-16)

In the exposure dataset, 39 (16%) patients were reported to have a dose delay of at least 3 days and 22 (9%) were reported to have a dose interruption. In the adverse event dataset, dose delays were reported in 64 (26%) patients and dose interruptions in 29 (12%) patients.

Relevant characteristics of the safety population:

Demographic information for patients in the integrated UC population is included in Section 6.1.2 above.

Adequacy of the safety database:

The safety database that includes AE data from the 242 patients treated with avelumab in the two UC cohorts of study EMR 100070-001 is adequate. The median age of patients on study is 68 years old, which is younger than the median age of diagnosis for urothelial carcinoma (73 years old). Older adults, including patients over 70 and minorities are underrepresented in these trials. The performance status of the patients entered on these trials is greater than the average performance status of patients with urothelial carcinoma as a whole.

7.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data quality for this study was acceptable. Datasets and patient narratives were reviewed and compared and were overall found to be concordant. The data submitted was well-organized and the quality was adequate to perform a complete review of the safety of avelumab. Multiple information requests were sent to the Applicant during the review of safety to confirm data, request additional data, narratives and case report forms, request alternative presentations of per patient safety data or clarify minor discrepancies in the pooled database. The Applicant provided sufficient responses including additional analyses and clarifications as required. Many of the narratives, following additional clarification and questions, did not provide adequate information concerning the reported adverse event.

Categorization of Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) were adequately defined within the protocol for Study EMR 100070-001. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 and AEs were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 criteria. Treatment emergent adverse events were defined as events reported up to 30 days after the last dose of study medication. Adverse events thought to be related to avelumab were collected at 10 weeks after the last dose. Serious adverse events thought to be related to avelumab were to be collected during the every 3 month survival follow ups.

The Applicant coded verbatim AE terms for the two UC cohorts of Study EMR 100070-001 and the integrated database using MedDRA version 18.1. Treatment-emergent adverse events (TEAEs) were defined as all AEs occurring from initiation of study drug through 30 days after the last dose of avelumab. For imARs the Applicant provided analyses based on a TEAE period extended to 90 days following the last dose of avelumab. NCI CTCAE Version 4.0 was used for toxicity grading.

The reviewer assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA preferred terms (PTs) for 100% of the ADAE.xpt dataset. Of the 2,587 line listings in the dataset, the reviewer used manual matching of verbatim and MedDRA PTs. The majority of nonidentical terms were due to spelling differences (e.g., anemia versus anaemia), abbreviations and full text (URI versus upper respiratory infection) and verbatim terms that included descriptors (e.g., intermittent nausea versus nausea). Overall, the MedDRA PTs listed in the dataset adequately represented the verbatim terms from the CRFs.

There were several exceptions and/or inconsistencies found, presented below, not thought to affect the overall integrity of the safety database:

Table 22: Possible Discrepancies Between Preferred Term and MedDRA PT Recorded

Preferred term (verbatim)	MedDRA PT
ACUTE ON CHRONIC RENAL INSUFFICIENCY (n=2)	Chronic kidney disease
MUSCLE SPASMS IN BACK DUE TO A FALL	(No MedDRA PT mapped in dataset)
TINY PULMONARY NODULES (BOTH LUNGS)	Pulmonary mass
WORSENING OF ACUTE KIDNEY INJURY ON CHRONIC KIDNEY DISEASE	Acute kidney injury

(Source: ADAE dataset, DCO 6-9-2016)

Routine Clinical Tests

Routine hematology and core chemistry laboratory assessments were performed within 18 days of enrollment and every two weeks prior to avelumab administration, and when medically necessary during Study EMR 100070-001. Vital signs, physical examination and performance score assessments were performed prior to each cycle. Adrenocorticotropic hormone (ACTH), antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor (RF), free thyroxine (free T4), and thyroid stimulating hormone (TSH) were collected at screening and every 3 months and as medically indicated. Human anti-human antibody (HAHA) was measured prior to avelumab infusion on Day 1, every 2 weeks for eight weeks and then every six weeks. A 12-lead ECG was assessed at screening, prior to infusion and 2 hours post-infusion every two weeks for eight weeks and then every 6 weeks thereafter while on treatment.

7.4.4. Safety Results

A summary of the overall safety data for the 242 platinum-exposed patients on the UC cohorts of Study EMR 100070-001 is presented below:

Table 23: Integrated Summary of Safety

Total number of patients with:	N= 242 (%)
Grade 5 AEs	14 (6%)
Grade 3-4 TEAEs	143 (59%)
Non-fatal SAEs	100 (41%)
AEs leading to Treatment Discontinuation	31 (13%)
Immune Mediated AEs	49 (20%)
Immune Mediated AEs Requiring High Dose Steroids	11 (5%)

(Source: ADAE, AESI and CM datasets, DCO:6-9-16)

Deaths

Review of the safety data submitted to the BLA based on the data cut-off date of June 9, 2016, revealed that of 242 platinum-exposed patients on the UC cohorts of Study EMR 100070-001, 141 patients (58%) had died. However, 24 of those deaths occurred after the DCO date of June 9, 2016, and no reason for death was initially provided for those cases. When the 90-day safety

update with a data cutoff date of September 30, 2016 was submitted to the BLA, the cause of death for an additional 19 of those patients was provided. Additionally, in response to an information request, the Applicant provided additional narratives on the circumstances surrounding the remaining 5 deaths that occurred after September 30, 2016. In two of these cases, cause of death was not indicated by investigator although both patients had discontinued therapy for radiographic disease progression.

Table 24: Deaths Overall

	Avelumab n (%)
Treated	242
Alive	101 (42%)
Deaths	141 (58%)
Progressive disease[a]	116 (48%)
Unknown/other	9 (4%)
Cause unknown, death within 30 days of end of treatment	1 (0.4%)
Cause unknown/other, within 60 days of first treatment, >30 days after end of treatment	4 (2%)
Cause unknown/other, death at least 30 days after end of treatment, >60 days after first treatment[b]	4 (2%)
Other: deaths occurred after DCO, full details unavailable[c]	2 (1%)
Grade 5 Adverse Events	14 96%)
Sepsis	4 (2%)
Urosepsis	1 (0.4%)
General Physical Health Deterioration	2 (1%)
Abdominal pain	1 (0.4%)
Cerebrovascular accident	1 (0.4%)
Death NOS	1 (0.4%)
Gastrointestinal hemorrhage	1 (0.4%)
Intestinal perforation	1 (0.4%)
Pneumonitis[d]	1 (0.4%)
Respiratory failure	1 (0.4%)

(Sources: Datasets ADSL, ADAE, narratives. DCO: 9-30-16)

[a]Includes one patient whose death was due to stage IV urothelial carcinoma

[b]All had discontinued therapy due to progressive disease. One died of a GI bleed not listed as a Grade 5 AE.

[c]Died after the September 30, 2016 data cutoff date. Both had discontinued therapy due to radiographic disease progression although reason for death was not definitively available. One death notification occurred via relative report, and the other was by public obituary notification.

[d]Pneumonitis was the only death attributed by investigator to study drug toxicity

The following 14 deaths were due to Grade 5 AEs not related to disease progression. The narratives and/or CRFs for each were reviewed and are summarized below. The only AE

considered by investigator to be related to **study drug was a case of pneumonitis, which was also considered an immune-mediated AE.**

Table 25: Deaths due to Grade 5 AEs Unrelated to Disease Progression

Patient ID	AE	Event summary
(b) (6)	Abdominal pain	51 year old F who received her first dose of Avelumab on (b) (6) and a second dose on (b) (6). She presented to the ED o , with abdominal pain and CT showed marked progression of disease in the abdomen. She died on (b) (6). ***Reviewer comment: This death appears unrelated to treatment and due to disease progression.***
	Gastrointestinal hemorrhage	59 year old M who received his first dose of Avelumab or (b) (6), and a second dose on (b) (6). He presented to the ED on (b) (6), with weakness, anorexia, and failure to thrive. He was found to have grade 4 AKI and atrial flutter. He developed a gastrointestinal hemorrhage on (b) (6), and died that day. No autopsy was performed. ***Reviewer comment: It is unclear what the etiology of the patient's gastrointestinal hemorrhage was, however, this does not appear to be treatment-related.***
	Death	75 year old F; first dose of avelumab was administered on (b) (6). Third and last infusion was on (b) (6). On (b) (6), 15 days after the most recent administration and 43 days after the first administration of avelumab, the subject died of an unknown cause. Patient was treated for LE edema as well as weakness and fatigue on (b) (6) and had also been treated with Keflex for LE edema from (b) (6). ***Reviewer comment: It is unclear what the etiology of the patient's death was, however, this does not appear to be obviously treatment-related.***
	Urosepsis	65-year-old who received one dose of avelumab on (b) (6). On (b) (6) the subject was admitted to the hospital and diagnosed with urosepsis, with blood cultures positive for proteus. Imaging showed worsening burden of intrathoracic metastatic disease. She died or (b) (6) ***Reviewer comment: This death does not appear to be treatment-related.***
	Respiratory failure	71-year-old M who received his first dose of therapy on (b) (6) and his second on (b) (6). On (b) (6) the patient experienced a grade 3 DVT leading to hospitalization, and a CT revealed multiple bilateral pulmonary emboli. He was discharged to hospice care on (b) (6). He died on (b) (6). ***Reviewer comment: This death does not appear to be treatment-related.***
	Septic shock	63-year-old F with hx of AKI and HTN who received one dose of avelumab on (b) (6). A Grade 5 event of septic shock occurred beginning 12 days after being dosed; the patient had klebsiella bacteremia and also had significant disease progression seen on imaging. She died on (b) (6). ***Reviewer comment: This death does not appear to be treatment-related.***
	Sepsis	81-year-old M who received one dose of avelumab on (b) (6). On (b) (6), 39 days later, the subject was hospitalized for sepsis thought to be due to right flank cellulitis or UTI. His condition worsened, he was transitioned to

Patient ID	AE	Event summary
(b) (6)		comfort care, and he died of septic shock on (b) (6). ***Reviewer comment: This death does not appear to be treatment-related.***
	Intestinal perforation	41-year-old M previously s/p cystoprostatectomy who received his first dose of avelumab on (b) (6) and his 12th dose on (b) (6). He was admitted to the hospital on (b) (6) with symptoms of dehydration. CT scan revealed intestinal obstruction. An exploratory laparotomy was performed and a J-tube was placed. He developed increased ascites and penile and scrotal swelling, with CT scan on (b) (6) reveling increased anasarca and intra-abdominal edema. The patient died on (b) (6). ***Reviewer comment: It is unclear if this death is related to disease progression or is in any way treatment-related.***
	Sepsis	60-year-old M with a hx of CAD; first dose of avelumab on (b) (6), 2nd dose on (b) (6). On (b) (6), the patient experienced a fall while getting out of bed, sustaining a humerus fracture. He had been experiencing worsening fatigue, poor appetite, and decreased ambulation prior to that time. He was admitted to the hospital, was febrile, and blood and urine cultures were positive. On (b) (6), palliative care was consulted and comfort care was instituted. The subject died on (b) (6). ***Reviewer comment: This death does not appear to be treatment-related.***
	Pneumonitis	54-year-old M with no prior history of pulmonary disease and no history of radiation received his first (only) dose of avelumab on (b) (6). He was admitted to the hospital on (b) (6) for diverticulitis (Grade 3), and Clostridium difficile colitis (Grade 3). On (b) (6) CT of thorax revealed bilateral pleural effusions and perihilar ground glass opacities likely reflecting pulmonary edema; extensive mediastinal and hilar lymphadenopathy. The subject was diagnosed with pneumonitis (Grade 3) and was transferred to intensive care unit; he received 125 mg methylprednisone IV on (b) (6), but died the following day. The investigator determined that the pneumonitis was related to avelumab. ***Reviewer comment: This death, although multifactorial, appears to be treatment-related.***
	General physical health deterioration	67-year-old F who received 1 dose of avelumab on (b) (6). A Grade 5 event of general physical health deterioration occurred 54 days afterwards. On (b) (6) the subject experienced an overall deterioration, and was admitted to hospital due to generalized carcinoma, significant pain and pre-terminal status. She died the following day. ***Reviewer comment: This death does not appear to be treatment-related.***
	Cerebrovascular accident	84-year-old F pmhx atrial fibrillation and DM. Her first dose of avelumab was administered on (b) (6), and the second was on (b) (6). On (b) (6), 25 days after the most recent administration of avelumab, she developed a generalized seizure that subsequently recurred, with CT showing no intracranial lesion. The decision was made to provide comfort care only to the patient and she died that day with no autopsy performed. A grade 1 CVA was previously diagnosed via brain MRI on (b) (6). ***Reviewer comment: Although there are several unclear details about the sequence of events causing, the death does not appear to be treatment-related.***
	General physical health	57-year-old M, with his first dose of avelumab on (b) (6) and his 5th dose on (b) (6). CT scan on (b) (6), had shown disease

Patient ID	AE	Event summary
	deterioration	progression compared to January scan. On (b) (6), the subject was admitted to hospital with asthenia, anorexia and weight loss and was found to have hypercalcemia and AKI. The patient died on (b) (6), with the investigator determining that disease progression was the primary cause of death. ***Reviewer comment: This death does not appear to be treatment-related.***
(b) (6)	Sepsis	70-year-old F pmhx DM, PE. A Grade 5 event of sepsis occurred 22 days after the first and only infusion of avelumab (b) (6) The subject died 3 days after onset of the event on (b) (6). On (b) (6), CT scans had shown diffuse disease progression. ***Reviewer comment: This death does not appear to be treatment-related.***

(Source: ADAE, ADSL, narratives; DCO: 9-30-16)

There were eight deaths within 30 days of treatment and an additional six deaths within 60 days of first treatment that were not related to progressive disease. Nine of these cases were due to Grade 5 AEs and overlapped with the deaths identified above. The remaining five were reviewed via review of the narratives and/or CRFs for each case and are presented below.

The additional death within 30 days of treatment, listed as primary cause unknown, is reviewed below:

Patient ID	AE	Event summary
(b) (6)	Unknown	62 year old M, hx of a fib, Wolff-Parkinson-White Syndrome, CKD who received his first dose of Avelumab on (b) (6), and a second dose on (b) (6), which was discontinued due to disease progression. He died on (b) (6). ***Reviewer comment: It is unclear what the attribution is for this death.***

Four additional deaths occurred not due to disease progression within 60 days of first treatment-

Patient ID	AE	Event summary
(b) (6)	AE not related to study drug As per ADAE- dehydration led to drug withdrawal	78 year old M, who received one dose of Avelumab on (b) (6), but developed grade 3 dehydration requiring hospitalization on (b) (6). He had previously developed poor appetite, with poor PO and fluid intake x 3 days. He had taken magnesium citrate for constipation on (b) (6), and then developed diarrhea on (b) (6) with 7-8 diarrheic stools over 24 hours and blood in his urine. Further evaluation revealed renal failure and altered mental status. He was admitted to the ICU for hydration on (b) (6). He died on (b) (6). ***Reviewer comment: It is unclear what the attribution is for this death but the ongoing series of events may be related to drug-related AEs.***
	"Other"	72 year old M who received avelumab from (b) (6) to (b) (6), with study drug discontinued due to disease progression on (b) (6) with an increase in size of liver metastases. On (b) (6) the subject started carboplatin and paclitaxel. The subject died on (b) (6), 31 days after the administration of the last dose of avelumab. The investigator indicated "other" as primary reason for death, specifying shock, severe sepsis with organ dysfunction and neutropenia. Review of the AEs for this patient revealed a hepatitis and GGT increase, grade 3 reported on (b) (6).

Patient ID	AE	Event summary
(b) (6)		This is likely related to progression of liver metastases, although the hepatitis was classified as an immune-mediated AE. ***Reviewer comment: This death was likely multifactorial and related to disease progression rather than to treatment with Avelumab.***
	Unknown	43-year-old F who received her first and last dose of avelumab on (b) (6). On (b) (6), the subject developed serious urosepsis (Grade 3). She was treated with nephrostomy and with IV antibiotics. On (b) (6), the subject recovered from urosepsis. During her hospitalization, imaging revealed disease progression. She died on (b) (6). ***Reviewer comment: This death was likely multifactorial and related to disease progression rather than to treatment with Avelumab.***
	Unknown	53-year-old M whose first and last dose of avelumab was administered on (b) (6). On (b) (6), 13 days after the first and last administration, the subject experienced serious hyponatremia (Grade 3) with Na = 121 requiring hospitalization. Initially it was thought that this might be an event of adrenal insufficiency but ACTH and cortisol levels were reportedly WNL. As disease progression was documented on CT done on (b) (6), the investigator concluded that the hyponatremia was due to paraneoplastic syndrome. He was discharged from the hospital on (b) (6) and supposed to be re-admitted to another hospital but was lost to follow-up; he died on (b) (6) ***Reviewer comment: This death in the setting of disease progression appears multifactorial, and the hyponatremia seems unrelated to treatment with avelumab, given the normal labs. Likely unrelated to avelumab.***

There were 4 remaining deaths that were due to unknown or other causes that occurred >30 days after the end of treatment and >60 days after initiating treatment. All patients had discontinued treatment for progressive disease. One patient's death was discovered via obituary notice, one died in hospice, one died >6 months after study termination with reason of death unknown and no further information available to investigator, and another died of a GI bleed (not listed as a grade 5 AE).

Additionally, deaths that occurred within 30 days of treatment and that were assessed by the investigator as being related to disease progression were reviewed. The following patients are highlighted from this review for either having clinical PD only, as review of dataset ADTUMOR and the narratives did not reference radiographic PD, or for having AEs that occurred around the time of death that could have been responsible for the subject's death. In all cases, investigator attribution of death was due to PD.

Table 26: Select deaths within 30 days of treatment, attributed by investigator to progressive disease

Patient ID	Event summary
(b) (6)	65-year old male. The first administration of avelumab was on (b) (6). The last dose was on (b) (6). On (b) (6), 11 days after the most recent administration and 25 days after the first administration of avelumab the subject experienced serious streptococcal bacteremia (Grade 3) and non-serious hypoxia (Grade 2). This involved prolonged hospitalization and the patient died

Patient ID	Event summary
(b) (6)	on (b) (6), with investigator attributing death to disease progression. CT scan while hospitalized showed worsening tumor burden as well as pneumonia and pleural effusion. ***Reviewer's comment- while there was disease progression evident on CT, infection may well have contributed significantly to the patient's death***
	65 M whose first dose of avelumab was administered on (b) (6). Study treatment was discontinued with the last administration of avelumab (2nd infusion) on (b) (6) due to disease progression. The subject died on (b) (6). The investigator indicated disease progression as primary cause of death. ***Reviewer's Comment: This may have been clinical progression, as no imaging documentation is provided. No radiographic PD recorded***
	69 M The first and only dose of avelumab was administered on (b) (6). On (b) (6), 8 days after the first and only administration, the subject developed non-serious fatigue (Grade 2) which worsened to non-serious Grade 3 on (b) (6). The patient died on (b) (6). ***Reviewer's comment- disease progression was the investigator's attribution, however, this may also be related to the AE that occurred shortly beforehand***
	75 F first dose of avelumab was administered on (b) (6). The most recent administration of avelumab (3rd infusion) was given on (b) (6). On (b) (6), 15 days after the most recent administration and 43 days after the first administration of avelumab, subject's death (Grade 5) of unknown cause was reported. The Investigator assessed death as not related to avelumab. The Investigator indicated disease progression as primary cause of death. The patient was treated for bilateral LE edema shortly prior to death, although no etiology was found on workup. **Reviewer's comment: The attribution for this death is unclear, with no documentation of disease progression provided other than the investigator's assessment. No radiographic PD recorded.**
	74 M whose first dose of avelumab was administered on (b) (6). The most recent administration of avelumab (2nd infusion) was given on (b) (6). On (b) (6), 14 days after the most recent administration and 28 days after the first administration of avelumab, the subject developed non-serious fatigue (Grade 3) assessed as not related to avelumab. The subject died on (b) (6) attributed by investigator to be due to disease progression. ***Reviewer's comment- no radiographic evidence of disease progression although death unlikely related to any other etiology. No radiographic PD recorded.***
	68 F who received one dose of avelumab on (b) (6). She developed PNA on (b) (6). She also developed other AEs (grade 1-2 including renal failure, cardiomyopathy, encephalopathy, CVA, PE, lactic acidosis. The investigator attributed her death on (b) (6) to disease progression although no radiographic evidence of progression was given. ***Reviewer's comment- unclear etiology of death in this case, likely multifactorial. No radiographic PD recorded.***
	71 M whose first dose of avelumab was administered on (b) (6). The most recent administration of avelumab (2nd infusion) was given on (b) (6). On (b) (6), 16 days after the most recent administration and 37 days after the first administration of avelumab, the subject developed serious respiratory failure (Grade 5). The subject was treated from (b) (6) (b) (6) with acetylsalicylic acid 81 mg orally once daily and since (b) (6) with enoxaparin sodium 120 mg subcutaneously once daily, all for peripheral embolism. The Investigator assessed the fatal respiratory failure as not related to avelumab. The investigator indicated disease progression as primary cause of death. ***Reviewer's comment: The attribution for this death is unclear. No documentation of radiographic PD. Patient may have suffered a PE.***
	86 M whose first and last dose of avelumab was administered on (b) (6). He was discontinued from therapy due to reason "other"- symptomatic deterioration. He died (b) (6), with disease progression listed as primary cause of death. ***Reviewer's comment: No radiographic evidence of PD, likely clinical deterioration.***

Patient ID	Event summary
(b) (6)	59 M hx of epilepsy. First dose of avelumab was administered on (b) (6). Study treatment was permanently discontinued with the last administration of avelumab (3rd infusion) on (b) (6) (b) (6) due to disease progression. Death from progressive disease occurred on (b) (6). ***Reviewer's comment: No radiographic evidence of PD provided***
	63 F hx of cerebral palsy. The first and only dose of avelumab was administered on (b) (6). On (b) (6), the subject experienced serious septic shock (Grade 5). CT showed significant progressive metastatic disease in liver and lung, new pleural effusions, and patchy opacities. Blood cultures were positive for gram negative rods. She died of disease progression (primary cause of death) on (b) (6). ***Reviewer's comment: Death likely multifactorial, with sepsis ruled by investigator to be unrelated to avelumab treatment. Patient was high risk for infection with enlarging pulmonary metastases, sacral ulcer, and nephrostomy tube.***
	69 F who received 7 doses of avelumab from (b) (6) but was discontinued due to disease progression. On (b) (6), a CT scan of chest showed acute sub-segmental pulmonary embolus and persistent metastases, although new pathologic fracture. The patient died on (b) (6) with investigator indicating progressive disease as primary cause of death. ***Reviewer's comment: Pulmonary embolus may also have contributed to death but this is not uncommon in the setting of extensive malignancy and likely unrelated to avelumab.***
	66 F who received one dose of avelumab on (b) (6) but was discontinued due to disease progression and died on (b) (6) due to progressive disease. ***Reviewer's comment: No radiographic evidence of PD provided.***
	65 F who received avelumab for 3 doses from (b) (6) and was discontinued due to disease progression. She died on (b) (6) due to progressive disease. ***Reviewer's comment: No radiographic evidence of progressive disease provided.***
	75 M whose first dose of avelumab was on (b) (6) and last dose was on (b) (6), with death due to disease progression on (b) (6). ***Reviewer's comment: the events surrounding the patient's disease progression are not included in the provided narrative.***

(Source: ADSL, ADTUMOR, narratives; DCO: 9-30-16)

Reviewer's Comment: Extensive review of the deaths not related to disease progression, as well as of those deaths that occurred within 30 days of drug dosing, reveals that there do not appear to be any cases other than the one highlighted case of pneumonitis in patient (b) (6) that are directly related to therapy with avelumab. In some cases of deaths attributed to disease progression, full details documenting radiographic progression of disease are not provided and in several cases, deaths appear multifactorial; however, the final attribution of deaths as being unrelated to therapy with avelumab other than in the one case above appears to be accurate overall.

Serious Adverse Event

Using a data cutoff of June 9, 2016, treatment-emergent non-fatal SAEs occurred to 100 patients (41%) overall of the 242 patients in the safety population. In 82 of those patients (34% overall), the SAE was grade 3 or 4. The number of SAEs increased to 45%, 36% grade 3-4 in the Safety Update with a data cutoff of September 30, 2017. Those SAEs affecting more than 1% of patients are presented below. The table does not include disease progression and related terms

when reported as SAEs. Note also that this table includes some composite terms. Please see the Appendix for grouping of the preferred terms.

The incidence of the various serious adverse events (SAEs) is similar in the original dataset and in the safety update and most SAEs are consistent with advanced urothelial cancer. Adverse events that are included here, but are not included in the common adverse event table include intestinal obstruction, sepsis/streptococcal bacteremia (non-urine related), bone fracture, dehydration, hematuria, respiratory failure, and hypotension.

Table 29: Serious Adverse Events Occurring in ≥1%

	Prior Platinum-based Therapy N = 242 (%)	
Any	100 (41)	108 (45)
Any (other than disease progression)	91	100 (41)
Blood Disorders		
Anemia	3 (1)	3 (1)
Gastrointestinal Disorders		
Abdominal Pain	6 (2)	6 (2)
Diarrhea	3 (1)	3 (1)
Intestinal Obstruction	5 (2)	5 (2)
General Disorders		
Asthenic Conditions	3 (1)	4 (2)
Pyrexia	5 (2)	5 (2)
Infections		
Urinary Tract Infection	11 (5)	12 (5)
Sepsis[1]	3 (1)	3 (1)
Pneumonia	4 (2)	5 (2)
Injury, Poisoning, and Procedural Complications		
Infusion-related Reactions	3 (1)	4 (2)
Bone Fracture	4 (2)	4 (2)
Investigations		
Elevated Transaminases	5 (2)	5 (2)
Metabolic Disorders		
Dehydration	5 (2)	5 (2)
Musculoskeletal Disorders		
Musculoskeletal Pain	6 (2)	6 (2)
Renal Disorders		
Creatinine Increased/Renal Failure	5 (2)	6 (2)
Hematuria	5 (2)	6 (2)
Respiratory Disorders		

	Prior Platinum-based Therapy N = 242 (%)	
Dyspnea	3 (1)	4 (2)
Respiratory Failure	1 (0.4)	3 (1)
Vascular Disorders		
Hypotension	4 (2)	4 (2)
Data Cutoff	June 9, 2016	September 30, 2017

[1]Not related to urinary infection or obstruction (Source: ADAE datasets)

Dropouts and/or Discontinuations Due to Adverse Effect

There were 31 patients with grade 1-4 TEAEs that led to drug discontinuations in the original BLA submission and 35 in the Safety Update. The AEs leading to drug discontinuation are presented below. The incidence of adverse events and the preferred terms are similar in the two datasets. In this grouping of adverse events, disease progression/ tumor pain are included since they may have been the cause of permanent treatment discontinuation.

The Applicant has set up their dataset (analysis and tabulation) so that the action taken with avelumab as the result of an adverse event can be categorized as multiple. The case report forms for each of these patients were examined to determine whether the action taken with avelumab was permanent discontinuation. If so, these pts are included in the table below. Note that in 1 patient, the term that led to discontinuation was changed from chronic kidney injury (original submission) to acute kidney injury (Safety Update).

Table 30: Grade 1-4 Adverse Events Leading to Permanent Discontinuation in > 1 Patient

	Prior Platinum-based Therapy N = 242 (%)	
Any Reported Event	30 (12)	33 (14)
Gastrointestinal Disorders		
Diarrhea	1 (0.4)	2 (0.8)
General Disorder		
Asthenic Conditions	3 (1)	4 (2)
Disease Progression/Tumor Pain	5 (2)	4 (2)
General Physical Health Deterioration[1]	2 (0.8)	2 (0.8)
Injury, Poisoning, and Procedural Complications		
Infusion-related Reactions	2 (0.8)	3 (1)
Investigations		
Transaminases Increased	2 (0.8)	3 (1)
Data Cutoff	June 9, 2016	September 30, 2017

[1]Includes general physical condition abnormal (Source: ADAE)

Dose delays due to 135 adverse events occurred in 79 patients (33%). In 21 patients (9%), dose delays occurred due to infusion-related reactions and in 67 patients (28%), dose delays occurred due to other AEs not categorized as infusion-related reactions. In the exposure dataset, 39 (16%) patients were reported to have a dose delay of at least 3 days and 22 (9%) were reported to have a dose interruption. Review of the 90-day safety update revealed that 156 treatment-emergent adverse events caused dose delays in 89 (37%) patients.

Table 27: AEs causing dose delay in >1% of patients

	Prior Platinum-based Therapy N = 242 (%)	
Any	79 (33)	89 (37)
Gastrointestinal Disorders		
Diarrhea	7 (3)	7 (3)
General Disorders		
Asthenic Conditions	5 (2)	6 (2)
Disease Progression/Tumor Pain	2 (0.8)	4 (2)
Infections		
Urinary Tract Infection	3 (1)	3 (1)
Injury, Poisoning, and Procedural Complications		
Infusion-related Reactions	21 (9)	28 (12)
Investigations		
Elevated Transaminases	5 (2)	5 (2)
Musculoskeletal Disorders		
Musculoskeletal Pain	3 (2)	3 (2)
Renal Disorders		
Creatinine Increased/Renal Failure	3 (2)	3 (2)
Respiratory Disorders		
Cough	2 (0.8)	3 (1)
Dyspnea	4 (2)	5 (2)
Skin Disorders		
Rash	3 (2)	4 (2)
Data Cutoff	June 9, 2016	September 30, 2017

(Source: ADAE datasets)

Reviewer's Comment: Infusion-related reactions were the most common cause of dose delays in Study EMR 100070-001. This toxicity appears to be unique to avelumab among the approved anti-PD-1 and anti-PD-L1 agents. This is likely due to the retained Fc portion of the antibody that makes patients on avelumab more likely to develop this toxicity despite protocol-mandated premedication. This toxicity is explored below in the section on infusion-related reactions.

Significant Adverse Events

There are two categories of significant adverse events mechanistically associated with treatment with avelumab.

Immune related reactions are thought to arise from the ability of avelumab to block programmed death receptor 1 (PD-1). Normally, binding to PD-1 inhibits T cell proliferation and cytokine production. Blocking this pathway releases the T cell from this inhibition, which may have the unintended effect of an increase in autoimmune disease.

Infusion reactions are thought to be a function of the fact that avelumab is a humanized monoclonal antibody. The fact that it is engineered with an intact Fc region may make these reactions more of a risk with avelumab than with other, similar PD-1/PD-L1 targeting drugs that do not have an intact Fc region.

These are explored in greater detail below.

Immune related reactions

The PTs included in the MedDRA query for identification of potential irAEs for subsequent medical review are summarized below (source: Summary of clinical safety, section 2.7.4).

Category	MedDRA Terms
Pneumonitis	PTs: Interstitial lung disease, Pneumonitis, and Acute interstitial pneumonitis
Colitis	HLT: Colitis (excl infective): Acute haemorrhagic ulcerative colitis, Allergic colitis, Autoimmune colitis, Colitis, Colitis erosive, Colitis ischaemic, Colitis microscopic, Colitis psychogenic, Colitis ulcerative, Crohn's disease, Enterocolitis haemorrhagic, Eosinophilic colitis, Inflammatory bowel disease, Necrotising colitis, Neutropenic colitis, Pseudopolyposis HLT: Diarrhoea (excl. infective) Diarrhoea, Diarrhoea haemorrhagic, Diarrhoea neonatal PT: Enterocolitis
Hepatitis	PTs: Acute hepatic failure, Alanine aminotransferase increased, Aspartate aminotransferase increased, Autoimmune hepatitis, Hepatic enzyme increased, Hepatic failure, Hepatitis, Hepatitis acute, Hepatotoxicity, Liver disorder, Liver function test abnormal, Liver injury, and Transaminases increased
Endocrinopathies	
Thyroid Disorders	
Hypothyroidism	HLT Thyroid hypofunction disorders: Autoimmune hypothyroidism, Hypothyroidic goitre, Hypothyroidism, Myxoedema, Primary hypothyroidism, Secondary hypothyroidism, Tertiary hypothyroidism, Thyroid atrophy, Transient hypothyroxinaemia of prematurity

Hyperthyroidism	HLT Thyroid hyperfunction disorders: Basedow's disease, Hyperthyroidism, Marine Lenhart syndrome, Primary hyperthyroidism, Secondary hyperthyroidism, Thyroid dermatopathy, Thyrotoxic crisis, Thyrotoxic periodic paralysis, Toxic goitre, Toxic nodular goiter
Thyroiditis	HLT Acute and chronic thyroiditis: Autoimmune thyroiditis, Thyroiditis, Thyroiditis acute, Thyroiditis chronic, Thyroiditis fibrous chronic, Thyroiditis subacute
Adrenal Sufficiency	HLT Adrenal cortical hypofunctions: Addison's disease, Adrenal androgen deficiency, Adrenal atrophy, Adrenal insufficiency, Adrenal suppression, Adrenocortical insufficiency acute, Glucocorticoid deficiency, Hypoaldosteronism, Mineralocorticoid deficiency, Primary adrenal insufficiency, Secondary adrenocortical insufficiency, and Steroid withdrawal syndrome
Type 1 Diabetes Mellitus	PTs: Type 1 Diabetes mellitus, Latent autoimmune diabetes in adults, Diabetic ketoacidosis, Diabetes Mellitus, and Hyperglycaemia
Pituitary Dysfunction	PTs: Hypophysitis and Hypopituitarism
Hypogonadism	PTs: Hypogonadism ,Hypogonadism female ,Hypogonadism male, Late onset hypogonadism syndrome, Primary hypogonadism, and Secondary hypogonadism
Nephritis and Renal Dysfunction	HLT Nephritis NEC: Autoimmune nephritis, Lupus nephritis, Nephritis, Nephritis haemorrhagic, Perinephritis, Tubulointerstitial nephritis, Tubulointerstitial nephritis and uveitis syndrome PTs: Acute renal failure, Renal failure, and Renal impairment
Rash	SMQ (narrow): Severe cutaneous adverse reactions and PTs: Erythema, Pemphigoid, Pruritus, Pruritus allergic, Pruritus generalised, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash popular, Rash pruritic
Other Immune-related Adverse Events	
Myositis	PTs: Myositis, Blood creatine phosphokinase increased
Other	PTs: Myocarditis, Uveitis, Iritis, Vitiligo, Psoriasis, Rheumatoid arthritis, Systemic inflammatory response syndrome, Sarcoidosis, Autoimmune disorder, Encephalitis, Encephalopathy, Guillain-Barre Syndrome, Myasthenia gravis, Pancreatitis, Autoimmune pancreatitis, and Pancreatitis acute

Additionally, the Applicant used a 2-level approach for analysis of potential irAEs (Source: SCS 2.7.4):

1. Level 1: A MedDRA PT query (as specified in the table above) was established for each event category (i.e., immune-related rash, colitis, pneumonitis, hepatitis, nephritis and renal dysfunction, endocrinopathies [with subcategories of thyroid disorders, adrenal insufficiency, Type 1 diabetes mellitus, and pituitary disorders, and hypogonadism], and other immune-related adverse reactions).

2. Level 2: AEs identified by the MedDRA PT queries were then medically reviewed using predefined case definitions for immune-related adverse reactions. More specifically, all potential irAEs were reviewed by 2 medically-qualified persons. If the 2 reviewers came to different assessments for a potential irAE, a third medically-qualified reviewer was asked to make the final assessment.

The following algorithm was used to review each adverse event to determine if it qualified as an irAE; all of the following criteria had to be met:

a. Onset: AE onset after first avelumab administration
b. Duration: AE does not spontaneously resolve (i.e., without corticosteroids/ immunosuppressant treatment) within 7 days after onset
c. Immunosuppressive therapy: AE treated with corticosteroid or other immunosuppressant therapy.
d. For endocrinopathies only: AE required hormone replacement and/or (corticosteroid or other immunosuppressive therapy). Hormone replacement was taken into account for specific endocrinopathies only as follows: (1) thyroid therapy (thyroid supplements and thyroid suppressants) for thyroid disorders, and (2) insulin for diabetes mellitus (including hyperglycemia).
e. Etiology: No other clear etiology or histopathology/biopsy consistent with an immune-related event.

On analysis of the data, there were 49/242 (20%) patients who were categorized as having immune related reactions that were treatment-emergent, including 33/242 (14%) treated with medications overall (including topical and high and low dose systemic steroids), and 11/242 (5%) treated with the equivalent of 40 mg or more of prednisone PO (high dose systemic steroids). The expected incidence of these events in derived from the avelumab package insert (PI). In general, the incidence of these AEs in patients with urothelial cancer is consistent with the expected incidence based on the avelumab PI.

Table 28: Immune Related Reactions Requiring Steroids

	Safety population n=242 N (%)	Expected Incidence %
Requiring high-dose steroids	11 (5)	3%
Requiring any steroids	33 (14)	7%[1]
Rash (includes rash pruritic, rash maculo-papular, rash erythematous)	15 (6)	4%
Pruritus	6 (2)	2%
Pneumonitis	3 (1)	1.2%
Hyperthyroidism	2 (0.8)	0.4%
Autoimmune hepatitis/AST increased	2 (0.8)	0.9%
Uveitis	1 (0.4)	0.1%
Rheumatoid arthritis	1 (0.4)	0.1%
Guillain-Barre syndrome	1 (0.4)	0.1%
Erythema/erythema multiforme	1 (0.4)	0.1%
Diarrhea/entercolitis	1 (0.4)	1.5%
Blood CPK increased	1 (0.4)	0.1%

[1]Excluding topical steroids (Source: AESI and CM dataset; DCO: June 9, 2016; expected incidence as per avelumab PI and clinical review of BLA 761049)

The actual number of patients experiencing some of these events is higher than shown in the table because most patients did not receive steroids. . Although these events were not treated with corticosteroids, they may be immune-related. The overall incidences of these events on Study EMR 100070-001 are bulleted below.

- Colitis: Diarrhea and entercolitis were reported in 43/242 patients (18%).
- Hepatitis: All grade hepatic AEs were reported in 29/242 patients (12%) and Grade 3 hepatic AEs were reported in 11/242 (5%) patients.
- Nephritis: All grade and grade 3-4 acute kidney injury, increased creatinine, and glomerular filtration rate decreased were reported in 38/242 (16%) and 7/242 (3%) patients, respectively.

Pneumonitis

Pneumonitis and interstitial lung disease (ILD) have been associated with treatment with immunotherapy. During the treatment and follow-up periods, 6 patients in the 242 patient safety population (2.5%) were reported to have pneumonitis (no patients were classified as having interstitial lung disease); all of these events were classified by the investigator as being related to avelumab. Two of these patients were never-smokers. Dosing was delayed in 1 patient and was withdrawn in 2 patients, including in one patient with a grade 5 event. The incidence of pneumonitis as reported in the avelumab product label is 1.2%. This rate is slightly lower but is overall consistent with the (2.5%) seen in the urothelial cohort.

Three patients with pneumonitis (50%) were treated with immune modulating medication, including all of those patients with grade>1 pneumonitis. These patients had grades 2, 3, and 5 pneumonitis, respectively. They were all treated with corticosteroids at dose of at least 40 mg prednisone systemically or equivalent; none had resolution of their pneumonitis. The median time to onset for the first pneumonitis event was 84.5 days (range 3-165 d). (Source: AESI and CM Dataset).

The narrative summary for the patient who died of a grade 5 pneumonitis event (b) (6) is reviewed in section 7.4.4; briefly, this was a 54 year old patient who developed pneumonitis on Day 20 and died on Day 24 despite high-dose corticosteroid therapy. Patient had received one prior avelumab infusion.

Safety data on broader treatment-emergent AEs related to pulmonary events and infectious lung events are presented below. The table below also provides information on the incidence of pneumonitis as well as other pulmonary events. Overall, there were 142 relevant pulmonary events in 86 patients.

Table 33: Pulmonary AEs in the Safety Population

	Safety population n=242

	Overall n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Cough/ productive cough	35 (14)	0	0
Dyspnea/ exertional dyspnea	41 (17)	6 (2)	0
Pneumonia/Respiratory Infection[a]	20 (8)	6 (2)	0
Acute respiratory failure	2 (0.8)	1 (0.4)	0
Pleural effusion/ pleurisy	9 (4)	2 (0.8)	0
Pneumonitis	6 (2)	1 (0.4)	1 (0.4)
Pulmonary congestion/ respiratory tract congestion/ Upper respiratory tract congestion	4 (2)	0	0
Lung disorder	2 (0.8)	0	0

[a]Includes bronchitis/lung infection/upper respiratory tract infection/ viral upper respiratory tract infection (Source: ADAE dataset; DCO: 6-9-16)

Two additional patients with pneumonitis, (b) (6) were reported in the Safety Update. Patient (b) (6) had underlying rheumatoid arthritis. On Day 124, following an initial diagnosis of exacerbation of underlying COPD, he was diagnosed with pneumonitis in the setting of lung metastases. He received high-dose steroids and infliximab and the event was said to resolve. He permanently discontinued avelumab. On Day 154, patient (b) (6) developed pneumonitis and received high-dose steroids. The event resolved and the patient resumed avelumab. A grade 3 infusion reaction requiring hospitalization occurred with the next dose and the patient permanently discontinued avelumab.

Reviewer's Comment: Pneumonitis was the cause of the single avelumab-related death in the UC cohorts. It is a known complication of this class of agents and appears in the avelumab PI in the Warnings and Precautions section, as this fatal pneumonitis case was known and was previously reviewed as part of the greater safety database. Although the reviewed case was fatal despite high-dose corticosteroids, other patients have improved with high-dose steroid treatment; this AE should be recognized immediately with a high index of suspicion and treated promptly.

Hepatitis

Hepatitis is a concern with avelumab, and the product label includes this in the Warnings and Precautions section. There were two patients in the overall safety database who experienced grade 5 immune mediated hepatitis events (0.1%). There is a theoretical concern that the ADCC activity of avelumab could possibly contribute to increased hepatotoxicity. PD-L1 is constitutively expressed in non-parenchymal cells in the liver and expression of PD-L1 may be induced in hepatocytes under certain conditions (e.g., viral infection or interferon-alpha and –gamma). ADCC activity in the liver may be a contributing factor, which is absent with the other products. It could be a secondary mechanism of the hepatic toxicity, or it may potentially exacerbate the development of autoimmune hepatitis "priming" the immune response in the liver by causing an initial damage through ADCC.

After the two fatal hepatotoxicity events occurred in the broader Study EMR 100070-001 population, the Applicant made changes to the LFT eligibility criteria and enhanced monitoring of LFTs; these changes affected all 242 patients enrolled on the urothelial cohorts. These changes are presented and include:

- Added safety visits at Weeks 2, 4, and 6 for blood draws for the analysis of liver enzymes for subjects with liver metastases
- Modified Inclusion Criterion 7 regarding hepatic function so that all subjects enrolled in the expansion cohorts must have had ALT and AST ≤ 2.5 × ULN for subjects
- Added weekly clinical monitoring x 7 weeks for subjects with liver metastases at baseline, as well as laboratory samples for ALT, AST, total bilirubin, and alkaline phosphatase at Weeks 2, 4, and 6.

(Source- EMR 100070-001 protocol version 10 date Dec 22, 2014).

There were no fatal events of autoimmune hepatitis in the urothelial cohorts of Study EMR 100070-001. There were 2 cases of autoimmune hepatitis that were treated with systemic steroids. One patient was a 67-year-old M (b) (6) who developed grade 3 AST elevation leading the investigator to discontinue avelumab. The AE resolved after 125 mg IV of solumedrol IV was administered for two days. This was categorized as an autoimmune hepatitis and started after the patient had been treated for almost 6 months.

The second patient (b) (6) was a 67-year old M who developed grade 1 autoimmune hepatitis and was treated with Dexamethasone up to 8 mg orally approximately 9 months after beginning therapy with avelumab. Dosing of avelumab was interrupted for this event. (Source: AESI and CM Dataset).

Reviewer's Comment: The delayed onset of the hepatitis events reported in the urothelial safety population is not atypical of immune-mediated hepatitis seen with avelumab. In the sixteen patients in the pooled safety population (n=1738) who developed autoimmune hepatitis and who were reviewed in the clinical review of BLA 761049, the median time to onset for hepatitis events was 3.3 months (range: 1 week to 15 months).

Further exploration of hepatic adverse events was undertaken in the broader dataset of AEs occurring in the urothelial cohorts. Overall, adverse events suggesting a hepatic injury were seen in 36/242 (15%) of patients in the urothelial cohorts including 6% (15/242) with grade 3-4 events and no grade 5 events. Among the 15 patients with Grade 3-4 events, adverse event outcome was reported in 13 patients, with 12 events ongoing and 1 recovered after dose interruption.

Both hepatic adverse events and AEs related to abnormal hepatic laboratories are included in the table below.

Table 29: Hepatic AEs in the Safety Population

	Safety population n=242	
	Overall n (%)	Grade 3-4 n (%)
Aspartate aminotransferase increased	16 (7)	5 (2)
Blood alkaline phosphatase increased	15 (6)	7 (3)
Gamma-glutamyltransferase increased	9 (4)	7 (3)
Alanine aminotransferase increased	8 (3)	2 (0.8)
Blood bilirubin increased/ Hyperbilirubinaemia	6 (2)	1 (0.4)
Transaminases increased	3 (2)	0
Activated partial thromboplastin time prolonged	3 (2)	0
Drug-induced liver injury	1 (0.4)	1 (0.4)
Ammonia increased	1 (0.4)	0
Cholestasis	1 (0.4)	0
Hepatic function abnormal	1 (0.4)	0
Hepatic steatosis	1 (0.4)	0
Ischemic hepatitis	1 (0.4)	0

(Source: ADAE Dataset; DCO:6-9-16)

In the Safety Update, patient (b) (6) was reported to have Grade 3 autoimmune hepatitis that led to discontinuation. At baseline, the patient had a non-target liver lesion and normal AST/ALT. The event began on Day 235 and liver enzymes worsened to grade 3. The patient received 60 and then 40 mg prednisone daily. End of treatment laboratories show a grade 1 ALT and grade 4 GGT.

Reviewer's Comment: Although the Applicant instituted the above-described precautions in terms of enrollment and monitoring related to LFTs, dose-modification guidelines included in the avelumab PI are consistent with the other labels of PD-L1/PD-1-directed agents, i.e. withhold for grade 2, and discontinue for grade 3-4, for all patients, with no distinction made for those with liver metastases.

Colitis/ Diarrhea

The overall incidence of diarrhea was 19% with 4% grade 3-4 events. This is consistent with what has been previously reported with avelumab (all grade incidence of diarrhea of 23% in the Merkel cell population, and 17% in the overall Study EMR 100070-001 population).

Immune modulating medication was initiated in 1 patient with diarrhea/entercolitis, a 76 year-old M (b) (6). He began therapy on (b) (6) and developed Grade 3 diarrhea on (b) (6) (day 7), beginning high-dose steroids with on (b) (6) with solumedrol 125 mg IV until (b) (6). His diarrhea resolved, but avelumab was permanently discontinued.

Other relevant gastrointestinal AEs were explored. These 169 treatment-emergent events occurred in 93 patients. The table below provides information on the incidence of diarrhea and other select gastrointestinal events.

Table 35: Incidence of Select Gastrointestinal AEs

	Safety population n=242		
	Overall n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain)	47 (19)	6 (2)	1 (0.4)
Intestinal obstruction/ duodenal obstruction/ small intestinal obstruction	6 (2)	5 (2)	0
Vomiting/retching	37 (15)	3 (2)	0
Diarrhea/enterocolitis	43 (18)	4 (2)	0
Intestinal perforation	1 (0.4)	0	1 (0.4)
Gastrointestinal hemorrhage	1 (0.4)	0	1 (0.4)
Abdominal abscess	1 (0.4)	1 (0.4)	0
Gastrointestinal inflammation	1 (0.4)	0	0

(Source: ADAE; DCO:6-9-16)

Thyroid disease

Hypothyroidism/thyroiditis/thyroxine decreased occurred in 12/242 (5%) treated urothelial patients. Among these 12 patients (4 Grade 1 and 8 Grade 2), only 2 events led to dose delay (both grade 2), and none led to permanent discontinuation. This is generally consistent with the 6% incidence reported in the greater safety population of Study EMR 100070-001.

Hyperthyroidism/blood thyroid hormone increased occurred in 6/242 (2%) treated urothelial patients, with 4 patients developing grade 2 toxicity and the other 2 developing grade 1 toxicity. Two of the events led to dose delay and none led to permanent discontinuation.

The median time to development of thyroid AEs was 12 weeks. Hypothyroidism was ongoing without resolution for 8 patients and hyperthyroidism/ blood TSH increased was ongoing without resolution for 2 patients.

Ten patients received hormone replacement therapy with levothyroxine and 2 patients received systemic steroids for hyperthyroidism, both at low doses.

Reviewer's Comment: It is not uncommon for thyroid-related immune-mediated adverse events that develop on avelumab to be ongoing/ not resolve. In the broader safety database, using a strict definition of resolution that required patients to be free of symptoms and/or

any ongoing need for medical management, only eight (8%) of the 98 patients with thyroid disorders had complete resolution. Most patients, though deemed clinically "resolved," were still receiving levothyroxine, thiamazole or cortisone at the data cutoff for the analysis. Thus, these events, while not life-threatening, often linger and require prolonged and ongoing management.

Hypophysitis
There were no cases of hypophysitis that occurred in the urothelial cohorts of Study EMR 100070-001.

Adrenal insufficiency

Two patients developed adrenal insufficiency. Patient (b) (6) experienced this Grade 2 AE on day 29 and it resolved after 4 days, after drug was interrupted. The patient was given dexamethasone and prednisone 60 mg/d.

Patient (b) (6) developed Grade 3 adrenal insufficiency on day 379, which caused the investigator to permanently discontinue avelumab, without resolution of the AE (although it downgraded to Grade 2 after 3 days). The patient was treated with hydrocortisone 100 mg/d. No narrative summary of the event was provided.

In the broader safety database, 8/1738 patients (0.5%) developed immune-mediated adrenal insufficiency, including 1 patient with a Grade 3 event.

Diabetes Mellitus

There were no de novo cases of diabetes reported in the urothelial cohorts of Study EMR 100070-001.
The incidence of hyperglycemia and other related AEs are presented below.

Table 36: Select Hyperglycemic Adverse Events

	Safety population n=242	
	Overall n (%)	Grade 3-4 n (%)
Hyperglycemia	11 (5)	4 (2)
Blood glucose increased	2 (0.8)	1 (0.4)
Diabetes[a]	1 (0.4)	1 (0.4)

[a]Patient with pre-existing DM Type II (Source: ADAE; DCO:6-9-16)

Nephritis

There were 91 treatment-emergent Grade 1-4 adverse events related to acute kidney injury, increased creatinine, and other select renal-related adverse events that were seen in 55/242 of the urothelial patients (23%). There were 6 patients (2%) in whom these AEs were thought to be related to study drug. Four events led to dose delay and one led to drug discontinuation. Median onset of these events was day 42 (range; day 4-322). Duration was available for 61 events. Median duration of events was 12 days, with a range of 1-144 days. No patients received immune modulating medications for these events. In the broader safety database, there was one patient who experienced an immune-mediated renal AE and another who experienced a serious Grade 1 acute kidney injury thought to possibly be attributable to avelumab.

The table below explores select renal-related adverse events affecting patients in the urothelial cohorts.

Table 30: Renal AEs in Safety populations

	Safety population n=242	
	Overall n (%)	Grade 3-4 n (%)
Blood creatinine increased/blood urea decreased/glomerular filtration decreased	22 (9)	2 (0.8)
Acute kidney injury	13 (5)	4 (2)
Hematuria/hemorrhage urinary tract	12 (5)	4 (2)
Renal failure/prerenal failure	9 (4)	1 (0.4)
Urinary retention	4 (2)	2 (0.8)
Urine tract obstruction	2 (0.8)	2 (0.8)
Urine flow decreased	1 (0.4)	0
Proteinuria	2 (0.8)	0
Chronic kidney disease	2 (0.8)	1 (0.4)

(Source: ADAE; DCO: 6-9-16)

Rash

There were 37/242 (15%) urothelial patients who developed rash. This is a grouped term that also Includes dermatitis acneiform, eczema, erythema, erythema multiforme, rash, and erythematous, macular, maculo-papular, papular, and pruritic rash. The median onset of these events was 70 days (range 1-350). Information on the duration of the event was available for 44 events. Median duration of the event in these patients was 17 days (range 1-133 days). Among these 37 patients, there were 57 events with 40 thought to be related to study drug. Dose was delayed for 3 events and discontinued for 1 event. There was only one patient with a grade 3 event of rash; all others were grades 1-2.

There were 15/242 (6%) patients with rash (grouped term) who received concomitant medication for their rash, including topical therapies, and 4 who received high dose systemic

corticosteroids. In patients who received high dose steroids, one patient had a dose delay and another had a dose discontinuation due to these AEs; in two of these patients, the AE of rash did not resolve.

This is generally consistent with the 5% of 1738 patients in the pooled safety population who experienced immune-mediated rash during avelumab treatment; none of these patients experienced Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

Neurologic events

There were 53 patients who experienced 94 AEs that were classified under the neurological disorders SOC. The most frequent event was headache, followed by dizziness, dysgeusia, and somnolence.

Table 31: Neurological Adverse Events in the Study Population

	Safety population n=242		
	Overall n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Headache	16 (7)	1 (0.4)	0
Dizziness	10 (4)	0	0
Dysgeusia	7 (3)	0	0
Somnolence	5 (2)	1 (0.4)	0
Peripheral sensory neuropathy	4 (2)	0	0
Cerebrovascular accident	3 (1)	1 (0.4)	1 (0.4)
Neuralgia	3 (1)	1 (0.4)	0
Paresthesia	3 (1)	0	0
Amnesia	2 (0.8)	0	0
Balance disorder	2 (0.8)	0	0
Carotid artery stenosis	2 (0.8)	0	0
Encephalopathy	2 (0.8)	1 (0.4)	0
Hyperesthesia	2 (0.8)	0	0
Hypoesthesia	2 (0.8)	0	0
Neuropathy peripheral	2 (0.8)	0	0
Seizure	2 (0.8)	2 (0.8)	0
Tremor	2 (0.8)	0	0
Apraxia	1 (0.4)	0	0
Ataxia	1 (0.4)	0	0
Carpal tunnel syndrome	1 (0.4)	0	0
Cognitive disorder	1 (0.4)	0	0
Coma	1 (0.4)	0	0

	Safety population n=242		
	Overall n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Coordination abnormal	1 (0.4)	0	0
Guillain-Barre syndrome	1 (0.4)	1 (0.4)	0
Hemiparesis	1 (0.4)	1 (0.4)	0
Lethargy	1 (0.4)	0	0
Memory impairment	1 (0.4)	0	0
Parkinson's disease	1 (0.4)	0	0
Peripheral motor neuropathy	1 (0.4)	1 (0.4)	0
Sciatica	1 (0.4)	0	0
Speech disorder	1 (0.4)	0	0

Select neurologic AEs are reviewed below:

Patient (b) (6) was an 84-year-old female who had a fatal CVA on day 40, deemed unrelated to avelumab.

Patient (b) (6) was an 80-year old M who developed Grade 3 Guillain-Barre syndrome on day 70, thought to be related to avelumab. An associated event of serious Grade 2 motor peripheral polyneuropathy occurred 21 days after the previous (third) administration of avelumab and 7 weeks after the first administration of avelumab. Grade 3 Guillain-Barre syndrome was diagnosed 13 days after the most recent (fourth) infusion of avelumab. The fourth infusion was given 4 weeks (rather than 2 weeks) after the third infusion due to polyarthritis. Electromyography showed a conduction block compatible with Guillain-Barre syndrome. The clinical picture (tremors in the 4 limbs and decrease in muscle strength) was compatible with Guillain-Barre, although the lumbar puncture result was not typical of Guillain-Barre syndrome. The subject received steroids and gamma globulin. The event improved to Grade 2 after approximately 3 weeks and further improvement to Grade 1 (ongoing) after an additional 6 months. Administration of avelumab was discontinued due to Guillain-Barre syndrome.

There were three reported cases of encephalopathy.
Patient (b) (6) was a 68-year-old F who received one dose of avelumab on (b) (6). She developed acute respiratory failure, pleural effusion, and pneumonia (Grade 3) on (b) (6), (b) (6) which was study day 11. By the next day, she developed ischemic hepatitis and septic shock, with renal failure developing a day later. By day 19, she developed cardiomyopathy, coma, and encephalitis, and she continued to develop complications including a cerebrovascular accident, pulmonary embolus, lactic acidosis, and increased ammonia, with her death on (b) (6) (day 24) attributed to disease progression. The encephalopathy in this case does not appear to be immune-mediated but rather multifactorial and related to overall deterioration due to pneumonia and related end-organ damage and shock.

Patient (b) (6) was an 81-year old male; he received one dose of avelumab and experienced sepsis Grade 4 on Day 39, dying of sepsis on Day 40. Causes of the sepsis were thought to possibly include flank cellulitis or urinary tract infection. He also experienced a Grade 3 encephalopathy, listed in the narrative as toxic-metabolic, on day 31, which was not thought to be related by the investigator to avelumab. He also developed grade 3 volume overload and Grade 4 hypotension prior to the encephalopathy.

Patient (b) (6) was a 79-year old male; he experienced serious asthenia requiring hospitalization on two occasions- day 23 (after his second dose of avelumab) and on day 36 (after his third and last dose of avelumab). He also had progression of hepatic metastases confirmed on day 36, and had discontinuation of avelumab related to disease progression. He had an episode of encephalopathy that occurred on day 62 of therapy, lasting 2 days, and occurring 36 days after his last dose of avelumab. This episode is not discussed in the narrative.

One patient was reported to have the AE of Parkinson's Disease, grade 1, with no accompanying narrative summary submitted by the Applicant. Patient (b) (6) was a 77-year-old male who developed the AEs of dyspnea, hypotension, tremor, and decreased weight on day 44 of treatment and then anxiety and non-cardiac chest pain on day 86, further developing depressive symptoms, memory impairment and Parkinson's Disease, and speech disorder on day 99. Further AEs included Grade 4 sepsis on day 121 and Grade 5 disease progression. The patient had no known history of Parkinson's and this AE was not thought to be related to avelumab by the investigator; no steroids were given for this AE. It is unclear if this is an immune-mediated event. The safety databases of the PD-1/L1 inhibitors will be followed for other reports of Parkinson's disease.

Ocular events

There were 15 ocular adverse events affecting 9 of the urothelial patients, one of which was a grade 3 event. Additionally, one patient experienced grade 2 uveitis requiring permanent discontinuation of avelumab therapy.

Table 32: Ocular AEs Occurring in the Safety Population

	All grades (n=242)	Grades 3-4 (n=242)
Dry eye	2	0
Vision blurred	2	0
Cataract	1	1
Conjunctival deposit	1	0
Conjunctivitis allergic	1	0
Diplopia	1	0

Eye pain	1	0
Eye pruritus	1	0
Lacrimation increased	1	0
Macular degeneration	1	0
Periorbital edema	1	0
Uveitis	1	0
Vitreous floaters	1	0

(Source: ADAE; DCO: 6-9-16)

Systemic Inflammatory Response Syndrome (SIRS)

This AE is known to occur with avelumab, and occurred to one patient in the broader avelumab safety database. The known event was a serious grade 3 SIRS that occurred four days after the fourth avelumab dose with no alternative etiology. Blood cultures were negative. The patient was treated with high dose corticosteroids and broad spectrum antibiotics and improved. There were two reported cases of SIRS in the urothelial cohorts of Study 001. The first was a grade 1 event occurring in a 64 year old male on day 107. It was not thought to be related to avelumab and was not treated with immunomodulatory medication. It did not result in dose modification or interruption of avelumab although it was ongoing at data cut-off.

The second SIRS case occurred in a 78-year-old male (b) (6) who received one dose of avelumab and had treatment permanently discontinued due to grade 3 dehydration, which occurred on day 25. Prior to that he had poor oral intake and constipation, but after taking magnesium citrate he developed diarrhea with 7-8 stools over 24 hours. He developed weakness and mental confusion as well as elevated WBC count to 24.7 and elevated creatinine to 1.97. His condition improved with hydration but he died on day 31; dehydration was ongoing at the time. The AE of grade 3 SIRS occurred on days 3-5 and resolved without immunomodulatory medication; it was not thought to be related to avelumab and is not described in the patient narrative.

Rheumatologic Disorders

Rheumatologic events of note occurred in the following patients:

Patient (b) (6) was an 81-year old male who developed the AE of polyarthritis Grade 2 on day 35 of treatment, worsening to Grade 3 on day 55 of treatment. The polyarthritis was thought to be related to avelumab and caused dose interruption. He then developed Guillain-Barre syndrome on Day 70, which was Grade 3 and caused permanent discontinuation of avelumab. Of note, he had a history of peripheral motor neuropathy and diabetes mellitus type II that predated his treatment with avelumab.

Patient (b) (6) was a 66-year old male who developed a non-serious, Grade 1 event of rheumatoid arthritis on day 23 of treatment (16th infusion). He had previously experienced

arthralgia Grade 1 on the day of his 3rd infusion of avelumab (day 28). On three subsequent occasions, the arthralgia worsened to Grade 2 and then improved to Grade 1; all events were categorized as non-serious. He was treated with low doses of oral prednisone intermittently; eventually, he was treated with an ongoing regimen of 7.5 mg of oral prednisone daily and discontinued from avelumab due to arthralgia. The rheumatoid arthritis was assessed as related to avelumab and was categorized as an immune-mediated adverse event.

There were no other rheumatologic events, such as Sjogren's syndrome or polymyalgia rheumatica in the integrated urothelial carcinoma population

Thrombocytopenia

There were 2 patients who had thrombocytopenic events that were explored further as being possibly immune-mediated.

Patient (b) (6) was a 67 year-old female with a platelet count of 17 $x10^9$/L at baseline. She developed transient Grade 3 thrombocytopenia on Day 15 of treatment, as well as Grade 3 platelets on Day 43. By the end of treatment, she had developed Grade 4 thrombocytopenia, with platelets of $12x10^9$/L. She died shortly after the development of thrombocytopenia due to general physical health deterioration, and also had Grade 3 anemia, renal and hepatic failure at the time of death. The narrative is inadequate to determine whether the patient had immune thrombocytopenia.

Patient (b) (6) was reported to have developed a Grade 3 AE of t hrombocytopenic purpura. His platelets were 246 $x10^9$/L at baseline and remained >200 $x10^9$/L throughout the time course of his treatment. He has one recorded value of platelets of 4 x 10^9/L on day 97 of treatment although the values recorded one week prior and one week subsequent are 301 x 10^9/L and 272 x 10^9/L, respectively. He did receive one platelet transfusion after the low value was recorded, and dosing of avelumab was interrupted for this AE. This does not appear to be a clinical case of thrombotic thrombocytopenic purpura or immune-mediated thrombocytopenia due to the single isolated low platelet value and the recovery to baseline with no immunomodulatory medications and the absence of other AEs, such as neurologic sequelae, around or after that time.

No other immune-mediated thrombocytopenia events were reported in the broader safety database.

Pancreatitis

Amylase and lipase were collected at baseline, Weeks 7 and 13, every 6 weeks, then 28 days and 10 weeks after the last dose. Patients were allowed to continue therapy despite Grade 4 amylase or lipase elevation if asymptomatic.

Review of the ADAE dataset revealed 9 patients who were reported to have experienced AEs of amylase increased or lipase increased, with 5 patients experiencing Grade 3-4 AEs, and 1 patient who experienced the AE of pancreatitis acute, grade 3. Review of available laboratory data showed that 23/178 patients (13%) developed grades 1-4 elevated amylase, with 4/178 (2%) developing Grade 3-4 events; 36/188 patients (19%) developed grades 1-4 elevated lipase, with 11/178 (6%) developing Grade 3-4 events.

There was one patient with a reported AE of acute pancreatitis. Patient (b) (6) was a 66-year old male who developed Grade 3 acute pancreatitis; no narrative is provided for this event. The pancreatitis began on day 148 and lasted 43 days. It was assessed as unrelated to avelumab, and the patient recovered.

There were no immune-mediated pancreatitis events that were identified in the broader safety database.

Infusion reactions

For defining an AE as an IRR, the onset of the event in relation to avelumab administration and time to resolution was considered if the following criteria were met: All AEs identified by the MedDRA PTs of infusion related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity, and Type 1 hypersensitivity, were considered potential IRRs when onset was within 24 hours of avelumab infusion (during or after the infusion. Pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria within 2 days of avelumab infusion were also considered potential IRRs.

Premedication with an antihistamine and with acetaminophen was mandatory for all the urothelial cohort patients (although it had been optional for patients enrolled on study EMR 100070-001 prior to a January 29, 2014 protocol amendment; this did not affect the urothelial patients and all patients received premedication prior to their first infusion). Premedication consisted of an antihistamine and acetaminophen approximately 30 to 60 minutes prior to each dose of avelumab (e.g., 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen). This regimen may have been modified based on local treatment standards and guidelines, as appropriate.

Review of the safety data in the urothelial cohorts reveals that there were 74/242 (31%) patients with 94 events who were categorized as having an infusion reaction (grouped term), including 71/242 (29%) who received concomitant medications for these reactions**,** only one of whom experienced a grade 3 reaction. The most commonly-used medications included diphenhydramine, acetaminophen, dexamethasone, hydrocortisone, and ibuprofen. There were 21 patients who received high-dose steroids for this indication (defined as a prednisone dose of 40 mg or greater). The can be compared to the 25% (439/1738) overall and 0.7% (12/1738) Grade 3-4 incidence of infusion reactions reported in the avelumab product label.

In 22 cases, drug interruption occurred and in two cases, drug was withdrawn.

Table 33: Infusion Related Reactions, Overall Safety Population

	Safety population n=242	
	Overall n (%)	Grade 3-4 n (%)
Any	71 (31)	1 (0.4)
Infusion related reaction	56 (23)	0
Chills	12 (5)	0
Pyrexia	8 (3)	0
Back pain	2 (0.8)	0
Flushing	2 (0.8)	0
Drug hypersensitivity	1 (0.4)	0
Dyspnea	1 (0.4)	1 (0.4)
Hypersensitivity	1 (0.4)	0
Hypotension	1 (0.4)	0

(Source: ADSI and CM datasets; DCO: 6-9-16)

Reviewer's Comment: IRRs reported with avelumab occur at a much higher than rate than the rate reported with similar-in-class agents. For example, atezolizumab reports a 2% incidence of IRRs, with no grade 3-4 events reported[6]. The higher incidence of IRR that occur with avelumab despite premedication is likely related the intact Fc region in this antibody which is not present in other, similar agents such as atezolizumab. Overall, the added toxicity is not thought to change the overall benefit: risk profile of avelumab for patients with metastatic urothelial carcinoma. Infusion related reactions appear in the Warnings and Precautions section of the avelumab PI, as 25% (439/1738) of patients in the broader safety database developed these reactions, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 events. It appears that premedication as used in the trial did not lower the incidence of IRRs but may have lessened the severity of the reaction. Monitoring and management guidelines for IRRs are addressed in product labeling. Because less than 1% of patients in the pooled population experienced their first infusion reaction at the fourth or later infusion, and none of the grade 3+ infusion reactions occurred after the second infusion, the avelumab PI only recommends premedication with an antihistamine and acetaminophen prior to the first 4 infusions.

An additional analysis was undertaken by the reviewers of this BLA as it became apparent that a substantial number of the IRRs occurring with avelumab occurred at a delayed interval, i.e. after the infusion of avelumab was already complete. It was felt that this information would be clinically relevant to those administering avelumab to patients to inform decisions about monitoring after completion of the avelumab infusion. This analysis is presented below.

Overall, there were 582 relevant AEs in 438 patients (25%) among the greater avelumab safety population of 1738. **There were 301 AEs in 245/1738 (14.1%) pts that were reported as occurring after the avelumab infusion completed, including 6 that occurred on the day after**

infusion. Among these 6 AEs were 4 that were considered to be related to avelumab; two occurred at the second or later avelumab infusion, including a patient with chills (grade 1) that occurred when dosed with avelumab on day 199.

Table 34: Infusion Related AEs in the Greater Avelumab Safety Database, N=1738

	# Adverse Events	During	After	Occurred the Day After Infusion
Any	**582**	**275**	**301**	**6**
Abdominal Pain	4	0	4	0
Anaphylactic Reaction	1	0	1	0
Back Pain	14	13	1	0
Chills	101	22	79	0
Drug Hypersensitivity	4	3	1	0
Dyspnea	6	4	2	0
Flushing	6	5	1	0
Hypersensitivity	3	2	1	0
Hypotension	6	3	3	0
Infusion-related Reaction	372	219	147	6
Pyrexia	64	3	61	0
Type 1 Hypersensitivity	1	1	0	0

(Source: ADAE, ISS dataset; DCO: 6-9-16)

Fifteen grade 3-4 AEs were reported in 12 patients in the overall safety database of 1738 patients (0.7%). In terms of timing of these grade 3-4 AEs, 11 occurred during and 4 after the avelumab infusion.

Reviewer's Comment: The fact that delayed infusion reactions occurring after the avelumab infusion had completed were reported in 14% of patients in the greater avelumab safety database was thought to be clinically relevant and was therefore added to the updated avelumab PI. Of note, the number used in the PI is 252 delayed events, as per the Applicant's own calculations using slightly different grouping parameters.

Treatment Emergent Adverse Events and Adverse Reactions

The table below provides information on the adverse events that occurred in at least 10% of patients within 30 days of their last dose of avelumab. Adverse events were to be collected up to 28 days after the last dose and related AEs between Day 29 and the 10 week follow up visit. Related SAEs were to be collected at each survival follow up. The table below includes AEs submitted in Amendment 4 (data cutoff June 9, 2016) and the Safety Update (data cutoff September 30, 2017). Several composite terms are used and the grouping of preferred is included in the Appendix. Disease progression (and related terms) is not included in the table.

The incidences of most of the adverse events were similar at these two cutoff dates. However, the adverse event hyponatremia increased to 11% with the Safety Update.
The common adverse events with avelumab are similar to the adverse events seen with atezolizumab and nivolumab. However, the incidence of infusion-related reactions (despite pre-medication) is higher with avelumab.

Note that the composite term creatinine increased/renal failure includes 20 patients identified by the terms acute kidney injury or renal failure. Creatinine increased identifies 17 additional pts, including 4 pts with grade 1 events. Inclusion of urosepsis and sepsis/bacteremia within the composite term urinary tract infection adds 3 patients. Sepsis/bacteremia was included in this term only used if it occurred on the same day as a UTI or urinary obstruction.

An increase in the incidence of infection was seen in a randomized trial of atezolizumab, another PD-L1 inhibitor. In a randomized study of non-small cell lung cancer, the incidence of infection was 43% in the atezolizumab arm and 34% with docetaxel. In a single-arm trial of atezolizumab in urothelial cancer, the incidence of infection was 38%. With avelumab, using all the preferred term under the system organ class Infections and Infestations, the incidence of infection was 42% (all grades), with 13% grade 3-4. Since data is only available from a single-arm study it is unclear whether the incidence of infection with avelumab is higher that the underlying incidence of infection in patients with cancer.

Table 35: Adverse Events Within 30 Days of Avelumab in ≥ 10% of Patients

	Urothelial Cancer and Prior Platinum-based Therapy N = 242			
	Grade 1-5	Grade 3-4	Grade 1-5	Grade 3-4
Any	237 (98)	143 (59)	239 (99)	155 (64)
Blood Disorders				
Anemia	45 (19)	18 (7)	48 (20)	20 (8)
Gastrointestinal Disorders				
Nausea	58 (24)	3 (1)	59 (24)	4 (2)
Abdominal Pain	47 (19)	6 (2)	49 (20)	6 (2)
Constipation	44 (18)	2 (1)	46 (19)	2 (1)
Diarrhea	43 (18)	4 (2)	46 (19)	4 (2)
Vomiting	37 (15)	3 (1)	39 (16)	4 (2)
General Disorders				
Asthenic Conditions	100 (41)	16 (7)	104 (43)	19 (8)
Peripheral Edema	41 (17)	1 (0.4)	42 (17)	1 (0.4)
Pyrexia	39 (16)	2 (1)	40 (17)	2 (1)
Infections				
Urinary Tract Infection	53 (22)	14 (6)	59 (24)	17 (7)
Injury, Poisoning, and Procedural Complications				
Infusion Reaction	74 (31)	1 (0.4)	73 (30)	2 (0.8)

	Urothelial Cancer and Prior Platinum-based Therapy N = 242			
	Grade 1-5	Grade 3-4	Grade 1-5	Grade 3-4
Investigations				
Weight Decreased	49 (20)	0	50 (21)	0
Metabolism and Nutrition Disorders				
Decreased Appetite	52 (21)	4 (2)	54 (22)	5 (2)
Hyponatremia	23 (9.5)	15 (6)	26 (11)	19 (8)
Musculoskeletal Disorders				
Musculoskeletal Pain	61 (25)	8 (3)	68 (28)	8 (3)
Renal Disorders				
Creatinine Increased/Renal Failure	38 (16)	7 (3)	40 (17)	8 (3)
Respiratory Disorders				
Dyspnea	41 (17)	6 (2)	44 (18)	7 (3)
Cough	35 (14)	0	41 (17)	0
Skin Disorders				
Rash	37 (15)	1 (0.4)	41 (17)	1 (0.4)
Pruritus	25 (10)	1 (0.4)	26 (11)	1 (0.4)
Vascular Disorders				
Hypertension	26 (11)	13 (5)	30 (12)	14 (6)
Data Cutoff	June 9, 2016		September 30, 2017	

(Source: ADAE)

The adverse event dataset submitted in Amendment 4 with a June 9, 2016 cutoff had 1 term (muscle spasms) that was not mapped to a preferred term and 4 events that were not graded. The term "muscle spasms" was mapped to myalgia during the review. The adverse event dataset submitted in the Safety Update with a September 30, 2017, cutoff had no unmapped adverse events and 8 adverse events that were not graded.

Adverse Events > 30 Days after the Last Dose of Avelumab

The table below provides information on AEs that were reported more than 30 days after the last dose of avelumab. Note that AE collection was limited beyond 28 days after the last dose. Among the 76 AEs in 30 pts, 7 AEs in 6 pts were considered related to avelumab. These include Guillain-Barre syndrome (previously reported), hypothyroidism, lipase increased, diarrhea, ALT increased, creatinine increased, and asthenia.

Table 36: Adverse Events Greater than 30 Days of Avelumab in > 1 Patient

	Urothelial Cancer and Prior Platinum-based Therapy N = 242 (%)	
	Grade 1-5	Grade 3-4
Any	30 (12)	13 (5)

	Urothelial Cancer and Prior Platinum-based Therapy N = 242 (%)	
	Grade 1-5	Grade 3-4
Asthenic Conditions	4 (2)	1 (0.4)
Abdominal Pain	3 (1)	1 (0.4)
Anemia	3 (1)	3 (1)
Creatinine Increased/Renal Failure	3 (1)	1 (0.4)
Thrombocytopenia	3 (1)	3 (1)
Atrial Fibrillation	2 (1)	0
Musculoskeletal Pain	2 (1)	0
Oral Candidiasis	2 (1)	0

(Source: ADAE; DCO: 9-30-17)

Laboratory Findings

Laboratories were obtained in all the patients at study entry. However, many were not accompanied by the normal range and the result was not graded by the Applicant. The number of patients with available laboratory values varied from 210-242, depending on the test. Given the study entry requirements, few grade 3-4 abnormalities were seen at baseline. Grade 3-4 abnormalities at baseline included: lymphopenia (0.9%), AKP increased (1%), GGT increased (4%), hyponatremia (3%), hyperglycemia (0.8%), hypophosphatemia (1%), elevated lipase (1%), elevated triglyceride (0.9%) and in 1 patient each ALT increased, hypokalemia, and increased CK.

The table below provides information on the on-study laboratory abnormalities (including the end of treatment visit).

Table 37: On Study Laboratory Abnormalities

Prior Platinum-based Therapy N = 242						
	N	Grade 1-4 N (%)	Grade 3-4 N (%)	N	Grade 1-4	Grade 3-4
Hematology						
Leukopenia	225	36 (16)	0	227	37 (16)	0
Neutropenia	221	26 (12)	2 (0.9)	221	27 (12)	2 (0.9)
Lymphopenia	219	138 (63)	25 (11)	221	145 (66)	27 (12)
Anemia	229	206 (90)	14 (6)	230	207 (90)	17 (7)
Thrombocytopenia	227	68 (30)	1 (0.4)	229	70 (31)	1 (0.4)
Liver Function Tests						
AST	232	72 (31)	7 (3)	234	76 (32)	8 (3)
ALT	232	52 (22)	2 (0.9)	234	54 (23)	3 (1)
Bilirubin	232	23 (10)	3 (1)	232	24 (10)	2 (0.8)

Prior Platinum-based Therapy N = 242						
	N	Grade 1-4 N (%)	Grade 3-4 N (%)	N	Grade 1-4	Grade 3-4
AKP	230	103 (45)	16 (7)	232	109 (47)	17 (7)
GGT	192	76 (40)	23 (12)	197	82 (42)	24 (12)
Electrolytes and Renal Function						
Creatinine	231	139 (60)	5 (2)	231	144 (62)	5 (2)
Hypernatremia	235	14 (6)	0	235	15 (6)	0
Hyponatremia	235	111 (47)	37 (16)	235	118 (50)	38 (16)
Hyperkalemia	235	61 (26)	8 (3)	235	67 (29)	8 (3)
Hypokalemia	235	26 (11)	1 (0.4)	235	30 (13)	2 (0.9)
Hypercalcemia	234	23 (10)	1 (0.4)	234	25 (11)	1 (0.4)
Hypocalcemia	234	77 (33)	3 (1)	234	78 (33)	3 (1)
Hyperglycemia	235	200 (85)	22 (9)	235	203 (86)	22 (9)
Hypoglycemia	235	17 (7)	2 (0.9)	235	19 (8)	2 (0.9)
Hypermagnesemia	232	16 (7)	2 (0.9)	232	17 (7)	3 (1)
Hypomagnesemia	232	68 (29)	1 (0.4)	232	73 (31)	2 (0.9)
Hypophosphatemia	233	62 (27)	13 (6)	233	67 (29)	14 (6)
Other Chemistries						
Elevated Amylase	178	23 (13)	4 (2)	181	26 (14)	5 (3)
Elevated Lipase	188	36 (19)	11 (6)	191	39 (20)	14 (7)
Elevated Cholesterol	187	48 (26)	2 (1)	188	53 (28)	2 (1)
Elevated Triglyceride	191	87 (46)	0	192	95 (49)	0
Elevated Creatine Kinase	167	18 (11)	2 (1)	172	22 (13)	2 (1)

At baseline, TSH was > 3xULN in 3/225 pts, > 10 xULN in 0 pts, and < LLN in 15 pts. Among the 15 pts who had a TSH < LLN at baseline, 2 had an elevated free T4. On study, 8/146 pts had a TSH > 3xULN and 5/146 a TSH > 10xULN. There appeared to be pts with both primary (high TSH, low T4) and secondary (low TSH and T4) hypothyroidism. Among the 16 pts who had a TSH < LLN on study, only 5 had an elevated free T4. Three of the 16 pts with a TSH < LLN on study had a TSH < LLN at baseline. Only 1 patient had laboratories consistent with hyperthyroidism followed by hypothyroidism.

Examination of the abnormal laboratory values in the table above found no explanation for the grade 3-4 hematological abnormalities seen on study. Both patients with grade 3 ANCs and 1 patient with grade 4 platelets had a transient decrease in counts. However, the other patient with grade 4 platelets, (b) (6) died shortly after the development of thrombocytopenia due to general physical health deterioration. At the time of death the patient had grade 3 anemia, renal, and hepatic failure. The narrative is inadequate to determine whether the patient had immune thrombocytopenia.

Liver enzymes were examined for patients who met biochemical criteria for Hy's law (AST/ALT > 3xULN and bilirubin > 2xULN). Two patients met these criteria, however, both had concomitant elevated alkaline phosphatase and an alternative etiology rather than avelumab-related toxicity, and these cases were not considered as Hy's Law cases.

1. Patient (b) (6) was an 85-year old male with liver metastases at baseline as per independent review. He received his first dose of avelumab on (b) (6) but was discontinued on 8/3/15 with reason for discontinuation being disease progression. He had developed grade 2 elevation in alkaline phosphatase by his week 3 day 15 visit; by his week 5 day 29 visit he had developed grade 3 elevation in alkaline phosphatase, grade 2 AST elevation, and grade 2 bilirubin. However, elevated alkaline phosphatase and progression of disease are alternative explanation for the elevated transaminases and bilirubin.

2. Patient (b) (6) was a 54-year-old male who developed elevated LFTs after his 4th infusion of avelumab, which was 14 days after the previous infusion and 56 days after his first infusion. He had concomitant grade 3 elevations in alkaline phosphatase, ALT, and bilirubin. He also had a CT scan that showed new innumerable liver lesions and lung lesions. He was treated with high doses of steroids x 4 days as well as mycophenolate mofetil, but the event was ongoing. He was discontinued from avelumab due to AST increased. The investigator assessed the AST increase as being related to progression of disease.

Among the chemistries, abnormalities were noted in creatinine, sodium, calcium, and amylase/lipase. The grade 3-4 elevations in creatinine on study appear to be related to obstruction or sepsis. Among the 38 pts with grade 3 hyponatremia in the Safety Update, 3 of these pts had grade 3 hyponatremia and baseline and an additional 12 had grade 1 hyponatremia. On study, only 1 had a grade 2-4 elevation in potassium at the time of grade 3 hyponatremia. Six had laboratory evidence of hypothyroidism. Examination of grade 3-4 hypocalcemia found that when corrected for albumin, 2 of the 3 pts had an improvement to grade 1-2 hypocalcemia. The third patient did not have an albumin at the time of the grade 4 calcium, but the most recent corrected calcium was grade 1. Among the 15 pts with grade 3-4 amylase and/or lipase, none had evidence of pancreatitis. However, 4 pts had an elevation in both amylase and lipase. One of these 4 reported intermittent nausea. Finally, 2 pts had grade 3-4 creatine kinase level. In both pts, the elevation in creatine kinase was associated with liver dysfunction.

Since avelumab has an intact Fc regions, lymphopenia was further examined on avelumab. At baseline, 2 pts had grade 3-4 lymphopenia. This increased to 27 (12%) pts on study. This is consistent with the incidence of grade 3-4 lymphopenia with atezolizumab (10%) and nivolumab (9%) in pts with urothelial cancer.

Vital Signs

Vital signs were not reviewed. As per the Applicant's analysis presented in the Summary of Clinical Safety, there was no overall evidence of any effect of avelumab on any vital sign parameters (weight, BMI, and diastolic and systolic blood pressure).

Changes in vital signs related to the administration of avelumab are considered under Infusion Related Reactions above.

Electrocardiograms (ECGs)

During Study EMR 100070-001, 12-lead ECGs were assessed during screening, prior to the infusion and 2 hours ± 20 minutes after the end of the infusion at each visit on Days 1, 15, 29, 43, 57, 71, and 85 and every six weeks thereafter while on treatment. The following criteria were used to identify potentially clinically significant abnormalities (PCSA) for ECG results.

Test	Potentially Clinically Significant Abnormalities (PCSA) Criteria
Heart rate	≤ 50 bpm and decrease from Baseline ≥ 20 bpm ≥ 120 bpm and increased from Baseline ≥ 20 bpm
PR interval	≥ 220 ms and increase from Baseline ≥ 20 ms
QRS	≥ 120 ms
QTcF, QTcB absolute	interval > 450 to ≤ 480 ms interval > 480 to ≤ 500 ms interval >500 ms
QTcF, QTcB change from Baseline	Increase from Baseline ≥ 30 ms and ≤ 60 ms Increase from Baseline > 60 ms

bpm: beats per minute; ms: milliseconds.

As per the Applicant, clinical ECG analyses, including ECG summary and exposure-QTc analysis, showed that avelumab does not have a clinically relevant effect on cardiac repolarization. The overall incidence of cardiac disorders in the urothelial carcinoma cohorts was 19/242 (8%), with tachycardia/sinus tachycardia being the most common AE 7/242 (3%). This is not unexpected given the demographic and clinical profile of this advanced urothelial cancer population.

QT

A thorough QT study was conducted using the ECG results from a pooled population of approximately 1600 patients treated in three open-label, single-arm studies of avelumab in patients with advanced solid tumors including patients from Study EMR 100070-001; these results are discussed in the clinical review of BLA 761049. Briefly, no large changes in the mean change from baseline QTc interval were detected when avelumab was administered at the intended marketing dose of 10 mg/kg.

With regard to the exposure-QTc analysis, there was no evident relationship between avelumab concentrations and ΔQTc. See the Clinical Pharmacology Review and QT-IRT consult in the review of BLA 761049 for additional information regarding QT abnormalities and for an assessment of the exposure-QTc analysis.

Immunogenicity

The blood samples for screening for human antihuman-antibody (HAHA) were collected prior to study drug administration and on Day 1. During treatment with avelumab, samples were collected within 2 hours prior to study drug infusion on Days 15, 29, 43 (every 2 weeks), then every 6 weeks thereafter while on treatment, and at the End-of-Treatment visit. The assay used to detect HAHA is not validated.

In the platinum-exposed urothelial cohorts of Study EMR 100070-001, 10 of 216 patients with a valid HAHA result tested positive (4.6%). Overall in Study EMR 100070-001, 53 of 1396 patients (4%) with a valid HAHA result tested positive. Although the numbers are limited, the incidence of TEAEs was similar in patients with HAHA positivity as compared to patients who were never positive. The rate of IRRs was 34% in those with a positive result as compared to 24% in patients with negative results; however, an association with HAHA positivity cannot be determined in this very limited sampling of patients. Further, only four of the patients experienced IRRs at or after HAHA was detected, and three of these patients discontinued treatment due to IRRs. (Source: HAHA dataset; clinical review of BLA 761049).

7.4.5. Analysis of Submission-Specific Safety Issues

See section 7.4.4 for a detailed analysis of immune mediated AEs and Infusion Related Reactions occurring during treatment with Avelumab.

7.4.6. Safety Analyses by Demographic Subgroups

Subgroup analysis based on race was not performed as the study population was largely White. Subgroup analyses based on age and gender are shown below.

Age was not reported in 3 patients and they are not included in the subset analysis. The number of grade 3-4 adverse events was similar in the 2 age groups. In those ≥ 65 years, there was an increase in asthenic conditions while there was an increase in UTIs in those < 65 years.

Table 38: All Grade Adverse Events in ≥20% of Patients by Age

	Prior Platinum-based Therapy N = 242

	< 65 Years N = 78 (%)	≥ 65 Years N = 161
All Grades	78 (100)	159 (99)
Grade 3-4	50 (64)	101 (63)
	All Grades	All Grades
Asthenic Conditions	30 (38)	72 (45)
Infusion-related	23 (29)	50 (31)
Musculoskeletal Pain	21 (27)	41 (25)
Nausea	19 (24)	40 (25)
Decreased Appetite	15 (19)	36 (22)
Urinary Tract Infection	21 (27)	34 (21)
Weight Decreased	16 (21)	32 (20)

Source: ADAE dataset; data cutoff June 9, 2016

Analysis of differences in the adverse event profile of avelumab in men and women should be interpreted with caution since the number of female patients is small. There appears to be an increased in grade 3-4 adverse event in women as well as an increase in infusion-related event and nausea. Men showed an increase in asthenic conditions, musculoskeletal pain, and weight loss.

Table 39: All Grade Adverse Events in ≥ 20% of Patients by Sex

	Prior Platinum-based Therapy N = 242	
	Male N = 175 (%)	Female N = 67 (%)
All Grades	171 (98)	66 (99)
Grade 3-4	102 (58)	44 (66)
	All Grades	All Grades
Asthenic Conditions	75 (43)	17 (25)
Infusion-related Reaction	50 (29)	23 (34)
Musculoskeletal Pain	52 (30)	10 (15)
Nausea	37 (21)	22 (33)
Decreased Appetite	35 (20)	16 (24)
Urinary Tract Infection	38 (22)	17 (25)
Weight Decreased	39 (22)	10 (15)

Source: ADAE dataset; data cutoff June 9, 2016

7.4.7. Specific Safety Studies/Clinical Trials

Not applicable.

7.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Carcinogenicity studies were not conducted for this anti-cancer drug.

Pediatrics and Assessment of Effects on Growth

Avelumab has not been studied in a pediatric population and the Applicant has received a waiver for this indication since urothelial carcinoma is rare in children.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Patients have received up to 20 mg/kg of avelumab. Experience is not available with a higher dose and no accidental overdoses have been reported. Drug abuse, withdrawal, and rebound are not applicable to avelumab.

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Avelumab has been granted accelerated approval as a new molecular entity in the treatment of metastatic Merkel cell carcinoma as of March 23, 2017. This approval occurred approximately one month prior to the anticipated approval date in the urothelial carcinoma setting, therefore, little cumulative postmarketing safety data is available.

Expectations on Safety in the Postmarket Setting

Not applicable.

7.4.10. Integrated Assessment of Safety

The evaluation of the safety of avelumab in patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy was primarily based on the 242 patients in the urothelial cohorts of Study EMR 100070-001, an open-label, multicenter, single arm trial. In select cases, a broader database provided by the Applicant looking at a pooled population of patients with various advanced solid tumors from Study EMR 100070-001 as well as patients from a single-arm trial of patients with Merkel cell carcinoma (Study 003) who received avelumab at a dose of 10 mg/kg every two weeks was also analyzed to support the safety review. The size of the pooled safety database (n=1738) was considered adequate to characterize the safety profile of avelumab.

In the urothelial cohorts of Study EMR 100070-001, there was one avelumab-related fatal AE, which was a case of pneumonitis. Non-fatal SAEs occurred in 41% (n=100) of patients, AEs

leading to permanent discontinuation occurred in 12% (n=30), and treatment-emergent Grade 3-4 AEs occurred in 59% (n=143) of patients. The most common AEs (≥20% of patients) in the urothelial patients enrolled in Study EMR 100070-001 included fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection. Similar incidences of these AE categories were observed in the pooled analysis.

Serious risks of avelumab are similar to those of other monoclonal antibodies acting in the PD - 1/PD-L1 pathway including imARs, including risk of fatal imARs and IRRs. ImARs occurred in 14% (n=33) of urothelial patients in Study EMR 100070-001, with one fatality (Grade 5 pneumonitis in one patient). Eleven patients received high-dose steroids defined as a dose equivalent to at least 40 mg of prednisone daily. Additionally, Grade 5 autoimmune hepatitis was previously reported in two patients in the broader avelumab safety database. ImARs experienced by patients in Study 003 (Merkel cell) were rash, thyroid disorders, diarrhea, pruritus, erythema, elevated transaminases, and nephritis. The majority of patients with imARs other than endocrinopathies required high-dose systemic corticosteroid administration. Additional imARs that occurred in at least two patients across the larger pooled analysis include pneumonitis, ALT/AST elevations, adrenal insufficiency, hepatitis, hepatic failure, myositis, thyroiditis, autoimmune disorder, and colitis. ImARs were mostly manageable with corticosteroid administration.

IRRs were common in the urothelial patients on Study EMR 100070-001 (31% overall, 0.4% grade 3-4) despite the mandatory premedication included in the protocol; this is likely related to the intact Fc region in the antibody structure. IRRs were manageable with temporary interruptions, infusion rate reductions, and administration of symptomatic treatments including antihistamines and corticosteroids.

Overall, the safety of avelumab is consistent with the expected toxicity profile of immunologically-mediated anticancer therapies. The safety data from the urothelial cohorts of Study EMR 100070-001 and the larger pooled database do not change the favorable benefit: risk assessment for avelumab for the treatment of patients with metastatic urothelial carcinoma.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

There are no outstanding statistical issues with the study design, statistical analysis plan, or efficacy analyses of the urothelial cohorts of Study EMD100070-001. However, it is noteworthy that while the statistical analysis plan included summary statistics of PFS and OS as secondary efficacy endpoints, these results are not considered interpretable in single arm trials.

7.6. Conclusions and Recommendations

Patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy represent a population with a serious and life-threatening disease for which there is no standardized therapy and no known curative therapy. Although UC is known to be a chemosensitive disease, off-label use of cytotoxic chemotherapy does not provide durable responses and has not demonstrated improvement in overall survival. While atezolizumab and nivolumab are FDA-approved in this setting, they have received Accelerated Approval only at this time, while the results of confirmatory trials are awaited to provide verification and description of clinical benefit.

The clinical benefit of avelumab for patients with metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy is based on the results of the urothelial cohorts of Study EMR 100070-001. Efficacy analyses conducted on 226 patients followed for at least 13 weeks after accrual demonstrate a confirmed, centrally reviewed ORR per RECIST v 1.1 of 13.3% (95% CI: 9.1, 18.4), including 9 patients (4.0%) with CR and 21 patients (9.3%) with PR. In 161 patients followed for at least 6 months, confirmed, centrally reviewed ORR per RECIST v 1.1 was 16.1% (95% CI: 10.8, 22.8), including 9 patients (5.6%) with CR and 17 patients (10.6%) with PR. Among the 30 responding patients, the median DOR was not reached (range 1.4+ to 17.4+ months). Among the 226 patients followed for $\geq$ 13 weeks, 73% (22/30) responding patients had an ongoing response at 6 months and 13% (4/30) at 1 year. Among the 161 patients followed for $\geq$ 6 months, 85% (22/26) of responders had at ongoing response at 24 weeks and 15% (4/26) at 52 weeks. Using a clinical trial assay to assess PD-L1 staining, with 15% of patients unevaluable, there were no clear differences in response rates based on PD-L1 tumor expression. Durable objective response rate is a valid surrogate endpoint considered reasonably likely to predict clinical benefit (i.e., improved survival) in this population, and the effect size of avelumab on ORR and DOR represents substantial improvement over off-label use of salvage chemotherapy.

The primary safety risks of avelumab are imARs and IRRs. In Study EMR 100070-001, 14% of patients experienced at least one imARs including one fatality due to pneumonitis; 5% of patients overall required high-dose steroids for management of an imAR. There were two cases of fatal autoimmune hepatitis in the broader avelumab safety database. The frequency and types of imARs in patients treated with avelumab are consistent with the safety profiles of other approved PD-1 and PD-L1 antibodies. Immune-mediated ARs were usually manageable with corticosteroids and hormone replacement therapy. Dose-modification and management guidelines for imARs are included in product labeling.

The frequency of occurrence of IRRs with avelumab observed during Study EMR 100070-001 despite premedication is higher than the frequency of occurrence of IRRs observed with other

approved PD-1 and PD-L1 antibodies. Infusion-related reactions that occurred with avelumab were generally low-grade in severity and manageable with temporary interruptions, infusion rate reductions, and administration of symptomatic treatments including antihistamines and corticosteroids. Premedication and management guidelines in case of IRRs are included in the product labeling.

Compared to other monoclonal antibodies directed against PD-1/L-1, avelumab is unique in that the Fc portion of the molecule is intact, allowing direct lysis of target cells by antibody-dependent cell-mediated cytotoxicity and complement fixation. Exposure-response analyses suggest that increased avelumab exposure was associated with response when adjusted for prognostic covariates. The intact Fc region is also the likely reason for the increase in observed IRRs compared to similar agents. (b) (4)

In summary, the benefit: risk assessment is favorable for the use of avelumab for the treatment of patients with metastatic MCC, at a dose of 10 mg/kg IV every 2 weeks. Avelumab has demonstrated statistically significant and clinically meaningful evidence of anti-tumor activity including confirmed ORR and evidence of durability of the responses in patients who have progressed on or following prior chemotherapy. These results are reasonably likely to predict clinical benefit in patients with metastatic MCC whether or not they have received prior chemotherapy for metastatic disease. The safety profile of avelumab is consistent with what is expected for an immunologically mediated anticancer therapy, is favorable as compared to cytotoxic chemotherapy, and is acceptable given the serious and life-threatening nature of metastatic MCC.

The reviewers recommend Accelerated Approval under Subpart E (21CFR601.41) for avelumab for the treatment of patients with (b) (4) metastatic UC, at a dose of 10 mg/kg IV every 2 weeks. Accelerated Approval is recommended given the uncertainty of the relation of ORR and DOR to ultimate outcomes of clinical benefit (i.e., improved survival) and to verify and describe the treatment effect of avelumab in patients with (b) (4) metastatic UC. Confirmatory evidence of clinical benefit will be based on submission and review of the results of Javelin Bladder 100, a phase III randomized trial of avelumab vs. best supportive care as a maintenance treatment in patients with locally advanced or metastatic UC whose disease did not progress after platinum containing chemotherapy.

The clinical and statistical reviewers do not recommend that a REMS be implemented for avelumab given the current safety profile and the experience of the medical community in managing imARs with other FDA-approved immune-modulating agents. Risk management based on labeling and routine pharmacovigilance will be employed to ensure the safe and effective use of avelumab.

Joyce Cheng, PhD Shenghui Tang, PhD

Primary Statistical Reviewer	Statistical Team Leader
Chana Weinstock, MD Primary Clinical Reviewer	Virginia E. Maher, MD Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this BLA.

9 Pediatrics

Trials with safety or efficacy data pertaining to pediatric patients were not submitted with this BLA. The BLA is exempt from the requirement to assess the safety and effectiveness of the product for the claimed indication in all pediatric age categories under 21 CFR 314.55(d), Exemption for Orphan Drugs.

10 Labeling Recommendations

10.1. Prescribing Information

The table below summarizes significant changes to the proposed prescribing information made by FDA. This labeling was under negotiation at the time of this review. Final labeling for BLA 761049 (metastatic Merkel Cell Carcinoma [mMCC]) was approved and incorporated into the BLA 761078 (UC) prescribing information during this review. The approved prescribing information for Bavencio will include information for both mMCC and advanced or metastatic urothelial carcinoma (UC).

Table 40: Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling *(As of April 19, 2017)*
Highlights		
Indications and Usage	*See comments below in FPI Indications and Usage for more information.*	
Dosage and Administration	*See comments below in FPI Dosage and Administration for more information.*	
Warnings and Precautions	*See comments below in FPI Warnings and Precautions for more information.*	
Adverse Reactions	Most common adverse reactions ((b) (4) ≥ 20% (b) (4)) were fatigue, nausea, infusion-related	FDA revised to add common adverse reactions (ARs) for musculoskeletal pain, nausea, urinary tract infection, (b) (4)

	reaction, and decreased appetite. (6.1) …	(b) (4). (6.1) …
Full Prescribing Information (FPI)		
1. Indications and Usage	BAVENCIO is a programmed death ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression on or after platinum-based therapy. (1) …	FDA revised the indication statement as follows: • Patients with locally advanced or metastatic urothelial carcinoma (UC) who: o Have disease progression during or following platinum-containing chemotherapy (1.2) o Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (1.2) …
2. Dosage and Administration	2.1 Recommended Dose … 2.2 Premedication … 2.3 Dose Modifications …	FDA moved the premedication information from 2.2 to 2.1. Important dosage information (i.e., required premedication) is typically listed first in Dosage and Administration if lack of this knowledge could result in serious adverse reactions. For Dose Modifications, FDA applied a tabular format, and re-organized this information using categories for immune-mediated ARs (imARs). *See "Labeling Recommendations" in the BLA 761049 (mMCC) Multi-disciplinary Review and Evaluation for more information.*

5. Warnings and Precautions	5.1 Immune-Mediated Pneumonitis – 5.6 Other Immune-Mediated Adverse Reactions …	The Warnings and Precautions (W&Ps) categories and subsections for imARs were revised. *See "Labeling Recommendations" in the BLA 761049 (mMCC) Multi-disciplinary Review and Evaluation for more information.* Since the incidence rates for imARs for UC were similar to the incidence for the overall safety database, FDA removed (b) (4) from the W&Ps subsections. …
	5.7 Infusion-Related Reactions …	Based on the FDA Clinical Safety Review, and to better clarify the time of onset for infusion-related reactions associated with Bavencio, FDA added the following information: "Fourteen percent of patients (252/1738) had infusion-related reactions that occurred after the BAVENCIO infusion was completed." *See 7.4.4 (Infusion Related Reactions) in this review for more information.*
6. Adverse Reactions	6.1 Clinical Trials Experience <u>Locally Advanced or Metastatic Urothelial Cancer</u> … In 242 patients with locally advanced or metastatic UC the most common adverse	FDA revised (and reordered) the UC subsection based on the FDA Clinical Safety Review as follows: … "Fourteen patients (6%) who were treated with BAVENCIO experienced pneumonitis,

	reactions (≥ 20%) were fatigue, nausea, infusion related reaction, and decreased appetite (b) (4) The most common Grade 3 and 4 adverse reactions (≥ 3%) were anemia, hyponatremia, fatigue, hypertension, and urinary tract infection. (b) (4) Serious adverse reactions reported in ≥ 2% of patients were (b) (4), (b) (4), abdominal pain, pyrexia, dehydration, (b) (4), urinary tract infection, and urosepsis. BAVENCIO was permanently discontinued for adverse reactions in (b) (4) % of patients; (b) (4) (> 1%) was fatigue. (b) (4) (> 1 %) were diarrhea, fatigue, (b) (4), urinary tract infection, (b) (4), and dyspnea.	respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death. BAVENCIO was permanently discontinued for Grade 1-4 adverse reactions in 30 (12%) patients. The adverse reaction that resulted in permanent discontinuation in > 1% of patients was fatigue. BAVENCIO was temporarily discontinued in 29% of patients for adverse reactions, excluding temporary dose interruption for infusion-related reactions where infusion was restarted the same day. The adverse reactions that resulted in temporary discontinuation in > 1% of patients were diarrhea, fatigue, dyspnea, urinary tract infection, and (b) (4). 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, musculoskeletal pain, abdominal pain, (b) (4), dehydration, hematuria, intestinal obstruction, and pyrexia. The most common Grade 3 and 4 adverse reactions (≥

		3%) were anemia, fatigue, hyponatremia, hypertension, urinary tract infection, musculoskeletal pain, (b) (4) . The most common adverse reactions (≥ 20%) were fatigue, infusion related reaction, musculoskeletal pain, nausea, decreased appetite, urinary tract infection, (b) (4) . 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)*]." FDA revised the Table 4 (Adverse Reactions) to reflect the FDA Clinical Safety Review. FDA added ARs for renal failure (All Grades = (b) (4)%; Grade 3-4 = 3%). *See 7.4.4 (Nephritis) in this review for more information.* FDA revised Table 5 (Laboratory Abnormalities) based on the FDA Clinical Safety Review. FDA added Grade 3-4 laboratory abnormalities for GGT increase (12%), increased alkaline phosphatase (7%), (b) (4), hyperkalemia (3%), (b) (4) , and

		increased creatinine (b) (4) . Hyperglycemia was also increased from (b) (4) to 9% based on FDA review.
8. Use in Specific Populations	8.5 Geriatric Use Of the (b) (4) patients with locally advanced or metastatic UC treated with BAVENCIO, (b) (4)% were 65 years or over. (b) (4)	FDA revised this subsection to provide additional details on the use of Bavencio in geriatric patients: … <u>Locally Advanced or Metastatic Urothelial Carcinoma</u> Of the 226 patients with locally advanced or metastatic UC treated with BAVENCIO, 68% were 65 years or over and 29% were 75 years or over. Among patients 65 years or over who were followed for at least 13 weeks, 14% (22/153) responded to BAVENCIO and 58% (89/153) developed a Grade 3-4 adverse reaction. No overall differences in safety or efficacy were reported between elderly patients and younger patients.
14. Clinical Studies	14.2 Locally Advanced or Metastatic Urothelial Cancer …	The Applicant's original efficacy information was based on (b) (4) patients from the JAVELIN Solid Tumor trial. During the review, FDA reached an agreement with the Applicant to resubmit the prescribing information (PI) based on updated 13-week follow up data for efficacy (n=226 patients). *See Section 1.2 (Conclusions on the*

	(b) (4)	*Substantial Evidence of Effectiveness) of this review for more information.* FDA revised the clinical trial description to clarify that 242 patients with locally advanced or metastatic urothelial carcinoma (UC) were included in the UC cohorts of the Javelin Solid Tumor trial (e.g., safety population for ARs). … FDA added the following clarification to the study enrollment criteria: "Patients were included regardless of their PD-L1 status." … FDA revised the enrolled patient population information for prior therapies to clarify the platinum chemotherapy experience and to add other clinically relevant disease characteristics as follows: "Nine (4%) patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy only. (b) (4) Seventeen percent of patients had hemoglobin <10 g/dL and 34%

		of patients had liver metastases at baseline." …
	…	FDA added the median time to [redacted] months (range: 1.3 to 11.0)] [redacted].
	…	…
	[redacted]	To be more accurate, since the PD-L1 results do not identify a clear difference in ORR or DOR with regards to PD-L1 expression, FDA revised this statement to "Using a clinical trial assay to assess PD-L1 staining, with [redacted]% of patients unevaluable, there were no clear differences in response rates based on PD-L1 tumor expression." *See 7.2.2 (Study Results, Primary Efficacy Endpoint, PD-L1 Subgroups) for more information.*
	…	… FDA revised Table 7 (Efficacy Results of the UC Cohorts) to include the Confirmed Overall Response Rate (ORR) and Duration of Response (DOR) results for patients with ≥ 13 weeks of follow up (n=226) and for patients with ≥ 6 months of follow up (n=161).

10.2. **Patient Labeling**

The Medication Guide approved with BLA 761049 for Bavencio (mMCC) was updated to include information related to the new indications for locally advanced or metastatic urothelial cancer. *See the consultative review from Patient Labeling Team: Morgan Walker (DMPP) and Nicholas*

Senior (OPDP) in BLA 761049 for more information.

Capt. William Pierce, PharmD
Associate Director for Labeling

11 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

None.

11.2. Conditions of Use to Address Safety Issue(s)

None.

11.3. Recommendations on REMS

None.

12 Postmarketing Requirements and Commitments

1. Since the indication will receive accelerated approval, the following postmarketing requirement will be issued:

   "Conduct "Javelin Bladder 100: A Phase III, 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."

   Trial completion is expected in September 2020 with Final Report Submission anticipated in March 2021.

2. The dose optimization issue discussed in the clinical pharmacology review in section 6 of this review is the basis of the following postmarketing commitment:

"Submit the final report and data for safety and efficacy of the ongoing clinical trial EMR100070-005 entitled "A Phase III, 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", including results of the exposure-response analysis."

Anticipated final report submission is October 2020.

13 Appendices

13.1. References

1. Siegel RL et al. Cancer Statistics 2016. CA Cancer J Clin 2016; 66:7-30

2. NCCN Guidelines v1 2016: Bladder Cancer

3. Park JC et al. Mutimodal management of muscle invasive bladder cancer. Curr Probl Cancer 2014; 38:80-108

4. Bellmunt J et al. Prognostic Factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 2010 38:1850

5. Bajorin D et al. Long-Term Survival in Metastatic Transitional-Cell Carcinoma and Prognostic Factors Predicting Outcome of Therapy. J Clin Oncol 1999: 3173-3181

6. FDA clinical review, BLA 761034

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study EMR 100070-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 950		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
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: _____ Significant payments of other sorts: X Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
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) 27		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

Not applicable to this submission; see review of BLA 761049.

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Summary of Applicant's E-R Analysis Method

E-R Analysis for Efficacy

Among patients included in Study EMR 100070-001, 153 diagnosed with UC and ≥6 month follow-up as of March 19, 2016, were included in the E-R analysis. Each subject was classified as "responder" or "non-responder". Responders are defined as subjects who had complete response (CR) or partial response (PR) according to RECIST 1.1. All the other subjects are defined as non-responders. PFS and OS were calculated for each subject.

A previously developed popPK model was used to predict individual exposure metrics using individual PK parameters and covariate values (Refer to Section 13.4.1 of the Multidisciplinary Review of BLA 761049, Applicant's Final Model). Three exposure metrics were considered in the analysis: predicted trough concentration at steady-state ($C_{trough,ss}$), predicted area under the concentration-time curve at steady-state (AUC_{ss}), predicted trough concentration after the first dose ($C_{trough,first}$).

The influence of exposure metrics on response was explored graphically, after which logistic regression with linear logit link or Cox proportional hazard model was applied to model the relationships between exposure, covariates, and the probability of being a responder:

$$logit(P) = log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 \cdot C_{trough,ss} + \beta_2 \cdot X_2 + \beta_3 \cdot X_3 + \cdots + \beta_n \cdot X_n \quad \text{Equation 1 (BOR)}$$

Where *P* is the probability of response, β_0 is the intercept, β_1, …, β_n are the regression coefficients for the n covariates (X_n), here using $C_{trough,ss}$ is an illustrative example for exposure metrics; or

$$h(t) = h_0(t) \cdot \exp(\beta_1 \cdot C + \beta_2 \cdot X_2 + \beta_3 \cdot X_3 + \cdots + \beta_n \cdot X_n) \quad \text{Equation 2 (PFS or ORS)}$$

Where hazard function $h(t)$ depends on a set of *n* covariates including the avelumab exposure metric *C*, whose effect is measured by the size of the respective regression coefficient (β_1, …, β_n).

Model development for probability of response and survival endpoints was performed in an aligned procedure. The variable selection for the multiple (logistic or Cox) regression was done with a stepwise approach separately for each explored exposure metric. Each inclusion step chooses the covariate with lowest effect p-value (from Chi-squared test) when below 0.15 and the subsequent elimination step(s) excludes a covariate with effect p-value above 0.40. The procedure stopped if no more covariates fulfill the inclusion criteria or the last included covariate needed to be excluded in the elimination step. The discriminatory power of the logistic models was assessed using receiver operating characteristic (ROC) curves. For survival models 95% CI for the hazard ratio for exposure metrics and other covariate effects were reported.

E-R Analysis for Safety

Dependent variables and exposure metrics of the E-R analysis for safety were summarized in Table 42:

Table 41: Exposure metrics Considered in the Analysis of Adverse Event Incidence

Adverse event category	Exposure metrics considered
Immune-related adverse events of grade ≥1 (irAE1)	AUC_{ss}, $C_{trough,first}$, $C_{trough,ss}$, none
Immune-related adverse events of grade ≥3 (irAE3)	AUC_{ss}, $C_{trough,first}$, $C_{trough,ss}$, none
Infusion-related reactions (IRR)	AUC_{first}, $C_{max,first}$, $C_{trough,first}$, none
Treatment-emergent adverse events of grade ≥1 (TEAE1)	AUC_{ss}, $C_{trough,first}$, $C_{trough,ss}$, none
Treatment-emergent adverse events of grade ≥2 (TEAE2)	AUC_{ss}, $C_{trough,first}$, $C_{trough,ss}$, none
Treatment-emergent adverse events of grade ≥3 (TEAE3)	AUC_{ss}, $C_{trough,first}$, $C_{trough,ss}$, none

[Source: BLA 761078/SDN 1, M&S Exposure-Safety Analysis Report, Table 13]

For each type of adverse event, subjects were classified as "AE" (experiencing the AE at least once during the duration of the study) or "non-AE" (not experiencing the AE). The influence of exposure metrics on AEs was explored graphically, followed by logistic regression:

$$logit(P) = log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 \cdot AUC_{ss} + \beta_2 \cdot X_2 + \beta_3 \cdot X_3 + \cdots + \beta_n \cdot X_n \quad \text{Equation 3}$$

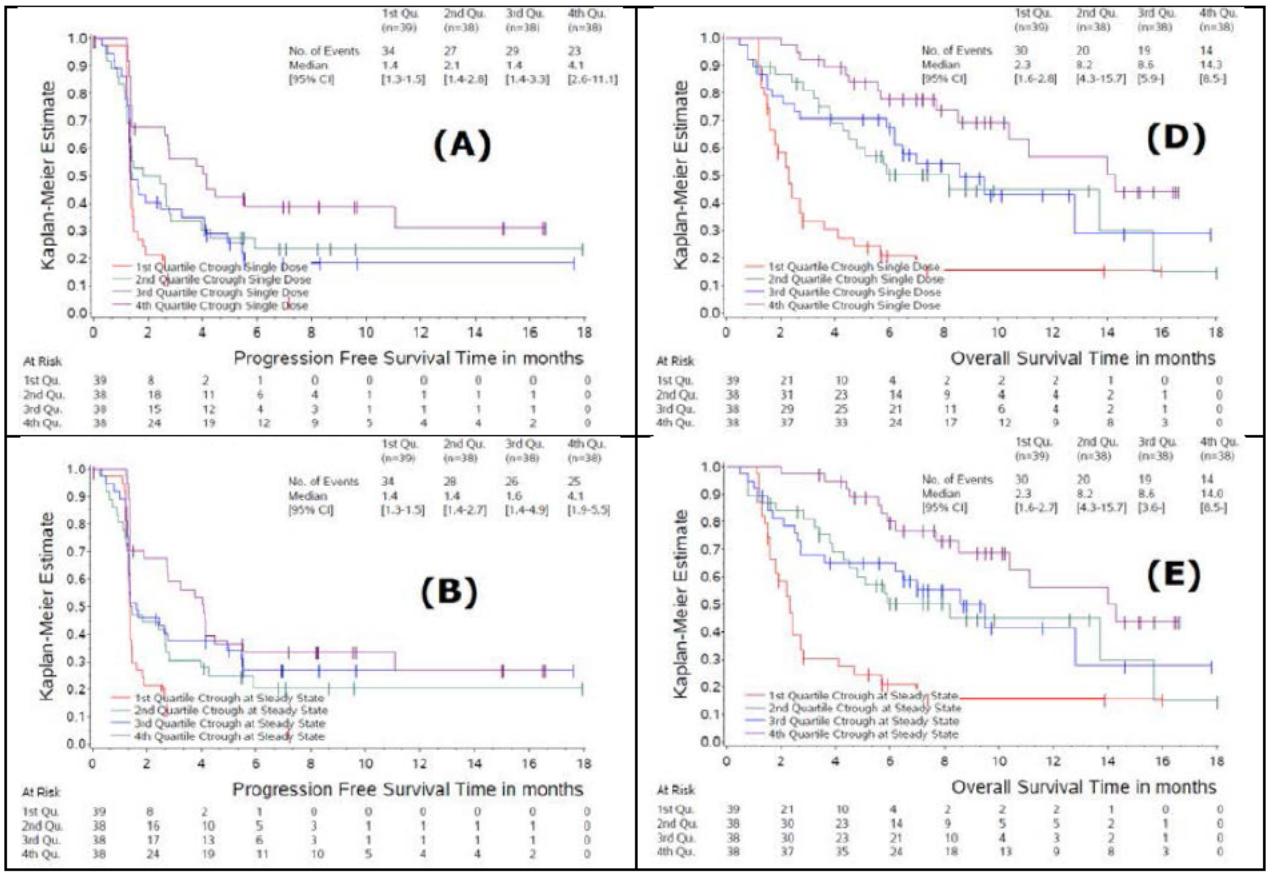
Here, *P* is the probability of having at least one adverse event during participation in the study, β_0 is the intercept, β_n are the regression coefficients for the *n* covariates (X_n) and explanatory, variables (using AUC_{ss} as an illustrative example).

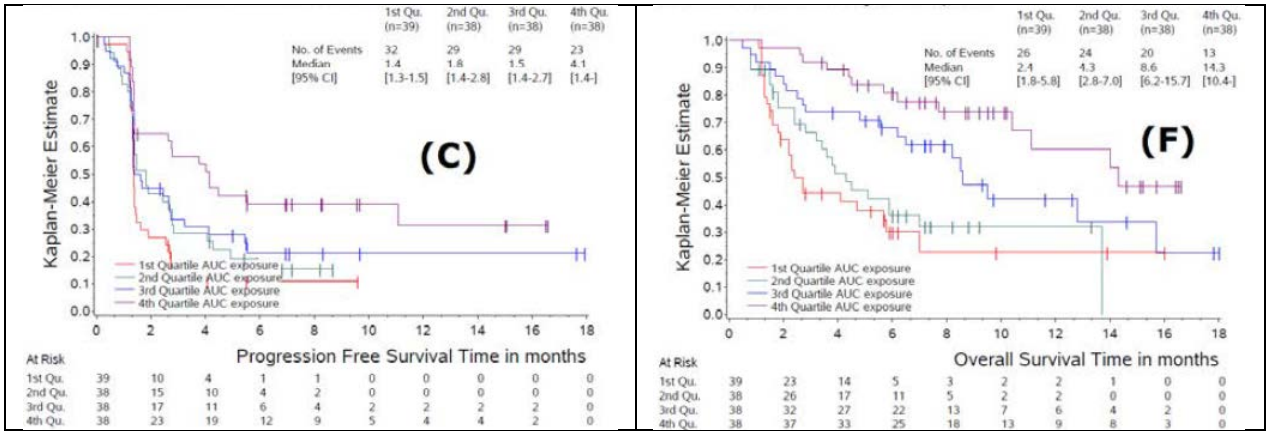
The basic model was a logistic regression, with explanatory variables added linearly. First, the univariate effect of each exposure metric was assessed. Next, the full model (the exposure metric as well as all covariates in scope) was fitted. Finally, a stepwise reduction process was performed, in which the least likely relationship was removed at each step based on its importance as assessed by the likelihood ratio test. The process was complete when all remaining relationships were assessed to be significant at the 5% level, given their degrees-of-freedom.

Since 95% confidence intervals on parameter estimates are based on estimated uncertainty and are therefore asymptotic, 95% confidence intervals for the intercept and the regression coefficients were obtained using nonparametric bootstrapping (using 2000 replicates), with bias correction, in order to provide an additional layer of assurance.

13.4.2. Applicant's E-R Analysis for PFS and OS

Figure 3. Kaplan-Meier Estimates for PFS (A: $C_{trough,first}$; B: $C_{trough,ss}$; C: AUC_{ss}) and OS (D: $C_{trough,first}$; E: $C_{trough,ss}$; F: AUC_{ss}) per Exposure





[Source: BLA 761078/SDN 1, M&S Exposure-Efficacy Analysis Report, Figure 15]

Table 42: Univariate Cox models for PFS and OS, per Exposure Metric

PFS	**AUC_{ss}**	**$C_{trough,ss}$**	**$C_{trough,first}$**
P value	0.0002	0.0006	0.0001
HR (95% CI)	0.946 (0.919 – 0.974)	0.975 (0.960 – 0.989)	0.958 (0.937 – 0.980)
OS	**AUC_{ss}**	**$C_{trough,ss}$**	**$C_{trough,first}$**
P value	<0.0001	<0.0001	<0.0001
HR (95% CI)	0.923 (0.894 – 0.954)	0.960 (0.942 – 0.977)	0.939 (0.915 – 0.964)

[Source: Adapted from BLA 761078/SDN 1, M&S Exposure-Efficacy Analysis Report, Table 18 and 19]

Table 43. Multivariable PFS Cox Models per Exposure Metric (Significant Effects in Bold).

Cox Model for PFS (AIC)	$C_{trough,first}$ Model (794.879)	AUC_{ss} Model (794.443)	$C_{trough,ss}$ Model (800.495)
Covariate effect estimate HR (95% CI)	$C_{trough,first}$ (µg/mL) **-0.03146** **0.969 (0.948 – 0.991)**	AUC (g·h/L) **-0.05749** **0.944 (0.912 – 0.978)**	$C_{trough,ss}$ (µg/mL) **-0.01547** **0.985 (0.970 – <1.000)**
PD-L1 expression (≥ 1%)	**-0.59384** **0.552 (0.366 – 0.832)**	**-0.56567** **0.568 (0.377 – 0.855)**	**-0.56101** **0.571 (0.378 – 0.862)**
Hemoglobin (g/L)	**-0.01797** **0.982 (0.969 – 0.996)**	-0.01393 0.986 (0.972 – 1.001)	**-0.01780** **0.982 (0.969 – 0.996)**
Metastatic site (liver metastases)	0.87935 2.409 (0.714 – 8.134)	0.86509 2.375 (0.701 – 8.047)	0.96580 2.627 (0.776 – 8.888)
Metastatic site (other metastases)	0.46172 1.587 (0.483 – 5.217)	0.40299 1.496 (0.454 – 4.930)	0.50639 1.659 (0.503 – 5.473)
No. of non-target lesions	0.06386 1.066 (0.981 – 1.159)	0.07534 1.078 (0.991 – 1.174)	
Tumor burden (mm)			0.00184 1.002 (0.999 – 1.005)
Bilirubin (µmol/L)		-0.04662 0.954 (0.901 – 1.011)	
Body weight (kg)		**0.01455** **1.015 (1.001 – 1.028)**	

[Source: BLA 761078/SDN 1, M&S Exposure-Efficacy Analysis Report, Table 20]

Table 44: Multivariable OS Cox Models per Exposure Metric (significant effects in bold).

Cox Model for OS (AIC)	$C_{trough,first}$ Model (632.844)	AUC_{ss} Model (632.693)	$C_{trough,ss}$ Model (634.195)
Covariate effect estimate HR (95% CI)	$C_{trough,first}$ (µg/mL) **-0.04589** **0.955 (0.929 – 0.982)**	AUC (g·h/L) **-0.06059** **0.941 (0.909 – 0.975)**	$C_{trough,ss}$ (µg/mL) **-0.02847** **0.972 (0.954 – 0.990)**
ECOG (≥ 1)	**0.97094** **2.640 (1.527 – 4.567)**	**1.02623** **2.791 (1.620 – 4.806)**	**0.99016** **2.692 (1.561 – 4.640)**
No. of non-target lesions	**0.10450** **1.110 (1.008 – 1.222)**	**0.11181** **1.118 (1.015 – 1.233)**	**0.12042** **1.128 (1.024 – 1.243)**
Metastatic site (liver metastases)	1.12417 3.078 (0.688 – 13.769)	1.04864 2.854 (0.631 – 12.905)	**1.48183** **4.401 (1.042 – 18.579)**
Metastatic site (other metastases)	0.75075 1.699 (0.389 – 7.419)	0.50211 1.652 (0.378 – 7.226)	0.80309 2.232 (0.532 – 9.374)
PD-L1 expression (≥ 1%)	-0.43476 0.678 (0.429 – 1.073)	-0.42261 0.655 (0.413 – 1.040)	
Visceral metastases (present)	0.65704 1.929 (0.795 – 4.863)	0.66062 1.936 (0.793 – 4.724)	

[Source: BLA 761078/SDN 1, M&S Exposure-Efficacy Analysis Report, Table 21]

13.4.3. Reviewer's E-R Analysis for Efficacy in Patients with ≥13 week or ≥6 month Follow-Up as of June 9, 2016

Efficacy data from the two UC expansion cohorts in Study EMR 100070-001 in 242 patients with UC whose disease progressed on or after platinum-based therapy were used to support the clinical evaluation of this application. The data cut-off date was June 9, 2016. 226 patients had ≥13 week follow-up and 161 patients had ≥6 month follow-up as of June 9, 2016. However, the Applicant's E-R analysis for efficacy was conducted based on an earlier cutoff date (March 19, 2016) and it included data from patients with UC who did not undergo prior platinum-based therapy. To evaluate the exposure-efficacy relationship in the most relevant population and to support the clinical evaluation, the FDA reviewer conducted independent analyses in the two subgroups of 242 patients with UC whose disease progressed on or after platinum-based therapy. Patients in Subgroup One had ≥13 week follow-up as of June 9, 2016, and patients in Subgroup Two had ≥6 month as of the same cutoff date.

Table 45: Univariate Logistic Regression on Exposure Metrics

≥13 week Follow-up (N=226)	**single dose C_{trough} ($C_{trough,first}$, µg/mL)**	**steady-state C_{trough} ($C_{trough,ss}$, µg/mL)**	**steady- state AUC (AUC_{ss}, g·h/L)**
P value	0.0003	0.0008	0.0003
Odds ratio (95% CI)	1.099 (1.046 – 1.159)	1.050 (1.021 – 1.082)	1.133 (1.062 – 1.215)
AIC	166.20	169.18	166.09
≥6 month Follow-up (N=161)	**single dose C_{trough} ($C_{trough,first}$, µg/mL)**	**steady-state C_{trough} ($C_{trough,ss}$, µg/mL)**	**steady- state AUC (AUC_{ss}, g·h/L)**
P value	0.0003	0.0014	0.0001
Odds ratio (95% CI)	1.098 (1.047 – 1.158)	1.047 (1.019 – 1.078)	1.145 (1.072 – 1.232)
AIC	131.02	135.48	129.10

Figure 4. Observed Objective Response Rate and Predicted Probability of Being a Responder versus AUC at Steady State (AUC_{ss})

≥13 week Follow-up (N=226)	**≥6 month Follow-up (N=161)**

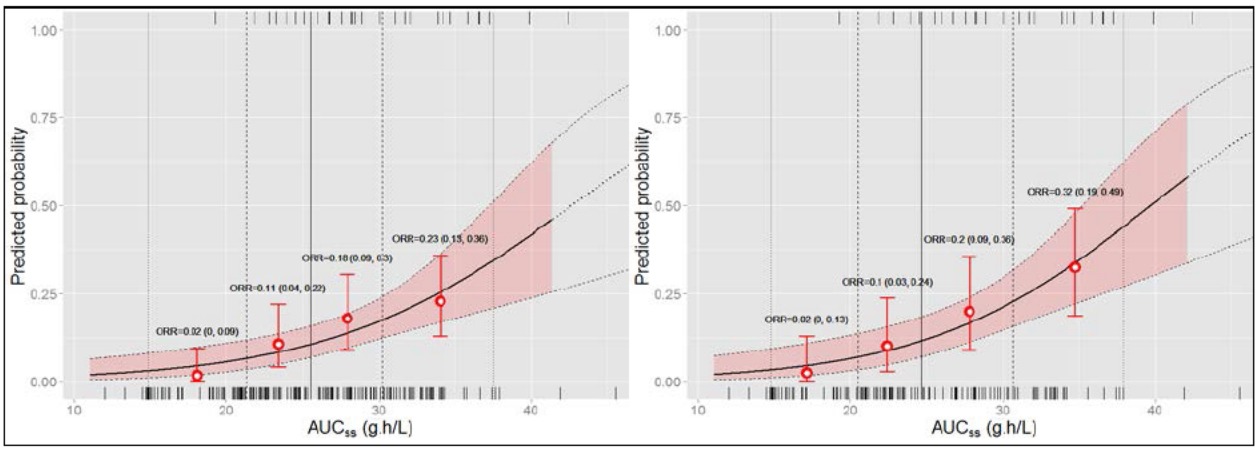
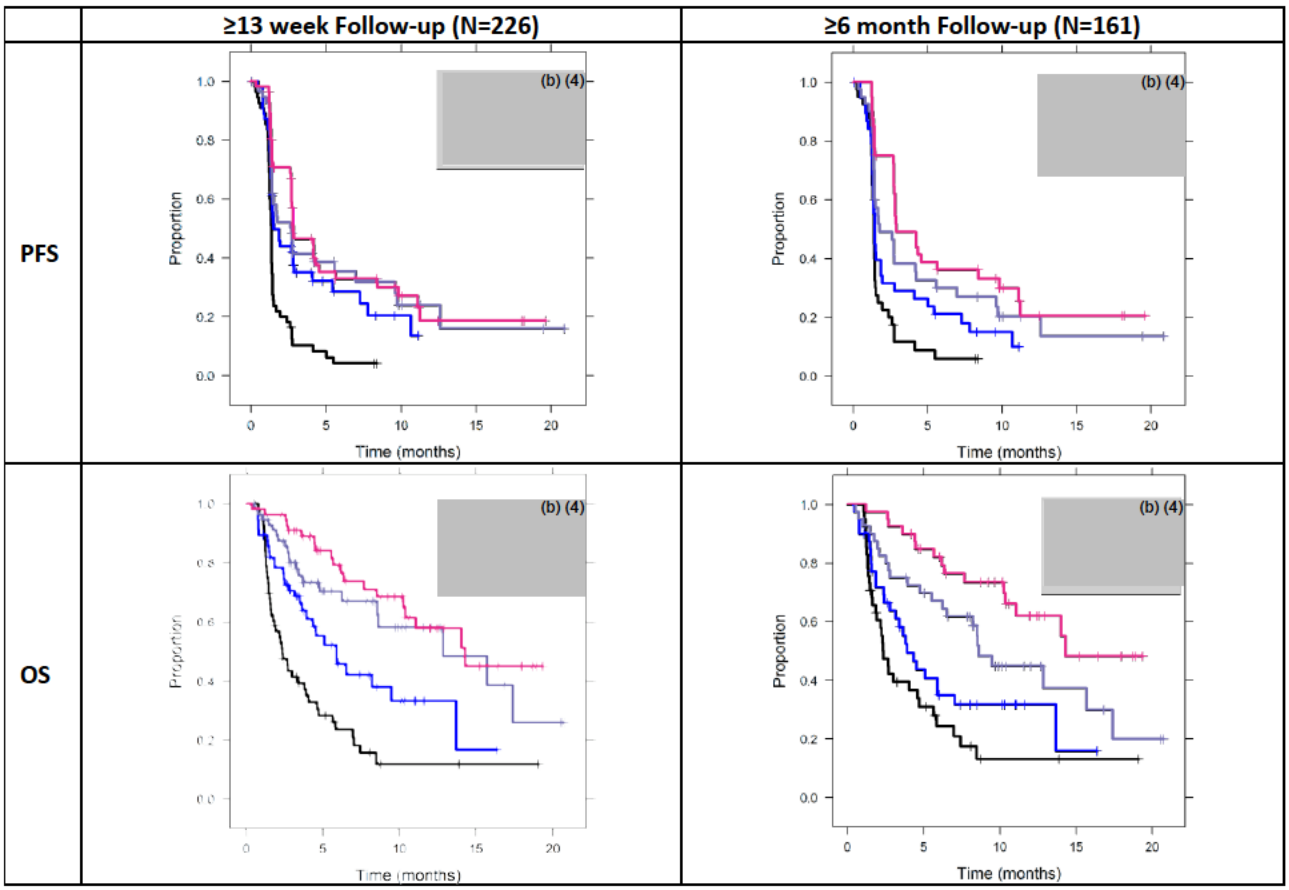


Table 46: Parameter Estimates for AUCss, $C_{trough,ss}$, and $C_{trough,first}$ in the Final Models of Multivariable Analysis of BOR. Significant effects were highlighted in Bold.

≥13 week Follow-up (N=226) Coefficient / Odds Ratio (95% CI)	AUCss (g·h/L) AIC (143.10)	$C_{trough,ss}$ (ug/mL) AIC (149.75)	$C_{trough,first}$ (ug/mL) AIC (146.49)
Exposure	**0.176 / 1.192 (1.089, 1.321)**	0.027 / 1.028 (0.994, 1.065)	**0.089 / 1.093 (1.026, 1.171)**
Intercept	-4.593 / 0.010 (0.000, 0.510)	-7.593 / 0.001 (0.000, 0.131)	-3.919 / 0.020 (0.000, 1.084)
Baseline Body Weight (kg)	**-0.046 / 0.955 (0.922, 0.985)**		-0.022 / 0.978 (0.949, 1.005)
Metastatic Site (other)	**-2.242 / 0.106 (0.024, 0.441)**	**-1.829 / 0.161 (0.043, 0.601)**	**-1.77 / 0.170 (0.043, 0.662)**
Metastatic Site (liver)	**-2.455 / 0.086 (0.015, 0.441)**	**-1.660 / 0.190 (0.035, 0.926)**	**-1.706 / 0.182 (0.032, 0.917)**
AST (IU/L)	**-0.075 / 0.928 (0.865, 0.980)**		
PD-L1 expression (≥1%)	**1.246 / 3.477 (1.385, 9.288)**	**1.059 / 2.883 (1.155, 7.554)**	**1.073 / 2.924 (1.163, 7.737)**
Hemoglobin (g/L)	**0.037 / 1.038 (1.007, 1.072)**	**0.035 / 1.036 (1.004, 1.070)**	**0.042 / 1.043 (1.011, 1.078)**
ALT (IU/L)		**-0.080 / 0.923 (0.865, 0.974)**	**-0.073 / 0.93 (0.873, 0.982)**
Baseline Tumor Size (mm)		-0.014 / 0.987 (0.97, 1.001)	-0.013 / 0.987 (0.970, 1.001)
Albumin (g/L)		0.104 / 1.11 (0.973, 1.281)	
≥6 month Follow-up (N=161) Coefficient / Odds Ratio (95% CI)	AUCss (g·h/L) AIC (107.69)	$C_{trough,ss}$ (ug/mL) AIC (113.87)	$C_{trough,first}$ (ug/mL) AIC (109.02)
Exposure	**0.208 / 1.231 (1.110, 1.393)**	0.033 / 1.034 (0.995, 1.075)	**0.102 / 1.107 (1.036, 1.192)**
Intercept	-12.790 / 0 (0.000, 0.025)	-12.930 / 0 (0.000, 0.004)	-14.130 / 0 (0.000, 0.002)
PD-L1 expression (≥1%)	**1.521 / 4.578 (1.474, 16.160)**	**1.515 / 4.551 (1.508, 15.520)**	**1.789 / 5.983 (1.890, 21.940)**
Hemoglobin (g/L)	**0.060 / 1.062 (1.020, 1.112)**	**0.052 / 1.054 (1.014, 1.100)**	**0.046 / 1.047 (1.006, 1.093)**
Baseline Body Weight (kg)	**-0.043 / 0.958 (0.917, 0.994)**		
RACE (non-white)	**-3.068 / 0.047 (0.001, 0.600)**	**-2.354 / 0.095 (0.004, 0.841)**	**-2.526 / 0.080 (0.003, 0.663)**
AST (IU/L)	**-0.108 / 0.898 (0.813, 0.976)**		
Metastatic Site (other)	**-2.014 / 0.133 (0.018, 0.906)**		
Metastatic Site (liver)	**-2.766 / 0.063 (0.005, 0.603)**		
EGFR (mL/min/1.73^2)	**0.031 / 1.032 (1.003, 1.064)**	**0.029 / 1.029 (1.004, 1.057)**	0.025 / 1.026 (1.000, 1.054)
Co-med Corticosteroids	-1.402 / 0.246 (0.038, 1.165)		
Age (years)	0.043 / 1.044 (0.989, 1.106)		
Baseline Tumor Size (mm)		-0.012 / 0.988 (0.969, 1.003)	-0.012 / 0.988 (0.969, 1.004)
ALT (IU/L)		**-0.083 / 0.92 (0.845, 0.985)**	**-0.083 / 0.921 (0.847, 0.984)**
ALB (g/L)		0.114 / 1.120 (0.960, 1.332)	0.130 / 1.139 (0.974, 1.357)
Visceral metastasis		-1.197 / 0.302 (0.073, 1.198)	
# of Anti-Cancer Treatment (>1)			-1.078 / 0.34 (0.102, 1.080)

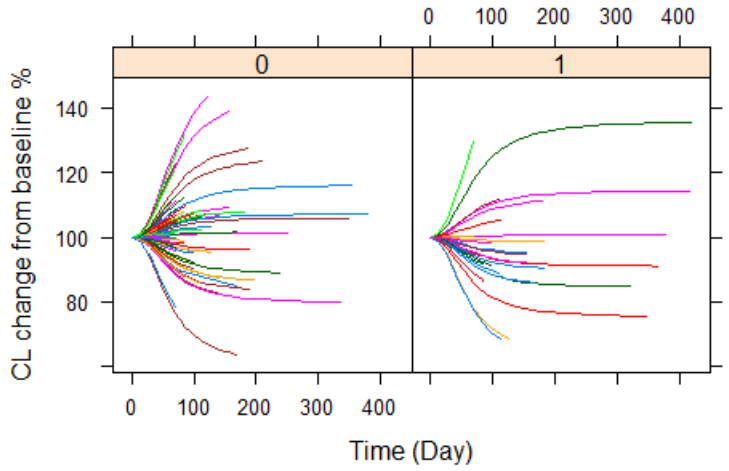
Figure 5. Kaplan-Meier Estimates for PFS and OS for AUCss (g·h/L)



13.4.4. Potential Interaction between Response Status and Avelumab Exposure in Patients with UC

158 patients who were diagnosed with UC contributed to the popPK dataset. 155 of them went through prior platinum-based therapy and had a minimum follow-up of 13 weeks by cutoff date June 9, 2017. A time-variant PK model was used to describe clearance change in the popPK dataset (refer to Section 13.4 of the Multidisciplinary Review of BLA 761049). A post hoc analysis of Applicant's Time-Variant model suggests a similar trend of CL change from baseline in responder (n=25) and non-responder (n=130) populations, and the mean maximal change (standard deviation) from baseline values were -5.6% (20.8%) and 1.9% (13.5%) in responder and non-responder populations, respectively.

Figure 6. Clearance Change from Baseline in Patients with UC. 0: non-responders; 1: responders.



13.5. Grouping of Preferred Terms

Composite Term	Preferred Terms
Abdominal Pain	Abdominal discomfort Abdominal pain Abdominal pain lower Abdominal pain upper Gastrointestinal pain
Anemia	Anemia Iron deficiency anemia
Asthenic Conditions	Asthenia Fatigue Malaise
Bone Fracture	Femur fracture Humerus fracture Rib fracture
Creatinine Increased/Renal Failure	Acute kidney injury Creatinine increased GFR decreased Renal failure
Cough	Cough Productive cough
Decreased Appetite	Decreased appetite Hypophagia
Diarrhea	Diarrhea Enterocolitis
Dyspnea	Dyspnea Dyspnea on exertion

Elevated Transaminases	ALT increased AST increased Autoimmune hepatitis Drug-induced liver injury Hepatic function abnormal Transaminases increased
Hematuria	Hematuria Urinary tract hemorrhage
Hypertension	Hypertension Hypertensive crisis Blood Pressure increased
Hypotension	Hypotension Orthostatic hypotension
Infusion-related Reactions	Select AEs with preferred terms of Back pain Chills Dyspnea Flushing Hypersensitivity Hypotension Infusion-related reaction Pyrexia
Intestinal Obstruction	Intestinal obstruction Small intestine obstruction
Musculoskeletal Pain	Back pain Musculoskeletal pain Myalgia Neck pain Pain in extremity
Peripheral Edema	Edema Generalized edema Peripheral edema Peripheral swelling
Pruritus	Generalized pruritus Pruritus
Pyrexia	Pyrexia Body Temperature Increased
Rash	Dermatitis acneiform Eczema Erythema Erythema multiforme Rash Rash erythematous

	Rash macular Rash maculo-papular Rash papular Rash pruritic
Respiratory Failure	Acute respiratory failure Respiratory failure
Sepsis	Sepsis (not urine related) Streptococcal bacteremia
Thrombocytopenia	Thrombocytopenia Platelet count decreased
Urinary Tract Infection	Bacteremia (if urine related) Cystitis Kidney Infection Pyuria Sepsis (if urine related) Urinary tract infection Urinary tract infection bacterial Urinary tract infection enterococcal Urinary tract infection fungal Urosepsis
Vomiting	Retching Vomiting

14 Division Director (DHOT)

Not Applicable

15 Division Director (OCP)

Nam Atiqur Rahman, PhD

16 Division Director (OB)

Rajeshwari Sridhara, PhD

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical)

Julia Beaver, MD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIM J ROBERTSON
05/05/2017

WEI CHEN
05/08/2017

TODD R PALMBY
05/08/2017

NAN ZHENG
05/08/2017

JINGYU YU
05/08/2017

PENGFEI SONG
05/08/2017

WILLIAM F PIERCE
05/08/2017

CHANA WEINSTOCK
05/08/2017

VIRGINIA E MAHER
05/08/2017

JOYCE H CHENG
05/08/2017

SHENGHUI TANG
05/08/2017

NAM ATIQUR RAHMAN
05/08/2017

RAJESHWARI SRIDHARA
05/08/2017

JULIA A BEAVER
05/08/2017

OFFICE OF CLINICAL PHARMACOLOGY MEMO

BLA	761078
Link to EDR	\\cdsesub1\evsprod\bla761078\
Applicant	EMD Serono, Inc.
Submission Date	12/27/2016 (SDN 1); 1/23/2017 (SDN 5); 2/2/2017 (SDN 7)
Submission Type	Original BLA (priority review)
Brand Name	BAVENCIO™
Generic Name	Avelumab
Dosage Form and Strength	Injectable/injection, 20 mg/mL
Route of Administration	Intravenous
Proposed Indication	(For Accelerated Approval) For the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression on or after platinum-based therapy.
Proposed Dosing Regimen	10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks.
Associated INDs	115747 (solid tumors), 119394 (MCC), (b) (4), (b) (4)
OCP Review Team	Nan Zheng, Ph.D., Jingyu (Jerry) Yu, Ph.D., Pengfei Song, Ph.D.
OCP Final Signatory	NAM Atiqur Rahman, Ph.D. (Division Director)

The Office of Clinical Pharmacology (OCP) review has been integrated to the Multidisciplinary Review and Evaluation, which will be documented into DARRTS. The proposed dose of 10 mg/kg administered as an intravenous infusion over 60 minutes every two weeks is acceptable based on clinical efficacy and safety demonstrated in two UC expansion cohorts in Study EMR 100070-001. However, this dose may not be optimal considering the short half-life relative to dosing interval, low steady state exposure, the positive E-R relationship on efficacy, a lack of E-R relationship on safety, as well as the fact that the maximum tolerated dose was not reached at 20 mg/kg dose level in the dose escalation phase of Study EMR 100070-001. As a dosing regimen of 10 mg/kg once weekly is being tested in an ongoing trial (EMR100070-005) in patients with non–small-cell lung cancer, the applicant agreed to submit the final study report of Study EMR100070-005 as well as exposure-response analysis as a post marketing commitment. Depending on the results of Study EMR100070-005 and exposure-response analysis, a trial to evaluate an alternate dosing regimen of avelumab in patients with UC may be necessary. There are no other outstanding issues in this BLA from a clinical pharmacology perspective.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NAN ZHENG
04/25/2017

JINGYU YU
04/26/2017

PENGFEI SONG
04/26/2017

NAM ATIQUR RAHMAN
04/27/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 761078 **Applicant: EMD Serono, Inc.** **Stamp Date: 12/27/2016**

Drug Name: Avelumab (MSB0010718C) **NDA/BLA Type: BLA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	x			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/LawsActsandRules/ucm084159 htm	x			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
10.	Has the applicant submitted a benefit-risk analysis for the product?	x			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?				
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?				
14.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: EMR100070-001 Study Title: A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumor and expansion to selected indications	x			A higher dose may be explored as part of a PMC.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 153 patients with UC. Treatment Arms: Single-arm study- Avelumab 10 mg/kg every 2 weeks Location in submission: 5.3.4.2				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 EMR100070-001 A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumor and expansion to selected indications Indication: Urothelial Carcinoma	x			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	x			
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?			x	
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
37.	Are all datasets to support the critical safety analyses available and complete?	x			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Chana Weinstock	3/14/17
Reviewing Medical Officer	Date
Virginia (Ellen) Maher	3/14/17
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHANA WEINSTOCK
03/14/2017

VIRGINIA E MAHER
03/14/2017

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 761078 **Applicant:** EMD Serono **Stamp Date:** 12/27/16

Drug Name: Avelumab **NDA/BLA Type:** BLA

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

File name: 5_Statistics Filing Checklist for BLA_761078

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE H CHENG
03/07/2017

SHENGHUI TANG
03/07/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

BLA Number	761078	**SDN**	1
Applicant	EMD Serono, Inc.	**Submission Date**	12/27/ 2016
Generic Name	Avelumab	**Proposed Brand Name**	Bavencio
Drug Class	A fully human IgG1 monoclonal antibody (mAb) directly against PD-L1		
Indication	For treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression after platinum-based therapy.		
Dosage Regimen	10 mg/kg every 2 weeks (Q2W), administered as IV infusion in 60 min		
Dosage Form	20 mg/mL sterile solution	**Route of Administration**	Intravenous
OCP Division	DCPV	**OND Division**	DOP1

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	NA	Pengfei Song
Pharmacometrics	Nan Zheng	Jingyu Yu
Genomics	NA	NA

Review Classification	☐ Standard ☐ Priority ☑ Expedited		
Filing Date	02/28/2017	**74-Day Letter Date**	03/11/3017
Review Due Date	04/17/2017	**PDUFA Goal Date**	08/28/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		

In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		1	Comparison of PK from Process A and Process B, pooled PK data from Phase 1 Studies EMR100070-001 (Study 001) & EMR100070-002 (Study 002) & Phase 2 Study EMR100070-003 Part A (Study 003)
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☑ Single Dose	2	Studies 001 and 002
	☑ Multiple Dose	3	Studies 001, 002, and Study 003
☐ Mass Balance Study			
☑ Other (e.g. dose proportionality)		1	Study 001
Intrinsic Factors			
☑ Race			PopPK analyses of pooled data from Studies 001, 002 & 003
☑ Sex			As above
☑ Geriatrics			As above
☐ Pediatrics			
☑ Hepatic Impairment			As above
☑ Renal Impairment			As above
☐ Genetics			
Extrinsic Factors			
☑ Effects on Primary Drug			PopPK analyses of pooled data from Studies 001, 002 & 003
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients		1	
☑ QT		1	
Pharmacometrics			
☑ Population Pharmacokinetics		1	PopPK analyses of pooled data from Studies 001, 002 & 003
☑ Exposure-Efficacy		1	
☑ Exposure-Safety		1	

Total Number of Studies	**In Vitro**	0	**In Vivo**	3
Total Number of Studies to be Reviewed		0		3

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data	☐Yes ☐No ☑N/A	

comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	**PK Reports:** RF6870, RF7010, 218-1407 & 15-IV104-V0 **ADA Reports:** TNJS13-170, TNJS13-170A1, IP190 & IP373
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-	☑Yes ☐No ☐N/A	

submission discussions, submitted in the appropriate format (e.g., CDISC)?		
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☐N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memorandum

Avelumab (MSB0010718C) is a fully human immunoglobulin G1 (IgG1) monoclonal antibody directed against the programmed death ligand 1 (PD-L1) molecule. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors, PD-1 and B7-1. This removes the suppressive effects of PD-L1 on cytotoxic CD8+ T cells, resulting in the restoration of antitumor T cell responses.

Indication: For the treatment of patients with locally advanced or metastatic urothelial cancer with disease progression after platinum-based therapy.

Drug Product: The drug product (DP) is a sterile solution in a single-dose glass vial containing 200 mg/10 mL (20 mg/mL) of avelumab drug substance (DS) and intended for IV infusion following dilution. Initially, the DP was formulated at a protein concentration of (b) (4) using avelumab DS from the initial manufacturing process (**Process A**) (b) (4). This formulation was used in non-clinical studies and Phase 1/2 clinical trials. An optimized formulation of avelumab at higher concentration (20 mg/mL) was developed on a later occasion using avelumab DS from a changed manufacturing process (**Process B**) and it contains acetic acid, D-mannitol, polysorbate 20, and sodium hydroxide at pH 5.2. DP produced using **Process A** has been used the treatment of 826 patients in Studies 001, 002, and 003. DP produced using **Process B** has been used for the treatment of a subset of 590 subjects in Studies 001 and 002, 183 subjects that were switched from Process A to the Process B during the study, and in ongoing clinical trials, at initiation of

all subsequent clinical trials, and commercial supply. Pop PK analysis of pooled PK data across Studies 001, 002 and 003 showed that there was no influence of the change in manufacturing process on avelumab PK.

Proposed Recommended Dosage: Administer 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. Premedicate for the first 4 infusions and subsequently as needed.

Justification for Recommended Dose: The recommended dose for treatment of mMCC is 10 mg/kg of avelumab, given by IV infusion once every 2 weeks. Safety and tolerability of the selected dose was demonstrated in the dose escalation phase of Study 001 where doses of 1, 3, 10 and 20 mg/kg were studied and MTD was not reached. In patients taking the 10 mg/kg Q2W dose, high target occupancy (93.2 ± 1.29%) of PD-L1 in peripheral blood mononuclear cells was achieve during the whole dose interval. Efficacy of the selected dose in the target population was demonstrated in the UC cohorts of Study 001.

Efficacy: Study 001 is an ongoing, global Phase Ib open-label dose-escalation study with concurrent parallel-group expansion in selected tumor types, including UC. Study 001 enrolled 2 cohorts of subjects with locally advanced or metastatic UC whose disease had progressed after treatment with at least 1 platinum-containing regimen for inoperable locally advanced or metastatic UC, or who were ineligible for cisplatin-based chemotherapy. The initial expansion cohort enrolled is referred to as the 'secondary expansion cohort,' and enrolled a total of 44 subjects. The subsequent expansion cohort to enroll subjects is referred to as the 'efficacy expansion cohort,' and enrolled 205 subjects. Enrollment of UC subjects in Study 001 is complete. The 2 UC cohorts had similar eligibility criteria, and the combined cohorts (N=242, excluding 7 subjects who were cisplatin naïve) provide the pivotal population. A total of 161 subjects have been followed for a minimum of 6 months as of the 9 June 2016 data cutoff date form the basis of the primary efficacy population. The data showed a confirmed Independent Endpoint Review Committee (IERC)-assessed ORR of 17.4% (95% confidence interval [CI]: 11.9, 24.1) and a 24-week durability of response of 92.3% (95% CI: 72.6, 98.0) among the 161 subjects with at least 6 months of follow up. Consistent results were observed in subjects who had ≥ 13 weeks of follow up (N=226) and in the ITT set (N=242).

Table 5 Confirmed Response According to Independent Endpoint Review Committee Assessment – Full Analysis Set

Efficacy Parameter per RECIST 1.1, IERC	ITT (N=242) n (%)	13 Weeks Follow up (N=226) n (%)	6 Months Follow up (N=161) n (%)
Confirmed BOR, n (%)			
Complete response (CR)	11 (4.5)	11 (4.9)	10 (6.2)
Partial response (PR)	24 (9.9)	24 (10.6)	18 (11.2)
Stable disease	70 (28.9)	62 (27.4)	36 (22.4)
Non-CR / non-PD	1 (0.4)	1 (0.4)	1 (0.6)
Progressive disease	93 (38.4)	86 (38.1)	67 (41.6)
Non-evaluable	43 (17.8)	42 (18.6)	29 (18.0)
Objective Response Rate (ORR)			
Response rate (CR + PR), n (%) 95% CI	35 (14.5) 10.3, 19.5	35 (15.5) 11.0, 20.9	28 (17.4) 11.9, 24.1
Disease Control Rate			
Rate (CR+PR+SD), n (%)	105 (43.4)	97 (42.9)	64 (39.8)
Time to Response			
Median (weeks)	11.57	11.57	11.64
Interquartile range (Q1; Q3)	6.00; 14.00	6.00; 14.00	5.93; 15.71
Minimum, maximum	5.6; 48.0	5.6; 48.0	5.6; 48.0
Duration of Response			
Median (weeks) 95% CI	ne (42.14, ne)	ne (42.14, ne)	ne (42.14, ne)
≥ 24 weeks by K-M, % (95% CI)	0.923 (0.726, 0.980)	0.923 (0.726, 0.980)	0.923 (0.726, 0.980)

Sources: Module 2.7.3 Addendum Table 5
BOR = best overall response, CI = confidence interval, CR = complete response, IERC = Independent Endpoint Review Committee, ITT = intent-to-treat, K-M = Kaplan-Meier, N/n = number of subjects, ne = not estimable, PD = progressive disease, PR = partial response, Q1 = quartile 1, Q3 = quartile 3, and SD = stable disease

Safety: Given the relatively small size of the UC study population (N=249), safety data from subjects with other advanced solid tumors from Study EMR100070-001 (N=1401) and MCC subjects from EMR100070-003 (N=88) (non-UC group N=1489) were analyzed and presented side by side with data from UC subjects (UC group) and in a pooled group (total group; N=1738). TEAEs were reported in > 90% of subjects in both the UC and non-UC groups. In the UC group, TEAEs reported in ≥ 15% of subjects were fatigue, nausea, infusion related reaction, decreased appetite, anemia, decreased weight, diarrhea, constipation, urinary tract infection, disease progression, abdominal pain, and pyrexia. In the non-UC group, TEAEs reported in ≥ 15% of subjects were fatigue, nausea, diarrhea, constipation, decreased appetite, vomiting, decreased weight, and infusion related reaction. Overall, the types of TEAEs and frequencies of each event were generally similar between the UC and non-UC groups. With the exception of irAEs and IRRs, the types of commonly reported TEAEs in both studies were consistent with the types of AEs commonly observed in patients with advanced or metastatic malignancies that have progressed after ≥ 1 lines of prior anti-cancer therapy. (See Applicant's tables below)

Table 9 Overview of Treatment Emergent Adverse Events - Safety Analysis Set – All Subjects

Event	UC (N=249) N (%)	Non-UC (N=1489) N (%)	Total (N=1738) N (%)
Any TEAE	244 (98.0)	1453 (97.6)	1697 (97.6)
TEAE, Grade ≥ 3	154 (61.8)	854 (57.4)	1008 (58.0)
Related TEAE	166 (66.7)	998 (67.0)	1164 (67.0)
Related TEAE, Grade ≥ 3	21 (8.4)	156 (10.5)	177 (10.2)
TEAE Leading to Permanent Treatment Discontinuation	40 (16.1)	204 (13.7)	244 (14.0)
TEAEs excluding IRRs Leading to Drug Interruption	70 (28.1)	293 (19.7)	363 (20.9)
Related TEAE Leading to Permanent Treatment Discontinuation	14 (5.6)	93 (6.2)	107 (6.2)
Related TEAEs Excluding IRRs Leading to Drug Interruption	21 (8.4)	103 (6.9)	124 (7.1)
Serious TEAE	117 (47.0)	660 (44.3)	777 (44.7)
Related Serious TEAE	19 (7.6)	89 (6.0)	108 (6.2)
TEAE Leading to Death	46 (18.5)	182 (12.2)	228 (13.1)
Related TEAE Leading to Death	1 (0.4)	3 (0.2)	4 (0.2)
irAE[a]	34 (13.7)	212 (14.3)	247 (14.2)
IRR[b]	75 (30.1)	364 (24.4)	439 (25.3)
Treatment Related IRR	73 (29.3)	349 (23.4)	422 (24.3)

Source: Refer to Module 2.7.4 Table 12.6.1.1

[a] The irAEs are defined by a pre-specified MedDRA PT query and a Level 2 medical review using a predefined case definition (updated irAE analysis version 2; for specific details, see Section 5.4)

[b] IRRs are defined by a pre-specified MedDRA PT query including signs and symptoms of IRRs and time of onset of the event (for specific details, see Section 5.5)

irAE = immune-related adverse event, IRR = infusion-related reaction, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, and TEAE = treatment-related adverse event

Clinical Pharmacology Studies Submitted in the BLA: The clinical pharmacology of avelumab (including PK, PK/PD, QTc, and immunogenicity assessments) has been characterized in Studies 001, 002, and 003 (See Applicant's tables below).

Table 1 Overview of Pivotal Study and Supportive Studies with Safety Data in This Submission

Study No.	Study Design	Subject Population	No. of Subjects
Pivotal Study EMR100070-001 (UC Cohorts)			
EMR100070-001 Conducted in US, Belgium, Czech Republic, France, Germany, Hungary, Korea, Poland, Taiwan, Republic of China, and UK	Phase I, open-label, treatment expansion phase in subjects with UC Objectives: Safety/tolerability, efficacy, and PK	UC Cohorts: Adult subjects with metastatic or locally advanced UC whose disease had progressed after treatment with at least one platinum-containing regimen or who were ineligible for cisplatin-based chemotherapy	249 subjects: 10 mg/kg every 2 weeks Efficacy 168 subjects with ≥ 13 weeks FU, with a subset of 153 subjects with ≥ 6 months FU Safety: 249 subjects

EMR100070-001 Conducted in US, Belgium, Czech Republic, France, Germany, Hungary, Korea, Poland, Taiwan, Republic of China, and UK	Phase I, open-label, 2-phase (dose escalation and treatment expansions) in solid tumors Objectives: Safety/tolerability, MTD, efficacy (treatment expansion phase only), and PK	Non-UC: Adult subjects with metastatic or locally advanced solid tumors and expansion to selected indications	Safety: 1401 non-UC subjects at 10 mg/kg and 38 subjects at 1, 3, or 20 mg/kg every 2 weeks
EMR100070-002 Conducted in Japan	Phase I, open-label, 2-phase (dose escalation and treatment expansion) in solid tumors Objectives: Safety/tolerability, MTD, efficacy, and PK	Adult subjects with metastatic or locally advanced solid tumors, with expansion in subjects with gastric cancer	Dose escalation (completed): 17 subjects: 5 at 3 mg/kg, 6 at 10 mg/kg, and 6 at 20 mg/kg every 2 weeks Dose expansion (ongoing): 34 subjects: 10 mg/kg every 2 weeks
EMR100070-003 Conducted in US, Australia, Austria, France, Germany, Italy, Japan, Spain, and Switzerland	Part A: Phase II, open-label, single-arm study Objectives: Efficacy, safety, biomarkers, PK	Part A: Adult subjects who have progressive disease after receiving at least 1 line of previous chemotherapy for the treatment of mMCC	Part A: 88 subjects (enrollment complete) 10 mg/kg every 2 weeks
	Part B: Phase II, open-label, single-arm study Objectives: Efficacy, safety, biomarkers, PK	Part B: Adult, systemic chemotherapy-naïve subjects with mMCC	No data from Part B are included in this submission

Source: Refer to Module 2.7.4 Table 2
FU = follow up, mMCC = metastatic Merkel cell carcinoma, MTD = maximum tolerated dose, PK = pharmacokinetics, UC = urothelial carcinoma, UK = United Kingdom, and US = United States

The PK of avelumab has been determined using both non-compartmental analyses (NCA) and population PK (PopPK) analyses. The results from the PopPK analyses are presented as follows:

- CL was estimated to be 0.0246 L/hr [95% confidence interval (CI): 0.0239, 0.0252] for a typical subject.
- Geometric mean V_{ss} was estimated to be 4.72 L (95% CI: 4.63, 4.82).
- Geometric mean $t_{1/2}$ was estimated to be 6.1 days (95% CI: 140, 152).
- Steady state is expected to be reached by the 3rd dosing cycle and the accumulation ratio is 1.25.
- Body weight was found to influence CL, central volume of distribution (V1) and peripheral volume of distribution (V2), with all 3 parameters increasing with increasing weight.
- Male subjects had a 19.9% higher CL and 20.3% higher V1 than female subjects after body weight effect is included. The difference in simulated AUC_{SS} between the sexes is regarded as clinically not meaningful.
- The model predicted that subjects with mMCC had a smaller CL of 22.4%, and a higher exposure than subjects with other tumor types. This observation had no impact on the recommended dose.
- There was an influence of baseline tumor size on avelumab CL. Avelumab CL increased with increasing baseline tumor size. This change is considered not clinically meaningful.
- There was an influence of albumin concentrations on avelumab CL. Avelumab CL decreased with increasing albumin concentration. The change is considered not clinically meaningful.
- The effect of immunogenicity was only significant on V2. No change in simulated AUCss was observed.
- There was no influence of renal or hepatic impairment on CL and thus, no dose adjustment is needed in patients with renal or hepatic impairment.
- The concomitant medications included in the popPK analysis did not have an influence on avelumab CL.
- Avelumab is not expected to have an effect on the PK of other drugs. Avelumab did not induce cytokines to concentrations needed to affect transporters involved in the distribution or CYP450 metabolism for small molecule drugs. Levels of several major circulating cytokines were measured in Study 001 over a period of 6 weeks, including interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-10, interferon-γ (IFNγ) and tumor necrosis factor-α (TNFα). After repeated administration of 10 mg/kg Q2W, IFNγ and TNFα concentrations remained low overall (e.g., 1.9±1.6 pg/mL on Day 15 for IFNγ). No apparent dose response was observed based on data collected from the 1 to 20 mg/kg cohorts.

Exposure-Efficacy Analyses: The exposure-efficacy analyses used data from 153 subjects with UC treated

with avelumab and with a minimum follow-up of 6-months (by cut-off date March 19, 2016) in Study 001. Logistic regression was used to assess the relationship between best overall response (BOR) of complete response or partial response and each of 3 predicted exposure metrics: AUC_{ss}, $C_{trough,ss}$, and concentration at the end of the first dose interval ($C_{trough,first}$). Cox proportional hazard models were used to assess the relationships between progression-free survival (PFS) and overall survival (OS) and avelumab exposure. Apparent exposure-BOR, exposure-PFS and exposure-OS relationships were identified for all 3 exposure metrics, where a higher exposure was associated with a higher rate of response or longer PFS.

Exposure-safety Analyses: The exposure-safety analyses used data from 1712 subjects treated with avelumab who had PK data in Studies 001, 002 and 003, including 241 subjects in 2 UC cohorts from Study 001 who received 10 mg/kg of avelumab as of 19 March 2016. Avelumab exposure was a weak factor associated with an increase in immune-related adverse event (irAE) incidence. The estimated probability of experiencing an irAE increased modestly with increasing avelumab exposure. The estimated probability of experiencing TEAEs or infusion-related reactions (IRRs) did not increase with increasing avelumab exposure.

Exposure-QTc Analysis: A total of 2194 time-matched singlet locally-read 12-lead ECG and avelumab concentrations were collected from a total of 689 study subjects from Studies 001, 002 and 003. Exposure-QTc analysis show that the effect of avelumab on QTc or QTc change from baseline (ΔQTc) is minimal for the QT corrected for heart rate by Fridericia's formula (QTcF) and the QT corrected via a project specific factor (QTcP), indicating that avelumab does not have a clinically meaningful effect on cardiac repolarization.

Immunogenicity Assessment: Based on data submitted in this BLA, the incidence of immunogenicity is low and ADA against avelumab did not appear to impact PK, safety, and efficacy.

- Treatment-emergent ADA incidence was 64 of 1558 subjects (4.1%) across the integrated safety analysis population. A similar treatment-emergent incidence was observed within the UC subjects: 10 of 200 subjects (5.0%). Titers were generally low across ADA ever-positive subjects, with no clear relationship between the duration of immunogenicity response and the maximum observed titer.
- ADA ever positive subjects had numerically lower C_{trough} than ADA never positive subjects. The trend is not statistically significant. Causality could not be established as C_{trough} within subjects was similar before and after seroconversion. Concentration at the end of infusion (CEOI) was similar between ADA ever positive subjects and ADA never positive subjects. ADA was only retained in the final PopPK model for V2. Together, the data suggest no clinically meaningful impact on PK.
- A greater percentage of ADA ever-positive subjects had an IRR (29 of 71; 40.8%) versus ADA never-positive subjects (392 of 1588; 24.7%) in the integrated safety analysis population. This appears to be an association rather than causation as only 13 of 71 ADA ever-positive subjects had at least 1 IRR at or after ADA seroconversion; 5 of these 13 subjects did discontinue treatment due to IRRs. No significant impact on safety profile was identified as the numerical increase does not represent a change in the risk assessment nor demonstrate a need to monitor immunogenicity separate from observing IRRs in the clinic.
- No apparent clinically meaningful impact of immunogenicity on efficacy was observed in the UC cohorts of Study 001.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NAN ZHENG
02/14/2017

PENGFEI SONG
02/14/2017

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA

BLA Number: 761078 **Applicant:** EMD Serono, Inc **Stamp Date:** December 27, 2017

Drug Name: Avelumab **BLA Type:** Commercial

On **initial** overview of the BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			n/a cross-reference to BLA 761049 No pharmacology/toxicology data are submitted.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			n/a
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			n/a
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			n/a
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			n/a
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			n/a
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			n/a
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			n/a

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	*x		* Issues generally identified during review
	Has the applicant addressed any abuse potential issues in the submission?			n/a
	If this BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			n/a

* Issues generally identified during review.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____yes____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Wei Chen, PhD 02/07/2017

Reviewing Pharmacologist Date

Todd Palmby, PhD

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEI CHEN
02/09/2017

TODD R PALMBY
02/09/2017