CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761049Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Non-Clinical
Clinical
Statistical
Clinical Pharmacology

BLA Multidisciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761049
Priority or Standard	Priority
Submit Date(s)	7/06/2016, 9/02/2016, 9/23/2016
Received Date(s)	9/23/2016
PDUFA Goal Date	5/23/2017
Division/Office	DOP2/OHOP
Review Completion Date	2/23/2017
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)	Metastatic Merkel cell carcinoma (MCC)
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma

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OBP=Office of Biotechnology Products
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
DMPP=Division of Medical Policy Programs
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ADCC	antibody dependent cell mediated cytotoxicity
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
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
	(b) (4)
CNS	central nervous system
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
Da	Daltons
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DOR	duration of response
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
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRC	independent central review committee
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

ITT	intent to treat
IV	intravenous
MCC	Merkel cell carcinoma
MCV	Merkel cell polyoma virus
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
ORR	Overall Response Rate
OS	Overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PD-L1	programmed death ligand 1
PDUFA	Prescription Drug User Fee Act
PFS	Progression free survival
PI	prescribing information
PK	pharmacokinetics
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
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

EMD Serono, Inc. submitted a Biologics License Application (BLA) for avelumab (Bavencio™) under the regulations for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses, 21 CFR 601 subpart E, as a rolling review with the final modules submitted on September 23, 2016. The indication proposed is: "BAVENCIO is a programmed death ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with metastatic Merkel cell carcinoma (MCC)." One open label, single arm, multicenter trial, Study EMR100070-003 (Study 003), entitled, "A Phase II, Open-label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab in Subjects with Merkel Cell Carcinoma," was submitted as the sole trial demonstrating the treatment effect of avelumab on the surrogate endpoint of durable overall response rate in patients with metastatic MCC. The results of Study 003 were considered in the context of an external population that included treatment-naïve or previously-treated patients with metastatic MCC who were treated with chemotherapy in observational Study 100070-Obs001 (Obs001), a retrospective, chart review of electronic medical records obtained in community and academic centers that collected information on the outcomes of untreated (first line) and previously treated (second line) patients with metastatic MCC. No formal statistical comparisons were made between Studies 003 and Obs001.

Primary reviews focused on Part A of Study 003 which enrolled 88 patients with metastatic MCC who had progressed following at least one prior systemic chemotherapy regimen. Patients received avelumab 10 mg/kg intravenously (IV) as a 60 minute infusion once every two weeks until disease progression or unacceptable toxicity. The major efficacy outcome measures of the trial were overall response rate (ORR) assessed by a blinded independent central review committee (IRC) and IRC-assessed duration of response. The efficacy analyses were conducted when the last patient enrolled had completed 12 months of follow-up. Additional information on the natural history of the disease in patients receiving available, off-label therapy that was considered by the clinical review team during the review process were the results from Obs001, which had a primary objective for the retrospective chart review of an evaluation of ORR as determined by the treating physician according to "clinical judgment" or by an independent auditor according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Characterization of safety for the BLA was derived primarily from Study EMR100070-001 (Study 001), a dose escalation and activity-estimating, multiple cohort expansion study of patients with various advanced solid tumors treated with avelumab at various doses. The safety database consisted of pooled data from 1738 patients enrolled in Study 001 and Study 003 who had been treated at the proposed recommended dosage regimen for labeling.

1.1. Product Introduction

Avelumab is a human monoclonal antibody on an immunoglobulin G1 framework. The recombinant antibody is produced in [redacted] (b) (4) and consists of two

heavy chains of 450 amino acid residues each and two light chains of 216 amino acid residues each with IgG_1 inter and intra chain disulfide bonds. The molecular mass of intact avelumab, calculated on the basis of the amino acid composition and predicted disulfide bonding without glycans, is 143'832 Daltons (Da), the mass including glycans is approximately 147'000 Da.

Avelumab is directed against the programmed death ligand 1 (PD-L1) molecule expressed as an immune-inhibitory checkpoint on epithelial and vascular endothelial cells, as well as by a number of immune cells. PD-L1 is utilized by tumor cells as an immune escape mechanism. Avelumab's main mechanism of action is based on the inhibition of the interaction between PD-L1 and its receptors PD-1 and B7-1 (CD80). This inhibition removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response. The biological activity (potency) of avelumab was evaluated through a cell based assay able to measure its capability to bind the PD-L1 receptor over-expressed on the recombinant HEK-293 (hPD-L1) cell line. PD-L1 target occupancy of > 90% is described in the application and is based on these *in vivo* and *in vitro* studies.

An additional mechanism of action proposed for avelumab is antibody dependent cell mediated cytotoxicity (ADCC) which is thought to occur as a result of the engagement of fragment crystalline receptors on cytotoxic natural killer cells and macrophages. This mechanism was confirmed by the Applicant in vitro using whole peripheral blood mononuclear cells or natural killer cells as effectors. While tumor xenograft models suggest that avelumab-induced ADCC contributes to the anti-tumor activity of avelumab, the relative contribution of this mechanism to anti-tumor activity is uncertain.

1.2. Conclusions on the Substantial Evidence of Effectiveness

It is recommended that approval for avelumab be granted under the provisions of accelerated approval delineated in 21 CFR 601, Subpart E for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC). All primary scientific discipline reviewers concur in this recommendation.
In this application, evidence for the effectiveness of avelumab for patients with metastatic MCC comes from the results of Part A of Study 003. Part A enrolled 88 patients with metastatic MCC who experienced tumor progression after receiving at least one prior chemotherapy regimen. The trial excluded patients with autoimmune disease; medical conditions requiring systemic immunosuppression; prior organ or allogeneic stem cell transplantation; prior treatment with anti-PD-1, anti-PD-L1 or CTLA-4 antibodies; central nervous system (CNS) metastases; infection with HIV; hepatitis B or hepatitis C; or ECOG performance score ≥ 2. The baseline characteristics of patients enrolled were a median age of 73 years (range: 33 to 88), 74% were male, 92% were White, and the ECOG performance scores were 0 (56%) or 1 (44%). Seventy-five percent of patients were 65 years or older, 35% were 75 or older, and 3% were 85 or older. Sixty-five percent of patients had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies. Fifty-three percent of patients had visceral metastases. All patients had tumor samples evaluated for PD-L1 expression by an investigational immunohistochemistry

assay; of these, 66% were PD-L1-positive (≥ 1% of tumor cells), 18% were PD-L1 negative, and 16% had non-evaluable results. Archival tumor samples were evaluated for Merkel cell polyomavirus (MCV) using an investigational assay; of the 77 patients with evaluable results, 52% had evidence of MCV.

All patients received avelumab 10 mg/kg IV every two weeks in an unblinded, non-randomized fashion. Treatment was continued until treatment failure, unacceptable toxicity, or withdrawal of patient consent. The primary endpoint of the study was confirmed best overall response rate (ORR). All major endpoints were determined by an IRC. The key secondary endpoint was duration of response (DOR); and progression-free survival (PFS) and overall survival (OS) were also followed.

Tumor response assessments were performed every 6 weeks using RECIST 1.1, and included radiologic imaging and physical examination of skin lesions. Patients who experienced a complete response (CR) as reported by an investigator could be treated for 6 to 12 months after confirmation of response, with treatment beyond 12 months permissible after a discussion with the sponsor. Re-initiation of treatment post relapse for patients with a confirmed CR prior to the end of the study was permitted at investigator discretion and agreement of the study medical monitor.

Efficacy analyses were conducted when all patients (N=88) had been treated or followed for at least 12 months from their first response. The trial results demonstrated a confirmed, centrally reviewed ORR of 33% (95% CI: 23, 44), including 10 patients (11%) with complete response (CR) and 19 patients (22%) with partial response (PR). Among the 29 responding patients, the median duration of response (DOR) was not reached (range 2.8 to 23.3+ months) and 72% (21/29) of patients had ongoing responses at the data cutoff. Eighty-six percent (25/29) of responding patients maintained responses of $\geq$ 6 months and 45% (13/29) maintained responses of $\geq$ 12 months in duration. Though the numbers were small, the treatment effect was consistent across relevant subgroups, i.e. those with visceral metastases, patients whose tumor tissue was MCV positive or negative, and PD-L1 expression status of the tumors.

The results in Study 003, Part A were considered in the context of a subgroup of the Study Obs001 database containing 686 patients with a diagnosis of MCC. A total of 39 potential patients were identified by the Applicant as having metastatic MCC with evidence of receiving second line chemotherapy for metastatic disease. Based on the Applicant's chart review, 19 of the 39 patients were excluded from the dataset because 11 patients did not have evidence of metastatic disease, 4 patients were participants in a clinical trial, 3 patients did not receive second-line therapy, and 1 patient did not receive one of the selected chemotherapeutic agents as first-line therapy. Of the remaining 20 patients, 6 patients were excluded from the assessment of ORR based on a history of autoimmune disease, medical conditions requiring systemic immunosuppression, and prior organ or allogeneic stem cell transplantation, i.e. those excluded from Study 003. For the remaining 14 patients, the ORR was 28.6% (95% CI: 8.4, 58.1), with a median duration of response of 1.7 months (95% CI: 0.5, 3.0). The data from this subset

analysis are of interest in the attempt to establish a baseline history of the disease treated in the current clinical environment; however, the data are limited, formal comparisons to the data from Study 003 were not made, and the data are subject to selection bias.

For patients with MCC in the setting of previously treated metastatic disease, durable objective response rate is deemed a valid surrogate endpoint considered reasonably likely to predict clinical benefit (i.e., improvement in survival, or how patients function or feel), and the treatment effect size for avelumab on ORR and DOR represents substantial improvement over use of salvage chemotherapy in this setting.

FDA considers extrapolation of the efficacy demonstrated for avelumab in patients with metastatic MCC who had progressed following at least one prior systemic chemotherapy regimen in Study 003 Part A to be scientifically justified for treatment of patients with metastatic MCC who have not been treated and for treatment of pediatric patients 12 years and older who have metastatic MCC.

The biology of metastatic MCC suggests no reason why the approximately 30% of patients who develop metastatic disease, and who have not been previously treated with chemotherapy, would respond differently or for a shorter duration than patients who have progressed on prior chemotherapy. There are no differences in histopathologic and virologic aspects of the disease between treated and untreated adults with MCC or between the disease in adults and pediatric patients. Because of the histomorphological features ofMCC, definitive diagnosis is made based on immunohistochemistry (IHC) for both adult and pediatric patients. Identification of cytokeratin 20 (CK20) is specific for the tumor type. Neuron-specific enolase (NSE) is also often positive. These positive stains along with negative staining for vimentin, S100, leukocute common antigen and thyroid transcription factor 1, distinguish MCC from other diagnoses such as small-cell lung cancer, small B-cell lymphomas, and anaplastic small-cell melanomas. There is also an association with the Merkel cell polyomavirus (MCV) that occurs in approximately 80% of adult patients who have the disease. In the pediatric age group, seropositivity for MCV appears to increase with age, occurring in approximately 60% of patients between the ages of 10 and 20[1]. Although there are no case series of pediatric patients with metastatic MCC to verify an association with the virus and the tumor, it is reasonable to conclude that such an association exists. In the absence of data to suggest otherwise, FDA believes that MCC in adults and pediatric patients 12 years and older is the same disease.

Supporting extrapolation of effectiveness between previously untreated and already treated adult patients with MCC are the similar outcomes observed for both groups of patients. The clinical reviewer cites a paper from Iyer, et.al. which evaluated a cohort of 62 patients having distant metastatic MCC. Among these patients, a platinum plus etoposide regimen was most commonly used in the first-line setting (69%). The ORR to first-line chemotherapy was 55% (34/62) with complete responses (CR) in 13% (8/62) and partial responses (PR) in 42% (26/62). Median DOR was 85 days. Among 30 patients who received second-line chemotherapy in this analysis, the ORR was 23% (7/30; 1 CR, 6 PR), and median DOR was 101 days. These data

suggest that although MCC is chemotherapy-sensitive, early development of resistance to chemotherapy based on the short duration of response is a hallmark of metastatic MCC, no matter the treatment setting, and support the argument that a treatment that does not result in disease progression within 2 to 3 months would be considered effective in adult patients with either untreated or previously treated MCC.

Additionally, the Applicant has provided data from a small group of previously untreated adult patients from the ongoing Part B of Study 003. The Investigator-assessed, confirmed ORR among 16 patients with three months of follow-up was 56% (95% CI 30, 80) which is similar to response rates to chemotherapy reported in the published literature. The caveats with these data are that the numbers are very small and the responses have not been verified by an independent review.

The Applicant has also provided data for patients who were followed beyond progression in Part A of Study 003. For 14 patients who were treated after progression on avelumab, three (21%) are reported to have had a partial response to chemotherapy: one patient to carboplatin and etoposide, one to carboplatin and paclitaxel, and one to cyclophosphamide, doxorubicin and vincristine. These three patients also had responses to one or more chemotherapy treatments prior to receiving avelumab. Although these data are also very limited, they suggest that treatment with avelumab does not appear to have a negative impact on responses to subsequent chemotherapy following disease progression; thus, salvage chemotherapy responses will very likely be preserved for patients who receive avelumab in the first line.

For adult patients with metastatic MCC, given the aforementioned data, the rarity of the disease, and the lack of available therapies, FDA considers the safety and effectiveness of avelumab to be favorable for adult patients with metastatic MCC regardless of whether or not they received prior chemotherapy.

Extrapolation of the effectiveness of avelumab to pediatric patients aged 12 and older who have metastatic MCC is also reasonable. Population pharmacokinetic (PK) modeling provided in the application included simulation of PK exposure at steady state after repeat intravenous dosing of avelumab 10 mg/kg every 2 week for patients with body weights of 30kg to 90 kg, which are equivalent to weights of adolescents. The PK data were obtained from patients aged 20 to 91 years who were treated with avelumab in Study 001, Study 3, and EMR 1000070-002 (Study 002). The results of this analysis demonstrate comparable PK between patients with body weights of 30 to 90 kg and adults. Also demonstrated were no differences in PK based on age. In addition, based on data from the population PK modeling simulating minimum concentration (Cmin) and the data from an in vitro target occupancy study provided by the Applicant, high target occupancy was predicted for pediatric patients 12 years and older during the entire dose interval at 10 mg/kg every 2 weeks.

Population PK modeling has long been utilized in the analyses of PK data to inform product labeling with regard to dosing recommendations in specific populations. Extrapolation of PK

findings from adults to pediatric patients 12 years and older is relied upon by FDA to inform labeling and these data contribute to support extrapolation of the indication for avelumab to the pediatric patients with metastatic MCC who are 12 years of age and older.

Additional support for the indication in pediatric patients comes from a review of the published literature performed by the Applicant that resulted in six case reports of patients with MCC in the pediatric age group, four patients in the age range 11 to 17, two of the patients had metastatic disease, one patient received chemotherapy and the remainder underwent surgical resection. All cases were diagnosed utilizing IHC. In addition to these patients, the Applicant submitted the report of a 10-year-old female patient diagnosed in January, 2014 with metastatic MCC who was initially treated with 6 cycles of cisplatin and etoposide and who experienced subsequent disease progression after receiving 3 doses of avelumab at 10 mg/kg under an emergency access single patient IND. During and after treatment with avelumab, the patient reportedly experienced pain, nausea and vomiting. While the numbers are small, the diagnosis and treatment of these patients is nearly identical to adults with metastatic MCC, as are the outcomes, and there are no data to suggest that treatment with avelumab will be less effective or tolerable.

Adult and pediatric patients aged 12 and older with advanced or metastatic MCC represent a population with a serious and life threatening disease. There is no available FDA-approved therapy for the disease, and no known therapy that is either curative or is known to improve overall survival (OS). Although MCC is known to be sensitive to chemotherapy, treatment of patients with cytotoxic chemotherapy has demonstrated neither durable responses (in general, for adults, less than 6 months) nor survival advantages for patients. Thus, a broad indication encompassing adults and pediatric patients 12 years and older is being recommended for avelumab in the setting of an accelerated approval. Additional data will be required to confirm the clinical benefit of avelumab for adult patients with metastatic MCC. A PMR will also be required to characterize the effects of treatment with avelumab for pediatric patients aged 12 years and older with solid tumors.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

The evidence for the effectiveness of avelumab for patients with metastatic MCC comes from the results of Part A of Study 003. Studied were patients with metastatic MCC who experienced tumor progression after receiving at least one prior chemotherapy regimen. The primary efficacy endpoint was overall response rate with duration of response being the key secondary endpoint. The results of the study are considered in the context of outcomes for previously-treated patients with metastatic MCC who had been treated with chemotherapy in observational Study Obs001, a retrospective chart review of electronic medical records obtained in community and academic centers that collected information on the outcomes of untreated (first line) and previously treated (second line) patients with metastatic MCC. The data from Study Obs001 are subject to selection bias, therefore no formal statistical comparisons were undertaken and the data are considered for informational purposes.

For Study 003, efficacy analyses were conducted when all patients (N=88) had been treated or followed for at least 12 months after accrual and the results demonstrated a confirmed, centrally reviewed ORR of 33% (95% CI: 23, 44), including 10 patients (11%) with complete responses (CR) and 19 patients (22%) with partial responses (PR). Among the 29 responding patients, the median duration of response (DOR) was not reached (range 2.8 to 23.3+ months) and 72% (21/29) of patients had ongoing responses at the data cutoff. Eighty-six percent (25/29) of responding patients maintained responses of > 6 months and 45% (13/29) had responses of > 12 months. Though the numbers are small, evidence of anti-tumor activity was present across relevant subgroups: those with visceral metastases, patients who were MCV-positive or MCV-negative, and patients whose tumors tested positive or negative for PD-L1 expression. In contrast for the relevant patient population in Study Obs001, the ORR was 28.6% (95% CI: 8.4, 58.1), with a median duration of response of 1.7 months (95% CI: 0.5, 3.0)

Study 003 demonstrated a clinically meaningful ORR that was significantly more durable than response rates observed for salvage chemotherapy, which is the current treatment standard. Because this application is being approved under the accelerated approval regulations, confirmation of the clinical benefit for avelumab is required.

The primary safety risks of avelumab are immune-related adverse reactions (imAR) and infusion-related reactions (IRR). In Study 003, 17% of patients experienced at least one imAR. The most common imARs in more than 2% of patients were hypothyroidism, rash, and diarrhea. Across the larger pooled safety population of > 1500 patients, imARs that occurred in more than 1% of patients include hypothyroidism, rash, pruritus, diarrhea and pneumonitis. Two percent of all immune-mediated events were Grade 3 or 4 in the pooled analysis. Serious imARs observed in less than 2% of patients across the avelumab development program include autoimmune hepatitis and myocarditis, for which fatal events were observed, colitis, nephritis, myositis, autoimmune thyroiditis, adrenal insufficiency, encephalopathy, uveitis, Guillain-Barre syndrome, bullous pemphigoid and systemic inflammatory response syndrome (SIRS). 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. ImARs were usually manageable with corticosteroids and hormone replacement therapy. Dose-modification and management guidelines for imARs are included in product labeling.

IRRs during Study 003 were low-grade in severity and no patient required permanent discontinuation of avelumab due to an IRR. The majority of patients received pre-medication with an antipyretic and antihistamine for the first four infusions of avelumab. IRRs that did occur were manageable with temporary treatment interruptions, infusion rate reductions, and administration of symptomatic treatments including antihistamines and

corticosteroids.

During Study 003, there were no avelumab-related fatal AEs. Avelumab-related SAEs occurred in 7% (n=6) of patients, AEs leading to permanent discontinuation occurred in 6% (n=5), and treatment-related Grade 3-4 AEs occurred in 8% (n=7) of patients. The most common AEs (more than 15% of patients) in Study 003 included fatigue, diarrhea, nausea, decreased appetite, peripheral edema, constipation, cough, arthralgia, anemia, extremity pain, and IRR. Similar incidences of these AE categories were observed in the larger, pooled analysis.

The principle strengths of this application are the duration of responses observed in a previously treated population of patients, as well as the fact that there is no FDA-approved treatment for this serious and life-threatening disease in a population of patients with an unmet medical need. The weaknesses of the application are that the results supporting it are not from a randomized trial, the historical data referenced are limited and subject to selection bias, and the data collected on time-to-event endpoints are not interpretable, therefore, it cannot be determined if PFS or OS are prolonged.

Recommendation: Under the Accelerated Approval regulations, approval is recommended for avelumab for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin, which can be distinguished from other skin cancers by its expression of cytokeratin 20 (CK20) and an association with the Merkel cell polyomavirus (MCV) • Factors associated with increased risk for developing MCC include ultraviolet (UV) radiation exposure, infection with MCV, advanced age, and immunosuppression, although the majority of patients with MCC are immunocompetent. The mean age at presentation is approximately 75 years • The 5-year survival rate for patients with MCC is 25% for tumors with distant metastases . More than 30% of patients will develop distant metastatic disease	Metastatic MCC is incurable and represents a disease without FDA-approved therapy, therefore, with a high unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are no FDA-approved products for the treatment of patients with metastatic MCC • The most common drugs used off-label are cisplatin or carboplatin in combination with etoposide, single agent topotecan, and cyclophosphamide, doxorubicin, and vincristine (CAV) • MCC is generally a chemo-sensitive tumor with response rates between 50-60% for patients with newly diagnosed metastatic MCC; however, responses are not durable (median duration of 85 days from reports in the published literature), and chemotherapy has not been shown to improve OS in patients with metastatic disease	There are few treatment options for patients with metastatic MCC. The existing treatments are not FDA-approved and offer limited benefit in terms of duration of responses, when responses are observed. Furthermore, there is no evidence that these existing treatments prolong survival or result in clinically meaningful delays in disease progression. Finally, the toxicity of chemotherapy includes serious and sometimes fatal adverse reactions, particularly in older patients.
Benefit	• The effectiveness of avelumab was demonstrated in Study 003, an open label, single arm, multicenter trial, of 88 patients with metastatic Merkel cell carcinoma who experienced tumor progression after receiving at least one prior chemotherapy regimen. • The primary efficacy endpoint was best overall response rate with duration of response being a key secondary endpoint. • Efficacy analyses were conducted when all patients (N=88) had been treated or followed for at least 12 months after accrual and demonstrated a confirmed, centrally reviewed ORR of 33% (95% CI: 23, 44), including 10 patients (11%) with complete response (CR) and 19 patients (22%) with partial response (PR). • Among the 29 responding patients, the median duration of response (DOR) was not reached (range 2.8 to 23.3+ months). Eighty-six percent (25/29) of responding patients maintained	Study 003 was a well-conducted trial demonstrating a clinically meaningful response rate for a serious and life threatening rare disease and with significantly longer response durations observed (Study Obs001) or reported with first-line chemotherapy. Response rates were similar in all subgroups studied. There is no biological reason to believe that the responses observed in Part A of Study 003 will not also apply to the population being studied in Part B of the trial, i.e., previously untreated patients with metastatic MCC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	responses of > 6 months and 45% (13/29) had responses of > 12 months. • In contrast, for the population of 14 patients with metastatic MCC treated in second line or greater in Study Obs001, the ORR was 28.6% (95% CI: 8.4, 58.1), with a median duration of response of 1.7 months (95% CI: 0.5, 3.0). For the 20 patients with metastatic MCC in Study Obs001 who received first line chemotherapy, the ORR was 29.4% (95% CI: 5.7, 43.7) • Though the numbers were small, the treatment effect was present across relevant subgroups: those with visceral metastases, patients who were MCV-positive or MCV-negative, and patients whose tumors tested positive or negative for PD-L1 expression. • Study 003 demonstrated a clinically meaningful ORR that was significantly more durable than response rates observed for salvage chemotherapy, the current treatment standard for this disease.	
Risk	• The safety evaluation was based on >1700 patients, including all patients in Study 003 as well as patients with various other solid tumors studied during the avelumab development program who were treated at the labeled dose. • In Study 003, the median duration of exposure to avelumab was 4 months (range: 2 weeks to 21 months). Forty percent of patients received the drug for more than 6 months and 14% were treated for more than one year • For the entire safety database, 24% of patients were exposed to avelumab for ≥ 6 months and 7% were exposed for ≥ 12 months.	Avelumab demonstrated ARs previously identified for this class of molecules, specifically imARs and IRRs. The incidences observed for imARs, IRRs, SAEs, AEs, dose interruptions, and permanent dose discontinuations were not excessive for this class of molecule in the treatment of a serious and life threatening disease. The known risks are reasonable for the intended population of patients with metastatic MCC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The primary safety risks of avelumab are immune-related adverse reactions (imAR) and infusion-related reactions (IRR). imARs that occurred in more than 1% of patients include hypothyroidism, rash, pruritus, diarrhea and pneumonitis. Two percent of all immune-mediated events were Grade 3 or 4 in the pooled analysis. Serious imARs observed at a lower frequency across the avelumab development program include autoimmune hepatitis and myocarditis, for which fatal events were observed, colitis, nephritis, myositis, autoimmune thyroiditis, adrenal insufficiency, encephalopathy, uveitis, Guillain-Barre syndrome, bullous pemphigoid and SIRS. • Dose-modification and management guidelines for imARs are included in product labeling. • IRRs during Study 003 were low-grade in severity and no patient required permanent discontinuation of avelumab due to an IRR. IRRs were manageable with temporary interruptions, infusion rate reductions and administration of symptomatic treatments including antihistamines and corticosteroids. • During Study 003, there were no avelumab-related fatal AEs. Avelumab-related SAEs occurred in 7% (n=6) of patients, AEs leading to permanent discontinuation occurred in 6% (n=5), and treatment-related Grade 3-4 AEs occurred in 8% (n=7) of patients. • The most common AEs (more than 15% of patients) in Study 003 included fatigue, diarrhea, nausea, decreased appetite, peripheral edema, constipation, cough, arthralgia, anemia, extremity pain, and	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	IRR. Similar incidence rates of these AE categories were observed in the pooled analysis.	
Risk Management	• Avelumab is intended to be prescribed by oncologists and administered intravenously by trained nursing staff in a controlled setting. • Oncologists are well versed in the identification and management of the toxicities associated with monoclonal antibodies	A Risk Evaluation and Mitigation Strategy (REMS) is not needed to ensure the risks of avelumab outweigh its risks.

X _____

Cross-Disciplinary Team Leader: Suzanne Demko

2 Therapeutic Context

2.1. Analysis of Condition

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine carcinoma of the skin, which can be distinguished from other cutaneous malignancies by its expression of cytokeratin 20 (CK20) and an association with the Merkel cell polyomavirus (MCV) in the majority (approximately 80%) of patients. The name of the tumor is taken from the Merkel cell which is located in the basal layer of the epidermis and characterized by neuroendocrine granules and CK20 expression. These shared characteristics have led to the common thinking that MCC originates from Merkel cells; however, the cell of origin is not definitive and the pathogenesis not completely understood [1].

MCC occurs in an estimated 1,600 new patients diagnosed each year in the U.S.; however, the annual incidence rate is increasing. Data from the Surveillance, Epidemiology and End Results (SEER) Program database estimated the annual incidence rate in 2011 as 0.79 per 100,000 persons. Factors associated with increased risk for developing MCC include ultraviolet (UV) radiation exposure, infection with the MCV, advanced age, and immunosuppression, although the majority of patients with MCC are immunocompetent. The mean age at presentation is approximately 75 years [2].

MCC usually presents as a firm, painless, rapidly enlarging, dome-shaped cutaneous nodule located in a sun-exposed area such as the head, neck or upper extremities [3]. Wide local excision with at least a 2-3cm minimum margin is the standard of care for localized MCC. Depending on the tumor location and the excision margins, adjuvant radiation may be administered following resection. For patients with disease present in local lymph nodes, the resection may include a wider dissection with lymphadenectomy, and adjuvant radiation is often administered [1,4]. For patients with distant metastatic disease, chemotherapy regimens similar to those used for small cell lung cancer are utilized, the most common being cisplatin or carboplatin in combination with etoposide. However, chemotherapy is generally tailored to the individual patient's age and baseline comorbidities, and the National Comprehensive Cancer Network (NCCN) guidelines suggest that a clinical trial, when available, is an appropriate first option as well [5]. Although MCC tends to be a chemosensitive tumor, responses are not durable, and chemotherapy has not been shown to improve overall survival in patients with metastatic disease. [6,7]. Chemotherapy is also associated with risk of severe toxicity and toxic death, particularly among older patients. Voog et al. performed a retrospective review of 107 patients with MCC who received chemotherapy for locally advanced or metastatic MCC between 1980 and 1995 and found an 8% risk of chemotherapy-related death during front-line treatment [8].

The 5-year survival rates for patients with MCC are 75%, 59%, and 25% for primary localized tumors, tumors with regional lymph node metastases (or local recurrences), and tumors with distant metastases, respectively [1]. More than 30% of patients will develop distant metastatic disease [8]. There are no large prospective studies reporting outcomes for patients with purely distant metastatic disease as many studies pool patients with locoregional and distant metastatic disease. A retrospective analysis of the treatment outcomes of 62 patients with MCC with distant metastases treated with chemotherapy demonstrated a median OS from start of chemotherapy for all patients of 9.5 months. The ORR with front-line chemotherapy was 55% (34/62). The median DOR from onset of response for first-line chemotherapy was 85 days (range 12–942 days). For the 30 patients who received salvage chemotherapy at recurrence, the ORR was 23% (7/30) with a median DOR of 101 days (range 6-226 days). In this case series, no patients died due to direct toxicity from chemotherapy; however, 7% of patients experienced febrile neutropenia and 5% of patients had septic events [9].

2.2. Analysis of Current Treatment Options

There are no FDA-approved products for the treatment of patients with metastatic MCC. Off-label use of chemotherapy regimens similar to those used for small cell lung cancer is generally employed in the frontline setting. The most common regimens are cisplatin or carboplatin in combination with etoposide, single agent topotecan, and cyclophosphamide, doxorubicin, and vincristine (CAV), although CAV is used less than the other regimens due to increased risk for toxicity. MCC is generally a chemo-sensitive tumor with response rates between 50-60% in newly diagnosed metastatic MCC; however, responses are not durable, and chemotherapy has not been shown to improve OS in patients with metastatic disease [5, 6, 8].

Multiple ongoing studies are evaluating the antitumor activity of various immune-checkpoint inhibitors for the treatment of MCC [2]. Nghiem et al. reported an ORR of 56% (95% CI: 35,76) in a prospective trial of 26 patients who received pembrolizumab for Stage IIIB (n=2) or Stage IV (n=24) newly diagnosed metastatic MCC. Among the 14 responders of the 25 patients included in the ORR calculation, the DOR ranged from at least 2.2 months to at least 9.7 months at data cutoff. Responses were observed in patients who had MCV-positive tumors and patients who had MCV-negative tumors. Similarly, responses did not correlate with PD-L1 expression [10].

There are published case reports and small case series of partial responses to kinase inhibitors including imatinib, cabozantinib, pazopanib and mTOR inhibitors in patients with metastatic MCC; however, no large prospective clinical trials have demonstrated evidence of effectiveness for any of these agents to date. Other drug classes under early investigation for metastatic MCC include cytokines, adoptive T-cell therapy, toll-like receptor 4 agonists, and somatostatin analogues [2].

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Avelumab is an NME and is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following summarizes the clinical presubmission regulatory activity for avelumab:

On November 13, 2012, IND 115747 was submitted to the Division of Oncology Products 2 for avelumab for the treatment of patients with advanced solid tumors. The IND was placed on partial hold on December 12, 2012, for insufficient information provided in the IND to assess whether the safety testing in the master cell bank (MCB) was sufficient to exclude contamination by (b) (4) adventitious agent. The initial feasibility study was allowed to proceed; however, the Applicant was required to provide data demonstrating that the MCB was free of adventitious agents (b) (4) . This information was submitted on July 3, 2013, and the partial hold was removed on August 1, 2013.

On January 14, 2014, a pre-IND teleconference was held between FDA and the Applicant to discuss the design of Study EMR 100070-003, entitled, "A Phase 2, Open-label, Multicenter Trial to Investigate the Clinical Activity and Safety of MSB0010718C in Patients with Merkel Cell Carcinoma." The initial proposed study was (b) (4)

- [redacted] (b) (4)
  - Based on this advice, the Applicant proposed to alternatively conduct a study in a narrower population: patients who have progressed after they have received chemotherapy for the treatment of metastatic disease and patients with metastatic MCC who are not suitable for treatment with chemotherapy because of underlying medical conditions. FDA provided the following feedback to this proposal:
    a) Provide specific objective criteria for eligibility and justification based on available literature that this population has an unmet medical need, i.e. that objective responses could not be obtained with lower dose or alternative chemotherapy.
    b) Provide justification for the proposed effect size and duration of effect to be considered evidence of direct benefit or likely to predict clinical benefit based on a lower limit of the confidence interval observed around the response rate.
    c) Time-to-event endpoints will not be interpretable in a single arm trial. Submit a proposal for a confirmatory study evaluating time-to-event endpoints for FDA review prior to initiating the study.

On March 4, 2014, IND 119394 was submitted and included the clinical protocol for Study EMR 100070-003 (Study 003), a single-arm, multi-center study of avelumab in patients with metastatic MCC who had received at least one line of previous chemotherapy. The primary endpoint of Study 003 was BOR according to the RECIST 1.1 based on independent review of tumor assessments. A safe to proceed memo was issued on April 2, 2014.

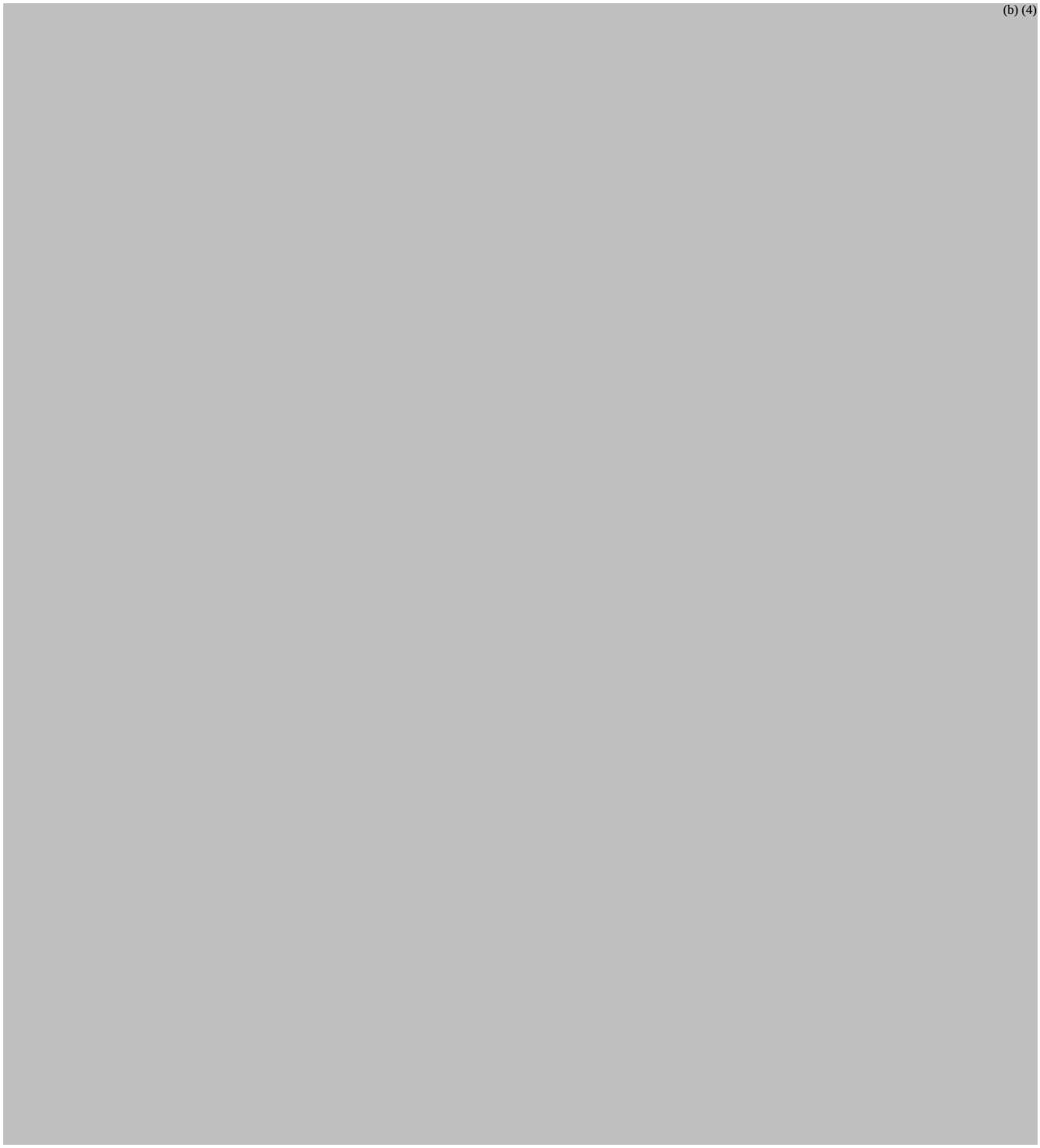
A Type B meeting was held on December 14, 2014 to discuss the scale-up activities and comparability for Process B drug substance. Process B material was intended for phase 3 development and is the intended commercial drug substance manufacturing process. Data supporting the comparability was submitted to the IND on March 10, 2015 and deemed sufficient for introduction into clinical trials.

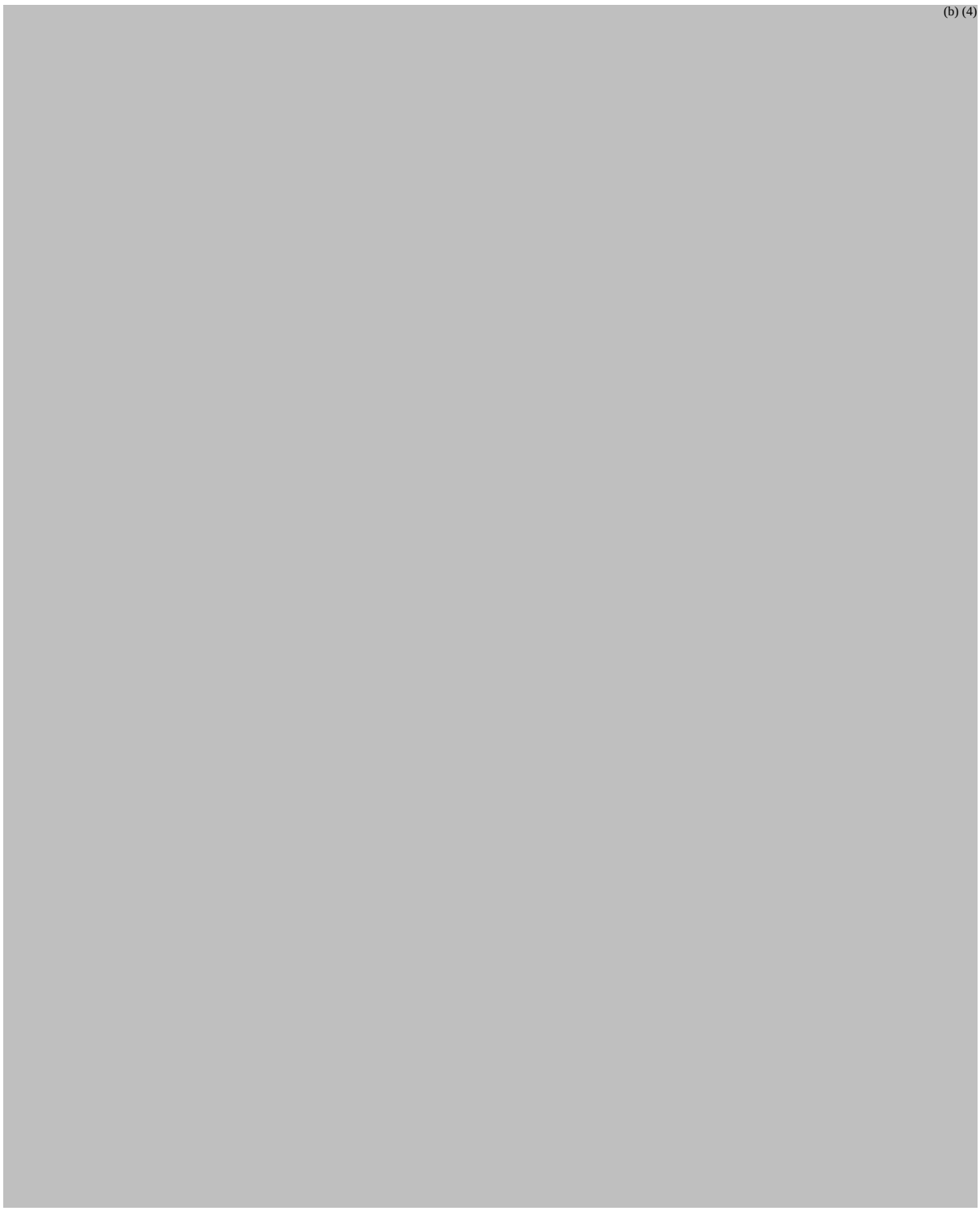
On July 1, 2015, a breakthrough therapy designation (BTD) preliminary advice teleconference was held to discuss whether a request for BTD for metastatic MCC was appropriate based on the data derived from the pre-specified futility analysis (n= 20 patients) performed during Study 003. FDA recommended that the BTD request be submitted when the Applicant had a minimum of three months, but preferably six months, of follow-up data on responders.

On August 14, 2015, the Applicant submitted a Fast Track Designation (FTD) request for avelumab for the treatment of metastatic MCC. On October 1, 2015, FTD was granted for the investigation of avelumab for the treatment of patients with metastatic MCC to demonstrate a clinically important and statistically robust improvement in PFS for patients treated with avelumab compared to available therapy.

On August 25, 2015, the Applicant submitted a draft protocol for Study EMR 100070-006 (Study 006), which was intended to provide confirmatory evidence of clinical benefit in patients with metastatic MCC such that a potential indication for metastatic MCC approved under accelerated approval could receive regular approval. The design of this trial was revised multiple times from August 2015 to September 2016:

(b) (4)





On September 18, 2015, the Applicant submitted a BTD request for the treatment of patients with metastatic MCC that has progressed after at least one prior chemotherapy regimen. Response and duration of response data from 28 patients enrolled in Study 003 with at least 24 weeks of follow-up were provided to support the BTD request. The ORR for these 28 patients

was 29% (CI:13, 49). The median DOR was not reached, and seven of the eight responding patients had ongoing responses ranging six months or longer. The clinical review team considered these data to be preliminary evidence of a substantial improvement over salvage chemotherapy treatment options. On November 17, 2015, BTD was granted.

On September 21, 2015, avelumab was granted orphan drug designation for the treatment of MCC.

On February 2, 2016, a Breakthrough Therapy-Initial Comprehensive Multidisciplinary Type B meeting was held. The following are key discussion points from this meeting:

- FDA stated that an improvement in DRR would be highly unlikely to provide direct evidence of clinical benefit, and that an application seeking regular approval would need to show improvement in survival or in how patients feel or function. The Applicant proposed the option of an external, historically-controlled comparison as an alternative confirmatory study design. FDA stated that such studies are challenging as it is difficult to establish that the study is well-controlled for both known and unknown prognostic factors, as well as excluding that differences cannot be attributed to changes in medical care over the period that a historically controlled population was treated.
- The proposal to pool the safety data from patients treated in Study 003 with data from patients treated with 10mg/kg avelumab in Study 001 for analyses included in the ISS was considered acceptable.
- FDA stated that the ISS should include case definitions for imARs (e.g. enterocolitis, hepatitis, pneumonitis, dermatologic events) with specific criteria used to distinguish these events from non-immune adverse events with similar symptoms and/or laboratory abnormalities. Criteria should include the treatment administered (dose and duration of corticosteroid use, need for additional immunomodulatory agents), additional interventions (e.g., biopsies, procedures), onset and duration of the event, requirement for dose modification or discontinuation, and other concurrent endocrinologic findings. A preferred terms MedDRA query that would be used to identify potential imARs was requested.
- With regard to analyses for IRRs, FDA stated that the ISS should include: a time-frame for identifying AEs thought to be related to IRRs (i.e., 24 hours following infusion); the preferred terms MedDRA query used to capture AEs commonly observed as infusion reactions, including but not limited to fever, rigors, flushing, cutaneous reactions, hypotension, dyspnea, wheezing, back pain, and abdominal pain; analysis of the incidence of infusion reactions by treatment cycle; analysis of interventions for management of infusion reactions, including medications administered and alterations of infusion rate; and analysis of the incidence of infusion reactions in patients with a previous infusion reaction.
- FDA stated that data from Study 100070-Obs001 should be included in the text for the ISE in order to put the study results in context and that these data could not be used for comparative labeling claims.

On February 5, 2016, the Applicant submitted a request for proprietary name review of

Bavencio. FDA determined that Bavencio was conditionally acceptable on April 28, 2016.

On June 16, 2016, a pre-BLA Type B meeting was held to discuss the content and format of the BLA for avelumab. The following are key discussion points from this meeting:

- FDA agreed that it would be acceptable to submit updated efficacy information on IERC-determined response duration concurrent with the 90 day safety update.
- The selection of MedDRA terms for case review on immune-mediated adverse events appeared adequate. However, FDA requested that the Applicant include hypogonadism related terms in immune-related endocrinopathy events. FDA also recommended a vigorous review process for immune-related endocrinopathy events so as to distinguish secondary hypofunction of thyroid, adrenals and gonads due to hypopituitarism/hypophysitis from primary hypofunction of these glands.
- FDA requested submission of patient narratives for all new immune-mediated adverse events in the safety update as well as updated narratives where new clinical information regarding a previously reported event was available.
- FDA agreed with the proposed timeline for rolling submission of components of the BLA.

On July 6, 2016, the first part of the rolling BLA was submitted: Module 4 (Nonclinical Study Reports).

On September 2, 2016, a Type B meeting (teleconference) was held to discuss the proposed confirmatory study (Part B of Study 003) to verify the clinical benefit of avelumab for the treatment of patients with metastatic Merkel Cell Carcinoma (see above for details). On October 26, 2016, the Applicant submitted a protocol amendment for Study 003 Part B to IND 119394 based on FDA advice provided during this teleconference.

On September 2, 2016, Module 3 (Quality) was submitted.

On September 23, 2016, the final portion of the BLA was submitted and included Module 5 (Clinical), Module 2.2 (Introduction), Module 2.3 (Quality Overall Summary), Module 2.4 (Nonclinical Overview), Module 2.5 (Clinical Overview), Module 2.6 (Nonclinical written and tabulated summaries), Module 2.7 (Clinical Summary) and Module 1 (administrative).

The following summarizes the important clinical post submission regulatory activity for avelumab:

On December 7, 2016, the Applicant submitted updated efficacy results for ORR and DOR based on a data cut-off date 12 months after the last enrolled patient started avelumab treatment as a Clinical Study Report (CSR) addendum (cutoff date September 3, 2016).

On December 23, 2016, the Applicant submitted the 90-day Safety Update Report and datasets including cumulative safety data through the data cut-off date of June 9, 2016. The Applicant

additionally submitted revised proposed labeling based on the 12 month efficacy data and the updated safety results.

On January 5, 2016, the Midcycle Communication teleconference was held with the Applicant. FDA stated that no significant review issues and no major safety concerns had been identified to date. FDA stated that there was no need for a REMS associated with the application. FDA requested submission of any available clinical data to support an indication for avelumab that includes patients with newly diagnosed metastatic Merkel cell carcinoma in addition to patients who have progressed following prior chemotherapy.

On January 30, 2017, the Applicant submitted available efficacy data from the ongoing Study 003 Part B. A teleconference was held with the Applicant to discuss these data on January 31, 2017. FDA determined that these results cannot be used to support an indication for avelumab for patients with chemotherapy-naïve metastatic MCC given the small sample size and very short follow-up which does not permit an adequate characterization of durable response rate.

APPEARS THIS WAY ON ORIGINAL

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

4.1. Office of Scientific Investigations (OSI)

The review team consulted the Office of Scientific Investigation (OSI) on October 20, 2016, to perform an audit of four clinical trial sites (Site #102, Dr. Kent Shih, Hermitage, TN; Site #133, Dr. Jeffery Russell, Tampa, FL; Site #204, Dr. Howard Kaufman, New Brunswick, NJ; Site #206, Dr. Shailender Bhatia, Seattle, WA), the Applicant site, and (b) (4) the contract research organization (CRO) that was responsible for developing the Imaging Review Charter, qualifying sites and investigators for image acquisition and image data transfer, selecting and training independent reviewers for the IERC and managing the IERC image review and correspondence with the Applicant. The Division, in consultation with OSI, selected clinical sites for inspection using the Center for Drug Evaluation and Research (CDER) risk-based Site Selection Tool and a manual assessment of the trends in screening and enrollment characteristics, patterns of protocol violations reported for the sites, patterns of efficacy reporting, and patterns of serious adverse event (SAE) reporting.

The OSI inspections identified underreporting of AEs at Site #102 and monitoring issues at the Applicant site that contributed to the underreporting of approximately 47 AEs at this site. At site #206, there was late-reporting for one serious AE and three patients did not have a post-infusion ECG per protocol for approximately 20% of the infusions received. No significant issues were identified at sites 133 or 204 and no issues of concern were identified at (b) (4) . Overall, OSI did not identify significant issues that could affect the quality and interpretation of the data submitted in the application

See OSI review for additional details regarding site inspections and findings.

4.2. Product Quality

Please see FDA CMC review by Arulvathani Arudchandran for details regarding avelumab quality. Per the CMC reviewer, the manufacture of avelumab is well controlled and produces a product that is pure, and potent; no novel excipients or impurities of concern were identified. The intended commercial drug substance will be manufactured using Process B. Process A was used for manufacturing drug substance for the drug product administered in Part A of Study 003. The Applicant provided sufficient data to demonstrate comparability between the two manufacturing processes. The commercial drug product will be manufactured at the same site (Merck Serono in Switzerland) used for the product supply for Study 003.

4.3. Clinical Microbiology

Please see FDA product quality microbiology reviews by Maria Candauchacon (drug substance reviewer) and Lakshmi Narasimhan (drug product reviewer) for further details. Per the reviewers, no microbiology issues of concern have been identified for avelumab.

4.4. Devices and Companion Diagnostic Issues

There is no device or companion diagnostic test for review in support of this BLA.

APPEARS THIS WAY ON ORIGINAL

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 pharmacology studies demonstrated the ability of avelumab to bind to human, mouse, and cynomolgus monkey PD-L1 with comparable affinities. Avelumab showed no detectable binding to PD-L1 paralogues, including PD-L2, B7.1, B7.2, B7-H2, or B7-H3. Further characterization of binding showed that avelumab was able to bind to PD-L1 expressed on the surface of various human tumor cell lines and human peripheral blood mononuclear cells (PBMCs). In vitro studies also confirmed the ability of avelumab to inhibit the interaction between PD-L1 and PD-1 or B7.1. Avelumab was incapable of mediating complement-dependent cytotoxicity (CDC) but was able to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro. The potential for avelumab to induce cytokine release was characterized in PBMCs isolated from human blood. The results were limited to a 5-7 fold increase in TNFα following 24 hours of exposure to avelumab at concentrations ≥ 14.4 ng/mL.

To assess the in vivo anti-tumor activity of avelumab, the Applicant utilized a syngeneic mouse model of colon cancer. In duplicate studies, avelumab demonstrated anti-tumor activity at all doses tested (100-800 µg, administered on Days 0, 3, and 6). A trend towards dose-dependency was noted at lower doses; however, the 800 µg dose of avelumab did not induce superior anti-tumor activity, compared to the 400 µg dose. Using spleens harvested from satellite animals on Day 9 showed that treatment with avelumab increased the percentages of $CD8^+/PD\text{-}1^+$ T cells and $CD8^+$ T effector memory (T_{EM}) cells.

Since avelumab was able to mediate ADCC in vitro, the Applicant examined whether avelumab-induced ADCC contributed to in vivo anti-tumor activity. In immune-competent mice implanted with a syngeneic murine model of colon cancer, treatment with avelumab (400 µg, administered on Days 0, 3, and 6) resulted in greater anti-tumor activity than treatment with either a deglycosylated form of the antibody or with avelumab given after systemic natural killer (NK) cell depletion. Both deglycosylation and NK cell depletion resulted in similar decreases in the anti-tumor activity of avelumab, suggesting that avelumab-induced ADCC contributes to the anti-tumor activity of avelumab.

The PD-1/PD-L1 signaling pathway has been implicated in the phenomenon of immune exhaustion and the maintenance of chronic infection (Barber et al., 2005). Blocking this pathway may lead to increases not only in the primary immune response but to secondary responses to infection. The Applicant did not include any studies to assess the potential for enhanced immune responses to vaccination or re-infection following treatment with avelumab. For this reason, a post-marketing commitment was recommended to investigate the effects of avelumab on the secondary immune response or memory response to antigen exposure.

Due to fatal hypersensitivity reactions after repeated administration of avelumab in mice and the low binding affinity of avelumab to rat PD-L1, rodents were not considered an appropriate species to characterize the long-term toxicity of avelumab. The cynomolgus monkey was, however, a pharmacologically relevant species for toxicity testing based on a similar avelumab binding affinity to cynomolgus monkey and human PD-L1 and the comparable cross-reactivity of avelumab across cynomolgus monkey and human tissues.

Thus, the toxicity of avelumab was evaluated in a GLP-compliant, 13-week toxicology study in cynomolgus monkeys. Monkeys received avelumab intravenously, once per week, at doses up to 140 mg/kg, resulting in avelumab exposure levels of up to 4700 µg/mL and 356514 µg*h/mL for C_{max} and AUC, respectively. Toxicity was limited to local inflammatory reactions at the injection site. Based on a mean C_{max} of ~300 µg/mL in humans at the end of the first 10 mg/kg infusion, the avelumab exposure level in monkeys was approximately 16-fold higher than in humans receiving the 10 mg/kg dose of avelumab. An in vitro assessment of target occupancy (TO) on human CD3+ T lymphocytes revealed that >95% TO was reached when avelumab blood concentrations were 1 µg/mL. Considering all patients that received 10 mg/kg of avelumab in a Phase 1 trial had serum concentrations ≥ 1 ug/mL, the 10 mg/kg dose of avelumab is projected to result in a consistent and high level of TO in patients.

The Applicant did not evaluate the transfer of avelumab to the fetus or to milk. As a result, the label includes advice for women not to breastfeed during treatment with avelumab and for (b) (4) months following the final dose. Reproductive and developmental toxicology studies were not conducted with avelumab. Instead, the Applicant submitted a non-product specific literature-based assessment of the potential reproductive safety effects of avelumab. Based on the literature, a central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. For example, blockade of PD-L1 signaling has been shown in some murine models of allogeneic pregnancy to disrupt tolerance to the fetus and to increase the rate of fetal loss (Guleria et al., 2005; D'Addio et al., 2011). Thus, based on the mechanism of action of avelumab, the potential risks of administering avelumab during pregnancy include increased rates of abortion or stillbirth. In addition, fetal exposure to avelumab may increase the risk of developing immune related disorders or altering the normal immune response. For these reasons, the label includes a warning for embryo-fetal toxicity. Similarly, the label advises females of reproductive potential to use contraception during treatment with Bavencio and for (b) (4) months after the final dose.

Finally, based on data from the literature and its mechanism of action, there may be a potential for inappropriate or severely enhanced immune responses to infection following treatment with avelumab. In the absence of PD-1 pathway signaling in mouse models of LCMV infection, CD8+ T cells killed virally infected endothelial cells, resulting in cardiovascular collapse (Frebel et. al., 2012; Mueller et. al., 2010). Similarly, in PD-1 deficient mice (C57BL/6), infection with M. tuberculosis resulted in decreased survival that correlated with uncontrolled bacterial proliferation in the lungs. Whether the decrease in survival in this model resulted from an inability to mount an appropriate antibacterial response or a failure to control the immune response leading to normal tissue destruction was not fully elucidated (Lazar-Molnar, et al., 2010). As this data represents a potential mechanistic risk associated with the use of a PD-1 signaling inhibitor, a brief description of this data is included in the label under Section 13.2. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of Bavencio for the treatment of the proposed patient population.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

The Applicant utilized surface plasmon resonance (SPR; Biacore systems) to measure the binding affinity of avelumab to PD-L1 derived from human, mouse, cynomolgus monkey, dog, rat, and rabbit (Study PEAT18052012CJW). As shown in Table 1, the binding affinity (Kd) of avelumab to PD-L1 was 0.7 nM. Similar binding affinities were noted in the mouse and cynomolgus monkey. The affinities to PD-L1 in dog, rat, and rabbit were approximately 6, 95, and 150-fold lower, respectively, than binding to human PD-L1.

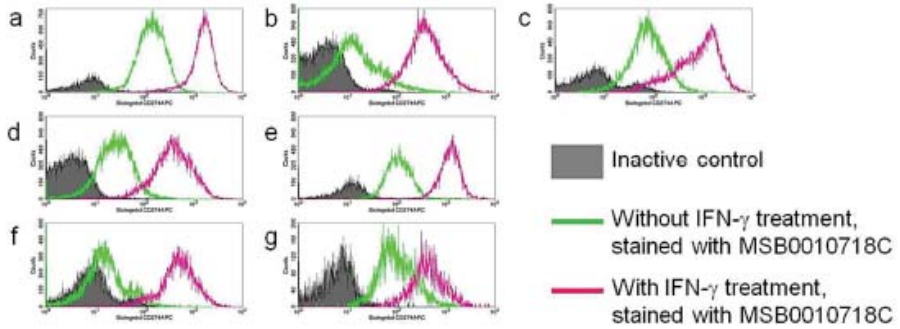
Table 1: Binding of Avelumab to PD-L1 in Various Species

Species	Dissociation constant (Kd)
Human	0.7 nM
Mouse	0.9 nM
Cynomolgus monkey	1.1 nM
Dog	4.5 nM
Rat	66.8 nM
Rabbit	105.4 nM

SPR was also used to evaluate the binding affinities of avelumab to PD-L1 and its paralogues from the B7 ligand family (Study PEAT20131213VS). Avelumab showed no detectable binding to PD-L2, B7.1, B7.2, B7-H2, or B7-H3 when tested at concentrations up to 1 µM (data not shown).

Fluorescence-activated cell sorting (FACS) was used to assess the ability of avelumab to bind PD-L1 expressed on the surface of human tumor cells lines (Study IONC201104051DZ). Two days prior to analysis, cells were seeded into 24-well plates in the absence or presence of 1000 U/mL of recombinant human IFN-γ to stimulate PD-L1 expression. A mutated form of avelumab (5 µg/mL) was used as an inactive/negative control. Cell pellets from the avelumab-treated and negative control samples were resuspended in 100 µl of FACS buffer containing DyLight 488 conjugated whole IgG Goat Anti-Human IgG, Fcγ antibody (1:300 diluted). The level of positive staining was measured by detecting DyLight 488 fluorescence using a FACSCalibur flow cytometer. As detailed in Figure 1, avelumab (MSB0010718C) demonstrated reactivity to human PD-L1 in various human tumor cell lines with or without IFN-γ treatment.

Figure 1: Avelumab Binding to Human Tumor Cell Lines

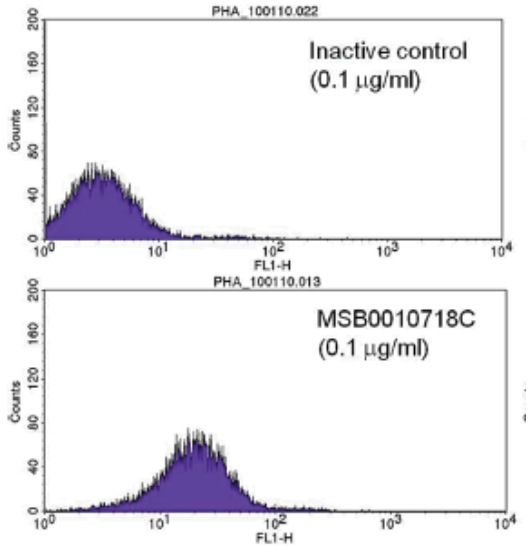


a. A431, epidermoid carcinoma cells; b. A549 lung adenocarcinoma cells; c. BxPC3 pancreatic carcinoma cells, d. HCT116 colorectal carcinoma cells, e. M24 melanoma cells; f. PC3mm2 prostate cancer cells, g. U-87 MG, glioblastoma cell line

(Applicant Figure reproduced from Study IONC201104051DZ)

FACS was also used to examine the ability of avelumab to bind human peripheral blood mononuclear cells (PBMCs; Study IONC201104051DZ). PBMCs were extracted from whole blood and stimulated with phytohemagglutinin (PHA) for 48 hours to induce PD-L1 expression. Cells were stained with 0.1 µg/mL of avelumab or a mutated inactive control antibody followed by secondary staining with a DyLight 488 conjugated Goat Anti-Human IgG Fcγ antibody. The level of positive staining was measured by detecting DyLight 488 fluorescence using a FACSCalibur flow cytometer. Avelumab (MSB0010718C) demonstrated reactivity against PHA-stimulated human PBMCs (Figure 2).

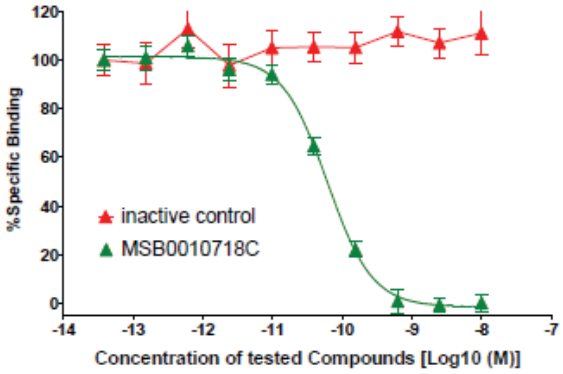
Figure 2: Avelumab Binding to Human PBMCs



(Applicant Figure reproduced from Study IONC201104051DZ)

The Applicant assessed the ability of avelumab to block the interaction between PD-L1 and PD-1 by conducting a competitive binding assay (Study IONC201104051DZ). Serial dilutions of avelumab or a mutated inactive control antibody were combined with radiolabeled (^{125}I) PD-L1-Fc to compete for binding to immobilized PD-1-Fc. Radiation counts were measured using a Packard Topcount scintillation counter. Avelumab (MSB0010718C) blocked the interaction between PD-L1 and PD-1 with an IC_{50} of 0.07 nM (Figure 3).

Figure 3: Avelumab Blockade of PD-L1 and PD-1 Interaction

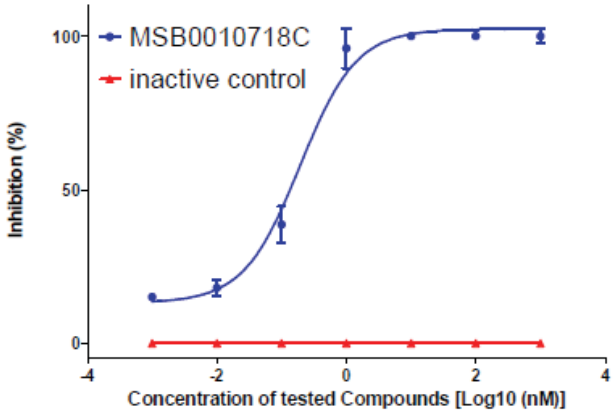


(Applicant Figure reproduced from Study IONC201104051DZ)

Avelumab also blocked the interaction between PD-L1 expressed on the surface of HEK293 cells and B7.1 (Study IONC201104051DZ). Serial dilutions of avelumab or a mutated inactive control antibody were combined with B7.1-Fc followed by secondary staining with a PE-labeled anti-human B7.1 antibody. Binding of the labeled B7.1 antibody, as measured by mean fluorescence intensity (MFI), was an indication of freely available PD-L1 on the cell surface. Data was

acquired using a FACSCalibur flow cytometer. As shown in Figure 4, avelumab (MSB001718C) blocked the interaction between B7.1 and PD-L1 with an IC_{50} of 0.2 nM.

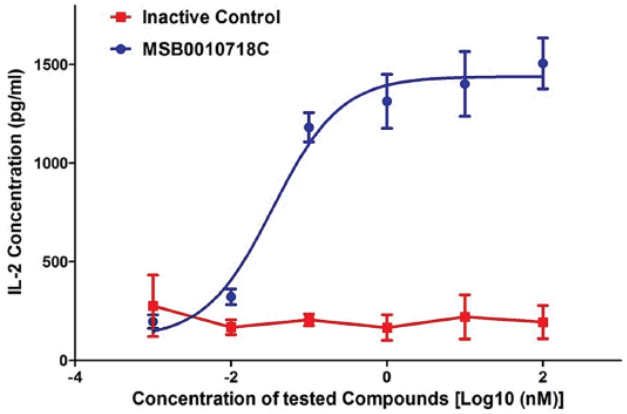
Figure 4: Avelumab Blockade of PD-L1 and B7.1 Interaction



(Applicant Figure reproduced from Study IONC201104051DZ)

To determine the ability of avelumab to enhance T cell function, the Applicant incubated serial dilutions of avelumab (up to ~15 µg/mL) or a negative control antibody with human PBMCs in the presence of staphylococcal enterotoxin A (200 ng/mL; SEA) for 96 hours (Study IONC201104051DZ). SEA activates CD4+ T cells by cross-linking of the T cell receptor (TCR) and major histocompatibility complex (MHC) class II molecules (Torres et al. 2001). Human IL-2 concentrations were measured in the supernatant by ELISA (Human IL-2 DuoSet, R&D Systems) and used as a surrogate measure of T cell activation. Incubation with avelumab (MSB0010718C) resulted in increased IL-2 production from SEA-stimulated PBMCs with an EC_{50} of 0.08 nM (Figure 5).

Figure 5: Increased IL-2 Production from SEA-Stimulated Human PBMCs



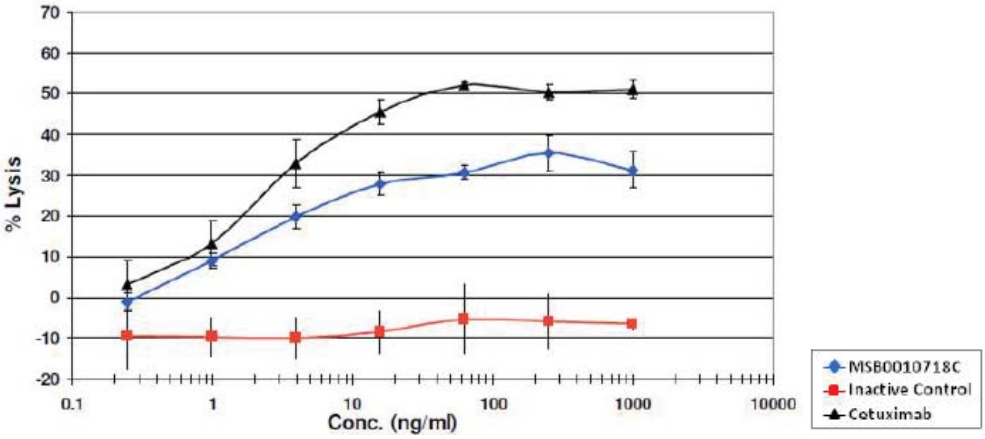
(Applicant Figure reproduced from Study IONC201104051DZ)

Serial dilutions of avelumab (10 µg/mL to 0.003 µg/mL) were also incubated with human whole blood from eight donors to determine the level of target occupancy (TO) towards PD-L1 on

CD3+ T lymphocytes (Study IONC19092014SM). The Applicant identified unoccupied PD-L1 binding sites using FACs analysis to compare avelumab-spiked and unspiked PBMCs after secondary staining with a biotinylated anti-PD-L1 and streptavidin–allophycocyanin. Overall, the mean avelumab concentration to achieve 50% TO (EC_{50}) was 0.122 µg/mL and the saturation plateau of >95% TO was reached in all donor blood samples at avelumab concentrations ≥ 1 µg/mL (data not shown).

The ability of avelumab to induce antibody-dependent cell-mediated cytotoxicity (ADCC) was assessed in two human tumor cell lines; A431 epidermoid carcinoma and A549 lung carcinoma (Study PEAT18052012AJW). Both cell lines were examined naïve or following stimulation with human IFN-γ to induce PD-L1 expression. Since FcγRIIIa polymorphic subtypes in PBMC effector cells influence ADCC activity through differences in affinity for the Fc regions, effector cells with each homozygous or heterozygous subtype were evaluated. Cancer cell lines were radiolabeled with ^{51}Cr and combined with human PBMCs at a ratio of 1:100 in the presence of either avelumab or an inactive control antibody, at concentrations up to 10,000 ng/mL. Cetuximab was used as a positive control. Lysis of the target cells was measured as the amount of radiolabeled chromium released into the supernatant. As shown in Figure 6, avelumab (MSB0010718C) induced ADCC activity mediated by effector cells from donors that were homozygous for the high affinity (VV) FcγRIIIa polymorphism (158V) in non-stimulated A431 cells. While stimulation with IFN-γ did not strongly affect ADCC activity in A431 cells due to the high levels of constitutive PD-L1 expression, IFN-γ stimulation of A549 cells potentiated the ADCC activity of avelumab by approximately 20% (data not shown). Using effector cells from donors that were heterozygous for the high affinity (VF) FcγRIIIa polymorphism (158V) yielded results similar to those from donors that were homozygous for the high affinity polymorphism, in both cell lines (data not shown). In contrast, effector cells from donors that were homozygous for the low affinity polymorphism (FF) displayed little to no ADCC activity in either cell line (data not shown).

Figure 6: ADCC in Non-stimulated A431 Cells using Effector Cells with the High-affinity (VV; homozygous) FcγRIIIa Polymorphism (158V)



(Applicant Figure reproduced from Study PEAT18052012AJW)

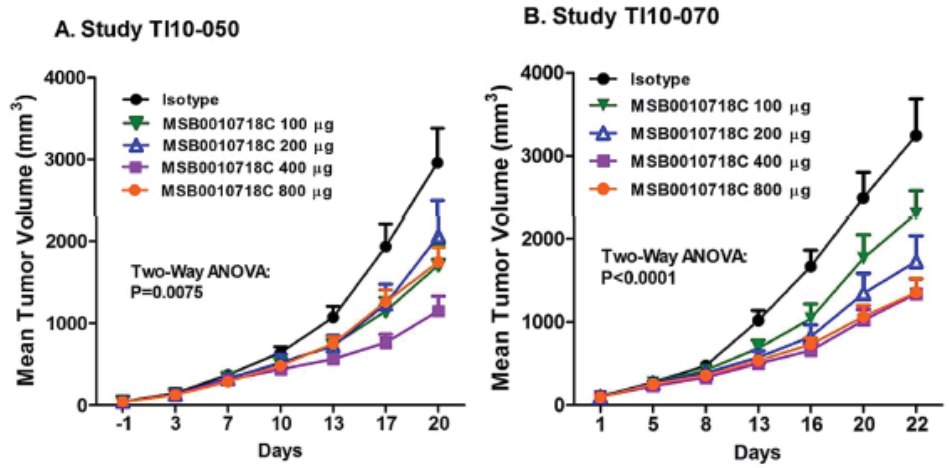
The potential of avelumab to induce complement-dependent cytotoxicity (CDC) was evaluated using three human tumor cell lines; A431 epidermoid carcinoma, A549 lung carcinoma, and M21 melanoma cells (Study PEAT18052012BJW). Target cells were radiolabeled with ^{51}Cr and then incubated with up to 10,000 ng/mL of avelumab in the presence of complete human complement. The amount of radiolabeled chromium released into supernatant was measured as an indicator of CDC activity. As a positive control, a previously characterized CDC competent antibody, 14.18.IL2, was tested against the M21 cell line. Cetuximab and an inactive version of avelumab were both used as negative controls. Avelumab was incapable of mediating CDC against any cell line tested (data not shown).

B. In Vivo Studies

To assess the in vivo anti-tumor activity of avelumab, the Applicant utilized a syngeneic mouse model of colon cancer (Study IONC20042011AKH). Duplicate studies (TI10-050 and TI10-070) were performed using identical methods. In both studies, 8 week old female C57BL/6 mice (Charles River Laboratories) were subcutaneously inoculated with $1x10^6$ MC38 colon carcinoma cells on the right flank. When tumors reached a mean volume of approximately 50 mm^3, mice (N=10/group) were administered 100, 200, 400, or 800 µg of avelumab via intraperitoneal injection on Days 0, 3, and 6. An inactive isotype-matched antibody (800 µg) was used as a negative control. Tumor volume and body weight were measured twice per week. Tumor weight was measured at sacrifice.

In both studies, all avelumab (MSB0010718C) dose groups demonstrated anti-tumor activity, compared to the isotype-matched control antibody, beginning on Day 13 (Figure 7). A trend towards dose-dependency was noted following administration of avelumab from 100 to 400 µg. Animals receiving 800 µg of avelumab did not show an increase in anti-tumor activity, compared to those at the 400 µg dose level.

Figure 7: Avelumab Inhibition of In Vivo MC38 Tumor Growth

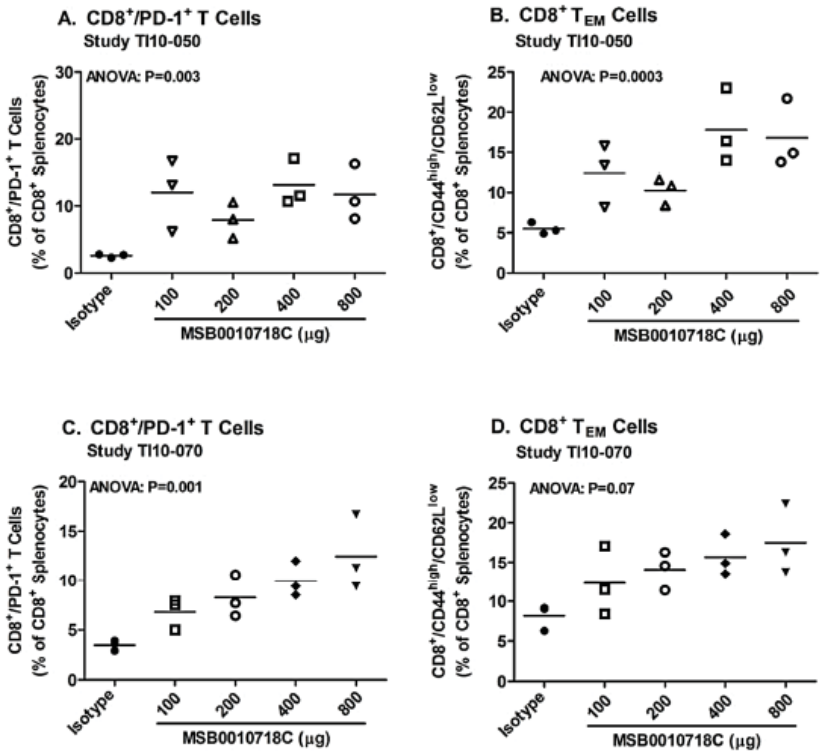


Female C57BL/6 mice were inoculated subcutaneously in the right flank with 1x10⁶ MC38 colon carcinoma cells. When tumors reached a mean volume of ~50 mm³, mice were sorted into treatment groups (N=14). Groups were administered avelumab intravenously at dose levels of 100, 200, 400, or 800 µg/mouse on days 0, 3, and 6. A control group was treated with an inactive isotype antibody. Tumors were measured twice weekly for the study duration via calipers. Data are mean ± SEM.

(Applicant Figure reproduced from Study IONC20042011AKH)

On Day 9 of these in vivo studies, investigators harvested spleens from satellite cohorts (N=3/group) of mice for FACS-based immunophenotyping. Spleens were dissociated into single cell suspensions and subsequently stained with fluorescently-labeled antibodies (CD8, PD-1, CD4, NK1.1, CD25, CD44, and CD62). As shown in Figure 8, administration of avelumab (MSB0010718C) resulted in a trend towards dose-responsive increases in the percentages of $CD8^+/PD\text{-}1^+$ T cells and $CD8^+$ T effector memory (T_{EM}) cells in the spleen.

Figure 8: Avelumab-induced Changes in Splenic CD8+ T cells in Mice

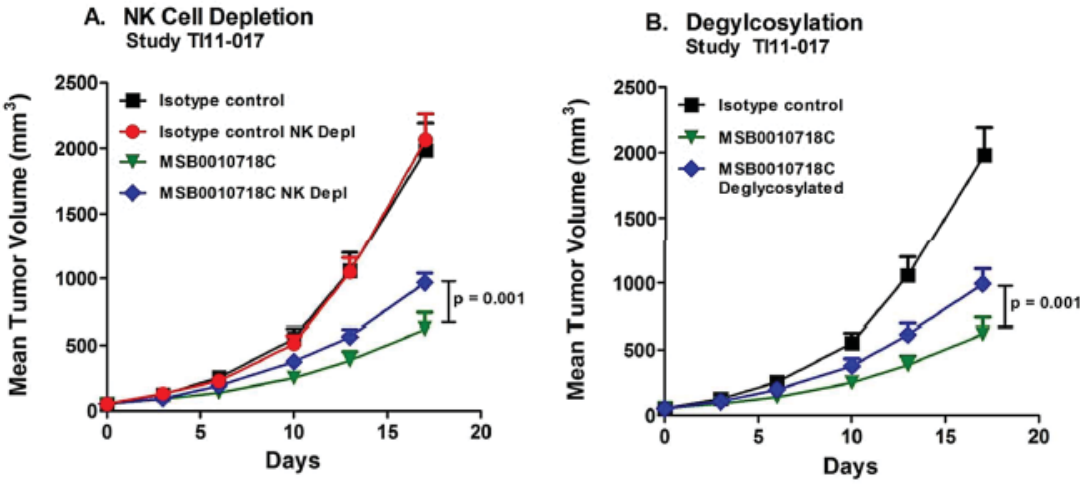


(Applicant Figure reproduced from Study IONC20042011AKH)

Since avelumab induced ADCC in vitro, the Applicant examined if avelumab-induced ADCC contributes to the in vivo anti-tumor activity of avelumab using a syngeneic mouse model of cancer (Study IONC08062012RT). MC38 colon carcinoma cells ($1x10^6$) were subcutaneously implanted into the right flank of C57BL/6 mice. Once tumors reached a mean volume of approximately 60 mm^3, 400 µg of avelumab (normally glycosylated or deglycosylated) was administered by intraperitoneal injection on Days 0, 3, and 6. An inactive control antibody was used as a negative control. Tumor volume and body weight were measured twice per week. A separate group of animals were pre-treated with 50 uL of anti-ASGM1 serum, intraperitoneally, once per week, to systemically deplete the animals of NK cells prior to administration of avelumab. Effective depletion of NK cells was confirmed by FACS analysis of peripheral blood, which showed a reduction in NK cell levels from ~5% to less than 1% (data not shown).

As shown in Figure 9, avelumab (MSB0010718C) significantly inhibited the growth of MC38 tumors, compared to the isotype control (A and B). Both NK cell depletion prior to administration of avelumab (A) and deglycosylation of avelumab (B) resulted in reduced anti-tumor activity, compared to administration of the normally glycosylated avelumab (MSB0010718C) in animals without NK cell depletion. The similar reductions in anti-tumor activity following deglycosylation or NK cell depletion, suggest that avelumab-induced ADCC can contribute to the anti-tumor activity of avelumab.

Figure 9: ADCC as a Secondary Mechanism of Anti-tumor Activity



(Applicant Figure reproduced from Study IONC08062012RT)

5.4. ADME/PK

Distribution, metabolism, and excretion studies were not conducted with avelumab because it is a monoclonal antibody.

Type of study	Major findings
Absorption MSB0010682 (Anti-PDL1): PK/PD Study After Single Intravenous Administration in Monkeys., Study # RF2120	Cynomolgus Monkeys C_{max} (µg/mL): 19 (0.8 mg/kg; LD) 98 (4 mg/kg; MD) 474 (20 mg/kg; HD) AUC (µg*h/mL): 807 (LD), 3270 (MD), 31100 (HD) $T_{1/2}$(hours): 32 (LD), 33 (MD), and 64 (HD) Clearance (mL/hr/kg): 1 (LD), 1.2 (MD), and 0.8 (HD)
TK data from general toxicology studies	Refer to Section 5.5

5.5. Toxicology

5.5.1. General Toxicology

Study Title / Number: MSB0010718 (Anti-PD-L1): 13-Week Toxicity Study in Cynomolgus Monkeys by Intravenous Infusion Followed by an 8-Week Recovery Period / RF4990

Key Study Findings:

- No mortalities occurred.
- Local toxicity was noted at the injection site.
- MSB0010718 did not induce cytokine or chemokine release.

Conducting laboratory and location:
(b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 20, 60, or 140 mg/kg/week
Route of administration:	IV infusion over 90 minutes
Formulation/Vehicle:	280mM mannitol, 10mM sodium acetate, 1.4 mM methionine, 0.05% Tween 20, pH 5.5
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	5 for control and high-dose group (2 continued through recovery period); 3 for low- and mid-dose group
Age:	3-4 years
Satellite groups/ unique design:	None / lymphocyte immunophenotyping and exploratory biomarker analysis
Dose justification:	The highest dose tested was the maximum feasible dose based on concentration and infusion volume.
Deviations from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Functional observational battery	Unremarkable
Ophthalmoscopy	Unremarkable
Electrocardiography	Unremarkable
Respiration rate	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	Unremarkable
Lymphocyte immunophenotyping	Unremarkable; no toxicologically significant changes were noted in counts of T cells subpopulations, B and NK cells, or in the expression of CD25, CD69, and PD1.
Exploratory biomarkers	Unremarkable; no toxicologically significant changes were noted in the levels of MCP-1, IP-10, TGF alpha, IL-2, IL-4, IL-10, IL-6, IFN-gamma, IL-1-beta, IL-17, and IL-1RA.
Urinalysis	Unremarkable
Gross Pathology	Generally consistent with histopathology findings
Organ Weights	Unremarkable
Histopathology **Adequate battery:** Yes	Local toxicity occurred at the injection site in all treatment and control groups. An increased incidence of inflammation was also noted at the injection site in HD animals.

Reversibility	Local toxicity at the injection site was reversible by the end of the recovery period.
Immunogenicity	Unremarkable
Toxicokinetics	C_{max} (Day 85; M/F; µg/mL): 20 mg/kg: 562 / 610 60 mg/kg: 2210 / 2183 140 mg/kg: 4700 / 4618 AUC (Day 85; M/F; µg*h/mL): 20 mg/kg: 33785 / 33980 60 mg/kg: 110702 / 140645 140 mg/kg: 356514 / 303662 Dose proportionality: Generally dose proportional from LD to MD and slightly greater than dose proportional from MD to HD. Accumulation: Minor accumulation was inconsistently noted. Gender differences: No significant differences.

LD: low dose; MD: mid dose; HD: high dose.

5.5.2. Genetic Toxicology

Not conducted per ICH S6.

5.5.3. Carcinogenicity

Not conducted per ICH S6, ICH S1, and ICH S9.

5.5.4. Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies were not conducted with avelumab. Instead, the Applicant submitted a non-product specific literature based assessment of the potential for avelumab to affect reproduction.

Based on the literature, a central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. For example, PD-L1 is expressed in the human placenta throughout pregnancy and on fetal trophoblast cells to potentially protect fetal cells against maternal leukocytes at the maternal-fetal interface (Holets et al. 2006, Petroff et al., 2003). In addition, blockade of PD-L1 signaling in murine models of allogenic pregnancy disrupted tolerance to the fetus and increased the rate of fetal loss (Guleria et al., 2005; D'Addio et al., 2011). This disruption of feto-maternal tolerance was associated with reduced regulatory T cells and was reversed by adoptive transfer of functional regulatory T cells (D'Addio et al., 2011).

Thus, based on the mechanism of action of avelumab, the potential risks of administering avelumab during pregnancy include increased rates of abortion or stillbirth. Fetal exposure to avelumab may increase the risk of developing immune related disorders or altering the normal immune response. For these reasons, the label includes a warning for embryo-fetal toxicity. Similarly, the label advises females of reproductive potential to use contraception during treatment with Bavencio and for (b) (4) months after the final dose.

5.5.5. Other Toxicology Studies

A pilot toxicity study of avelumab was conducted in CD-1 mice (N=20/group) by intravenously administering 20, 40, or 140 mg/kg of avelumab once per week, for 4 weeks. The vehicle was used as the negative control. Mortality occurred within 30 minutes after the 3rd administration of avelumab at all dose levels and was not dose-responsive. Adverse clinical signs consisted of paralysis of hind limbs, sternal recumbency, sedation, and dyspnea immediately after injection. These clinical signs and histopathological findings (vascular immunocomplex deposition) were suggestive of hypersensitivity reactions in mice. Due to these fatal hypersensitivity reactions in mice and the low binding affinity of avelumab to rat PD-L1, rodents were not considered an appropriate species to characterize the long-term toxicity of avelumab. The cynomolgus monkey was, however, a pharmacologically relevant species for toxicity testing based on a similar avelumab binding affinity to cynomolgus monkey and human PD-L1 and the comparable cross-reactivity of avelumab across cynomolgus monkey and human tissues.

To further support monkeys as a relevant species for toxicity testing, the cross-reactivity of avelumab (1 and 15 ug/mL) was assessed across cryosections of normal human tissues (3 donors per tissue; Study 20015186) and normal cynomolgus monkey tissues (2 donors per tissue; Study 20015187). Staining of adipocytes, megakaryoytes, ovarian granulosa cells, and testicular interstitial cells was only present in human. Staining of ovarian stromal cells and oocytes was only present in the cynomolgus monkey. Overall, except for these differences, avelumab staining of normal human and cynomolgus tissues was generally comparable.

The potential for avelumab to induce cytokine release was characterized in human PBMCs isolated from the blood of 16 donors (8 males and 8 females; Study T17986). Multiple Th1 and Th2 cytokines were measured using the human cytokine 10-Plex multiplex bead immunoassay panel (xMAP Luminex multiplex assay, Invitrogen) at concentrations up to 14383 ng/mL. Cytokines were measured after 6 or 24 hours of exposure to avelumab. The positive control, lipopolysaccharide (LPS), induced the release of the expected pro-inflammatory cytokines. The results were limited to a 5-7 fold increase in TNFα following 24 hours of exposure to avelumab at concentrations ≥ 14.4 ng/mL. Avelumab was unable to enhance the release of TNFα in cells pre-incubated with the superantigen SEA.

X X

6 Clinical Pharmacology

6.1.Executive Summary

For the current indication, the proposed dosage is 10 mg/kg avelumab administered by intravenous (IV) infusion over 60 minutes once every two weeks (Q2W). The Clinical Pharmacology Section of this BLA is supported by single and repeat dose PK studies of avelumab in patients with advanced solid tumors and patients with metastatic MCC, as well as the following evaluations: population pharmacokinetics (popPK) analysis, exposure-response (E-R) analysis, immunogenicity assessment, and assessment of the potential for QT/QTc prolongation. The popPK analysis demonstrated that age, body weight, gender, race, ECOG, PD-L1 status, tumor type, albumin concentration, tumor burden, anti-drug antibody (ADA) status, mild or moderate renal impairment, and mild or moderate hepatic impairment had no clinically meaningful effect on the steady state exposure of avelumab (simulated AUC_{SS}). The E-R analysis was conducted with efficacy data from 88 patients with mMCC in Study 003 at a dose 10 mg/kg given Q2W. E-R relationships were observed between avelumab steady state exposure metrics and the best objective response (BOR), OS, and PFS. However, the E-R analysis for efficacy is limited for this single-arm trial due to the potential interaction between response status and late-exposure metrics for a monoclonal antibody. The E-R analysis with safety data from 1629 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.

6.1.1 Recommendations

The proposed dosing regimen of 10 mg/kg Q2W administered by IV infusion over 60 minutes appears acceptable based on results pooled from the 3 clinical trials submitted. From a Clinical Pharmacology standpoint, the BLA is acceptable to support approval provided that the Applicant and the FDA reach an agreement regarding the labeling language. The clinical pharmacology program for avelumab is summarized below:

The proposed dosing regimen of 10 mg/kg is supported by efficacy and safety results submitted in the current application. The effect of anti-avelumab antibodies on efficacy, safety, and exposure could not be assessed due to low incidence resulting in the limited number of patients with treatment-emergent anti-avelumab antibodies.

6.2.Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Distribution

Based on popPK analysis of data from a total of 1629 subjects [n=1490 from Study 001, n=51 from Study 002, and n=88 from Study 003], geometric mean (%CV) volume of distribution at steady state (V_{SS}) [calculated as the sum of V_1 and V_2] was 4.72 L (44.5%) in patients receiving 10 mg/kg Q2W.

Metabolism

Avelumab, as an immunoglobulin, is expected to be catabolized in various body tissues through proteolytic degradation into amino acids and recycled into other proteins. CYP450 enzymes do not contribute to its metabolism.

Elimination

Because of its large molecular mass (147 kDa), avelumab is not expected to be excreted in urine. It is metabolized into peptides and amino acids that re-utilized by the body for de novo synthesis of proteins or excreted by the kidney. A 2-compartment PK model with linear elimination predicted geometric mean (%CV) total clearance (CL) and elimination half-life ($t_{1/2}$) values of 0.0267 L/h (29.9%) and 6.1 days (91.5%), respectively, in patients taking the 10 mg/kg Q2W dose. In a post hoc analysis, avelumab clearance was found to decrease over time in patients with MCC, with a mean maximal reduction (% coefficient of variation [CV%]) from the baseline value of approximately 41.7% (40.0%).

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 2 weeks until disease progression or unacceptable toxicity. The single-arm Study 003 evaluated the efficacy and safety of avelumab at this dosing regimen in 88 patients with mMCC who had received at least one line of previous chemotherapy. The proposed dose appears acceptable from a clinical pharmacology perspective. A mean TO of 93.2±1.3% was obtained *in vivo* at 10 mg/kg Q2W prior to the second dose (Day 15).

Therapeutic Individualization

Comparability

A non-compartmental PK analysis with data from 658 subjects who received only the drug product manufactured by Process A (early clinical formulation) and data from 543 subjects who

received only the DS manufactured by Process B (late clinical and commercial formulation) at the 10 mg/kg Q2W dose in Study 001 (advanced solid tumors), Study 002 (advanced solid tumors), and Study 003 (mMCC) indicated that the two processes were comparable. The geometric mean (%CV) serum concentration of avelumab at the end of infusion (C_{EOI}) after the first dose (Day 1) was 224 µg/mL (36%, n=134) for Process A and 219 µg/mL (28%, n=425) for Process B. After the fourth dose (Day 43), geometric mean (%CV) C_{EOI} was 256 µg/mL (26%, n=80) for Process A and 240 µg/mL (31%, n=249) for Process B. Thus, the pharmacokinetic profile with drug product manufactured according to Process A and Process B appear comparable.

Population Pharmacokinetic (popPK) Analysis

A popPK analysis of data from a total of 1629 subjects in Studies 001 (n=1490), 002 (n=51) and 003 (n=88) at doses ranging from 1.0 to 20 mg/kg Q2W demonstrated that body weight was positively correlated with total systemic clearance in poppK analysis. No clinically meaningful differences in avelumab PK were observed based on age (20 to 91), sex, race, PD-L1 status, tumor burden, mild [calculated creatinine clearance (CLcr) 60-89 mL/min, n=623 as estimated by the Cockcroft-Gault formula], moderate [CLcr 30 to 59 mL/min, n=320] or severe [15 to 29 ml/min, n=4] renal impairment and mild [bilirubin less than or equal to ULN and AST greater than ULN or bilirubin between 1 and 1.5 times ULN, n=217] or moderate [bilirubin between 1.5 and 3 times ULN; n=4] hepatic impairment. There are limited data from patients with severe hepatic impairment [bilirubin greater than 3 times ULN, n=1] and the effect of severe hepatic impairment on the pharmacokinetics of avelumab is unknown.

Exposure-Response (E-R) Relationships for Efficacy and Safety

The E-R analysis for efficacy was conducted with efficacy data from 88 patients with mMCC in Study 003 at a dose 10 mg/kg given Q2W. E-R relationships were observed between avelumab steady state exposure metrics and best objective response (BOR), OS, and PFS. However, the E-R analysis for efficacy is limited for a single arm monoclonal antibody trial in cancer patients due to the potential interaction between response status and late-exposure metrics.

The E-R analysis for safety was conducted with safety data from 1629 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.

Immunogenicity

Of 1558 patients treated with BAVENCIO 10 mg/kg as an intravenous infusion every 2 weeks who were evaluable for immunogenicity, 64 (4.1%) tested positive for treatment-emergent anti-drug antibodies (TE-ADA) as per the 90-Day Safety Report dated 1/31/2017 (SND 32). These results were reported in the labeling. The development of TE-ADA against avelumab did not appear to alter the pharmacokinetic profile of avelumab. There was a trend for C_{trough} to be 40% lower in ADA ever positive subjects compared to the ADA never positive subjects;

however, the popPK analysis predicted no change in the exposure of avelumab (simulated AUC_{SS}) at the 10 mg/kg Q2W dose. The applicant plans to conduct neutralizing antibody (NAb) testing as a post-marketing commitment (PMC).

Drug-Drug Interaction (DDI) Potential

No DDI studies have been conducted for avelumab. Avelumab, as an immunoglobulin, is eliminated by intracellular lysosomal proteolytic degradation throughout the entire body, and therefore is not expected to be affected by small molecule drugs via CYP450 inhibition/induction or transporter modulation. Avelumab, as a mAb, is also not expected to have a direct DDI effect on other small molecule drugs.

QT Prolongation

The IRT-QTc review team concluded that no large changes in the mean change from baseline QTc interval were detected when avelumab was administered at the therapeutic dose of 10 mg/kg. QTcF >500 ms was detected in a total of 33 subjects (2.1%) within the 10 mg/kg dose cohorts from all three studies. ΔQTcF > 60 ms was noted for 63 subjects (4.1%) within the 10 mg/kg dose cohorts.

Outstanding Issues

The clinical pharmacology reviewer requested one PMC for the conduct and assessment of neutralizing ADA responses with a validated assay. Refer to Section 12 of this review for details

6.2.3. General Pharmacology and Pharmacokinetic Characteristics

Bioanalytical Method: **PK Assessment:** A validated sandwich immunoassay method on the Gyrolab™ platform was used to measure avelumab concentrations in serum samples from Studies 001, 002 and 003. The lower limit of quantitation (LLOQ) was 0.2 µg/mL. This assay was developed and validated at (b) (4) (Refer to Appendix 4.1, Reports RF6870 and RF7010). The originator laboratory (b) (4) was subsequently transferred and validated at (b) (4) (Refer to Appendix 4.1, Report 218-1407). A cross-validation was conducted between the two laboratories (b) (4) using serum samples from Study 001 (Refer to Appendix 4.1, Report 15-IV104-V0). A total of 15 spiked prepared samples and a total of 75 incurred samples which were already analyzed by the originator (b) (4) laboratory from Study 001 were shipped to (b) (4) and tested at both laboratories. All of the 15 spiked prepared samples met the acceptance criterion of within ±20% and 72% (54/75) of incurred samples met the acceptance criterion of within ±30% (Refer to Applicant's Tables 7 and 8, respectively, Appendix 4.1, Report 15-IV104-V0).

Immunogenicity Assessment: A validated electrochemiluminescence method was used to detect anti-drug antibodies (ADA) in serum samples from Studies 001, 002 and 003. The limit of

detection (LOD) was 15.5 ng/mL of the positive control antibody in the absence of avelumab (Refer to Appendix 4.1, Report TNJS13-170 and its Addendum Report TNJS13-170A1).

PD-L1 Target Occupancy (TO) Testing: A validated flow cytometry method was used to detect TO on human peripheral blood mononuclear cells (PBMCs) in whole blood samples collected in Study 001 (refer to Appendix 4.1, Report IONC-IB-DZ-080312013).

Pharmacokinetics: The PKs of avelumab have been determined using both non-compartmental (NCA) and popPK analyses. Studies 001 and 002 used both intensive (dose escalation phase) and sparse PK (expansion phase) sampling schemes, whereas Study 003 used only a sparse PK sampling scheme. A summary of NCA PK parameters is presented in **Table 2** and **Table 3**.

Table 2 Single Dose Geometric Mean (%CV) NCA PK Parameters for Avelumab after the First Infusion on Day 1

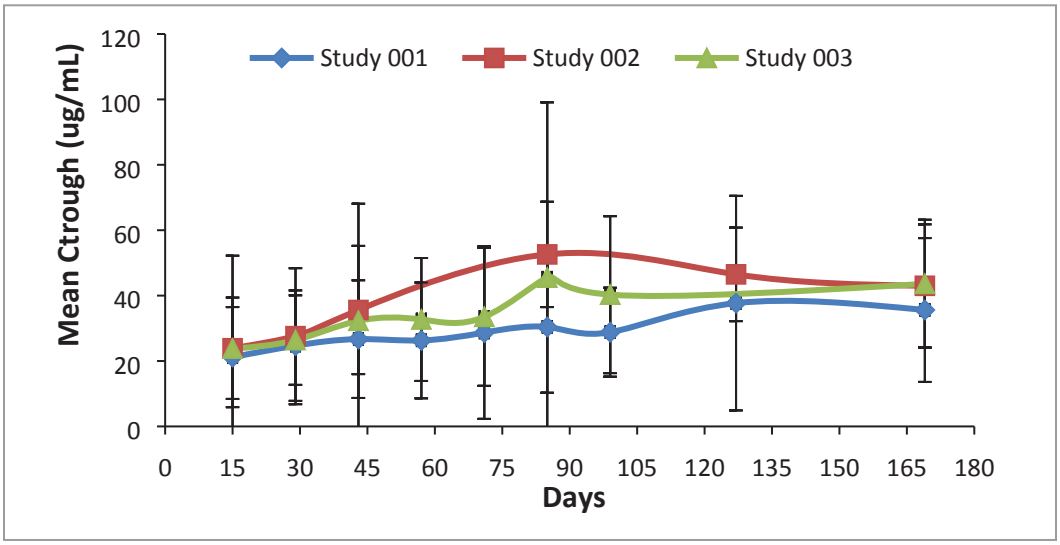
Dose (n)	C_{MAX} (µg/mL)	$AUC_{0\text{-}336h}$ (µg.h/mL)	$AUC_{0\text{-}inf}$ (µg.h/mL)	$t_{1/2}$ (d)	CL (mL/h/kg)	V_z (mL/kg)
	Study 001					
1 mg/kg (n=4)	18.4 (22%)	1179 (52%)	1203 (57%)	2.48 (37%)	0.825 (58%)	70.8 (18%)
3 mg/kg (n=13)	78.9 (29%)	6078 (32%)	6521 (35%)	3.38 (30%)	0.461 (34%)	54.1 (28%)
10 mg/kg (n=48)	297.1 (32%)	25154 (25%)	27654 (27%)	3.94 (22%)	0.362 (27%)	49.4 (25%)
20 mg/kg (n= 21)	470.0 (30%)	38298 (42%)	42710 (47%)	4.13 (30%)	0.469 (47%)	67.1 (30%)
	Study 002					
3 mg/kg (n=4)	63.9 (22%)	5632 (28%)	6055 (32%)	3.55 (26%)	0.495 (32%)	61.0 (25%)
10 mg/kg (n=6)	179.1 (20%)	18729 (36%)	21510 (45%)	4.53 (36%)	0.471 (44%)	73.8 (17%)
20 mg/kg (n=6)	458.9 (14%)	46966 (23%)	53717 (24%)	4.68 (12%)	0.373 (24%)	60.6 (21%)

Table 3 Avelumab Geometric Mean (%CV) C_{trough} (µg/mL) over Time after Repeated Administration of 10 mg/kg Avelumab in subjects with Solid Tumors

Day	Study 001				Study 002			Study 003
	1 mg/kg Q2W	3 mg/kg Q2W	10 mg/kg Q2W	20 mg/kg Q2W	3 mg/kg Q2W	10 mg/kg Q2W	20 mg/kg Q2W	10 mg/kg Q2W
15	0.23 (173%)	3.5 (74%)	21.2 (72%)	50.1 69%)	3.3 (72%)	23.9 (65%)	44.4 (34%)	23.8 (119%
29	NC	NC	24.7 (68%)	NC	4.6 (47%)	27.6 (75%)	54.6 (26%)	26.4 (52%)
43	NC	NC	26.7 (67%)	NC	6.3 (43%)	35.6 (55%)	64.1 (37%)	32.3 (110%)
57	NC	NC	26.3 (67%)	NC	NC	NC	NC	32.7 (57%)
71	NC	NC	28.7 (92%)	NC	NC	NC	NC	33.5 (63%)
85	NC	NC	30.4 (66%)	NC	6.8 (45%)	52.6 (30%)	70.0 (31%)	45.5 (118%)
99	NC	NC	28.8 (47%)	NC	NC	NC	NC	40.3 (60%)
127	NC	NC	37.7 (87%)	NC	9.3 NC, n=1	46.5 (31%)	64.1 NC, n=1	NC
169	NC	NC	35.6 (62%)	NC	9.3 NC, n=1	43.0 (44%)	76.8 NC, n=1	43.6 (45%)

NC=Not Calculated

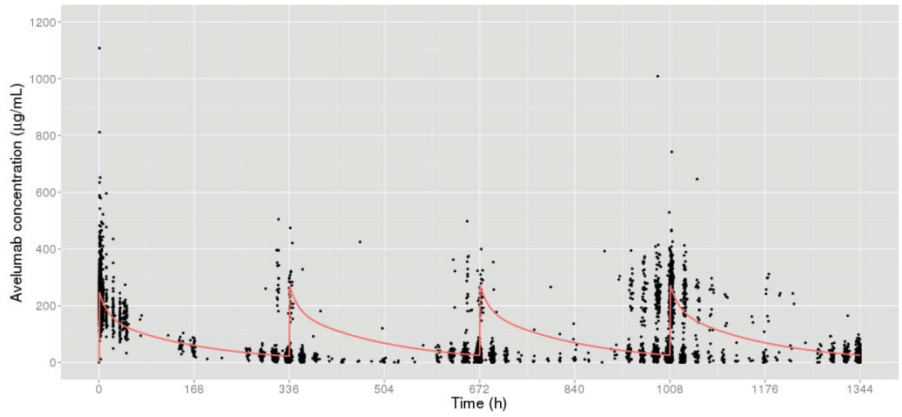
Figure 10 Arithmetic Mean (± SD) C_{trough} *versus* Weeks at 10 mg/kg Q2W



Based on the NCA after the first dose (Day 1), the results from Studies 001 and 002 showed that avelumab exposure (C_{MAX} and $AUC_{0\text{-}336h}$) increased more than dose proportionally between 1 and 10 mg/kg dose levels, but increased proportionally between the 10 and 20 mg/kg dose levels; this may be due to the presence of target mediated drug disposition (TMDD). Mean $t_{1/2}$ after the first dose increased from 2.5 days to 3.4 days with the increase of dose from 1 mg/kg to 3 mg/kg while it was similar between the 10 and 20 mg/kg doses (3.9 days and 4.1 days), respectively. Steady state is expected to reach by the 3rd dosing cycle (Day 29) which is consistent with the $t_{1/2}$ of 6 days.

Based on popPK analysis of pooled data from Studies 001, 002 and 003, geometric mean (%CV) CL, V_{ss} (calculated as the sum of V_1 and V_2) and $t_{1/2}$ was 0.0267 L/h (29.9%), 4.72 L (44.5%) and 6.1 days (146 hours) (91.5%), respectively, for for patients receiving the 10 mg/kg Q2W dose. An accumulation ratio of 1.25 is obtained based on a $t_{1/2}$ of 6.1 days for a dosing interval of two week (14 days). **Figure 11** below shows the PK profile for patients receiving 10 mg/kg Q2W. The predicted data superimposed the observed data.

Figure 11 Predicated and Observed Avelumab Concentration *versus* Time Profiles after the First Four Doses



[Source: BLA 761049/ SDN 5, M&S Population Analysis Report, pp 63]

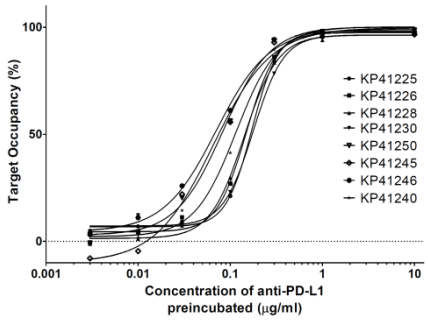
6.2.4. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The primary evidence of effectiveness in this BLA submission was obtained from the single-arm Study 003 in 88 patients with mMCC who had received at least one line of previous chemotherapy. All subjects received avelumab at the proposed 10 mg/kg Q2W dose regardless of their PD-L1 and MCC polyomavirus status. At this dose, the confirmed objective response rate (ORR) was 31.8% (95% CI: 22.3, 42.6) in the intent-to-treat population (n=88) with 9% of subjects achieved Complete response. The dose-response relationship for PD-L1 Target Occupancy (**TO**) (concentrations of unbound PD-L1 on $CD3^+$ T lymphocytes) provided additional

supportive mechanistic evidence for effectiveness. *In vitro* TO was measured in peripheral blood $CD3^+$ T cells after spiking of human whole blood samples from 8 healthy volunteers. The mean concentration of all blood samples required to achieve 50% TO (EC_{50}) was 0.122±0.042 µg/ml for the 8 donors. The saturation plateau (>95% TO) was reached in all blood samples at 1 µg/ml of avelumab (See **Applicant's figure** below). At the 10 mg/kg dose, all patients exceeded the serum concentration of 1 µg/ml that would lead to a >95% saturating TO. In **Study 003**, the avelumab geometric mean (%CV) C_{trough} at 10 mg/kg Q2W was estimated to be 18.5 µg/ml (72%) prior to the second infusion (Day 15) in patients with mMCC which is about 18-fold higher than the TO required concentration.

	KP41225	KP41226	KP41228	KP41230	KP41250	KP41245	KP41246	KP41240
EC50	0.1725	0.1498	0.1414	0.1784	0.08340	0.06530	0.07050	0.1159



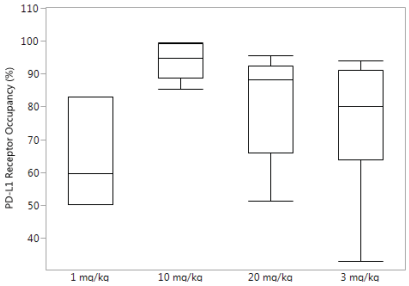
[Source: BLA 761049/SDN 5, *In Vitro* Report IONC19092014SM, PP 24]

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

The current proposed avelumab dosage of 10 mg/kg given Q2W was used in the Study 003. This dose was selected based on the adequate safety and tolerability data obtained in the dose escalation phase 1 Study 001 which investigated doses up 20 mg/kg. Safety data obtained from this study indicated that avelumab was well tolerated with no dose-limiting toxicities observed up to a dose of 20 mg/kg administered Q2W.

An *ex vivo* PD-L1 target occupancy (TO) measured in PBMCs by flow cytometry on serum samples from subjects participated in the dose escalation cohorts of Study 001 indicated a mean TO of 94.2±5.2% at the 10 mg/kg Q2W dose (n=5) throughout the dosing interval. A mean TO of 64.3±13.7%, 75.6 ±17.8% and 79.8±15.1% were obtained at the 1 mg/kg (n=3), 3 mg/kg (n=11) and 20 mg/kg (n=9) Q2W doses, respectively (See **Figure 12** below).

Figure 12 PD-L1 Target Occupancy by Dose Prior to the Second Infusion from Study 001 (Day 15)



[Source: BLA 761049/SDN 5, Study EMR100070-001 CSR, Table 15.5.2.1V, Listing 16.2.13.1V]

Based on these results, avelumab dose of **10 mg/kg** administered **Q2W** appears reasonable and was used in the Study 003.

Exposure-Response (E-R) Relationships for Efficacy, Safety and QTc

Exposure-Efficacy Analysis

The Applicant's table below summarizes the efficacy data obtained from Study 003 (**Part A**) with a cutoff date of 3/3/2016 in 88 patients with mMCC who received avelumab 10 mg/kg Q2W. The ORR was 32% (95% CI: 21.9, 43.1) with 9% of patients having Complete Response.

Best Overall Response by RECIST v1.1*	N=88
Complete response, n (%)	8 (9.1)
Partial response, n (%)	20 (22.7)
Stable disease, n (%)	9 (10.2)
Progressive disease, n (%)	32 (36.4)
Non-CR/non-PD, n (%)	1 (1.1)
Non-evaluable, n (%)	18 (20.5)
Objective response rate, % (95.9% CI)†	**31.8 (21.9, 43.1)**

* Confirmed best overall response according to independent review committee assessment.
† A repeated CI for ORR (95.9% CI for the primary analysis) was calculated to account for the group sequential testing approach.

E-R relationships were observed between avelumab steady state exposure metrics and BOR, OS, and PFS. 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 of avelumab may be more efficacious. However, the E-R analysis for efficacy is limited for a single arm monoclonal antibody trial in patients with cancer due to potential interaction between response status and late-exposure metrics. Because mMCC is an orphan disease and because Study 003 provided acceptable effectiveness, no additional study to further optimize the dose is recommended based on the current available information.

Exposure-Safety Analysis

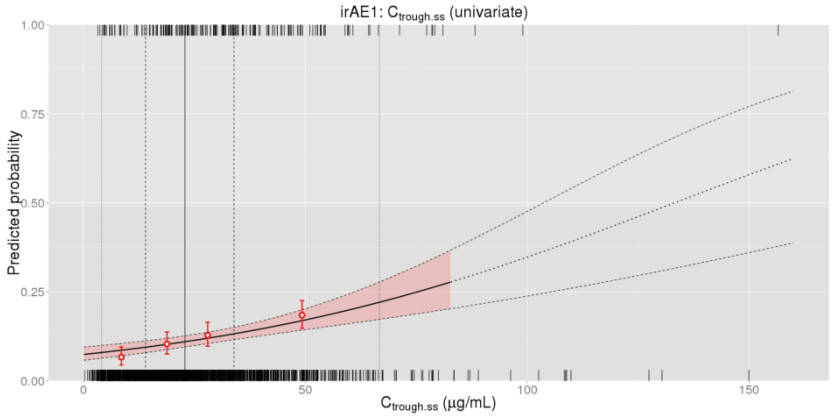
Table 4 below summarizes the most common treatment-emergent adverse events (TEAEs) occurred in ≥10% of subjects in Study 001 and Study 003 (**Part A**) as a cutoff date of 3/3/2016.

Table 4 Incidence of TEAEs occurred in ≥10 of Subjects at 10 mg/kg Q2W

TEAEs	Study 001 (N = 1452) n (%)	Study 003 (N = 88) n (%)	Integrated Safety Database (N = 1540) n (%)
irAEs	165 (11.4)	14 (15.9)	179 (11.6)
Nausea	326 (22.5)	18 (20.5)	344 (22.3)
Constipation	248 (17.1)	15 (17.0)	263 (17.1)
Diarrhea	242 (16.7)	20 (22.7)	262 (17)
Vomiting	214 (14.7)	10 (11.4)	224 (14.5)
Fatigue	418 (28.8)	33 (37.5)	451 (29.3)
Weight decreased	225 (15.5)	12 (13.6)	237 (15.4)
IRR	246 (16.9)	13 (14.8)	259 (16.8)
Drug-related TEAEs leading to permanent discontinuation	90 (6.2)	1 (1.1)	91 (5.9)

The E-R analysis for safety was performed on the pooled data from Studies 001, 002, and 003 in a total of 1629 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 univariate models using $C_{trough,ss}$ as the exposure metric, avelumab exposure was positively associated with irAE (any grade) incidence with an odds ratio of 1.019 per µg/mL increase in $C_{trough,ss}$ (Figure 13). Increasing avelumab exposure was not associated with an increased incidence of IRR or TEAEs of any grade.

Figure 13 Relationship between Probability of irAE (grade ≥1) and $C_{trough,ss}$



[Source: BLA 761049/ SDN 5, M&S Exposure-Safety Analysis Report, PP 52]

Exposure-QTc Analysis

Exposure-QTc analysis was performed on pooled ECG data from Studies 001, 002 and 003 for which at least one matched pair of PK and ECG measurement pre-dose and at least one matched pair of PK and ECG measurements within 0-2 hours post the end of infusion was available. There were 1474, 51, and 86 subjects included in the dataset from studies 001, 002 and 003, respectively. QT was corrected for heart rate using a project-specific (QTcP) formula or Fridericia's formula (QTcF). The relationships between QTc change from baseline (ΔQTcF and ΔQTcP) and avelumab concentrations were investigated using linear mixed-effects modeling. The results of this analysis demonstrated that there was no evident relationship between avelumab concentrations and ΔQTcF or ΔQTcP (See **Table 5 Table 5** and **Figure 14** and **Figure 15** below). QTcF >500 ms was detected in a total of 33 subjects (2.1%) in the 10 mg/kg dose cohorts from all three studies. ΔQTcF > 60 ms was noted for 63 subjects (4.1%) in the 10 mg/kg dose cohorts.

Table 5 4 Point Estimates and 90% Confidence Intervals for Avelumab at Last Visit (FDA Analysis)

Study	Treatment	ΔQTcF (ms)			
		N	Mean	Lower 90% CI Limit	Upper 90% CI Limit
001	10.0 mg/kg	15	1.4	-6.7	9.5
	10.0 mg/kg Expansion	1418	1.7	0.6	2.8
002	10.0 mg/kg	6	23.1	14.7	31.4
	10.0 mg/kg Expansion	34	0.4	-4.9	5.8
003	10.0 mg/kg Expansion	73	1.9	-1.7	5.5

[Source: QTc-IRT review in DARRTS, Reference ID: 4026388, PP 2]

Figure 14 QTcF vs. Avelumab Concentrations

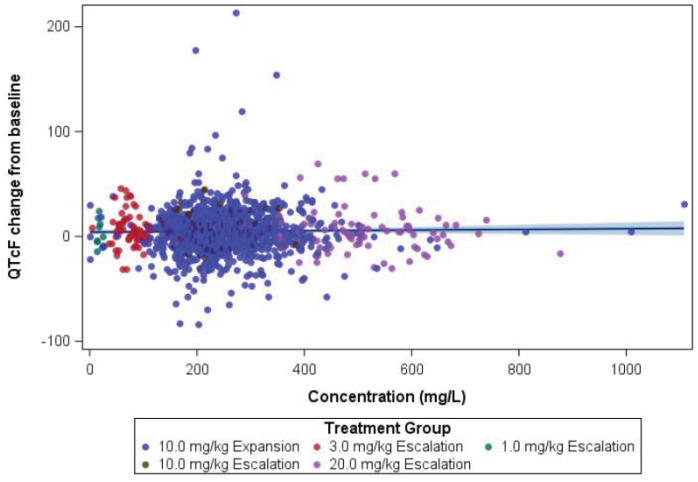
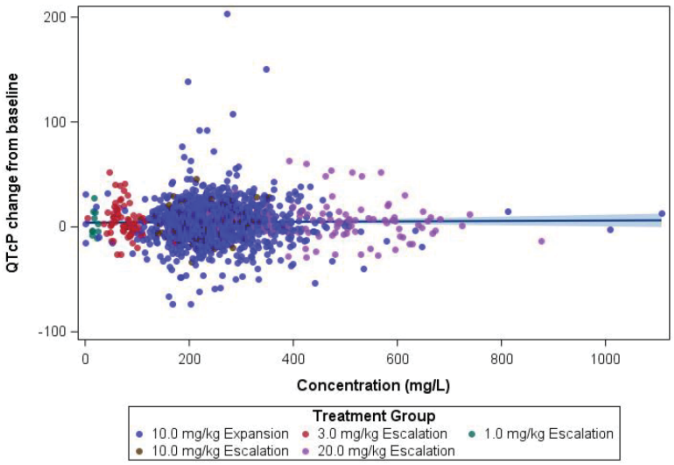


Figure 15 QTcP vs. Avelumab Concentrations



[Source: QTc-IRT review in DARRTS, Reference ID: 4026388, PP 24]

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

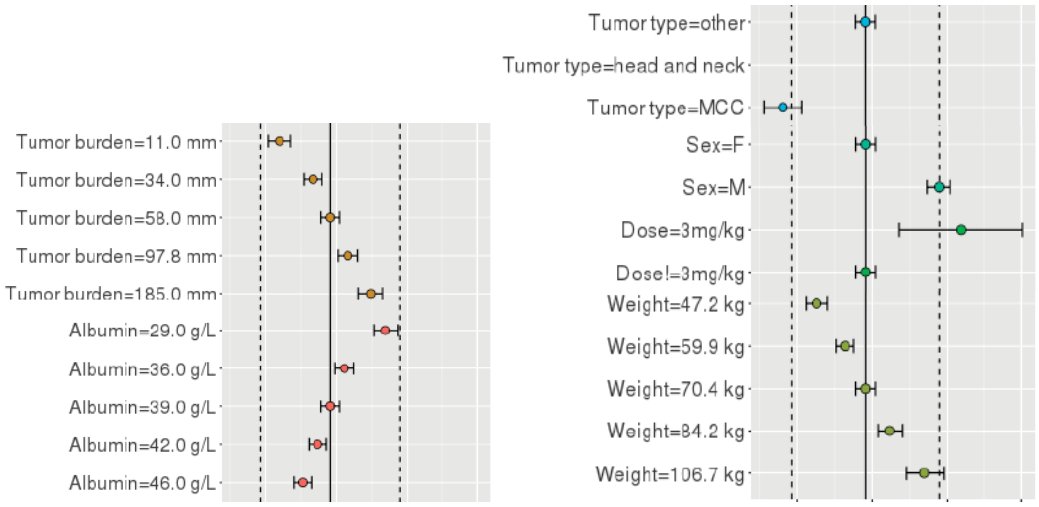
No, dose adjustment based on intrinsic factors is not needed based on the popPK analysis.

PopPK analysis was performed on the PK data from a total of 1629 subjects from Study 001 (n=1490 advanced solid tumors), Study 002 (n=51 advanced solid tumors) and Study 003 (n=88 mMCC) at avelumab doses ranging from 1.0 to 20 mg/kg Q2W to determine the effect of various covariates on the exposure to avelumab. Subjects ranged in age between 20-91 years (median=63 years) and baseline body weight ranged between 30.4-204 kg (median=70.5 kg). Fifty percent of subjects were males and 80% were Whites. Subjects were classified by baseline ECOG PS as restricted (ECOG = 1) or fully active (ECOG = 0) in this analysis.

The final popPK model estimated a geometric mean (%CV) CL value of 0.0267 L/h (29.9%) in patients receiving10 mg/kg Q2W. A geometric mean (%CV) of 4.72 L (44.5%) was estimated for volume of distribution at steady state (V_{SS}) (calculated as the sum of V_1 and V_2). Geometric mean $t_{1/2}$ was estimated to be 6.1 days (91.5%).

The applicant's final model contains 17 parameter-covariate relationships: baseline body weight, baseline albumin, baseline tumor burden, dose, sex and tumor type (MCC) on CL; acetaminophen premedication and tumor type (MCC and NSCLC) on Q; baseline body weight and sex on V1; and eGFR, acetaminophen premedication, tumor type (head and neck, ovarian and MCC) and immunogenicity on V2. Extreme values of these covariates do not induce clinically meaningful changes in avelumab clearance / exposure as compared with the typical value. Age, renal function, and hepatic function were not identified as statistically significant factors in the population PK model.

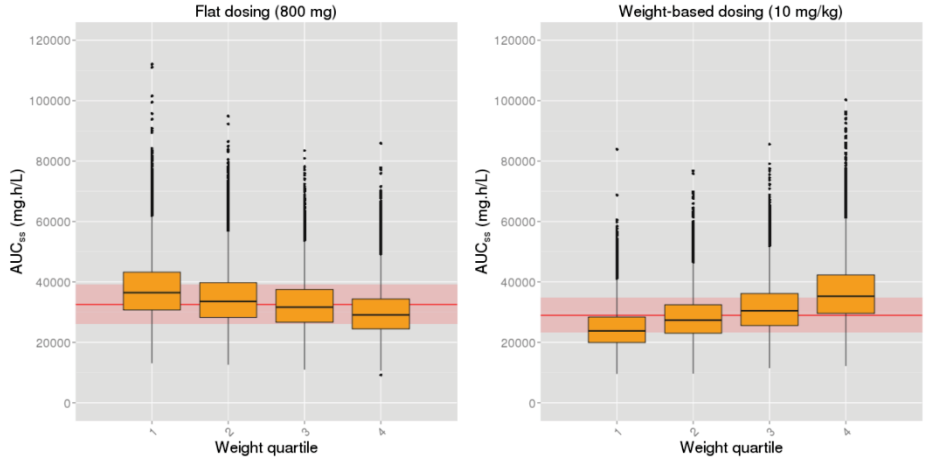
Figure 16 Forest Plot Showing Covariate-CL Relationships in the Final Model (run124). Dashed vertical lines are 80% and 120% of parameter values. !=; not equal to.



[Source: emr100070-001-002-003-population-pk-report.pdf, Figure 10]

Figure 17 shows the effect of body weight on simulated AUC_{SS} after the 10 mg/kg Q2W dose. These simulations suggested that the overall variability in exposure is similar for both body weight based and flat dosing schemes. A flat dosing regimen should be acceptable.

Figure 17 Simulated AUC_{SS} by Body Weight



N=100,000 simulated datasets. Black horizontal lines are medians. Boxes are interquartile range. Solid red horizontal line represents AUCss for population median of body weight. Red shaded area represents 80-120% range. All other covariates set to population median or most common category.

[Source: BLA 761049/ SDN 5, M&S Population Analysis Report, pp 65]

Immunogenicity

Serum samples for the analysis of anti-drug antibodies (ADAs) were collected in Studies 001, 002 and 003 at baseline prior to drug administration on Day 1, within 2 hours prior to infusion on Days 15, 29, 43 (every 2 weeks) and then every 6 weeks thereafter while on treatment, and at the end-of-treatment visit. EMD Serono plans to perform neutralizing antibody (Nab**)** testing

with a validated assay and will submit the results of this testing it as a PMC final study report. Immunogenicity results are shown in Table 5 as of cutoff date of 11/20/2015 (SDN 5).

Table 6 5 Incidence of Immunogenicity in the 10 mg/kg Q2W Dose Cohorts in Studies 001, 002 and 003 and the Integrated Safety Database

Category	Study 001 (N=1437)	Study 002 (N=34)	Study 003 (N=88)	Integrated Safety Database* (N = 1540)
Ever Positive n/N0 (%)	53/1385 (3.8%)	2/34 (5.9%)	3/88 (3.4%)	56/1484 (3.8%)
Pre-existing n/N1 (%)	7/1218 (0.6%)	0/34	0/85	7/1315 (0.5%)
Treatment boosted n/N2 (%)	0/1132	0/31	0/79	0/1221
Treatment-emergent n/N3 (%)	46/1291 (3.6%)	2/31 (6.5%)	3/82 (3.8%)	49/1383 (3.5%)

*Included both dose escalation and expansion cohorts at 10 mg/kg Q2W from Studies 001 and 003
N0 = Number of subjects with at least 1 valid result.
N1 = Number of subjects with valid baseline result.
N2 = Number of subjects with valid baseline and at least 1 valid post-baseline result.
N3 = Number of subjects with at least 1 valid post-baseline result and without positive baseline results.

[Source: BLA 761049/ SDN 5, Summary of Clinical Pharmacology Studies, Section 2.2.3, Page 91]

In the Integrated Safety Database as of the cutoff date of 11/20/2015 (SDN 5), 49 of 1383 subjects (3.5%) were reported as having at least 1 positive ADA result post-baseline with negative baseline result, after the 10 mg/kg Q2W dose. However, according to the 90-Day Safety Report dated 1/31/2017 (SND 32), immunogenicity results showed that among subjects with at least 1 ADA result, 4.3% of subjects (71 of 1659) had a positive ADA at any time point including baseline (3.8% [56 of 1484]. Among subjects who did not have positive results at baseline, 4.1% (64 of 1558) had treatment-emergent ADA (3.5% [49 of 1383]). The results from this 90-Day Safety Report were reported in the labeling by the FDA.

In conclusion, according to the 90-Day Safety Report dated 1/31/2017 (SND 32), immuno-genicity results showed that among subjects with at least 1 valid ADA result after the 10 mg/kg Q2W dose, 4.3% of subjects (71 of 1659) had a positive ADA at any time point including baseline (3.8% [56 of 1484]. These results were reported in the labeling by the FDA.

Effect of Immunogenicity on PK

Table 7, **Table 8**, **Figure 27,** and **Figure 28** below summarize of avelumab serum concentrations (C_{EOF} and C_{trough}, respectively) by ADA status at 10 mg/kg Q2W observed in the Integrated Safety Database.

Table 7 Avelumab Serum Concentration at the End of Infusion (C_{EOI}) Following 10 mg/kg Q2W by ADA Status

	ADA Status					
	Ever Positive			Ever Negative		
Day	N	Mean (µg/mL)	%CV	N	Mean (µg/mL)	%CV
1	25	207	24%	559	235	35%
15	NC	NC	NC	41	276	32%
29	NC	NC	NC	40	267	29%
43	12	213	21%	336	256	31%
85	7	234	24%	186	262	26%
127	NC	NC	NC	11	284	23%
169	2	252	35%	54	297	22%
253	1	298	NC	14	320	23%
337	1	381	NC	5	372	14%
421	1	489	NC	3	441	19%

NC = Not Calculable due to insufficient number of subjects

Figure 18 Arithmetic Mean (±SD) C_{EOI} by ADA Status Following 10 mg/kg Q2W

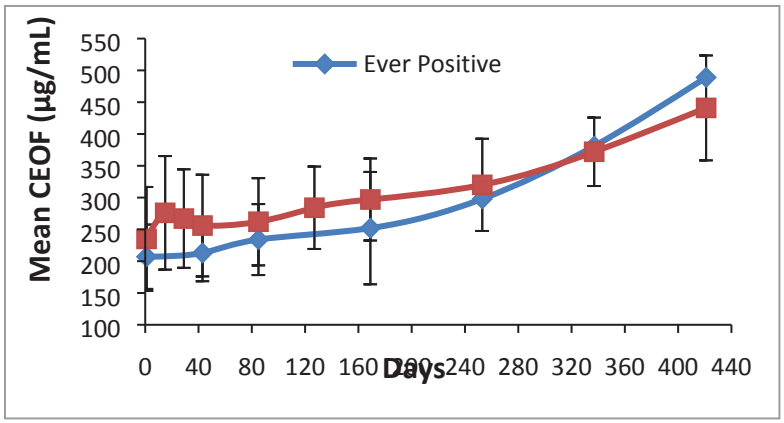
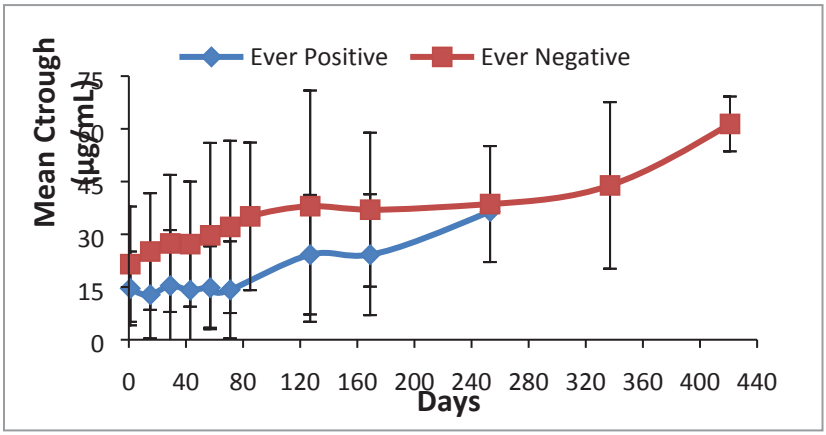


Table 8 Avelumab Serum Trough Concentrations (C_{trough}) Following 10 mg/kg Q2W by ADA Status

Day	ADA Status					
	Ever Positive			Ever Negative		
	N	Mean (µg/mL)	%CV	N	Mean (µg/mL)	%CV
1	51	14.6	72%	1268	21.5	76%
15	50	12.8	97%	1159	25.1	66%
29	37	15.4	103%	933	27.4	71%
43	23	14.1	106%	756	27.2	65%
57	23	14.8	80%	678	29.7	89%
71	20	14.2	97%	533	32.1	76%
85	2	37.4	9%	66	35.1	60%
127	10	24.2	70%	207	38.0	87%
169	8	24.2	71%	200	37.0	59%
253	1	36.5	NC	10	38.6	43%
337	NC	NC	NC	4	43.9	5%
421	NC	NC	NC	2	61.4	NC

NC = Not Calculable due to insufficient number of subjects

Figure 19 Arithmetic Mean (±SD) C_{trough} by ADA Status Following 10 mg/kg Q2W



Avelumab C_{EOI} concentrations were comparable between subjects with ever positive ADA and those with never positive for ADA (mean C_{EOI} on average = 296 µg/mL *versus* 301 µg/mL, respectively).

Avelumab C_{trough} concentrations trended lower in subjects with a positive ADA at any time than in those never positive for ADA (40% on average). Given the high variability in general between subjects [e.g., mean C_{trough} at Day 43 was 14.1 µg/mL (CV=106%) in ADA ever positive and 27.2 µg/mL (CV=65%) in ADA never positive], this trend may not be clinically significant. In addition, the popPK analysis demonstrated that treatment-emergent ADAs (HAHA) did not affect the exposure to avelumab (simulated AUC_{SS}) at the 10 mg/mg Q2W dose.

Effect of Immunogenicity on Safety

The incidence of treatment-related irAEs, IRR and TEAEs by immunogenicity status across Studies 001 and 003 (Integrated Safety Database) is presented in **Table 9**.

Table 9 Safety Sub-Analysis by Immunogenicity Status across Studies 001 and 003

Safety Measure n (%)	ADA Status				
	[a]Treatment-emergent-ADA	[a]Not Treatment-emergent-ADA	[b]Ever Positive ADA	[b]Never positive ADA	[c]All Subjects
	N=49	N=1435	N=56	N=1428	N=1540
irAEs	4 (8.2%)	146 (10.2%)	5 (8.9%)	145 (10.2%)	151 (9.8%)
IRRs	17 (34.7%)	331 (23.1%)	18 (32.1%)	330 (23.1%)	344 (23.1%)
TEAEs (Grade ≥ 3)	5 (10.2%)	139 (9.7%)	5 (8.9%)	139 (9.7%)	150 (9.7%)
Serious TEAEs	3 (6.1%)	82 (5.7%)	3 (5.4%)	82 (5.7%)	90 (5.8%)
TEAEs Leading to permanent Discontinuation	7 (14.3%)	84 (5.9%)	7 (12.5%)	84 (5.9%)	91 (5.9%)

[a]Treatment-emergent ADA are all subjects without a positive baseline test and at least 1 positive post-treatment sample**.**

[b]Non-treatment emergent are the sum of subjects negative at all time points and subjects positive prior to first treatment. Ever positive ADA are all subjects with at least 1 positive ADA, at either baseline or post-treatment. Never positive are subjects negative at all time points.

[c]All patients includes the 56 subjects that do not have valid ADA results

[Source: Summary of Clinical Pharmacology Studies, Section 4.1.5, Table 28, Page 98].

The incidences of irAEs, TEAEs Grade ≥ 3 and serious TEAEs were similar between the ever positive and never positive subjects.

The incidence of IRRs was higher in the ever positive subjects than the never positive subjects (32.1% versus 23.1%, respectively). As per the 90-Day Safety Report submitted on 1/31/2017 (SDN 32), IRRs remain higher in ADA ever-positive subjects (40.8%) versus never-positive subjects (24.7%). The association continues to not indicate causality, as only 13 subjects

experienced IRRs at or after ADA seroconversion, 5 of which discontinued treatment due to IRRs.

The incidence of TEAEs Grade ≥ 3 and serious TEAEs was comparable between the ever positive and never positive subjects. The percentage of subjects experiencing TEAEs leading to permanent discontinuation was higher in the ever positive subjects than in the never positive subjects (12.5% versus 5.9%, respectively), although the comparison was limited by the low incidence of immunogenicity.

Effect of Immunogenicity on Efficacy

ADA was tested as one of the covariates in the exposure-efficacy analysis using data from Study 003. However, because only 3 patients of 82 with mMCC (3.7%) tested ADA- positive in this study, a quantitative assessment of an association between efficacy and the incidence of ADA could not be performed. Table 9 below summarizes the characteristics of these three ADA positive subjects at 10 mg/kg Q2W.

Table 10 Characteristics of the Three ADA Positive Subjects from Study 003 at 10 mg/kg Q2W

Parameter	Subject 1010003	Subject 1010004	Subject 2060004
Demographics: Age, Sex, Race	82 years, Male, White	73 years, Male White	55 years, Female, White
Titer	4	8	8
Day tested ADA positive	85	43	127
C_{trough}	10.62 µg/mL	No trough sample taken on Day 43	Not calculated
Status as a cutoff date of 3/3/2016	Discontinued the study	Discontinued the study for disease progression	Continued in the study

[Source: Summary of Clinical Pharmacology Studies, Section 4.1.6, Page 100]

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

The popPK analysis indicated that concomitant medications (such as paracetamol, ibuprophen, acetylsalicylic acid, opioids) or premedication (with acetaminophen and diphenhydramine) did not have a significant effect on the total CL of avelumab ($p>0.05$). Avelumab, as a mAb, is eliminated by intracellular lysosomal proteolytic degradation throughout the entire body and therefore is not expected to be affected by small molecule drugs via CYP450 inhibition/induction or transporter modulation. Avelumab, as a mAb, is also not expected to have a direct DDI effect on other small molecule drugs.

Are the PK parameters reported in the label supported by PopPK analysis?

Yes, PK parameters in the proposed label are generally supported by the applicant's popPK analysis**.**

A trend for a time-dependent increase in exposure, especially in patients with MCC, was observed with multiple cycle avelumab treatment. In addition, a decrease in CL over time was also suggested by the goodness-of-plots of the applicant's popPK analysis. In a post hoc analysis that included a time-variant CL popPK model with tumor type as a covariate on CL change over time, the average (s.d.) maximal change is -3.1% (18.6%) and -41.7% (40.0%) in the entire PPK population (n=1629) and the MCC (n=88) subgroup. The clinical relevance of the CL change (especially -41.7% in MCC subpopulation) is unclear, but dose adjustment according to the CL change does not seem necessary because the proposed 10 mg/kg Q2W was well studied in clinical trials and the benefit/risk is acceptable.

X X

Primary Reviewer: Safaa Burns Team Leader: Jeanne Fourie Zirkelbach

7 Statistical and Clinical and Evaluation

7.1.Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Table 10 lists the clinical trials included in the original BLA submission. The primary evidence to support the clinical efficacy and safety of avelumab in patients with metastatic MCC is from 88 patients enrolled in Part A of Study 003. A pooled population (N=1540) comprised of patients with various advanced solid tumors who received avelumab at a dose of 10 mg/kg every two weeks in Study 001 and patients in Study 003 was analyzed to support the safety review. During the review, the Applicant submitted additional efficacy and safety data reflective of longer term exposure to avelumab for patients in both studies. The updated safety analyses were based on a pooled database consisting of 1738 patients as Study 001 was ongoing and had accrued additional patients at the time of the later data cutoff.

In addition to the prospective clinical trials of avelumab, the Applicant conducted an observational study (Study 100070-Obs001) which consisted of a multicenter retrospective chart review of patients treated with chemotherapy for distant metastatic MCC. The intent of this study was to characterize the natural history of metastatic MCC with respect to treatment outcomes for two cohorts of patients: those with metastatic MCC treated with frontline chemotherapy and those treated with one or more salvage chemotherapy regimens for refractory disease. In this study, radiology reports and relevant progress notes were independently reviewed by clinical reviewers to characterize response rates to chemotherapy according to RECIST. The descriptive analyses and results of Study Obs001 were considered exploratory and reviewed only in order to further characterize the risk: benefit profile of avelumab in metastatic MCC in the context of the natural history of MCC and treatment outcomes with cytotoxic chemotherapy. See Additional Efficacy Considerations in Section 7.4.

Table 11. Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety							
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	First patient enrolled Jul 3, 2014. At primary analysis (6 months after last patient initiated treatment) the median duration of treatment was 15 weeks.	88	Patients with metastatic MCC with progressive disease following at least one line of prior chemotherapy	38 sites across 8 countries
Studies to Support Safety							
EMR100070-001	Open-label, dose-escalation with expansion phase consisting of several disease-specific cohorts	<u>Dose-escalation:</u> Avelumab 1, 3, 10 or 20 mg/kg IV every 2 weeks <u>Expansion:</u> 10 mg/kg IV every two weeks	-Safety -PK -Determine MTD -BOR according to RECIST 1.1	First patient enrolled Jan 31, 2013. At the interim analysis (data cutoff date Nov 20, 2015), the median duration of treatment was 12 weeks.	1490* (interim analysis CSR)	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 11countries

*1490 was the sample size for ongoing Study 001 in the interim CSR submitted in the original BLA. The Applicant submitted an updated analysis as part of the 90-day safety update comprised of 1650 patients from Study 001 and 88 patients from Study 003.

7.1.2. Review Strategy

The statistical and clinical review team consisted of one primary statistical reviewer of efficacy and one primary clinical reviewer of safety and efficacy.

The BLA submission contained data from one single-arm, multicenter trial entitled "A Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma" as primary support for the proposed indication. The clinical review of efficacy focused on Part A of the trial which enrolled patients with metastatic MCC who had progressed following at least one prior systemic chemotherapy regimen.

The statistical and clinical review of safety and efficacy included the following:

- Review of the current literature on MCC epidemiology and treatment and the Applicant's orientation materials
- Review of Trial 003, including the clinical study report (CSR), protocol, protocol amendments, statistical analysis plan (SAP) and SAP amendments
- Review of Trial 001, including the CSR, protocol, and protocol amendments
- Review and assessment of Applicant analyses of avelumab safety and efficacy in the clinical study reports and the ISS
- Review of datasets submitted as SAS transport files
- Review of patient narratives of SAEs, deaths, and adverse events of special interest (AESI)
- Review of minutes of key meetings conducted during the avelumab development program for MCC
- Review and assessment of the Module 2 summaries including the Summary of Clinical Efficacy (SCE) and the Summary of Clinical Safety (SCS)
- Review of the 90 day safety update and proposed labeling modifications
- Review of updated Study 003 efficacy data and analyses submitted to the BLA on December 7, 2016 and relevant proposed labeling modifications
- Review of consultation reports from the Interdisciplinary Review Team for QT Studies (QT IRT), Office of Scientific Investigation (OSI), Office of Prescription Drug Promotion (OPDP) and Patient Labeling Team (PLT)
- Review of Applicant responses to multiple FDA requests for additional analyses and clarifications throughout the review
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling

Data Sources

The electronic submission including protocols and protocol amendments, SAP, CSRs, clinical summaries, patient listings, case report forms, supporting literature, SAS transport datasets in legacy, SDTM, and ADAM format, and SAS codes for the BLA submission are located in the following network paths:

Original submission: \\CDSESUB1\evsprod\BLA761049\761049.enx

Data and Analysis Quality

The submission contained all of the required components of the electronic Common Technical Document (eCTD) and was of adequate quality and integrity to allow for review of the clinical trial data supporting the proposed indication. The primary analysis dataset was reproducible, and FDA was able to confirm the Applicant's analyses of the primary and secondary endpoints.

Multiple information requests were sent to the Applicant during the review cycle. Examples of these were requests to clarify the location of specific components in the application, to obtain additional case report forms, to obtain updated information regarding specific patients, and to provide alternative presentations of specific efficacy results. During the midcycle communication, the Applicant was asked to submit any available data and datasets from Part B of Study 003 to support the proposal for a broad indication for avelumab for the treatment of metastatic MCC.

The Applicant was also asked to conduct additional analyses to allow further characterization of the safety profile of avelumab. Examples include various analyses of imARs, the duration and resolution of specific adverse reactions (e.g., endocrinopathies), the potential risk for immune-mediated cardiac toxicity (i.e., myocarditis), and anemia risk in patients treated with avelumab. The additional safety data was requested for the purpose of evaluating specific identified safety concerns with the intent to adequately describe the risk-benefit profile of avelumab in the product label. The Applicant was able to provide timely responses to satisfy all FDA information requests.

The applicant submitted documentation of data quality assurance procedures in the clinical study reports for Study 001 and 003. These procedures included a site Monitor performing routine visits to study sites and permission for representatives of the Sponsor's Quality Assurance unit as well as Health Authorities to inspect all study-related documents and other materials at each site. Additionally, each step of the data capture procedures, and the handling of the data, including creation of the final CSR, were subject to independent Quality Assurance audits which could be conducted at any time during or after the study.

7.2.Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Trial EMR 100070-003

7.2.2.

Trial Design and Endpoints

Part A of Trial EMR 100070-003 (Study 003) was a multi-center, international, open-label study in patients with metastatic MCC who have progressed on at least one line of chemotherapy. Patients were excluded from the study based on history of autoimmune disease, medical conditions requiring systemic immunosuppression, prior organ or allogeneic stem cell transplantation, prior treatment with anti-PD-1, anti-PD-L1 or CTLA-4 antibodies, central nervous system (CNS) metastases, infection with HIV, hepatitis B or hepatitis C, or ECOG performance score $\geq$ 2. Patients received avelumab 10mg/kg once every two weeks. Tumor measurements were performed every 6 weeks to determine response by RECIST 1.1 criteria, and included radiologic imaging and physical examination of skin lesions. Treatment continued until therapeutic failure, unacceptable toxicity, withdrawal of consent, or the fulfillment of any criteria for withdrawal as defined by the study protocol (Section 9.3.3).

Patients who experienced a complete response (CR) as reported by investigator could be treated for 6 to 12 months after confirmation of response, with treatment beyond 12 months permissible after a discussion with the sponsor. Re-initiation of treatment post relapse for patients with a confirmed CR prior to the end of the study was allowed at investigator discretion and agreement of the study Medical Monitor.

The primary endpoint of the study was confirmed best overall response (BOR) as per RECIST 1.1 as determined by Independent Endpoint Review Committee Assessment (IERC). Secondary endpoints included duration of response (DOR), progression-free survival (PFS) time according to RECIST 1.1 as determined by IER, and overall survival (OS) time.

Statistical Analysis Plan

The primary endpoint of Study 003 is the confirmed BOR of complete response (CR) or partial response (PR) according to RECIST 1.1. Tumor response was determined by IERC and BOR was defined as the best response among all tumor assessments at each time point, from study onset to documented disease progression. Any CR or PR must have been confirmed at a subsequent tumor assessment to occur no less than 5, but preferably 6 weeks after the initial observation of response.

There was one interim analysis for futility after 20 patients were enrolled and observed for at least 3 months and one interim analysis for efficacy 6 months after 56 patients were enrolled. If there were no unconfirmed responses according to RECIST 1.1 at the time of the interim analysis for futility, then enrollment was to be stopped until the SMC made a recommendation as to whether the study should continue. The primary analysis of efficacy was conducted 6 months after the final patient was enrolled, and a 12-month efficacy update was conducted 12 months after the last patient was enrolled, which was also the end of the study.

A sample size of 84 patients was planned for the study assuming an overall response rate (ORR) of 35%, and overall alpha of 0.025, and 87% power for rejecting the null hypothesis. The null

hypothesis for BOR, which was tested at both the interim as well as the primary analysis, was a response rate ≤ 20%. This hypothesis was tested in the ITT population and the overall type I error rate was controlled at 0.025 (1-sided). The interim analysis for efficacy was allocated a nominal p-value threshold of 0.0045. If the analysis of BOR is statistically significant in favor of the alternative hypothesis at the time of the interim analysis, enrollment continued to enroll the full number of patients to collect further data. Otherwise, the primary analysis conducted at 6 months was allocated an alpha of 0.0205.

The Clopper-Pearson confidence intervals (CI) were used for BOR analyses, and the repeated CI method was used to construct the 2-sided CI for the interim and the primary analysis. Kaplan-Meier estimates were used to determine the medians and 95% CI for duration of response.

In a single arm trial, FDA will not use inferential procedures to evaluate the trial results. Instead the efficacy decision will be based on whether the lower limit of 95% confidence interval of the response rate exceeds a clinically irrelevant response rate and whether the duration of response is adequate.

Protocol Amendments

Table 12 lists major modifications to Study 003 protocol with each amendment. This table was adapted from information located in Table 5 (page 88) of the Study 003 CSR.

Table 12. Protocol Amendments, Study 003

Amendment Date	Major changes introduced into the protocol
April 10, 2014	• Revised to state that radiotherapy administered to superficial lesions is not allowed if such lesions are considered target lesions or may influence efficacy evaluation • Clarified required premedication and allow for flexibility based on local treatment standards
June 6, 2014	• Added response status at 6 and 12 months as a secondary objective • Updated PK sampling to provide additional post infusion samples for characterization of population PK • Added additional immunogenicity sampling in the follow-up period • Added a comparison of the TTP on last prior anticancer therapy to PFS time on treatment as an exploratory objective • Added an exploratory analysis repeating the analysis of secondary and exploratory objectives that will be conducted 12 months after the accrual of the last subject • Added health-related quality of life questionnaires (the EuroQol EQ-5D and Functional Assessment of Cancer Therapy – Melanoma questionnaires)
September 5, 2014	• Added optional patient interviews to the health-related quality of

Amendment Date	Major changes introduced into the protocol
	life assessments and a new exploratory endpoint regarding the subjects experience with their disease and treatment • Revised to allow for archival biopsy at screening if fresh biopsy was not feasible
November 17, 2014	• Revised to remove the mandate that patients with CR must discontinue treatment, and state that patients with confirmed CR should stay on treatment for a minimum of 6 months and maximum of 12 months • Added an algorithm for the treatment of immune-related AEs • Added language stipulating that Grade 3 and 4 diagnostic tests (for example, ECGs, laboratory findings) must be reported as an AE
December 22, 2014	• Added new visits at Week 2, 4, and 6 for blood draws for the analysis of liver enzymes for patients with liver metastases • And revised eligibility criteria such that all patients were to have ALT and AST $\leq 2.5 \times$ ULN • Added new eligibility criterion of estimated life expectancy of 12 weeks
February 26, 2015	• Introduced product name: avelumab • Added tumor shrinkage as exploratory objective and added to endpoints
January 8, 2016	• Added a new cohort (Part B) of patients who had not received any prior systemic treatment for metastatic MCC.

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*).

The review team consulted the OSI on October 20, 2016 to perform an audit of select clinical sites. Sites were selected based on the number of patients enrolled, the relative number of protocol violations recorded, frequency of SAEs and specific efficacy results determined from data collected at the site. Four domestic sites were chosen for inspection: Sites 102, 133, 204, and 206. Additionally, EMD Serono, Inc. and one study CRO, (b) (4) were inspected. The CRO was responsible for creating the IRC, qualifying sites for image acquisition and data transfer, selecting and training independent reviewers, and overseeing the image review performed centrally by the IERC.

There were no significant issues identified at two of the four clinical sites and no issues identified upon inspection of the CRO (b) (4) The inspections conducted by OSI identified the following items:

- Monitoring issues at EMD Serono that contributed to approximately 46 unreported adverse events (AEs) from one site and evidence of underreporting AEs at that site
- Late reporting of one SAE (nine days late) at one site
- No ECG assessment post infusion in 3 patients approximately 20% of the time for each patient at one site.

These events 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 761049; the table indicates for each investigator whether the investigators have provided a Certification (FORM 3454), a Disclosure Statement (FORM 3455) or if the financial disclosure information is missing. During the review, FDA requested that the Applicant submit certification that they acted with due diligence but were unable to obtain the missing information (option 3 on FORM FDA 3454). This certification was submitted and included a table listing the investigators for whom financial disclosure information was missing and the reason why it was not obtained.

A total of one investigator (from Study 001) who participated in the conduct of clinical studies of avelumab supporting this application disclosed financial arrangements. Of the 27 investigators for Study 001 who initially had missing disclosure information, five were actually on file (due to a name change), and nine did not participate in the trial. 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. Only one investigator from Study 003 did not have financial disclosure information available, and the documented reason was site closure.

Patient Disposition

A total of 125 patients were screened for participation in Study 003; 88 patients (100%) received at least 1 dose of study drug and comprise the intent to treat (ITT) and safety populations for the study. At the data cutoff for the primary analysis, 26 patients (30%) were continuing on active treatment, and 62 patients had discontinued avelumab. Table 13 summarizes the reasons for discontinuation.

Table 13. Patient disposition, primary analysis

Disposition	Avelumab n (%)
Number screened	125
Reasons for exclusion during screening	
Eligibility criteria	29
Withdrawal of informed consent	2
Adverse event	1
Death	1
Other[a]	4
Number receiving at least one dose of avelumab	88 (100)
Treatment ongoing at data cutoff	26 (30)
Off treatment	62 (71)
Reasons for discontinuation	
Progressive disease	44 (50)
Death	7 (8)
Withdrawal of consent	4 (5)
Adverse event	3 (3)
Other[b]	3 (3)
Non-compliance[c]	1 (1)
Lost to follow-up	1 (1)
Patients in post-treatment follow-up at cutoff	15 (17)

Source: ADSL.xpt, primary analysis

[a] The Investigator's "other" reasons were choice of an alternative treatment, occurrence of an SAE, screening window > 18 days limit, and ECOG performance score of 2

[b] Two patients experienced CRs and one patient with a stable PR discontinued after almost one year of treatment.

[c] Patient missed Weeks 13, 15, and 17 for non-medical reasons.

Protocol Violations/Deviations

Major protocol deviations were pre-specified in the SAP for Study 003 and included:

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

Protocol deviations were categorized as: "Study Procedures Criteria," or "Concomitant Medication Criteria" or "Eligibility and Entry Criteria". There were 15 major violations in 12 patients. Table 14 summarizes the major protocol deviations identified in Study 003. The

description of the protocol deviation is adapted from that provided by the Investigator.

Table 14. Major protocol deviations during Study 003, primary analysis

PATIENT ID*	PROTOCOL DEVIATION
Concomitant Medication Criteria	
1020002	Tylenol was not given as a pre-medication prior to 3 infusions.
2040007	Patient received steroid medication to treat non immune-related adverse event while being on study treatment between the wk9 and wk11 visits.
2060002	Patient has needed steroid medication either as an oral medication or an IV injection prior to treatments which is prohibited by the protocol.
2060004	Patient took dexamethasone as premedication on two dates of avelumab administration. This medication is prohibited by the protocol.
9510001	Patient was given steroids as premedication at wk 5 and wk 7.
9550002	Patient received steroid medication to treat non immune-related adverse event while being on study treatment between the w3 and w5 visits.
Eligibility and Entry Criteria	
2040004	Patient was enrolled onto the study although the patient was ineligible due to lymphocytes <0.5 at screening.
2040007	Previous therapy with prohibited medication: PF-05082566 (antibody that stimulates signaling through CD137 which is found on T-cells)
2040008	Patient was enrolled onto the study although the patient was ineligible due to their lymphocyte being below the required level at a screening.
6050005	Patient was included in the study although the exclusion criteria 8 (previous malignant disease within the last 5 years...) was not fulfilled. The patient had a renal carcinoma which was resolved 4.5 years before the enrollment.
8010001	The patient was enrolled with brain metastases which met exclusion criterion #8. The brain CT/MRI was performed only after the first avelumab dose because of site oversight.
Study Procedures Criteria	
1020001	Wk23 premedication administration time is the same as avelumab administration start time (i.e., no premedication at infusion start).

PATIENT ID*	PROTOCOL DEVIATION
6080001	Pre-medication was not given prior to dosing.

Source: ADPD.xpt, Study 003; *Patients counted once within each category if they had more than one deviation.

Reviewer: 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.

Table of Demographic Characteristics

A total of 88 patients were enrolled in Study 003. Of these 88 patients, which represents the ITT analysis set, 65 (74%) were male and 81 (92%) were White. A majority of patients were from North America (58%), a sizable group was from Western Europe (33%), and the remaining patients from Australia (6%) and Asia (3%). All patients had a baseline ECOG performance status of 0 (56%) or 1 (44%).

Table 15. Demographic characteristics of all enrolled patients

Demographic Characteristics	Avelumab (N=88) Mean (SD) or n (%)
Age	69.7 (10.7)
Sex	
Male	65 (73.9%)
Female	23 (26.1%)
Race	
White	81 (92.0%)
Asian	3 (3.4%)
Unknown	4 (4.5%)
Geographic Region	
North America	51 (58.0%)
Europe	29 (33.0%)
Australia	5 (5.7%)
Asia	3 (3.4%)

Demographic Characteristics	Avelumab (N=88) Mean (SD) or n (%)
ECOG	
0	49 (55.7%)
1	39 (44.3%)

Source: ADSL.xpt, primary analysis

Other Baseline Characteristics

All patients enrolled in Study 003 had distant metastatic disease at study entry, and all patients had progressed during or after receiving systemic chemotherapy for the treatment of metastatic disease. The majority of patients (76%) had primary tumors located in the skin. Fifty-three percent of patients had visceral metastatic disease at study entry. Seventy-four patients had PDL-1 expression status assessed from tumor specimens, and the majority of patients had at least 1% of cells that tested positive for PDL-1 expression. Approximately half of the patients' specimens tested positive for MCV.

Sixty-five percent of patients (n=57) had received one prior systemic therapy and 35% (n=31) had received two or more lines of systemic therapy for metastatic MCC. Table 16 summarizes the disease characteristics for patients enrolled in Study 003. The most common prior chemotherapy regimens included etoposide for 61 patients (69%), carboplatin for 45 patients (51%), cisplatin for 25 patients (28%), and doxorubicin for 9 patients (10%). Three patients had been treated with kinase inhibitors, and three patients had received somatostatin analogs. One patient received and progressed on an experimental T cell co-regulator antibody (considered a protocol deviation) prior to study entry. Other prior systemic treatments included everolimus, interferon, melphalan, tumor-necrosis factor alpha, and inteleukin-2 (one patient each). The best overall response to the last prior anticancer therapy included: CR for nine patients (10%), PR for 13 patients (15%), SD for 20 patients (23%), and PD for 39 patients (44%). Seven patients did not have prior response data.

It is notable that 47 patients (53%) enrolled in Study 003 had medical histories significant for prior neoplasms including 17 patients (19%) with basal cell carcinoma, 12 patients (14%) with squamous cell carcinoma, 3 patients (3%) with breast cancer, 2 patients (2%) with prostate cancer, and two patients (2%) with non-Hodgkin's lymphoma. Various other benign and malignant neoplasms were reported in individual patients.

Table 16. Disease characteristics, primary analysis

Characteristic	Avelumab N=88 n (%)
Presence of visceral metastatic disease	47 (53)
PD-L1 Expression	
≥5% of cells with any staining	19 (22)
1-5% of cells with any staining	39 (44)
<1% of cells with any staining	16 (18)
Not Evaluable	14 (16)
MCV ICH status[a]	
Positive	46 (60)
Negative	31 (40)
Visceral metastases at study entry	47 (53)
Primary Tumor site Skin Lymph nodes Other[b] Missing	 67 (76) 12 (14) 2 (2) 7 (8)
Prior Lines of Therapy (All)	
1	52 (59)
2	26 (30)
3 or 4	10 (11)
Types of Prior Anticancer Therapy	
Chemotherapy for metastatic Disease	88 (100)
Chemotherapy for non-metastatic. Disease	3 (3)

Kinase inhibitor	4 (5)
Octreotide/Lanreotide	4 (5)
Antibody therapy	1 (1)
Exp. T cell co-regulator	1 (1)
Other[c]	4 (5%)

Source: ADSL.xpt, primary analysis
[a]77 patients had MCPyV immunohistochemistry testing
[b] Other sites in patient listings were "cheek mucosa" and "rectosigmoid junction"
[c]Other includes everolimus, interferon, melphalan, tumor-necrosis factor alpha, and interleukin-2

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was not analyzed because avelumab was administered as an intravenous infusion at the clinic. One patient was discontinued due to protocol noncompliance after missing three infusions for nonmedical reasons. Premedication with an antihistamine and acetaminophen prior to each avelumab infusion was mandatory. Use of rescue medication is not applicable to the study treatment mechanism of action.

Efficacy Results

Primary Efficacy Endpoint: Overall Response

Of the 88 patients enrolled in Study 003, there were 29 patients who had confirmed responses at the time of the 12 month efficacy analysis, which was also the end of the study. This corresponds to a 33% best overall response rate (95% CI: 23%, 44%). Table 17 provides further details of the responses for the ITT population. Ten patients (11%) had confirmed complete responses and 19 (22%) patients had confirmed partial responses. Non-responding patients were classified as having stable disease (9 patients), progressive disease (32 patients), and not-evaluable (18 patients). Of the patients whose responses were not evaluable, 14 were due to no post-baseline assessment, 2 were due to insufficient or missing radiologic scans, 1 was due to a new anticancer therapy stated prior to first post-baseline assessment, and 1 was due to an SD of insufficient duration.

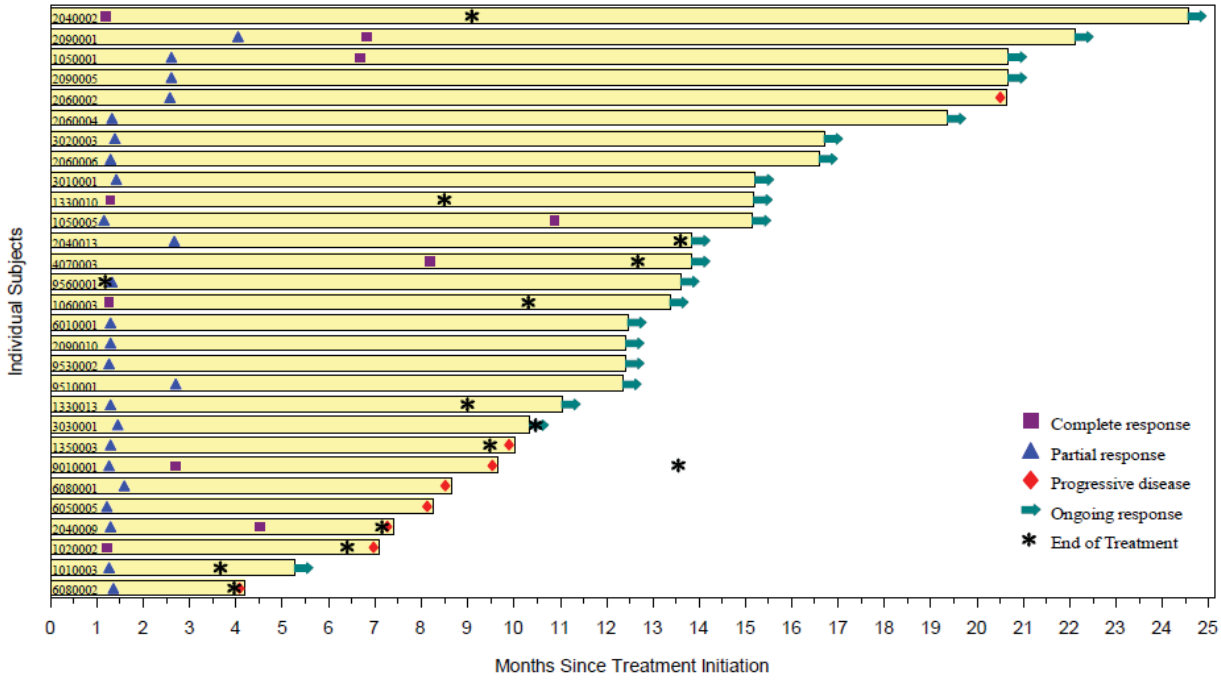
Table 17. Primary Efficacy Analysis: Confirmed Best Overall Response According to IERC Assessment (All enrolled patients)

	Avelumab (N=88) n (%)
Confirmed Responses	29 (33.0%)
Complete Responses	10 (11.4%)
Partial Responses	19 (21.6%)
Stable Disease	9 (10.2%)
Progressive Disease	32 (36.4%)
Not evaluable*	18 (20.5%)

Secondary Efficacy Endpoints: Duration of Response

Figure 20 provides a graphic representation of the duration of response of the confirmed responders of Study 003. Of the 29 responders, 23 patients (82%) had an ongoing response at the end of the study, 8 patients (18%) had progressive disease, and 0 patients died. The median duration of response was not reached, and the lower limit of the Kaplan-Meier estimate of the 95% CI is 8.3 months (the upper limit is not reached). The range of the duration of response was 2.8 months to 23.3 months (ongoing). The Kaplan-Meier estimate for the percent of patients with a 6-month duration of response is 93% (95% CI: 74%, 98%), and the estimate for the percent of patients with a 12-month duration of response is 75% (95% CI: 53%, 87%).

Figure 20. Duration of Response of Responders (Adapted from CTR-EMR100070-003 Addendum 1 Figure 15.2.2.20)



Subgroup Analyses

Response rates were compared across several subgroups of interest to examine consistency of effect. These subgroups were defined by number of prior systemic therapies (1 vs. 2 or more), PD-L1 tumor expression (≥1% vs. <1% and ≥5% vs. <5%), and MCV status (positive vs. negative). The comparison of response rates across these subgroups are presented in Table 18.

Of the 52 patients with 1 prior line of therapy for MCC, 21 patients (40%) had a response. This is compared to the 8 patients (22%) with a response in the subpopulation of 36 patients with 2 or greater lines of prior therapy. When comparing durability of response, 6 patients (12%) had progressive disease after response in the group of patients with 1 prior line of therapy and 2 patients (6%) had progressive disease after response after response in the subgroup of patients with 2 or more lines of previous therapy. Duration of response ranged from 2.8 months to 18.0 months (ongoing) in patients with 1 prior line of therapy and from 5.6 months (ongoing) to 23.3 months (ongoing) in patients with 2 or more prior lines of therapy.

Responses in PD-L1 positive and PD-L1 negative subpopulations are compared across different testing thresholds defining PD-L1 status. When defining positive status as ≥1% of cells testing positive for PD-L1 tumor expression, 21 of 58 PD-L1 positive patients (36%) had a confirmed response compared to 3 of 16 PD-L1 negative patients (19%) with a confirmed response. When the PD-L1 positive status threshold is defined as ≥5% of cells testing positive for PD-L1 tumor expression, 11 of 19 PD-L1 positive patients (58%) had a confirmed response compared to 13 of

55 PD-L1 negative patients (24%) with a confirmed response.

Finally, response rate was compared in patients testing positive and negative for MCV as determined by the MCPyV immunohistochemistry (IHC). In the 46 patients who tested positive for MCV, 13 patients (28%) had a confirmed response, compared to 11 confirmed responses (35%) out of the 31 patients who tested negative for MCV.

Table 18. BOR Compared Across Subgroups of Interest

	Avelumab (N=88)
Number of Prior Systemic Therapies	
1 vs. ≥2	40% vs. 22%
PD-L1 tumor expression	
≥1% vs. <1%	36% vs. 19%
≥5% vs. <5%	58% vs. 24%
MCV Status	
Positive vs. Negative	28% vs. 35%

7.3.Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

As discussed, data from a single trial were submitted as the primary support for this BLA. The effectiveness of avelumab in patients with metastatic MCC is based upon the results of Study 003, an international, multi-center, single-arm trial of avelumab in 88 patients with metastatic MCC who had disease progression after at least one prior chemotherapy regimen in the metastatic setting.

Efficacy Endpoints

The assessment of efficacy in this application is based on the endpoints of confirmed ORR and DOR according to RECIST 1.1 and as determined by the IERC for patients with metastatic MCC treated with avelumab at a dose of 10 mg/kg IV every two weeks. The primary analysis was conducted when all patients had been treated or followed for at least six months. An updated efficacy analysis was conducted when all patients had been followed for at least 12 months, and these results, which further characterize the durability of responses, will be described in the product label. At the time of the 12-month analysis, the ORR was 33% (95% CI: 23, 44). Twenty-nine of 88 patients had an objective response; 10 patients (11%) had a CR and 19 patients (22%) had a PR. The median DOR was not reached (range 2.8 to 23.3+ months) and

72% (n=21 of 29 responders) of the responses were ongoing. Twenty-five of 29 patients experienced responses of ≥ 6 months and 13/25 patients experienced responses of ≥ 12 months. It is notable that some patients within the group of responders have maintained prolonged responses after discontinuation of avelumab; two patients remained in CR for 15 months and 7 months, and one patient had a PR that was sustained for approximately 12 months after stopping avelumab.

Subpopulations

Similar response rates were observed in males and females, patients under or over the age of 65, and in patients with or without visceral metastases at study entry. The treatment effect of avelumab was observed in patients with tumors that were PD-L1 positive as well as patients with PD-L1 negative tumors. Objective responses also occurred in patients with tumors positive or negative for MCV by IHC. With limited sample sizes and wide CIs, neither PD-L1 status nor MCV status are considered reliable biomarkers for predicting response. See Table 18.

Additional Efficacy Considerations

Study 100070-Obs001 (Obs001)

The Applicant conducted Study Obs001, a retrospective, chart review and registry-based study designed to collect information on the treatment outcomes of patients with metastatic MCC and serve as a historic reference for Study 003. Part A of the study included patients treated in community oncology centers in the U.S. and Part B of the study included European patients primarily treated in academic centers. The Applicant evaluated outcomes for both previously untreated (frontline) and previously treated (second line and beyond) patients with metastatic MCC. The primary objective of the study was to determine the ORR to chemotherapy. For Part A, the assessment of response was determined by independent chart reviewers trained in categorizing response according to RECIST 1.1 who evaluated all radiologic scan reports and relevant progress notes for patients included in the primary analysis. If two reviewers were not able to definitively categorize the response based on review of scans and notes, the Principal Investigator was consulted to make the final assessment.

Part A (U.S. population) of Study Obs001 initially identified 686 patients in the iKnowMed electronic health record database. Most patients did not meet the criteria for inclusion in the primary analysis due to not having metastatic disease (n=431), having had additional solid tumors (n=27), no continuity of care to allow for follow-up (n=18), no prior chemotherapy (n=62), had chemotherapy but the regimen did not include qualifying agents (n=12), evidence of only one line of chemotherapy (n=97). Of the remaining 39 patients, 19 were excluded for other reasons after the chart review (e.g., did not have metastatic disease, treated in another interventional trial), and of the 20 patients who were treated with second line chemotherapy, 14 were determined to be immunocompetent. The immunocompetent group was chosen as

the reference group because these patients, according to the Applicant, most closely mimicked the Study 003 population. The ORR in these 14 patients was 28.6% (95% CI: 8.4, 58.1), with a median duration of response of 1.7 months (95% CI: 0.5, 3.0).

The results of Study Obs001 are consistent with the limited published literature on outcomes for patients treated with second line chemotherapy. Iyer et. al. published the largest retrospective case series describing response rates to frontline and second line chemotherapy in 62 patients with distant metastatic MCC. For the 30 patients who received second line chemotherapy, the ORR was 23% (7/30) with a median DOR of 101 days (range 6-226 days) [9].

Acknowledging these data are limited and subject to selection bias and other problems inherent in the use of an external historical control, the response rate and DOR results of Study 003 compare favorably with the results of Study Obs001 and the Iyer study.

Proposal for a Line-Agnostic Indication

The proposed indication for avelumab is for the treatment of patients with metastatic MCC. The Applicant asserts that a broad indication for all patients with metastatic disease, regardless of having received prior chemotherapy or not, is appropriate based on biologic rationale and unmet medical need. FDA requested that the Applicant submit clinical data to support an indication for avelumab for patients with metastatic MCC not previously treated with off-label chemotherapy since the data submitted in the BLA are from patients treated in second-line and beyond. FDA also requested that the Applicant provide evidence that use of avelumab in the frontline setting would not negatively impact any potential response to subsequent chemotherapy administered to patients who progress on or following avelumab treatment.

The Applicant submitted preliminary efficacy data from the ongoing Part B of Study 003 which is designed to assess ORR and DOR in patients with metastatic MCC who have not received prior chemotherapy for metastatic disease. As of the data cutoff date of January 26, 2017, 25 patients had received avelumab and had at least six weeks of follow-up; 16 of these patients had at least 13 weeks of follow-up. Given the small sample size with very limited follow-up to allow an adequate characterization of the durability of responses, FDA has not reviewed these data in support of this application. According to the Applicant, the Investigator-assessed, confirmed ORR among the 16 patients with three months of follow-up was 56% (95% CI 30, 80) which is similar to response rates to chemotherapy reported in the literature; however, the response rate in this population is expected to be as durable as in Part A. The IERC results were not yet available. FDA considers extrapolation of efficacy from patients treated in the second line setting and beyond (Part A of Study 003) to chemotherapy-naive patients to be justified for the reasons discussed earlier in this review.

The Applicant was also able to provide information regarding response to subsequent chemotherapy following progression on avelumab for 14 patients who were treated in Study 003. Three of the 14 patients (21%) are reported to have had a partial response to chemotherapy following progression on avelumab: one patient responded to carboplatin/etoposide, one to carboplatin/paclitaxel and one to cyclophosphamide/

doxorubicin/vincristine. These three patients had responses to one or more chemotherapy treatments prior to receiving avelumab. Although these data are very limited, it does not appear that avelumab has a negative effect on subsequent response to chemotherapy.

In addition to accepting extrapolation of efficacy data from chemotherapy-refractory patients to patients with chemotherapy-naive metastatic MCC and having limited data showing no adverse effects on potential subsequent responses to chemotherapy following avelumab treatment, FDA considered the following relevant factors in determining the approved broad indication: 1)there is an ongoing clinical trial of avelumab in the frontline setting (Part B of Study 003) which will characterize the durable response rate; 2) there is an unmet need for patients with metastatic MCC who have no FDA-approved therapy and where there is a short duration of response to off-label use of chemotherapy; and 3) avelumab has a relatively favorable toxicity profile as compared to cytotoxic chemotherapy. FDA has concluded that the totality of evidence supports the proposed indication for avelumab under the accelerated approval regulations.

7.3.2. Integrated Assessment of Effectiveness

The Applicant is seeking approval of avelumab for patients with metastatic MCC under the Accelerated Approval regulations. Durable objective response rate of sufficient magnitude is a surrogate endpoint that is reasonably likely to predict clinical benefit (i.e., improved survival) in patients with metastatic MCC. The effect size of avelumab on ORR [33% (95% CI: 23, 44)], and DOR (45% of responding patients with response durations ≥ 12 months) demonstrated in Part A of Study 003 represents substantial evidence of effectiveness. The durability of responses provides an advance over that observed with off-label use of chemotherapy which produces nondurable response rates (reported and observed median durations of response less than 3 months). Extrapolation of efficacy from patients who received avelumab following progression on prior chemotherapy to the frontline treatment of metastatic MCC is justified for the reasons discussed earlier in this review. A trial of avelumab which will characterize the durable response rate in chemotherapy-naïve patients is ongoing, the results will provide confirmatory evidence of clinical benefit for avelumab in patients with metastatic MCC.

7.4. Review of Safety

7.4.1. Safety Review Approach

The safety of avelumab based on common adverse reactions was evaluated in 88 patients with metastatic MCC who progressed after at least one line of prior chemotherapy enrolled in Part A of Study 003. 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. The primary safety analysis was conducted when all patients had been followed for at least six months from initiating avelumab treatment (data cut-off date of March 3, 2016).

A pooled population of patients (N=1540) with various advanced solid tumors who received avelumab at a dose of 10 mg/kg every two weeks in Studies 001 (N=1452) and 003 (N=88) was also analyzed to support the safety review. Study 001 is an ongoing dose-escalation trial with multiple parallel expansion cohorts in various solid tumor indications. The data cut-off date for Study 001 analyses was November 20, 2015. Since Study 001 was ongoing at the cutoff date, additional analyses were performed on the subgroup of patients from Study 001 who were followed for at least three months from initiation of avelumab treatment to ensure that the incidence of specific adverse events (e.g., imARs) was not underestimated due to inclusion of a group of patients with relatively short exposure and follow-up (i.e., less than 12 weeks).

The Applicant also submitted a 12 month safety analysis with corresponding datasets (data cut-off date of June 9, 2016), for both Studies 001 (N=1650) and 003 (N=88) to supplement the SCS as part of the 90-day safety update. The pooled safety population in the updated analysis included 1738 patients. The Applicant's side-by-side safety data from the primary 6 month analysis and the 12 month updated analyses were reviewed for cumulative safety results with longer exposures to avelumab and summarized in relevant sections of the review. Narratives of deaths and SAEs from both studies were reviewed for events that occurred up until the final data cutoff date of June 9, 2016. Key safety analyses from the 12 month dataset were verified by the reviewer for the purpose of informing the product label. Specifically, the updated pooled database (N=1738) was used to describe imARs in the Warnings and Precautions section of the label, and the updated Study 003 database (N=88) was used to describe the MCC safety data in the Adverse Reactions section of the label.

7.4.2. Review of the Safety Database

Overall Exposure

All enrolled patients in Study 003 (n=88) 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 17 weeks, and patients received between 1 and 35 infusions. In Study 001, the median exposure for the subset of patients who received avelumab at the 10 mg/kg dose at the data cut-off date was 12 weeks, and patients received between 1 and 51 infusions. Table 19 summarizes avelumab exposure during both studies.

Table 19. Exposure Summary, primary analysis

	Study 003 N=88	Study 001 N= 1452
Duration of treatment in weeks		
Median	17	12
Mean	23	15
Range	2-76	2-108
Number of infusions		
Median	7	5
Mean	11	7
Range	1-35	1-51
Cumulative dose (mg/kg)		
Median	70	50
Mean	111	74
Range	9-351	3-510
Dose intensity (mg/kg/cycle)		
Median	10	10
Mean	10	10
Range	5-11	2-11
Relative dose intensity (%)		
Median	99	100
Mean	95	97
Range	50-105	22-112

Source: ADEX.xpt, primary analysis

Relevant characteristics of the safety population:

The safety population from Study 003 was comprised of patients with distant metastatic MCC who had received at least one prior chemotherapy regimen. Consistent with the epidemiology and natural history of MCC, the median age was 73 years. Seventy five percent of patients were over the age of 65, and 5% were over the age of 75. This differed from Study 001 in which 56% of the study population was under the age of 65 years. The Applicant provided subgroup safety analyses to evaluate the impact of age on adverse event frequency in Study 003 and the pooled population. Additional exploratory analyses were conducted based on gender, race, performance score, body mass index (BMI) and tumor type. Limitations of these subgroup analyses are the small sample sizes in Study 003 and lack of internal control in both studies.

Adequacy of the safety database:

Overall, the safety database submitted by the Applicant was adequate. No major deficiencies were identified. Although the median exposure time at the time of the primary analysis of Study 001 data was relatively short (less than 12 weeks), the AE incidence rates in the subset of patients that were followed for at least 3 months in Study 001 were similar to those of the entire group, and the 12 month update with extended exposure for all patients did not identify any major differences in the safety profile for patients who had longer follow-up. The size of the safety database was sufficient to identify adverse events that occur at an incidence of approximately 1%.

7.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

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.

Categorization of Adverse Events

The Applicant coded verbatim AE terms for Study 003 and the integrated database using MedDRA version 18.1 for the primary analyses and MedDRA version 19 for the analyses submitted at the 90 day safety update. 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 Study 003 primary AE.xpt dataset. Of the 1017 line listings in the dataset, the reviewer used matching of identical verbatim and MedDRA PTs (n=381 line listings) as well as manual evaluation of the remaining verbatim terms (n=636 line listings). 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.

Routine Clinical Tests

Routine hematology and core chemistry laboratory assessments were performed within 18 days of enrollment and every two weeks prior to avelumab administrations, and when medically necessary during Study 003. Vital signs, physical examination and performance score assessments were performed prior to each cycle. Adrenocorticotropic hormone (ACTH), antinuclear antibody (ANA), antineutrophil 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 antihuman 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

Deaths

At the time of the primary analysis for Study 003, 43 patients (49%) had died; 40 died from progressive disease and for the other three patients, the primary cause of death was listed as "unknown" on the CRF. Twelve patients died within 30 days of receiving avelumab. One of the three unknown cases involved a death within 30 days of avelumab administration. An Information Request was issued to the Applicant during the BLA review to provide any available updated information and CRFs for the three patients with unknown cause of death. The primary cause of death remained "unknown" in the updated CRFs (data cutoff of June 9, 2016). For all three patients, the overall response to avelumab was progressive disease, and PD is listed as the reason for avelumab discontinuation in the CRFs. The Applicant was able to collect additional information on one of the patients (2040007) from the study site.

Patient 1020001: Narrative was not provided because death occurred six months after last dose of avelumab. CRF was reviewed and ADSL.xpt and ADAE.xpt datasets were reviewed to verify the CRF. The patient was a 71 year old male who had been on study for approximately six months prior to discontinuation for PD. At the (b) (6) EOT visit the ECOG PS was 0 according to the CRF. The date of death was approximately six months for the last dose of avelumab. The primary cause of death listed in the CRF is "unknown." This patient experienced three nonserious drug-related AEs during study including grade 2 oral thrush, and grade 1 fatigue and nausea.

Reviewer: Based on the date of death six months after the last dose of avelumab and the patient's relatively few treatment related AEs all of which resolved by the EOT visit, the reviewer concludes that avelumab is unlikely to have contributed to this patient's death.

Patient 1050003: 62 yo female who developed PD after three infusions of avelumab. Date of death was 9 months after the last dose of avelumab. CRF states cause of death as "unknown" and states that the date of death was identified from the public record. According to the CRF, this patient did not have further follow-up because the study consent was withdrawn as the patient did not want to complete additional laboratory assessments after stopping avelumab. During the study, the patient experienced two drug related nonserious AEs: hypersensitivity and elevated AST; both resolved.

Reviewer: Based on the date of death nine months after the last dose of avelumab and the patient's relatively few treatment related AEs, the reviewer concludes that avelumab did not contribute to this patient's death.

Patient 2040007: 61 year old male who received avelumab for approximately four months prior to discontinuation for PD. The patient died four weeks after the last dose of avelumab, and the CRF lists the primary cause of death as unknown. The treatment site informed the Applicant that after discontinuation of avelumab the patient sought palliative care and that disease progression is listed as the cause of death in the most recent documentation in the medical chart at the site.

Reviewer: Based on the review of the CRF and the updated information provided by the treatment site, this patient did not have a drug-related death.

During Study 003, there were eight treatment emergent AEs that had a fatal outcome. For five of the patients, both the AE and the primary cause of death were reported as disease progression. For three of the patients, disease progression was present at the time of death, but the AE triggering hospitalization prior to death was an event other than progressive disease. These three cases are summarized in the table below. For all cases, the reviewer agrees that it is unlikely that avelumab was a direct causal factor in the patient's death.

Table 20. TEAEs with a fatal outcome*, Study 003

Patient ID	AE	Event Summary
2040008	Hepatic failure	66 year old male with primary metastatic MCC and "bulging hepatic lesion." Experienced liver failure on Day 9 and death on Day 23. CRF reviewed. Patient had underlying liver, peripancreatic and gastrohepatic ligament nodal metastases. Patient received one infusion and presented on Day 9 with nausea, vomiting, intestinal obstruction and biliary obstruction. Stent was placed. No corticosteroids administered. Investigator assessed death as

Patient ID	AE	Event Summary
		unrelated to avelumab and related to underlying disease.
6080005	Pneumonia	76 year old obese male experienced AE of pneumonia on Day 52. Third and last avelumab infusion was Day 44. CRF and narrative were reviewed. Patient had fallen and was found unconscious at home. Diagnosed with pneumonia, urosepsis, bacteremia, rhabdomyolysis (from lying in one position after fall) and progressive disease. Investigator assessed death as unrelated to avelumab and related to both the pneumonia and underlying disease.
6080006	Ileus	74 year old male experienced AE of ileus on Day 33. He had received two avelumab infusions. He had been on oxycodone 20mg twice daily for approximately one month for pain. He was noted to have constipation and a CT scan demonstrating obstipation at a clinic visit prior to presenting with hematemesis and obstructive GI symptoms four days after last avelumab infusion. No steroids were given and no autopsy performed. The patient aspirated and deteriorated rapidly and did not have scheduled gastroscopy. Investigator assessed ileus and death as unrelated to avelumab and death as related to underlying disease. The Applicant suggested opioid use as a potential causal factor for the ileus.

*Does not include patients who died from the AE "disease progression"

Deaths during Study 001 were also reviewed as supportive safety information given the small sample size for the 003 trial. At the time of the interim analysis for Study 001, 545 patients (38%) had died; 29% from disease progression, 3% from an AE not related to avelumab, 0.4% had a treatment related AE, 4% were unknown, and 1% had a documented cause of death of "other." For the subgroup of 158 (11%) patients who died within 30 days of receiving avelumab, six patients had an AE related to avelumab, five (0.3%) had cause of death as "other" and four (0.3%) had cause of death listed as "unknown." Narratives were provided for the six patients who died from an AE related to study drug and the four patients who died within 30 days of avelumab with an "unknown" cause of death. These are briefly summarized here.

Patient 100070-001-1200014: 51 year old patient with metastatic breast cancer with liver metastases. Patient presented with nonserious **autoimmune hepatitis** on Day 35 with elevated liver enzymes (grade 2). Her condition became Grade 3 and serious four days later with associated grade 4 anemia and thrombocytopenia requiring transfusion. She was treated for presumed autoimmune hepatitis with high dose prednisone orally on Days 40 to 44, followed

by high dose methylprednisolone and hydrocortisone on Days 44 to 47, and with acetylcysteine for acute liver failure on Day 46. She died on Day 47. She had received three avelumab infusions prior to this event. No autopsy was performed.

Reviewer: Although this patient had progressive disease and liver metastases, given the timing of her death relative to avelumab doses and the known safety profile of PD-1 inhibitors with regard to immune-mediated adverse events including hepatitis, avelumab treatment resulting in autoimmune hepatitis is a likely cause for this patient's death.

Patient 100070-001-9080003: 50 year old patients with gastric and gastroesophageal junction cancer with no underlying liver metastases and normal screening labs experienced grade 3 **autoimmune hepatitis** followed by grade 4 hepatic failure on Day 14 and died on Day 15. Concomitant medications included lansoprazole, rebamipide, phazyme, and oxycodone. The patient had had one avelumab infusion. There was an acute rise in liver enzymes and bilirubin which did not improve despite administration of high dose steroids and mycophenylate. Her condition worsened leading to oligouria, confusion and dyspnea with hypoxemia. She died on Day 15. No autopsy was performed.

Reviewer: The event occurred after only one dose of avelumab; however autoimmune hepatitis was likely caused by avelumab treatment in this patient who had normal screening liver function and no liver metastases.

Patient 100070-001-2080029: 54 year old patient with urothelial carcinoma who experienced **pneumonitis** on Day 20 and had a fatal outcome on Day 24. The patient initially presented with left groin pain. He was not in respiratory distress on admission. The patient also had symptomatic C.difficile positive diarrhea. His creatinine was 1.9 and this was considered the result of dehydration secondary to diarrhea. He was hospitalized with initial improvement; however, developed acute shortness of breath. A CT scan revealed bilateral pleural effusions perihilar ground glass opacities, and a possible superimposed pneumonia. There were also mediastinal and hilar lymphadenopathy and hepatic and bony metastases noted. The patient was diagnosed with pneumonitis and began high dose steroid treatment in addition to broad spectrum antibiotics. He worsened to grade 4 and was intubated. The plan was to administer infliximab if there was no improvement. The patient died on Day 24. No autopsy was performed.

Reviewer: *The event occurred after only one dose of avelumab; however autoimmune pneumonitis caused by avelumab treatment is possible as there was no evidence of underlying lung metastases or chronic lung disease and the radiologic findings were consistent with pneumonitis. Infectious pneumonia also may have led to death.*

Patient 100070-001-1720004: 71 year old female patient with non-small cell lung cancer (NSCLC) and medical history significant for fibromyalgia and hyperthyroidism followed by hypothyroidism. She had prior lung radiation in December 2013. The patient enrolled in Study 001 in (b) (6) and had had one prior infusion of avelumab. On Day 11, she presented with dyspnea and abdominal pain. A CT demonstrated a new large right pleural effusion and new pulmonary nodules. The effusion was drained and the pathology showed malignant cells. She

was diagnosed with **radiation pneumonitis** and treated with oxygen, prednisone 60 mg orally once daily and ampicillin-sulbactam for pneumonitis. No autopsy was performed. On Study Day 18, she was discharged to hospice care and she died the next day. The investigator initially attributed the death to avelumab treatment, but subsequently stated that progressive disease was the cause of death. The Applicant assessed avelumab as not related to this death.

Reviewer: Given the patient's lung irradiation within four months of starting treatment with avelumab, the presentation of pneumonitis soon after the first dose of study drug, no improvement with steroid administration and very progressive lung disease noted on admission, the reviewer's opinion is that the patient had radiation pneumonitis and progressive disease which led to a fatal outcome and that is less likely that avelumab treatment caused a fatal autoimmune pneumonitis.

Patient 100070-001-1390004: 40 year old patient with metastatic breast cancer and underlying liver metastases. She experienced **respiratory distress and sepsis** on Day 23 and died on Day 40. She had received two prior avelumab infusions. Her CT scan at the time revealed progressive pulmonary metastases, including necrotic lesions. She was hospitalized and treated with broad spectrum antibiotics and high dose steroids. Her condition worsened. No autopsy performed. The Investigator assessed the respiratory distress as related to avelumab and the sepsis as not related to avelumab. The Investigator also indicated "adverse event related to study treatment" as the primary cause of death.

Reviewer: Avelumab cannot be completely excluded from the causality analysis; however, this patient's underlying progressive pulmonary disease and potential lung infection are confounders in the attribution analysis.

Patient 100070-0014030013: 69 year old male patient with previously treated NSCLC and medical history significant for emphysema, bronchopulmonary aspergillosis in 2014, dyspnea, respiratory failure, and hypoxia. He experienced **acute respiratory distress syndrome (ARDS)** on Day 1 which had a fatal outcome and was the primary cause of death on Day 6. The patient experienced chills and fever 30 minutes after the first avelumab infusion. He was hypoxic and had rales. Blood cultures were negative. Virology testing during the workup revealed **fulminant hepatitis E**. He was being treated with high dose steroids, antibiotics and spiramycin. He had several episodes of respiratory distress while in-house and died on Day 6. He was diagnosed with sepsis complicated by several acute respiratory decompensations in the setting of chronic respiratory failure and acute fulminant hepatitis E. He had received 1 infusion of avelumab. The Investigator assessed the ARDS as related to avelumab and an "adverse event related to study treatment" as primary cause of death.

Reviewer: The patient's initial symptoms seem consistent with a possible infusion reaction (i.e., anaphylaxis). It appears that the patient entered the study with compromised lung function due to underlying disease, emphysema, prior fungal infections and respiratory failure such that the development of ARDS was serious and potentially fatal in itself. The concurrent hepatitis E infection may be contributory to the patient's rapid deterioration, but the infectious factors in this case are unclear. In summary, there are multiple confounders,

but avelumab cannot be excluded as contributing to this fatal event as anaphylactic reactions can trigger ARDS.

Four patients enrolled in Study 001 died within 30 days of the last treatment administration with a primary cause of "unknown." Brief summaries are provided here:

Patient 100070-001-1120007: 67 year old patient with ovarian cancer was reported to have died on Day 35, 20 days after the last avelumab administration. The cause of death was unknown and not provided in the study record.

Patient 100070-001-1640009: 35 year old patient with gastric and GEJ carcinoma was reported to have died on Day 5, 4 days after the last avelumab administration. The cause of death was listed as unknown in the case report form; however, according to the CSR and the 90 day safety update, medical notes state that the patient expired at home of cardiac arrest. The event was reported as an SAE of Grade 5 cardiac arrest that was considered unrelated to study treatment by the Investigator.

*Patient 100070-001-*1670028: 81 year old patient with head and neck squamous cell carcinoma was reported to have died on Day 95, 24 days after the last avelumab administration. The cause of death was listed as unknown; the patient reportedly died in her sleep while on vacation, no other information was available.

Patient 100070-001- 1930019: 79 year old patient with NSCLC was reported to have died on Day 42, 27 days after the last avelumab administration. The cause of death was unknown; however, the patients was noted to have transitioned to hospice care and was lost to follow-up thereafter.

Reviewer: The above four patients died within 30 days of avelumab infusion. The available information was limited. Although one patient was on hospice care and another died from cardiac arrest at home, avelumab cannot be excluded from the causality analysis in any of these deaths without additional information. These four patients represent 0.3% of the Study 001 population. If we pooled these patients with the six patients who had treatment-related deaths, the incidence of deaths due to adverse reactions to avelumab would be 0.6%. This incidence does not change the benefit-risk ratio for avelumab in patients with refractory cancers.

The 90 day safety update reported that one additional patient from Study 003 died from disease progression. There were no new deaths from any related or unrelated AE that occurred within 30 days of the last dose of avelumab in Study 003. For Study 001, 53% of patients had died at the time of the safety update as compared to 38% of patients at the data cutoff date for the primary analysis. The most common reason for the increased number of deaths was disease progression. The incidence of treatment-related deaths decreased from 0.6% to 0.4% because investigators changed the cause of death to disease progression (patient 100070-001-172-

0004) and ARDS (patient 100070-001-403-0013) in two of the six patients described above. There were an additional 18 patients in Study 001 who died from AEs not related to avelumab at the time of the safety update.

Reviewer: The updated information on deaths provided in the 90 day safety update does not change the benefit: risk profile for avelumab in patients with metastatic MCC.

Serious Adverse Events

SAEs, including Grade 5 events, occurred in 36 patients (41%) in Study 003. Nonfatal SAEs occurred in 32 patients (36%). Five patients (6%) experienced a SAE that was considered related to avelumab. The most common SAE was disease progression. SAEs that occurred in more than one patient during Study 003 included anemia, abdominal pain, asthenia, general health deterioration and cellulitis. Of the eight patients in Study 003 who experienced a fatal SAE, three were SAEs other than progressive disease (hepatic failure, pneumonia, and ileus) and are described above in Table 20. Table 21 summarizes all SAEs that occurred in at least one patient in Study 003.

Table 21. Serious adverse events, Study 003, primary analysis

Preferred Term	All grades N=88 n (%)	≥ Grade 3 N=88 n (%)
Any SAE	36 (41)	33 (38)
Disease progression[a]	6 (7)	6 (7)
Anemia[b]	5 (6)	5 (6)
Acute kidney injury	4 (5)	1 (1)
Abdominal pain	2 (2)	2 (2)
General physical health deterioration	2 (2)	2 (2)
Dyspnea[c]	2 (2)	2 (2)
Gastric hemorrhage[d]	2 (2)	1 (1)
Squamous cell carcinoma[e]	2 (2)	2 (2)
Asthenia	2 (2)	0
Cellulitis	2 (2)	0
Leukocytosis	1 (1)	1 (1)
Atrial flutter	1 (1)	1 (1)
Pericardial effusion	1 (1)	1 (1)
Fecaloma	1 (1)	1 (1)
Eyelid function disorder	1 (1)	1 (1)
Glaucoma	1 (1)	1 (1)
Retinal artery occlusion	1 (1)	1 (1)
Ileus	1 (1)	1 (1)
Eesophageal spasm	1 (1)	1 (1)

Preferred Term	All grades N=88 n (%)	≥ Grade 3 N=88 n (%)
Chest pain	1 (1)	1 (1)
Fatigue	1 (1)	1 (1)
Non-cardiac chest pain	1 (1)	1 (1)
Pain	1 (1)	1 (1)
Hepatic failure	1 (1)	1 (1)
Liver injury	1 (1)	1 (1)
Erysipelas	1 (1)	1 (1)
Klebsiella sepsis	1 (1)	1 (1)
Lung infection	1 (1)	1 (1)
Pneumonia	1 (1)	1 (1)
Streptococcal sepsis	1 (1)	1 (1)
Urinary tract infection	1 (1)	1 (1)
Transaminases increased	1 (1)	1 (1)
Diabetes mellitus	1 (1)	1 (1)
Hyponatraemia	1 (1)	1 (1)
Bone pain	1 (1)	1 (1)
Flank pain	1 (1)	1 (1)
Musculoskeletal pain	1 (1)	1 (1)
Metastases to meninges	1 (1)	1 (1)
Pericardial effusion malignant	1 (1)	1 (1)
Post herpetic neuralgia	1 (1)	1 (1)
Confusional state	1 (1)	1 (1)
Delirium	1 (1)	1 (1)
Pleural effusion	1 (1)	1 (1)
Deep vein thrombosis	1 (1)	1 (1)
Superior vena cava syndrome	1 (1)	1 (1)
Tachycardia	1 (1)	0
Ulcerative keratitis	1 (1)	0
Enterocolitis	1 (1)	0
Diabetic foot infection	1 (1)	0
Infusion related reaction	1 (1)	0
Chondrocalcinosis	1 (1)	0
Synovitis	1 (1)	0
Encephalopathy	1 (1)	0
Anxiety	1 (1)	0
Tubulointerstitial nephritis	1 (1)	0

Source: ADAE.xpt, primary dataset
[a]Disease progression includes “neoplasm progression” and “malignant neoplasm progression”
[b] Anemia includes “Normochromic normocytic anaemia” and “microcytic anemia”
[c] dyspnea includes “dyspnea” and “exertional dyspnea”

[d] Gastric hemorrhage includes "gastric hemorrhage" and "gastrointestinal hemorrhage"
[e] Squamous cell carcinoma includes "squamous cell carcinoma" and "squamous cell carcinoma of the skin"

Treatment-related SAEs

Five patients (6%) experienced nonfatal treatment-related SAEs during Study 003. Narratives for these patients were reviewed and are summarized here.

Patient 105 0002: 69 year old male with medical history significant for grade 1 jaundice and metastatic pancreatic masses causing biliary obstruction and requirement for biliary stent. The patient developed grade 2 elevation in transaminases on Day 14 which increased to **grade 3 elevation of transaminases** on Day 18. Avelumab was discontinued. He had received one dose. The patient was treated for two days with methylprednisolone 30 mg orally every 8 hours and with prednisone 50 mg orally twice daily from 12/18/2014 to 2/25/15 for the transaminitis. Approximately four weeks after the initial event, the patient's transaminases improved to grade 2. A CT scan at this time demonstrated evidence of stent occlusion and infiltrative pancreatic mass. The next day, an endoscopic retrograde cholangiopancreatography was performed and a new biliary stent was placed. The patient is reported to have recovered from the SAE five weeks later. This SAE was categorized as a SAE and an immune-related AE based on steroid administration and no clear alternative etiology.

Reviewer: Agree with the assessment of this event as serious and potentially immune-mediated given the improvement with steroids and the length of time it took the patient to fully recover. The confounding factor is the occluded biliary stent, but replacement of a new stent should have led to a quicker recovery if the etiology was solely the occlusion.

Patient 4070002: 34 year old male who was diagnosed with serious **synovitis** (Grade 2) and serious **chondrocalcinosis** (Grade 2) during treatment with avelumab. The patient had had nine prior infusions. The clinical presentation also included lower limbs and scrotum erysipelas and fever. Subcutaneous blood culture was positive for Streptococcus pyogenes and the patient was treated with antibiotics with improvement. The patient was subsequently hospitalized for surgical treatment of the knee arthritis and the shoulder synovitis. Arthroscopic exploration and lavage of the right knee was performed; the fluid was sterile but showed persistent biological inflammatory syndrome. Avelumab was temporarily interrupted and restarted. The Investigator assessed the events synovitis and chondrocalcinosis as related to avelumab. The Sponsor considered the events synovitis and chondrocalcinosis as not related to avelumab.

Reviewer: This patient had had prior right knee surgery for resection of MCC and baseline chronic arthralgia. Prior surgeries are likely the cause of the arthritis and the chondrocalcinosis. It is unclear whether the left shoulder synovitis is related to study drug. The patient was febrile, was treated for infection with some improvement, but was not treated with steroids. It seems more plausible that there was an infectious etiology for the synovitis though the joint fluid cultures were negative. Avelumab cannot be excluded from the causality analysis as synovitis could be immune-mediated inflammation, but the

reviewer considers an infectious etiology to be more likely for the SAE synovitis in this patient.

Patient 6080006: 74 year old male who experienced the SAE s of **infusion-related reaction** and **ileus** while being treated with avelumab. The SAE ileus was considered unrelated to avelumab, but it was fatal and is described in Table 20. The infusion reaction was grade 2 and serious in that it required hospitalization for monitoring. The patient did recover and complete the dose after 30 minutes at 50% of the initial rate. The patient had received appropriate premedications. This occurred during the first infusion of avelumab. The Investigator considered the infusion reaction to be related to avelumab but assessed the ileus as not related to avelumab.

Reviewer: Agree with Investigator's assessment. The SAE of infusion reaction was related to avelumab. With regard to the SAE ileus, this patient had been on chronic narcotics for approximately one month prior to presenting with symptoms of ileus. The patient also had CT evidence of obstipation at the clinic visit prior to being admitted to the hospital for management of the ileus. The patient did not receive steroids.

Patient 9010001: 75 year old male who experienced the SAE of **enterocolitis** after his 17th infusion of avelumab and then **ileus** after 14 months of being on study. The enterocolitis was Grade 2 but required hospitalization. Avelumab was temporarily held and then restarted. No steroids were administered according to the narrative. Five months later, the patient presented with intractable vomiting and was diagnosed with ileus. The patient was treated with high-dose corticosteroids with a taper. The patient recovered for this event. Avelumab was permanently discontinued due to the SAE ileus.

Reviewer: Agree with Investigator's assessment. Both SAEs could be related to avelumab treatment. The enterocolitis improved without steroids and could have been infectious, but avelumab cannot be ruled out in the causality analysis. The SAE ileus seems most likely to be related to avelumab treatment. This patient was treated with corticosteroids with an improvement.

Patient 9560001: 71 year old female with the SAE **immune-related tubulointerstitial nephritis** that occurred after her fourth infusion of avelumab. The event required hospitalization. The patient had a normal baseline creatinine at screening. The patient was admitted for elevated creatinine and decreased filtration rate. Renal ultrasound showed no masses or hydronephrosis. An ultrasound guided renal biopsy revealed diffuse changes of acute tubular injury in association with a diffuse interstitial inflammatory cell infiltrate associated with tubulitis. The infiltrate was comprised of predominantly lymphocytes but also included lesser numbers of plasma cells and eosinophils. Tubular atrophy and interstitial fibrosis involved less than 5% of the sampled cortex. The patient was treated with high dose corticosteroids followed by a taper over the following two months. The patient recovered. Avelumab was permanently discontinued.

Reviewer: Agree with Investigator's assessment that this SAE of immune-mediated nephritis was related to treatment with avelumab.

In the pooled population of 1540 patients treated in Studies 001 and 003, the incidence of SAEs was generally comparable to that reported in Study 003. SAEs occurred in 40% of the pooled population (n=614) and 41% (n=36) of patients in Study 003. Disease progression was the most common SAE reported in both studies. SAEs that were reported in greater than or equal to 2% more of patients in Study 003 as compared to the pooled population were anemia, general health deterioration and acute kidney injury. Additionally, the incidence of SAEs in all patients from Study 001 (n=1452) as compared to the incidence in patients in Study 001 with more than 3 months follow-up time (n=1206) was very similar (40 and 42% respectively).

The 90 day safety update included two additional SAEs that occurred in patients enrolled in Study 003. The SAE ileus in patient 9010001 is described above. There was also a SAE of hypothyroidism in one patient (Patient 3030001). The case report form and narrative were reviewed. This patient developed Grade 3 hypothyroidism 21 days after the last dose of avelumab. The patient had been on treatment for approximately one year. Avelumab had been discontinued one week prior to the hypothyroidism diagnosis for elevated creatine kinase (treatment-related). The patient was treated with steroids and oral thyroid replacement therapy (levothyroxine) according to the CIOMS report. Duration of the AE was not reported. The thyroid function returned to normal with replacement therapy.

Discontinuations Due to Adverse Effects

Adverse events that led to permanent discontinuation of avelumab occurred in 3% of the patients treated in Study 003 in the primary analysis. These AEs were pericardial effusion, elevated transaminases, and immune-mediated nephritis, each occurring in one patient. The pericardial effusion was a malignant effusion and unrelated to avelumab. The AEs of elevated transaminases (patient 1050002) and the immune mediated nephritis (patient 9560001) are described above under SAEs.

The 90 day safety update included narratives for three additional patients enrolled in Study 003 who discontinued avelumab due to an adverse event: ileus, creatine kinase elevation, and alanine aminotransferase (ALT) increased and gamma-glutamyltransferase (GGT) increased.

Patient 901001*:* 75 year old male who experienced grade 3 **ileus** four days after last avelumab infusion and after 14 months of being on treatment. The patient was treated with corticosteroids and recovered. Details of this case and the reviewer's impression are provided above under "Treatment-related SAEs."

Patient 3030001: 74 year old male who experienced grade 3 **elevation of creatine kinase** and grade 3 hypothyroidism, both related to study treatment. The patient recovered from the grade 3 creatine kinase elevation in 20 days. The grade 3 hypthyroidism was treated with levothyroxine, and the patient had improvement, but was deemed "recovered with sequelae".

Levothyroxine was discontinued approximately two months after the diagnosis of hypothyroidism.

Patient 1330013: 75 year old male who experienced treatment-related **ALT and GGT elevation** noted 14 days after his 20th infusion of avelumab. He was treated with high dose oral prednisone followed by a taper and had improvement.

With these additional patients, a total of 6 (7%) patients with metastatic MCC had permanent discontinuation of avelumab due to an adverse reaction. This incidence is slightly less than that for Study 001 in which 13% of patients experienced AEs leading to permanent discontinuation. Excluding patients with progressive disease events, IRRs were the only AE that led to permanent treatment discontinuation in ≥ 1% of patients in the pooled safety database.

Significant Adverse Events

Dose Interruptions
The case report forms did not differentiate between an interruption of avelumab for an IRR and an interruption of avelumab for an AE that led to delays in the next dose administration. The Applicant therefore excluded IRRs causing temporary dose interruptions from the analysis. This was acceptable since an immediate and short term interruption (usually less than two hours with completion of the infusion the same day) for an IRR would not cause a delay in the next treatment administration whereas withholding the study drug while a patient recovers from a non-IRR adverse event would lead to a true dose delay.

The Study 003 primary safety dataset showed that 29 patients experienced any AE that required an action of "drug interrupted." Eight patients with interruptions due to IRRs were excluded from the analysis (preferred terms: IRR, back pain, hypersensitivity, hypotension). Therefore, the incidence of temporary discontinuations due to AEs during Study 003 was 24% (n=21). All AEs leading to dose delays are listed in Table 22. Of the listed events, there was one grade 4 AE (Klebsiella sepsis). Grade 3 AEs included anemia in 3 patients, and gastric hemorrhage, acute kidney injury, ALT increased, blood creatine kinase increased, bone pain, delirium, diabetes mellitus, erysipelas, flank pain, hypokalemia, hypophosphatemia, pericardial effusion, superior vena cava syndrome, tubulointerstitial nephritis, and urinary tract infection in one patient each. AEs that were considered drug-related include diarrhea, herpes zoster, blood creatine phosphokinase increased, synovitis, enterocolitis, and tubulointerstitial nephritis.

Table 22. AEs leading to dose delays, Study 003, Primary analysis

Preferred Term	All grades N=88 n(%)
Anemia	3 (3)
Gastric hemorrhage	2 (2)

Preferred Term	All grades N=88 n(%)
Acute kidney injury	1 (1)
Alanine aminotransferase increased	1 (1)
Blood creatine phosphokinase increased	1 (1)
Bone pain	1 (1)
Delirium	1 (1)
Diabetes mellitus	1 (1)
Diarrhoea	1 (1)
Dyspnea exertional	1 (1)
Enterocolitis	1 (1)
Erysipelas	1 (1)
Flank pain	1 (1)
Herpes zoster	1 (1)
Hypokalaemia	1 (1)
Hypophosphataemia	1 (1)
Klebsiella sepsis	1 (1)
Lung infection	1 (1)
Pericardial effusion	1 (1)
Pseudomonal bacteraemia	1 (1)
Superior vena cava syndrome	1 (1)
Synovitis	1 (1)
Tubulointerstitial nephritis	1 (1)
Urinary tract infection	1 (1)

Source: ADAE.xpt, primary analysis

In the pooled analysis, the incidence of temporary discontinuations secondary to AEs was lower than that for Study 003 (15% as compared to 24% of patients). AEs that led to interruptions in greater than or equal to 2% of patients in Study 003 as compared to the pooled population were anemia and gastric hemorrhage. The small difference may be due to less exposure time for the patients enrolled in Study 001. At the time of the 90 day safety update, the incidence of AEs leading to temporary discontinuation were reported in 24% of patients (the same as in the primary analysis) in Study 003 and in 21% of patients in Study 001. The safety update results did not reveal any new safety concerns.

Grade 3-4 AEs

Fifty-seven percent (n=50) of patients in Study 003 experienced at least one Grade 3 or 4 AE at the cutoff for the primary analysis. Four patients had Grade 3 or 4 AEs that were related to avelumab. These included lymphopenia (n=2), elevation of creatine kinase (n=1) and transaminases increased (n=1). Table 23 lists treatment emergent Grade 3 and 4 AEs that occurred in more than one patient in Study 003.

Table 23. Grade 3-4 adverse events, Study 003, primary analysis

Preferred Term	N=88 n (%)
Anemia	9 (10)
Lymphopenia	6 (7)
Hypertension	5 (6)
Gamma-glutamyltransferase increased	3 (3)
Lipase increased	3 (3)
Fatigue	2 (2)
Decreased appetite	2 (2)
Abdominal pain	2 (2)
Alanine aminotransferase increased	2 (2)
Hyponatraemia	2 (2)
Hypotension	2 (2)
Pleural effusion	2 (2)
Leukocytosis	2 (2)
General physical health deterioration	2 (2)

Source: ADAE.xpt, primary analysis dataset

The incidence of Grade 3-4 AEs in Study 001 at the time of the primary analysis was 47%. Ten percent of these AEs were considered related to treatment with avelumab. Overall, the incidences of specific grade 3-4 AEs were similar between the patients enrolled in Study 003 and the pooled population.

Treatment Emergent Adverse Events and Adverse Reactions

The primary safety database for Study 003 was analyzed at each level of the MedDRA hierarchy for common AEs. The tables in this section summarize the incidence of TEAEs, defined as AEs that occurred from the time of the first dose until 30 days following the last dose of avelumab. Almost all patients (98%) treated had at least one AE during treatment with avelumab in the primary analysis.

At the system organ class (SOC) level, the most frequently affected systems (> 20% incidence) were general disorders/administrative site conditions, gastrointestinal disorders, musculoskeletal and connective tissue disorders, investigations, skin and subcutaneous disorders, infections and infestations, nervous system disorders, metabolism and nutrition disorders, respiratory, thoracic and mediastinal disorders, vascular disorders, injury, poisoning and procedural complications, blood and lymphatic system disorders, and psychiatric disorders. Table 24 summarizes all AEs by SOC.

Table 24. Adverse events by SOC, Study 003, primary analysis

System Organ Class	N=88 N (%)
General disorders and administration site conditions	61 (69)
Gastrointestinal disorders	51 (58)
Musculoskeletal and connective tissue disorders	43 (49)
Investigations	36 (41)
Skin and subcutaneous tissue disorders	35 (40)
Infections and infestations	33 (38)
Nervous system disorders	31 (35)
Metabolism and nutrition disorders	30 (34)
Respiratory, thoracic and mediastinal disorders	30 (34)
Vascular disorders	23 (26)
Injury, poisoning and procedural complications	21 (24)
Blood and lymphatic system disorders	20 (23)
Psychiatric disorders	20 (23)
Cardiac disorders	15 (17)
Eye disorders	10 (11)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (10)
Renal and urinary disorders	8 (9)
Endocrine disorders	5 (6)
Hepatobiliary disorders	5 (6)
Reproductive system and breast disorders	5 (6)
Immune system disorders	2 (2)
Ear and labyrinth disorders	1 (1)

Source: ADAE.xpt, primary analysis

At the PT level, AEs that occurred in more than 15% of patients treated with avelumab included fatigue, diarrhea, nausea, decreased appetite, peripheral edema, constipation, cough, arthralgia, anemia, pain in extremity, and IRR. Grade 3 and 4 AEs were infrequent. Grade 3-4 AEs that occurred in at least 2% of patients included anemia, hypertension, lymphopenia, elevated GGT, elevated ALT, elevated aspartate aminotransferase (AST), hyponatremia, decreased appetite, abdominal pain, fatigue and hypotension. Table 25 summarizes common TEAEs in Study 003 by preferred term.

Table 25. TEAEs in at least 5% of patients, Study 003, primary analysis

Preferred Term	Any Grade N=88 n (%)	Grade 3-4 N=88 n (%)
Fatigue	33 (38)	2 (2)
Diarrhea	20 (23)	0
Nausea	18 (20)	0
Decreased appetite	17 (19)	2 (2)
Edema peripheral	16 (18)	0
Constipation	15 (17)	1 (1)
Cough	15 (17)	0
Rash[a]	15 (17)	0
Abdominal pain[b]	14 (16)	2 (2)
Arthralgia	14 (16)	1
Anemia	13 (15)	9 (10)
Pain in extremity	13 (15)	1
Infusion related reaction	13 (15)	0
Weight decreased	12 (14)	0
Hypertension	11 (13)	5 (6)
Asthenia	11 (13)	0
Dizziness	11 (13)	0
Vomiting	10 (11)	0
Back pain	9 (10)	0
Dyspnea[c]	8 (9)	1 (1)
Headache	8 (9)	0
Pruritus	8 (9)	0
Lymphopenia	6 (7)	6 (7)
Alanine aminotransferase increased	6 (7)	2 (2)
Chills	6 (7)	0
Pyrexia	6 (7)	0
Nasopharyngitis	6 (7)	0
Muscle spasms	6 (7)	0
Insomnia	6 (7)	0
Hyponatremia	5 (6)	2 (2)
Aspartate aminotransferase increased	5 (6)	1 (1)
Upper respiratory tract infection	5 (6)	0
Blood creatinine increased	5 (6)	0
Anxiety	5 (6)	0
Gamma-glutamyltransferase increased	4 (5)	3 (3)
Hypotension	4 (5)	2 (2)
Urinary tract infection	4 (5)	1 (1)
Blood creatine phosphokinase increased	4 (5)	1 (1)
Acute kidney injury	4 (5)	1 (1)

Preferred Term	Any Grade N=88 n (%)	Grade 3-4 N=88 n (%)
Lymphedema	4 (5)	1 (1)
Hypothyroidism	4 (5)	0
Abdominal discomfort	4 (5)	0
Sinusitis	4 (5)	0
Dehydration	4 (5)	0
Myalgia	4 (5)	0
Dry skin	4 (5)	0

Source: ADAE.xpt, primary analysis
Disease progression events are not included in the table.
[a]Rash includes terms "rash" and "maculopapular rash"
[b]Abdominal pain includes terms "abdominal pain" and "abdominal pain upper"
[c] Dyspnea includes terms "dyspnea" and "dyspnea exertional"

Table 26 shows a side by side comparison of the incidence of common TEAEs in Study 003 and the pooled analysis. TEAEs (related and unrelated) that occurred in 5% or more of the Study 003 group as compared to the pooled population were fatigue, diarrhea, peripheral edema, cough, rash, extremity pain, hypertension, asthenia and dizziness. The increase in specific TEAEs in the Study 003 group may be the result of the relatively older patient population enrolled in Study 003 (median age of 73 as compared to 63 years in Study 001), longer avelumab exposure, and eligibility requirements for presence of distant metastatic disease and prior treatment with cytotoxic chemotherapy. Additionally, except for fatigue, asthenia and rash, there was a less than 3% difference in the incidence of all treatment-related TEAEs between the two populations. Treatment-related fatigue occurred in 24% of patients in Study 003 and 17% of patients in the pooled population. Treatment-related rash occurred in 13% of patients in Study 003 and 6% of patients in the pooled database. Treatment related asthenia occurred in 8% of patients in Study 003 and 3% of patients in the pooled population.

Table 26. Common AEs in ≥ 5% of patients, Study 003 and pooled analysis

Preferred Term	Study 003 N=88	Pooled population N=1540
Fatigue	33 (38)	451 (29)
Diarrhea	20 (23)	262 (17)
Nausea	18 (20)	344 (22)
Decreased appetite	17 (19)	249(16)
Edema peripheral	16 (18)	147 (10)
Constipation	15 (17)	263 (17)
Cough	15 (17)	183 (12)
Rash[a]	15 (17)	146 (9)
Abdominal pain[a]	14 (16)	263(17)

Preferred Term	Study 003 N=88	Pooled population N=1540
Arthralgia	14 (16)	149 (10)
Anaemia	13 (15)	201 (13)
Pain in extremity	13 (15)	82 (5)
Infusion related reaction	19 (22)	371 (24)
Weight decreased	12 (14)	237 (15)
Hypertension	11 (13)	114 (7)
Asthenia	11 (13)	115 (8)
Dizziness	11 (13)	93 (6)
Vomiting	10 (11)	224 (15)
Back pain	9 (10)	163 (11)
Headache	8 (9)	131 (9)
Pruritus	8 (9)	94 (6)
Dyspnea[c]	8 (9)	270 (18)
Lymphopenia	6 (7)	23 (1)
Alanine aminotransferase increased	6 (7)	70 (5)
Chills	6 (7)	139 (9)
Pyrexia	6 (7)	187 (12)
Nasopharyngitis	6 (7)	26 (2)
Muscle spasms	6 (7)	47 (3)
Insomnia	6 (7)	83 (5)
Hyponatremia	5 (6)	81 (5)
Aspartate aminotransferase increased	5 (6)	79 (5)
Upper respiratory tract infection	5 (6)	58 (4)
Blood creatinine increased	5 (6)	55 (4)
Anxiety	5 (6)	78 (5)
Gamma-glutamyltransferase increased	4 (5)	39 (3)
Hypotension	4 (5)	48 (3)
Urinary tract infection	4 (5)	121 (8)
Blood creatine phosphokinase increased	4 (5)	18 (1)
Acute kidney injury	4 (5)	31 (2)
Lymphedema	4 (5)	12 (1)
Hypothyroidism	4 (5)	70 (5)
Abdominal discomfort	4 (5)	15 (1)
Sinusitis	4 (5)	16 (1)
Dehydration	4 (5)	90 (6)
Myalgia	4 (5)	75 (5)
Dry skin	4 (5)	37 (2)

Source: ADAE.xpt (Study 003 and ISS datasets) primary analysis
Disease progression events are not included in the table.
[a]Rash includes terms “rash” and “maculopapular rash”
[b]Abdominal pain includes terms “abdominal pain” and “abdominal pain upper”

[c] Dyspnea includes terms “dyspnea” and “dyspnea exertional”

Given the relatively short median exposure time (12 weeks) for the primary analysis of Study 001 and because the trial was continuing to enroll patients who potentially had very limited exposure to avelumab at the time of data cut-off, the Applicant additionally analyzed AE frequency in the subset of patients in Study 001 who had a minimum follow-up time of three months (N=1206). The incidences of general AEs did not substantially increase when these patients were compared to all patients treated in Study 001. The frequency of imARs was also similar (11% in patients overall and 13% in patients with at least 3 months follow up). See Table 27 (copied from the Summary of Clinical Safety). FDA verified the data in this table.

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Table 27. TEAE incidence by SOC and PT, Study 001, primary analysis

Body System or Organ Class Preferred term	All 001 Subjects (N=1452) n (%)	001 Subjects with > 3 mo Follow Up (N=1206) n (%)
Number of Subjects With At Least One Event	1359 (93.6)	1172 (97.2)
Blood and lymphatic system disorders	254 (17.5)	233 (19.3)
Anaemia	188 (12.9)	174 (14.4)
Endocrine disorders	100 (6.9)	91 (7.5)
Hypothyroidism	66 (4.5)	60 (5.0)
Gastrointestinal disorders	850 (58.5)	762 (63.2)
Nausea	326 (22.5)	295 (24.5)
Constipation	248 (17.1)	230 (19.1)
Diarrhoea	242 (16.7)	223 (18.5)
Vomiting	214 (14.7)	190 (15.8)
Abdominal pain	184 (12.7)	167 (13.8)
Abdominal pain upper	65 (4.5)	60 (5.0)
Abdominal distension	54 (3.7)	51 (4.2)
Dry mouth	50 (3.4)	48 (4.0)
Dysphagia	51 (3.5)	48 (4.0)
Ascites	46 (3.2)	42 (3.5)
Gastrooesophageal reflux disease	45 (3.1)	41 (3.4)
General disorders and administration site conditions	870 (59.9)	777 (64.4)
Fatigue	418 (28.8)	381 (31.6)
Pyrexia	181 (12.5)	156 (12.9)
Oedema peripheral	131 (9.0)	125 (10.4)
Chills	133 (9.2)	112 (9.3)
Disease progression	125 (8.6)	117 (9.7)
Asthenia	104 (7.2)	89 (7.4)
Non-cardiac chest pain	70 (4.8)	64 (5.3)
Influenza like illness	65 (4.5)	60 (5.0)
Infections and infestations	432 (29.8)	389 (32.3)
Urinary tract infection	115 (7.9)	106 (8.8)
Pneumonia	59 (4.1)	55 (4.6)
Upper respiratory tract infection	53 (3.7)	49 (4.1)
Injury, poisoning and procedural complications	342 (23.6)	307 (25.5)
Infusion related reaction	246 (16.9)	218 (18.1)
Investigations	529 (36.4)	479 (39.7)
Weight decreased	225 (15.5)	206 (17.1)
Aspartate aminotransferase increased	74 (5.1)	68 (5.6)
Alanine aminotransferase increased	64 (4.4)	56 (4.6)
Weight increased	58 (4.0)	54 (4.5)
Blood creatinine increased	50 (3.4)	46 (3.8)
Blood alkaline phosphatase increased	53 (3.7)	47 (3.9)
Metabolism and nutrition disorders	531 (36.6)	480 (39.8)
Decreased appetite	232 (16.0)	216 (17.9)
Dehydration	86 (5.9)	77 (6.4)

Body System or Organ Class Preferred term	All 001 Subjects (N=1452) n (%)	001 Subjects with > 3 mo Follow Up (N=1206) n (%)
Hypokalaemia	83 (5.7)	78 (6.5)
Hyponatraemia	76 (5.2)	69 (5.7)
Hypomagnesaemia	61 (4.2)	57 (4.7)
Hypoalbuminaemia	50 (3.4)	46 (3.8)
Hyperglycaemia	47 (3.2)	46 (3.8)
Musculoskeletal and connective tissue disorders	523 (36.0)	482 (40.0)
Back pain	154 (10.6)	146 (12.1)
Arthralgia	135 (9.3)	127 (10.5)
Pain in extremity	69 (4.8)	64 (5.3)
Musculoskeletal pain	74 (5.1)	71 (5.9)
Myalgia	71 (4.9)	66 (5.5)
Musculoskeletal chest pain	53 (3.7)	50 (4.1)
Nervous system disorders	382 (26.3)	354 (29.4)
Headache	123 (8.5)	116 (9.6)
Dizziness	82 (5.6)	78 (6.5)
Psychiatric disorders	205 (14.1)	194 (16.1)
Insomnia	77 (5.3)	75 (6.2)
Anxiety	73 (5.0)	71 (5.9)
Respiratory, thoracic and mediastinal disorders	565 (38.9)	510 (42.3)
Cough	168 (11.6)	159 (13.2)
Dyspnoea	163 (11.2)	148 (12.3)
Dyspnoea exertional	99 (6.8)	95 (7.9)
Pleural effusion	66 (4.5)	58 (4.8)
Skin and subcutaneous tissue disorders	334 (23.0)	302 (25.0)
Pruritus	86 (5.9)	76 (6.3)
Rash	77 (5.3)	73 (6.1)
Vascular disorders	227 (15.6)	202 (16.7)
Hypertension	103 (7.1)	87 (7.2)
Hypotension	44 (3.0)	42 (3.5)

Source: BLA 761049 SCS, pages 59-60

The Applicant's analysis of longer term safety data submitted with the 90 day safety update was also reviewed, and key analyses were performed on the 12 month data to confirm the Applicant's results and inform the product label. Note that the cutoff for the safety update was three months after the data cutoff for the primary analysis of Study 003. In general, there were very slight increases in the frequency of some common AEs and no new safety signals identified in the Study 003 patients. The only additional AEs that occurred in two or more patients at the later data cutoff were dyspnea (three additional patients) and rash (two additional patients).

The data cutoff for the updated safety results for Study 001 was almost seven months after the primary analysis. Note that this study was ongoing such that the sample size increased for the updated analysis (N=1650 as compared to 1452 in the primary analysis), but the median exposure remained the same at 12 weeks. No new safety signals were detected. TEAEs that occurred at an incidence of at least 2% higher than that for the primary analysis were fatigue

and nausea (both 3% more) and anemia, diarrhea, peripheral edema, upper respiratory infection, urinary tract infection, decreased appetite, dyspnea, and hypertension (each 2% more).

Laboratory Findings

In Study 003, laboratory tests to assess liver function (alkaline phosphatase, ALT, AST, bilirubin), chemistries (sodium, potassium, chloride, BUN, creatinine, glucose), and minerals (magnesium, phosphorus, calcium) were measured every two weeks. Hematology assessments were performed every two weeks. The reviewer analyzed the ADLB.xpt data from the primary and 12 month analyses. Table 28 summarizes the common laboratory abnormalities for patients in Study 003. Grade 3 or 4 chemistry abnormalities in more than 2% of patients included elevations in serum lipase, glucose, ALT and amylase.

Anemia was common in patients enrolled in Study 003. It is important to note that the inclusion criteria allowed patients with preexisting anemia to participate in the trial if a hemoglobin level > 9 g/dl could be reached by means of blood transfusion, and only 27% of patients had a normal hemoglobin at study entry. Fifty-two percent of patients had grade 1, 19% had grade 2 and one patient had grade 3 anemia at baseline. Thirty of the 85 patients (35%) with available post-baseline values had lower hemoglobin values during treatment with avelumab; eight of the 85 patients (9%) worsened to a Grade ≥ 3 anemia. Anemia was considered an adverse event in 13 patients during Study 003, and one patient was reported to have treatment-related anemia. The unrelated anemia events had other causal factors documented including "tumor/disease-related," "past illness," "small intestine ulcer," and "GI bleed." Grade 3 lymphopenia occurred in 21% of patients. Lymphopenia was reported as an adverse event by Investigators in 7% of patients; grade 3 lymphopenia was considered treatment-related in two patients (2%).

Reviewer: Baseline low-grade anemia and lymphopenia could be manifestations of prior cytotoxic chemotherapy administered for metastatic MCC and the relatively older patient population enrolled in Study 003.

Table 28. Laboratory abnormalities, Study 003

Laboratory Test	Avelumab N=88	
	All grades n (%)	Grades 3-4 n (%)
Chemistry		
Increased serum creatinine	36 (41)	0
Increased serum creatine kinase (CK)*	18 (20)	1 (1)
Hyperglycemia	5 (6)	2 (2)

Laboratory Test	Avelumab N=88	
	All grades n (%)	Grades 3-4 n (%)
Increased lipase	15 (17)	4 (5)
Increased amylase	7 (8)	1 (1)
Increased alanine aminotransferase	22 (25)	4 (5)
Increased aspartate aminotransferase	43 (49)	1 (1)
Increased alkaline phosphatase*	26 (30)	1 (1)
Increased bilirubin	6 (7)	1 (1)
Hematology		
Anemia	77 (88)	9 (10)
Lymphopenia	60 (68)	18 (21)
Neutropenia	5 (6)	1 (1)
Thrombocytopenia	31 (35)	1 (1)

Source: ADLB.xpt, Safety Update Report; Safety Update tables Section 12.8
Incidences based on patients with at least one grade 1 abnormality during treatment
*CK and alkaline phosphatase results based on ADLB.xpt, primary analysis

The Applicant also provided an analysis of common laboratory abnormalities occurring in Study 003 and in the pooled safety population. This analysis reports incidence rates based on a denominator that includes all patients who had non-missing baseline and on-treatment values and only includes patients who experienced a laboratory abnormality that was worse than their baseline abnormality (if present). Therefore, grade 1 anemia events, for example, would not be listed if the patient had a baseline grade 1 anemia at study entry. The following table was copied from the Applicant's response to an FDA Information Request submitted to the BLA on February 9, 2017.

Table 29. On-treatment worsening of laboratory measures compared to baseline, Study 003 and pooled database, updated analysis

Parameter	EMR 100070-003 (N=88)						Pooled analysis (N=1738)					
	Subjects available		Grade ≥ 1		Grade ≥ 3		Subjects available		Grade ≥ 1		Grade ≥ 3	
	n	%	n	%	n	%	n	%	n	%	n	%
Creatinine increased	85	96.6	28	32.9	0	0.0	1673	96.3	348	20.8	9	0.5
Lipase increased	80	90.9	11	13.8	3	3.8	1349	77.6	199	14.8	68	5.0
Serum amylase increased	79	89.8	6	7.6	1	1.3	1348	77.6	144	10.7	26	1.9
Hyperglycemia	84	95.5	NA	-	6	7.1	1682	96.8	NA	-	95	5.6
Serum creatine kinase (CPK) increased	71	80.7	12	16.9	1	1.4	1273	73.2	153	12.0	14	1.1
Blood bilirubin increased	86	97.7	5	5.8	1	1.2	1673	96.3	141	8.4	28	1.7
Alanine aminotransferase increased	86	97.7	17	19.8	4	4.7	1679	96.6	356	21.2	40	2.4
Alkaline phosphatase increased	85	96.6	20	23.5	1	1.2	1659	95.5	520	31.3	70	4.2
Aspartate aminotransferase increased	86	97.7	29	33.7	1	1.2	1679	96.6	492	29.3	63	3.8
Hypokalemia	85	96.6	11	12.9	2	2.4	1688	97.1	257	15.2	33	2.0
Hypocalcemia	84	95.5	17	20.2	1	1.2	1682	96.8	440	26.2	12	0.7
Hypercalcemia	84	95.5	1	1.2	0	0.0	1682	96.8	164	9.8	11	0.7
Hypomagnesemia	83	94.3	10	12.0	0	0.0	1662	95.6	310	18.7	11	0.7
Hypophosphatemia	82	93.2	25	30.5	4	4.9	1632	93.9	384	23.5	77	4.7
Hematology												
Anemia	85	96.6	30	35.3	8	9.4	1651	95.0	741	44.9	83	5.0
Lymphocyte count decreased	83	94.3	41	49.4	16	19.3	1584	91.1	752	47.5	233	14.7
Neutrophil count decreased	84	95.5	5	6.0	1	1.2	1603	92.2	147	9.2	13	0.8
Platelet count decreased	85	96.6	23	27.1	1	1.2	1649	94.9	230	13.9	12	0.7

Source: Response to FDA IR, submitted to BLA 2/9/17

The Applicant conducted an analysis of laboratory changes of AST/ALT, total bilirubin, and alkaline phosphatase during the on-treatment period to identify potentially drug-induced liver injury (DILI). There were no cases of potential DILI in Study 003. In Study 001, 25 patients (1%), developed concurrent elevation of total bilirubin ≥ 2 × upper limit of normal (ULN) and ALT/AST ≥ 3 × ULN. The analysis for potential Hy's Law cases defined as laboratory findings of bilirubin ≥ 2 × ULN, ALT/AST ≥ 3 × ULN without concomitantly elevated alkaline phosphatase yielded 2 patients (0.1%). A causality analysis was conducted for each of the 25 patients, and other causal factors were identified in all patients including progressive disease, liver metastases, biliary obstruction, and viral hepatitis. See Table 30 copied from the 90-day Safety

Table 30. Laboratory abnormalities suggestive of potential drug-induced liver injury

Criteria	001 (N=1650) n (%)	003 (N=88) n(%)	Total (N=1738) n (%)
Concurrent (ALT or AST) ≥ 3 x ULN and TBILI ≥ 2 x ULN	25 (1.5)	0 (0.0)	25 (1.4)
Concurrent (ALT or AST) ≥ 3 x ULN and TBILI ≥ 2 x ULN and ALP > 2 x ULN	23 (1.4)	0 (0.0)	23 (1.3)
Concurrent (ALT or AST) ≥ 3 x ULN and TBILI ≥ 2 x ULN and ALP ≤ 2 x ULN or missing	2 (0.1)	0 (0.0)	2 (0.1)

Source: SUR Table 12.8.3.1
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, TBIL = total bilirubin, and ULN = upper limit of normal
Concurrent measurements are those occurring on the same date.

Source: 90-day Safety Update Report, page 154

Vital Signs

Vital signs were assessed and recorded at baseline and every two weeks in clinic on the day of the avelumab infusion. There were no clinically significant changes in vital signs in patients treated in Study 003 during avelumab infusions. Vital sign changes during an infusion reaction were captured as part of the infusion reaction AE. Observations made from evaluating the vital sign data for Study 003:

- Fever was not common during avelumab infusions. One patient experienced a temperature of 38.2^{o} C, and the greatest change from baseline temperature was an increase of 1.6^{o} C in one patient. The majority of patients had less than 1^{0}C change from baseline.
- Three patients experienced an increase in heart rate of more than 40 BPM on the day of avelumab dosing. The majority of patients remained within 20 BPM of baseline heart rate.
- Among patients with a baseline systolic blood pressure of < 140 mm Hg, 44% of patients experienced a maximal increase of $\leq$ 20 mm Hg and 10% experienced an increase of $\geq$ 40 mm Hg.
- Twenty-two patients had a systolic blood pressure of 160 mm Hg or higher at least once; this was an increase of 20 mm Hg or more from baseline for 12 of these patients.
- Twelve patients had a respiratory rate > 20 breaths per minute at least once during the study; the highest respiratory rate was 28 breaths per minute.

Electrocardiograms (ECGs)

During Study 003, 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.

Table 31. PCSA Criteria for interpretation of 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.

Source: Clinical Study Report, Study 003, page 86

One patient had an ECG-related SAE of grade 4 atrial flutter on Day 120 (Patient 2090009). The patient had discontinued avelumab one week prior to the event due to disease progression. The patient died from disease progression approximately three months after the diagnosis of atrial flutter. The patient had a normal ECG at study entry, but had other ECG abnormalities noted during treatment including sinus rhythm with first degree atrioventricular block, with moderate left axis deviation on Day 57 and intra-atrial conduction delay on Day 85. The patient discontinued study drug due to disease progression. The Investigator assessed the event of atrial flutter as unrelated to study treatment.

AEs that were categorized under the SOC of Cardiac Disorders occurred in 17% of patients (n=15). Cardiac AEs that occurred in more than one patient during Study 003 were tachycardia (n=3), sinus bradycardia (n=3), palpitations, atrial flutter and atrial fibrillation (n=2 each). All cardiac AEs were assessed as unrelated to avelumab treatment except the two AEs of palpitations. These were grade 1 in severity, and avelumab dosing continued without interruption.

Reviewer: These cardiac AEs were mostly unrelated to avelumab treatment and not atypical for the elderly patient population enrolled in Study 003.

QT

An assessment of effects on QT 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 (Studies 001, 002, and 003). 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. An on-treatment QTc > 500 msec was note in 33 patients (2.1%) treated at the 10 mg/kg dose. The ECGs were centrally reviewed for 12 of the patients;

one of the 12 patients with QTc > 500 msec was confirmed (QTc=513 msec) after central review. The patient had a baseline QTc of 510 msec and had received premedication with the antihistamine dexchlorpheniramine. The patient also had medical history significant for ischemic cardiomyopathy, atrioventricular block, pacemaker insertion, and hypertension. Seven ECGs for this patient were available for central read, and all showed a paced ventricular rhythm. According to the Applicant, this may have impacted the accuracy of the QTc measurement.

In Study 003, there were no AEs with the preferred term of "ECG QT prolonged" or "Torsade's de pointes" reported. Sixteen percent of patients (n=14) experienced a >450 msec and ≤ 480 msec QTc reading, 8% (n=7) had at least one > 480 msec and ≤ 500 msec QTc, and 3% (n=3) experienced at least one QTc of > 500 msec. In Study 001, a treatment-related AE of "electrocardiogram QT interval prolonged" was reported for seven patients (0.5%); however, six of the seven patients had QTc reads less than 500 msec. One patient had a QTc greater than 500 msec, but central review was not available for this ECG. The patient had medical history significant for alcohol abuse and use of loratadine. Treatment with avelumab was not interrupted for any of the seven patients.

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 for additional information regarding QT abnormalities and an assessment of the exposure-QTc analysis.

Immunogenicity

The blood samples for screening for human antihuman-antibody (HAHA) responses 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 was not validated.

In Study 003 three of 88 patients (3%) had at least one positive HAHA result. In Study 001, 53 of 1396 patients (4%) with an available 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.

Reviewer: The development of treatment-emergent ADA against avelumab did not appear to alter the pharmacokinetic profile or risk of IRRs. See Clinical Pharmacology (Section 6) Review for details.

7.4.5. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest
Adverse events of special interest (AESI) for avelumab are imARs and IRRs.

Immune-mediated adverse reactions (imARs)
The Applicant used the following two-level case definition for the analysis if imARs that occurred in patients treated with avelumab in Study 003 and Study 001 (definition adapted from Summary of Clinical Safety, page 101-102).

- Level 1: A MedDRA PT query 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 other immune-related adverse reactions).

  Level 2: AEs identified by the MedDRA PT queries were then medically reviewed using pre-defined case definitions for immune-related adverse reactions. All potential imARs were reviewed by 2 medically-qualified persons. If the 2 persons came to different assessments for a potential irAE, a third medically-qualified reviewer was asked to make the final assessment. The following criteria were used by the medical reviewers:

  - Onset: AE onset after first avelumab administration until up to 90 days after last dose (end of AE collection period in the studies)
  - Duration: AE does not spontaneously resolve (i.e., without corticosteroids / immunosuppressant treatment) within 7 days after onset
  - Immunosuppressive therapy: AE treated with corticosteroid or other immunosuppressant therapy. For endocrinopathies only: AE required hormone replacement and / or (corticosteroid or other immunosuppressive therapy)
  - Etiology: No other clear etiology or histopathology/biopsy consistent with immune-related event.

The analysis of imARs searched for reactions that occurred within 90 days from the last dose of avelumab given the potential for late-onset AEs with immunotherapeutic agents. The PTs included in the MedDRA query to identify potential imARs that would undergo medical review are listed in Table 32.

Table 32. Categories and preferred terms use to search for potential imARs

Category	SMQ/Preferred Terms
Pneumonitis	Interstitial lung disease, Pneumonitis, and Acute interstitial pneumonitis.
Colitis	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, Diarrhoea, Diarrhoea haemorrhagic, Diarrhoea neonatal, and Enterocolitis.
Hepatitis	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	HLT Thyroid hypofunction disorders: Autoimmune hypothyroidism, Hypothyroidic goiter, Hypothyroidism, Myxoedema, Primary hypothyroidism, Secondary hypothyroidism, Tertiary hypothyroidism, Thyroid atrophy, Transient hypothyroxinaemia of prematurity 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 HLT Acute and chronic thyroiditis: Autoimmune thyroiditis, Thyroiditis, Thyroiditis acute, Thyroiditis chronic, Thyroiditis fibrous chronic, Thyroiditis subacute
Adrenal Sufficiency	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	Type 1 Diabetes mellitus, Latent autoimmune diabetes in adults, and Diabetic ketoacidosis
Pituitary Dysfunction	Hypophysitis and Hypopituitarism
Nephritis and Renal Dysfunction	Autoimmune nephritis, Lupus nephritis, Nephritis, Nephritis haemorrhagic, Perinephritis, Tubulointerstitial nephritis, Tubulointerstitial nephritis and uveitis syndrome, Acute renal failure, Renal failure, and Renal impairment
Rash	Severe cutaneous adverse reactions (SMQ); narrow and Erythema, Pemphigoid, Pruritus, Pruritus allergic, Pruritus generalized, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash popular, Rash pruritic
Other Immune-related Adverse Events	Myocarditis, Uveitis, Iritis, Vitiligo, Psoriasis, Myositis, Rheumatoid arthritis, Systemic inflammatory response syndrome, Sarcoidosis, Autoimmune disorder, Encephalitis, Encephalopathy, Guillain-Barre Syndrome, Myasthenia gravis, Pancreatitis, Autoimmune pancreatitis, and Pancreatitis acute

Source: Refer to 5.3.5.3 SCS SAP Table 9
HLT = high level term, PT = preferred term, and SMQ= Standard MedDRA Query

Source: copied from SCS, page 100

In addition to an analysis of treatment-emergent imARs (i.e., up to 30 days following last dose of avelumab), an analysis of all events occurring up to 90 days following the last dose of

avelumab was conducted. The incidence did not substantially increase; three additional patients across both studies were identified with the longer follow-up period. Overall, 11.8% of patients had at least one imAR with the 90 day safety period as compared to 11.6% during the TEAE period. The Applicant also provided a side-by-side analysis of imARs that occurred in all patients treated in Study 001 (n=1452) and the subset of Study 001 patients who had at least three months of follow-up since starting treatment (n=1206). The incidence of imARs was similar in the two groups: 11% (n=165) in the total population and 13% (n=156) in the group with at least three months follow-up. There were no significant increases noted for any specific imAR or category of imARs in the group with at least three months of follow-up.

Table 33 lists all imARs by preferred term that occurred in Study 003 and in the pooled population up to 90 days following the most recent dose of avelumab. Rash and hypothyroidism were the only adverse imARs that occurred in more than 2% of patients in both Study 003 and the pooled data. Most imARs were Grade 1-2. The only imAR in Study 003 that was $\geq$ Grade 3 was a grade 3 elevation of transaminases, and this event led to discontinuation of avelumab (see narrative below for patient 1050002). This analysis confirms the results of the analysis performed by the Applicant, but the reviewer has grouped similar preferred terms differently as described in the table footnotes.

Table 33. Immune-mediated adverse reactions, primary analysis

Preferred Term	Study 003 N=88 n (%)		Pooled Analysis N=1540 n (%)	
	All grades	Grade 3-5	All grades	Grade 3-5
Rash[a]	4 (5)	0	63 (4)	2 (0.1)
Hypothyroidism	4 (5)	0	61 (4)	1 (0.1)
Diarrhea	2 (2)	0	13 (1)	1 (0.1)
Hyperthyroidism	2 (2)	0	9 (1)	0
Pruritus	1 (1)	0	26 (2)	0
Erythema	1 (1)	0	5 (0.3)	0
Transaminases increased	1 (1)	1 (1)	1 (0.1)	1 (0.1)
Tubulointerstitial nephritis	1 (1)	0	1 (0.1)	0
Pneumonitis	0	0	12 (1)	4 (0.3)
Alanine aminotransferase increased	0	0	9 (1)	2 (0.1)
Aspartate aminotransferase increased	0	0	9 (1)	3 (0.2)
Adrenal insufficiency[c]	0	0	7 (0.5)	1 (0.1)
Autoimmune hepatitis	0	0	4 (0.3)	4 (0.3)
Myositis	0	0	4 (0.3)	1 (0.1)
Thyroiditis[d]	0	0	4 (0.3)	0

Autoimmune disorder	0	0	2 (0.1)	2 (0.1)
Autoimmune hypothyroidism	0	0	2 (0.1)	0
Colitis	0	0	2 (0.1)	2 (0.1)
Hepatic failure[e]	0	0	2 (0.1)	2 (0.1)
Acute kidney injury	0	0	1 (0.1)	0
Dermatitis exfoliative	0	0	1 (0.1)	0
Encephalopathy	0	0	1 (0.1)	0
Erythema multiforme	0	0	1 (0.1)	0
Guillain-Barre syndrome	0	0	1 (0.1)	1 (0.1)
Hypopituitarism	0	0	1 (0.1)	0
Iritis	0	0	1 (0.1)	0
Pemphigoid	0	0	1 (0.1)	0
Psoriasis	0	0	1 (0.1)	0
Rheumatoid arthritis	0	0	1 (0.1)	0
Uveitis	0	0	1 (0.1)	0

Source: ADAE.xpt, ISS dataset, primary analysis (events up to 90 days following last study treatment included)
[a]Rash includes "rash", "rash maculopapular", "rash macular", "rash papular", "rash erythematous", rash pruritic", and "rash generalized"
[b]Pruritis includes "pruritis" and "pruritis generalized"
[c]Adrenal insufficiency includes "Adrenal insufficiency" and "Adrenocortical insufficiency acute"
[d]Thyroiditis includes "thyroiditis" and "autoimmune thyroiditis"
[e]Hepatic failure includes "hepatic failure and "acute hepatic failure"

The median time to onset of any imAR in Study 003 and in the pooled population in the primary analysis was nine weeks. Immune-mediated adverse reactions led to permanent discontinuation of avelumab in one patient (1%) in Study 003 and 18 patients (1%) in the pooled population of 1540 patients who received avelumab at a dose of 10 mg/kg every 2 weeks. Sixty-three percent of the patients in the pooled dataset who experienced an imAR received systemic corticosteroids for the reaction, and 28% received high dose corticosteroids (i.e., $\geq$ 40 mg prednisone equivalent). At the data cutoff for the primary analysis, approximately 60% of patients in the pooled population had ongoing events while 40% had experienced resolution of the imAR. Three patients had a fatal outcome from the imAR (one grade 5 pneumonitis and two grade 5 autoimmune hepatitis); see narrative summaries for patients *100070-001-2080029, 100070-001-1200014, 100070-001*-9080003 under "Deaths" in Section 7.4.4 of the review.

In the 90-day safety update report, the Applicant provided a side-by-side comparison of the incidence of imARs in Studies 001, 003 and the pooled population at the time of the later cutoff date for both studies (June 9, 2016). These data were verified for the purpose of informing the product label with incidence rates reflective of longer exposure to avelumab. The following summary table was copied from the 90-day safety update report.

Table 34. Immune-mediated adverse reactions, updated analysis, cutoff date June 9, 2016

	001 (N=1650)		003 (N=88)		Overall (N=1738)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Number of Subjects with at least one Event	235 (14.2)	12.59 ; 16.02	15 (17.0)	9.87 ; 26.55	250 (14.4)	12.77 ; 16.12
Hypothyroidism	87 (5.3)	4.24 ; 6.46	4 (4.5)	1.25 ; 11.23	91 (5.2)	4.24 ; 6.39
Rash	36 (2.2)	1.53 ; 3.01	5 (5.7)	1.87 ; 12.76	41 (2.4)	1.70 ; 3.19
Pruritus	26 (1.6)	1.03 ; 2.30	1 (1.1)	0.03 ; 6.17	27 (1.6)	1.03 ; 2.25
Diarrhoea	19 (1.2)	0.69 ; 1.79	2 (2.3)	0.28 ; 7.97	21 (1.2)	0.75 ; 1.84
Pneumonitis	21 (1.3)	0.79 ; 1.94	0 (0.0)	0.00 ; 4.11	21 (1.2)	0.75 ; 1.84
Rash maculo-papular	19 (1.2)	0.69 ; 1.79	1 (1.1)	0.03 ; 6.17	20 (1.2)	0.70 ; 1.77
Aspartate aminotransferase increased	9 (0.5)	0.25 ; 1.03	1 (1.1)	0.03 ; 6.17	10 (0.6)	0.28 ; 1.06
Alanine aminotransferase increased	8 (0.5)	0.21 ; 0.95	1 (1.1)	0.03 ; 6.17	9 (0.5)	0.24 ; 0.98
Adrenal insufficiency	8 (0.5)	0.21 ; 0.95	0 (0.0)	0.00 ; 4.11	8 (0.5)	0.20 ; 0.90
Hyperthyroidism	6 (0.4)	0.13 ; 0.79	1 (1.1)	0.03 ; 6.17	7 (0.4)	0.16 ; 0.83
Rash pruritic	7 (0.4)	0.17 ; 0.87	0 (0.0)	0.00 ; 4.11	7 (0.4)	0.16 ; 0.83
Rash generalised	6 (0.4)	0.13 ; 0.79	0 (0.0)	0.00 ; 4.11	6 (0.3)	0.13 ; 0.75
Autoimmune hepatitis	5 (0.3)	0.10 ; 0.71	0 (0.0)	0.00 ; 4.11	5 (0.3)	0.09 ; 0.67
Blood creatine phosphokinase increased	5 (0.3)	0.10 ; 0.71	0 (0.0)	0.00 ; 4.11	5 (0.3)	0.09 ; 0.67
Colitis	5 (0.3)	0.10 ; 0.71	0 (0.0)	0.00 ; 4.11	5 (0.3)	0.09 ; 0.67
Erythema	4 (0.2)	0.07 ; 0.62	1 (1.1)	0.03 ; 6.17	5 (0.3)	0.09 ; 0.67
Myositis	5 (0.3)	0.10 ; 0.71	0 (0.0)	0.00 ; 4.11	5 (0.3)	0.09 ; 0.67
Psoriasis	5 (0.3)	0.10 ; 0.71	0 (0.0)	0.00 ; 4.11	5 (0.3)	0.09 ; 0.67
Rash erythematous	4 (0.2)	0.07 ; 0.62	0 (0.0)	0.00 ; 4.11	4 (0.2)	0.06 ; 0.59
Rash macular	3 (0.2)	0.04 ; 0.53	0 (0.0)	0.00 ; 4.11	3 (0.2)	0.04 ; 0.50
Transaminases increased	2 (0.1)	0.01 ; 0.44	1 (1.1)	0.03 ; 6.17	3 (0.2)	0.04 ; 0.50
Autoimmune hypothyroidism	2 (0.1)	0.01 ; 0.44	0 (0.0)	0.00 ; 4.11	2 (0.1)	0.01 ; 0.42
Autoimmune thyroiditis	2 (0.1)	0.01 ; 0.44	0 (0.0)	0.00 ; 4.11	2 (0.1)	0.01 ; 0.42
Rash papular	2 (0.1)	0.01 ; 0.44	0 (0.0)	0.00 ; 4.11	2 (0.1)	0.01 ; 0.42
Rheumatoid arthritis	2 (0.1)	0.01 ; 0.44	0 (0.0)	0.00 ; 4.11	2 (0.1)	0.01 ; 0.42
Thyroiditis	2 (0.1)	0.01 ; 0.44	0 (0.0)	0.00 ; 4.11	2 (0.1)	0.01 ; 0.42
Acute hepatic failure	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Adrenocortical insufficiency acute	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Autoimmune colitis	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Dermatitis exfoliative	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Diabetes mellitus	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Enterocolitis	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Erythema multiforme	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Guillain-Barre syndrome	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Hepatic failure	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Hepatitis	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Hyperglycaemia	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Hypopituitarism	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Pemphigoid	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Pruritus generalised	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Systemic inflammatory response syndrome	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32
Tubulointerstitial nephritis	0 (0.0)	0.00 ; 0.22	1 (1.1)	0.03 ; 6.17	1 (0.1)	0.00 ; 0.32
Uveitis	1 (0.1)	0.00 ; 0.34	0 (0.0)	0.00 ; 4.11	1 (0.1)	0.00 ; 0.32

Source: Safety Update Report submitted December 23, 2016, page 90-91

At the time of the updated analysis, 17% (up from 16%) of patients in Study 003 and 14% (up

from 12%) of patients across the two trials experienced at least one imAR during avelumab treatment. The median time to onset of any imARs in Study 003 remained 9 weeks, and that for the pooled population was 12 weeks. Immune-mediated adverse reactions led to permanent discontinuation of avelumab in two patients (2%) in Study 003 and 2% (up from 1%) of patients across the pooled population. There were no additional fatal imARs with the longer follow-up period.

The Applicant presented analyses of imARs by disease subcategories based on the safety profile of avelumab and other antibodies targeting the PD-L1 protein and PD-1 receptor protein. This section of the review will focus on the cumulative safety results from the pooled population (N=1738) at the cutoff date for the 90-day safety update report to best characterize relatively common and rare imARs by disease category across the larger safety population with longer follow-up.

Immune-mediated pneumonitis

Twenty-one (1.2%) of 1738 patients in the pooled safety population experienced immune-mediated pneumonitis during avelumab treatment including one patient (0.1%) with Grade 5, one patient (0.1%) with Grade 4, and five patients (0.3%) with Grade 3 pneumonitis. The narrative summary for the patient who experienced a fatal pneumonitis (Patient *100070-001-2080029)* is found in Section 7.4.4 under "Deaths." There were no pneumonitis events in patients with metastatic MCC treated in Study 003.

The median time to onset for pneumonitis events was 2.6 months (range: 3 days to 11 months), and the median duration of pneumonitis was 5 weeks (range: 4 days to 3.8+ months).
All patients were treated with systemic corticosteroids. Eighty-one percent (17/21) of patients who experienced pneumonitis received high-dose corticosteroids (i.e., $\geq$ 40 mg prednisone equivalent). High-dose corticosteroids were administered for a median duration of eight days (range: 1 day to 10 weeks). Immune-mediated pneumonitis led to permanent discontinuation of avelumab in 3 of 21 patients. Immune-mediated pneumonitis had resolved in 57% (12/21) of patients at the time of data cut-off. Table 35 summarizes $\geq$ grade 3 pneumonitis events during avelumab treatment across the pooled database.

Table 35. Grade 3-5 pneumonitis reactions, pooled database, updated safety analysis

Patient ID	Grade	Description
100070-001-2080029	5	54 year old patient developed pneumonitis on Day 20 and died on Day 24 despite high-dose corticosteroid therapy. Patient had received one prior avelumab infusion. See narrative summary in Section 7.4.4.
100070-001-172-0001	4	64 year old patient experienced pneumonitis approximately seven weeks after start of avelumab therapy. He had received four infusions. Presented with dyspnea and was hypoxic 8 days after the last infusion. Chest CT scan and X-ray indicated drug-induced pneumonitis versus pneumonia. The patient had medical history significant for COPD and

Patient ID	Grade	Description
		asthma. Treated with broad spectrum antibiotics and high dose corticosteroids. Improved to grade 3. Discharged from the hospital, but the patient withdrew consent and there was no additional follow-up.
100070-001-102-0042	3	33 year old patient with metastatic breast cancer developed pneumonitis 5 days after second avelumab infusion. Presented with fever, dyspnea, and CT findings consistent with pneumonitis and no evidence of pulmonary embolism. Treated with broad spectrum antibiotics and high dose corticosteroids with a prolonged taper. Pneumonitis resolved. Patient developed progressive disease, was discontinued from treatment and was not rechallenged.
100070 001-118-0003	3	56 year old with adrenocortical carcinoma developed SAE of pneumonitis following the 11th infusion of avelumab. Presented with dyspnea, fever, wheezing. Chest x-ray and CT findings consistent with pneumonitis. Treated with broad spectrum antibiotics and high dose corticosteroids with a taper. Pneumonitis resolved. Patient developed progressive disease, was discontinued from treatment and was not rechallenged.
100070 001-135-0026	3	65 year old patient with history of pulmonary fibrosis, urothelial carcinoma and lung metastases developed pneumonitis following the first infusion of avelumab. CT scan showed ground-glass opacities and increased size of lung metastases. Treated with antibiotics and high dose corticosteroids and patient improved to Grade 1. Patient discontinued avelumab due to pneumonitis and died from progressive disease one month later.
100070-001-117-0033	3	80 year old with NSCLC developed SAE of pneumonitis two weeks after last infusion of avelumab. Patient had been treated for six months prior to the event. Patient received antibiotics and IV steroids and valganciclovir. Patient improved to Grade 2. Developed concurrent CMV pneumonia after pneumonitis improved. Discontinued avelumab due to pneumonitis.
100070-001-908-0008	3	46 year old with gastric cancer experienced pneumonitis after one month of study treatment and five days following the last dose of avelumab. The patient had been hospitalized for pain management at the time the pneumonitis symptoms (dyspnea) started. The patient had low grade fever and a CT scan showed multifocal ground glass opacities in both lungs. There was a mild pericardial effusion as well. Treated with antibiotics and high dose corticosteroids. The patient improved, but died due to disease progression approximately five weeks following the start of pneumonitis and 10.5 weeks following initiation of avelumab.

Immune-mediated hepatitis
Sixteen (0.9%) of 1738 patients in the pooled safety population experienced immune-mediated hepatitis during avelumab treatment including two patients (0.1%) with Grade 5, and 11 patients (0.6%) with Grade 3 hepatitis. The narrative summaries for the patients who experienced fatal hepatitis (Patients *100070-001-1200014 and 100070-001-9080003)* are found in Section 7.4.4 under "Deaths."

The median time to onset for hepatitis events was 3.3 months (range: 1 week to 15 months), and the median duration of hepatitis was 26 days (range: 1 day to 5 months). All patients were treated with systemic corticosteroids; 15 (94%) of the 16 patients received high-dose corticosteroids for a median duration of 14 days (range: 1 day to 2.5 months). Immune-mediated hepatitis led to permanent discontinuation of avelumab in nine (0.5%) patients. Immune-mediated hepatitis had resolved in 69% (11/16) of patients at the time of data cut-off.

The majority of the grade 3 hepatitis events were elevations of liver transaminases that were treated with corticosteroids. In Study 003, two patients developed grade 3 immune-mediated hepatitis manifested by elevated transaminases and required permanent discontinuation of avelumab.

> *Patient 1050002*: 69 year old male with medical history significant for grade 1 jaundice and metastatic pancreatic masses causing biliary obstruction and presence of biliary stent. The patient developed grade 2 elevation in transaminases on Day 14 and this increased to grade 3 transaminases increased on Day 18. Patient was treated with high-dose corticosteroids. Avelumab was discontinued after one prior infusion. See narrative summary under "Serious adverse events" in Section 7.4.4.
>
> *Patient 1330013*: 75 year old male who experienced ALT and GGT elevation 14 days after his 20th infusion of avelumab. He was treated with high dose oral prednisone followed by a taper for the events. Avelumab was permanently discontinued.

Immune-mediated colitis
Twenty-six (1.5%) of 1738 patients in the pooled safety population experienced immune-mediated colitis during avelumab treatment. There were no Grade 4 or 5 events. Seven patients (0.4%) in Study 001 had Grade 3 colitis. There were no Grade 3 events in Study 003. The median time to onset for colitis events was nine weeks (range: 2 days to 11 months), and the median duration of colitis was 26 days (range: 1 day to 14+ months). All patients were treated with systemic corticosteroids; 15 (58%) of the 26 patients received high-dose corticosteroids for a median duration of 19 days (range: 1 day to 2.5 months). Immune-mediated colitis led to permanent discontinuation of avelumab in eight (0.5%) patients. Immune-mediated colitis had resolved in 77% (20/26) of patients at the time of data cut-off.

In Study 003, two patients (2%) with metastatic MCC developed grade 2 immune-mediated colitis. Neither case was reported as an SAE.

> *Patient 1020004*: Patient with medical history significant for psoriasis developed **grade 1-2 diarrhea over seven weeks** following 3rd avelumab infusion. Patient was treated with high dose corticosteroids followed by a taper. Avelumab was temporarily discontinued and then restarted when patient recovered from the diarrhea. The patient died from disease progression 10 days later.
>
> *Patient 2040007*: Patient with medical history significant for chronic constipation. Developed **grade 2 diarrhea** after 5th avelumab infusion. The patient was treated with loperamide and steroids and recovered and was able to restart treatment.

Immune-mediated thyroid disorders

Ninety-eight (6%) of 1738 patients in the pooled safety population experienced immune-mediated thyroid disorders during avelumab treatment. There were no Grade 4 or 5 events. Three patients (0.2%) experienced grade 3 autoimmune thyroid disorders. Hypothyroidism occurred in 91 (5%) patients, hyperthyroidism in 7 (0.4%) patients, and thyroiditis in 4 (0.2%) patients treated with avelumab. The median time to onset for any immune-mediated thyroid disorder was three months (range: 2 weeks to 13 months). Immune-mediated thyroid disorders led to permanent discontinuation of avelumab in one (0.1%) patient.

Reviewer: The Applicant reported resolution in 22 (22%) of the 98 patients who experienced an immune-mediated thyroid disorder; however, this was based on the Investigator's assessment of clinical resolution of the adverse reaction. FDA requested that the Applicant provide an analysis of the safety data defining "resolution" of the adverse reaction as asymptomatic with no further need for corticosteroids, hormone replacement therapy or any ongoing medical management of the immune-mediated condition. Using this definition of "resolution," only eight (8%) of the 98 patients with thyroid disorders had complete resolution. Most patients, though deemed clinically "resolved," were still receiving levothyroxine, thiazimole or cortisone at the data cutoff for the analysis.

In Study 003, 6% (5/88) of patients with metastatic MCC developed immune-mediated thyroid disorders. These included four hypothyroidism events and one hyperthyroid event. All were Grade 1-2 in severity except one grade 3 hypothyroidism event.

> *Patient 3030001*: 74 year old patient who developed **serious grade 3 hypothyroidism** three weeks after the last avelumab infusion and approximately one year after starting study treatment. The patient had already discontinued avelumab six days prior to the diagnosis of hypothyroidism due to a grade 3 elevation in creatine kinase, also considered drug-related. The patient was treated with steroids and levothyroxine. The patient had improvement, but

was deemed "recovered with sequelae." Levothyroxine was discontinued approximately two months after the diagnosis of hypothyroidism.

Immune-mediated adrenal insufficiency

Eight (0.5%) of 1738 patients in the pooled safety population experienced immune-mediated adrenal insufficiency during avelumab treatment. There were no grade 4 or 5 events. One patient (0.1%) experienced grade 3 adrenal insufficiency. The median time to onset for any immune-mediated adrenal insufficiency was 2.6 months (range: 1 day to 9 months). All patients were treated with systemic corticosteroids; four (50%) of the eight patients received high-dose corticosteroids. Immune-mediated adrenal insufficiency led to permanent discontinuation of avelumab in one patient. The Investigator assessed one of the eight patients as "resolved;" however, re-analysis of the safety data such that patients were only considered resolved if they were clinically asymptomatic and had discontinued all steroid or hormone replacement therapy demonstrated that this patient was continuing to receive hormone replacement therapy at data cutoff.

Narratives were reviewed for the patient who experienced grade 3 adrenal insufficiency and for the patient who required permanent discontinuation of avelumab due to adrenal insufficiency.

Patient 100070-001-1320002: 68 year old male with metastatic gastric cancer who experienced **grade 3 primary adrenal insufficiency** 15 days after the most recent avelumab infusion and 7 months after starting the study. The patient presented with fatigue, anorexia, decreased appetite, nausea, lethargy, and low blood pressure. Labs showed low sodium and low cortisol. The patient had medical history significant for hyperthyroidism treated with methimazole and his labs showed evidence of conversion to hypothyroidism at the same time as the adrenal insufficiency with elevated TSH. The hypothyroidism was managed with levothyroxine. The patient received high dose hydrocortisone with an improvement in symptoms and normalization of cortisol. Avelumab was temporarily interrupted and restarted 14 days later without further symptoms. The patient continued to received avelumab with concomitant hydrocortisone replacement therapy.

Patient 100070-001-1220015: 61 year old female with NSCLC experienced **non-serious grade 2 adrenal insufficiency** 3 days after the fourth infusion of avelumab. The patients had had a normal baseline ACTH. The narrative reports that the patient had low ACTH levels on three occasions, four weeks apart while on treatment. The patient was treated with dexamethasone twice daily starting approximately eight weeks after the first low ACTH was documented. Avelumab was permanently discontinued due to the adrenal insufficiency. The event was ongoing at data cutoff.

Immune-mediated diabetes mellitus

Type 1 diabetes mellitus (DM) without an alternative etiology occurred in two (0.1%) of 1738 patients receiving avelumab. Both events were serious grade 3 reactions that led to permanent discontinuation of avelumab. Additionally, a patient with pre-existing Type II DM enrolled in Study 003 experienced an exacerbation of DM that was coded as Type I DM and required insulin treatment; however, the Investigator considered this even unrelated to avelumab and related to a longstanding history of diabetes.

Patient 100070-001-1640004: 69 year old patient was hospitalized with **serious Grade 3 diabetes with diabetic ketoacidosis**. Medical history was significant for intermittent hyperglycemia, hypertension and obesity. Her glucose was 102 mg/dL at baseline and 140 mg/dL on the day of her fifth avelumab infusion. A hyperglycemic episode with glucose of 691 mg/dL occurred two weeks after her seventh infusion. She was treated with metformin followed by glipizide and sitagliptin. One month later, she was hospitalized with dehydration, diarrhea, and diabetic ketoacidosis requiring insulin drip and admission to the ICU. Her condition improved with insulin, and she was discharged on long-acting and short-acting insulin preparations. The event led to permanent discontinuation of avelumab.

Patient 100070-001-1350005: 60 year old patient with mesothelioma experienced **serious Grade 3 hyperglycemia**, 6 days after the 41st infusion of avelumab. Her non-fasting glucose was 545 mg/dL and insulin was started at 10 units. Insulin therapy was started, and three weeks later, her blood glucose was 200 mg/dL, and remained at this elevated value after 12 weeks. Avelumab was permanently discontinued due to this event. The Investigator changed the event term to Type I DM after the primary data cutoff. Type I DM was ongoing at the data cutoff.

Patient 100070-003-9010001: 75 year old male with metastatic MCC and medical history of Type II DM experienced **grade 3 diabetes mellitus** approximately three months after start of avelumab. The patient presented with a glucose was 412 mg/dL, leading to hospitalization and requiring treatment with insulin. Avelumab was temporarily discontinued for the event and later restarted. The patient subsequently experienced grade 1 DM on Day 258 concurrent with the SAE of enterocolitis (see SAE narratives in Section 7.4.4) and required insulin therapy. The Investigator assessed the first presentation as related to the patient's underlying Type 2 DM and the later event as related to avelumab.

Immune-related Pituitary Dysfunction

One patient (0.1%) in the pooled safety population experienced an immune-mediated hypotituitarism (Patient 100070-001-122-0023). The patient was a 67 year old female with NSCLC who experienced **non-serious Grade 2 hypopituitarism** three weeks after her 35th avelumab infusion. At screening, she had a normal ACTH and TSH. At the time of diagnosis of hypopituitarism, her ACTH and TSH were low. She was treated with levothyroxine and prednisone (10 mg orally twice daily followed by a taper over the next 2 months. Avelumab had been discontinued for progressive disease prior to the diagnosis of hypopituitarism. The

outcome was recorded as ongoing at the end of treatment visit. The Investigator assessed the hypopituitarism as related to avelumab.

Immune-mediated nephritis

One patient in Study 003 experienced a serious immune-mediated nephritis that led to permanent discontinuation of avelumab. Another patient in Study 001 experienced a non-serious grade 1 acute kidney injury that was considered by the Investigator and Applicant as unrelated to avelumab treatment. This case is also summarized as the Reviewer does not believe treatment with avelumab can be completely excluded from the attribution analysis.

Patient 100070-003-9560001: 71 year old female experienced a serious **immune-mediated tubulointerstitial nephritis** that occurred after her fourth infusion of avelumab. The event required hospitalization. The patient had a normal baseline creatinine at screening. The patient was admitted for elevated creatinine and decreased filtration rate. Renal ultrasound showed no masses or hydronephrosis. An ultrasound guided renal biopsy revealed diffuse changes of acute tubular injury in association with a diffuse interstitial inflammatory cell infiltrate associated with tubulitis. The infiltrate comprised predominantly lymphocytes but also included lesser numbers of plasma cells and eosinophils. Tubular atrophy and interstitial fibrosis involved less than 5% of the sampled cortex. The patient was treated with high dose corticosteroids followed by a taper over the following two months. The patient recovered. Avelumab was permanently discontinued.

Patient 100070-001-1860012: 67 year old male patient with urothelial carcinoma experienced **non-serious grade 1 acute kidney injury** concurrently with the events serious grade 3 AST increased, serious grade 4 blood creatine kinase increased, non-serious grade 1 ALT increased, and non-serious grade 2 hypothyroidism. These events occurred 13 days following the 12th infusion of avelumab. The patient was hospitalized for management of AST elevation and hypothyroidism per the narrative. The patient had a creatinine of 141.47 µmol/L (converts to 1.6 mg/dL) and a creatinine clearance of 61.56 ml/min/1.73m^2 while in the hospital. No biopsy was performed. The patient was treated with high-dose steroids for the AST increased and blood creatine phosphokinase increased. The patient improved and was discharged in three days. The administration of avelumab was permanently discontinued due to AST increased. The Investigator assessed the event of acute kidney injury as not related to avelumab, and it was ongoing at data cutoff.

Reviewer: While this patient is reported to have had chronic renal insufficiency and potentially an acute on chronic kidney injury while ill with autoimmune hepatitis and hypothyroidism, avelumab cannot be ruled out as a causal factor in this patient's condition. The patient received corticosteroids for possible autoimmune hepatitis and creatine kinase elevation which may have treated an immune-mediated renal injury as well.

Immune-mediated skin adverse reactions

Ninety (5%) of 1738 patients in the pooled safety population experienced immune-mediated rash during avelumab treatment. In Study 003, seven patients (5%) had at least one immune-mediated skin rash during avelumab treatment. Across the two trials, there were no Grade 4 or 5 events. There were no reported cases of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) in the pooled population. One patient (0.1%) in Study 001 had Grade 3 rash, and one patient experienced a SAE of "rash generalized." A third patient had a grade 3 rash that was recoded to grade 2 at the time of the safety update. These patients are described below. PTs for the rash subcategory of imARs that were reported in more than 0.5% of patients included rash (n=35; 2.1%), pruritus (n=25; 1.5%), and rash maculo-papular (n=19; 1.2%). The median time to onset for any grade immune-mediated skin reactions was nine weeks (range: 2 days to 2+ years). Twenty-six patients were treated with systemic corticosteroids; 15 (60%) of the 26 patients received high-dose corticosteroids for a median duration of 6 days (range: 1 to 18 days). Immune-mediated rash led to permanent discontinuation of avelumab in three (0.2%) patients.

Patient 100070-001-5020006: 63 year old female who experienced **grade 3 rash** eight days after the 4th infusion of avelumab. The rash, described as macular, reddish, and epidermal, was pruritic and covered approximately 50% of her body surface on the thorax, back, abdomen, face, proximal thighs, and upper arms. She had no other symptoms. No biopsy was performed. The patient was treated with intravenous high-dose corticosteroids followed by a prolonged taper. The rash improved to grade 1 within three days of starting steroids. Avelumab was temporarily discontinued and restarted two weeks later.

Patient 100070-001-1020037: 72 year old female patient experienced a **grade 3 pruritic rash, a grade 2 erythematous rash and a grade 1 rash** starting following the third infusion of avelumab and following the ninth infusion. The patient was treated both times with oral methylprednisolone and topical desonide, fluocinonide and desoximetasone and recovered from the rash. Avelumab was temporarily held and restarted with the second event. Note that the grade 3 serious generalized rash was downgraded to grade 2 event in the 90 day safety update report.

Patient 100070-001-1020037: The patient was a 77 year old male with NSCLC who had **serious, grade 2 "rash generalized" and non-serious grade 1 pruritus** on Day 84, seven days after the most recent avelumab infusion. The patient was treated with high dose oral prednisone and topical diphenhydramine hydrochloride and triamcinolone. Avelumab was withheld temporarily. The patient recovered and was able to restart treatment.

Three additional patients experienced a rash that led to permanent discontinuation of avelumab. The rashes were considered nonserious grade 2 rashes by the Investigator. These included bullous phemphigoid, rash, and maculopapular rash. The patient with the pemphigoid rash experienced concurrent immune-mediated hypothyroidism.

Other immune-mediated adverse reactions

Other preferred terms that that fell under the prespecified MedDRA search query (Table 32) for imARs and were reported at least once across the pooled population included myositis, blood creatine kinase increased, myocarditis, uveitis, iritis, vitiligo, psoriasis, rheumatoid arthritis, systemic inflammatory response syndrome (SIRS), sarcoidosis, autoimmune disorder, encephalopathy, Guillain-Barre syndrome, pancreatitis, and acute pancreatitis. After the second level medical review, 19 patients were identified as having at least one of these other imARs during avelumab treatment. Table 36 summarizes these patients.

No immune-mediated vitiligo, iritis, sarcoidosis, encephalitis, encephalopathy, myasthenia gravis, or pancreatitis was identified after the second-level medical review across the pooled population. One patient in Study 001 experienced an event reported as myopericarditis which was not considered immune-mediated and is not included in the summary table. This event is described in the following section of the review (Immune-mediated myocarditis).

Table 36. Other ImARs, 90-day safety update

Preferred Term	Any grade N=1738 n (%)	Grade 3-4 N=1738 N (%)
Blood creatine phosphokinase increased	5 (0.3)	3 (0.2)
Myositis	5 (0.3)	2 (0.1)
Psoriasis	5 (0.3)	1 (0.1)
Rheumatoid arthritis	2 (0.1)	0
Guillain-Barre syndrome	1 (0.1)	1 (0.1)
Systemic inflammatory response syndrome	1 (0.1)	1 (0.1)
Uveitis	1 (0.1)	0

Source: ADAE.xpt, 90-day SUR

Myositis

Nine patients (0.5%) experienced either elevated creatine kinase or myositis considered to be immune-mediated after medical review. Five of these patients experienced grade 3-4 elevations in creatine kinase, four patients had SAEs and five of the nine patients required permanent discontinuation of avelumab. Four patients had either grade 3 or 4, or serious, concurrent events of myositis. One patient with a serious grade 4 myositis was hospitalized for severe muscle weakness and needed intubation and remained ventilator dependent at data cutoff. This patient also had thymoma. All nine patients were treated with corticosteroids, and 7 (78%) received high dose corticosteroids. Two-thirds (6/9) of the patients had resolution of the immune-mediated myositis and/or creatine kinase elevation.

Twenty-one additional patients (not included in the table above) experienced elevations of creatine kinase during avelumab treatment; 12 were considered related to avelumab by

Investigators, and four of the related events were Grade 3 elevations. These cases did not meet criteria for designation as an immune-mediated event during the second level medical review.

Psoriasis

Five patients experienced immune-mediated psoriasis during avelumab treatment. Four of the patients had medical history of psoriasis. Of the five events, four were grade 2 and nonserious, and one was grade 3 and serious (described below).

> *Patient 100070-001-8070010:* 61 year old male with medical history of for the most part asymptomatic psoriasis and chronic fungal infections of the fingers and toes. Seven days after the third avelumab infusion, a **grade 3 and serious psoriatic rash** occurred on his back and buttocks. Skin biopsies revealed "diffuse parakeratosis with loss of granular layer and collections of neutrophils within the parakeratin. Psoriasiform epidermal hyperplasia with mild pallor to the keratinocytes in the superficial layers was noted. The epidermis overlying the dermal papillae showed spongiosis and some lymphocyte exocytosis. There was moderate to marked oedema of the papillary dermis and a mild perivascular sprinkling of lymphocytes was observed in the dermis. Immunoglobulin G (IgG), IgM, IgA and complement component 3 (C3) were not detected (direct immunofluorescence)." The patient also had palmar plantar erythodysesthesia with severe desquamation of the sole heels of the feet at this time. The patient was treated topically with calcipotriol/ betamethasone dipropionate followed by clobetasone butyrate/calcium oxytetracycline/ nystatin and calcipotriol. Avelumab was temporarily interrupted and restarted, but he only received one additional dose due to progression of disease. The skin adverse reaction was considered ongoing at data cutoff.

Guillain-Barre syndrome

One patient (0.1%) in the pooled analysis experienced Guillain-Barre Syndrome. This 81 year old male presented with leg weakness. An electromyography (EMG) on that day revealed that the subject had no motor conduction block but severe peripheral motor polyneuropathy. It was thought that this was due to prior chemotherapy with cisplatin and paclitaxel and poorly controlled diabetes. The patient was hospitalized, and two weeks later, a repeat EMG demonstrated a conduction block compatible with Guillain-Barre syndrome. The patient was treated with high dose corticosteroids and immunoglobulin. There was an improvement to grade 2 severity, but the event was ongoing at data cutoff. Avelumab was permanently discontinued due to Guillain-Barre syndrome.

Other imARs included in the 90-day safety update were one case of grade 2 uveitis requiring permanent discontinuation, two cases of grade 1-2 rheumatoid arthritis (one required permanent discontinuation) and one serious grade 3 systemic inflammatory response syndrome (SIRS). This patient presented four days after the fourth avelumab dose with hypotension, hypoxia, and was confused. Blood cultures were negative. The patient was treated with high dose corticosteroids and broad spectrum antibiotics and improved. The SIRS

was categorized as immune-mediated because it was treated with corticosteroids in the absence of other clear alternative etiologies.

Reviewer: Overall, the Applicant's case definition for imARs included adequate search terms, and the second level medical review algorithm was reasonable for identifying events that are truly immune-mediated and related to avelumab. The incidence of specific categories of imARs may appear to be less when compared to other available drugs in the class due to utilization of the second level medical review of specific criteria consistent with imARs following the initial MedDRA query. The individual adverse reactions described in this section of the review are probably related to avelumab treatment and were most often assessed as related by Investigators. None of the events would be considered unexpected for this class of drugs.

Immune-mediated myocarditis
Immune-mediated myocarditis was an identified risk in the avelumab development program based on a fatal case of myocarditis that occurred in a trial evaluating the combination of avelumab and axitinib in patients with renal cell carcinoma (Patient 100070-002-1012105*)*. This patient was not included in the pooled safety population supporting the present application; however, the Applicant provided the narratives for this event and three additional events identified across the Adverse Reaction Information System global (ARISg) safety database up to the data cutoff date of September 30, 2016; this database is comprised of approximately 2600 patients who have received a range of doses of avelumab.

Patient 100070-002-1012105: 69 year old male with renal cell carcinoma who was receiving avelumab plus axitinib in a clinical trial. Five days after the second infusion of avelumab 10 mg/kg, the patient complained of chest pain and nausea. The patient's wife stated that the home blood pressure machine would not provide a reading. While she was on the telephone with the on-call service, the patient collapsed. Cardiopulmonary resuscitation was initiated, but the patient died. Corticosteroids were not given for the event. An autopsy was performed, and the findings reported were "…severe infiltration by lymphocytes and macrophages with significant myocardial muscle atrophy and destruction. This was seen throughout the myocardium and not confined to one area. Histology revealed heavy infiltration of histiocytes and lymphocytes which were mainly T cells as confirmed by CD3 and CD5. An equally large number of histiocytes as demonstrated by CD68 were also seen."

Reviewer: Agree with Investigator assessment of an avelumab-related myocarditis. The autopsy findings support an immune-mediated etiology for this patient's condition.

Patient 100070-004-3530043: 55 year old male with NSCLC and medical history significant for coronary artery disease and cardiac bypass surgery. Prior to randomization, this patient had an event reported as grade 3 "inflammation induced by cancer." The ECG showed a suspect lateral infarction and the CK And CK-MB were both elevated. The troponins were normal. The patient started treatment 10 days later. Two weeks after the first dose of avelumab, the patient presented with dyspnea, tachycardia and fatigue. His liver was enlarged and stiff and his general condition was described as "moderate to poor." An echocardiogram showed acute

heart failure with hypokinesia and an ejection fraction of 30 percent, left ventricular systolic function disorder, and small, compressed right cavities. The patient had elevated liver enzymes and bilirubin. Imaging revealed progressive disease in the liver. His CK and CK-MB and troponin were elevated. High dose corticosteroids were administered and these levels improved; however, the patient continued to worsen. The patient was also noted to have a fungal infection in the lungs. The patient experienced cardiac and respiratory failure and could not be resuscitated.

Reviewer: Avelumab cannot be excluded as a potential causal factor for this patient's cardiac and other organ problems; however, there are multiple confounding factors including the patient's cardiac history, surgical history, concurrent extensive progressive disease and infection that could lead to a lower threshold for cardiac failure. The CK and CK-MB levels improved with corticosteroids, but the patient did not clinically improve and no biopsy was obtained to provide more definitive evidence of an immune-mediated etiology.

Patient *100070*-001-1010026: 46 year old female with malignant thymoma experienced a grade 3 serious "autoimmune disorder" three days after the second infusion of avelumab 20 mg/kg. She had medical history significant for non-cardiac chest pain and anxiety. Prior to receiving avelumab in Study 001, the patient had undergone a left thoracotomy, right radical pleurectomy, mediastinal lymph node dissection, resection of mediastinal mass, diaphragmatic resection and pericardial resection in 2011. She also had received radiation therapy to the superior left mediastinum in 2011. On the day of her second infusion, the patient complained of epigastric band like pain, muscle ache in arms and thighs, and a bruised feeling. She also reported dyspnea after climbing two flights of stairs and positional dizziness. Her CK was elevated but CK isoenzymes were normal. The Investigator stopped the second infusion five minutes after it started. Three days later, the CK-MB and troponin I were elevated. ECG showed a right bundle branch block. CT angiogram of the chest revealed no filling defects in the pulmonary arteries. An echocardiogram showed no wall-motion abnormality and a normal ejection fraction of 60-65%. She was started on fluids and furosemide for potential rhabdomyolysis. The patient also started high dose corticosteroid treatment with a prolonged taper over the following two months. The patient reported decreased dyspnea. One week later, she complained of dyspnea and was re-admitted to the hospital. Her liver enzymes were normal; her CK was normal. The troponin had improved to 0.59, but was still elevated. The electromyography (EMG) did not demonstrate a problem with the neuromuscular junction. The cardiology diagnosis was right bundle branch block and troponin leak related to myocarditis, which was most likely of the same etiology of diffuse myositis. The CK and troponin were within normal limits two days later. A subsequent ECG the following month revealed sinus rhythm and right bundle branch block and the repeat echocardiogram done on an unknown date in Jan 2014 showed no valve dysfunction and efficiency as 65%. The patient recovered from the event two weeks later.

Reviewer: Immune-mediated myocarditis cannot be ruled out in this patient who had evidence of CK and CK cardiac isoenzyme elevation and was complaining of chest pain and

had an arrhythmia. The patient was also treated with corticosteroids. Still, the patient had an echocardiogram at the time of the lab abnormalities that did not reveal any muscle wall abnormalities or low ejection fraction. Additionally, the patient had history of thymoma and multiple local surgical procedures at the mediastinum and radiation to the mediastinum which could contribute to her longstanding history of intermittent non-cardiac chest pain. The cardiology assessment of myocarditis as part of a larger diffuse myositis is not unreasonable. There are multiple confounding factors in this case and no biopsy to provide further support for the diagnosis of immune-mediated myocarditis. Although this patient was enrolled in Study 001, this event was not captured in the pooled safety database supporting the BLA because the patient was treated with 20 mg/kg avelumab.

Patient 100070-001-1710009: 63 year old male with head and neck cancer metastatic to anterior mediastinum. The patient presented with chest pain and trouble breathing 10 days after the 15th infusion of avelumab and was diagnosed with grade 2 myopericarditis and bilateral pleural effusion. CK-MB and troponin were elevated. High dose corticosteroids were administered in addition to nitroglycerin and narcotics. Pericardium and myocardium biopsies showed minimal scattered chronic inflammation. Investigator assessed cause of carditis as malignant chylothorax and not avelumab-related. Avelumab had been discontinued at the time of the last infusion due to progressive disease.

Reviewer: Agree with Investigator's assessment of chylothorax due to malignant effusions as the underlying causal factor. The lack of immune cell infiltrate on biopsies of the myocardium the day following the symptoms makes an immune-mediated etiology less likely.

Reviewer: These four case reports of myocarditis represent an incidence of 0.15% across the 2600 patient database. While two of the cases point toward a potential immune-mediated etiology for the cardiac adverse reactions, the other two events seem less likely related to study treatment, although avelumab cannot be completely excluded from the attribution analysis in any of the cases. Avelumab and other drugs in the same class have the potential for causing autoimmune adverse events in any organ system, including the heart. It is important to adequately inform patients and providers of these risks in the product label and continue to follow with routine pharmacovigilance in the postmarketing phase of development. At this time, the reviewer does not believe the cardiac risks outweigh the treatment benefits of avelumab in patients with metastatic MCC.

Infusion-related reactions (IRRs)

The Applicant initially used the following case definition for identifying possible IRRs: An event was considered an IRR if the event had the preferred term of infusion related reaction, drug hypersensitivity, hypersensitivity, Type 1 hypersensitivity, or anaphylactic reaction, and the onset of the event was on the same day or the next day following avelumab administration.

FDA requested that the Applicant propose a broader search for IRRs for the Integrated Summary of Safety that would consider the 24 hour time period following the infusion and include preferred terms to capture AEs commonly observed as infusion reactions, including but not limited to fever, rigors, flushing, cutaneous reactions, hypotension, dyspnea, wheezing, back pain, and abdominal pain. The Applicant modified the case definition to include nine additional symptoms with an onset date at the day of infusion and a recovery within 2 days.

In the updated IRR analysis, the onset of the event in relation to avelumab administration and time to resolution was considered if the following criteria were met:

(1) 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 on the day of avelumab infusion (during or after the infusion) or the day after the avelumab infusion (irrespective of resolution date; 'IRR diagnoses')

(2) All AEs identified by the MedDRA PT query describing the most commonly observed signs and symptoms of infusion-related reactions in association with avelumab therapy (i.e., pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria) were considered potential IRRs when onset was on the day of avelumab infusion (during or after infusion) and the event resolved with an end date within 2 days after onset ('IRR symptoms').

Premedication

Premedication with an antihistamine and acetaminophen was required according to the Study 003 protocol. Premedication was optional for the first part of Study 001 until the protocol was amended to mandate premedication on July 30, 2014 such that 1527 of the 1650 patients in Study 001 at the cutoff date for the updated safety analysis used premedication prior to their first infusion of avelumab. The frequency of any grade IRRs during the first infusion in patients treated in Study 001 was similar in patients who received premedication (20.2%) and those who did not receive premedication (19.5%). The severity of IRRs with avelumab was less in patients who received premedication with an incidence of grade 3-4 IRRs of 0.3% as compared to 1.6% in patients who did not receive premedication.

Incidence of IRRs

In Study 003, 22% of patients had at least one IRR, and in Study 001, the IRR incidence was 26% at the cutoff for the 90 day safety update. Table 37 summarizes the incidence of IRRs in Study 003 and in the pooled population. The most common events in both studies were infusion related reaction, chills, and pyrexia. There were no fatal events. There were no grade 3 or 4 IRRs in Study 003, and most IRRs were low grade in both trials. Three patients in Study 001 experienced a grade 4 IRR (two events were prior to the incorporation of the requirement for premedication into the protocol). Twelve patients experienced an IRR of $\geq$ grade 3 severity; all

of the twelve patients had resolution of the event. Twenty patients (0.1%) across the pooled safety population experienced a serious IRR.

Table 37. Summary of IRRs in Study 003 and pooled analysis, safety update

	Study 003 N=88 n (%)		Pooled analysis N=1738 n (%)	
Preferred Term	**Any Event**	**Grade ≥ 3**	**Any Event**	**Grade ≥ 3**
Any IRR	19 (22)	0	439 (25)	12 (1)
Infusion related reaction	13 (15)	0	296 (17)	10 (1)
Chills	2 (2)	0	94 (5)	0
Pyrexia	2 (2)	0	62 (4)	0
Back pain	1 (1)	0	9 (1)	0
Dyspnea	0	0	6 (0.3)	1 (0.1)
Hypotension	1 (1)	0	6 (0.3)	0
Drug hypersensitivity	1 (1)	0	5 (0.3)	0
Flushing	0	0	5 (0.3)	0
Abdominal pain	0	0	4 (0.2)	0
Hypersensitivity	1 (1)	0	0 (0.2)	0
Anaphylactic reaction	0	0	0 (0.1)	1
Type I hypersensitivity	0	0	0 (0.1)	0

Source: ADAE.xpt, 90-day SUR

Grade 4 IRRs
Three patients in Study 001 experienced serious grade 4 IRRs requiring permanent discontinuation of avelumab.

Patient 100070-001-1510001: 62 year old male experienced shortness of breath, facial flushing, hypertension, and rigidity approximately 8 minutes after beginning the second infusion of avelumab. The infusion was stopped immediately. He had a heart rate of 70 bpm and blood pressure of 183/80 mm Hg. He was placed on a non-rebreather mask and a cardiac monitor; diphenhydramine and dexamethasone were administered. He recovered quickly. Treatment with avelumab was discontinued. The patient had not received premedication.

Patient 100070-001-1070004: 67 year old male experienced shortness of breath, wheezing with oxygen desaturations, chills, shaking, and pain after receiving his first dose of avelumab. Maximum blood pressure was 154/101 and lowest blood pressure was 107/49. He was treated with oxygen and epinephrine and recovered 30 minutes after avelumab was stopped. Treatment with avelumab was discontinued. The patient had not received premedication.

Patient 100070-001-1150021: 53 year old male experienced wheezing, tachypnia, and rigors 38 minutes into the first infusion of avelumab. The infusion was stopped immediately, and he was given meperidine followed by dexamethasone. An oxygen saturation was not gotten at the time, but he was given oxygen by nasal cannula, albuterol and intramuscular epinephrine. Diphenhydramine was administered as well. At approximately 45 minutes into the reaction, he "began to stabilize" according to the narrative. He remained under observation for another 2 hours and had fully recovered to baseline by the time of discharge. Avelumab was permanently discontinued for this IRR. The patient had been premedicated with diphenhydramine and acetaminophen.

Reviewer: IRRs are expected adverse reactions with monoclonal antibodies. The frequency of IRRs with avelumab is higher than that for other drugs in class. This increased incidence may be related to avelumab-induced ADCC. It appears that premedication did not lower the overall incidence of IRRs but may have lessened the severity of the reactions. While serious, the above grade 4 events (0.6% of the reported IRRs across the pooled database) do not change the overall benefit: risk profile of avelumab for patients with metastatic MCC. Oncologist prescribers will have experience in managing IRRs that are expected events with other FDA-approved immune-modulating agents. Monitoring and management guidelines for IRRs will be addressed in product labeling.

Timing and management of IRRs
The majority of first occurrence IRRs were during or following the first infusion. Less than 1% of patients in the pooled population experienced their first infusion reaction at the fourth or later infusions. In Study 003, all first occurrences of IRRs were related to the first (n=16) or second (n=3) dose of avelumab. In Study 001, all IRRs ≥ grade 3 (n=12) occurred with the first (n=7) or second infusion (n=5).

In Study 003, there were no permanent discontinuations of avelumab for IRRs. In Study 001, 35 patients (2%) required permanent discontinuation of avelumab for an IRR. Across both studies, 9% of patients (n=152) required at least one interruption of the infusion due to an IRR and 7% (n=124) required at least one infusion rate reduction due to an IRR.

In Study 003, 18% (n=16) of patients had only one IRR during the trial and 2% (n=2) had 2 IRRs. One patient (1%) experienced five IRRS over the course of the study. This patient presented with grade 2 back pain during 5 separate infusions of avelumab and required temporary interruption of the infusion each time. In Study 001, 22% of patients had only one IRR, 3% had two IRRs, 1% had 3 IRRs, and 0.1% had more than 3 IRRs during the trial.

The majority of IRRs across both studies were successfully managed with an analgesic (most commonly acetaminophen) and an antihistamine such as diphenhydramine. Approximately 25% of patients were treated with systemic corticosteroids. Ten percent of patients required anti-nausea medications and 4% of patients received albuterol or a similar product for managing

respiratory symptoms of obstructive airway disease. Table 38 summarizes the common medications that were administered to patients for IRRs with avelumab treatment.

Table 38. Medications administered for IRRs, pooled analysis

Drug Class	Patients with any IRR N=439 n (%)
Analgesics (e.g., acetaminophen)	427 (97)
Antihistamines for systemic use	402 (92)
Antipruritics, including antihistamines, anesthetics	376 (86)
Psycholeptics (e.g., diphenhydramine, promethazine)	350 (80)
Corticosteroids, dermatological preparations	109 (25)
Corticosteroids for systemic use	109 (25)
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	56 (13)
Antiemetics and antinauseants	42 (10)
Drugs for obstructive airway diseases (e.g., albuterol)	17 (4)

Source: ADAESI.xpt and CM.xpt, 90-day safety update

7.4.6. Safety Analyses by Demographic Subgroups

Age: Twenty-five percent of patients in Study 003 were less than 65 years old, 40% were between 65 and 75 years of age, 32% were between 75 and 85, and 3% (n=3) were 85 or older. Almost all specific TEAEs were similar across age groups except vomiting which occurred at a 5% increased incidence in patients over 65 years of age.

Table 39. AEs by age subgroups, Study 003, primary analysis

Age Subgroups	Any grade event n (%)	Grade 3-5 events n (%)
< 65 (N=22)	22 (100)	14 (64)
≥ 65 - < 75 (N=35)	35 (100)	24 (69)
≥ 75 (N=31)	29 (94)	16 (52)

Source: ADAE.xpt, primary analysis

Gender: There were 65 male and 23 female patients in Study 003. There were no obvious differences in AE incidence between male and female patients. Almost all patients had at least one any grade AE and 62% of males and 61% of females had at least one ≥ grade 3 AE. Immune-mediated adverse reactions occurred in 15% of males and 17% of females. IRRs occurred in 23% of males and 17% of females.

Reviewer: Age and gender comparisons should be considered exploratory and limited by the small number of patients.

Race: No conclusions can be drawn with regard to the effect of race on safety as there were a limited number of non-White patients (N=7) in Study 003.

7.4.7. Specific Safety Studies/Clinical Trials

None.

7.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct carcinogenicity studies.

Pediatrics and Assessment of Effects on Growth

Avelumab was granted orphan designation for the MCC indication and is therefore exempt from the requirements of the Pediatric Research Equities Act (PREA) for this indication. Avelumab has not been studied in the pediatric population. See section 9 of this review for a discussion on extrapolating the indication to pediatric patients 12 years and older.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No studies have been conducted to evaluate the abuse potential with avelumab. There is no evidence that suggests a risk for dependence on avelumab. No cases of withdrawal symptoms were reported during human clinical trials.

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable. Avelumab is a new molecular entity with no prior approval history.

Expectations on Safety in the Postmarket Setting

Avelumab is being approved under the provisions in 21 CFR Part 601 Subpart E (accelerated approval); therefore, a confirmatory trial(s) is required to verify and describe the clinical benefit of avelumab in patients with metastatic Merkel cell carcinoma.

Clinical PMRs:

- Conduct and submit the results of a multicenter clinical trial confirming the clinical benefit of avelumab in patients with metastatic Merkel cell carcinoma (MCC) who have not received prior systemic therapies for metastatic MCC. The trial will enroll at least 100 patients to be followed for a minimum of 12 months to establish the objective response rate and characterize the durability of response. Overall survival will be followed until at least 70% of patients have died to characterize effects on survival. An analysis of overall survival compared to historical control data will be provided.
- Conduct a trial in a sufficient number of pediatric patients age(s) 12-18 to adequately characterize baseline risk factors, safety outcomes, and clinical responses following exposure to avelumab.

7.4.10. Integrated Assessment of Safety

The evaluation of the safety of avelumab in patients with metastatic MCC was primarily based on Study 003, an open-label, multicenter, single arm trial in 88 patients with metastatic MCC who had progressed on or following at least one prior chemotherapy regimen. A pooled population of patients from Study 003 and patients from Study 001 (N=1540 in the primary analysis and N=1738 in 90-day safety update analysis) with various advanced solid tumors 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 was considered adequate to characterize the safety profile of avelumab.

During Study 003, there were no avelumab-related fatal AEs. Cumulative safety data up until the data cutoff date for the 90 day safety update demonstrated that avelumab-related SAEs occurred in 7% (n=6) of patients, AEs leading to permanent discontinuation occurred in 6% (n=5), and treatment-related Grade 3-4 AEs occurred in 8% (n=7) of patients. The most common AEs (more than 15% of patients) in Study 003 included fatigue, diarrhea, nausea, decreased appetite, peripheral edema, constipation, cough, arthralgia, anemia, extremity pain, and IRR. 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, as well as the risk of fatal imARs and IRRs. ImARs occurred in 17% (n=15) of patients in Study 003 and in 14% of patients in the pooled database. There were no fatal imARs during Study 003, three fatal imARs were observed in Study 001 (Grade 5 pneumonitis in one patient and Grade 5 autoimmune hepatitis in two patients), and an

additional fatal, immune-mediated myocarditis was identified in the ARIS database. ImARs experienced by patients in Study 003 were rash, thyroid disorders, diarrhea, pruritis, erythema, elevated transaminases and nephritis. The majority of patients with imARs other than endocrinopathies required high-dose systemic corticosteroid administration. Two percent of patients in Study 003 required permanent discontinuation of avelumab for imARs. 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 slightly more common during Study 001 as compared to Study 003 (26% versus 22%) and of greater severity; this is partly due to the mandatory premedication included in the protocol for Study 003 that was not initially part of Study 001. IRRs during Study 003 were grade 1-2 in severity and no patient required permanent discontinuation of avelumab due to an IRR. 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 Study 003 and the larger pooled database do not change the favorable benefit-risk assessment for avelumab for the treatment of adult patients with metastatic MCC.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

There are no outstanding statistical issues with the study design, statistical analysis plan, or efficacy analyses of Part A of Trial EMD100070-003. However, it is noteworthy that while the statistical analysis plan of the trial included summary statistics of PFS and OS as secondary efficacy endpoints, these results were not presented in this review as analyses of time-to-event endpoints are not interpretable in single arm trials.

7.6. Conclusions and Recommendations

Patients with metastatic MCC represent a population with a serious and life-threatening disease for which there is no FDA-approved therapy and no known curative therapy. Although MCC 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 as compared to no treatment.

The clinical benefit of avelumab for patients with metastatic MCC who have progressive disease following at least one prior line of chemotherapy is based on the results of Part A of Study 003. Efficacy analyses conducted when all patients (N=88) had been treated or followed for at least 12 months after accrual demonstrate a confirmed, centrally reviewed ORR per RECIST v 1.1 of 33% (95% CI: 23, 44), including 10 patients (11%) with CR and 19 patients (22%) with PR. Among the 29 responding patients, the median DOR was not reached (range 2.8 to 23.3+ months) and 72% (21/29) had ongoing responses at data cutoff. Eighty-six percent (25/29) of responding patients maintained responses of $\geq$ 6 months and 45% (13/29) had responses of $\geq$ 12 months. Efficacy was consistent across relevant subgroups: those with visceral metastases, patients who were MCV-positive or MCV-negative, and patients whose tumors tested positive or negative for PD-L1 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. Acknowledging the limitations of the small sample size and selection bias inherent in the use of historical control data, the ORR and DOR results of Study Obs001 in immunocompetent patients with metastatic MCC treated with second line chemotherapy [ORR 28.6% (95% CI: 8.4, 58.1); median DOR 1.7 months (95% CI: 0.5, 3.0)], provided context for the natural history of MCC with chemotherapy.

The clinical benefit of avelumab for patients with chemotherapy-naive metastatic MCC is based on extrapolation of efficacy demonstrated in patients treated in second line and beyond (Study 003, Part A). Clinical data from the ongoing Part B of Study 003 are immature and do not adequately characterize the effectiveness of avelumab in the frontline setting. Extrapolation of efficacy from previously-treated patients with MCC is scientifically justified to patients with no prior therapy because there are no examples across the field of oncology where a drug which is not targeted to a specific resistance mutation did not result in achieving durable response rates of at least the same or greater magnitude in patients who have not been previously treated with chemotherapy than that observed in patients who have progressed on prior chemotherapy. Additionally, treatment with avelumab does not appear to negatively affect the likelihood of achieving a response to subsequent chemotherapy following disease progression based on the data in patients who received chemotherapy following disease progression on avelumab in Study 003. Finally, given the lack of available therapies for patients with metastatic MCC and the more favorable toxicity profile of avelumab as compared to cytotoxic chemotherapy, FDA considers the clinical benefit for avelumab to be favorable for patients with metastatic MCC regardless of whether or not they received prior chemotherapy for metastatic disease.

The primary safety risks of avelumab are imARs and IRRs. In Study 003, 17% of patients experienced at least one imAR. The most common imARs in more than 2% of patients were hypothyroidism, rash, and diarrhea. Across the larger pooled safety population, imARs that occurred in more than 1% of patients include hypothyroidism, rash, pruritus, diarrhea and pneumonitis. Two percent of all immune-mediated events were Grade 3 or 4 in the pooled analysis. Serious imARs observed at a lower frequency across the avelumab development

program include autoimmune hepatitis including fatal hepatitis, myocarditis including fatal myocarditis, colitis, nephritis, myositis, autoimmune thyroiditis, adrenal insufficiency, encephalopathy, uveitis, Guillain-Barre syndrome, bullous pemphigoid and SIRS. 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. ImARs were usually manageable with corticosteroids and hormone replacement therapy. Dose-modification and management guidelines for imARs are included in product labeling.

IRRs during Study 003 were common but low-grade in severity and no patient required permanent discontinuation of avelumab due to an IRR. IRRs were 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.

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. A trial of avelumab evaluating durable response rates in the frontline setting is ongoing and the results are intended to serve as confirmatory evidence of clinical benefit. 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 metastatic MCC, 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 and to verify and describe the treatment effect of avelumab in patients with chemotherapy-naïve metastatic MCC. Confirmatory evidence of clinical benefit will be based on a demonstration of a statistically significant and clinically meaningful durable response rate in patients with untreated metastatic MCC that are followed for at least 12 months from initiation of avelumab. The Applicant will additionally evaluate OS as compared to historical control data and incorporate assessments of other measures of the effect of avelumab on tumor-related symptoms, physical functioning and disfiguring lesions (when present). Depending on the demonstrated effect size, these data may be sufficient to support granting regular approval for this indication.

The clinical and statistical reviewers did not find that a REMS is required to ensure the safe and effective use of avelumab, given the observed 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.

X	X
Primary Statistical Reviewer: Pallavi Mishra-Kalyani	Statistical Team Leader: Kun He
X	X
Primary Clinical Reviewer: Denise Casey	Clinical Team Leader: Suzanne Demko

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. The Division has been attempting to obtain the advice of a Special Government Employee (SGE), a practicing oncologist with expertise in MCC and a patient advocate; however, clearance for these SGEs was not able to be obtained prior to the completion date for this review.

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 under 21 CFR 314.55(d), Exemption for Orphan Drugs.

The indication statement will include pediatric patients 12 years and older based on extrapolation of PK from the adult to the adolescent population.

Extrapolation of the effectiveness of avelumab to pediatric patients aged 12 and older who have metastatic MCC is reasonable. Population pharmacokinetic (PK) modeling includes simulation of PK exposure at steady state after repeat intravenous dosing of avelumab 10 mg/kg every 2 week for patients with body weights of 30kg to 90 kg, which are equivalent to weights of adolescents. The PK data were obtained from patients aged 20 to 91 years who were treated with avelumab in Study 001, Study 3, and EMR 1000070-002 (Study 002). The results demonstrate comparable PK between patients with body weights of 30 to 90 kg and adults. Also demonstrated were no differences in PK based on age. In addition, based on data from the population PK modeling simulating minimum concentration (Cmin) and the data from an in vitro target occupancy study provided by the Applicant, high target occupancy was predicted for pediatric patients 12 years and older during the entire dose interval at 10 mg/kg every 2 weeks.

Population PK modeling is performed routinely in analyses of PK data, and FDA requires this modeling in applications to support labeling.

Additional support for an indication in pediatric patients comes from a review of the published literature performed by the Applicant that resulted in six case reports of patients with MCC in the pediatric age group, four patients in the age range 11 to 17, two of the patients had metastatic disease, one patient received chemotherapy and the remainder underwent surgical resection. All cases were diagnosed utilizing IHC. In addition to these patients, the Applicant submitted the report of a 10-year-old female patient diagnosed in January, 2014 with metastatic MCC who was initially treated with 6 cycles of cisplatin and etoposide and who experienced subsequent disease progression after receiving 3 doses of avelumab at 10 mg/kg under an emergency access single patient IND. During and after treatment with avelumab, the patient reportedly experienced pain, nausea and vomiting. While the numbers are small, the diagnosis and treatment of these patients is nearly identical to adults with metastatic MCC, as are the outcomes, and there are no data to suggest that treatment with avelumab will be less effective or tolerable.

Adult and pediatric patients aged 12 and older with advanced or metastatic MCC represent a population with a serious and life threatening disease. There is no available FDA-approved therapy for the disease, and no known therapy that is either curative or is known to improve

overall survival (OS). Although MCC is known to be sensitive to chemotherapy, treatment of patients with cytotoxic chemotherapy has demonstrated neither durable responses nor survival advantages for patients. A broad indication encompassing adults and pediatric patients 12 years and older is being recommended for avelumab in the setting of an accelerated approval. A PMR will be also be required to characterize the effects of treatment with avelumab on pediatric patients aged 12 and older with solid tumors.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations were ongoing at the time of completing this review. The table below summarizes significant changes to the proposed label made by FDA prior to negotiations. The package insert for Bavencio will include the finalized prescribing information.

Summary of Significant Labeling Changes		
Section	**Proposed Labeling**	**Approved Labeling**
2.2 Premedication	Premedication recommended prior to the first four infusions and then based on clinical judgment thereafter	Although the protocol for Study 003 required premedication for all infusions, the Applicant provided sufficient rationale for the alternative recommendation for premedication for the first four infusions and then as deemed clinically appropriate. Of 1738 patients in the pooled safety population, there were 439 IRRs; 12 (3%) of the 439 were Grade 3 or 4, and all of these occurred during the first or second infusion. Additionally, only six (1.4%) of the 439 patients experienced an IRR during the 5th or greater infusion. Given these results and the ability to successfully manage grade 1-2 IRRs without the need to discontinue study drug, FDA considers the proposed labeling recommendation to be reasonable.
2.3 Dose Modifications	Bullet format guidelines (b) (4) [redacted]	FDA incorporated a table format organized by specific categories of imARs (e.g., colitis, pneumonitis, hepatitis etc.). Additionally, during labelling negotiations, FDA requested that the Applicant provide evidence-based guidelines for (b) (4) [redacted] The proposed

		recommendation to (b) (4) [redacted] is vague and not informative for prescribers.
5 Warnings and Precautions	Categories included were pneumonitis, colitis, hepatitis, endocrinopathies, and other. Other included monitoring guidelines for myocarditis.	FDA included an additional category of immune-mediated nephritis and removed (b) (4) [redacted] FDA recommended removal. FDA added other serious imARs that were identified in less than 1% of patients with avelumab or have been identified with other drugs in class: psoriasis, rheumatoid arthritis, exfoliative dermatitis, erythema multiforme, bullous pemphigoid rash, bullous dermatitis, hypopituitarism, hypophysitis, uveitis, iritis, Guillain-Barré syndrome, systemic inflammatory response, Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), pancreatitis, myasthic syndrome, rhabdomyolysis, demyelination and lymphadenitis.
6 Clinical Trials Experience		FDA added a description of Study 001 and the eligibility criteria for Study 003 to better characterize the patients included in the pooled analysis. FDA described the case definition that was used to diagnose imARs. FDA reorganized the adverse reaction table and laboratory abnormalities table to summarize events in decreasing incidence rate. FDA added a column in the lab abnormality table for “any grade”

		events. In Section 6.2 (Immunogenicity), FDA added the recommended language based on the labeling guidance for this section
8.5 Geriatric Use	(b) (4)	FDA described the age ranges in Study 003 and stated that a determination cannot be made as to whether geriatric patients respond differently as Study 003 treated only 88 patients.
12.3 Pharmacokinetics		FDA removed subsection (b) (4) . FDA removed (b) (4) and incorporated the relevant information under "specific populations"
14 Clinical Studies	The Applicant included (b) (4) .	FDA added description of patient population enrolled in Study 003, a description of the PD-L1 and MCV status across patients. FDA removed (b) (4) FDA summarized response and DOR in table format. FDA removed (b) (4) as these descriptions are not useful to prescribers.
17 Patient Counseling		FDA reorganized subsections and changed formatting. (b) (4) were removed since it falls under (b) (4)

10.2. Patient Labeling

See consult review from Patient Labeling Team: Morgan Walker, (DMPP) and Nicholas Senior (OPDP).

11 Risk Evaluation and Mitigation Strategies (REMS)

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

Serious risks of avelumab are immune-mediated adverse reactions, including fatalities, and infusion-related reactions.

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

Avelumab will be administered in clinics experienced with infusions of chemotherapy. Premedications will be required for the first four infusions based on data from the applicant demonstrating that the majority of infusion –related reactions occurred during these infusions.

The label includes listings of immune-related reactions that have been observed across the class as well as dose modifications and treatment for these events. As this class of drugs is admitting newly approved members regularly over the past few years, prescribers have become more experienced with monitoring and treating these types of events, and generally, oncologists are experienced in the monitoring and management of these serious risks.

11.3. Recommendations on REMS

It is not recommended that a risk evaluation and mitigation strategy (REMS) be implemented for avelumab. Recommendations for safe and effective use of avelumab, including adequate safety monitoring for immune-mediated adverse reactions and infusion reactions, will be addressed in the product label.

12 Postmarketing Requirements and Commitments

The Application was approved with an Accelerated Approval requirement to confirm clinical benefit, and one FDAAA PMR to assess in pediatric patients a known serious risk of immune mediated adverse reactions. Additionally, there are two postmarketing commitments: one nonclinical PMC requesting an animal study to further characterize the effect of avelumab on the immune response, and one clinical pharmacology PMC regarding binding and neutralizing anti-drug antibody responses.

The data provided in the Application are sufficient to support approval of Bavencio (avelumab) as treatment for patients with metastatic Merkel cell carcinoma (MCC). However, data for avelumab as a treatment for patients with metastatic MCC who have not received prior systemic chemotherapy (i.e., frontline) is limited. Metastatic MCC is a rare and life-threatening illness with no available therapy. There is reasonable biologic rationale to support extrapolation of the efficacy results from the second-line setting in which patents received prior chemotherapy to the initial frontline setting, and to pediatric patients 12 years and older. The trial required in chemotherapy-naïve adult patients for confirmation of clinical benefit is necessary to more accurately characterize response rate and durability of responses for adults with metastatic MCC in the frontline setting. The PMR for pediatric patients 12 and older will assess a known serious risk of immune mediated adverse reactions for avelumab in this population of patients.

The postmarketing requirements and commitments are as follows:

Accelerated Approval PMR under 21 CFR 601.41 Subpart E

Conduct and submit the results of a multicenter clinical trial confirming the clinical benefit of avelumab in patients with metastatic Merkel cell carcinoma (MCC) who have not received prior systemic therapies for metastatic MCC. The trial will enroll at least 100 patients followed for a minimum of 12 months, in order to establish the objective response rate and characterize the durability of response for first-line treatment of metastatic MCC. All patients will be followed for overall survival until at least 70% of patients have died in order to characterize effects on survival. An analysis of overall survival compared to historical control data will be provided.

FDAAA Postmarketing Requirement under 505(o)

Conduct a trial in a sufficient number of pediatric patients age(s) 12-18 to adequately characterize baseline risk factors, safety outcomes, and clinical responses following exposure to avelumab.

Postmarketing Commitments under 506B

- Conduct an animal study that will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody

responses to antigen challenge (e.g. KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include an evaluation of cytokine production by T cells at appropriate time points.

- Conduct an assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses with validated assays (including an updated cutpoint for the screening and confirmatory ADA assays and for the neutralizing assay as requested in 3185-5) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least 300 avelumab-treated patients. The final report will include information on the level of avelumab in each patient's test sample at each sampling point with an appropriate cutpoint.

13 Appendices

13.1. References

CDTL References
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13.2. Financial Disclosure

Covered Clinical Study: Study EMR100070-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 340		
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): 0		
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: 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) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

Not applicable

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRIC REVIEW

1 Summary of Findings

The current indication is based on the registration study EMR10070-003 Part A (Study 003), a Phase II, open-label, single-arm trial to investigate the clinical activity and safety of avelumab 10 mg/kg every 2 weeks (Q2W) in subjects with metastatic MCC after failing first-line chemotherapy. The intention to treat population consists of 88 subjects. The primary endpoint is confirmed objective response rate (ORR) by IERC according to RECIST 1.1 and the secondary endpoints include progression-free survival (PFS), overall survival (OS), duration of response, response rate at 6-month, and safety. 28 (31.8%, 95% CI: 21.9%-43.1%) patients were confirmed responders. Median PFS was 2.7 (95% CI: 1.4, 6.7) months, and median OS was 11.3 (95% CI: 7.5, 14.0) months.

Based on data submitted in this application, the proposed 10 mg/kg Q2W dosing regimen is acceptable from the pharmacometrics (PM) perspective. Dose adjustment based on intrinsic or extrinsic factors is not necessary. The sponsor's proposed clinical pharmacology labeling language is generally acceptable.

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the proposed 10 mg/kg Q2W dosing regimen justified from the clinical pharmacology perspective?

Yes, the proposed dosing regimen is justified based on Study 003 outcome, *ex vivo* data, and exposure-response (E-R) analyses for efficacy and safety.

The rationale for the 10 mg/kg given once every 2 weeks was based on the safety and tolerability data obtained from the dose-escalation phase of Study 001 where patients were treated at 1, 3, 10, and 20 mg/kg doses Q2W with no MTD reached. Ex vivo target occupancy (TO) in PBMCs, measured by flow cytometry on serum samples from subjects with advanced solid tumors who participated in the dose escalation cohort of Study 001, demonstrated TO of 93.2±1.29% at doses of 10 mg/kg Q2W throughout the dose interval. A mean TO of 90.0±8.1% and 85.0±8.7% were obtained at the 3 mg/kg and the 20 mg/kg Q2W dose levels, respectively.

E-R relationships were observed between avelumab steady state exposure metrics and best objective response (BOR), OS, and PFS. 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 of avelumab may be more efficacious. However, the E-R analysis for efficacy is limited for a single arm monoclonal antibody (mAb) trial in patients with cancer due to potential interaction between response status and late-exposure metrics. Because mMCC is a rare disease, and Study 003 provided acceptable effectiveness, no additional study to further optimize the dose is recommended based on the current available information. No substantial E-R relationship was observed for safety. The proposed 10 mg/kg Q2W dosing regimen is justified given the positive outcome of Study 003, the high ex vivo TO results, and the E-R relationships identified in the current submission.

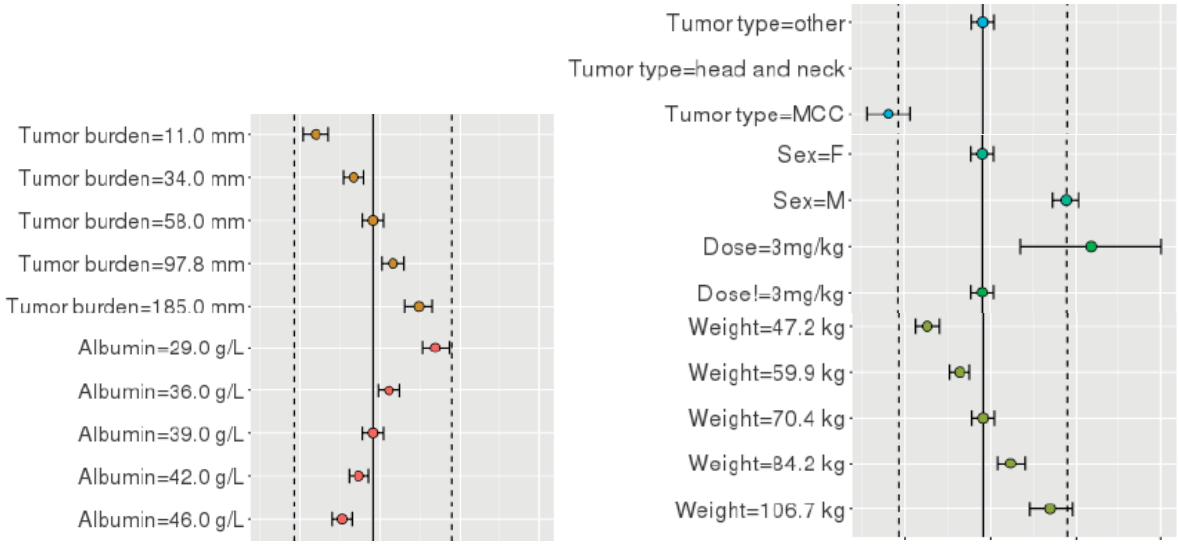
Population pharmacokinetics (PPK) analysis suggests that a flat dosing regimen (800 mg Q2W) would be acceptable as well, because the overall variability in exposure is similar to that observed with the proposed 10 mg/kg Q2W dosing regimen.

1.1.2 Does PPK analysis suggest any need for dose adjustment based on intrinsic and extrinsic factors?

No, dose adjustment based on intrinsic and extrinsic factors is not needed based on PPK analysis.

The sponsor's final model contains 17 parameter-covariate relationships: baseline body weight, baseline albumin, baseline tumor burden, dose, sex and tumor type (MCC) on CL; acetaminophen premedication and tumor type (MCC and NSCLC) on Q; baseline body weight and sex on V1; and eGFR, acetaminophen premedication, tumor type (head and neck, ovarian and MCC) and immunogenicity on V2. Extreme values of these covariates do not induce clinically meaningful change in avelumab clearance / exposure as compared with the typical value. Age, renal function, and hepatic function were not identified as statistically significant factors in the population PK model.

Figure 21: Forest Plot Showing Covariate-CL Relationship in the Final Model (run124). Dashed vertical lines are 80% and 120% of parameter values. !=; not equal to.



Source: emr100070-001-002-003-population-pk-report.pdf, Figure 10.

1.1.3 Are the PK parameters reported in the label supported by PPK analysis?

Yes, PK parameters in the proposed label are generally supported by the sponsor's PPK analysis.

A trend of time-dependent increase in exposure especially in MCC patients was observed with avelumab multiple cycle treatment and decrease in clearance (CL) over time was also suggested by the goodness-of-plots of the sponsor's PPK analysis. PPK analysis of individual estimates of CL for the 1629 subjects who contributed to the PPK analysis was further conducted using data from first treatment cycle only. The average decrease between CL estimated from overall multiple-cycle dataset and CL estimated from the first treatment cycle is <5%. However, the analysis based on the studied overall population may be affected by patient factors (e.g., tumor type, tumor burden, etc.), treatment factors (e.g., avelumab dose, treatment duration, etc.) and response status (e.g., CR, PR, SD, and DP). In a post hoc analysis that including a time-variant CL PPK model with tumor type as a covariate on CL change over time,, the average (s.d.) maximal change is -3.1% (18.6%) and -41.7% (40.0%) in the entire PPK population (n=1629) and the MCC (n=88) subgroup. The clinical relevance of the CL change (especially -41.7% in MCC subpopulation) is unclear, but dose adjustment according to the CL change does not seem necessary because the proposed 10 mg/kg Q2W was well studied in clinical trials and the benefit/risk is acceptable.

2 Pertinent Regulatory Background

Avelumab clinical development program started with the submission of IND 115747 in 2012, for the treatment of patients with various solid tumors. On January 14, 2014, Pre-IND teleconference was held to discuss the development program for the treatment of MCC. In 2015, Orphan Drug, Fast Track, and Breakthrough Therapy designations were granted for the treatment of MCC. On September 23, 2016, EMD Serono submitted BLA 761049 (rolling submission) for the treatment of patients with metastatic MCC. Major clinical studies to support this submission include:

- EMR100070-001 (Study 001): The first-in-man trial of avelumab. In the escalation part of this clinical trial, multiple doses of 1, 3, 10, and 20 mg/kg every two weeks (Q2W) were administered to subjects with metastatic or locally advanced solid tumors. In an expansion part, 10 mg/kg Q2W were administered to subjects with selected indications.
- EMR100070-002 (Study 002): A Phase I trial in Japanese subjects. In an escalation part Japanese subjects with metastatic or locally advanced solid tumors were dosed with 3, 10, or 20 mg/kg Q2W. In an expansion cohort, 10 mg/kg Q2W were administered to Japanese subjects with gastric cancer.
- EMR100070-003 Part A (Study 003): The registration study. A Phase II, open-label, multicenter, single-arm trial to investigate the clinical activity and safety of avelumab 10 mg/kg Q2W in subjects with mMCC after failing first-line chemotherapy.

3 Sponsor's Population Pharmacokinetics and E-R Analysis

3.1 PPK Analysis

3.1.1 Objectives

- To describe the concentration versus time data obtained after multiple infusions of avelumab;
- To identify covariates explaining (part of) the between patient PK variability;
- To estimate the residual PK inter-individual variability; and
- To compare avelumab exposures following weight-based vs flat dosing using simulations.

3.1.2 Data

Intermediate results from Study 001 (cut-off date: November 20, 2015), Study 002 (cut-off date: November 20, 2015), and Study 003 (cut-off date: March 03, 2016) are included in the PPK analysis. The dataset consists of 10220 concentration observations from 1629 subjects: 1490 from Study 001, 51 from Study 002, and 88 from Study 003. Table 45 in Appendix summarizes demographics, laboratory, disease metrics and other baseline information in the dataset.

3.1.3 Software

NONMEM, PsN, Pirana, Xpose, and R.

3.1.4 Methods

Base model: Two-compartment models including various main covariates or having various variance covariance structures were tested using the available data. Point estimates and inter-individual variability for the PK parameters as well as residual variability were derived.

Covariate model: The influence of additional demographics (age, weight at baseline, sex, race), laboratory parameters (albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, total protein, immune globulin, prothrombin, eGFR, disease related values (tumor size at baseline, tumor type, PD-L1 expression of tumor, the Eastern Cooperative Oncology Group (ECOG) status), medication (number of previous anti-cancer drug therapies, previous medication with biologics, concomitant medication (paracetamol, ibuprofen, acetylsalicylic acid dose, opioids, corticosteroids or biologics), pre-treatment with medication (acetaminophen or diphenhydramine), dose, formulation or immunogenicity (human anti-human antibody, HAHA) was further assessed by stepwise covariate model (SCM) building (forward: $p<0.001$; backward: $p<0.0005$).

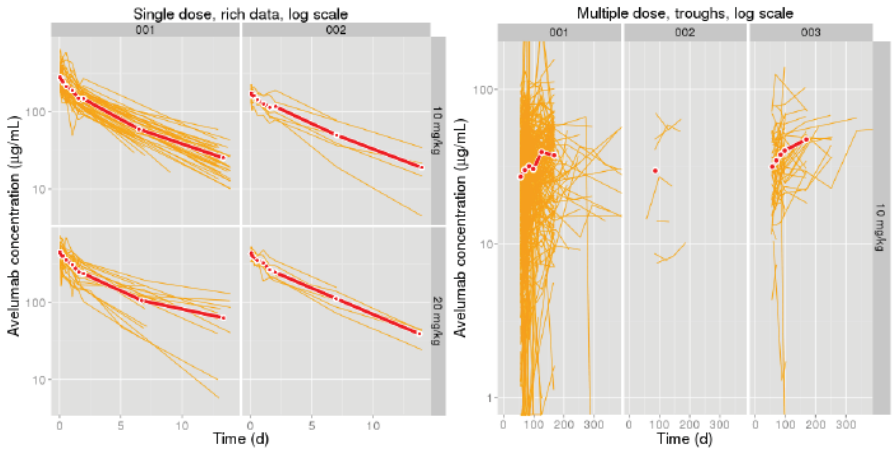
Final model: Clinical relevance of covariates selected by SCM was checked in terms of their influence on PK parameters. If parameters did not change by >15% across the 90% range of recorded covariate values, the covariate relationship was excluded. Model selection and qualification were based on goodness-of-fit plots and visual predictive checks, as well as predefined statistical criteria.

3.1.5 Results

Although avelumab is a monoclonal antibody (mAb), no evidence of significant target-mediated drug disposition was observed at dose level 10 mg/kg and above in concentration-time curves (Figure 22, Left). However, trough concentrations appeared to increase over time in the multiple cycle treatment, especially in Study 003 (Figure 22, Right).

Reviewer's comments: Given the relatively short elimination half-life of 6 days compared to the dosing interval of 2 weeks, and the limited accumulation (with ratio of 1.25), it is likely that there is a dynamic change of avelumab kinetics especially in MCC patients.

Figure 22: Avelumab PK Profile for Rich-Sample Patients in the First Dosing Cycle, by Study and Dose Level (Left) and Pre-Dose Trough Concentration by Study for the 10 mg/kg Dose Level (Right).



Source: emr100070-001-002-003-population-pk-report.pdf, Figures 1 and 2.

Given the lack of graphical evidence for TMDD and the PK behavior of other mAbs in the same class (pembrolizumab, ipilimumab and nivolumab), the Sponsor used a two-compartment model with linear kinetics (run001) as the starting point to identify any remaining outliers (CWRES>4, run001). After removing these outliers, the model was fit against the updated dataset. Log-normally distributed IIV was included on CL, central volume of distribution (V1), peripheral volume of distribution (V2) and inter-compartmental clearance (Q). Body weight at baseline was explored as a covariate during structural model development owing to its allometric importance, and included a priori on CL and V1 before the start of SCM process. Various variance-covariance structures were explored; the complexity of the variance-covariance matrix was reduced from a full block to a version including covariance only between IIV on CL and IIV on V1 to increase model stability. The residual error was described by an additional and proportional error model.

PK parameters and basic diagnostic plots of the base model (run 042) are provided in Table 46 and Figure 32 in Appendix. PK parameters were generally well-estimated, although shrinkage for IIV on Q was high, suggesting that graphical diagnostics and graphical covariate exploration for this parameter would be of limited use. Basic diagnostic plots suggest an acceptable fit of the model to the data, except a systematic deviation from the line of identity observed for the plot of conditional weighted residuals against time, primarily in Study 003.

The magnitude of inter-occasional variability (IOV, 9.1%) is less than IIV (30.3%) in the base model (run 047), indicating that variability within individuals is considerably smaller than between individuals. IOV was not included in the final model for reasons of parsimony.

The final model (Table 40, Figure 23, and Figure 24) was estimated using NONMEM's MCETA option, with 1000 samples. Parameters for the final avelumab population PK model were generally well-estimated. Shrinkage on CL was acceptable, but relatively higher for V1, V2 and

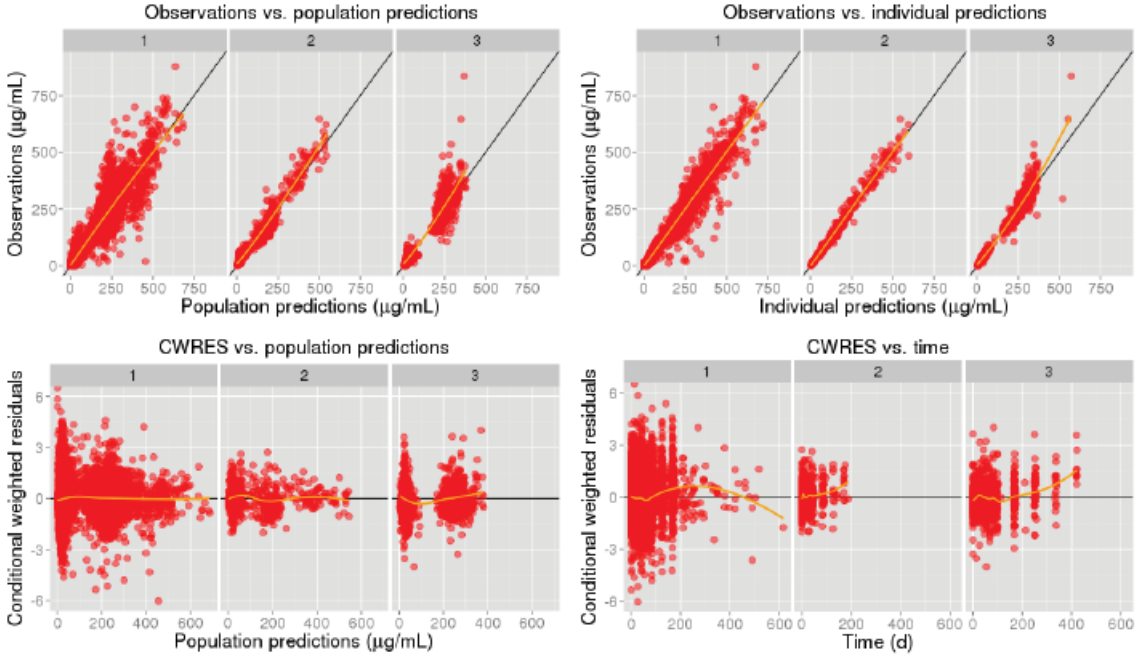
especially Q. Predictions and residuals are symmetrically distributed without any significant trends, except for Study 003.

Table 40: Parameter Estimates for the Final Model (run 124)

Parameter	Estimate	%RSE	95% CI	Shrinkage
Clearance (CL, L/h)	0.0246	1.32	0.0239-0.0252	
Central volume (V_1, L)	2.83	1.22	2.76-2.89	
Peripheral volume (V_2, L)	1.17	6.90	1.01-1.33	
Intercompartmental clearance (Q, L/h)	0.0526	9.21	0.0431-0.0622	
Baseline weight on CL	0.358	10.2	0.286-0.430	
Baseline albumin on CL	-0.500	4.86	-0.547--0.452	
3 mg/kg dose level on CL	0.260	33.9	0.0874-0.432	
Sex (male) on CL	0.199	10.6	0.158-0.241	
Baseline tumor burden on CL	0.0948	8.70	0.0787-0.111	
Tumor type (MCC) on CL	-0.224	11.0	-0.272--0.176	
Acetaminophen premedication (none) on Q	-0.56	5.88	-0.625--0.496	
Tumor type (NSCLC) on Q	-0.692	6.31	-0.778--0.607	
Tumor type (MCC) on Q	-0.864	1.84	-0.895--0.833	
Baseline weight on V_1	0.367	8.19	0.308-0.426	
Sex (male) on V_1	0.203	9.69	0.165-0.242	
eGFR on V_2	-0.507	27.9	-0.785--0.230	
Acetaminophen premedication (none) V_2	-0.233	13.3	-0.294--0.172	
Tumor type (head and neck) on V_2	0.726	40.5	0.149-1.30	
Tumor type (ovarian) on V_2	-0.336	26.9	-0.513--0.159	
Tumor type (MCC) on V_2	8.58	25.2	4.34-12.8	
Immunogenicity (ever) on V_2	-0.667	12.4	-0.830--0.505	
Interindividual variability				
IIV on CL (ω^2_{CL}, variance)	0.0634	5.16	0.057-0.0699	19.0
cov(CL,V_1) ($\omega_{CL,V1}$, covariance)	0.0217	9.96	0.0175-0.0259	
IIV on V_1 (ω^2_{V1}, variance)	0.0335	5.83	0.0297-0.0374	37.8
IIV on V_2 (ω^2_{V2}, variance)	1.11	8.49	0.924-1.29	40.1
IIV on Q (ω^2_{Q}, variance)	0.154	29.8	0.0644-0.245	78.1
Residual variability				
Proportional residual error (σ_{add})	0.164	0.654	0.162-0.166	12.2
Additive residual error (σ_{add}, μg/mL)	2.91	1.39	2.83-2.99	

Source: emr100070-001-002-003-population-pk-report.pdf, Table 10.

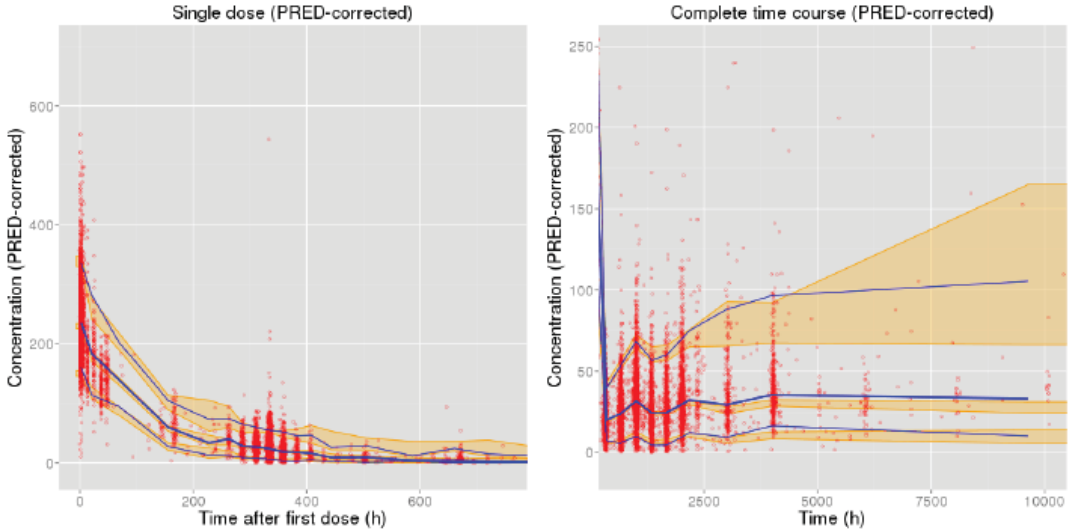
Figure 23: Basic Diagnostic Plots for the Final PPK Model for Avelumab by Study (run 124)



Points are observations. Orange lines are loess smooths through the data. Black lines are lines of identity or zero lines as appropriate. CWRES=conditional weighted residuals

Source: emr100070-001-002-003-population-pk-report.pdf, Figure 11.

Figure 24: Prediction-Corrected Visual Predictive Check for the Final Model, for the First Dosing Interval and the Complete Time Course (run 124)



Red points are observations. Blue lines are observed median, 5th and 95th percentiles. Orange shaded areas are 95% confidence intervals for simulated median, 5th and 95th percentiles.

Source: emr100070-001-002-003-population-pk-report.pdf, Figure 14.

Geometric mean CL in the study population was 0.0268 L/h (CV 30.4%, asymptotic 95% CI 0.0264-0.0272 L/h). Geometric mean CL in the 10 mg/kg group was 0.0267 L/h (CV 29.9%, asymptotic 95% CI 0.0263-0.0271 L/h). The predicted area under the concentration-time curve

at steady-state (AUC_{ss}) for the 10 mg/kg dose group had a geometric mean of 26214 mg·h/L (CV 35.4%, asymptotic 95% CI 25773-26662 mg·h/L; estimated using each individual's CL estimate and the median dose they received over the duration of their treatment). Volume of distribution at steady state (Vss) was calculated as the sum of V1 and V2 for each individual, and had a geometric mean in the population of 4.73 L (CV 44.2%, asymptotic 95% CI 4.63-4.82 L) for the total population, and 4.72 L (CV 44.5%, asymptotic 95% CI 4.63-4.82 L) for the 10 mg/kg dose group. Geometric mean terminal elimination half-life for the total population was calculated to be 145 h (CV 90.3%, asymptotic 95% CI 140-151 h), and 146 h (CV 91.5%, asymptotic 95% CI 140-152 h) for the 10 mg/kg dose group. Based on an elimination half-life (t1/2) of 145 h, accumulation ratio is 1.25 for a dosing interval of 336 h. Note that this estimate applies only to the first 4 months of biweekly dosing, given that the observed time-dependent increase in concentrations beyond this point is not captured by the model.

The increase in AUC_{ss} for MCC is highest among tested tumor types (based on an estimated decrease in clearance of 22.4%). Other tumor types identified in the model (head & neck, NSCLC and ovarian) produced less marked differences in exposure. CL was estimated to be similar for dose levels of 1 mg/kg, 10 mg/kg and 20 mg/kg, although the 3 mg/kg dose level was estimated to have a typical CL that was 26.0% greater. Subjects having at least once a HAHA-positive result show slightly lower trough concentration after the first dose ($C_{trough,first}$) and $C_{trough,ss}$. Pre-medication with acetaminophen and eGFR show a marginal influence on exposure metrics. Male patients have lower exposure than female patients, assuming other covariates are the same, although in practice collinear differences in weight (and dose) would reduce this apparent difference. With increasing tumor size at baseline and decreasing albumin levels at baseline, the exposure of avelumab decreases. No relationships were found between any population PK parameter and formulation process or age.

Figure 33 in Appendix show the effect of weight on exposure metrics AUC_{ss} and $C_{trough,ss}$ (after fourth dose) for different dosing regimens. These simulations suggest that the overall variability in exposures is similar for both weight-based and flat dosing schemes.

Reviewer's Comments:

- *The sponsor PPK models appear to be able to reasonably characterize the PK profiles in studied overall population. Run042 and run124 were repeated. There is no apparent error in the dataset or analysis code. PK parameters in the proposed label are supported by sponsor's PPK analysis.*
- *The two-compartmental linear model adequately describes the concentration of avelumab over time (up to 125 days) across three studies, in 1629 subjects with different types of cancer. However, trough concentrations appeared to increase over time, especially in Study 003, although the elimination half-life of 6 days compared to the dosing interval of 2 weeks is relatively short and the PK accumulation is expected to be limited (with ratio of 1.25). It is likely that there is a dynamic change of avelumab kinetics especially in MCC. The magnitude of the time-dependent under-prediction at later time points is further explored in Section 4 of this review.*
- *The FDA reviewer agrees with sponsor's assessment that dose adjustment is not needed based on age, gender, hepatic or renal function.*
- *Based on sponsor's analysis, patients with MCC tumor type has a CL which is 22.4% lower than that in a patient with other tumor types. This tumor type effect on CL is not considered*

clinically relevant because safety and efficacy at the proposed dose level has been demonstrated in the MCC population (Study 003).

- *Simulations comparing weight-based (10 mg/kg) and flat dosing (800 mg) suggested that the overall variability in exposures is similar for both the dosing schemes (Figure 33). However, the sponsor is not seeking flat dose regimen at this stage.*

3.2 E-R Analysis

3.2.1Exposure-Efficacy Analysis

Objectives

- To explore relationship between avelumab exposure and the probability of being a responder
- To evaluate covariates which may have an effect on the probability of being a responder
- To assess the relationship between avelumab exposure parameters and OS/PFS

Data, Software, and Methods

A total of 88 subjects in Study 003 A were included in the 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. OS and PFS information was available for these 88 subjects. The base PPK model was used to predict individual exposure metrics using individual pharmacokinetic parameters (Figure 34 in Appendix).

Six exposure metrics were considered in the analysis for BOR: predicted $C_{trough,ss}$, predicted AUC_{ss}, predicted average concentration (C_{ave}), predicted $C_{trough,first}$, observed trough concentration at steady-state ($C_{obs\text{-}trough,ss}$) and observed trough concentration after the first dose ($C_{obs\text{-}trough,first}$). E-R relationship was explored graphically followed by logistic regression with linear logit link. A stepwise approach was used for covariate selection. In the first step each covariate was fitted by a univariate model and all predictors significant at a level p1=0.10 were selected for the second step. In the second step all significant covariates were subject to backward selection to eliminate non-significant variables at a level p2=0.05. Model discriminatory performance was assessed using receiver operating characteristic (ROC) curves.

A Cox proportional hazards model was used to assess the relationship for OS and PFS versus avelumab exposure metrics including predicted minimum avelumab serum concentration (Cmin), maximum avelumab serum concentration (Cmax), and area under the curve (AUC) after single dose and at steady-state. After a stepwise covariate selection (p1=0.10, p2= 0.05), all possible two-way interaction terms were added and the backward selection was applied using p3=0.05. Goodness of Fit plots and ROC curves were examined to assess the model adequacy.

All data preparation and processing and analyses were performed using R version 3.2.2.

Results - BOR

An apparent exposure response relationship was observed between BOR and the following exposure metrics: predicted $C_{trough,first}$, predicted $C_{trough,ss}$, observed $C_{trough,ss}$, predicted AUC_{ss} and C_{ave} using univariate analysis. Among them, $C_{trough,ss}$ was the strongest predictor (p=0.0001) for response (Table 41). $C_{trough,ss}$ shows "good" discrimination power based on ROC curves. At the

end of backward elimination, only $C_{trough,ss}$ remains. Therefore, the final model is the univariate model using $C_{trough,ss}$. Parameter estimates for the final model is presented in Table 42.

Table 41: Univariate Logistic Regression on Exposure Metrics

Exposure metric	single dose Ctrough ($C_{trough,first}$) (µg/mL)	steady-state Ctrough ($C_{trough,ss}$) (µg/mL)	steady-state AUC (AUC_{ss}) (mg·h/L)	Cave (AUC_{ss}/tau) (µg/mL)	Observed $C_{trough,first}$ (µg/mL)	Observed $C_{trough,ss}$ (µg/mL)
P value	0.0379	0.0001	0.0005	0.0005	0.1033	0.0171
Odds radio (95% CI)	1.0611 (1.0049 – 1.1254)	1.0737 (1.0387 – 1.1177)	1.0001 (1.0001 - 1.0002)	1.0481 (1.0228 - 1.0790	1.0376 (0.9967 - 1.0904)	1.0432 (1.0097 – 1.0837)
AUROC	0.651	0.854	0.78	0.78	0.618	0.742

Source: ms-emr100070-003-exposure-efficacy-report-final.pdf, Table 6.

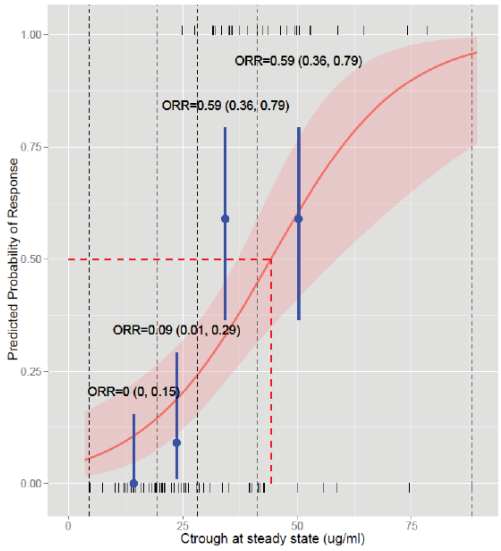
Table 42: Final Model Parameter Estimates Using Univariate Analysis of BOR by $C_{trough,ss}$.

Variable	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-3.14815	0.68777	-4.577	4.71E-06
Ctrough,ss	0.07115	0.01855	3.835	0.000125

Source: ms-emr100070-003-exposure-efficacy-report-final.pdf, Table 8.

The E-R relationship based on predicted $C_{trough,ss}$ is shown in Figure 25, along with the observed BOR and all the observations (rugs). Beyond $C_{trough,ss}$ value of 50 µg/mL, large prediction confidence intervals are demonstrated due to limited observations. Based on this relationship, the probability of BOR is predicted to be 50% (95% CI: 35% ~ 65%) at $C_{trough,ss}$ of 44 µg/mL. Based on the 95% CI from the estimated odds radio, the prediction interval of $C_{trough,ss}$ corresponding to 50% response rate is estimated to be 37 µg/ml ~ 59 µg/ml.

Figure 25: Relationship between Probability of Response and $C_{trough,ss}$.



Source: ms-emr100070-003-exposure-efficacy-report-final.pdf, Figure 4.

Despite of a strong, positive association between avelumab exposure and BOR, extrapolation from this logistic model to a higher dose would not be recommended. The logistic model

assumes linear relationship with exposure, meaning that probability of response can theoretically reach 100% given a very high exposure. This underlying assumption requires interpretation of the results with caution. For example, the observed ORR values for the 3rd and 4th exposure quartile are identical, a plateau may already be reached when $C_{trough,ss}$ is higher than 28 µg/ml (median of MCC population). Given that the exposure range in MCC population was generated from a single dose (10mg/kg) and the linear assumption between exposure and response, extrapolation from this logistic model to a higher dose would not be recommended.

Results – OS and PFS

In the univariate analysis, both AUC_{ss} and $C_{trough,ss}$ were highly significant (as judged by the p-values) for OS and PFS. Final models were summarized in Table 43.

Table 43: Final Multivariate Model for Overall Survival (Upper) and PFS (Lower).

Variable	Estimate	Standard Error	z-value	p-value
Steady-state AUC	-0.3334	0.0677	-4.9238	<0.0001
ECOG	-0.1691	0.6403	-0.2640	0.7918
Lactate Dehydrogenase	-0.0124	0.0037	-3.3260	0.0009
PDL1 Expression ≥ 1%	-1.7490	0.7387	-2.3675	0.0179
Steady-state AUC/LDH Interaction	0.0004	0.0001	3.6742	0.0002
ECOG/LDH Interaction	0.0037	0.0012	3.2095	0.0013
LDH/PDL1 Interaction	0.0026	0.0012	2.1282	0.0333

Variable	Estimate	Standard Error	z-value	p-value
Steady-state AUC	-0.0547	0.0253	-2.1577	0.0310
Lactate Dehydrogenase	0.0012	0.0003	3.3266	0.0009
PDL1 Expression ≥ 5%	8.0962	2.8724	2.8186	0.0048
Steady-state AUC/PLD1 Interaction	-0.2637	0.0989	-2.6649	0.0077
Lactate Dehydrogenase/PDL1 Interaction	-0.0038	0.0011	-3.4586	0.0005

Source: pmar-eqdd-b999a-dp2-644-final-signed.pdf, Table 13 and 14.

It was noted that for several of the covariates, there is an imbalanced distribution in different exposure quantiles, regardless of which exposure parameter is selected. For instance, ECOG status of 1 is more prevalent among patients in the lower quartiles, and the lowest quartile is imbalanced by subjects with extra-large tumors, early deaths, and subjects experiencing more than 2 prior chemotherapy regimens, suggesting that the lowest quartile may be affected by subjects with more advanced disease.

Conclusions

- An apparent exposure response relationship was observed between BOR and the following exposure metrics: predicted $C_{trough,first}$, predicted $C_{trough,ss}$, observed $C_{trough,ss}$, predicted AUC_{ss} and C_{ave}. $C_{trough,ss}$ was the strongest predictor (p=0.0001) with odds ratio of 1.074 (95% CI: 1.039 – 1.118) per unit increase in trough concentration at steady state.
- An apparent exposure response relationship was observed between predicted AUC_{ss} (and $C_{trough,ss}$) and both PFS and OS.

Reviewer's Comments: Although apparent E-R relationships were observed, E-R analysis for efficacy is difficult for a single arm mAb trial in cancer patients. Potential interaction between response status and late-exposure metrics is likely to confound the analysis. E-R relationship

between observed $C_{trough,first}$ and BOR (p=0.103) was weaker than that between observed $C_{trough,ss}$ and BOR (p=0.017) (Table 41), further suggesting a dynamic interaction between response and late exposure metrics.

3.2.2Exposure-Safety Analysis

Objectives

- To explore the influence of avelumab exposure on the probability of adverse events (AEs)
  - Immune-related adverse events of grade ≥1 (irAE) or ≥3 (irAE3)
  - Infusion-related reactions (IRR)
  - Treatment-emergent adverse events of grade ≥1 (TEAE1), ≥2 (TEAE2), or ≥3 (TEAE3)
- To identify other covariates that may have an effect on the probability of adverse events

Data, Software, and Methods

A total of 1629 subjects from Studies 001, 002, and 003 were included in the analysis. The primary metric of exposure considered was predicted $C_{trough,ss}$, AUC_{ss}, and $C_{trough,first}$. For IRR, area under the concentration-time curve after a single dose (AUC_{first}, calculated as first dose divided by clearance) and Cmax after a single dose ($C_{max,first}$) were used as secondary metrics.

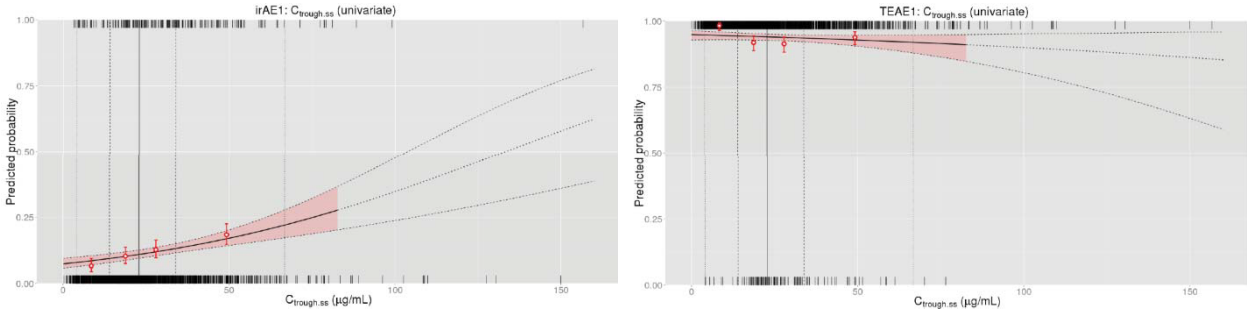
Model fitting was performed by first fitting a univariate model using each exposure metric, and then the full model (exposure metric as well as all covariates in scope). Predictors were then removed in a stepwise fashion based on the outcome of a likelihood ratio test applied to each, until all those remaining were assessed as being significant at the 5% level.

95% CI for the intercept and the regression coefficients were obtained using nonparametric bootstrapping (using 2000 replicates), with bias correction. Relationships between exposure metrics, covariates and probability of adverse event incidence were explored graphically and odds ratios were reported. Discriminatory performance was assessed using ROC curves.

Results and Conclusions

Avelumab exposure metrics were generally weak predictors of AEs as assessed by ROC curves. For univariate models using $C_{trough,ss}$ as exposure metric, avelumab exposure was positively associated with irAE1 incidence with odds ratio of 1.019 per µg/mL increase in $C_{trough,ss}$. Avelumab exposure was not associated with increased incidence of IRR or TEAEs of any grade.

Figure 26: Relationship between $C_{trough,ss}$ and Probability of irAE1 (Left), TEAE1 (Right),



Source: ms-emr100070-001-002-003-exposure-safety-report.pdf, Figures 7 and 24.

4 Reviewer's Analysis

4.1 Introduction

The firm's PPK analysis shows a time-dependent under-prediction of concentration after 125 days of treatments when the typical two-compartment linear model was applied to describe the concentration-time data. The FDA reviewer conducted PPK analysis to explore the magnitude of this time-dependent CL change and to confirm the firm's proposed, clinical pharmacology labeling language.

4.2 Objectives

The FDA reviewer's analyses were to

- Confirm Sponsor's PPK analysis and the proposed clinical pharmacology label language.
- Explore the magnitude of time-dependent CL change and evaluate its impact on labeling.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 44.

Table 44 Summary of datasets used in the FDA reviewer's analysis.

Name	Link to EDR
avelumab-pa-260816a-csv.csv	\\cdsesub1\evsprod\bla761049\0007\m5\datasets\emr100070-001-002-003\analysis\adam\datasets\avelumab-pa-260816a-csv.csv
adresp.xpt	\\cdsesub1\evsprod\bla761049\0014\m5\datasets\emr100070-003\analysis\adam\datasets\adresp.xpt

- "avelumab-pa-260816a-csv.csv" was used to generate NONMEM dataset with log-transformed concentration data. The dataset was run against a two-compartment linear model (run005: body weight ~ CL and V1, IIV on all PK parameters, covariance between IIV on CL and V1, log-additive error model) to remove remaining outliers (CWRES>=6). The updated dataset "avelumab_260816a_NM_005.csv" was used in further analysis and served as the basis for:
  - Dataset "avelumab_260816a_NM_005_1dose.csv": PK data after the first dosing cycle
  - Dataset "avelumab_260816a_NM_005_cov_new_02.csv": certain covariate values were reassigned for exploratory covariate model development
- "adresp.xpt" was used to derive response status for patients in Study 003.

4.3.2 Software

NONMEM (v7.3), Pirana (2.9.0), and R (v3.2.2) were used for the FDA reviewer's analysis.

4.3.3 Analysis Method

To evaluate the extent of time-dependent PK, the FDA reviewer first analyzed the ratio of CL as derived from PK data in the first dosing cycle (run310) verse CL as derived from PK data in all available dosing cycles (run304). No covariates were included except for body weight on CL, V1, and V2. In the second step, with PK data from all available dosing cycles, a time-varying component was added to the CL term based on the following equations:

$$CL_{TDPKi} = TVCL \cdot e^{\frac{(T_{\max} + \eta_{T_{\max}}) \cdot DAY^{\gamma}}{T50 + DAY^{\gamma}}} \cdot Cov \cdot e^{\eta_i} \quad \text{, Equation 1}$$

Post hoc analysis of individual estimate of Tmax was reported as a measure of the magnitude of time-dependent CL change.

4.4 Results

The FDA reviewer's exploratory covariate model (run211) identified age, baseline albumin level, concomitant opioid use, dose level 3 mg/kg, dose level 1 mg/kg, pre-medication with diphenhydramine, gender, baseline tumor size, and body weight as significant covariates on CL. None of these covariates had clinically meaningful impact on avelumab exposure (Figure 35). This is consistent with proposed labeling language (i.e. no dose adjustment based on intrinsic and extrinsic factors). The geometric mean CL based on FDA reviewer's model is 0.0269 L/h, geometric mean Vss is 4.246 L, geometric mean terminal elimination half-life is 123 h, and the accumulation ratio is 1.18. These values are close to those in the propose label.

Individual CL estimates obtained from first dose data (CL-firstDose) are slightly higher than those obtained from all dose data (CL-allDose) (Figure 27). The average ratio between CL-firstDose and CL-allDose 0.958 (Median: 0.945).

Figure 27: Comparison of the Distribution of Individual Estimates of CL from the First Dose Cycle and from All Dose Cycles

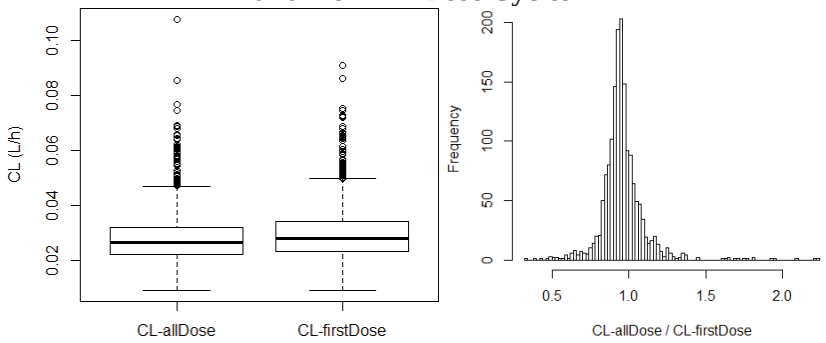


Figure 35: The Effect of Selected Covariates on AUCss (run211, 10 mg/kg dose only). Red lines represents 80-125% of AUCss in a typical patient (amount = 705 mg, CL = 0.0253 L/h).

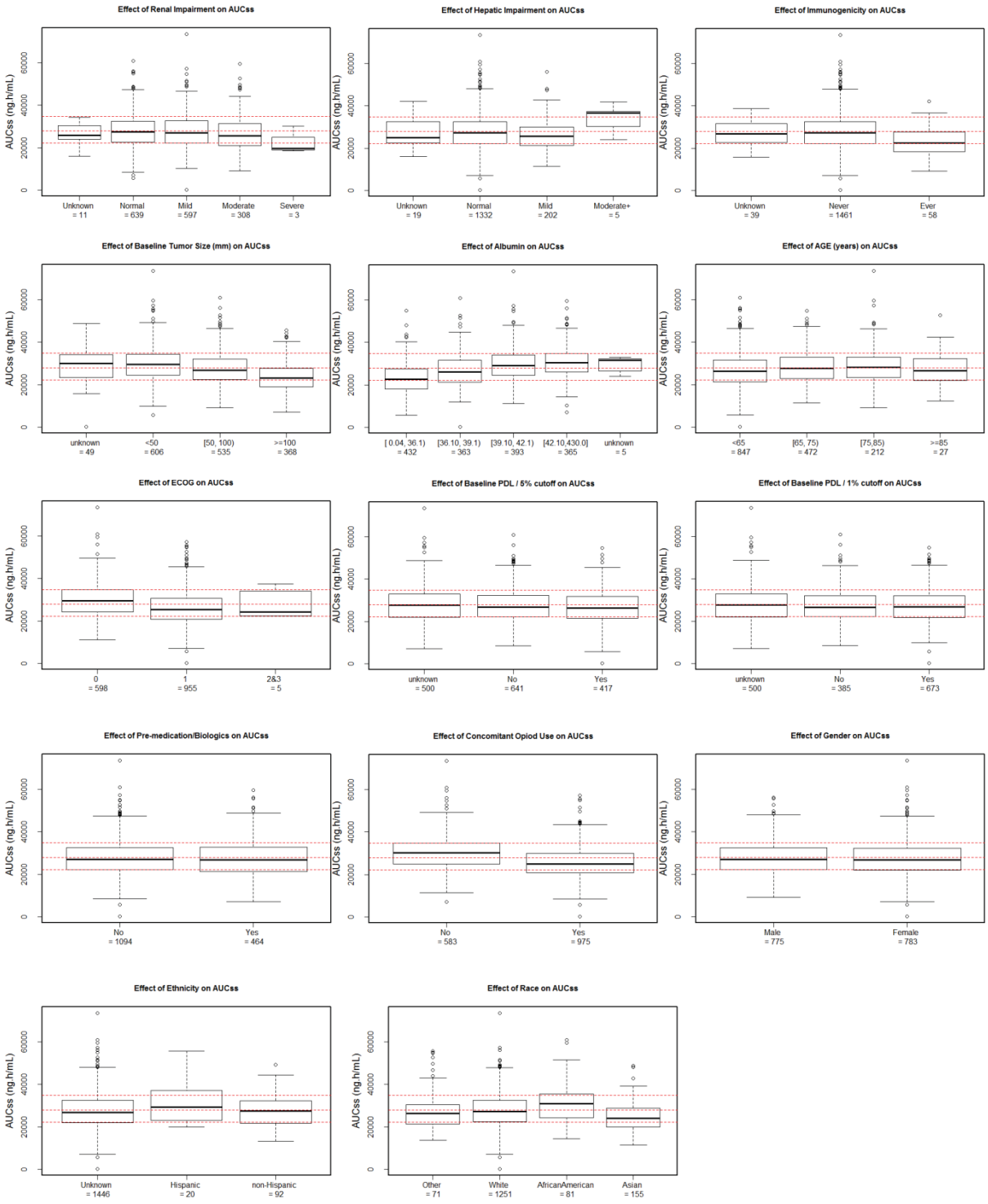


Table 47 in Appendix provides a comparison of model parameters where the time-varying CL model was excluded or incorporated (run211 vs 328: OFV -10465.5 vs -11530.9 and AIC -10423.5 vs. -11476.9 for a net increase of 6 parameters). The population estimate of Tmax is close to 0 while "MCC" and "solid tumor" types have significant effect on Tmax. It should be noted that all of the 88 MCC patients were from Study 003. In addition, "solid tumor" type was

the only tumor type defined at the dose escalation phase of Study 001 and 002, and it was the only tumor type that was associated with 1, 3, and 20 mg/kg dose levels. The effect of "solid tumor" type on CL is a mixture of different tumor types (e.g. ovarian cancer, breast cancer, NSCLC, etc.) and different dose levels.

Based on FDA reviewer's analysis, the median and average decrease from baseline CL after 6 months is -1.3% and -3.0%, respectively, indicating that the extent of time-dependent CL change is minimal in the entire study population. In MCC and solid tumor patients, the median percentage decrease at 6-month post dose is and 21.2% and 13.7% respectively. Post hoc analysis of individual Tmax (run328) renders an average (s.d.) Tmax of 0.00464 (0.262), -0.276 (0.255), and -0.161 (0.206) in the entire PPK population (n=1629), the MCC population (n=88), and the solid tumor population (n=70). A comparison of CWRES vs. TIME plots by study for run211 and 328 (Figure 28) suggests that the time-varying CL models does help reducing under-prediction at later time points, however, the impact is limited. There appears to be a trend where responders in MCC population have a more prominent time-dependent CL change as compared to non-responders (Figure 29), and a more consistent trend of decreasing CL over time as compared to non-responders (Figure 30).

Figure 28: CWRES vs TIME Plots Based on Study ID (run211-Upper; run328-Lower).

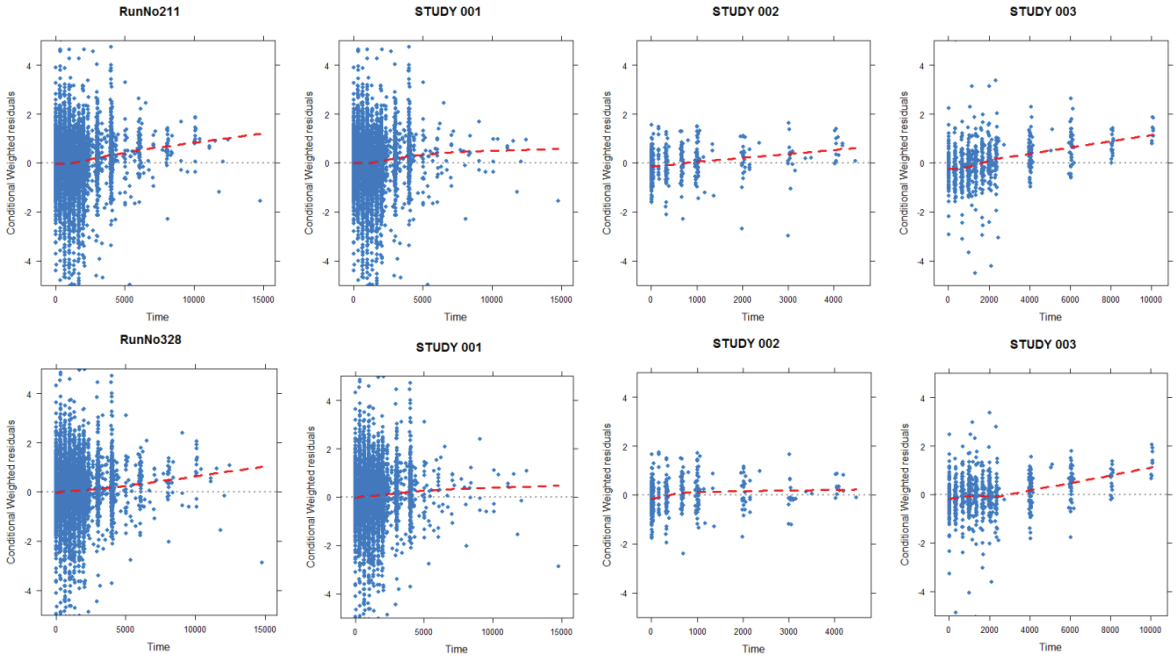


Figure 29 CWRES vs TIME Plots Based on Responder Status (run328, MCC population).

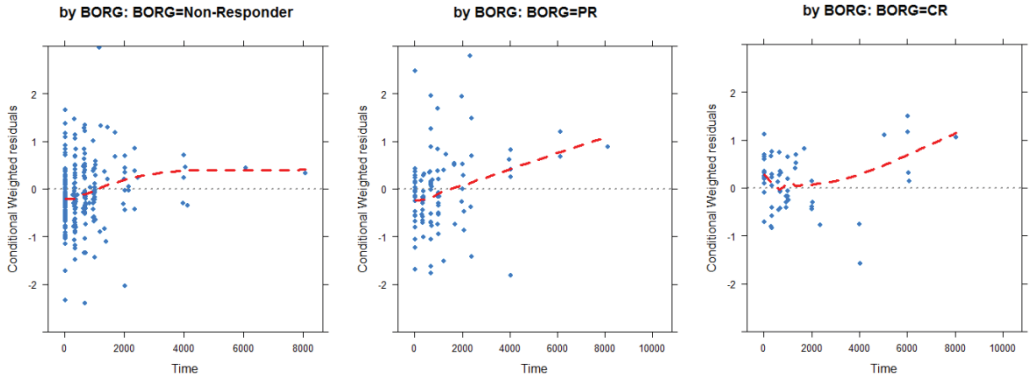
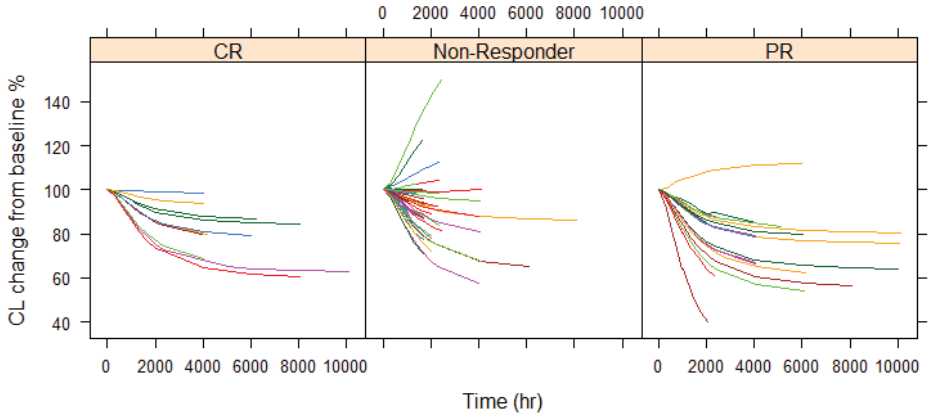
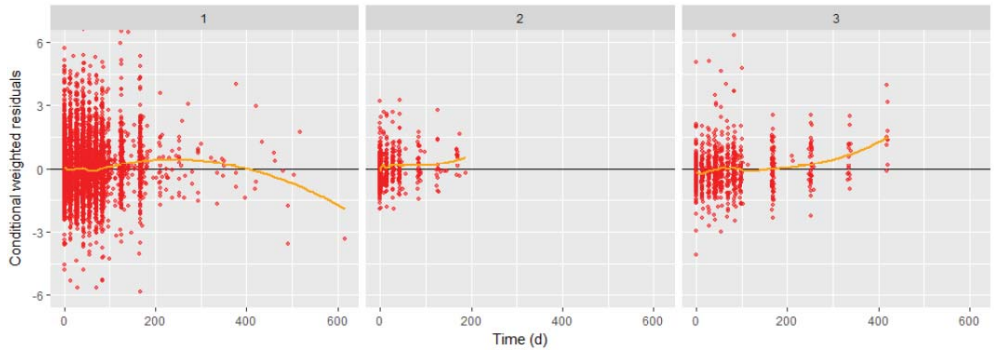


Figure 30: CL Change from Baseline over Time Based on Responder Status (run328, MCC population)



Reviewer's observation of CL decreasing over time was communicated with the sponsor. In response to information request (received on February 2, 2017 [redacted] (b) (4) the sponsor submitted updated PPK analyses including the time-variant CL. With the updated time-variant model, the OFV decreases by 674.1 (run143 compared to run124 in the original submission) for a net increase of 14 structural model parameters. Visual inspection of diagnostic plots suggested marginal improvement compared to the time-invariant PPK model (Figure 31). A post hoc analysis with the sponsor's updated model (run143) indicated that the average (s.d.) maximal change from baseline is -3.1% (18.6%), -41.7% (40.0%), and -24.1% (15.8%) in the entire PPK population (n=1629), the MCC (n=88) subgroup, and the solid tumor (n=70) subgroup. The FDA reviewer was able to repeat the sponsor's updated analysis. [redacted] (b) (4)

Figure 31: CWRES versus Time Plots for Sponsor's Time-Dependent PPK Model (run143).



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5 Appendix

Table 45: Summary of Covariate Information in the Dataset. *(Source: emr100070-001-002-003-population-pk-report.pdf, Table 5)*

Covariate	EMR100070-001	EMR100070-002	EMR100070-003	Total
Dose level				
1 mg/kg	4 (0.268%)	0 (0%)	0 (0%)	4 (0.246%)
3 mg/kg	13 (0.872%)	5 (9.8%)	0 (0%)	18 (1.1%)
10 mg/kg	1452 (97.4%)	40 (78.4%)	88 (100%)	1580 (97%)
20 mg/kg	21 (1.41%)	6 (11.8%)	0 (0%)	27 (1.66%)
Treatment duration (d)	84 {75.3} (14-769) [0]	84 {87.7} (14-728) [0]	126 {114} (14-532) [0]	84 {77.4} (14-769) [0]
Age (y)	63 {60.4} (20-91) [0]	62 {60.1} (30-77) [0]	72.5 {68.7} (33-88) [0]	63 {60.8} (20-91) [0]
Weight (kg)	70.6 {71.1} (30.4-204) [4]	55.5 {55.3} (35.2-89.3) [0]	82.7 {80.9} (47-153) [1]	70.5 {71} (30.4-204) [5]
Height (cm)	168 {168} (135-195) [25]	163 {161} (138-177) [0]	173 {171} (150-185) [1]	168 {168} (135-195) [26]
Sex				
Male	711 (47.7%)	35 (68.6%)	65 (73.9%)	811 (49.8%)
Female	779 (52.3%)	16 (31.4%)	23 (26.1%)	818 (50.2%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Race				
White	1227 (82.3%)	0 (0%)	81 (92%)	1308 (80.3%)
Black or African American	81 (5.44%)	0 (0%)	0 (0%)	81 (4.97%)
Asian	113 (7.58%)	51 (100%)	3 (3.41%)	167 (10.3%)
American Indian or Alaska Native	5 (0.336%)	0 (0%)	0 (0%)	5 (0.307%)
Native Hawaiian or other Pacific Islander	4 (0.268%)	0 (0%)	0 (0%)	4 (0.246%)
Other	60 (4.03%)	0 (0%)	1 (1.14%)	61 (3.74%)
Missing	0 (0%)	0 (0%)	3 (3.41%)	3 (0.184%)
Ethnicity				
Hispanic or Latino	16 (1.07%)	0 (0%)	4 (4.55%)	20 (1.23%)
Not Hispanic or Latino	0 (0%)	51 (100%)	58 (65.9%)	109 (6.69%)
Missing	1474 (98.9%)	0 (0%)	26 (29.5%)	1500 (92.1%)
BSA (m^2)	1.8 {1.8} (1.2-2.62) [30]	1.6 {1.58} (1.27-2.01) [0]	1.96 {1.93} (1.43-2.47) [2]	1.8 {1.8} (1.2-2.62) [32]
AST (U/L)	22 {23.4} (2-210) [5]	24 {24.1} (12-122) [0]	26 {27.7} (10-113) [0]	23 {23.7} (2-210) [5]
ALT (U/L)	19 {NC} (0-185) [5]	16 {16.4} (6-70) [0]	18.5 {18.3} (5-62) [0]	19 {NC} (0-185) [5]
Total Bilirubin (μmol/L)	6.84 {6.9} (0.51-12000) [8]	10.3 {9.13} (3.42-20.5) [0]	6.84 {7.19} (3.3-26) [0]	6.84 {6.98} (0.51-12000) [8]
Albumin (g/L)	39 {38.3} (0.04-430) [5]	37 {39} (21-310) [0]	40.4 {39.8} (24.1-53) [0]	39 {38.4} (0.04-430) [5]
Prothrombin (intl. normalized ratio)	1 {1.08} (0.71-72) [6]	1.03 {1.04} (0.93-1.24) [0]	1.04 {1.08} (0.84-2.94) [0]	1 {1.08} (0.71-72) [6]
Creatinine (μmol/L)	72.5 {74.7} (17.7-2560) [10]	62.8 {66.7} (33.6-114) [0]	81.3 {83} (34.5-194) [0]	73.4 {74.8} (17.7-2560) [10]
Creatinine clearance (mL/min)	83.1 {82.4} (2.2-150) [11]	73 {75.5} (40.8-139) [0]	77 {79.3} (41.7-150) [0]	82.3 {82} (2.2-150) [11]
Total protein (g/L)	70 {68.2} (0.06-689) [8]	64 {64.7} (49-77) [0]	69 {68.9} (53-89) [0]	70 {68.2} (0.06-689) [8]
eGFR (mL/min/1.73 m^2)	86.6 {84.9} (1.3-398) [10]	106 {102} (51.4-178) [10]	75.2 {78.4} (32.6-177) [10]	86.5 {85.0} (1.3-398) [10]
Renal impairment[1]				
None	628 (42.1%)	18 (35.3%)	25 (28.4%)	671 (41.2%)
Mild	560 (37.6%)	20 (39.2%)	43 (48.9%)	623 (38.2%)
Moderate	287 (19.3%)	13 (25.5%)	20 (22.7%)	320 (19.6%)
Severe	4 (0.268%)	0 (0%)	0 (0%)	4 (0.246%)
Missing	11 (0.738%)	0 (0%)	0 (0%)	11 (0.675%)
Formulation				
Process A only	557 (37.4%)	40 (78.4%)	88 (100%)	685 (42.1%)
Process B only	482 (32.3%)	9 (17.6%)	0 (0%)	491 (30.1%)
Both Process A and Process B	128 (8.59%)	1 (1.96%)	0 (0%)	129 (7.92%)
At least one missing lot number	323 (21.7%)	1 (1.96%)	0 (0%)	324 (19.9%)

Covariate	EMR100070-001	EMR100070-002	EMR100070-003	Total
Baseline immunogenicity status (HAHA)				
Negative (0)	1423 (95.5%)	48 (94.1%)	88 (100%)	1559 (95.7%)
Positive (1)	11 (0.738%)	0 (0%)	0 (0%)	11 (0.675%)
Missing	56 (3.76%)	3 (5.88%)	0 (0%)	59 (3.62%)
Immunogenicity status (HAHA, ever)				
Never positive (0)	1396 (93.7%)	48 (94.1%)	85 (96.6%)	1529 (93.9%)
Ever positive (1)	55 (3.69%)	3 (5.88%)	3 (3.41%)	61 (3.74%)
Missing	39 (2.62%)	0 (0%)	0 (0%)	39 (2.39%)
Hepatic impairment[2]				
None	1279 (85.8%)	42 (82.4%)	67 (76.1%)	1388 (85.2%)
Mild	188 (12.6%)	9 (17.6%)	20 (22.7%)	217 (13.3%)
Moderate	3 (0.201%)	0 (0%)	1 (1.14%)	4 (0.246%)
Severe	1 (0.0671%)	0 (0%)	0 (0%)	1 (0.0614%)
Missing	19 (1.28%)	0 (0%)	0 (0%)	19 (1.17%)
PD-L1 expression (%)	2 {NC} (0-100) [521]	0 {NC} (0-95) [11]	2 {NC} (0-100) [14]	2 {NC} (0-100) [546]
PD-L1 expression (1%)				
Negative (<1%)	352 (23.6%)	31 (60.8%)	16 (18.2%)	399 (24.5%)
Positive (>=1%)	617 (41.4%)	9 (17.6%)	58 (65.9%)	684 (42%)
Missing	521 (35%)	11 (21.6%)	14 (15.9%)	546 (33.5%)
PD-L1 expression (5%)				
Negative (<5%)	575 (38.6%)	31 (60.8%)	54 (61.4%)	660 (40.5%)
Positive (>=5%)	394 (26.4%)	9 (17.6%)	20 (22.7%)	423 (26%)
Missing	521 (35%)	11 (21.6%)	14 (15.9%)	546 (33.5%)
Tumor burden (mm)	60 {NC} (0-750) [49]	55.5 {58.5} (15-195) [1]	60 {NC} (0-404) [0]	60 {NC} (0-750) [50]
Number of non-target lesions				
1	309 (20.7%)	20 (39.2%)	13 (14.8%)	342 (21%)
2	297 (19.9%)	11 (21.6%)	12 (13.6%)	320 (19.6%)
3	216 (14.5%)	10 (19.6%)	9 (10.2%)	235 (14.4%)
4	100 (6.71%)	3 (5.88%)	10 (11.4%)	113 (6.94%)
5	80 (5.37%)	2 (3.92%)	13 (14.8%)	95 (5.83%)
6	36 (2.42%)	0 (0%)	10 (11.4%)	46 (2.82%)
7	28 (1.88%)	0 (0%)	3 (3.41%)	31 (1.9%)
8	19 (1.28%)	0 (0%)	4 (4.55%)	23 (1.41%)
9	6 (0.403%)	0 (0%)	1 (1.14%)	7 (0.43%)
10	9 (0.604%)	0 (0%)	2 (2.27%)	11 (0.675%)
11	5 (0.336%)	0 (0%)	0 (0%)	5 (0.307%)
12	1 (0.0671%)	0 (0%)	1 (1.14%)	2 (0.123%)
13	0 (0%)	0 (0%)	0 (0%)	0 (0%)
14	1 (0.0671%)	0 (0%)	0 (0%)	1 (0.0614%)
15	1 (0.0671%)	0 (0%)	0 (0%)	1 (0.0614%)
16	0 (0%)	0 (0%)	0 (0%)	0 (0%)
17	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18	1 (0.0671%)	0 (0%)	2 (2.27%)	3 (0.184%)
Missing	381 (25.6%)	5 (9.8%)	8 (9.09%)	394 (24.2%)
Relative dose intensity (%)	100 {96.6} (21.6-112) [0]	99.9 {98.6} (84.8-109) [0]	99.4 {94.8} (50-105) [0]	100 {96.6} (21.6-112) [0]
Number of prior anti-cancer therapies (NACT)				
1	406 (27.2%)	4 (7.84%)	52 (59.1%)	462 (28.4%)
2	332 (22.3%)	14 (27.5%)	26 (29.5%)	372 (22.8%)
3	221 (14.8%)	15 (29.4%)	7 (7.95%)	243 (14.9%)
4	141 (9.46%)	13 (25.5%)	3 (3.41%)	157 (9.64%)
5	94 (6.31%)	3 (5.88%)	0 (0%)	97 (5.95%)
6	58 (3.89%)	1 (1.96%)	0 (0%)	59 (3.62%)
7	36 (2.42%)	0 (0%)	0 (0%)	36 (2.21%)
8	25 (1.68%)	0 (0%)	0 (0%)	25 (1.53%)
9	14 (0.94%)	1 (1.96%)	0 (0%)	15 (0.921%)
10	11 (0.738%)	0 (0%)	0 (0%)	11 (0.675%)
11	4 (0.268%)	0 (0%)	0 (0%)	4 (0.246%)
12	1 (0.0671%)	0 (0%)	0 (0%)	1 (0.0614%)
13	1 (0.0671%)	0 (0%)	0 (0%)	1 (0.0614%)
14	1 (0.0671%)	0 (0%)	0 (0%)	1 (0.0614%)
Missing	145 (9.73%)	0 (0%)	0 (0%)	145 (8.9%)

Covariate	EMR100070-001	EMR100070-002	EMR100070-003	Total
ECOG status				
Fully active (0)	550 (36.9%)	35 (68.6%)	49 (55.7%)	634 (38.9%)
Restricted in physically strenuous activity (1)	935 (62.8%)	16 (31.4%)	39 (44.3%)	990 (60.8%)
Ambulatory, capable of selfcare but unable to work (2)	4 (0.268%)	0 (0%)	0 (0%)	4 (0.246%)
Capable of only limited selfcare (3)	1 (0.0671%)	0 (0%)	0 (0%)	1 (0.0614%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Concomitant paracetamol				
No	61 (4.09%)	1 (1.96%)	0 (0%)	62 (3.81%)
Yes	1429 (95.9%)	50 (98%)	88 (100%)	1567 (96.2%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Concomitant ibuprofen				
No	1174 (78.8%)	51 (100%)	72 (81.8%)	1297 (79.6%)
Yes	316 (21.2%)	0 (0%)	16 (18.2%)	332 (20.4%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Concomitant acetylsalicylic acid				
No	1245 (83.6%)	51 (100%)	67 (76.1%)	1363 (83.7%)
Yes	245 (16.4%)	0 (0%)	21 (23.9%)	266 (16.3%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Concomitant opioids				
No	552 (37%)	32 (62.7%)	32 (36.4%)	616 (37.8%)
Yes	938 (63%)	19 (37.3%)	56 (63.6%)	1013 (62.2%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Concomitant systemic corticosteroids				
No	1020 (68.5%)	33 (64.7%)	65 (73.9%)	1118 (68.6%)
Yes	470 (31.5%)	18 (35.3%)	23 (26.1%)	511 (31.4%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Concomitant biologics				
No	988 (66.3%)	36 (70.6%)	85 (96.6%)	1109 (68.1%)
Yes	502 (33.7%)	15 (29.4%)	3 (3.41%)	520 (31.9%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Previous biologics				
No	1028 (69%)	40 (78.4%)	88 (100%)	1156 (71%)
Yes	462 (31%)	11 (21.6%)	0 (0%)	473 (29%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Premedication with diphenhydramine				
No	401 (26.9%)	7 (13.7%)	29 (33%)	437 (26.8%)
Yes	1089 (73.1%)	44 (86.3%)	59 (67%)	1192 (73.2%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Premedication with acetaminophen				
No	334 (22.4%)	4 (7.84%)	28 (31.8%)	366 (22.5%)
Yes	1156 (77.6%)	47 (92.2%)	60 (68.2%)	1263 (77.5%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Continuous covariates are shown as median {geometric mean} (range) [missing]. Categorical covariates are shown as count (%). NC=not calculable.

1 Renal impairment was defined as follows: Normal renal function: creatinine clearance (CRCL)>=90 mL/min, Mild renal impairment: CRCL >= 60 and < 90 mL/min, Moderate renal impairment: CRCL >= 30 and < 60 mL/min, Severe renal impairment: CRCL < 30 mL/min.

2 Hepatic impairment defined as follows: Normal hepatic function: bilirubin (BILI)<= Upper limit of normal (ULN) and AST <= ULN, Mild hepatic impairment: (BILI<= ULN and AST> ULN) or (BILI > 1*ULN and BILI <= 1.5 * ULN and any AST), Moderate hepatic impairment: BILI > 1.5*ULN and BILI <= 3 * ULN, Severe hepatic impairment: BILI >3*ULN.

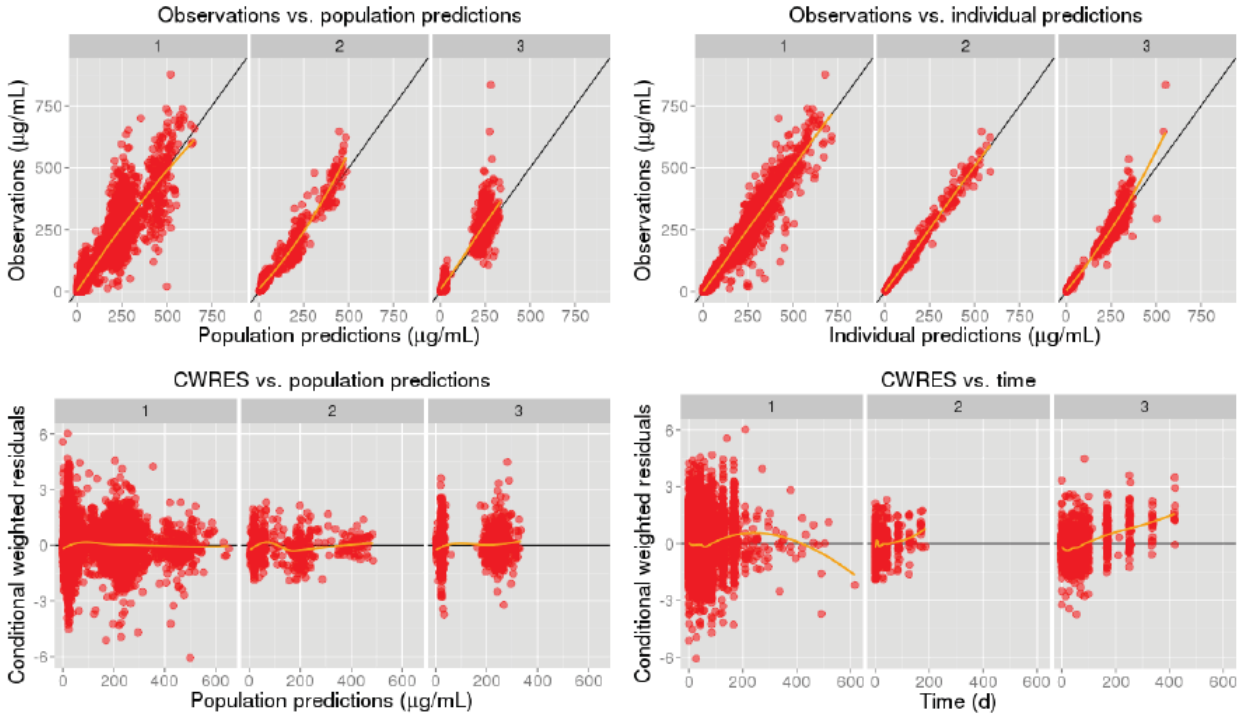
Extreme values of covariates were observed in two patients (total bilirubin in 4050009, and creatinine, creatinine clearance and eGFR in 1010021). These are likely to reflect errors in the data. Extreme values likely to inappropriately influence covariate selection during modeling were capped as described in section 5.4.3.

Table 46: Parameter Estimates for the Base Model (run 042)

Parameter	Estimate	%RSE	95% CI	Shrinkage
Clearance (CL, L/h)	0.0268	1.04	0.0263-0.0274	
Central volume (V_1, L)	3.16	0.832	3.11-3.21	
Peripheral volume (V_2, L)	1.01	6.5	0.878-1.13	
Intercompartmental clearance (Q, L/h)	0.0263	7.73	0.0223-0.0303	
Baseline weight on CL	0.462	8.34	0.387-0.538	
Baseline weight on V_1	0.509	6.03	0.449-0.569	
Interindividual variability				
IIV on CL (ω^2_{CL}, variance)	0.0919	5.00	0.0829-0.101	16.1
cov(CL,V_1) ($\omega_{CL,V1}$, covariance)	0.0322	8.92	0.0265-0.0378	
IIV on V_1 (ω^2_{V1}, variance)	0.0394	5.79	0.0349-0.0439	35.3
IIV on V_2 (ω^2_{V2}, variance)	1.28	7.83	1.09-1.48	37.9
IIV on Q (ω^2_{Q}, variance)	0.150	29.6	0.0629-0.237	81.8
Residual variability				
Proportional residual error (σ_{add})	0.169	0.648	0.166-0.171	12.7
Additive residual error (σ_{add}, µg/mL)	2.79	1.49	2.71-2.87	

Source: emr100070-001-002-003-population-pk-report.pdf, Table 6.

Figure 32: Basic Diagnostic Plots for the Base Population PK Model for Avelumab (run 042)



Source: emr100070-001-002-003-population-pk-report.pdf, Figure 5.

Figure 33: Simulated AUC_{ss} (Upper) and $C_{trough,ss}$ (Lower) by Body Weight. N=100,000 simulated datasets. Black horizontal line: median. Box: interquartile range. Solid red horizontal line: population median of body weight. Red shaded area: 80-120% range. Other covariates set to population median or most common category. (Source: emr100070-001-002-003-population-pk-report.pdf, Figures 17 and 19)

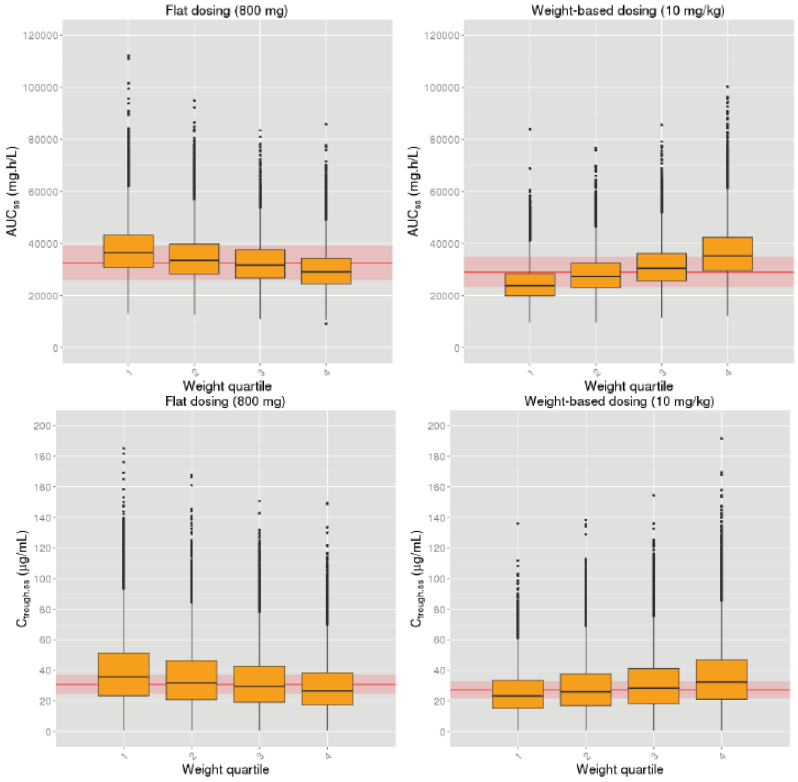


Figure 34: Comparison of Individual Predictions from the Base Model (run 042) and the Final Model (run 124) (*Source: emr100070-001-002-003-population-pk-report.pdf, Figure 44*).

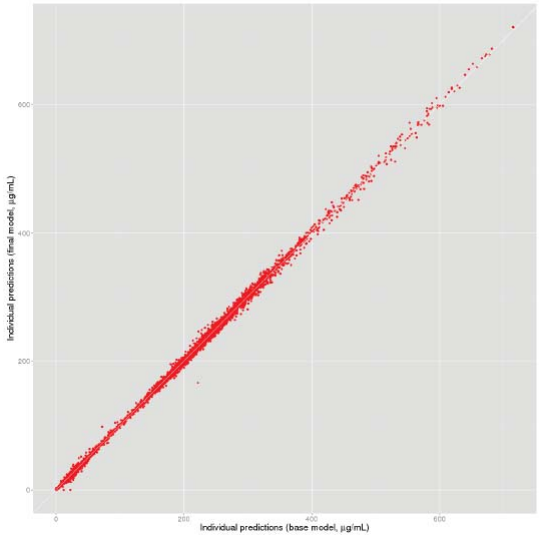


Figure 35: The Effect of Selected Covariates on AUCss (run211, 10 mg/kg dose only). Red lines represents 80-125% of AUCss in a typical patient (amount = 705 mg, CL = 0.0253 L/h).

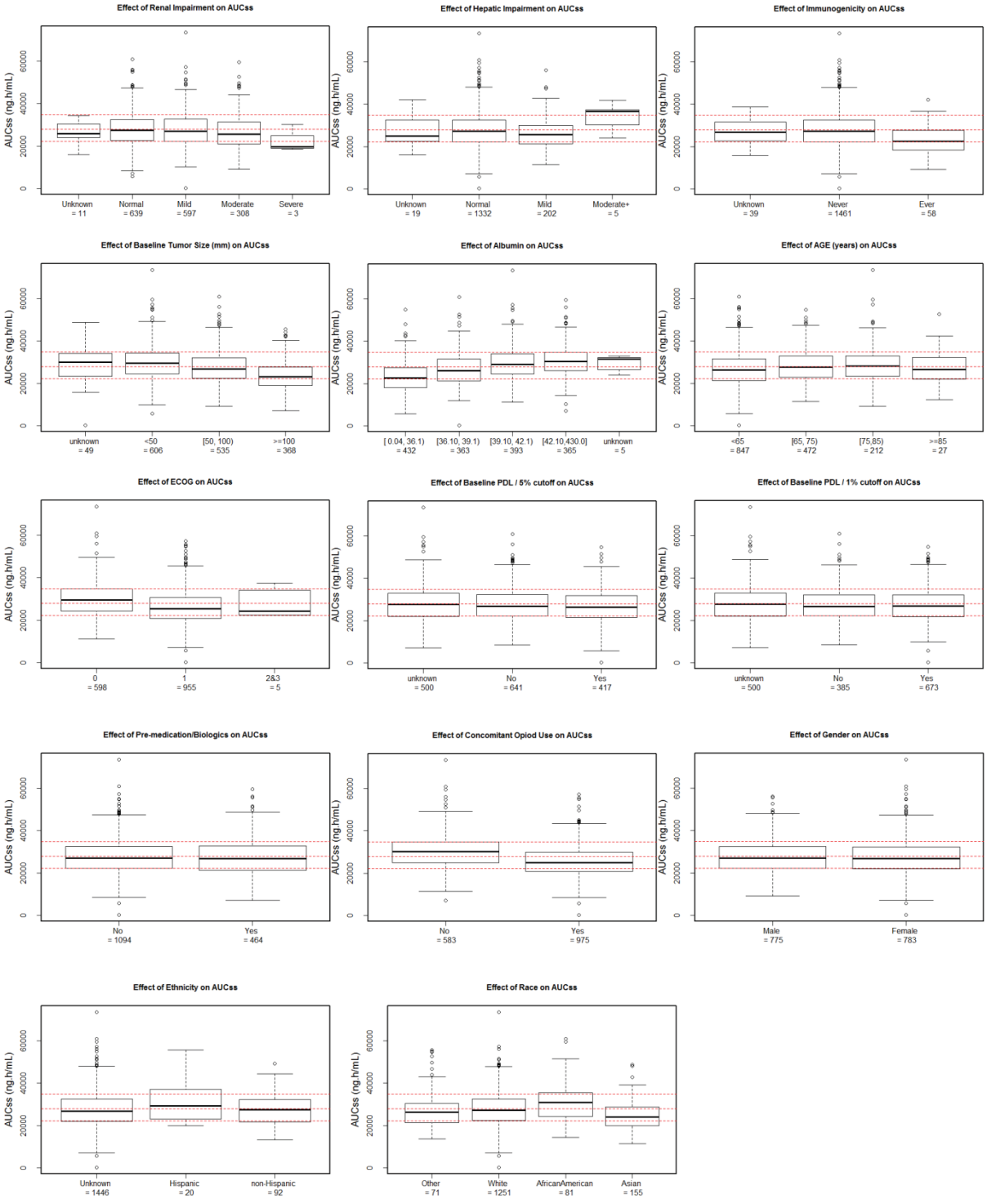


Table 47: Summary of FDA Reviewer's Model Parameters. Parameters are presented as "estimate / RSE% / shrinkage% (if applicable)".

	run304	run211	Run328
Description	base model	covariate model	covariate mode + Equation 1
OFV	-9968.9	-10465.5	-11530.9
AIC	-9942.9	-10423.5	-11476.9
Theta			
CL	0.0266 / 1% /	0.0253 / 1% /	0.0255 / 1% /
V1	3.13 / 1% /	3.14 / 1% /	3.14 / 1% /
V2	0.86 / 8% /	0.837 / 9% /	0.744 / 9% /
Q	0.0216 / 11% /	0.0218 / 12% /	0.0229 / 14% /
Log-additive Error	0.274 / 0 /	0.273 / 0 /	0.24 / 0 /
CL_AGE_power		-0.0024 / 24% /	-0.0019 / 29% /
CL_ALB_linear		-0.591 / 8% /	-0.594 / 8% /
CL_opioid_linear		-0.105 / 13% /	-0.0877 / 15% /
CL_3mg/kg_linear		0.221 / 37% /	0.261 / 30% /
CL_1mg/kg_linear		0.423 / 89% /	0.453 / 71% /
CL_PREDIP_linear		0.0514 / 8% /	0.0148 / 28% /
CL_SEX_linear		0.081 / 21% /	0.0891 / 18% /
CL_TSB_linear		0.0015 / 9% /	0.0014 / 9% /
CL_WTB_linear	0.488 / 9% /	0.0064 / 7% /	0.0066 / 9% /
V1_WTB_power	0.498 / 7% /	0.502 /7% /	0.511 / 6% /
V2_WTB_power	0.602 / 38% /	0.656 / 34% /	0.527 / 49% /
Tmax			0.0225 / 74% /
SolidTumor_Tmax_linear			-0.197 / 44% /
MCC_Tmax_linear			-0.307 / 21% /
T50			71 / 4% /
gamma			1.8 / 4% /
Omega			
CL	0.0977 / 5% /13%	0.0644 / 5% /17%	0.0619 / 5% /17%
V1	0.0304/ 7% /42%	0.0305/ 7% / 45%	0.0331/ 7% / 42%
V2	1.45 / 8% / 39%	1.41 / 8% / 37%	1.08/ 11% / 42%
Q	0.425/ 15% / 77%	0.541/ 20% / 76%	0.651 / 11% / 47%
Tmax			0.142 / 9% / 32%
T50			
Sigma	1 / / 12%	1 / / 12%	1 / / 15%

Table 48: Comparison of Parameter Estimates from Sponsor's Time-Invariant (BLA Model) and the Time-Variant (Model 1) PPK models.

	BLA Model	Model 1 (Wang)
Clearance (CL/CL_L, L/h)	0.02457 (1.32)	0.02495 (1.29)
Time-varying CL (CL_T, L/h)	-	-
Central volume (V1, L)	2.826 (1.23)	2.805 (1.24)
Peripheral volume (V2, L)	1.173 (6.90)	1.113 (6.55)
Intercompartmental clearance (Q, L/h)	0.05265 (9.21)	0.04867 (9.11)
T_{max} (solid tumors)	-	-0.2435 (25.3)
T_{max} (MCC)	-	-0.4203 (19.7)
T_{max} (other tumor types)	-	0 (-)
T_{50} (d, GEJ)	-	62.08 (5.78)
T_{50} (d, UC)	-	66.15 (10.9)
T_{50} (d, NSCLC)	-	73.93 (2.66)
T_{50} (d, metastatic breast)	-	89.08 (7.97)
T_{50} (d, MCC)	-	151.7 (26.8)
T_{50} (d, other tumor types)	-	68.8 (5.45)
Gamma (γ, solid)	-	0.7253 (22.5)
Gamma (γ, GEJ)	-	3.022 (13.7)
Gamma (γ, ovarian)	-	2.544 (14.6)
Gamma (γ, UC)	-	2.334 (17.2)
Gamma (γ, NSCLC)	-	3.644 (11.1)
Gamma (γ, metastatic breast)	-	2.623 (13.1)
Gamma (γ, MCC)	-	1.598 (14.2)
Gamma (γ, other tumor types)	-	2.853 (8.52)
Decay coefficient (k_{des}, solid)	-	-
Decay coefficient (k_{des}, MCC)	-	-
Decay coefficient (k_{des}, other tumor types)	-	-
Baseline weight on CL	0.358 (10.2)	0.3486 (10.2)
Baseline weight on V1	0.3668 (8.19)	0.3640 (8.27)
Baseline albumin on CL	-0.4997 (4.86)	-0.4974 (5.61)
3 mg/kg dose level on CL	0.2597 (33.9)	0.2951 (32.2)
Male sex on CL	0.1992 (10.6)	0.2022 (10.1)
Baseline tumor size on CL	0.09483 (8.70)	0.0882 (8.59)
MCC tumor type on CL	-0.2241 (11.0)	-
Premedication with acetaminophen on Q	-0.5601 (5.88)	-0.4624 (12.1)
NSCLC tumor type on Q	-0.6922 (6.31)	-0.365 (34.9)
MCC tumor type on Q	-0.8638 (1.84)	-0.7013 (13.7)
Male sex on V1	0.2032 (9.69)	0.2097 (9.46)
eGFR on V2	-0.5074 (27.9)	-0.3832 (34.2)
Premedication with acetaminophen on V2	-0.2331 (13.3)	-0.2303 (13.6)
Head & neck tumor type on V2	0.7260 (40.5)	0.9694 (29.2)
Ovarian tumor type on V2	-0.3363 (26.9)	-0.2311 (41.2)
MCC tumor type on V2	8.578 (25.2)	-
HAHA (ever) on V2	-0.6674 (12.4)	-0.6696 (13.4)
IIV on CL (exponential, %CV)	25.2 (5.16[a])	24.2 (5.20[a])
IIV on V1 (exponential, %CV)	18.3 (5.83[a])	18.4 (5.79[a])
IIV on V2 (exponential, %CV)	105.2 (8.49[a])	89.4 (9.16[a])
IIV on Q (exponential, %CV)	39.3 (29.8[a])	-
IIV on T_{max} (additive, SD)	-	0.261 (9.79[a])
IIV on K_{des} (additive, SD)	-	-
Proportional residual error (%)	16.4 (0.654[a])	15.7 (0.613[a])
Additive residual error (SD, µg/mL)	2.91 (1.39[a])	2.41 (1.41[a])

Source: Response to FDA Request for Information No. 2_ 12 Jan 2017.pdf, submitted on Feb 2, 2017, (b) (4).

14 Division Director (DHOT): John Leighton

X

15 Division Director (OCP): Nam Atiqur Rahman

X

16 Division Director (OB): Rajeshwari Sridhara

X

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical): Patricia Keegan

X

18 Office Director (or designated signatory authority): Richard Pazdur

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