# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761334Orig1s000

# MULTI-DISCIPLINE REVIEW

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

# BLA Multi-disciplinary Review and Evaluation

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

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|---|---|
| **Application Type** | NME, 351(a) |
| **Application Number(s)** | BLA 761334 |
| **Priority or Standard** | Priority |
| **Submit Date(s)** | August 6, 2022 |
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| **Division/Office** | Division of Oncology 3/Office of Oncologic Diseases |
| **Review Completion Date** | Refer to electronic stamp date |
| **Established Name** | Retifanlimab-dlwr |
| **(Proposed) Trade Name** | Zynyz |
| **Pharmacologic Class** | PD-1 blocking antibody |
| **Code name** | INCMGA00012 |
| **Applicant** | Incyte Corporation |
| **Formulation(s)** | Injection |
| **Dosing Regimen** | 500 mg/20 mL (25 mg/mL) |
| **Applicant Proposed Indication(s)/Population(s)** | For the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma. |
| **Recommendation on Regulatory Action** | Accelerated Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | For the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma. |

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OMPI=Office of Medical Policy Initiatives
DMPP= Division of Medical Policy Programs

# Glossary

| | |
|---|---|
| ADA | antidrug antibodies |
| ADCC | antibody-dependent cell-mediated cytotoxiciy |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BLA | Biologics License Application |
| BLQ | below the limit of quantification |
| BMI | body mass index |
| CDC | complement-dependent cytotoxicity |
| CD4 | cluster of differentiation 4 |
| CD8 | cluster of differentiation 8 |
| CI | confidence interval |
| CL | clearance |
| COVID-19 | corona virus disease 2019 |
| CR | complete response |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| DCR | disease control rate |
| DDI | drug-drug interaction |
| DMC | data monitoring committee |
| DOR | duration of response |
| DP | drug product |
| DS | drug substance |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eGFR | estimated glomerular filtration rate |
| ELISA | enzyme-linked immunosorbent assay |
| EMA | European Medicines Agency |
| EOT | end of treatment |
| E-R | exposure-response |
| FAS | full analysis set |
| Fc | fragment crystallizable |
| FDA | Food and Drug Administration |
| FTD | Fast Track Designation |
| GVHD | graft-versus-host-disease |
| HIV | human immunodeficiency virus |
| HRP | horseradish peroxidase |
| HSCT | hematopoietic stem cell transplantation |
| ICH | International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICR | independent central radiographic review |
| IFN-γ | interferon gamma |
| IgG | immunoglobulin G |
| IgG4 | immunoglobulin G4 |
| IHC | immunohistochemistry |
| irAE | immune-related adverse event |

| | |
|---|---|
| ISI | Integrated Summary of Immunogenicity |
| ISS | Integrated Summary of Safety |
| IV | intravenous(ly) |
| LDH | lactate dehydrogenase |
| LPLV | last participant last visit |
| mAb | monoclonal antibody |
| MCC | Merkel cell carcinoma |
| MCPyV | Merkel cell polyomavirus |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MSD-ECL | Meso Scale Discovery electroluminescence |
| NAb | neutralizing antibody |
| NCA | noncompartmental analysis |
| NCCN | National Comprehensive Cancer Network |
| NE | not estimable |
| NME | New molecular entity |
| NR | not reached |
| NSCLC | non-small cell lung cancer |
| ORR | objective response rate |
| OS | overall survival |
| PBS | phosphate buffered saline |
| PD | progressive disease |
| PD-1 | programmed death receptor-1 |
| PD-L1/2 | programmed death receptor-ligand 1/2 |
| PFS | progression-free survival |
| PK | pharmacokinetic(s) |
| PPK | population pharmacokinetic |
| PR | partial response |
| PT | preferred term |
| QT | QT interval in electrocardiogram tracings |
| QTc | QT interval corrected |
| QxW | every x weeks |
| RECIST v1.1 | Response Evaluation Criteria in Solid Tumors version 1.1 |
| SCAC | squamous carcinoma of the anal canal |
| SD | stable disease |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| Tim-3 | T-cell immunoglobulin mucin 3 |
| TPF | time pressure filled |
| TSH | thyroid-stimulating hormone |
| ULN | upper limit of normal |
| US | United States |
| UV | ultraviolet |

# 1 Executive Summary

## 1.1. Product Introduction

Retifanlimab-dlwr (retifanlimab) is a is a humanized, hinge-stabilized, IgG4κ monoclonal antibody that recognizes human PD-1, and it contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1–expressing cells, including T cells, and restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2. At the time of submission of the current Biologics Licensing Application (BLA) 761334 on August 6, 2022, retifanlimab was not yet approved for any indication in the United States. The Applicant's proposed indication is for the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data that provide substantial evidence of the safety and effectiveness of retifanlimab for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) administered at a dose of 500 mg every 4 weeks (q4w). (b) (4) (b) (4)

The review team concluded that the submitted data provide substantial evidence of the safety (n=105) and efficacy (n=65) of retifanlimab for the adult patients with MCC. This conclusion is based on the results of Study INCMGA 0012-201 (POD1UM-201), an open-label, multiregional, single-arm study in 65 patients ≥12 years of age with metastatic or recurrent locally advanced MCC who had not received prior systemic therapy for their advanced disease. Patients received retifanlimab 500 mg q4w until disease progression, unacceptable toxicity, or up to 24 months. The primary efficacy endpoint was objective response rate (ORR) as assessed by an independent central review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. ORR of an individual drug generally can be interpreted in a single-arm setting because tumors generally do not shrink on their own.

The ORR in the primary efficacy analysis population of Study 201 was 52% (34/65) (95% confidence interval [CI]: 40, 65) with 12 patients experiencing a complete response. Of the 34 patients who experienced an objective response, duration of response (DOR) was ≥6 months for 76% of patients and ≥12 months for 62% of patients.

As a supportive analysis based on updated data submitted to the BLA, FDA also analyzed ORR and DOR in all chemotherapy-naïve MCC patients enrolled in PODIUM-201. Per ICR assessment, among 101 patients, 52 were responders (16 with CR and 36 with PR) with ORR of 51.5% (95%

CI: 41%, 62%); 67% of responding patients had DOR ≥6 months and 40.4% had DOR ≥12 months. Per Investigator assessment, among 101 patients, 59 were responders (19 with CR and 40 with PR) with ORR of 58% (95% CI: 48%, 68%); 76% of responding patients had DOR ≥6 months and 52.5% had DOR ≥12 months. In an additional supportive analysis, the applicant reported that three of six patients with chemotherapy refractory disease responded to treatment.

The safety of retifanlimab has been adequately characterized based on the data from PODIUM-201 in 105 adult patients with MCC and by additional supportive data from other studies in the retifanlimab development program. Anti-PD-1 antibodies have a well-characterized safety profile. During the review, FDA noted the safety profile is generally consistent with the known safety profile of other anti-PD-1 antibodies. Per the Office of Scientific Investigations, underreporting of adverse events (AEs) was found at 2 of the 3 sites that were inspected. The unreported AEs were not serious and did not lead to study discontinuation and there were no other unreported adverse events upon review of the patient charts at the site.

The review team recommends granting Accelerated Approval to retifanlimab for the treatment of adult patients with metastatic or recurrent locally advanced MCC. Data from additional patients with MCC will be requested to verify and confirm the durability of the clinical effect on overall response rate.

## 1.3. Benefit-Risk Assessment (BRA)

**Benefit-Risk Summary and Assessment**

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin that typically affects sun-exposed skin of older adults and has a high propensity for recurrence and metastases. The global incidence of MCC ranges from 0.1 to 1.6 cases per 100,000 people per year. MCC is more common in males, occurs most commonly in the head and neck, and in immunosuppressed individuals (Walsh, et al). The prevalence of MCC varies among ethnic groups and geographic areas. The most typical patient is an elderly white male in his seventies or eighties with a history of extensive sun exposure, although MCC has also been reported in Black, Asian, American Indian, and Pacific Islander patients. MCC is approximately 25 times more common in whites compared to other ethnic groups. Incidence rates based on epidemiologic studies in Northern Europe align closely with US figures (Coggshall). Tumors that are positive for Merkel cell polyomavirus (MCPyV) large tumor antigen have a relative better prognosis, including reduced risk of recurrence and improved disease-specific survival. MCPyV is a nonenveloped, double-stranded DNA virus that has been causally linked to the development of MCC. A 2015 meta-analysis of 23 studies found an overall MCPyV prevalence of 79 % (95% CI: 72, 84) in Merkel cell tumors versus 12% (95% CI: 8, 9) in control skin samples (Santos-Juanes J et al). The preferred treatment for MCC is with the immune checkpoint inhibitors (ICI) avelumab and pembrolizumab. Avelumab and pembrolizumab have accelerated approval for the patients with advanced or metastatic MCC. If patients have a contraindication to ICI, cytotoxic chemotherapy is the treatment of choice (NCCN 2022). Five-year overall survival estimates are 76%, 56%, and 23% for local, nodal, and distant disease, respectively. (SEER data)

The efficacy of retifanlimab (n=65) for the proposed indication is supported by the results from PODIUM-201, an open-label, single-arm, multicenter study that enrolled patients with metastatic or recurrent locally advanced MCC who had not received prior systemic therapy for their advanced disease. The major efficacy endpoint was overall response rate (ORR) assessed by an independent central review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The ORR was 52% (34/65), 95% confidence interval [CI]: 40, 65) with 12 (18%) experiencing a complete response. Of the 34 patients who experienced an objective response, duration of response was ≥6 months for 76% of patients and ≥12 months for 62% of patients.

Safety data supporting the indication reflected exposure to retifanlimab in 105 patients with MCC enrolled on the PODIUM study which includes the 65 patients in the primary efficacy population. The safety profile of anti-PD-1 antibodies has been well-characterized from other approvals in this drug class. The safety profile of retifanlimab is consistent with the known safety profile of other anti-PD-1 antibodies. No new

safety signals for this class of drug was identified.

A favorable risk:benefit has been established for retifanlimab for the treatment of adult patients with metastatic or recurrent locally advanced MCC based on the results of a single study, PODIUM. Given the rarity of MCC and small sample size, there are limited data to draw conclusions regarding subgroup analyses (i.e., race, age, sex, etc.) from this application.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin.<br>• The highest incidence of MCC was observed in whites, males, and in people older than 65 years.<br>• Data from the Surveillance, Epidemiology, and End Results (SEER) Program database indicate that in the United States, the estimated annual incidence rate rose from 0.5 cases per 100,000 persons in 2000 (95% CI 0.4-0.5) to 0.7 cases per 100,000 persons in 2013 (95% CI 0.7-0.8)<br>• Merkel cell polyomavirus (MCPyV) is present in 80% of patients with MCC<br>• Five-year overall survival estimates of 76%, 56%, and 23% for local, nodal, and distant disease, respectively. | Patients with metastatic and recurrent MCC represent a rare patients population with a serious and life-threatening disease. |
| **Current Treatment Options** | • There are two available therapies for MCC<br>• Avelumab was approved in 2017 for adults and pediatric patients ≥12 with metastatic MCC. The overall response rate was 33%. Duration of response (DOR) was ≥6 months for 86% of patients and ≥12 months for 45% of patients.<br>• Pembrolizumab was approved in 2018 for adult and pediatric patients with recurrent locally advanced or metastatic MCC. The ORR was 56% | There are two available treatments for patients with recurrent of metastatic MCC approved under the accelerated approval pathway. Confirmation of clinical benefit has not been established for either drug. There is no data to support either drug prolongs survival. Therefore, an unmet medical need |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | and duration of response was ≥6 months for 96% of patients and ≥12 months for 54% of patients. | remains in this patient population. |
| **Benefit** | • The efficacy of retifanlimab was evaluated in the PODIUM study.<br>• The ORR was 52% (95% confidence interval [CI]: 40, 65) with 12 (18%) experiencing a complete response<br>• Of the 34 patients who experienced an objective response, duration of response was ≥6 months for 76% of patients and ≥12 months for 62% of patients | The PODIUM study demonstrated a clinically meaningful and durable response rate.<br>The submitted data meets the evidentiary standards for accelerated approval in the proposed patient population. |
| **Risk and Risk Management** | • Well characterized toxicities appeared to occur at a lower incidence than other anti-PD-1 antibodies. | The overall risk profile for retifanlimab is acceptable for the treatment of a serious and life-threatening condition and is consistent with the well characterized safety profile of other anti-PD-1 antibodies. |

## 1.4. Patient Experience Data

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

| | | | | | |
|---|---|---|---|---|---|
| X | The patient experience data that was submitted as part of the application, include: | | | | Section where discussed, if applicable |
| | □ | Clinical outcome assessment (COA) data, such as | | | |
| | | | X | Patient reported outcome (PRO) | Section 9.2.5 and Tables 3.7.1 and 3.7.2 of the CSR |
| | | | □ | Observer reported outcome (ObsRO) | |
| | | | □ | Clinician reported outcome (ClinRO) | |
| | | | □ | Performance outcome (PerfO) | |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | | |
| | □ | Observational survey studies designed to capture patient experience data | | | |
| | □ | Natural history studies | | | |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | | |
| | □ | Other: (Please specify) | | | |
| □ | Patient experience data that was not submitted in the application, but was considered in this review. | | | | |

PODIUM-201 study assessed PRO data as an exploratory endpoint using the EuroQol-5D (EQ-5D) and Functional Assessment of Cancer Therapy – Melanoma (FACT-M). No formal analysis was performed.

X

Leslie Doros, MD
Cross-Disciplinary Team Leader

# 2 Therapeutic Context

## 2.1. Analysis of Condition

The Applicant's Position:

Merkel cell carcinoma is an ultra-rare, aggressive, life threatening, cutaneous malignancy. Approximately 2500 cases are diagnosed each year in the US (Bradford 2020, Paulson 2018). The approximate annual incidence is 0.13 per 100,000 in Europe (van der Zwan 2013).

Merkel cell carcinoma is an immunogenic tumor. Cell surface expression of PD-L1 by tumor cells and tumor infiltrating lymphocytes is present in approximately half of MCC tumor specimens (Lipson 2013). Approximately 80% of MCCs are associated with MCPyV infection (Feng 2008). The MCPyV DNA integrates in the host cell genome, resulting in persistent expression of MCPyV T antigens (Feng 2008). Peripheral blood and tumors from most patients with MCPyV-positive MCC contain MCPyV-specific T cells (Lipson 2013). PD-1, as well as Tim-3, are frequently highly expressed on MCPyV-specific T cells and MCC-infiltrating lymphocytes (Afanasiev 2013). The remainder of MCCs that are not MCPyV-positive are associated with UV exposure, which results in DNA damage and multiple oncogenic mutations that may generate neoantigens for immune recognition (Goh 2009, Harms 2015, Knepper 2019, Wong 2015).

The principal environmental risks for MCC are UV radiation and MCPyV infection; as a result, elderly, fair-skinned individuals with a history of chronic sun exposure have the highest risk of developing MCC (Dellambra 2021Dellambra 2021, Gauci 2022, Harms 2016, Paulson 2018). Approximately two-thirds of cases are diagnosed in males; non-White patients represent only 2.2% to 3.5% of cases (Gauci 2022, Harms 2016, Paulson 2018, Yaghi 2022). Immunocompromised status (eg, due to other malignancies, HIV, or solid organ transplant) is also a recognized risk factor for MCC (Clarke 2015, Dellambra 2021, Engels 2002, Koljonen 2009, Paulson 2018, Yaghi 2022).

In individuals younger than 30 years, MCC is rare (< 1% of cases; Paulson and Nghiem 2019). Six case reports of patients in the pediatric age group have been published (Bajciova 2013Bajciova 2013, Dunker 1988, Gherardi 1990, Köksal 2009, Marzban 2011, Schmid 1992). The disease in younger patients tends to present at more advanced stages and with more frequent distant spread (Paulson and Nghiem 2019). The disease in younger patients tends to present at more advanced stages and with more frequent distant spread (Paulson and Nghiem 2019). Because of the histomorphological features of MCC, definitive diagnosis is made based on IHC for both adult and pediatric patients. Identification of cytokeratin 20 is specific for the tumor type (NCCN 2022). In the pediatric age group, seropositivity for MCPyV appears to increase with age, occurring in approximately 60% of patients between the ages of 10 and 20 years (Viscidi 2011); as a result, it is reasonable to assume that MCC in adults and pediatric patients is the same disease.

Presentation of MCC is usually with a nonspecific, erythematous lesion in sun-exposed areas. Lesions may grow and metastasize quickly; 26% to 36% of patients present with lymph node involvement, and 6% to 16% of patients present with distant metastatic disease

(Agelli and Clegg 2003Agelli and Clegg 2003, Albores-Saavedra 2010, Harms 2016, Hodgson 2005, Lemos 2010, Sridharan 2016). MCC metastasizes first to lymph nodes and spread is typically to lung, adrenal glands, pancreas, liver, brain, and bones (Dellambra 2021).Dellambra 2021). Surgery and/or radiation therapy are indicated and, potentially, curative for local-regional disease (Bhatia 2011). Recurrence is common (~40%), however, and often incurable (Bhatia 2011, McEvoy 2022). The 5-year survival rates for patients with MCC are 51% for local disease, 35% for nodal involvement, and 14% for metastatic disease (Harms 2016, Trinidad 2019).

The FDA's Assessment:

FDA generally agrees with the Applicant's analysis. The incidence of MCC rises with age, with the median age at diagnosis of 74 years (Agelli and Clegg 2003). In a retrospective analysis of the Surveillance Epidemiology and End Results (SEER) database which included 3,870 individuals with a diagnosis of MCC (Albores-Saavedra, Batich et al. 2010), 62% of patients were male, 38% female, 24% age 50-69, 72% age 70 years or greater, 95% were white, 1% black, with the head and neck being the most common primary tumor location.

(b) (4)

## 2.2. Analysis of Current Treatment Options

The Applicant's Position:

**Chemotherapy for Merkel Cell Carcinoma**

Historically, metastatic MCC has been treated with chemotherapy regimens similar to those used for small cell lung cancer. Initial therapy with platinum-based chemotherapy provides response in approximately half of patients, however, these are of short duration (median DOR of approximately 3 months; Iyer 2016; see Table 1). No survival advantage has ever been demonstrated for chemotherapy (Cassler 2016, Gauci 2022, Hughes 2014, Lebbe 2015, NCCN 2022, Voog 1999). Management of patients with recurrent, locally advanced, unresectable MCC is also challenging (Becker 2017). Similar to distant metastatic disease, patients with recurrent, unresectable MCC require systemic therapy to achieve disease control. Chemotherapy is both less effective in the salvage setting (Iyer 2016), and also associated with risk of severe toxicity and toxic death, particularly among older patients who, as noted, have the highest incidence of the disease (Gauci 2022, Lebbe 2015, Voog 1999). Consequently, current guidelines recommend against the use of chemotherapy in this setting (NCCN 2022).

**Immunotherapy in Merkel Cell Carcinoma**

Immunotherapy is a promising approach to treatment of locally advanced or metastatic MCC due to the highly immunogenic nature of both MCPyV-positive and MCPyV-negative tumors. Additionally, PD-(L)1 inhibitors have been granted accelerated approval in the US for the treatment of adults and pediatric patients 12 years and older with metastatic MCC (avelumab)

or for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic MCC (pembrolizumab). These approvals were based on the high proportions of durable RECIST v1.1 responses in single-arm studies (Table 1). Current practice guidelines include a recommendation for PD-(L)1 inhibitors as the preferred treatment for disseminated or locally recurrent (incurable) MCC (Gauci 2022, NCCN 2022, Silk 2022).

**Table 1: Immunotherapies and Other Therapies for MCC**

| Agent | MCC Study Population | | ORR, % (95% CI) | CRR, % | mDOR, months (range) | DOR ≥ 12 months, % | mPFS, months (95% CI) | mOS, months (95% CI) |
|---|---|---|---|---|---|---|---|---|
| **PD-(L)1 Inhibitors** | | | | | | | | |
| Avelumab* D'Angelo 2020, D'Angelo 2021 | Distant metastatic | Chemo-naïve (n = 116) | 39.7 (30.7, 49.2) | 16.4 | 18.2 (1.2-28.3) | 26.7[a] | 4.1 (1.4, 6.1) | 20.3 (12.4, NE) |
| | | Chemo-refractory (n = 88) | 33.0 (23.3, 43.8) | 11.4 | 40.5 (2.8-41.5) | 20.7[a] | Not reported | 12.6 (7.5, 17.1) |
| Pembrolizumab* Nghiem 2021 | Distant metastatic or locoregional | Chemo-naïve[c] (n = 50) | 58 (43.2,71.8) | 30 | NR (1.0+-51.8+) | 54[b] | 16.8 (4.6, 43.4) | NR (26, NE) |
| Nivolumab Topalian 2017 | Unresectable local or metastatic | Chemo-naïve and refractory (n = 25) | 64[d] (43-82) | 32 | NR (3.5-12.1) | Not reported | NR | NR |
| **Chemotherapy** | | | | | | | | |
| Cytotoxic chemotherapy Iyer 2016 | Distant metastatic | Chemo-naïve (n = 62) | 55 | 13 | 2.8 | 2 of 34 | 3.1 | 9.5 |
| Cytotoxic chemotherapy Voog 1999 | Locally advanced or metastatic | Chemo-naïve (n = 107) | 60 | 38.6 | 8 | Not reported | Not reported | 9 |

Note: CRR = complete response rate; mDOR = median DOR; mPFS = median PFS; mOS = median OS; NE = not estimable; NR = not reached.

[a] NCT02155647 ClinicalTrials.gov results posting (May 4, 2021).

[b] Bradford 2020.

[c] Adjuvant chemotherapy completed > 6 months prior to study treatment was permitted.

[d] Responses are not ICR assessed.

*FDA-approved under accelerated approval

Though initial results with PD-(L)1 inhibitors are encouraging, a survival benefit has yet to be demonstrated, and approximately half of the metastatic MCC population does not respond, or experiences disease progression, after treatment. The Q2W dose administration schedule for avelumab, and requirement for preadministration prophylaxis for infusion reactions, is also burdensome for patients, most of whom are elderly. Thus, there remains an unmet need for new therapies to treat metastatic or recurrent locally advanced MCC.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the therapeutic options used in the management of advanced MCC. Although there is an ongoing need for the management of patients with advanced MCC who have progressed on immune checkpoint inhibitors, PODIUM-201 was not designed to address that unmet medical need. Additionally, FDA does not agree with the

selective description of increased burden of either the q2W administration or the need for pre-administration prophylaxis for infusion reactions with avelumab, neither of which were quantitatively nor qualitatively assessed as part of PODIUM-201. Furthermore, FDA has granted accelerated approval to pembrolizumab for MCC which can be dosed using an every six weeks regimen.

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Retifanlimab is an NME and is not currently marketed in the U.S. or in any other country.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The following summarizes the clinical presubmission regulatory activity for retifanlimab:

On August 26, 2016, IND 130952 was submitted to the Division of Oncology Products 2 for retifanlimab for the treatment of patients with advanced cancer and the Study May Proceed letter for the first-in-human study (INCMGA 0012-101 [formerly CP-MGA012-01]) was issued on September 24, 2016.

On June 8, 2018, IND 139181 was submitted and included the clinical protocol for Study INCMGA 0012-201 (Study 201), a single-arm, multicenter study of retifanlimab in patients with metastatic MCC who had not received prior systemic therapy. The primary endpoint of Study 201 was ORR according to RECIST 1.1 based on independent review of tumor assessments. A Study May Proceed letter was issued on July 5, 2018.

In an Advice/Information Request Letter dated August 9, 2018, FDA provided the following comments:

- Your proposed clinical trial, Study 201, has the potential to be a registrational trial. As such, ensure that your CMC development is in line with the manufacturing and product quality that would be needed in support of a registrational trial.
- In accordance with the ICH S9 guidance, the reports of 13-week GLP-compliant toxicology studies in dogs and rats are expected to be submitted prior to submission of a protocol intended to support product registration.
- We acknowledge your June 27, 2018, revisions to the SAP and sample size calculation in the study protocol based on the higher target effect size. While the proposed effect size may be more relevant for the expected study population, which includes patients with distant metastatic disease who may or may not have received chemotherapy, the study sample size should also be large enough to ensure adequate characterization of safety of retifanlimab at the intended dose in patients with MCC.

- The proposed dose of 500 mg Q4W appears to be acceptable. However, given that the dose/exposure-response relationship for safety and efficacy is not established for retifanlimab, we recommend that you evaluate these relationships based on available data and continue to evaluate whether further dose optimization may be needed.

In a Type B EOP1 meeting on December 16, 2018 (IND 141702), FDA agreed that the nonclinical toxicology plan supports the development of retifanlimab.

In an Advice/Information Request letter dated May 13, 2019, FDA advised the Applicant that the primary analysis of Study 201 should be based on all patients who have received at least one dose of study drug, without regard to replacement. The Applicant amended the primary analysis population to include all patients who received at least 1 dose of study drug while retaining central confirmation of disease for supporting analyses.

A Type C meeting was held on May 4, 2020 (IND 130952) to discuss the proposed comparability assessment between DP lots manufactured from (b) (4) DS lots. Data supporting the comparability was submitted to IND 130952 and deemed sufficient for introduction into clinical trials.

A Type B EOP2 meeting was held on August 24, 2020 to discuss the data from Study 201 and to obtain the Agency's feedback and advice on the proposed approval pathway for retifanlimab for the treatment of patients with recurrent locally advanced or metastatic MCC including a proposal to provide confirmatory evidence of the clinical benefit of retifanlimab in patients with MCC. FDA provided the following feedback to the Applicant:

- FDA stated that the observed response rate and DOR in patients with metastatic or recurrent locally advanced MCC should be of sufficient magnitude to conclude that retifanlimab is reasonably likely to provide clinical benefit and provides an advantage over available therapy in the intended use population.
- FDA recommended following patients for at least 6 months after a confirmed response to allow for adequate evaluation of DOR. To support an application for regular approval, longer follow-up duration will be expected.
- The Agency stated that the proposal to (b) (4) (b) (4)
- FDA stated that the BLA should include details regarding the extent of expected follow-up at the time of the proposed analyses including estimates of OS based on the proposed data cutoff dates.

On October 26, 2020, retifanlimab was granted orphan drug designation for the treatment of MCC.

On September 15, 2020, the Applicant requested FTD for the treatment of patients with metastatic or recurrent locally advanced MCC. FTD was granted on November 6, 2020.

On April 2, 2021, the Applicant requested a Type C meeting to discuss and reach agreement with FDA on the proposed safety and efficacy analysis plans and content and format of the marketing application for retifanlimab for the treatment of adult (b) (4) patients (b) (4) (b) (4) with metastatic or recurrent locally advanced MCC. Written responses were issued

on May 5, 2021 and FDA provided the following recommendations:

- FDA agreed to the proposed pooling strategy for the ISS and recommended that AE datasets include separate flags for MCC and other solid tumor populations and the pooled safety population only include patients treated with the same dose of monotherapy retifanlimab.
- FDA agreed to the proposed subgroup analysis for the ISS and recommended analyses based upon HIV status.

The Applicant requested a Type B Pre-BLA meeting on September 27, 2021 and FDA provided the following comments on October 18, 2021:

- FDA requested that all patients with a confirmed response in Study 201 should have at least 6 months of follow-up from the onset of response.
- FDA recommended that the Applicant conduct an animal study that will measure the effect of PD-1 inhibition on the magnitude of the primary (first vaccination) and recall (second vaccination) antibody responses to antigen challenge.
- FDA stated that Bioresearch Monitoring data should be submitted for all major trials used to support safety and efficacy.
- FDA agreed with the Applicant's proposed plan for submitting clinical datasets.
- FDA requested that the Sponsor submit a Diversity Plan.
- FDA requested that the Sponsor include information with respect to how protocol conduct or data collection were impacted by COVID or COVID-related procedures.

The Applicant submitted BLA 761209 for retifanlimab for the treatment of adult patients with locally advanced or metastatic SCAC on November 25, 2020. A CRL was issued on July 22, 2021.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment and adds the following information regarding the use of retifanlimab for the treatment of SCAC:

An Oncology Drug Advisory Committee (ODAC) Meeting was held on June 24, 2021, to discuss the Applicant's initial Biologics License Application (BLA) submission (BLA 761209) for retifanlimab, seeking approval in patients with locally advanced or metastatic squamous carcinoma of the anal canal (SCAC). The application was based on the safety and efficacy of Study PODIUM-202, where 94 patients with locally advanced or metastatic SCAC who were intolerant or ineligible for platinum-based chemotherapy received retifanlimab 500 mg by intravenous infusion every 4 weeks. The objective response rate (ORR) was 14% (95% CI: 8, 22). The major review issue identified was whether the reported ORR was reasonably likely to predict clinical benefit. The majority (13 voted 'Yes' and 4 voted 'No') of the ODAC members voted for the regulatory decision on retifanlimab for the treatment of locally advanced or metastatic SCAC be deferred until further data are available from the randomized clinical trial PODIUM-303.

This application (BLA 761334) was granted priority review because the other available immunotherapy options for the treatment of MCC remain under accelerated approval status.

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

## 4.1. Office of Scientific Investigations (OSI)

Inspections by the CDER Office of Scientific Investigations (OSI) were requested by the Division of Oncology 3 (DO3). Three clinical investigators (CIs), Drs. Burgess (Site 1), De Braud (Site 506), and Guida (Site 502) were inspected for Study INCMGA 0012-201 given they were high enrolling sites with high treatment effect. One clinical investigator, Dr. Girda (Site US005), was inspected for Study INCMGA 0012-101.

There were some regulatory violations related to unreported adverse events (AEs) at Dr. Girda's site, these events were not serious and did not lead to study discontinuation. They were determined by the CI not to be related to the study drug and some have been included in the labeling proposed by the sponsor. There were also regulatory violations at Dr. Burgess's site related to late reporting of serious adverse events (SAEs), missed reconsenting of subjects of new versions of the informed consent form, and unreported adverse events. All SAEs were subsequently reported, and all subjects signed the initial informed consent and eventually were reconsented on updated versions of the informed consent form. The unreported adverse events were not serious and did not lead to study discontinuation and there were no other unreported adverse events upon review of the subject charts at the site.

Despite these regulatory violations, the conducted onsite inspections did not find significant concerns regarding the management of the clinical trial, GCP compliance, or the data generated for Study INCMGA 0012-201 and Study INCMGA 0012-101.

Site Inspections and Reviewer's Comments:
At all inspected sites the source documents were reviewed for protocol compliance, eligibility, informed consent, and data accuracy. The reviewed records included informed consent forms and subject medical records including electronic medical records and RECIST reports. Study related documents were also reviewed protocol deviations, adverse event reports, case report forms, IRB approvals, sponsor communications regarding adverse event, Form FDA 1572s, site protocols, training records, delegation of responsibilities log, and investigational product (IP) accountability/disposition records.

**Site US005 – Dr. Eugenia Girda**
Dr. Girda was inspected on October 11-18, 2022, as an onsite surveillance inspection for Study INCMGA 0012-101. This was the first FDA inspection for this investigator. This was the first FDA inspection for this investigator. There were 38 patients screened, and 28 patients enrolled and treated at the site. Radiographic scans and related investigators assessments were performed as specified in the protocol and there were no discrepancies with the data listings. No unreported protocol deviations were identified.

There were 3 patients who had the following unreported adverse events:

1. Patient US005 (b) (6) – Nausea, anorexia, arthralgia bilateral hands, urinary frequency
2. Patient US005 - taste change. black stools
1. Patient US005 - Constipation, vaginal itching, urinary incontinence, fall, whooshing sensation bilateral ears

*Reviewer's Comments: Dr. Girda stated that none of the AEs were related to the study drug, nausea and arthralgias are listed in the proposed product labeling as adverse events. These events were not serious and did not lead to study discontinuation. There were no other unreported adverse events upon review of the subject charts at the site. These events were recorded into the CRF during the inspection and recorded as protocol deviations. Her corrective action and preventive action (CAPA) was acceptable.*

**Site 506 - Dr. Filippo de Braud**

Dr. de Braud was inspected on November 14-18, 2022, as an onsite surveillance inspection for Study INCMGA 0012-201. This was the first FDA inspection for this investigator. Six patients were screened, and 6 patients enrolled and treated at the site.

Radiographic scans were performed as specified in the protocol and all local imaging studies were sent to the central radiology facility and had a central interpretation in the listings. No unreported adverse events were identified. No unreported protocol deviations were identified.

**Site 502: Dr. Michele Guida**

Dr. Guida was inspected on November 7-11, 2022, as an onsite surveillance inspection for Study INCMGA 0012-201. This was the first FDA inspection for this investigator. Six patients were screened, and 6 patients enrolled and treated at the site.

There were three unreported adverse events for Subject 502 (b) (6) from (b) (6): lumbosciatalgia Grade 2, hyperuricemia Grade 1, and impotence Grade 1; all were determined by the CI to be unrelated to the study drug. No other unreported adverse events or protocol deviations were identified.

*Reviewer's Comment: These adverse events were likely not related to the study drug and all low grade. They were correctly identified and reported at an (b) (6) monitoring visit. Since they were identified after the data cutoff date, they were not in the data listings. There were no additional unreported adverse events, suggesting adequate management of adverse event reporting at the site.*

**Site 1: Dr. Melissa Burgess**

Dr. Burgess was inspected on November 9-16, 2022, as an onsite surveillance inspection for Study INCMGA 0012-201. This was the first FDA inspection for this investigator. Six patients

were screened, and 5 patients enrolled and treated at the site.

Radiographic scans were performed as specified in the protocol and all local imaging studies were sent to the central radiology facility and had a central interpretation in the listings. No unreported protocol deviations were identified.

There were 3 unreported adverse events:

1. Patient 001 (b) (6) Sciatic nerve pain
2. Patient 001 Diarrhea
3. Patient 001 Constipation and poor appetite

Three SAEs, involving two subjects, were not reported to the sponsor within 24 hours of the investigator being aware of the events.

1. Patient 001 (b) (6) Gastric Hemorrhage – 1 Day late, Hypoglycemia – 2 days late
2. Patient 001 Pneumonia – 6 days late

3 patients were not re-consented following the IRB approval of Informed Consent version 4.

*Reviewer's Comments: Diarrhea (b) (4) are listed in the proposed product labeling as adverse events. These events were not serious and did not lead to study discontinuation. Per the protocol serious adverse events are required to be reported to the sponsor within 24 hours (9.4 Reporting of Serious Adverse Events). It does not appear that there were any subject safety violations as the SAEs were eventually reported. Dr. Burgess did not receive a regulatory violation during the inspection; a voluntary action indicated (VAI) letter, highlighting the objectionable findings during FDA inspection, was issued to Dr. Burgess on January 22, 2023.*

## 4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) did not identify any product quality issues that would preclude approval of retifanlimab. Refer to the OPQ review of this application for additional information. No safety or efficacy concerns were identified during this review that related to Chemistry, Manufacturing, and Controls (CMC).

## 4.3. Clinical Microbiology

The Office of Biotechnology Products, Office of Pharmaceutical Quality (OPQ) did not identify any product quality issues that would preclude approval of retifanlimab. Refer to the OPQ review of this application for additional information. No safety or efficacy concerns were identified during this review that related to Chemistry, Manufacturing, and Controls (CMC).

### 4.4. Devices and Companion Diagnostic Issues

This submission does not require a companion diagnostic.

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

Retifanlimab is an IgG4κ monoclonal antibody that recognizes PD-1 and blocks its interaction with PD-L1 and PD-L2. Retifanlimab has an approximate molecular weight of 148 kDa. Binding of the PD-1 ligands PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Based on the nonclinical data submitted in the BLA, the established pharmacological class (EPC) of "programmed death receptor-1 (PD-1) blocking antibody" is scientifically valid.

In vitro studies showed retifanlimab bound to human and cynomolgus monkey PD-1 with nanomolar affinity (0.6 and 3.6 nM, respectively) and did not cross react with rodent or canine PD-1, supporting the use of cynomolgus monkeys as the single pharmacologically relevant species for toxicity assessment. Retifanlimab blocked the binding of human PD-1 to human PD-L1 and PD-L2 in an NSO/PDCD1 cell-based bioassay at an EC50 of 0.138 µg/mL. In a cell-based PD-1 assay, incubation with retifanlimab blocked PD-1/PD-L1 interaction promoting T-cell activation measured by enhanced TCR-mediated NFAT-driven luciferase signaling by a PD-1 expressing cell line. Retifanlimab increased dose-dependent secretion of IFN-γ from human PBMCs stimulated with staphylococcal enterotoxin B (SEB). Retifanlimab did not have in vitro complement-dependent cytotoxicity (CDC) activity or antibody-dependent cellular cytotoxicity (ADCC) activity.

The Applicant evaluated the toxicity of retifanlimab in a 13-week GLP-compliant repeat-dose toxicology study in cynomolgus monkeys. Monkeys received once weekly intravenous administration of retifanlimab at doses up to 100 mg/kg. There were no mortalities. Findings included an increase in histologic mononuclear cell and mixed inflammatory cell infiltration at the injection site. Tissue cross reactivity of retifanlimab in normal human tissues indicated staining of lymphocytes and lymphoid organs as expected.

Embryo-fetal developmental toxicology studies were not conducted with retifanlimab. Rather, consistent with the alternative approach to providing information on the potential for reproductive toxicity described in ICH S6(R1) and ICH S9, the Applicant provided a weight-of-evidence assessment of the potential reproductive toxicity of retifanlimab. Data from the literature indicates the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy. In allogeneic mouse models of

pregnancy, blockade of PD-1/PD-L1 signaling resulted in an increased incidence of fetal loss but no fetal malformations. There are no reports of fetal malformations associated with PD-1 deficiency in mice; however, late onset autoimmunity can occur. Based on these findings, potential risks of administering retifanlimab during pregnancy include increased rates of abortion or stillbirth and an increased risk in offspring developing immune-related disorders or altered immune response. Product labeling for retifanlimab reflects the risk for embryo fetal toxicity. Based on a human half-life of 18.4 days, females of reproductive potential are advised to use effective contraception during treatment with retifanlimab and for 4 months after the last dose. The Applicant did not evaluate transfer of retifanlimab to the fetus or milk, but IgG antibodies can be present in milk. Because of potential adverse effects of retifanlimab on a breastfeeding infant, proposed product labeling for retifanlimab reflects advice not to breastfeed during treatment with retifanlimab and for 4 months after the last dose. Genetic toxicology and carcinogenicity studies were not warranted.

Based on data from the literature and its mechanism of action, there may be a potential for severely enhanced immune responses to infection following treatment with retifanlimab. 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 proposed label under Section 13.2.

There are no approvability issues from a pharmacology/toxicology perspective.

## 5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
The nonclinical pharmacology/toxicology data to support this BLA was previously submitted under BLA 761209. No new information is provided in the current submission.

## 5.3. Pharmacology

Primary pharmacology
Programmed death receptor-1 (PD-1) blocking antibody (EPC)

The Applicant determined the binding affinities of MGA012 (retifanlimab) for human and cynomolgus monkey PD-1 using surface plasmon resonance (SPR-Biacore; Study # MGA012-15-1002). The binding affinity (Kd) of retifanlimab for human PD-1 was 0.6 nM. Retifanlimab

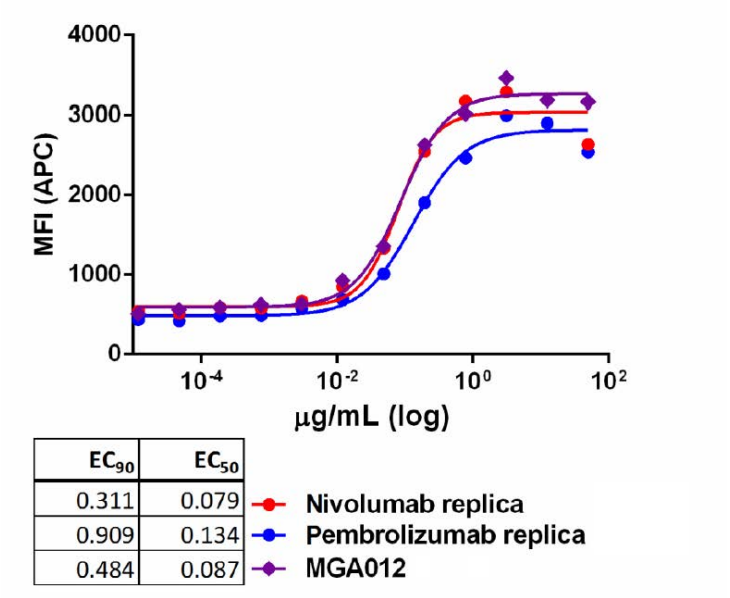
binding to human PD-1 was approximately 6-fold higher than binding to cynomolgus monkey PD-1 (Table 2). Cynomolgus monkeys were a pharmacologically relevant species for toxicity assessment based on sequence homology and binding. As assessed by flow cytometry, retifanlimab bound to PD-1 on NSO/PDCD1 cells in a dose-dependent manner (EC50 0.087 µg/ml) (see Figure 1 and Table 3; Study # MGA012-15-1001).

**Table 2: Equilibrium Dissociation Constants (KD) for Binding of Human or Cynomolgus Monkey PD-1 Protein to Captured Retifanlimab**

| Antigens | $k_a$ (± SD) [a] ($M^{-1}s^{-1}$) | $k_d$ (± SD) [a] ($s^{-1}$) | $K_D$ (± SD) [a] (nM) |
|---|---|---|---|
| Human PD-1 | 4.3 (± 0.06) x $10^5$ | 2.4 (± 0.30) x $10^{-4}$ | 0.6 (± 0.06) |
| Cynomolgus monkey PD-1 | 1.8 (± 0.1) x $10^5$ | 6.4 (± 0.46) x $10^{-4}$ | 3.6 (± 0.46) |

*(Applicant Table Reproduced from Study MGA012-15-1002)*

**Figure 1: EC50 and EC90 Values of Anti-PD-1 mAb Binding to NS0/PDCD1 Cells**




*(Applicant Figure Reproduced from Study MGA012-15-1001)*
NS0 (myeloma) cells were engineered to express the human PDCD1 gene (NS0/PDCD1 cells)
MGA012 - retifanlimab

**Table 3: EC50 and EC90 Values of Anti-PD-1 mAb Binding to NS0/PDCD1 Cells**

| | $EC_{50}$ Values (µg/mL) | | | $EC_{90}$ Values (µg/mL) | | |
|---|---|---|---|---|---|---|
| | Nivolumab replica | Pembrolizumab replica | Retifanlimab | Nivolumab replica | Pembrolizumab replica | Retifanlimab |
| Mean | 0.158 | 0.140 | 0.138 | 1.546 | 1.162 | 0.661 |
| SD | 0.116 | 0.095 | 0.093 | 1.769 | 1.268 | 0.344 |
| SEM | 0.058 | 0.048 | 0.046 | 0.884 | 0.634 | 0.172 |

*(Applicant Table Reproduced from Study MGA012-15-1001)*

Retifanlimab was also evaluated in NSO/PDCD1 cells for binding to PD-1 and subsequent interaction with soluble PD-L1 and PD-L2 ligands. Flow cytometry was used to detect mean fluorescence on NS0/PDCD1 cells incubated with serially diluted anti-PD-1 mAbs in the presence of human PD-L1 and PD-L2 ligands. Retifanlimab inhibited binding of PD-L1 and PD-L2 to PD-1 expressing NSO/PDCD1 cells in a dose-dependent manner (Table 4).

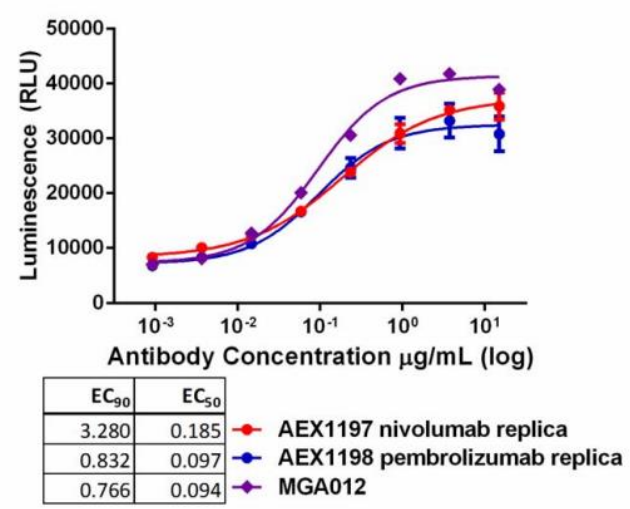
**Table 4: IC50 and IC90 Values of anti-PD-1 mAb-mediated Inhibition of sPD-L1 and sPD-L2 Binding to NS0/PDCD1 Cells**

| | $IC_{50}$ Values (µg/mL) | | | $IC_{90}$ Values (µg/mL) | | |
|---|---|---|---|---|---|---|
| | Nivolumab replica | Pembrolizumab replica | Retifanlimab | Nivolumab replica | Pembrolizumab replica | Retifanlimab |
| sPD-L1 | 0.016 ± 0.005 | 0.014 ± 0.001 | 0.010 ± 0.001 | 0.078 ± 0.012 | 0.080 ± 0.014 | 0.052 ± 0.002 |
| sPD-L2 | 0.028 ± 0.004 | 0.028 ± 0.003 | 0.021 ± 0.001 | 0.159 ± 0.067 | 0.092 ± 0.004 | 0.062 ± 0.004 |

*(Applicant Table Reproduced from Study MGA012-15-1001)*

The Applicant investigated the effect of retifanlimab on PD-1/PD-L1 signaling using a human T cell-based PD-1 bioassay (Study #MGA012-15-1001). In the assay, CD3-positive Jurkat reporter cells constitutively express human PD-1 and a luciferase reporter gene under the control of NFAT promoter triggered by TCR activation. Jurkat cells are co-cultured with a CHO-stimulator cell line that stably expresses human PD-L1 with a TCR activator (anti-CD3). NFAT signaling is inhibited by the PD-1/PD-L1 interaction between the Jurkat and CHO/PD-L1 cells. In the presence of blocking anti-PD-1 mAbs, this inhibition is repressed allowing increased NFAT signaling measured optically through luciferase reporter gene activity (Figure 2). The mean EC50 value for retifanlimab in the bioassay was 0.090 µg/mL (Table 5).

**Figure 2: Retifanlimab-mediated PD-1/PD-L1 Signaling Inhibition through Induction of NFAT Gene Expression within a Reporter Assay System**




*(Applicant Figure Reproduced from Study MGA012-15-1001)*
*Release of PD-1/PD-L1-mediated inhibition is measured by an increased luminescence under the control of TCR-mediated NFAT signaling in the presence of anti-PD-1 mAbs.*
MGA012 - retifanlimab

**Table 5: EC50 and EC90 Values of Anti-PD-1 mAb Inhibition of PD-1/PD-L1 Signaling**

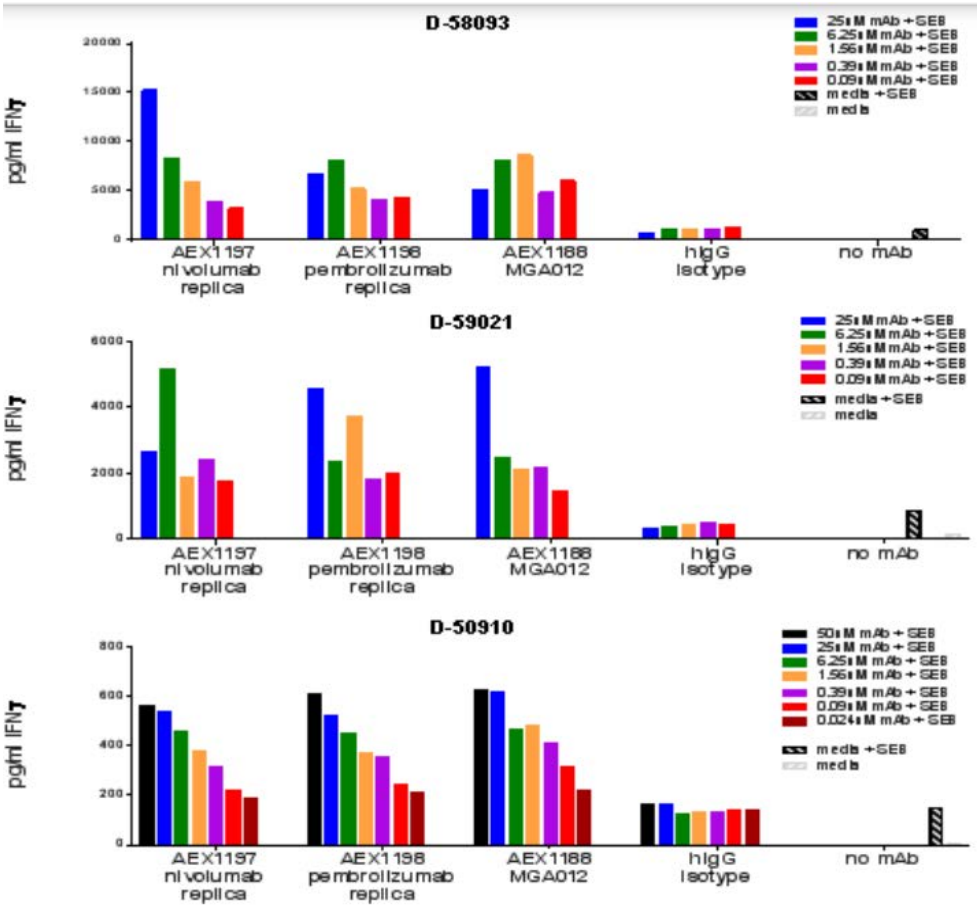
| | $EC_{50}$ Values (µg/mL) | | | $EC_{90}$ Values (µg/mL) | | |
|---|---|---|---|---|---|---|
| | AEX1197 nivolumab replica | AEX1198 pembrolizumab replica | MGA012 | AEX1197 nivolumab replica | AEX1198 pembrolizumab replica | MGA012 |
| Experiment 1 | 0.137 | 0.079 | 0.075 | 1.204 | 1.026 | 0.411 |
| Experiment 2 | 0.185 | 0.097 | 0.094 | 3.280 | 0.832 | 0.766 |
| Experiment 3 | 0.192 | 0.132 | 0.103 | 1.896 | 0.618 | 0.778 |
| **Mean** | **0.171** | **0.103** | **0.090** | **2.127** | **0.825** | **0.651** |
| SD | 0.030 | 0.027 | 0.014 | 1.057 | 0.204 | 0.208 |
| SEM | 0.017 | 0.016 | 0.008 | 0.610 | 0.118 | 0.120 |

*(Applicant Table Reproduced from Study MGA012-15-1001)*
MGA012 - retifanlimab

Retifanlimab was examined for its ability to promote secretion of cytokines and enhance the T cell response. The Applicant incubated human peripheral blood mononuclear cells (PBMCs) with Staphylococcal enterotoxin B (SEB, 0.5 ng/mL) and retifanlimab (up to 25 nM), anti-PD-1 mAbs, or an isotype control antibody for 48 hours (Study MGA012-15-1001). IFN-γ secretion

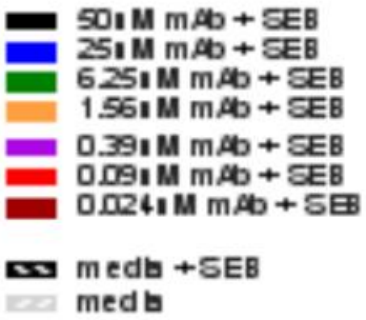
was measured using an ELISA assay. Retifanlimab had comparable IFN-γ secretion to other anti-PD-1 mAbs (Figure 3).

**Figure 3: Evaluation of MGA012 to Enhance IFN-γ Signaling Following SEB Stimulation of Human PBMCs**




*(Applicant Figure Reproduced from Study MGA012-15-1001)*

Example donor responses

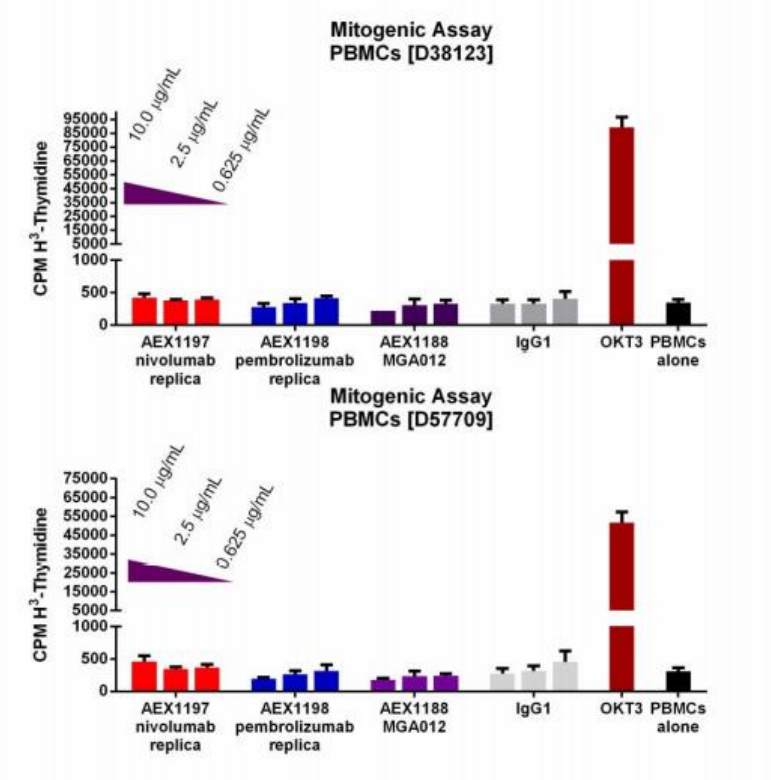



*(Applicant Figure Legend Reproduced from Study MGA012-15-1001)*

MGA012 – retifanlimab

The proliferative potential of retifanlimab was examined using the 3H-thymidine incorporation assay by incubation of resting human PBMCs for 2 days with retifanlimab, anti-PD1 mAbs (10.0, 2.5, or 0.625 µg/mL), an isotype control, or an anti-CD3 mAb (OKT3 clone positive control). There was no mitogenic activity in any of the anti-PD-1 mAbs compared to activity in the controls (Figure 4).

**Figure 4: Evaluation of Intrinsic Mitogenicity of MGA012**



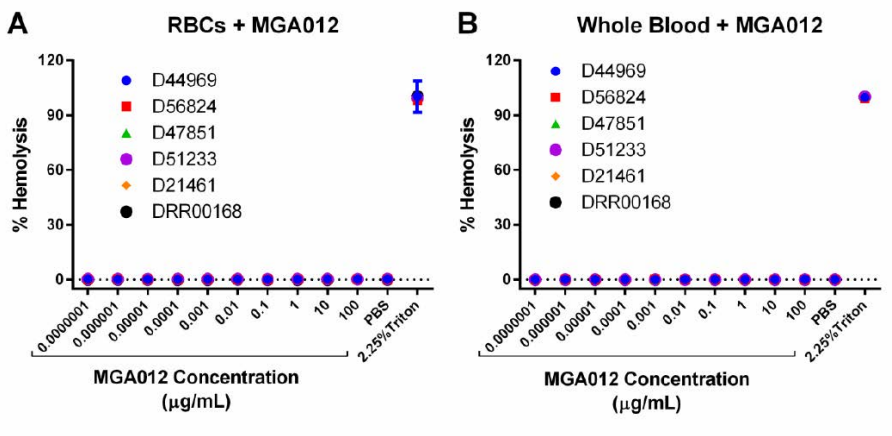

*(Applicant Figure Reproduced from Study MGA012-15-1001)*
MGA012 - retifanlimab

Secondary Pharmacology

The FDA's Assessment:

Hemolysis was analyzed using purified human red blood cells (RBCs) or whole blood from 6 individual healthy human donors. Samples were incubated with retifanlimab (up to 100 µg/mL) and examined for hemolysis (Study # MGA012-15-1007). No hemolytic activity was observed with retifanlimab at any concentration tested (Figure 5).

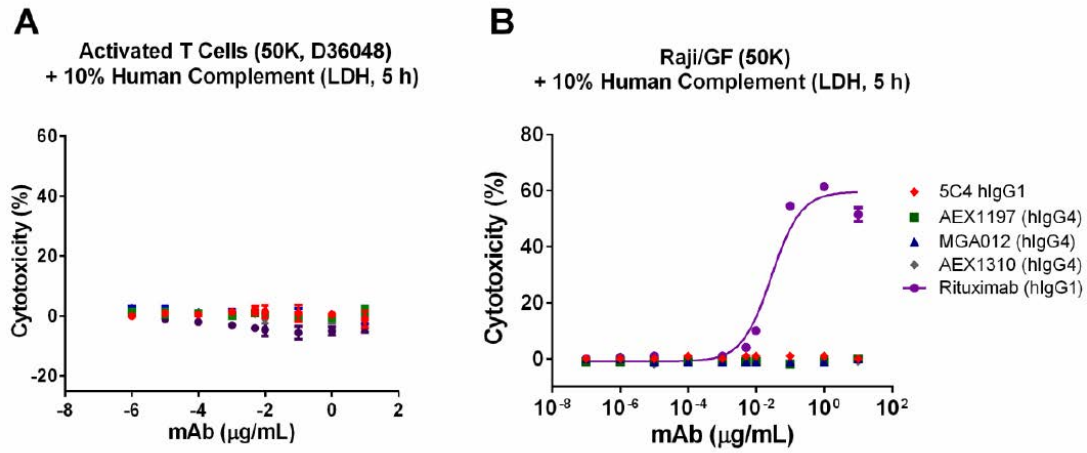
**Figure 5: Lack of Hemolysis with Retifanlimab in Purified RBCs or Whole Blood**




*(Applicant Figure Reproduced from Study MGA012-15-1007)*
MGA012 - retifanlimab

Retifanlimab did not have complement-dependent cytotoxicity (CDC) activity at concentrations up to 10 µg/mL in PD-1-positive activated human primary T cells (Study MGA012-15-1006) (Figure 6).

**Figure 6: Lack of CDC Activity Mediated by Retifanlimab in Target Cells**

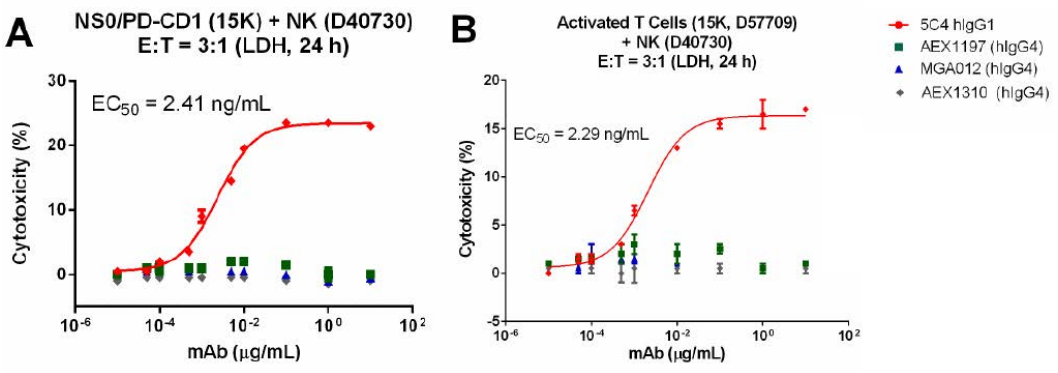



*(Applicant Figure Reproduced from Study MGA012-15-1006)*
5C4 hIgG1 - anti-PD-1 control mAb with wild-type human IgG1 Fc domain; AEX1197 - nivolumab replica; AEX1310 - palivizumab replica; MGA012 - retifanlimab

The ability of retifanlimab to induce antibody-dependent cell-mediated cytotoxicity (ADCC) was assessed with an effector cell (purified human NK cells) to target cell (NS0/PDCD1 cells or activated human primary T cells from 3 independent human donors) ratio of 3:1. A lactate dehydrogenase (LDH) assay was used to measure cell viability (Study MGA012-15-1006). There

was no retifanlimab-mediated ADCC activity up to 10 µg/mL, the highest concentration test (Figure 7).

**Figure 7: Lack of ADCC Activity Mediated by Retifanlimab in Target Cells**




*(Applicant Figure Reproduced from Study MGA012-15-1006)*

5C4 hIgG1 - anti-PD-1 control mAb with wild-type human IgG1 Fc domain; AEX1197 - nivolumab replica; AEX1310 - palivizumab replica; MGA012 - retifanlimab

## 5.4. ADME/PK

The FDA's Assessment:

| Type of Study | Major Findings |
|---|---|
| **Absorption**<br>Pharmacokinetics Study of AEX1188, AEX1197, MK-3475, AEX1214 and AEX1228 Following Single Dose Intravenous Infusion in Cynomolgus Monkeys/ 20077288 | Cynomolgus Monkeys: AEX1188 (retifanlimab) (10 mg/kg)<br>Cmax (µg/mL): 194<br>AUC (hr*µg /mL): 30222<br>T1/2 (hrs): 68.6<br>Clearance (mL/hr/kg): 0.345 |
| **TK data from general toxicology studies** | Refer to **Section** Error! Reference source not found.**.1** of this BLA review |

## 5.5. Toxicology

### 5.5.1. General Toxicology

The FDA's Assessment:

**Study title/ number:** A Toxicity and Toxicokinetic Study following 13 weekly Intravenous administrations of INCMGA00012 in Cynomolgus Monkeys (GLP)/ T18-02-10

- There were no mortalities during the study.
- Anti-drug antibodies (ADA) were detected in 10/30 animals. After repeat administration, changes in INCMGA00012 exposure (serum) were measured in 8/10, 3/10, and 1/10 animals in 5, 20, and 100 mg/kg dosing groups, respectively.
- Minimal to mild immune cell infiltration at the injection site and in various tissues.

GLP compliance: Yes

Methods

| | |
|---|---|
| Dose and frequency of dosing: | 0, 5, 20, or 100 mg/kg, once weekly for 13 weeks |
| Route of administration: | Intravenous infusion |
| Formulation/Vehicle: | 0.9% sodium chloride injections, USP |
| Species/Strain: | Cynomolgus monkeys |
| Number/Sex/Group: | 5/sex/group |
| Age: | Males 2–3 years, Females 3–4 years |
| Satellite groups/ unique design: | None |
| Deviation from study protocol affecting interpretation of results: | No |

Table 6, Table 7, and Table 8 summarize the results.

**Table 6: Observations and Results (Changes from Control)**

| Parameters | Major findings |
|---|---|
| **Mortality** | There were no mortalities during the study. |
| **Clinical Signs** | Unremarkable |
| **Body Weights** | Unremarkable |
| **Ophthalmoscopy** | Unremarkable |
| **ECG** | Unremarkable: within normal limits. |
| **Hematology** | |
| • Measured on Days -12 or -9, -5 or -4, 2, 28, and 88 in control and INCMGA00012-treated monkeys.<br>• Decreased absolute lymphocyte (10^9/L) counts occurred on Day 2 in males administered > 5 mg/kg<br>• Increased fibrinogen occurred on Day 2 in treated groups. | |
| **Clinical Chemistry** | Unremarkable |
| **Urinalysis** | Unremarkable |
| **Gross Pathology** | Unremarkable |
| **Organ Weights** | Unremarkable |
| **Histopathology**<br>Adequate battery: Yes | An increased incidence of infiltration of mixed inflammatory and mononuclear cells was noted at the injection site in all dose groups relative to control animals. Mononuclear cell infiltration of minimal to mild severity was also noted in the adrenal gland, thyroid gland, trachea, and uterus occurred at a higher incidence than control animals. |
| **Flow Cytometry** | Unremarkable: parameters examined included changes in T cells, B cells, natural killer cells, and monocytes. |

Laboratory values of absolute lymphocytes (10^9/L) were measured on Days -12 or -9, -5 or -4, 2, 28, and 88 in control and INCMGA00012-treated monkeys. Laboratory values of fibrinogen (mg/dL) were measured on Days -12 or -9, 2, 28, and 88 in control and INCMGA00012-treated monkeys.

**Table 7: Toxicokinetics in Monkeys**

| Sex | Week | Parameter | 5 mg/kg QW (Group 2) | 20 mg/kg QW (Group 3) | 100 mg/kg QW (Group 4) |
|---|---|---|---|---|---|
| Male | 1 | N | 5 | 5 | 5 |
| | | $C_{max}$ (µg/mL) | 120±8.4 | 467±44 | 2525±152 |
| | | $t_{max}$ (h) | 0.70±0.4 | 0.70±0.4 | 1.10±0.5 |
| | | $AUC_{0\text{-}167.5h}$ (h*µg/mL) | 9477±338 | 35157±5004 | 195165±6032 |
| | | $t_{½\ term}$ (h) | 212.30±55.8 | 227.34±56.1 | 215.86±36.3 |
| | | $AUC_{inf,pred}$ (h*µg/mL) | 21479±3292 | 84070±24149 | 442980±53380 |
| | | $CL_{pred}$ (mL/h/kg) | 0.237±0.038 | 0.257±0.084 | 0.228±0.025 |
| | | $V_{ss,pred}$ (mL/kg) | 68.2±7.7 | 76.1±8.0 | 67.2±3.6 |
| | | $MRT_{inf,pred}$ (h) | 296.81±78.3 | 315.03±77.7 | 298.74±50.1 |
| | 4 | N | 1 | 4 | 5 |
| | | $C_{max}$ (µg/mL) | 192 | 832±190 | 4105±426 |
| | | $t_{max}$ (h) | 4.50 | 0.75±0.5 | 1.70±1.6 |
| | | $AUC_{0\text{-}167.5h}$ (h*µg/mL) | 21344 | 73245±15330 | 369924±59801 |
| | | $t_{½}$ term (h) | 197.63 | 136.91±38.7 | 196.67±25.3 |
| | 13 | N | 1 | 3 | 5 |
| | | $C_{max}$ (µg/mL) | 307 | 968±341 | 5243±224 |
| | | $t_{max}$ (h) | 1.50 | 1.50±0 | 2.10±1.3 |
| | | $AUC_{0\text{-}71.5h}$ (h*µg/mL) | 16860 | 50618±23347 | 267361±23071 |
| | | $t_{½}$ term (h) | 190.02 | 133.14±90.7 | 166.54±40 |
| Female | 1 | N | 5 | 5 | 5 |
| | | $C_{max}$ (µg/mL) | 114±8.7 | 497±70 | 2545±128 |
| | | $t_{max}$ (h) | 0.70±0.4 | 0.90±0.5 | 1.10±0.5 |
| | | $AUC_{0\text{-}167.5h}$ (h*µg/mL) | 8709±762 | 36608±2344 | 179059±12029 |
| | | $t_{½}$ term (h) | 166.57±55 | 221.37±40.6 | 207.86±87.3 |
| | | $AUC_{inf,pred}$ (h*µg/mL) | 16502±2836 | 83452±15294 | 396767±139007 |
| | | $CL_{pred}$ (mL/h/kg) | 0.310±0.054 | 0.246±0.042 | 0.277±0.093 |
| | | $V_{ss,pred}$ (mL/kg) | 68.7±14 | 72.4±4.1 | 70.3±8.3 |
| | | $MRT_{inf,pred}$ (h) | 230.82±72.6 | 302.38±57.9 | 285.48±120.9 |
| | 4 | N | 1 | 5 | 4 |
| | | $C_{max}$ (µg/mL) | 187 | 838±127 | 3711±445 |
| | | $t_{max}$ (h) | 0.50 | 0.50±0 | 1.00±0.6 |
| | | $AUC_{0\text{-}167.5h}$ (h*µg/mL) | 19103 | 69127±18778 | 322399±76836 |
| | | $t_{½}$ term (h) | 179.22 | 193.07±93.1 | 161.24±49.3 |
| | 13 | N | 1 | 4 | 5 |
| | | $C_{max}$ (µg/mL) | 304 | 953±93 | 4520±1196 |
| | | $t_{max}$ (h) | 1.50 | 1.00±0.6 | 0.90±0.5 |
| | | $AUC_{0\text{-}71.5h}$ (h*µg/mL) | 17183 | 53082±7882 | 206563±36012 |
| | | $t_{½}$ term (h) | 142.54 | 105.62±25.3 | 90.02±30.0 |

*(Applicant Figure Reproduced from Study T18-02-10)*

**Table 8: Immunogenecity in Monkeys**

| Animal ID | Gender | Dose (mg/kg) | Time When Aberrant TK Was Observed | ADA response | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | D-5 | D-4 | D8 | D29 | D85 |
| 2001 | M | 5 | w4, w13 | - | NA | - | + | + |
| 2002 | M | 5 | w4, w13 | - | NA | - | + | + |
| 2003 | M | 5 | w4, w13 | - | NA | - | + | + |
| 2004 | M | 5 | w4, w13 | - | NA | - | + | + |
| 2501 | F | 5 | w4, w13 | NA | NA | - | + | + |
| 2502 | F | 5 | w4, w13 | NA | - | - | + | + |
| 2503 | F | 5 | w4, w13 | NA | - | - | + | + |
| 2505 | F | 5 | w4, w13 | NA | - | - | + | + |
| 3004 | M | 20 | w13 | - | NA | - | - | + |
| 3005 | M | 20 | w4, w13 | - | NA | - | + | + |
| 3505 | F | 20 | w13 | NA | - | - | - | - |
| 4502 | F | 100 | w4 | NA | - | - | - | - |

NA = not available.

*(Applicant Figure Reproduced from Study T18-02-10)*

### 5.5.2. Genetic Toxicology

The FDA's Assessment:
Genetic toxicology studies were not warranted.

### 5.5.3. Carcinogenicity

The FDA's Assessment:
Carcinogenicity studies were not warranted.

### 5.5.4. Reproductive and Developmental Toxicology

The FDA's Assessment:
Reproductive and developmental toxicology studies were not conducted with retifanlimab. Instead, the Applicant submitted a weight-of-evidence reproductive risk assessment for retifanlimab.

Scientific literature suggests that the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy. PD-L1 is expressed in the human placenta throughout pregnancy and at the maternal-fetal interface in human fetal villous syncytiotrophoblasts and cytotrophoblasts (Petroff, et al. 2003; Miko, et al. 2019). In an allogeneic mouse model of pregnancy (CBA x C57BL/6), PD-L1 expression was detected at the uteroplacental interface of the placenta as early as 10.5 days post-conception (Guleria, et al. 2005; La Rocca, et al. 2014; Tripathi and Guleria, 2015; Miko, et al. 2019). Intraperitoneal administration of 250–500 µg of a murine anti-PD-L1 monoclonal antibody to allogeneic pregnant mice on 6.5, 8.5, 10.5, and 12.5 days post-conception resulted in an increased incidence of resorptions (86%) compared to isotype control (18%) (Guleria, et al. 2005). Allogenic fetal rejection was T-cell dependent in this experiment. In addition, increased rates of resorptions occurred in female PD-L1 homozygous knockout (PD-L1 -/-) mice compared to

female PD-L1 heterozygous knockout mice (Guleria, et al. 2005). Pregnant PD-L1 -/- mice, as well as mice administered an anti-PD-L1 antibody, exhibited an increase in IFN-γ-producing Th1 cells at the maternal-fetal interface compared to appropriate controls (Guleria, et al. 2005). In other preclinical studies, depletion of regulatory T cells (Tregs) abrogated the effect of PD-L1 blockade on fetal resorption and survival in pregnant C57BL/6 mice, whereas adoptive transfer of Tregs from wild-type mice to PD-L1 -/- mice improved fetal survival (Habicht, et al. 2007), suggesting that PD-L1-expressing Tregs are responsible for tolerance to fetal alloantigens. Conversely, in a CBA/J x DBA/2J mouse model of pregnancy, blockade of PD-1 abrogated the protective effects of Tregs, resulting in a higher rate of abortion in abortion-prone mice compared to controls (Wafula, et al. 2009).

Notably, blockade of PD-1/PD-L1 signaling in PD-L1 -/- mice or via an anti-PD-1/PDL1 antibody did not result in overt malformations in offspring (Guleria, et al. 2005; Habicht, et al. 2007, Wafula et al 2009). The maternal-fetal interface of mice is similar to that of humans, suggesting that findings from mouse models of allogeneic pregnancy are applicable to humans. Based on its mechanism of action and findings from murine models of pregnancy, administration of retifanlimab is likely to disrupt the maintenance of normal pregnancy (e.g., increased rates of abortion and stillbirth). PD-1 -/- mice develop late onset autoimmune phenotypes (Okazaki and Honjo 2007; Miko, et al. 2019) and therefore fetal exposure to retifanlimab increased the risk of developing immune-related disorders or alterations in the 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 retifanlimab and for four months after the last dose.

### 5.5.5. Other Toxicology Studies

The FDA's Assessment:

In a tissue cross-reactivity study of retifanlimab (0.25 and 2.5 µg/mL) was assessed across cryosections of normal human tissues (3 donors per tissue; Study 20085103). Staining was observed in expected tissues and was limited to lymphocytes.

X

Matthew Thompson
Reviewer/Team Leader

# 6 Clinical Pharmacology

## 6.1. Executive Summary Executive Summary

The FDA's Assessment:

Retifanlimab is a programmed death receptor 1 (PD-1) blocking monoclonal antibody that recognizes and blocks PD-1 from interacting with PD-L1 and PD-L2. The proposed dosing regimen is 500 mg IV infusion over 30 min every four weeks (Q4W) for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC).

The primary evidence of effectiveness is from the first 65 chemotherapy-naïve participants in the pivotal single-arm clinical trial INCMGA 0012-201 in adult patients with advanced or metastatic MCC (n=107). Treatment with retifanlimab at 500 mg Q4W resulted in an objective response rate (ORR) of 52.3%, including 18% complete responses (CR) and 34% partial responses (PR). The safety profile of retifanlimab was consistent with the PD-(L)1 inhibitor class. Rates for Grade ≥ 3 treatment-emergent adverse events (TEAEs), serious treatment-emergent adverse events (SAEs), and TEAEs leading to treatment discontinuation were 30%, 23%, and 17%, respectively. See Section **Error! Reference source not found.** for more details on the e fficacy and safety assessment for retifanlimab. The incidence of treatment-emergent anti-drug antibodies (ADAs) was 2.9% (3 out of 102 patients) in the pivotal clinical trial INCMGA 0012-201. Among the three patients who tested positive for ADAs, two patients tested positive for neutralizing antibodies against retifanlimab. Given the low ADA incidence, the impact of ADA on PK, efficacy, and safety of retifanlimab is inconclusive.

Population pharmacokinetics (PopPK) analysis including 634 participants with solid tumors indicated that there was no clinically meaningful effect of various covariates, including age, sex, body weight, race, ECOG performance status, tumor burden, corticosteroid coadministration, mild or moderate renal impairment, mild hepatic impairment, clinical laboratory values, cancer type, drug product administered, and infusion time. Therefore, no dosage adjustment was required for these covariates in patients with MCC. Flat exposure-response (E-R) relationships were observed for efficacy endpoints (ORR and DOR) in chemotherapy-naïve participants with MCC and flat E-R relationships were observed for safety endpoints (AESIs and irAEs) in all cancer population and the MCC population over the evaluated dose levels of 1, 3, and 10 mg/kg Q2W, 3 and 10 mg/kg Q4W, 500 and 750 mg Q4W, and 375 mg Q3W.

**Recommendations**
The Office of Clinical Pharmacology has reviewed the information and data submitted in BLA 761334. This BLA is approvable from a clinical pharmacology perspective with no major review issues as shown in Table 9.

**Table 9 Review Issues and Recommendations/Comments**

| Review Issue | Recommendations/Comments |
|---|---|
| Pivotal or supportive evidence of effectiveness | The primary evidence of effectiveness came from the first 65 chemotherapy-naïve participants in the full analysis set (FAS) in the ongoing pivotal study INCMGA 0012-201. Treatment with retifanlimab resulted in an ORR of 52.3% (95% CI: 39.5, 64.9), including CR occurred in 12 patients (18.5%) and PR occurred in 22 patients (33.8%). Median duration of response (DOR) was not reached, with 76% of patients having DoR greater than 6 months and 62% of patients having DoR greater than 12 months.<br><br>Flat E-R relationships were observed for efficacy endpoints (ORR and DOR) in chemotherapy-naïve participants with MCC. |
| General dosing instructions | The proposed dosing regimen for retifanlimab is 500 mg Q4W (IV infusion over 30 min) for adult patients. This dosing regimen is supported by the results of the dose finding study, the clinical benefit in terms of ORR and DoR with manageable safety profile observed in the pivotal Study INCMGA 0012-201, and flat E-R relationships for efficacy and safety. |
| Dosing in patient subgroups (intrinsic and extrinsic factors) | No dosage adjustment is recommended for intrinsic and extrinsic factors (age, sex, body weight, race, ECOG performance status, tumor burden, corticosteroid coadministration, mild or moderate renal impairment, mild hepatic impairment, clinical laboratory values, cancer type, drug product administered, and infusion time) according to the results of PopPK analyses.<br><br>The effect of moderate or severe hepatic impairment (total bilirubin > 1.5xULN and any AST) on the exposure of retifanlimab has not been evaluated. |
| Immunogenicity | The incidences of treatment emergent ADAs were 2.9% in patients with MCC and 1.7% in all cancer population. Given the low ADA incidence, the impact of ADAs on PK, efficacy and safety of retifanlimab is inconclusive. Two out of three patients tested positive for neutralizing antibody against retifanlimab. |

| Review Issue | Recommendations/Comments |
|---|---|
| Labeling | The proposed labeling for the clinical pharmacology section is acceptable with minor recommended formatting revisions. |

From a clinical pharmacology perspective, if approved, no post-marketing requirements (PMRs) or post-marketing commitments (PMCs) would be required.

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

**Mechanism of Action**

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Retifanlimab is a humanized, hinge-stabilized, IgG4 κ mAb that recognizes human PD-1 and contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1–expressing cells, including T cells, and restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1, and PD-L2.

**Pharmacokinetics**

The PKs of retifanlimab were evaluated in 634 patients with various solid tumors, including 102 patients with MCC. Retifanlimab exhibited linear PK over the dose range of 1 mg/kg to 10 mg/kg (including flat doses of 375 mg, 500 mg, and 750 mg). At 500 mg Q4W, the geometric mean retifanlimab concentrations (CV%) at steady state ranged between a $C_{min}$ of 41.0 mg/L (50.8%) and a $C_{max}$ of 193 mg/L (24.1%). Steady-state exposure was achieved after approximately 308 days (approximately 10 months) of treatment and systemic accumulation was 1.6-fold for the Q4W dose in consideration of time-varying clearance and at Cycle 6 (approximately 6 months) and 1.3-fold, respectively, without consideration of time-varying clearance. The geometric mean $V_{ss}$ of retifanlimab was 6.05 L (20.2% CV). Retifanlimab CL (CV%) after the first dose was 0.314 L/day (36.0%) and decreased over time by 23.6%, resulting in a steady state CL of 0.240 L/day (33.6%). The elimination half-life (CV%) at steady state was 18.7 days (28.7%).

Population PK analyses showed that the following factors had no clinically meaningful effect on the exposure of retifanlimab: sex, race, age, body weight, ethnicity, cancer type (EC, MCC, SCAC, NSCLC, and others), AST level, ALP level, albumin level, bilirubin level, estimated glomerular filtration rate (MDRD equation), HIV status, corticosteroid used for AE management, infusion time, DP (produced by P1 and P2 process), and renal and hepatic function. Pharmacokinetic exposures were similar among participants with normal renal function and participants with mild or moderate renal impairment and among participants with normal

hepatic function and participants with mild hepatic impairment.

A total of 65 chemotherapy-naïve participants with MCC from Study 201, including 34 responders, were included in the E-R efficacy analysis dataset. A non–statistically significant relationship was seen between any PK exposure and ORR, DOR, DCR, PFS, and OS.

Flat E-R curves were observed for the safety endpoints of irAEs, ≥ Grade 3 treatment-related TEAEs, and most TEAEs with a frequency > 10% for the All Cancer Population. The effect of retifanlimab exposures on each TEAE with a frequency > 10% in the All Cancer Population was considered not clinically relevant.

Moderate increases in PK exposures were predicted in adolescents as compared to adults when 500 mg Q4W was administered for both populations. However, these increases are not clinically significant. Retifanlimab demonstrated full saturation of the PD-1 receptor on CD4+ and CD8+ cells at trough at all clinical doses in adults (b) (4)

(b) (4)

Eleven (1.7%) of 640 evaluable participants tested positive for treatment-emergent anti-retifanlimab antibodies and only 1 participant persistently tested positive. Of those who were ADA positive, neutralizing antibodies were detected in only 4 participants (0.6% of the total). There were no clinically significant alterations of the PK, efficacy, or safety profile of retifanlimab in the positive participants.

A cardiac safety analysis was performed using 12-lead ECG data from 240 participants treated with retifanlimab at doses up to 10 mg/kg Q2W and 750 mg Q4W in Study 101. A large QT/QTc effect (> 20 milliseconds) can be excluded within the observed range of retifanlimab serum concentrations. Retifanlimab at the studied doses up to 10 mg/kg Q2W or 750 mg Q4W did not have a relevant effect on cardiac conduction (ie, the PR and QRS intervals).

These findings from the retifanlimab population PK analyses, E-R analyses, and immunogenicity analyses support the proposed dosing regimen of 500 mg as a 30-minute IV infusion Q4W in adult (b) (4) patients (b) (4) with MCC.

The FDA's Assessment:

FDA generally agrees with the Applicant's position regarding pharmacology and clinical pharmacology of retifanlimab, except for the calculation of incidence of neutralizing antibodies (Nab). However, Nab incidence should be calculated relative to the incidence of ADAs, rather than the total patient number. The correct Nab incidences in MCC population and all cancer population are 66.7% and 36.3%, respectively. Given the low ADA incidence, the impact of ADA on PK, efficacy, and safety of retifanlimab is inconclusive.

## 6.2.2. General Dosing and Therapeutic Individualization

### 6.2.2.1. General Dosing

The Applicant's Position:

The recommended dosing regimen of retifanlimab is 500 mg as a 30 minute IV infusion Q4W in (b) (4) patients with MCC.

In Study 101, retifanlimab was initially administered in dose escalation as weight-based doses (ranging from 1 to 10 mg/kg Q2W). Retifanlimab was well-tolerated over the entire dosing range, and a maximum tolerated dose was not reached. Flat dose regimens of 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W were also explored in the cohort expansion of Study 101 in addition to the weight-based dose of 3 mg/kg Q2W.

The proposed dosing regimen of 500 mg Q4W was based on nonclinical results and Phase 1 clinical results. The latter included a population PK analysis with 37 participants from the dose escalation phase of Study 101.

The 500 mg Q4W regimen resulted in steady-state exposure that was similar to the 3 mg/kg Q2W regimen ($C_{trough}$). Full PD-1 receptor occupancy was observed on PD-1–expressing CD4+ and CD8+ cells with effects on circulating cytokines that are typical for a PD-1 inhibitor in all dose regimens of Study 101. Therefore, the 500 mg Q4W dose was selected as a dose for further development in MCC.

This dose regimen was further supported by the linear PK of retifanlimab. Although body weight was identified as a predictor for CL, $V_c$, and $V_p$, the exponents for power function were less than 0.5, indicating a mild impact of body weight on PK exposures. A comparison between the population PK model-simulated PK profile for the 3 mg/kg Q2W dosing regimen and the 500 mg Q4W dosing regimen was also conducted. Comparable PK profiles were observed between the flat 500 mg Q4W dose and body weight–based 3 mg/kg Q2W dose, with mean $AUC_{0\text{-}28d,ss}$ of the 500 mg Q4W dose approximately 14.8% higher than that of the 3 mg/kg Q2W dose. In addition, the mean $C_{max1}$ and $C_{min1}$ of the 500 mg Q4W dose were only 131% and 13.9% higher than that of the 3 mg/kg Q2W dose; the mean $C_{min,ss}$ and $C_{max,ss}$ were only 16.3% lower and 69.4% higher than those after 3 mg/kg Q2W dosing.

Furthermore, no meaningful E-R relationships for safety variables (irAEs, AESI, > 10% TEAEs, and ≥ Grade 3 treatment-related TEAEs) in the MCC Population and the All Cancer Population were identified, indicating no difference in safety between the 3 mg/kg Q2W and 500 mg Q4W dose regimens. The simulated $C_{min,ss}$ and $AUC_{0\text{-}28d,ss}$ were comparable between the 2 dosing regimens. Hence, the safety data from the 3 mg/kg Q2W cohorts, the safety and efficacy data from the 500 mg Q4W dose in participants with MCC, and similar exposures following 3 mg/kg Q2W and 500 mg Q4W support the proposed dosing regimen of 500 mg Q4W.

Infusion time had no impact on the retifanlimab PK parameters. The comparison between 500 mg Q4W administered as a 30-minute IV infusion and 60 minute IV infusion indicates that serum concentration profiles overlap and the exposures ($C_{max}$, $C_{min}$, and $AUC_{0\text{-}28d}$) were comparable.

(b) (4)

The FDA's Assessment:
FDA generally agrees with the Applicant's position on general dosing in adult patients with MCC. The proposed dosage of 500 mg Q4W through 30-minute IV infusion in adults is supported by the results of the dose-finding study, the efficacy demonstrated in PODIUM-201 in the MCC population, the acknowledged safety profile (in reference to the observed efficacy), and flat E-R relationships for efficacy (in MCC) and safety (in MCC and all cancer populations). Refer to section 6.3.2.2 for further details. (b) (4) (b) (4)

#### 6.2.2.2. Therapeutic Individualization

The Applicant's Position:
The clinical pharmacology of retifanlimab, as well as the importance of various intrinsic and extrinsic factors influencing retifanlimab PK, has been characterized in 5 clinical studies of participants with cancer. Overall, the clinical pharmacology profile of retifanlimab is supportive of the proposed dosing regimen of 500 mg as an IV infusion over 30 minutes Q4W in adults (b) (4) (b) (4) with MCC. The main findings include the following:

- In total, retifanlimab PK data were collected in 634 participants with various solid tumors, including 102 participants with MCC.
- Population PK analyses showed that the following factors had no clinically meaningful effect on the exposure of retifanlimab: age, sex, body weight, race, ethnicity, cancer type (EC, MCC, SCAC, NSCLC, and others), AST level, ALP level, bilirubin level, albumin level, estimated glomerular filtration rate (MDRD equation), HIV status, corticosteroid used for AE management, infusion time, and DP (produced by P1 and P2 process), and renal and hepatic function.
- Simulation based on the population PK model showed moderate but nonclinical significant increases in PK exposures in adolescents compared with adults when 500 mg Q4W was administered for both populations. Pharmacokinetic exposures were similar between participants with normal renal function and participants with mild or moderate renal impairment and between participants with normal hepatic function and participants with mild hepatic impairment.
- It is unlikely that retifanlimab would be a victim or perpetrator of PK DDIs.
- Flat E-R relationships were generally observed for efficacy endpoints in MCC participants.
- Flat E-R relationships were generally observed for safety endpoints in the All Cancer Population and the MCC Population.
- The overall incidence of treatment-emergent ADAs was low (1.7%). The presence of retifanlimab ADAs appears not to alter the PK, efficacy, and safety of retifanlimab.
- A large QT/QTc effect (> 20 milliseconds) can be excluded up to the highest dose level studied.

In summary, the findings from the retifanlimab population PK analyses, E-R analyses on safety and efficacy, and immunogenicity analysis support the proposed dosing regimen of 500 mg as a 30-minute IV infusion Q4W in adult (b) (4) patients with MCC.

The FDA's Assessment:
FDA agrees with the Applicant's position that no dosage adjustment is required for adult patients with MCC based on intrinsic and extrinsic factors, including sex, race, age, body weight, ethnicity, cancer type, AST level, ALP level, albumin level, bilirubin level, estimated glomerular filtration rate (MDRD equation), HIV status, corticosteroid used for AE management, infusion time, DP, and renal and hepatic function, because the PopPK analyses showed no clinically significant effect of these covariates on PK exposure.

#### 6.2.2.3. Outstanding Issues

The Applicant's Position: Not applicable.

The FDA's Assessment: There are no outstanding issues.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

***Bioanalytical Method:*** **PK Assessment:** The bioanalytical methods validated for determination of retifanlimab concentrations in human serum used 2 types of assay platforms, the ELISA and the MSD-ECL. Both the ELISA and the MSD-ECL methods were used in the sample analysis for Study 101. The MSD-ECL method was also used for sample analysis for Studies 104, 201, 202, and 203. The ELISA method (DMB-19.168) was originally developed and fully validated at (b) (4) Subsequently, the ELISA method was transferred to and fully validated at (b) (4) (DMB-18.85). In the ELISA methods, an assay plate coated with murine anti-retifanlimab mAb for capture. The captured retifanlimab was detected by the sequential addition of biotinylated murine anti-retifanlimab biotin (detector mAb), followed by HRP-SA. The bound HRP activity was quantified by the luminescence light generation using the Pico substrate. The luminescence light intensity was measured by a plate reader. The standard curve was generated by fitting the relative light intensity signal from retifanlimab standards with a 4 PL model. The concentration of retifanlimab in the serum samples was determined by interpolation from a standard curve using a 4-parameter curve fit relating the light intensity to the concentration of retifanlimab. The validated assay range was 23.3 ng/mL to 625 ng/mL with a dilution factor of up to 1:25000 verified. In order to ensure data quality and assay robustness, a new MSD-ECL method was subsequently validated at (b) (4). The MSD-ECL method (DMB-19.155) consisted of an ECL immunoassay, where recombinant human PD 1 was coated overnight onto an MSD standard plate (ECL capable). Retifanlimab was captured on the coated plate in the calibration standards, QC samples, controls, and other samples. After thorough washing of the wells to remove the unbound antibody, ruthenylated anti-retifanlimab (clone 4E3.1) was added to the wells so that the conjugate would bind to the captured retifanlimab. Excess unbound conjugate was removed by further washing of the wells followed by addition of MSD read buffer. The assay plate was then read using an MSD-ECL plate reader. The ECL signal generated relative to the amount of retifanlimab present in the calibration standards, QC samples, controls and other samples was recorded. The nonregression model used was a

4-parameter curve fit. The concentration of retifanlimab was back calculated from the regression analysis. The assay range was 200 to 6000 ng/mL and a dilution factor of 1:1600 was verified. This assay was put into effect for quantitative bioanalysis of retifanlimab in DEC 2018. The MSD-ECL assay was cross validated against both ELISA methods at (b) (4) and at (b) (4), using incurred samples from Study 101. The cross validation demonstrated that the results generated from the methods are comparable (DMB-20.71).

**Immunogenicity Assessment:** A bridging ELISA method was validated that was able to sensitively detect anti-retifanlimab antibodies. The procedure consisted of 3 assays: a screening assay, a confirmatory assay, and a titration assay. In the screening assay, the assay plate was coated with retifanlimab and stored overnight. The next day, the assay plate was blocked with 5% bovine serum albumin in PBS. In a dilution plate, test samples were treated with acetic acid. The acid-treated samples were then incubated to dissociate retifanlimab from anti-retifanlimab antibodies if present. At the end of the incubation, retifanlimab biotin in neutralization buffer and acidified serum samples were then transferred sequentially to the retifanlimab-coated assay plate. The neutralized sample mixture was incubated. The assay plate was then washed and the second detector, HRP-SA, was added. After incubation, the bound HRP activity was quantified by the color conversion of the HRP substrate, TMB, and the absorbance was measured. The confirmatory assay was performed similarly to the screening assay, except that samples were incubated with excess retifanlimab to demonstrate the specificity of the presumptive antibody response. Samples that were determined to be positive in the confirmatory assay are tested on the titration assay, which would quantify the antibody response. The ADA assay (DMB-19.169) was originally developed and fully validated at (b) (4). Subsequently, this method was transferred to (b) (4) and underwent method transfer validation (DMB-19.156). Serum samples from participants in Study 101 obtained before APR 2018 were analyzed for ADAs with the validated ELISA at (b) (4). For serum samples obtained from Study 101 after APR 2018, and for serum samples from all other clinical studies, ADA sample bioanalysis was performed with the validated ELISA method at (b) (4). In addition, results from an ADA cross validation tests demonstrated that the methods generated similar results using incurred samples from Study 101. A cell-based NAb assay (DMB-21.111) was validated at (b) (4) and applied to the detection of neutralizing antibodies to retifanlimab in human serum for the confirmed ADA positive samples. The assay starts with an acidification step of the drug/NAb complex. The NAb is then immunocaptured using Dynabeads coated with retifanlimab drug. The eluted NAb (samples and controls) are then processed with PathHunter PD-1 Signaling Bioassay, which relies on the well-established PathHunter EFC technology to interrogate receptor activity. EFC consists of a split β-gal enzyme: the ED and EA fragments, which independently have no β-gal activity. However, when forced to complement they form an active β-gal enzyme that hydrolyzes substrate to produce a chemiluminescent signal. Addition of an antagonist (eg, antibody to PD-L1, PD-L2, or PD-1) blocks PD-1 signaling, and prevents complementation, resulting in a loss of signal. The presence of NAb binds to the drug and reverses the blockage in a dose dependent manner and restores the signal. This method was used for Studies 101, 201, 202, and 203.

**PD-L1 Target Occupancy Testing:** Retifanlimab receptor occupancy of PD-1 on CD8+ and CD4+ T cells from participants dosed with retifanlimab in Study 101 was measured by 2 complementary flow cytometry methods evaluating 1) percent of maximal binding over time (as measured by anti-IgG4 to detect retifanlimab), and 2) loss of retifanlimab binding over time to confirm binding (as measured by loss of commercially labeled anti-PD-1 mAb, which competes with retifanlimab). Peripheral blood from dose escalation and flat dose expansion (500 mg Q4W and 750 mg Q4W) cohorts were collected at various time points after dosing (TRS-20.15). In the first method, receptor occupancy was measured as percent of maximal binding over time from individual patients and was determined by the percentage of retifanlimab-positive CD8+ cells (detected with an anti-IgG4Fc Ab) at the time following retifanlimab infusion divided by the percentage of retifanlimab-positive CD8+ cells at the same time following retifanlimab infusion measured in the presence of an excess amount of exogenously added retifanlimab (representing maximal binding ~100%). A second complementary method used an AlexFlur488-labeled anti-PD-1 mAb (eJBio105 clone) that competes with retifanlimab for PD-1 binding sites to measure receptor occupancy is presented as a function of loss of PD-1 staining over time (representing blockade of binding ~0%). The second method was employed to confirm retifanlimab binding.

***Pharmacokinetics:*** The PK of retifanlimab have been determined using both NCA and PPK analyses. In Study 101 and Study 104, sparse PK sampling was performed after the first cycle of retifanlimab. For this reason, only first dose PK and selected steady-state PK parameters were evaluated using NCA. In Study 201, Study 202, and Study 203, only sparse PK samples were collected and no NCA was performed. The main PK evaluation was based on a population-based PK approach, combining results from monotherapy in all 5 clinical studies. (Table 10)

**Table 10: Summary of Pharmacokinetic Parameters of Retifanlimab From Study 101**

| | | First Dose | | | | | | | Steady State | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose | N | $C_{max}$ (mg/L) | $T_{max}$ (h) | $t_{1/2}$ (day) | $AUC_t$ (day·mg/L) | $AUC_\infty$ (day·mg/L) | CL (L/day) | $V_z$ (L) | $C_{trough}$ (mg/L) | $C_{max,ss}$ (mg/L) |
| 1 mg/kg Q2W | 3 | 16.5 ± 4.94 (15.9, 34.6%) | 1.1 (1.0-1.2) | 7.97 ± 1.80 (7.84, 23.0%) | 93.6 ± 21.4 (92.0, 22.5%) | 135 ± 43.2 (131, 30.6%) | 0.442 ± 0.0297 (0.441, 6.62%) | 5.03 ± 0.857 (4.99, 16.9%) | NA | NA |
| 3 mg/kg Q2W[a] | 131 | 62.9 ± 20.5 (60.1, 31.0%) | 1.3 (0.9-144) | 7.65 ± 2.10 (7.39, 26.4%) | 369 ± 102 (353, 32.6%) | 534 ± 172 (507, 34.2%) | 0.449 ± 0.153 (0.427, 32.3%) | 4.73 ± 1.40 (4.56, 27.7%) | 44.0 ± 18.8 (39.1, 59.8%) | 106 ± 34.0 (100, 33.6%) |
| 3 mg/kg Q4W | 9 | 67.9 ± 13.5 (66.6, 21.4%) | 1.2 (1.0-7.0) | 12.7 ± 4.79 (11.6, 53.1%) | 555 ± 139 (539, 26.9%) | 719 ± 218 (685, 34.9%) | 0.415 ± 0.135 (0.397, 32.0%) | 7.12 ± 2.61 (6.66, 41.6%) | 18.1 | 77.3 |
| 10 mg/kg Q2W | 7 | 208 ± 55.2 (201, 27.0%) | 1.1 (1.1-1.3) | 9.35 ± 2.27 (9.13, 23.6%) | 1140 ± 300 (1110, 24.2%) | 1740 ± 576 (1680, 29.9%) | 0.453 ± 0.119 (0.437, 30.9%) | 5.98 ± 1.70 (5.76, 30.6%) | NA | NA |

| Dose | | N | First Dose | | | | | | | Steady State | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $C_{max}$ (mg/L) | $T_{max}$ (h) | $t_{1/2}$ (day) | $AUC_t$ (day·mg/L) | $AUC_\infty$ (day·mg/L) | CL (L/day) | $V_z$ (L) | $C_{trough}$ (mg/L) | $C_{max,ss}$ (mg/L) |
| 10 mg/kg Q4W | | 5 | 225 ± 41.7 (223, 17.4%) | 1.2 (1.0-7.0) | 15.6 ± 5.82 (14.8, 37.4%) | 1920 ± 308 (1900, 17.3%) | 2640 ± 654 (2570, 25.8%) | 0.336 ± 0.169 (0.304, 53.9%) | 7.07 ± 3.36 (6.46, 49.7%) | 70.6, 51.5 | 285, 246 |
| 375 mg Q3W[b] | | 15 | 114 ± 32.7 (110, 30.4%) | 1.2 (1.0-7.0) | 12.9 ± 3.72 (12.4, 28.9%) | 786 ± 238 (752, 31.6%) | 1170 ± 410 (1100, 39.2%) | 0.366 ± 0.151 (0.341, 39.2%) | 6.26 ± 1.41 (6.09, 25.0%) | 43.0 ± 15.0 (41.3, 31.5%) | 175 ± 32.5 (172, 18.7%) |
| 500 mg Q4W[c] | | 97 | 192 ± 144 (175, 37.8%) | 1.3 (1.0-7.3) | 15.6 ± 6.68 (14.6, 36.7%) | 1430 ± 395 (1380, 30.2%) | 1980 ± 675 (1870, 35.2%) | 0.284 ± 0.107 (0.267, 35.2%) | 5.90 ± 1.99 (5.61, 33%) | 55.4 ± 27.3 (47.7, 68.8%) | 269 ± 307 (229, 47.4%) |
| 750 mg Q4W[d] | | 13 | 215 ± 66.5 (206, 29.5%) | 1.2 (1.0-22) | 17.6 ± 5.21 (16.9, 31.0%) | 1830 ± 532 (1760, 29.3%) | 2600 ± 741 (2490, 31.8%) | 0.316 ± 0.115 (0.301, 31.8%) | 7.59 ± 2.06 (7.35, 27.3%) | 37.5 ± 8.72 (36.8, 25.7%) | 264 ± 18.5 (264, 7.02%) |
| Total (280) | Escalation | 33 | — | 1.13 (1.0-7.1) | 10.6 (7.6-17.6) | — | — | 0.427 ± 0.124 (0.408, 33.6%) | 6.30 ± 2.35 (5.90, 37.9%) | — | — |
| | Expansion | 247 | — | 1.3 (0.9-144) | | — | — | 0.371 ± 0.156 (0.343, 41.2%) | 5.41 ± 1.85 (5.14, 32.7%) | — | — |

NA = not available.
Note: Values are presented in the format of mean ± STD and geometric mean (CV%) if N > 2 except that $T_{max}$ is reported as median (range).
[a] n = 46 for steady state.
[b] n = 4 for steady state.
[c] n = 57 for steady state.
[d] n = 3 for steady state.

Retifanlimab exhibited linear PK over the dose range of 1 mg/kg to 10 mg/kg (including flat doses of 375 mg, 500 mg, and 750 mg; Table 10). At 500 mg Q4W, the geometric mean retifanlimab concentrations (CV%) at steady state ranged between a $C_{min}$ of 41.0 mg/L (50.8%) and a $C_{max}$ of 193 mg/L (24.1%). Steady-state exposure was achieved after approximately 308 days (approximately 10 months) of treatment and systemic accumulation was 1.6-fold for the Q4W dose in consideration of time-varying clearance and at Cycle 6 (approximately 6 months) and 1.3-fold, respectively, without consideration of time-varying clearance.

Population PK analyses showed that the following factors had no clinically meaningful effect on the exposure of retifanlimab: sex, race, age, body weight, ethnicity, cancer type (EC, MCC, SCAC, NSCLC, and others), AST level, ALP level, albumin level, bilirubin level, estimated glomerular filtration rate (MDRD equation), HIV status, corticosteroid used for AE management, infusion time, DP (produced by P1 and P2 process), and renal and hepatic function. Pharmacokinetic exposures were similar among participants with normal renal function and participants with mild or moderate renal impairment and among participants with normal

hepatic function and participants with mild hepatic impairment.

The geometric mean $V_{ss}$ of retifanlimab was 6.05 L (20.2% CV). Retifanlimab CL (CV%) after the first dose was 0.314 L/day (36.0%) and decreased over time by 23.6%, resulting in a steady-state CL of 0.240 L/day (33.6%). The elimination half-life (CV%) at steady state was 18.7 days (28.7%).

Moderate increases in PK exposures were predicted in adolescents as compared to adults when 500 mg Q4W was administered for both populations. However, these increases are not clinically significant. Retifanlimab demonstrated full saturation of the PD-1 receptor on CD4+ and CD8+ cells at trough at all clinical doses in adults (TRS-20.15) (b) (4)

(b) (4)

Eleven (1.7%) of 640 evaluable participants tested positive for treatment-emergent anti-retifanlimab antibodies and only 1 participant persistently tested positive. Of those who were ADA positive, neutralizing antibodies were detected in only 4 participants (0.6% of the total). There were no clinically significant alterations of the PK, efficacy, or safety profile of retifanlimab in the positive participants.

A cardiac safety analysis was performed using 12-lead ECG data from 240 participants treated with retifanlimab at doses up to 10 mg/kg Q2W and 750 mg Q4W in Study 101. A large QT/QTc effect (> 20 milliseconds) can be excluded within the observed range of retifanlimab serum concentrations. Retifanlimab at the studied doses up to 10 mg/kg Q2W or 750 mg Q4W did not have a relevant effect on cardiac conduction (ie, the PR and QRS intervals; DMB-20.60).

These findings from the retifanlimab population PK analyses, E-R analyses, and immunogenicity analyses support the proposed dosing regimen of 500 mg as a 30-minute IV infusion Q4W in adult (b) (4) patients (b) (4) with MCC (DMB-22.69).

The FDA's Assessment:

FDA agrees with the Applicant's summary of the PK, PD, and immunogenicity characteristics of retifanlimab as it applies to the proposed indication in adult patients with advanced or metastatic MCC.

### 6.3.2. Clinical Pharmacology Questions

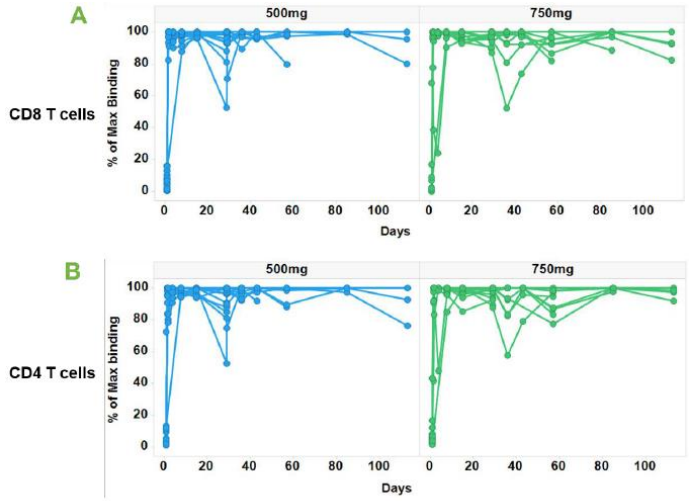
#### 6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

The primary evidence of effectiveness in this BLA submission was obtained from the single-arm Study 201 in 65 patients with metastatic or recurrent locally advanced MCC. All patients received retifanlimab at the proposed 500 mg Q4W dose. At this dose, the confirmed ORR by ICR was 52.3% (95% CI: 39.5, 64.9) in the intent-to-treat population (n=65) with 18.5% of patients achieving a CR. The 65 chemotherapy-naïve participants with MCC from Study 201, including 34 responders, were included in the E-R efficacy analysis dataset. A non–statistically significant relationship was seen between any PK exposure and ORR, DOR, DCR, PFS, and OS.

Retifanlimab receptor occupancy of PD-1 on CD8+ and CD4+ T cells from patients dosed with retifanlimab in Study 101 was measured. PD-1 receptor expression was observed on 15-45% of CD8 and CD4 cells across patients as measured in whole blood prior to retifanlimab infusion. Despite patient variation in PD-1 expression, full retifanlimab receptor occupancy was observed at all the time points sampled post-retifanlimab infusion, at all doses tested in dose escalation (TRS-20.15). Both methods utilized to measure receptor occupancy support full occupancy on both PD-1 expressing CD4+ and CD8+ T cells. All tested doses of retifanlimab evaluated also demonstrated full saturation of the PD-1 receptor at trough on circulating CD4+ and CD8+ T cells. Receptor occupancy analysis from 30 participants receiving flat doses of retifanlimab (500 mg Q4W [n = 15] and 750 mg Q4W [n = 15]) also demonstrated full occupancy in both dosing cohorts (**Error! Reference source not found.**). Specifically, average receptor occupancy f or both CD4+ and CD8+ T cells was above 90% at all-time points assessed.

**Figure 88 PD-1 Receptor Occupancy Following Dosing in the Flat Dosing Cohorts**




Panel A in CD8+ cells and Panel B in CD4+ cells.

The FDA's Assessment:

The pivotal single-arm clinical trial INCMGA 0012-201 in adult patients with advanced or metastatic MCC (n=107) provided the primary evidence of effectiveness, based on data from the first 65 chemotherapy-naïve participants in full analysis set (FAS). Treatment with retifanlimab 500 mg Q4W resulted in an ORR of 52% with18 % of patients experiencing CRs and 34% of patients experiencing PRs.

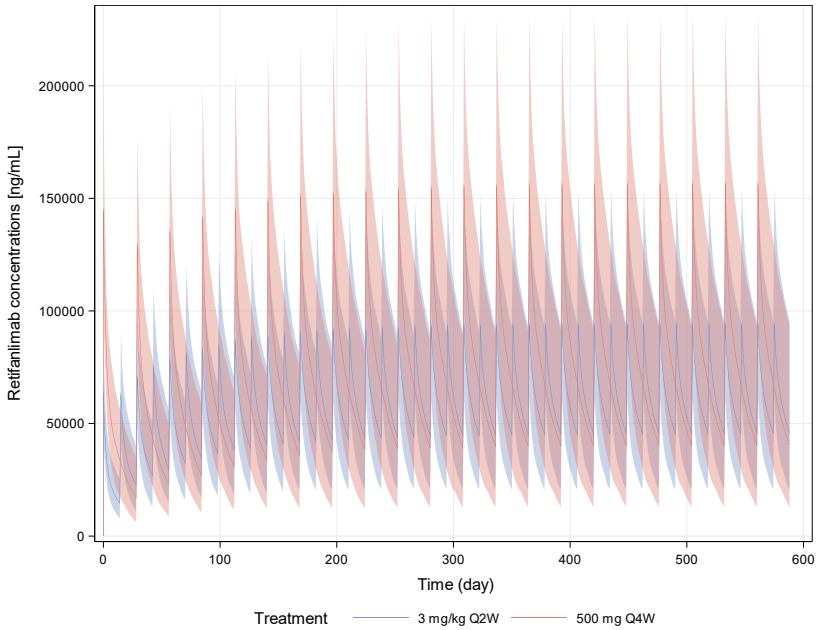
### 6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

The current proposed retifanlimab dosage of 500 mg given Q4W was used in Study 201. The proposed dosing regimen of 500 mg Q4W was based on nonclinical results and Phase 1 clinical results. The latter included a PPK analysis with 37 participants from the dose escalation phase

of Study 101. In Study 101, retifanlimab was initially administered in dose escalation as weight-based doses (ranging from 1 to 10 mg/kg Q2W). Retifanlimab was well-tolerated over the entire dosing range, and a maximum tolerated dose was not reached. Flat dose regimens of 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W were also explored in the cohort expansion of Study 101 in addition to the weight-based dose of 3 mg/kg Q2W. A comparison between the PPK model-simulated PK profile for the 3 mg/kg Q2W dosing regimen and the 500 mg Q4W dosing regimen is provided in Figure 99. Comparable PK profiles were observed between the flat 500 mg Q4W dose and body weight–based 3 mg/kg Q2W dose, with mean $AUC_{0\text{-}28d,ss}$ of the 500 mg Q4W dose approximately 14.8% higher than that of the 3 mg/kg Q2W dose. In addition, the mean $C_{max1}$ and $C_{min1}$ of the 500 mg Q4W dose were only 131% and 13.9% higher than that of the 3 mg/kg Q2W dose; the mean $C_{min,ss}$ and $C_{max,ss}$ were only 16.3% lower and 69.4% higher than those after 3 mg/kg Q2W dosing.

**Figure 99: Comparison of Model-Simulated Pharmacokinetic Profiles Following 500 mg Q4W Versus 3 mg/kg Q2W Retifanlimab**




Note: The blue line and shadow indicate the median and 95% quantile of 3 mg/kg Q2W, and the red line and shadow indicate the median and 95% quantile of 500 mg Q4W.
Source: Module 2.7.2, Figure 25.

(b) (4)

(b) (4)

The Applicant's Position:

Body weight–based doses (ranging from 1 to 10 mg/kg) were initially administered in dose escalation cohorts of Study 101. Flat dose regimens of 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W were also explored in expansion cohorts. Retifanlimab was well-tolerated over the entire dose range, and a maximum tolerated dose was not reached. The proposed dose regimen of 500 mg Q4W was based on nonclinical results, the Phase 1 clinical experience, and results from a population PK analysis with 37 participants from the dose escalation portion of Study 101. The 500 mg Q4W regimen resulted in similar steady-state exposure when compared to the 3 mg/kg Q2W regimen (trough concentration). Full PD-1 receptor occupancy was observed on PD-1–expressing CD4+ and CD8+ cells with effects on circulating cytokines that are typical for a PD-1 inhibitor in all dose regimens of Study 101 (TRS-20.15). Therefore, the 500 mg Q4W dose was selected for further development in MCC based on the comparable benefit-risk profiles to weight–based dose administration, similar PK exposures, longer dose intervals, and the many practical advantages inherent to flat dose regimens, such as easier dose preparation, reduced drug waste, and a reduced risk of dose calculation error (Bai 2012, Wang 2009). The 500 mg Q4W dose regimen is further supported by the approximate linear PK of retifanlimab, population PK results, and the comparable simulated PK profiles for the flat 500 mg Q4W dose and body weight 3 mg/kg Q2W dose. Furthermore, no meaningful E-R relationships for safety variables (eg, irAEs, TEAEs) in the MCC Population and the All Cancer Population were identified, indicating no difference in safety between the 3 mg/kg Q2W and 500 mg Q4W dose regimens. The 3 mg/kg Q2W previously demonstrated clinical activity in participants with advanced solid tumors in Study 101, and the results from Study 201 demonstrate that 500 mg Q4W is an active dose in participants with MCC. Hence, the safety and efficacy data from 3 mg/kg Q2W cohorts, the safety and efficacy data from 500 mg Q4W in participants with MCC, and similar exposures of 3 mg/kg Q2W and 500 mg Q4W support the proposed dose regimen of 500 mg Q4W. (b) (4)

(b) (4)

The FDA's Assessment:

The Applicant's proposed dosage of 500 mg Q4W is acceptable for adult patients with metastatic or recurrent locally advanced MCC. The proposed dosing regimen in adults is supported by the observed clinical safety, efficacy, PK/PD data, PopPK, and E-R analyses:.

- Comparable steady-state exposures were observed between the flat dosage of 500 mg Q4W and the body weight–based dosage of 3 mg/kg Q2W, which achieved the highest efficacy response rates in Phase 1 study INCMGA 0012-101. PopPK suggested there was no clinically meaningful impact of body weight on PK exposures, which supports the proposed flat dose for retifanlimab.
- Full PD-1 receptor occupancy was observed in all dose regimens evaluated in Study INCMGA 0012-101.
- Flat E-R relationships for efficacy endpoints (ORR and DoR) and safety variables (irAEs, AESI,

>10% TEAEs) were observed.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:

No. Dose adjustment based on intrinsic factors is not needed based on the PPK analysis.

PPK analyses showed that the following factors had no clinically meaningful effect on the exposure of retifanlimab: age, sex, body weight, race, ethnicity, cancer type, AST level, ALP level, bilirubin level, albumin level, estimated glomerular filtration rate (MDRD equation), HIV status, corticosteroid used for AE management, infusion time, and DP (produced by P1 and P2 process), and renal and hepatic function.

(b) (4)

(b) (4) Pharmacokinetic exposures were similar between participants with normal renal function and participants with mild or moderate renal impairment and between participants with normal hepatic function and participants with mild hepatic impairment.

The FDA's Assessment:

FDA agrees with the Applicant's justification that no dose adjustment is warranted for the above intrinsic and extrinsic factors based on PopPK assessment. Although PK of retifanlimab has not been studied in patients with moderate or severe hepatic impairment, the impact of hepatic dysfunction on PK of retifanlimab is expected to be minimal, given that retifanlimab is anticipated to be catabolized into amino acids by the general protein degradation process.

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

Data:

Retifanlimab belongs to the class of IgG antibodies that are administered parenterally and cleared by protein catabolism; thus, extrinsic factors such as food and DDI are not anticipated to affect the exposure of retifanlimab. Specifically, drugs that affect cytochrome P450 and other metabolizing enzymes are not expected to interfere with the catabolism of retifanlimab (Sheng 2017, FDA 2020). It is unlikely that retifanlimab would be a victim of PK DDI (EMA 2012, FDA 2020). Dedicated DDI studies of retifanlimab have not been performed.

Corticosteroids were used in the studies to treat some irAEs, so the coadministration of corticosteroids was explored as a time independent predictor for PK variability in the PPK model. Corticosteroid coadministration was not identified as a significant predictor for PK parameter variabilities. Therefore, no dose adjustments based on corticosteroids are

recommended. Retifanlimab is known to increase some proinflammatory cytokine levels (TRS-20.15). This is a known class effect of checkpoint inhibitory mAbs (Feun 2019Feun 2019, Matsuo 2019) but is unlikely to modulate cytochrome P450 enzymes or drug transporters, based on clinical evidence with other agents of this class (Sheng 2017).

The Applicant's Position:

Retifanlimab, 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. Retifanlimab, as a mAb, is also not expected to have a direct DDI effect on other small molecule drugs.

The FDA's Assessment:

FDA agrees with the Applicant's position that food-drug or drug-drug interaction are not anticipated, given that retifanlimab is a humanized monoclonal antibody administered via IV route.

X

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# 7 Sources of Clinical Data

## 7.1. Table of Clinical Studies

The Applicant's Position:
The clinical studies to support efficacy and safety that are relevant to this BLA are summarized in Table 11.

**Table 11: Listing of Clinical Trials Relevant to this BLA**

| Trial Identity | Trial Design | Regimen | Study Endpoints | Treatment Duration | No. Of Patients | Study Population | No. of Centers |
|---|---|---|---|---|---|---|---|
| ***Uncontrolled Studies to Support Efficacy and Safety*** | | | | | | | |
| INCMGA 0012-201<br>NCT03599713 | Phase 2, open-label, multiregional, multicenter | Retifanlimab 500 mg Q4W IV | **Primary:** ORR according to RECIST v1.1 by ICR<br>**Secondary:** DOR, DCR, and PFS according to RECIST v1.1 by ICR; OS | Up to 2 years or until meeting protocol-specific discontinuation criteria | 107[a] | Participants with metastatic or locally advanced recurrent Merkel cell carcinoma | 34 sites across 11 countries |
| ***Studies to Support Safety*** | | | | | | | |
| INCMGA 0012-101<br>NCT03059823 | Phase 1, open-label, multiregional, multicenter, dose-escalation and cohort expansion | Retifanlimab 1 mg/kg Q2W, 3 mg/kg Q2W and Q4W, 10 mg/kg Q2W and Q4W, 500 mg Q4W, 750 mg Q4W, 375 mg Q3W; IV | **Primary:** Safety and tolerability<br>**Secondary:** PK; ORR, DOR, and PFS according to RECIST v1.1 by investigator and ICR; OS | Up to 2 years or until meeting protocol-specific discontinuation criteria | 315 | Participants with advanced solid tumors | 56 sites across 16 countries |
| INCMGA 0012-104<br>NCT03910530 | Phase 1b, open-label, multicenter | Retifanlimab 500 mg Q4W IV | **Primary:** Safety and tolerability<br>**Secondary:** PK; ORR, DOR, and DCR according to RECIST v1.1 by investigator | Up to 2 years or until meeting protocol-specific discontinuation criteria | 6 (in retifanlimab monotherapy arm) | Japanese participants with advanced solid tumors | 2 sites in 1 country |
| INCMGA 0012-202<br>NCT03597295 | Phase 2, open-label, single-arm, multiregional, multicenter | Retifanlimab 500 mg Q4W IV | **Primary:** ORR according to RECIST v1.1 by ICR<br>**Secondary:** DOR, DCR, and PFS according to RECIST v1.1 by ICR; OS; safety; PK | Up to 2 years or until meeting protocol-specific discontinuation criteria | 94 | Participants with locally advanced or metastatic SCAC | 40 sites across 9 countries |
| INCMGA 0012-203<br>NCT03679767 | Phase 2, open-label, multiregional, multicenter | Retifanlimab 500 mg Q4W IV | **Primary:** ORR according to RECIST v1.1 by investigator<br>**Secondary:** DOR, DCR, and PFS according to RECIST v1.1 by investigator; OS; safety; -PK | Up to 2 years or until meeting protocol-specific discontinuation criteria | 121 | Participants with metastatic or locally advanced NSCLC, UC, melanoma, or RCC | 34 sites across 8 countries |

[a] Data for all 107 participants enrolled and treated with retifanlimab as of the 21 JAN 2022 data cutoff date are included in Study 201 CSR. Safety data for participants who received a dose of retifanlimab as of 16 JUN 2021 (N = 105) are included in the pooled safety analyses in the ISS.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the clinical studies to support efficacy and safety. FDA clarifies the sample size of the efficacy population submitted in this BLA application consists of the initial 65 chemotherapy-naïve patients with locally advanced recurrent or metastatic MCC enrolled into PODIUM-201 who received at least 1 dose of retifanlimab as of the enrollment cutoff date of October 15, 2020. The safety population included 105 patients treated on PODIUM-201, including 6 patients with chemotherapy-refractory MCC, with a data cutoff for safety of June 16, 2022. The total pooled population for the studies to support safety comprise of 440 patients who have received at least 1 dose of retifanlimab monotherapy administered 500 mg IV every 4 weeks.

# 8 Statistical and Clinical Evaluation

## 8.1. Review of Relevant Individual Trials Used to Support Efficacy

Study 201 is the primary study that supports retifanlimab efficacy and safety claims in participants with metastatic or recurrent locally advanced MCC. This study is the only retifanlimab monotherapy study to enroll participants with MCC.

### 8.1.1. Study INCMGA 0012-201 (Study 201)

**Trial Design**
The Applicant's Description:
Study 201 is an ongoing, Phase 2, open-label, single-arm, multiregional study designed to assess the clinical activity and safety of retifanlimab in participants with metastatic or recurrent locally advanced MCC. Participants with locally advanced disease were eligible only if they had a recurrence following locoregional therapy and were not considered amenable to curative therapy with surgery or radiation. All participants receive retifanlimab 500 mg Q4W IV by 60-minute infusion.
Efficacy is assessed based on tumor assessments obtained at screening, Q8W for the first 12 months, and Q12W thereafter. Tumor response is evaluated by ICR based on RECIST v1.1 criteria. Based on regulatory guidance (EMA 2017, FDA 2018), tumor response for efficacy analysis is independently and centrally assessed based on standard RECIST v1.1 criteria (Eisenhauer 2009) using a 2-reader plus adjudication paradigm. Details of the independent review (ICR Charter) are provided in CSR, Appendix 16.1.4. Objective assessment of tumor status is also performed by the site investigators, who remain blinded to the ICR assessment. Treatment continues for up to 2 years, or until disease progression, unacceptable toxicity, death, or any decision by the physician or participant to prematurely discontinue treatment.

**Trial location**
The study is being conducted at 34 sites in Italy, France, the United States, Poland, Canada, Switzerland, Hungary, the Czech Republic, Germany, Spain, and the United Kingdom.

**Choice of control group**
Given that ORR is a direct measure of antitumor activity, a noncomparative study with ORR supported by DOR is appropriate to demonstrate the efficacy of retifanlimab (EMA 2017, FDA 2018). Based on these guideline recommendations and the ultra-rare incidence of MCC, controlled studies against a chemotherapy comparator are not believed to be feasible or appropriate (Bradford 2020, Gauci 2022).

**Study treatments**
All participants receive retifanlimab 500 mg Q4W.

**Dose selection**
Refer to Section 6.

**Assignment to treatment**
After determining that a participant was eligible at screening, site staff contacted the interactive response technology to obtain the participant number.

**Dose modification/discontinuation**
Permitted retifanlimab dose modifications for TEAEs include delay of the next scheduled dose (up to 12 weeks), infusion interruption, and discontinuation. The Protocol provides guidelines for management of specific irAEs known to be associated with the PD-1 inhibitor class, supplemented by ASCO, ESMO, and NCCN irAE guidelines. Action taken with the study drug, concomitant medications, and nondrug therapies are recorded on the appropriate eCRF.

**Administrative structure**
Incyte is the study Sponsor and is responsible for medical monitoring, study oversight, vendor oversight, database development and maintenance, collection and processing of serious AEs, regulatory submissions of relevant case reports, storage and distribution of clinical supplies to sites, and site and vendor audits. An independent DMC reviews safety data on an ongoing basis and reviewed interim efficacy data.

**Procedures and schedule**
Objective assessment of tumor status is performed Q8W for the first year of treatment and Q12W thereafter. The recommended method for measuring and following tumor burden is CT scan. Each image is evaluated by ICR for tumor response according to RECIST v1.1 and in accordance with the ICR Charter. Tumor response is also evaluated by the investigator. A central pathology laboratory tested tumor samples for MCPyV status, PD-L1 CPS, and confirmed the MCC diagnosis.
Safety is assessed continuously throughout the treatment period by monitoring the frequency, duration, and severity of AEs; performing physical examinations; measuring vital signs and clinical laboratory blood and urine samples; and conducting 12-lead ECGs. In addition to standard laboratory parameters, HIV viral load and CD4+ cell count are assessed in participants known to be HIV-positive.
Blood samples for PK analysis are obtained on Day 1 of Cycles 1 and 6 preinfusion and 10 minutes and 4 hours post-infusion and on Day 1 of Cycles 2, 4, and 7. Blood samples for ADA analysis are obtained preinfusion on Day 1 of Cycles 1, 2, 4, 6, and 8, every 2 cycles thereafter, and at EOT or safety follow-up. Health-related quality of life is assessed using validated patient

reported outcome tools (FACT-M and EQ-5D-5L questionnaires) on Cycle 1 Day 1 and then every other cycle and at EOT.

**Concurrent medications**

Permitted concomitant medications include highly active antiretroviral therapy for participants known to be HIV-positive, supportive measures for specific toxicities, growth factors, bisphosphonates, anticoagulants, and transfusional support. The incidence of infusion-related reactions with retifanlimab is low, and premedication prophylaxis is recommended only for participants who have had prior clinically significant reactions to infusion of a protein product. Prohibited concomitant medications include other anticancer therapies, probiotic dietary supplements, immunosuppression in excess of physiologic maintenance corticosteroid doses (with the exception of acute AE treatment), and live virus vaccines.

**Treatment compliance**

Retifanlimab is administered by healthcare professionals under the supervision of the investigator. Treatment administration records are maintained by site staff. The study monitor reviews these records as well as medication accountability during study site visits and at the completion of the study.

**Subject completion discontinuation, or withdrawal**

Treatment may continue for up to 2 years in the absence of disease progression, intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation for any other reason. Participants who have been treated for at least 6 months and achieve a confirmed CR may discontinue retifanlimab per the discretion of the investigator. The follow-up period begins once a participant has completed 2 years of study drug treatment or prematurely discontinues from study drug. The safety follow-up visit occurs approximately 28 days after the last dose of study drug. Participants are followed up for AEs up to 90 days after the last dose of study drug or until the start of a new anticancer therapy, whichever occurs first.

The FDA's Assessment:

FDA agrees with the Applicant's description and that the study appeared adequate to characterize the response rate and duration of response in patients with MCC treated with retifanlimab. FDA clarifies that in addition to baseline imaging, photographic imaging of the skin tumor(s) being followed as target lesions were required and followed the schedule of events for clinical tumor assessments. In the BLA, the Applicant provided the details of the Independent Central Review (ICR) review charter that comprises details of the team, the scope, roles and responsibility of the independent radiology and oncology (review of photography) review. (Eisenhauer 2009).

**Eligibility Criteria**

The Applicant's Description:

Men and women aged 18 or older (or as applicable per local country requirements) with a diagnosis of MCC with distant metastatic disease or recurrent advanced locoregional disease not amenable to surgery or radiation were enrolled in this study. Participants who were known

to be HIV-positive were allowed to enroll, as long as their CD4+ count was ≥ 300 cells/µL, they had an undetectable viral load, and they were receiving highly active antiretroviral therapy. As of Protocol Amendment 5, only chemotherapy-naïve participants were permitted to enroll.

**Key inclusion/exclusion criteria**

*Key Inclusion Criteria*

- Signed informed consent.
- Diagnosis of MCC with distant metastatic disease or recurrent, advanced locoregional disease not amenable to surgery or radiation.
- ECOG performance status of 0 to 1.
- Measurable disease according to RECIST v1.1.
- Availability of tumor tissue (fresh or archival) for central pathology review.
- Willingness to avoid pregnancy or fathering children.

*Key Exclusion Criteria*

- Prior systemic therapy for MCC, including chemotherapy and prior PD-(L)1 directed therapy.
- Treatment with anticancer drugs or participation in another interventional clinical study within 21 days before the first administration of study drug.

The FDA's Assessment:

FDA agrees with the Applicant's summary. FDA clarifies that women of childbearing potential were required to have a negative pregnancy test during screening and consent to the use of highly effective contraception from screening through 120 days after the last dose of study treatment. Men were required to use barrier contraception during the study and for 6 months after the end of the treatment. Additional exclusion criteria were consistent with other studies evaluating ICIs. The study excluded patients with clinically significant autoimmune disorders, cardiopulmonary disorders, infections hepatitis, and brain metastases, so the results of PODIUM-201 cannot be extrapolated to these groups. Patients less than 18 years were excluded from PODIUM-201. (b) (4)

(b) (4)

**Study Endpoints**

The Applicant's Description:

Primary and secondary endpoints are listed in Table 12. Because ORR can be directly attributed to the drug administered, single-arm studies can be used to assess the efficacy of the drug in refractory tumor types without available treatment options (FDA 2018). Tumor response is evaluated independently by ICR using a 2-reader plus adjudication paradigm and according to standard RECIST v1.1 criteria (Eisenhauer 2009, EMA 2017, FDA 2018).

**Table 12: Primary and Secondary Endpoints**

| | |
|---|---|
| **Primary** | ORR, defined as the percentage of participants having an objective response (CR or PR), according to RECIST v1.1, as determined by ICR. |
| **Secondary** | DOR, defined as the time from an initial objective response (CR or PR) according to RECIST v1.1 until disease progression as determined by ICR, or death due to any cause. |
| | DCR, defined as the proportion of participants with either an objective response or SD according to RECIST v1.1 lasting at least 6 months, as determined by ICR. |
| | PFS, defined as the time from the start of therapy until disease progression according to RECIST v1.1, as determined by the ICR, or death due to any cause. |
| | OS, defined as the time from the start of therapy until death due to any cause. |
| | Safety, determined by the number, frequency, duration, and severity of AEs using CTCAE v5.0; laboratory tests; vital signs; and ECGs. |
| | The PK of retifanlimab when given to participants with advanced/metastatic MCC. |
| | |

The FDA's Assessment:

FDA agrees with the Applicant's description of the study endpoints. FDA clarifies that the patients enrolled into PODIUM-201 were predominantly chemotherapy-naïve and had not received prior immune checkpoint inhibitors, thus would not be classified as treatment refractory. The rationale for the use of a single-arm study and the chosen primary endpoint of ORR centered around the epidemiology of MCC and the lack of feasibility of conducting a randomized controlled study as the first-line management of patients with locally advanced or metastatic unresectable MCC is acceptable. ORR (in context with DOR) has been used as an intermediate endpoint to support accelerated approval as response is directly related to study drug. Time-to-event endpoints, i.e., PFS and OS are not interpretable in the absence of a comparator arm.

**Statistical Analysis Plan and Amendments**

The Applicant's Description:

***Analysis Sets***

The safety evaluable population includes all enrolled participants who received at least 1 dose of study drug as of the 21 JAN 2022 data cutoff date. The primary analysis of ORR by ICR was based on the chemotherapy-naïve participants in the FAS (Chemotherapy-Naïve MCC FAS), which includes the 65 chemotherapy-naïve participants who received at least 1 dose of retifanlimab as of the enrollment cutoff date of 15 OCT 2020.

***Efficacy Analyses***

The date for this Protocol-specified analysis was selected to allow for at least 60 chemotherapy-naïve participants to be followed for at least 6 months after the first response assessment. Participants who did not have sufficient baseline data to ascertain a response were included in the denominators in the calculation of ORR.

The SAP was finalized prior to database lock. The ORR and 95% CI calculated based on the exact method for binomial distributions are provided. The ORR by investigator assessment is provided as a sensitivity analysis for the primary endpoint.

The Kaplan-Meier estimate of the distribution function was constructed for DOR. The estimated median was reported with 95% CIs. The DCR, defined as CR, PR, or SD lasting for 6 months, was

reported with the 95% CI. Time-to-event analyses for PFS and OS were performed using Kaplan-Meier methods.

***Sample Size Determination***

With the assumed response rate of 48% for retifanlimab treatment, a sample size of approximately 60 chemotherapy-naïve participants would provide > 80% probability to have a 95% CI with a lower limit of > 30% (Section 3.4 of the Statistical Analysis Plan).

***Futility Analysis***

There was 1 planned analysis for futility after approximately 20 chemotherapy-naïve participants were evaluable for response. As of Protocol Amendment 6, the DMC has reviewed the data for the interim analysis. The preliminary efficacy based on the ORR assessed by ICR exceeded the futility threshold, and the DMC recommended the study to proceed as planned.

***Subgroup Analysis***

Exploratory analysis of ORR using RECIST v1.1 based on ICR was performed for the following subgroups:

- Sex: Male, Female
- Baseline ECOG performance status: 0 vs 1
- Age: < 65 years vs ≥ 65 years and < 75 years vs ≥ 75 years
- Race: Caucasian, other
- Region: North America, Europe
- Ethnicity: Non-Hispanic or Latino, other
- PD-L1 status determined by central pathology review: < 1%,< 1% or missing, ≥ 1%
- MCPyV status by central pathology review: positive, negative/equivocal/missing
- Cancer stage: advanced/metastatic

***Handling of Dropouts or Missing Data***

No participants were replaced. Data recorded on the eCRF are included in data listings. In general, missing observations were treated as missing at random and were not imputed. The handling of missing cancer diagnosis date, prior and concomitant medication, and partial death dates is described in Section 4.1.6 of the Statistical Analysis Plan.

***Multiple Comparisons/Multiplicity***

No adjustments for multiplicity were made.

The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical analysis plan and adds the following:

1. The original statistical analysis plan (SAP) was issued on 13 March 2019 and underwent 2 amendments with key changes summarized below:

   Amendment 1 (1 Jun. 2020):

- Discontinued enrollment of chemotherapy-refractory patients and revised the sample size from a total enrollment of 90 to 60 chemotherapy-naïve patients.
- Moved ORR, DOR, PFS, OS in the full study population, which include chemotherapy naïve and refractory patients, from secondary to exploratory endpoints.
- Revised the definition of full analysis set (FAS) as patients who receive at least one unit of study drug and used the FAS for primary efficacy analysis.
- Updated the interim analysis to coincide with the confirmed BOR definition. All participants enrolled with at least 2 postbaseline response assessments or participants who discontinued early were to be included in the futility analysis.

Amendment 2 (19 May 2021):

- The target chemotherapy-naïve population was increased to 100 in the final analysis, and approximately 60 chemotherapy-naive participants will be included in the primary analysis.

**Protocol Amendments**

The Applicant's Description:

The original protocol was finalized on 25 APR 2018 and has been amended globally 7 times. Substantial protocol changes are summarized below (Protocol Appendix E).

Amendment 1 (27 JUN 2018):

- Based on FDA feedback, assessment of the primary endpoint of ORR was limited to the chemotherapy-naïve study population. The ORR in the full study population, comprised of both chemotherapy-naïve and chemotherapy-refractory participants, was revised to be a secondary endpoint. Statistical analyses and sample size estimates were updated to align with the revised population for the primary analysis.

Amendment 2 (04 OCT 2018):

- Based on additional regulatory feedback, stricter safety measures were added, including an independent DMC to provide review of safety and efficacy data during the study.

Amendment 3 (05 DEC 2018):

- Eligibility criteria were revised to allow enrollment of participants who are HIV-positive and participants with liver metastases if ALT or AST are ≤ 5 × ULN. The requirement for premedication prophylaxis before the first dose of retifanlimab was removed.

Amendment 4 (16 AUG 2019):

- Eligibility criteria were expanded to include participants with recurrent locoregional advanced disease based on their similar prognosis.
- Based on FDA guidance, the primary analysis population was updated to include all participants who received a dose of study drug.
- The irAE guidance was updated to align with current ASCO clinical practice guidelines.

Amendment 5 (09 APR 2020):

- The study design and eligibility criteria were adjusted to exclude participants who have received prior systemic therapy for MCC.

- Protocol was updated to clarify that tumor lesions located in areas that have received prior locoregional therapy may be selected as target lesions if progression has been demonstrated in these lesions.

Amendment 6 (22 OCT 2020):

- The number of participants to be enrolled was increased to 100 chemotherapy-naïve participants. The study duration section was updated to clarify that the study will end after every participant receiving active treatment has been followed for at least 6 months after confirmed response or until all participants have been followed for survival for a minimum of 2 years. The statistical section was also updated to clarify how the populations will be analyzed for the primary and final analyses.

Amendment 7 (16 DEC 2021):

- The irAE management guidelines were revised to reflect updated published guidance and to provide guidance on the management of participants during the COVID-19 pandemic.

The FDA's Assessment:
FDA agrees with the Applicant's description of key protocol changes.

### 8.1.2. Study Results

Overall, 107 participants were enrolled; enrollment is now complete. The geographic distribution of the study population is presented in Table 13. The Applicant provided a Diversity Plan with this BLA.

**Table 13: Geographic Distribution of Study Population**

| Country, n (%) | N = 107 |
|---|---|
| Italy | 40 (37.4) |
| France | 22 (20.6) |
| United States | 16 (15.0) |
| Poland | 9 (8.4) |
| Canada | 7 (6.5) |
| Switzerland | 3 (2.8) |
| Hungary | 3 (2.8) |
| Other | 7 (6.5) |

The efficacy data are from the Protocol-defined primary efficacy analysis of 65 chemotherapy-naïve participants (Chemotherapy-Naïve MCC FAS) with a data cutoff date of 21 JAN 2022, when all ongoing confirmed responses have been followed for a minimum of 6 months. An additional 6 participants with chemotherapy-refractory disease were also enrolled.

**Compliance with Good Clinical Practices**

The Applicant's Position:
This study was conducted in accordance with the ICH E6 Guideline for Good Clinical Practice,

including the archiving of essential documents, the principles of the Declaration of Helsinki, and other applicable local ethical and legal requirements. Study 201 is a global study that is being conducted at 34 centers, including 5 centers in the US. All clinical sites outside of the US were not conducted under a US IND but meet the requirements of 21 CFR 312.120. All investigators and clinical sites were selected based on ICH E6 criteria. The Protocol and all amendments were reviewed and approved by qualified IRBs/IECs before enrollment of participants at each site. Before initiation of the study, the Sponsor received documentation of the IRB/IEC approvals. Informed consent was obtained from each participant before Protocol-specific screening assessments were performed. Any information supplied to the participant to obtain informed consent, including written informed consent forms and other relevant documents (eg, advertisements), was reviewed and approved by qualified IRBs/IECs before the enrollment of participants.

The FDA's Assessment:
FDA acknowledges the Applicant's position on compliance with good clinical practice during the conduct of this study.

FDA clarifies that the Applicant submitted a Diversity Plan with this BLA submission. However, the initiatives covered in the proposal pertains to enrollment of underrepresented racial and ethnic participants in ongoing retifanlimab studies in non-MCC patient population. Study INCMGA 0012-201 (PODIUM-201) had completed enrollment at the time of the BLA submission.

Although 107 patients were enrolled, 65 were eligible for efficacy analysis at the time of the data cutoff. The 65 patients enrolled as of the data cutoff were included in the primary efficacy population for the rest of the efficacy review.

**Financial Disclosure**

The Applicant's Position:
The financial interests of Study 201 clinical investigators were tracked and disclosed. Financial disclosure details are presented in Section 0. The integrity of Study 201 data were not affected by financial interest of the investigators.

The FDA's Assessment:
FDA acknowledges the Applicant's position. For further details see Section 19.2.

**Patient Disposition**

Data:

**Table 14: Participant Disposition (Primary Efficacy Population)**

| Variable, n (%) | Chemotherapy-Naïve MCC (N = 65) |
|---|---|
| Participants treated | 65 (100.0) |
| Participants with ongoing treatment | 17 (26.2) |
| Participants who completed treatment[a] | 11 (16.9) |
| Participants who discontinued treatment | 37 (56.9) |
| Disease progression | 20 (30.8) |
| AE | 13 (20.0) |
| Death | 2 (3.1) |
| Physician decision | 2 (3.1) |
| Withdrawal by participant | 0 (0.0) |
| Other | 0 (0.0) |
| Participants ongoing in study | 43 (66.2) |
| Participants who withdrew from study | 22 (33.8) |
| Death | 18 (27.7) |
| Withdrawal by participant | 4 (6.2) |

[a] Participants who received 2 years of treatment or who were treated for at least 6 months and achieved a confirmed CR.
Source: Table 1.1.2.2.

The Applicant's Position:

As of the data cutoff date (21 JAN 2022), 17 participants (26.2%) continued to receive treatment. The most common reason for treatment discontinuation was progression of disease. The most common reason for study withdrawal was death (Table 14).

The FDA's Assessment:

The primary efficacy population included 65 patients that were eligible for analyses as of the data cutoff. FDA agrees with the Applicant's description of patient disposition. FDA confirmed that the most common reason for treatment discontinuation was disease progression, with no adverse event leading to treatment discontinuation occurring in more than one patient.

**Protocol Violations/Deviations**

The Applicant's Position:

Protocol deviations were classified as per the ICH E3 classification of protocol deviations as important (those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being) or not important. Among the participants enrolled in the primary analysis population and assigned to treatment in the study, there were 4 participants with protocol deviations that were considered clinically important:

- One participant had an entry criterion deviation (locoregional disease, not recurrent).
- Three participants each had a single Grade 2/3 TEAE for which study drug was not held. None of these affected participant safety.

No participant data were excluded from analyses due to deviations. No deviations, including deviations related to the COVID-19 pandemic, significantly affected the completeness,

accuracy, and/or reliability of the study data, the study conclusions, or participant safety (CSR Section 7.7).

The FDA's Assessment:

A summary of the four protocol deviations in PODIUM-201 provided by the Applicant is outlined below:

- Patient (b) (6) The patient had an entry criterion deviation (locoregional disease, not recurrent
- Patient (b) (6) The patient had Grade 3 AST increased, for which Cycle 2 Day 1 dosing was not held.
- Patient (b) (6) The patient had Grade 2 acute kidney injury starting on Day 114, for which Cycle 5 Day 1 dosing was not held The TEAE resolved on Day 124.
- Patient (b) (6) The patient had Grade 3 hypokalemia and hypocalcemia starting on Day 332, for which dosing was not held. On Day 345, hypokalemia and hypocalcemia resolved. On Day 377, the patient was diagnosed with Grade 3 hypophysitis, and retifanlimab was discontinued.

FDA clarifies that for Patient (b) (6) the patient was subsequently hospitalized on Day 54 following an episode of swollen tongue, shortness of breath, and visual disturbance. The patient was diagnosed with infusion related reaction, and retifanlimab was discontinued. The LFT abnormalities had not recovered at the time of treatment discontinuation. Infusion related reaction was listed as a reason for treatment discontinuation in the retifanlimab USPI.

FDA clarifies that Patient (b) (6) the diagnosis of hypophysitis was made after the cut-off date for safety and was not included in the agreed upon USPI of retifanlimab. Nevertheless, the labeling contains a warning regarding the potential for severe/serious autoimmune events including hypophysitis, and oncologists / endocrinologists are experienced with this toxicity given the widespread use of PD-(L)1 inhibitors in clinical practice.

FDA agrees that the significant protocol deviations did not affect the overall assessment of safety and efficacy within the trial.

**Table of Demographic Characteristics**

Data:

**Table 15: Demographic Characteristics (Primary Efficacy Population)**

| Variable | Chemotherapy-Naïve MCC (N = 65) |
|---|---|
| Age, years | |
| Mean (STD) | 71.4 (10.26) |
| Median (minimum, maximum) | 71.0 (44, 90) |
| Age group, n (%) | |
| < 65 years | 14 (21.5) |
| ≥ 65 years | 51 (78.5) |
| < 75 years | 41 (63.1) |
| ≥ 75 years | 24 (36.9) |
| Sex, n (%) | |
| Male | 42 (64.6) |
| Female | 23 (35.4) |
| Race, n (%) | |
| White/Caucasian | 51 (78.5) |
| Asian | 1 (1.5) |
| Other[a] | 13 (20.0) |
| Ethnicity, n (%) | |
| Not Hispanic or Latino | 52 (80.0) |
| Not reported | 13 (20.0) |
| ECOG performance status, n (%) | |
| 0 | 48 (73.8) |
| 1 | 17 (26.2) |
| HIV infection, n (%) | |
| Positive | 1 (1.5) |
| Negative/unknown | 64 (98.5) |

[a] Other includes participants from France, where information on race is not collected per regulatory requirements.
Source: CSR Tables 1.2.1.2 and 1.3.1.2 and Listing 2.4.1.

The Applicant's Position:

The median age was 71.0 years (range: 44-90 years), and the majority of participants were male. Among the participants with a reported race and/or ethnicity, most participants were White and not Hispanic or Latino. All participants had ECOG scores of 0 (73.8%) or 1 (26.2%; Table 15). The demographic characteristics of the study population were consistent with the reported epidemiology of MCC (Dellambra 2021).Dellambra 2021).Dellambra 2021).Dellambra 2021).

The FDA's Assessment:

FDA agrees with the Applicant's summary of demographic characteristics. Out of the 65 chemotherapy-naïve patients, 15 (23%) were from North America: 11 (17%) from United States, 4 (6%) from Canada and 50 (77%) were from Europe. The prevalence of MCC varies among ethnic groups and geographic areas. The most typical patient is an elderly white male in his

seventies or eighties with a history of extensive sun exposure, although MCC has also been reported in black, Asian, American Indian, and Pacific Islander patients. MCC is approximately 25 times more common in whites compared to other ethnic groups. Incidence rates based on epidemiologic studies in Northern Europe align closely with US figures (Coggshall).

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

Data:

**Table 16: Baseline Disease Characteristics (Primary Efficacy Population)**

| Variable | Chemotherapy-Naïve MCC (N = 65) |
|---|---|
| Time since initial diagnosis, months | |
| Mean (STD) | 12.78 (14.727) |
| Median (minimum, maximum) | 8.94 (0.2, 64.0) |
| Liver metastasis, n (%) | |
| Yes | 6 (9.2) |
| No | 59 (90.8) |
| MCPyV status by central laboratory, n (%) | |
| Positive | 46 (70.8) |
| Negative | 15 (23.1) |
| Equivocal | 1 (1.5) |
| Missing | 3 (4.6) |
| PD-L1 CPS, n (%) | |
| < 1% | 9 (13.8) |
| ≥ 1% | 52 (80.0) |
| Missing | 4 (6.2) |
| Visceral metastases at baseline per ICR, n (%)[a] | |
| Present | 25 (38.5) |
| Absent | 40 (61.5) |

[a] Presence of visceral metastases was determined based on location of target and nontarget lesions as identified by ICR at baseline. Participants were considered to have visceral metastases if they had at least 1 lesion (target or nontarget) with an anatomical location other than lymph nodes, skin/subcutaneous, soft tissue, or bone.

Source: CSR Table 1.3.1.2.

The Applicant's Position:

The baseline disease characteristics observed were as anticipated for participants with metastatic or recurrent locally advanced MCC, and the study population is representative of the patient population intended for retifanlimab treatment in the US (Table 16). All participants had Stage 3 or 4 disease at the time of study entry. Merkel cell polyomavirus status by central laboratory testing was positive in a majority of participants (46 out of the 62 participants for whom test results were available). PD-L1 CPS was ≥ 1% in 52 out of the 61 participants for whom test results were available.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the other baseline disease characteristics.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

The Applicant's Position:

**Treatment Compliance:** Retifanlimab is administered as an IV infusion at the study site by qualified study staff. Treatment infusions were recorded by the site staff and monitored by the Sponsor/designee. The majority of participants were treated as planned (Q4W) without infusion interruption or dose delay (CSR Table 3.1.2).

**Concomitant Medications:** Sixty-four of 65 participants reported receiving at least 1 concomitant medication. The most frequently reported concomitant medication was paracetamol (CSR Table 1.4.2).

**Rescue Medication Use:** Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA clarifies that in the efficacy population (N=65) there were four (6.2%) infusion related reactions (IRRs), one (1.5%) was Grade 3 and led to treatment discontinuation. The most common (>10%) concomitant medications were paracetamol (53%); viral vaccine (26%); prednisone (23%); acetylsalicylic acid and levothyroxine sodium (13% each); enoxaparin sodium and ramipril (12% each); and cholecalciferol, chlorphenamine, famotidine, furosemide, sodium chloride, and cetirizine (10% each). As of January 21, 2022, 22 (34%) of the efficacy population had received systemic glucocorticoids, the most commonly prescribed was prednisone (N=15 [23%]).

**Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)**

Data:

**Table 17: ORR and DOR Based on ICR by RECIST v1.1 (Primary Efficacy Population)**

| Efficacy Endpoint (based on ICR) | Chemotherapy-Naïve MCC (N = 65) |
|---|---|
| **Objective response rate** (95% CI)[a] | 52.3% (39.5, 64.9) |
| Complete response (CR) | 18.5% |
| Partial response (PR) | 33.8% |
| Stable disease (SD) | 20.0% |
| Progressive disease (PD) | 18.5% |
| Not evaluable | 9.2% |
| **Disease control rate** (95% CI)[a] | 61.5% (48.6, 73.3) |
| **Duration of response,** median in months (95% CI)[b] | NR (14.0, NE) |
| Range in months | 1.1-24.9+ |
| Median follow-up in months | 13.9 (range: 1.1-24.9) |
| Participants with DOR ≥ 6 months[c] | 76.5% |
| Participants with DOR ≥ 12 months[c] | 61.8% |

[a] CI calculated based on the exact method for binomial distributions.

[b] CI calculated using Brookmeyer and Crowley's and Klein and Moeschberger's methods with log-log transformation.

[c] Observed proportion of participants with DOR over 6 or 12 months.

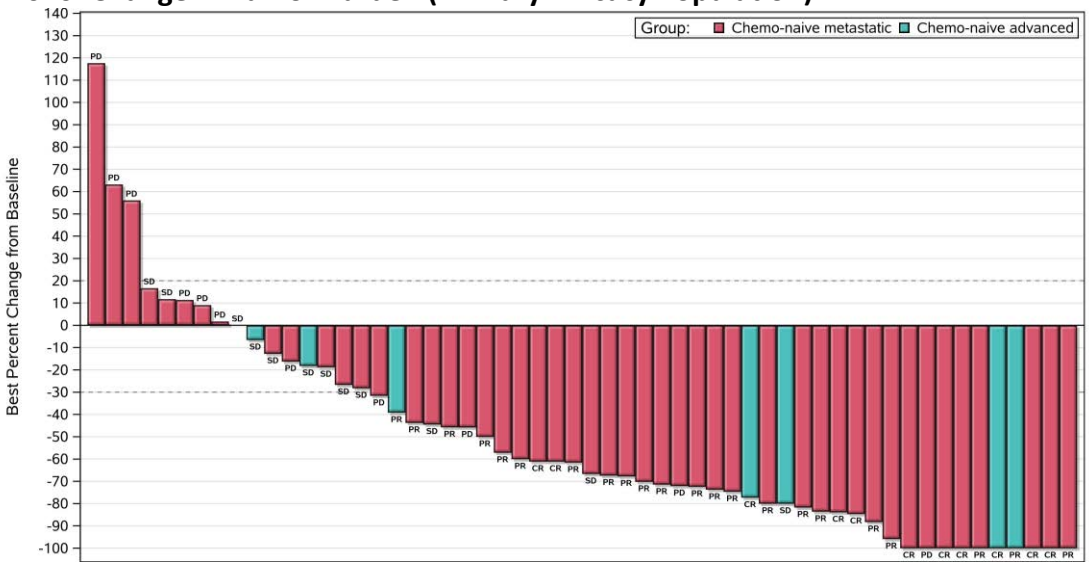
Source: Module 2.7.3 Tables 5 and 6. + indicates ongoing response.

The Applicant's Position:

Retifanlimab elicits clinically meaningful, durable tumor responses in a high proportion of participants with advanced MCC. The ORR was 52.3% (95% CI: 39.5, 64.9) based on confirmed RECIST v1.1 responses by ICR (Table 1Table 17). At the time of the data cutoff, median DOR based on K-M analysis had not been reached (95% CI: 14.00, NE), with a median follow-up time of 13.9 months (range: 1.1-24.9 months). Efficacy results based on investigator assessment were consistent with the ICR results (CSR Section 9.2.3).

Nearly all participants had clinically meaningful reduction in tumor burden (Figure 1010).

**Figure 1010: Change in Tumor Burden (Primary Efficacy Population)**




Source: CSR Figure 4.3.2.1. Note: Nine of 65 participants had missing baseline or postbaseline target lesion assessments.

The FDA's Assessment:

FDA agrees that PODIUM-201 demonstrated a clinically meaningful ORR of 52.3% (95% CI: 39.5, 64.9) with 61.8% of responding patients having DOR ≥12 months for the chemotherapy-naïve MCC population. Although responses have been historically observed with cytotoxic chemotherapy in MCC, such responses are typically of short duration and no demonstrated effect on OS have been observed. As has been demonstrated with this class of drugs, responses to retifanlimab appear of greater magnitude and longer duration.

In addition, FDA adds the following:

- Among the 34 responders, 8 had PD, 2 died and 24 were censored for DOR. Among responders who were censored, 3 patients were censored due to the start of new anti-cancer therapy, 1 patient completed/discontinued the study, and 20 patients had study ongoing.
- Concordance between ICR and Investigator-assessed ORR was generally high, i.e.,

78.5%, in the 65 chemotherapy-naïve MCC patients. A sensitivity analysis of ORR per Investigator assessment showed consistent results. The number of responders was 40 (13 with CR and 27 with PR) with ORR of 61.5% (95% CI: 48.6, 73.3). 77.5% of responding patients had DOR ≥12 months for the chemotherapy-naïve MCC population.

- As a supportive analysis, FDA also analyzed ORR and DOR in all chemotherapy-naïve MCC patients enrolled in PODIUM-201. Per ICR assessment, among 101 patients, 52 were responders (16 with CR and 36 with PR) with ORR of 51.5% (95% CI: 41.3, 61.6); 67.3% of responding patients had DOR ≥6 months and 40.4% had DOR ≥12 months. Per Investigator assessment, among 101 patients, 59 were responders (19 with CR and 40 with PR) with ORR of 58.4% (95% CI: 48.2, 68.1); 76.3% of responding patients had DOR ≥6 months and 52.5% had DOR ≥12 months.

**Data Quality and Integrity**

The Applicant's Position:

The following steps, visits, and procedures were conducted to ensure accurate, consistent, and complete data collection and to assure quality:

- Site selection was performed to assess the adequacy of the site and associated study personnel.
- Study initiation visits and an investigator meeting were performed to discuss and develop a common understanding of the Protocol, eCRFs, and procedural requirements with the investigator and associated study personnel.
- Qualified representatives of the Sponsor or Sponsor designees ("study monitors") continue to monitor the study according to a predetermined monitoring plan.
- An external DMC has made recommendations on study performance based on reviews of safety and interim efficacy data.
- An eCRF is used to permit consistent collection of data; source-verified data are subject to both manual and electronic checks to ensure data integrity and accuracy.
- Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.
- An ICR is used for all imaging response assessments.

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

The FDA's Assessment:

FDA did not identify any issues regarding data integrity and submission quality during review of PODIUM-201.

**Efficacy Results – Secondary and other relevant endpoints**

The Applicant's Position:

**Disease Control Rate**

The DCR, defined as the proportion of participants with either an objective response or SD lasting at least 6 months, was 61.5% (95% CI: 48.6, 73.3) based on ICR (Table 17).

**Progression-free Survival**

Estimated median PFS was 16.0 months (95% CI: 9.33, NE; Table 18), with a median follow-up time of 10.2 months.

**Table 18: PFS Based on ICR According to RECIST v1.1 (Primary Efficacy Population)**

| Variable | Chemotherapy-Naïve MCC (N = 65) |
|---|---|
| Number (%) of participants with events | 30 (46.2) |
| Disease progression | 25 (38.5) |
| Death | 5 (7.7) |
| Number (%) of participants censored | 35 (53.8) |
| Median PFS, months (95% CI)[a] | 16.03 (9.33, NE) |
| Month 3 PFS rate (95% CI) | 0.77 (0.65, 0.86) |
| Month 6 PFS rate (95% CI) | 0.67 (0.54, 0.77) |
| Month 9 PFS rate (95% CI) | 0.64 (0.50, 0.74) |
| Month 12 PFS rate (95% CI) | 0.54 (0.40, 0.66) |
| Median follow-up time, months (minimum, maximum) | 10.2 (0.0, 26.8) |

[a] Median PFS time was estimated by Kaplan-Meier method, and CI by Brookmeyer and Crowley method.
Source: CSR Table 2.2.3.

**Overall Survival**

As of the data cutoff, 46 participants (70.8%) were alive and censored for OS at the last date known alive. Estimated median OS had not been reached based on Kaplan-Meier analysis (Table 19), with a median follow-up of 18.5 months (range: 0.7-33.9 months).

**Table 19: Overall Survival (Primary Efficacy Population)**

| Variable | Chemotherapy-Naïve MCC (N = 65) |
|---|---|
| Number (%) of participants with: | |
| Death | 19 (29.2) |
| Censoring | 46 (70.8) |
| Median OS, months (95% CI)[a] | NR (25.82, NE) |
| Month 3 OS rate (95% CI) | 0.94 (0.84, 0.98) |
| Month 6 OS rate (95% CI) | 0.89 (0.79, 0.95) |
| Month 9 OS rate (95% CI) | 0.84 (0.73, 0.91) |
| Month 12 OS rate (95% CI) | 0.81 (0.69, 0.89) |
| Median follow-up time, months (minimum, maximum) | 18.5 (0.7, 33.9) |

[a] Median OS time was estimated by Kaplan-Meier method, and CI by Brookmeyer and Crowley method.
Source: CSR Table 2.2.4.

**Chemotherapy-Refractory Population**

The ICR-confirmed ORR in the 6 participants with chemotherapy-refractory disease was 50.0%. These responses were also durable. The estimated median DOR was not reached, with a median follow-up time of 19.6 months (range: 10.2-26.4 months).

The FDA's Assessment:

FDA agrees with the Applicant's analysis results presented above. Among 65 chemotherapy-

naïve MCC patients, 12 had best overall response (BOR) of complete response (CR), 22 had partial response (PR), 13 had stable disease (SD), 12 had progressive disease (PD) and 6 were not evaluable. Per the Applicant, disease control rate (DCR) was defined as proportion of participants with a confirmed overall response (CR and PR) at any postbaseline visit, or SD (non-CR/non-PD) lasting at least 6 months from start of treatment, until the first PD or new anticancer therapy. Among the 13 patients with BOR of SD, only 6 had SD lasted over 6 months, and DCR was 61.5% (95% CI: 48.6, 73.3).

In addition, FDA notes the small sample size of patients with chemotherapy-refractory disease and that efficacy of retifanlimab in this patient population is considered exploratory. Additionally, time-to-event endpoints (such as PFS and OS) are not interpretable in a single-arm study.

**Dose/Dose Response**

The Applicant's Position:

There was no statistically significant relationship between PK exposure and efficacy endpoints.

The FDA's Assessment: Although FDA in general agrees with this statement for a single-dose level, the study was not designed to demonstrate a statistically significant effect between PK exposure and efficacy. Refer to FDA assessments in sections 6.2.1 and 19.4 for additional details.

**Durability of Response**

The Applicant's Position: Duration of response is presented in Table 17.

FDA acknowledges the Applicant's position. Refer to FDA's assessment of Efficacy Results – Primary Endpoint (Section 8.1.2) for additional details.

**Persistence of Effect**

The Applicant's Position:

Persistence of efficacy is demonstrated by the durability of confirmed tumor responses. At the time of the data cutoff, the median DOR had not been reached, with a median DOR follow-up of 13.9 months (Table 17). Twenty-six of 34 responders (76.5%) had a DOR ≥ 6 months, and 21 responders (61.8%) had a DOR ≥ 12 months. Secondary efficacy endpoints of PFS and OS further support the persistence of clinical benefit elicited by retifanlimab.

No formal analyses to assess the persistence of efficacy after treatment discontinuation have been conducted. There are no known tolerance effects with retifanlimab.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to FDA's assessment of Efficacy Results – Primary Endpoint (Section 8.1.2) for additional details.

**Efficacy Results –Exploratory Clinical outcome assessment (COA)/(PRO) endpoints**

The Applicant's Position:

Mean and median EQ-5D-5L EuroQol visual analogue scale scores and FACT-M scores were relatively stable during the treatment period (CSR Section 9.2.5).

The FDA's Assessment:
FDA reviewed the data presented in the CSR assessing patient-reported outcome (PRO) using the EQ-5D-5L EuroQol visual analogue scale scores and FACT M scores but did not conduct independent analyses to replicate all the results. Per the Applicant, EQ-5D-5L EuroQol visual analog scale and FACT M were included as exploratory endpoints in the PODIUM-201 Study.

For reference, FDA notes that PRO was assessed at Cycle 1 Day 1 (C1D1) and then every 2 cycles while on treatment and at the end of treatment (EOT) visit. For each of the PRO endpoints, actual score and change from baseline were summarized descriptively at each visit in the FAS population.

For EQ-5D-5L EuroQol visual analog scale, the completion rates for chemotherapy-naïve patients, defined as the number of patients who completed the PRO assessment form divided by the number of patients in the FAS, were 91% at baseline (C1D1), 66% at Cycle 3 and remained >50% until Cycle 7.

For FACT M, the completion rates were 92% at baseline, 69% at Cycle 3 and remained >50% until Cycle 9 for the melanoma subscale; for emotional, functional, physical and social/family well-being subscales, the completion rates were 91-92% at baseline, 71% at Cycle 3 and remained >50% until Cycle 9.

FDA considers all PRO analyses for PODIUM-201 to be exploratory and emphasizes that no definitive conclusions should be drawn based on the observed PRO analysis results. Further, FDA notes that results of PRO analyses are difficult to interpret in the context of a single-arm study without a comparator arm.

**Additional Analyses Conducted on the Individual Trial**
The Applicant's Position: Not applicable.

The FDA's Assessment: Not applicable.

### 8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
Evidence of clinically meaningful activity of retifanlimab 500 mg Q4W was observed in patients with chemotherapy-naïve metastatic or recurrent locally advanced MCC (N=65) from PODIUM-201, with the overall response rate of 52.3% (95% CI: 39.5%, 64.9%). DOR was durable with 21 (62%) patients having a response lasting at least 12 months.

### 8.1.4. Assessment of Efficacy Across Trials

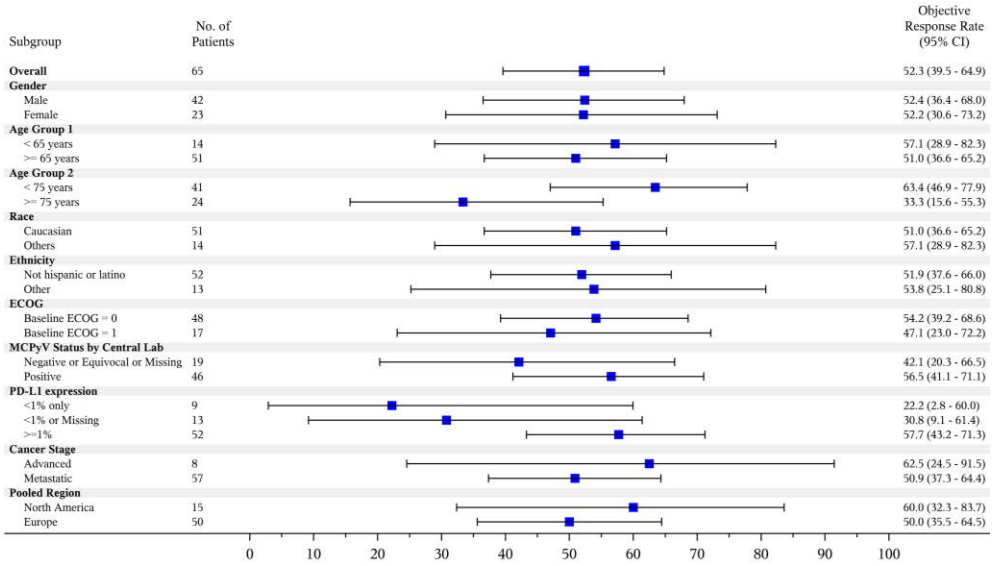
The Applicant's Position: The data to support this BLA are from a single study, and thus an analysis of efficacy across trials is not applicable.

The FDA's Assessment:
Not applicable.

**Subpopulations**

Data:

**Figure 1111: ORRs Based on Predefined Subgroups (Primary Efficacy Population)**




Note: Other includes participants from France, where race is not collected per regulatory requirements.
Note: PD-L1 expression was based on CPS.
Source: CSR Figure 4.3.4.1.

The Applicant's Position:
Preplanned, exploratory, subgroup analyses of ORR were performed. Objective responses were observed in all subgroups of interest (Figure 1111).

The FDA's Assessment:
FDA agrees with the exploratory subgroup analyses results presented by the Applicant. In general, the subgroup analyses of ICR-assessed ORR showed that there were no outlier subgroups and the treatment effect was generally consistent with that of the FAS population. For patients with age ≥75 years (n=24), the point estimate for ORR was 33.3% (95% CI: 15.6%, 55.3%), which is lower than the ORR of 63.4% (95% CI: 46.9, 77.9) for patients with age <75 years (n=41). In addition, the ORR for patients with PD-L1 expression <1% (n=9) was 22.2% (95% CI: 2.8%, 60.0%), which is lower than the ORR of 57.7% (95% CI: 43.2, 71.3) for patients with PD-L1 expression ≥1% (n=52). However, given the small sample size in these subgroups and the resulting wide confidence intervals, FDA considers the results of subgroup analyses to be exploratory and they should be interpreted with caution.

### 8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

Efficacy data from a well-characterized population (N = 65) with chemotherapy-naïve metastatic or recurrent locally advanced MCC in Study 201 demonstrate that retifanlimab 500 mg Q4W elicits clinically meaningful, durable tumor responses in a high proportion of participants with advanced MCC. The multiregional, single-arm study design is robust and incorporates all regulatory guidance. The primary endpoint of ORR was independently and centrally assessed based on standard RECIST v1.1 criteria. Characteristics of the study population are consistent with those of the intended population. Therefore, the efficacy data presented in this BLA are generalizable to the US population and US medical practice.

Objective response rate, defined as the proportion of participants with confirmed CR or PR, is a direct measure of antitumor activity. The clinical endpoint of ORR is meaningful because, in general, tumors do not regress spontaneously (EMA 2017, FDA 2018). The antitumor activity of retifanlimab is evident based on the confirmed ORR of 52.3% (18.5% CR) by ICR in participants with metastatic or recurrent locally advanced MCC. The study met the predefined efficacy threshold (the lower limit of the 95% CI exceeded 30%). Tumor responses occurred in all subgroups of interest. Furthermore, responses were durable. With a median follow-up duration of 13.9 months, median DOR by ICR was not reached, with a range of 1.1 to 24.9+ months; 76.5% of responders maintained response for at least 6 months and 61.8% maintained responses for at least 12 months, which favorably compares to other therapies that have been used to treat MCC (Table 1).

Objective response rate has routinely served as the basis for determining clinical benefit of PD-(L)1 inhibitors in advanced MCC due to the ultra-rare nature of the disease and infeasibility of conducting a randomized, controlled comparison to chemotherapy in this setting. The efficacy of retifanlimab in Study 201 is comparable to efficacy that has been reported with PD-(L)1 inhibitor monotherapy in MCC and responses are more durable than historical experience with chemotherapy (Table 1). Favorable activity was also observed in participants with chemotherapy-refractory disease (ORR: 50%; median DOR: NR), which provides further evidence for clinical benefit.

The FDA's Assessment:

Although 107 patients were enrolled, FDA's and the Applicant's primary efficacy assessment was based on the primary outcome of objective response rate (ORR) in 65 chemotherapy-naïve, metastatic or recurrent locally advanced MCC in PODIUM-201 as of the data cutoff.. The confirmed ORR per RECIST v1.1 by independent central review was 52% (95% CI: 40%, 65%), with 18% having a complete response (CR). The median DOR was not reached. The DOR ranged from 1.1 to 24.9+ months with 62% of the responding patients had a DOR ≥12 months. FDA notes that retifanlimab was only assessed in 6 patients with chemotherapy refractory disease, these patients were not included in the primary efficacy analysis. Although, an ORR of 50% in this patient population is generally supportive of retifanlimab approval for the proposed indication, the efficacy in the chemotherapy refractory patient population is considered

exploratory. Nevertheless, in current practice, it is expected that ICI therapy is administered in the first-line metastatic setting, rather than chemotherapy.

The magnitude of the durable ORR is sufficient to serve as an endpoint that is reasonably likely to predict clinical benefit to patients, and is acceptable to support granting accelerated approval of retifanlimab for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma. Prior to the AAs of avelumab and pembrolizumab, off-label use of chemotherapy was typically used to treat MCC (e.g., a platinum in combination with etoposide, topotecan, or cyclophosphamide, doxorubicin, and vincristine). Although these drugs could induce responses, responses were typically short-lived (e.g., median less than 3 months) and associated with considerable toxicity. Given these factors and the rarity of MCC, randomization is felt to not be feasible given the anti-tumor effects observed to date with ICIs including retifanlimab.

## 8.2. Review of Safety

Data from the 5 clinical studies summarized in Section 7 were pooled for the safety analysis of retifanlimab 500 mg Q4W monotherapy. The primary safety analyses are based on the following populations:

**MCC Population** (N = 105) includes all participants with MCC who received at least 1 dose of retifanlimab 500 mg Q4W monotherapy as of 16 JUN 2021. All participants in the MCC Population were enrolled in Study 201. This population includes the 65 participants in the primary efficacy population.

**All Cancer 500 mg Q4W Population** (N = 440) includes all participants with solid tumors who received at least 1 dose of retifanlimab 500 mg Q4W as monotherapy. This population includes the MCC Population and provides a larger dataset for identifying less common, potentially important events.

Safety data from an additional 201 participants who received retifanlimab at doses other than 500 mg Q4W were summarized in the ISS and demonstrate that the safety profile of retifanlimab is consistent across the evaluated dose levels.

The FDA's Assessment:

FDA agrees with the Applicant's description of the safety population included in the primary safety analyses. FDA clarifies that the summary of the PODIUM-201 patients who have received retifanlimab at doses other than 500 mg Q4W were not included in the primary safety analyses.

The primary safety analysis was performed on patients that were enrolled to PODIUM-201 (n=105 who received at least one dose of study drug and included all 65 patients in the primary efficacy analysis) and the pooled safety population included patients who had received at least 1 dose of retifanlimab. The data cutoff date for the primary safety analysis was June 16, 2021. A safety update was provided on November 7, 2022, which consisted of data from 452 patients that had received retifanlimab at the proposed dose of 500 mg Q4W monotherapy across the

studies cited above, including 107 patients enrolled to PODIUM-201. The data cutoff date for the safety update for the MCC population was May 20, 2022. The data was reviewed for congruence with the primary safety analysis.

### 8.2.1. Safety Review Approach

The Applicant's Position:

Based on the known pharmacology, nonclinical toxicology data, clinical experience with retifanlimab to date, and well-characterized class effects, key safety concerns associated with retifanlimab are irAEs and infusion-related reactions. Standard safety assessments were performed for each of the clinical studies. Immune-related AEs were monitored throughout the studies with appropriate guidance on assessment and management provided to investigators. Overall, the safety data presented in this marketing application demonstrate that retifanlimab 500 mg Q4W is tolerable and has an acceptable safety profile that is predictable and manageable, with no unique immune-related toxicities.

The FDA's Assessment:

The FDA safety review focused on the incidence of treatment emergent adverse events (TEAEs), regardless of causality assessment. An adverse event (AE) was considered a TEAE, if reported either for the first time or worsening of a pre-existing AE after the first dose of retifanlimab until 90 days after the last dose. The safety analysis including fatal and non-fatal SAEs, AEs leading to permanent treatment discontinuation, treatment interruption and delay, and an assessment of immune-mediated adverse events (imAE).

FDA analysis utilized clinically relevant grouped terms independent of the analyses provided by the Applicant; therefore there may be some discrepancy between the results for the safety table present in this section. The groupings are all highlighted within the FDA-generated tables. FDA and Applicant agreed upon FDA groupings to be included within the retifanlimab USPI.

The Applicant had submitted their list of preferred terms that comprised preselected adverse events of special interest (AESI) categories on April 02, 2021. The categorization permitted for assessment, regardless of causality, to determine the incidence of imAEs and infusion-related reactions (IRR) with retifanlimab. IRRs occurring anytime during the treatment period and symptoms of infusion reaction that occurred within 1 day of infusion and resolved within 2 days from onset are included as an IRR. The AESI categorization is listed in Table 45. FDA performed independent analyses using the predefined grouped terms to evaluate the incidence of imAE and IRR within the development program.

### 8.2.2. Review of the Safety Database

**Overall Exposure**

Data:

**Table 20: Retifanlimab Exposure**

| Variable | MCC (N = 105) | All Cancer 500 mg Q4W (N = 440) |
|---|---|---|
| Total number of infusions[a] | | |
| Mean (STD) | 8.0 (6.61) | 8.0 (6.52) |
| Median (minimum, maximum) | 6.0 (1, 26) | 6.0 (1, 26) |
| Duration of treatment (months)[b] | | |
| Mean (STD) | 6.8 (6.45) | 6.7 (6.23) |
| Median (minimum, maximum) | 5.6 (0.03, 23.3) | 4.6 (0.03, 27.0) |
| Dose intensity (mg/day)[c] | | |
| Mean (STD) | 17.32 (1.107) | 17.32 (1.165) |
| Median (minimum, maximum) | 17.86 (11.3, 18.2) | 17.86 (8.2, 18.9) |
| Participants treated – n (%) | | |
| ≤ 1 month | 29 (27.6) | 97 (22.0) |
| > 1 to ≤ 3 months | 12 (11.4) | 87 (19.8) |
| > 3 to ≤ 6 months | 15 (14.3) | 65 (14.8) |
| > 6 to ≤ 9 months | 12 (11.4) | 44 (10.0) |
| > 9 to ≤ 12 months | 15 (14.3) | 52 (11.8) |
| > 12 to ≤ 15 months | 9 (8.6) | 38 (8.6) |
| > 15 to ≤ 18 months | 3 (2.9) | 29 (6.6) |
| > 18 to ≤ 21 months | 7 (6.7) | 16 (3.6) |
| > 21 to ≤ 24 months | 3 (2.9) | 11 (2.5) |

[a] Total number of infusions: total number of infusions per participant with a nonzero dose of retifanlimab.
[b] Duration of treatment (months) = (date of last dose of retifanlimab − date of first dose + 1) / 30.4375.
[c] Dose intensity (mg/day) = total dose administered (mg) / (duration of treatment [days] + cycle length − 1).
Source: ISS Table 3.1.1.

The Applicant's Position:

A total of 440 participants were included in the All Cancer 500 mg Q4W Population. As of the data cutoff date, the median duration of treatment was 4.6 months (range: 0.03-27.0 months), and 95 participants (21.6%) had received retifanlimab for > 12 months (see Table 20). Among the 105 participants in the MCC Population, the median duration of retifanlimab treatment was 5.6 months (range: 0.03-23.3 months), and 22 participants (21.0%) had received retifanlimab for > 12 months. Relative dose intensity was 100% in both populations.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA notes that the overall exposure was similar between the two safety populations and is adequate to characterize the safety profile. A limitation of the safety database for MCC is that the data were derived from a single arm trial, and therefore it can be difficult to differentiate a treatment-related adverse event from underlying symptoms of malignancy or concomitant medical conditions. Nevertheless, consistent with FDA practice, for labeling, FDA took the approach to list all TEAEs without making a post hoc determination of relatedness.

## Relevant characteristics of the safety population:

The Applicant's Position:

In the MCC Population, demographics and baseline characteristics are representative of the proposed treatment population (Dellambra 2021).Dellambra 2021). Median age was 71.0 years

(range: 38-90 years), and most participants (67.6%) were male. Among the participants with a reported race and/or ethnicity, most were White and not Hispanic or Latino. All participants had a baseline ECOG performance status of 0 (71.4%) or 1 (28.6%). One participant was HIV-positive. Consistent with eligibility criteria, most participants (94.3%) had not received prior systemic therapy, none had received prior immunotherapy, and 37.1% had received prior radiotherapy.

In the All Cancer 500 mg Q4W Population, median age was 67.0 years (range: 36-94 years), and 43.2% of participants were male. Among the participants with a reported race and/or ethnicity, most participants were White and not Hispanic or Latino. Most participants had an ECOG performance status of 0 (48.6%) or 1 (50.7%) at baseline. The most common cancer types were MCC (23.9%), EC (23.2%), SCAC (21.4%), melanoma (8.0%), renal cell carcinoma (7.7%), bladder cancer (6.6%), and NSCLC (5.2%). Ten participants (2.3%) were HIV-positive at baseline. The proportions of participants reporting prior systemic therapy and prior radiotherapy (58.0% and 50.7%, respectively) were higher than in the MCC Population.

The FDA's Assessment

FDA agrees with the Applicant's assessment. FDA adds the following demographic and disease characteristics of the two safety populations (Table 21).

**Table 21: Safety Populations: Demographics**

| | **PODIUM-201 MCC N = 105** | **POOLED SAFETY "All Cancer" N = 440** |
|---|---|---|
| **Age group** n (%) | | |
| < 65 years | 27 (26) | 261 (59) |
| ≥ 65 years | 78 (74) | 179 (41) |
| **Race** n (%) | | |
| White | 83 (79) | 342 (78) |
| Black or African American | 0 (0) | 3 (1) |
| Asian | 1 (1) | 21 (5) |
| Not Reported[a] | 21 (20) | 74 (16) |
| **Region Enrolled** n (%) | | |
| North America | 23 (22) | 59 (13) |
| Europe | 82 (78) | 360 (82) |
| Other | 0 | 21 (5) |

Source: FDA Analysis

[a]Race and ethnicity data from France was not reported

**Adequacy of the safety database:**

The Applicant's Position:

The primary safety analyses of retifanlimab are based on the 105 participants in the MCC Population and the 440 participants in the All Cancer Population who received the recommended retifanlimab 500 mg Q4W as monotherapy. As of the individual study data cutoff dates, the median duration of retifanlimab treatment was 5.6 months in the MCC Population and 4.6 months in the All Cancer 500 mg Q4W Population. The median duration of safety follow-up was 6.5 months (range: 1 day-28.2 months) in the All Cancer 500 mg Q4W Population and 6.4 months (range: 1 day-25.6 months) in the MCC Population (ISS Table 3.2.25.1). The size of the safety database and duration of safety follow-up are considered sufficient for identifying less common, potentially important events. Demographics and baseline characteristics of the participants in the MCC Population are representative of the proposed treatment population. Therefore, the safety of retifanlimab as detailed in this marketing application is generalizable to clinical practice.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA notes that although MCC occurs much less frequently in Black/African American, Asian and American Indian/Alaskan Native patients, the few numbers of patients who are members of these demographic categories limits the assessment of safety in these groups.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

**Issues Regarding Data Integrity and Submission Quality**

The Applicant's Position:

There are no substantial issues regarding data integrity and submission quality. Multiple standard steps are in place to ensure the integrity and quality of the data. Qualified representatives of the Sponsor or Sponsor designees monitor the study according to a predetermined monitoring plan. An independent DMC makes recommendations on study performance based on reviews of safety and interim efficacy data. An eCRF is used to permit consistent collection of data; source-verified data are subject to both manual and electronic checks to ensure data integrity and accuracy. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Part of this study was conducted during the COVID-19 pandemic. Twenty-eight of the 107 participants who were treated with retifanlimab in this study were enrolled prior to 20 JAN 2020 (first CDC-documented case of COVID-19 in the US). No changes in study conduct were implemented in response to the pandemic. COVID-19-related data, including deviations, were collected. None of the Protocol deviations associated with the pandemic significantly affected the completeness, accuracy, and/or reliability of the study data or participant safety.

The FDA's Assessment:

FDA acknowledges the Applicant's position. FDA review did not uncover any data integrity

issues.

**Categorization of Adverse Events**

The Applicant's Position:

The overall safety assessment included TEAEs (treatment-related, serious, Grade 3 or higher, fatal, and leading to treatment discontinuation/interruption/dose delay), and laboratory values. Adverse events were defined and categorized as follows:

Treatment-emergent AEs (TEAEs) were defined as any AE either reported for the first time or worsening of a pre-existing event after the first dose of study drug until 90 days after the last dose of study drug and before initiation of new anticancer therapy use. Analysis of AEs was limited to TEAEs, but data listings include all AEs regardless of their timing in relation to study drug administration. Treatment-emergent AEs were tabulated by MedDRA PT and SOC using MedDRA v23.1.

Treatment-related TEAEs were the subset of TEAEs assessed by the investigator to be related to study drug. If the investigator did not specify the relationship of the TEAE to study drug, the TEAE was considered to be treatment-related.

Severity of AEs was graded using the NCI CTCAE v5.0 for Studies 104, 201, 202, and 203 and NCI CTCAE v4.03 for Study 101.

Immune-related AEs included predefined PTs (and a list of potential symptoms) for irAE diagnosis that were programmatically identified and grouped into categories by the Sponsor and used to identify irAEs independent of investigator's assessment of causality or management of the event.

Concomitant medications for irAEs were identified based on timing of administration, drug classes of interest, and appropriateness of each drug class for the event.

Infusion-related reactions included AEs with a PT indicating a diagnosis of infusion-related reaction, PTs of symptoms that potentially indicated an infusion-related reaction if the symptoms occurred within 1 day of infusion and resolved within 2 days from onset, and all AEs assessed by the investigator as an infusion-related reaction.

The FDA's Assessment:

FDA agrees with the Applicant's categorization of adverse events used for this application. FDA conducted an audit of the coding terms in the dataset. Verbatim terms for adverse events were accurately coded using the MedDRA dictionary. FDA analyses were conducted irrespective of attribution.

**Routine Clinical Tests**

The Applicant's Position:

Clinical safety laboratory analyses (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, lipid panel, and urinalysis) were performed in certified local laboratories. Laboratory data were classified according to NCI CTCAE v5.0.

The FDA's Assessment:
FDA agrees with the Applicant's statement. Blood chemistries, hematology assessments and pregnancy test were conducted at baseline and on day 1 of every cycle. Lipid, coagulation, and endocrine panels were collected at baseline and every third cycle starting with cycle 4.

### 8.2.4. Safety Results

**Deaths**

Data:
The majority of deaths on study were due to disease progression (ISS Table 3.2.28.1). Fatal TEAEs are summarized in Table 22.

**Table 22: Fatal TEAEs**

| MedDRA PT, n (%) | MCC (N = 105) | All Cancer 500 mg Q4W (N = 440) |
|---|---|---|
| Acute respiratory failure | 1 (1.0) | 1 (0.2) |
| Asthenia | 1 (1.0) | 1 (0.2) |
| Cerebrovascular accident | 0 (0.0) | 1 (0.2) |
| Concomitant disease progression | 1 (1.0) | 1 (0.2) |
| COVID-19 pneumonia | 0 (0.0) | 1 (0.2) |
| Death | 0 (0.0) | 1 (0.2) |
| Femur fracture | 0 (0.0) | 1 (0.2) |
| General physical health deterioration | 0 (0.0) | 1 (0.2) |
| Haemorrhage | 0 (0.0) | 1 (0.2) |
| Hypercalcaemia | 0 (0.0) | 1 (0.2) |
| Interstitial lung disease | 0 (0.0) | 1 (0.2) |
| Large intestinal stenosis | 0 (0.0) | 1 (0.2) |
| Lymphangiosis carcinomatosa | 0 (0.0) | 1 (0.2) |
| Pancreatic carcinoma | 0 (0.0) | 1 (0.2) |
| Pelvic infection | 0 (0.0) | 1 (0.2) |
| Peritonitis | 0 (0.0) | 1 (0.2) |
| Pleural effusion | 0 (0.0) | 1 (0.2) |
| Pneumocystis jirovecii pneumonia | 0 (0.0) | 1 (0.2) |
| Renal failure | 0 (0.0) | 1 (0.2) |
| Right ventricular failure | 0 (0.0) | 1 (0.2) |
| Sepsis | 0 (0.0) | 1 (0.2) |
| Septic shock | 0 (0.0) | 1 (0.2) |
| Tumour embolism | 0 (0.0) | 1 (0.2) |

Source: ISS Table 3.2.16.1.

The Applicant's Position:
TEAEs with a fatal outcome were consistent with the diseases under study, an advanced oncology population, and the limited life expectancy for many of these participants, which is less than the Protocol-defined safety follow-up periods. Fatal TEAEs occurred in 3 of the 105 participants (2.9%) in the MCC Population. By PT, fatal TEAEs in the MCC Population were acute respiratory failure, asthenia, and concomitant disease progression in 1 participant each.

Fatal TEAEs occurred in 20 additional participants in the larger All Cancer 500 mg Q4W Population (23 of the 440 total participants [5.2%]), with no event occurring in more than 1 participant by PT (Table 22). Two fatal events in the All Cancer 500 mg Q4W Population were assessed by the investigator as having a reasonable possibility of being related to retifanlimab due to possible hyperprogression of an existing malignancy (lymphangiosis carcinomatosa and progression of concomitant chronic lymphocytic leukemia). The Sponsor assessed both events as not related to retifanlimab.

The FDA's Assessment:
As of the safety data cutoff, 12 (11%) patients in PODIUM-201 and 134 (38%) patients in the pooled safety population died from disease progression. Case narratives of all patients who died as a result of an adverse event were reviewed. FDA disagrees with the Applicant's causality assessment of hyper progression of an existing malignancy (progression of concomitant chronic lymphocytic leukemia). Treatment-emergent adverse events with a fatal outcome in PODIUM-201 and FDA reviewer comments are outlined in Table 23.

**Table 23: TEAEs with Fatal Outcome in PODIUM-201**

| Patient ID | Primary cause of death by Investigator | Applicant attribution to study treatment | FDA Reviewer Comments |
|---|---|---|---|
| **PODIUM-201** | | | |
| # (b) (6)<br>Male<br>82 Years | Asthenia | Not Related - Disease Progression | Patient received 2 doses of retifanlimab and had known bone metastasis with associated bone pain prior to starting treatment. He was noted to have increasing analgesia requirement on Day 15. On Day 44, the patient was hospitalized for worsening in general physical function. During the course of this admission, the patient had clinical evidence of progressive disease and subsequently discontinued treatment on Day 51, he died 38 days following his last retifanlimab dose.<br><br>*FDA considers asthenia as possibly related to retifanlimab and the reason for treatment discontinuation, this was added to the retifanlimab USPI. With the known sites of metastatic disease, medical comorbidities and clinical concerns for disease* |

| Patient ID | Primary cause of death by Investigator | Applicant attribution to study treatment | FDA Reviewer Comments |
|---|---|---|---|
| | | | *progression, the diagnosis of disease progression leading to death appears most likely.* |
| # (b) (6)<br>Female<br>70 years | Concomitant Disease Progression of CLL | Not Related<br>- Progression of CLL | Patient received 3 doses of retifanlimab and had a prior diagnosis of CLL that was under surveillance and never treated prior to starting treatment with retifanlimab. The patient developed worsening anemia (Grade 3) requiring transfusion, with concomitant neutropenia (Grade 2) and thrombocytopenia (Grade 2). With the worsening multilineage cytopenia and transfusion dependence, the patient discontinued treatment with retifanlimab and started CLL directed therapy with obinutuzumab and chlorambucil. The patient died on Day 97, no autopsy was performed.<br><br>*FDA disagrees with the Applicant's assessment of causality. With the patient having stable CLL under surveillance prior to starting treatment, accelerated disease progression of CLL due to retifanlimab cannot be excluded due to the temporal association and the reason for discontinuation has been added to the USPI.* |
| # (b) (6)<br>Male<br>86 Years | Acute Respiratory Failure | Not Related<br>- Disease progression | Patient received 1 dose of retifanlimab and had known pleural and pericardial effusion at baseline prior to starting treatment. On Day 22, the patient attended the emergency room in acute respiratory failure and died the same day. No |

| Patient ID | Primary cause of death by Investigator | Applicant attribution to study treatment | FDA Reviewer Comments |
|---|---|---|---|
| | | | autopsy or further information was possible.<br><br>*FDA agrees with the investigator that the event leading to death is unlikely to be related to retifanlimab, given the acuity of presentation and the known baseline pericardial and pleural effusion being more consistent with the underlying disease.* |

Abbreviations: CLL- Chronic Lymphocytic Leukemia
Source: Reviewer generated table from case narratives

**Table 24: Summary of Deaths**

| | PODIUM-201 MCC | Pooled Safety All Cancer |
|---|---|---|
| | N = 105 | N = 440 |
| | N (%) | N (%) |
| **Total Deaths** | 16 (15) | 167 (38) |
| **Within 30 days after last dose of retifanlimab** | 3 (2.9) | 22 (5) |
| **Beyond 30 days after last dose of retifanlimab** | 13 (12) | 145 (33) |

Source: FDA analysis

The majority of deaths at the time of the safety data cutoff occurred beyond 30 days after the last dose of retifanlimab (n=13 [12%]) (Table 24). FDA sent an information request to the Applicant to ensure there was no change in mortality within 30 days from the original cutoff date (June 16, 2021 and update was provided on November 7, 2022). As of May 20, 2022, there have been an additional 3 patients (total 6 (5.6%]) patients enrolled into PODIUM-201 who have died within 30 days of the last dose of retifanlimab. A review of the incidence and causes of death did not reveal any unexpected safety signals with retifanlimab monotherapy used for the treatment of patients in the locally advanced unresectable or metastatic setting.

**Serious Adverse Events**

Data:

Serious TEAEs are summarized in Table 25.

**Table 25: Serious TEAEs in > 2 Participants in All Cancer 500 mg Q4W Population**

| MedDRA PT, n (%) | MCC (N = 105) | All Cancer 500 mg Q4W (N = 440) |
|---|---|---|
| Pneumonia | 1 (1.0) | 10 (2.3) |
| Urinary tract infection | 2 (1.9) | 10 (2.3) |
| Abdominal pain | 0 (0.0) | 6 (1.4) |
| Anaemia | 0 (0.0) | 6 (1.4) |
| Asthenia | 3 (2.9) | 6 (1.4) |
| Sepsis | 1 (1.0) | 6 (1.4) |
| Acute kidney injury | 0 (0.0) | 4 (0.9) |
| Chronic obstructive pulmonary disease | 0 (0.0) | 4 (0.9) |
| General physical health deterioration | 0 (0.0) | 4 (0.9) |
| Hypercalcaemia | 0 (0.0) | 4 (0.9) |
| Pneumonitis | 2 (1.9) | 4 (0.9) |
| Pyrexia | 0 (0.0) | 4 (0.9) |
| Atrial fibrillation | 2 (1.9) | 3 (0.7) |
| Back pain | 0 (0.0) | 3 (0.7) |
| Bone pain | 2 (1.9) | 3 (0.7) |
| Cerebrovascular accident | 0 (0.0) | 3 (0.7) |
| Dyspnoea | 1 (1.0) | 3 (0.7) |
| Hepatocellular injury | 0 (0.0) | 3 (0.7) |
| Pelvic pain | 0 (0.0) | 3 (0.7) |
| Pleural effusion | 0 (0.0) | 3 (0.7) |

Source: ISS Table 3.2.9.1.

The Applicant's Position:

Serious TEAEs (including the fatal TEAEs described above) occurred in 149 participants (33.9%) in the All Cancer 500 mg Q4W Population, including 23 participants (21.9%) in the MCC Population. By PT, the most common (> 2%) serious TEAEs were pneumonia and urinary tract infection (10 participants [2.3%] each) in the All Cancer 500 mg Q4W Population and asthenia (3 participants [2.9%]) in the MCC Population (Table 25). By PT, the only treatment-related serious TEAE in more than 2 participants in the All Cancer 500 mg Q4W Population was pneumonitis (3 participants [0.7%]). No treatment-related serious TEAE occurred in more than 1 participant in the MCC Population (Module 2.7.4 Section 2.1.8).

The FDA's Assessment:

FDA agrees with the Applicant's description of the incidence of overall SAEs in the MCC and pooled population. FDA clarifies that in the pooled patient population 6 (1.4%) patients had the SAE of pneumonitis (grouped term: pneumonitis, interstitial lung disease).

FDA disagrees with the Applicant's assessment that there were no treatment-related SAEs that occurred in more than one patient in the MCC population. The most frequent (≥2% of patients) SAEs occurring in the MCC population enrolled into PODIUM-201 were fatigue, arrhythmia, and pneumonitis (3 [2.9%] patients each). The USPI for retifanlimab has been updated accordingly.

**Dropouts and/or Discontinuations Due to Adverse Effects**

Data:

Treatment-emergent AEs leading to retifanlimab discontinuation are summarized in Table 26.

**Table 26: TEAEs Leading to Retifanlimab Discontinuation by Preferred Term**

| MedDRA PT, n (%) | MCC (N = 105) | All Cancer 500 mg Q4W (N = 440) |
|---|---|---|
| Hepatitis | 0 (0.0) | 2 (0.5) |
| Renal failure | 0 (0.0) | 2 (0.5) |
| Sepsis | 0 (0.0) | 2 (0.5) |
| Acute kidney injury | 0 (0.0) | 1 (0.2) |
| Alanine aminotransferase increased | 0 (0.0) | 1 (0.2) |
| Asthenia | 1 (1.0) | 1 (0.2) |
| Atrial fibrillation | 1 (1.0) | 1 (0.2) |
| Autoimmune hepatitis | 0 (0.0) | 1 (0.2) |
| Azotaemia | 0 (0.0) | 1 (0.2) |
| Blood bilirubin increased | 0 (0.0) | 1 (0.2) |
| Blood creatinine increased | 0 (0.0) | 1 (0.2) |
| COVID-19 pneumonia | 0 (0.0) | 1 (0.2) |
| Chronic obstructive pulmonary disease | 0 (0.0) | 1 (0.2) |
| Concomitant disease progression | 1 (1.0) | 1 (0.2) |
| Demyelinating polyneuropathy | 1 (1.0) | 1 (0.2) |
| Diarrhoea | 0 (0.0) | 1 (0.2) |
| Diffuse large B-cell lymphoma | 0 (0.0) | 1 (0.2) |
| Dry mouth | 0 (0.0) | 1 (0.2) |
| Dry skin | 0 (0.0) | 1 (0.2) |
| Eosinophilic fasciitis | 1 (1.0) | 1 (0.2) |
| General physical health deterioration | 0 (0.0) | 1 (0.2) |
| Haemorrhage | 0 (0.0) | 1 (0.2) |
| Hepatic failure | 0 (0.0) | 1 (0.2) |
| Hepatocellular injury | 0 (0.0) | 1 (0.2) |
| Immune-mediated enterocolitis | 0 (0.0) | 1 (0.2) |
| Infusion-related reaction | 1 (1.0) | 1 (0.2) |
| Iritis | 0 (0.0) | 1 (0.2) |
| Large intestinal stenosis | 0 (0.0) | 1 (0.2) |
| Lung disorder | 1 (1.0) | 1 (0.2) |
| Myelodysplastic syndrome | 0 (0.0) | 1 (0.2) |
| Myositis | 0 (0.0) | 1 (0.2) |
| Palmar-plantar erythrodysaesthesia syndrome | 0 (0.0) | 1 (0.2) |
| Pancreatitis | 1 (1.0) | 1 (0.2) |
| Pleural effusion | 0 (0.0) | 1 (0.2) |
| Pneumonia | 0 (0.0) | 1 (0.2) |
| Pneumonitis | 0 (0.0) | 1 (0.2) |
| Polyarthritis | 1 (1.0) | 1 (0.2) |
| Polymyalgia rheumatica | 0 (0.0) | 1 (0.2) |
| Pseudomonas infection | 0 (0.0) | 1 (0.2) |
| Radiculopathy | 1 (1.0) | 1 (0.2) |
| Right ventricular failure | 0 (0.0) | 1 (0.2) |

| MedDRA PT, n (%) | MCC (N = 105) | All Cancer 500 mg Q4W (N = 440) |
|---|---|---|
| Septic shock | 0 (0.0) | 1 (0.2) |
| Transaminases increased | 1 (1.0) | 1 (0.2) |
| Transitional cell carcinoma | 0 (0.0) | 1 (0.2) |

Source: ISS Table 3.2.20.4.

The Applicant's Position:

Most common TEAEs did not lead to retifanlimab discontinuation. Treatment-emergent AEs leading to discontinuation occurred in 47 participants (10.7%) in the All Cancer 500 mg Q4W Population, including 11 participants (10.5%) in the MCC Population. In the All Cancer 500 mg Q4W Population, by PT, the only TEAEs that led to retifanlimab discontinuation in more than 1 participant were hepatitis, renal failure, and sepsis in 2 participants (0.5%) each, and the only treatment-related TEAE leading to retifanlimab discontinuation in more than 1 participant was hepatitis in 2 participants (0.5%; Table 26).

The FDA's Assessment:

FDA agrees with the Applicant's assessment on the overall incidence of TEAEs leading to discontinuation of retifanlimab in PODIUM-201 and in the pooled population. The MedDRA preferred terms leading to treatment discontinuation are listed Table 26. FDA agrees that there were no TEAEs leading to treatment discontinuation that occurred in more than one patient in PODIUM-201 and the terms are included in the retifanlimab USPI.

FDA clarifies that in the pooled population, 8 (1.8%) patients had evidence of hepatic dysfunction (alanine aminotransferase increased [N=1], autoimmune hepatitis [N=1], bilirubin increased [N=1], hepatitis [N=2], hepatic failure [N=1], hepatocellular injury [N=1], transaminases increased [N=1]), 4 (0.9%) patients had evidence of renal dysfunction [(acute kidney injury [N=1], azotemia [N=1], renal failure [N=2]) and 3 (0.7%) patients had sepsis (sepsis [N=2], septic shock [N=1]) leading to treatment discontinuation.

**Dose Interruption/Reduction Due to Adverse Effects**

Data:

Dose reductions were not permitted. Dose interruptions were permitted; TEAEs leading to dose interruption are summarized in Table 27.

**Table 27: TEAEs Leading to Dose Delay in >2 Participants in All Cancer 500 mg Q4W Population**

| MedDRA PT, n (%) | MCC (N = 105) | All Cancer 500 mg Q4W (N = 440) |
|---|---|---|
| Pyrexia | 3 (2.9) | 8 (1.8) |
| Diarrhoea | 1 (1.0) | 7 (1.6) |
| Pneumonia | 1 (1.0) | 6 (1.4) |
| Rash | 1 (1.0) | 6 (1.4) |
| Alanine aminotransferase increased | 4 (3.8) | 5 (1.1) |
| Aspartate aminotransferase increased | 3 (2.9) | 5 (1.1) |

| MedDRA PT, n (%) | MCC (N = 105) | All Cancer 500 mg Q4W (N = 440) |
|---|---|---|
| Blood creatinine increased | 1 (1.0) | 5 (1.1) |
| Lipase increased | 3 (2.9) | 5 (1.1) |
| Abdominal pain | 1 (1.0) | 4 (0.9) |
| Amylase increased | 3 (2.9) | 4 (0.9) |
| Arthralgia | 1 (1.0) | 4 (0.9) |
| COVID-19 | 4 (3.8) | 4 (0.9) |
| Urinary tract infection | 1 (1.0) | 4 (0.9) |
| Blood alkaline phosphatase increased | 2 (1.9) | 3 (0.7) |
| Cough | 1 (1.0) | 3 (0.7) |
| Hepatocellular injury | 0 (0.0) | 3 (0.7) |
| Myalgia | 1 (1.0) | 3 (0.7) |
| Pneumonitis | 2 (1.9) | 3 (0.7) |
| Sepsis | 1 (1.0) | 3 (0.7) |

Source: ISS Table 3.2.19.12.

The Applicant's Position:

Treatment-emergent AEs leading to dose delay occurred in 114 participants (25.9%) in the All Cancer 500 mg Q4W Population, including 25 participants (23.8%) in the MCC Population. By PT, the most frequent TEAE leading to dose delay was pyrexia (1.8%) in the All Cancer 500 mg Q4W Population and ALT increased and COVID-19 (3.8% each) in the MCC Population.

The FDA's Assessment:

Treatment-emergent adverse events leading to treatment interruption occurred in 117 (27%) patients in the pooled safety population, including 26 (25%) patients in PODIUM-201. The most frequent (≥2%) TEAEs leading to treatment interruption are listed in Table 28. (b) (4)

**Table 28: TEAEs Leading To Treatment Interruption in ≥2% of Patients in Either PODIUM-201 or the Pooled Safety Population**

| MedDRA Preferred Term | PODIUM-201 MCC N = 105 N (%) | POOLED SAFETY "All Cancer" N = 440 N (%) |
|---|---|---|
| **Any TEAE leading to treatment interruption** | **26 (25)** | **117 (27)** |
| Alanine Aminotransferase Increased | 4 (3.8) | 5 (1.1) |
| Covid-19 | 4 (3.8) | 4 (0.9) |
| Amylase Increased | 3 (2.9) | 4 (0.9) |
| Aspartate Aminotransferase Increased | 3 (2.9) | 5 (1.1) |

| MedDRA Preferred Term | PODIUM-201 MCC N = 105 N (%) | POOLED SAFETY "All Cancer" N = 440 N (%) |
|---|---|---|
| Lipase Increased | 3 (2.9) | 6 (1.4) |
| Pneumonitis[a] | 3 (2.9) | 4 (0.9) |
| Pyrexia | 3 (2.9) | 8 (1.8) |
| Dermatitis/rash[b] | 2 (1.9) | 12 (2.7) |

Abbreviations: MCC – Merkel Cell Carcinoma; TEAE: Treatment emergent adverse event
Source: FDA Analysis
[a]Pneumonitis (GT) includes: pneumonitis, interstitial lung disease, organizing pneumonia
[b]Dermatitis/Rash (GT) includes: rash, dermatitis, dermatitis bullous, rash erythematous, rash maculo-papular, rash papular, and rash pruritic

**Treatment-Emergent Adverse Events and Adverse Reactions**

The Applicant's Position:

An overall summary of TEAEs is presented in Table 29.

**Table 29: Overall Summary of TEAEs**

| Participants (n [%]) With a: | MCC (N = 105) | All Cancer 500 mg Q4W (N = 440) |
|---|---|---|
| TEAE | 81 (77.1) | 399 (90.7) |
| Treatment-related TEAE | 59 (56.2) | 279 (63.4) |
| Serious TEAE | 23 (21.9) | 149 (33.9) |
| Grade 3 or higher TEAE | 29 (27.6) | 183 (41.6) |
| Fatal TEAE | 3 (2.9) | 23 (5.2) |
| Serious treatment-related TEAE | 9 (8.6) | 26 (5.9) |
| Grade 3 or higher treatment-related TEAE | 13 (12.4) | 53 (12.0) |
| Infusion interruption due to TEAE | 2 (1.9) | 5 (1.1) |
| Dose delayed due to TEAE | 25 (23.8) | 114 (25.9) |
| Discontinued study drug due to TEAE | 11 (10.5) | 47 (10.7) |
| Discontinued study drug due to treatment-related TEAE | 9 (8.6) | 27 (6.1) |

Source: ISS Tables 3.1.1 and 3.2.1.1.

In both populations, common TEAEs were consistent with AEs anticipated for an advanced cancer population or with PD-(L)1 inhibitor treatment. By PT, the most common TEAE was asthenia in both populations (Table 30). The majority of the most common TEAEs were predominantly Grade 1 or Grade 2 in severity in both populations.

**Table 30: TEAEs in ≥ 5% (All Grades) of the All Cancer 500 mg Q4W Population**

| | MCC (N = 105) | | All Cancer 500 mg Q4W (N = 440) | |
|---|---|---|---|---|
| MedDRA PT, n (%) | All Grades | ≥ Grade 3 | All Grades | ≥ Grade 3 |
| Participants with ≥ 1 TEAE | 81 (77.1) | 29 (27.6) | 399 (90.7) | 183 (41.6) |
| Asthenia | 21 (20.0) | 2 (1.9) | 97 (22.0) | 8 (1.8) |
| Diarrhoea | 14 (13.3) | 0 (0.0) | 71 (16.1) | 2 (0.5) |
| Pruritus | 19 (18.1) | 0 (0.0) | 68 (15.5) | 0 (0.0) |
| Anaemia | 5 (4.8) | 2 (1.9) | 64 (14.5) | 26 (5.9) |
| Fatigue | 10 (9.5) | 0 (0.0) | 60 (13.6) | 3 (0.7) |
| Nausea | 11 (10.5) | 0 (0.0) | 57 (13.0) | 0 (0.0) |
| Pyrexia | 11 (10.5) | 0 (0.0) | 54 (12.3) | 2 (0.5) |
| Arthralgia | 11 (10.5) | 1 (1.0) | 52 (11.8) | 3 (0.7) |
| Constipation | 9 (8.6) | 0 (0.0) | 52 (11.8) | 0 (0.0) |
| Decreased appetite | 4 (3.8) | 0 (0.0) | 52 (11.8) | 3 (0.7) |
| Urinary tract infection | 7 (6.7) | 1 (1.0) | 49 (11.1) | 6 (1.4) |
| Hypothyroidism | 8 (7.6) | 0 (0.0) | 40 (9.1) | 0 (0.0) |
| Rash | 4 (3.8) | 0 (0.0) | 39 (8.9) | 2 (0.5) |
| Cough | 7 (6.7) | 0 (0.0) | 37 (8.4) | 0 (0.0) |
| Vomiting | 6 (5.7) | 0 (0.0) | 36 (8.2) | 1 (0.2) |
| Abdominal pain | 3 (2.9) | 0 (0.0) | 34 (7.7) | 6 (1.4) |
| Dyspnoea | 4 (3.8) | 1 (1.0) | 34 (7.7) | 7 (1.6) |
| Back pain | 5 (4.8) | 0 (0.0) | 32 (7.3) | 4 (0.9) |
| Headache | 5 (4.8) | 0 (0.0) | 28 (6.4) | 1 (0.2) |
| Oedema peripheral | 3 (2.9) | 0 (0.0) | 28 (6.4) | 1 (0.2) |
| Hyperthyroidism | 5 (4.8) | 0 (0.0) | 23 (5.2) | 0 (0.0) |
| Hypokalaemia | 2 (1.9) | 0 (0.0) | 22 (5.0) | 4 (0.9) |

Source: ISS Tables 3.2.1.1, 3.2.3.1, 3.2.6.1, and 3.2.7.1.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of TEAEs listed in Table 29. FDA clarifies that the incidence of TEAEs leading to treatment interruption was 25% in PODIUM-201 and 27% in the pooled safety population (Table 27). FDA's independent analyses were conducted irrespective of the Applicant's causality assessment. FDA's analysis of the frequency and severity of the most common (≥ 5%) TEAEs are listed in the table below Table 31. FDA agrees that the majority of the TEAEs in the MCC and pooled safety population were of Grade 1 and 2 severity.

**Table 31: Any Grade TEAE occurring in ≥ 5% of Patients in Either PODIUM-201 or the Pooled Safety Population**

| | Merkel Cell Cancer | | All Cancer | |
|---|---|---|---|---|
| | N = 105 | | N = 440 | |
| | All grades | Grades 3-4 | All grades | Grades 3-4 |
| | N (%) | N (%) | N(%) | N (%) |
| **Patients with TEAEs** | 81 (77) | 26 (25) | 399 (91) | 160 (36) |

| | Merkel Cell Cancer | | All Cancer | |
|---|---|---|---|---|
| | N = 105 | | N = 440 | |
| | All grades | Grades 3-4 | All grades | Grades 3-4 |
| | N (%) | N (%) | N(%) | N (%) |
| **General Disorders And Administration Site Conditions** | | | | |
| Fatigue[a] | 29 (28) | 1 (1.0) | 151 (34) | 10 (2.3) |
| Pyrexia[b] | 11 (10) | 0 (0.0) | 55 (13) | 2 (0.5) |
| Edema[c] | 5 (4.8) | 0 (0.0) | 34 (8) | 1 (0.2) |
| **Musculoskeletal And Connective Tissue Disorders** | | | | |
| Musculoskeletal Pain[d] | 23 (22) | 3 (2.9) | 113 (26) | 11 (2.5) |
| **Gastrointestinal Disorders** | | | | |
| Diarrhea[e] | 16 (15) | 0 (0.0) | 73 (17) | 2 (0.5) |
| Nausea | 11 (10) | 0 (0.0) | 57 (13) | 0 (0.0) |
| Constipation | 9 (9) | 0 (0.0) | 52 (12) | 0 (0.0) |
| Vomiting | 6 (6) | 0 (0.0) | 36 (8) | 1 (0.2) |
| **Skin And Subcutaneous Tissue Disorders** | | | | |
| Pruritus | 19 (18) | 0 (0.0) | 68 (15) | 0 (0.0) |
| Rash[f] | 12 (11) | 1 (1.0) | 73 (17) | 5 (1.1) |
| **Endocrine Disorders** | | | | |
| Hypothyroidism | 9 (9) | 0 (0.0) | 43 (10) | 0 (0.0) |
| Hyperthyroidism | 5 (4.8) | 0 (0.0) | 23 (5) | 0 (0.0) |
| **Investigations** | | | | |
| Lipase Increased | 7 (7) | 2 (1.9) | 13 (3.0) | 3 (0.7) |
| Alanine Aminotransferase Increased | 6 (6) | 2 (1.9) | 21 (4.8) | 7 (1.6) |
| Aspartate Aminotransferase Increased | 6 (6) | 1 (1.0) | 21 (4.8) | 3 (0.7) |
| **Infections And Infestations** | | | | |
| Urinary Tract Infection[g] | 7 (7) | 1 (1.0) | 62 (14) | 7 (1.6) |
| Covid-19 | 6 (6) | 2 (1.9) | 9 (2.0) | 2 (0.5) |
| **Respiratory, Thoracic And Mediastinal Disorders** | | | | |
| Cough[h] | 8 (8) | 0 (0.0) | 40 (9) | 0 (0.0) |
| Dyspnea[i] | 5 (4.8) | 1 (1.0) | 42 (10) | 7 (1.6) |
| **Nervous System Disorders** | | | | |
| Headache | 5 (4.8) | 0 (0.0) | 28 (6) | 1 (0.2) |
| Neuropathy Peripheral[j] | 3 (2.9) | 0 (0.0) | 24 (5) | 2 (0.5) |
| **Blood And Lymphatic System Disorders** | | | | |
| Anemia | 5 (4.8) | 2 (1.9) | 64 (15) | 26 (6) |

Abbreviations: GT: Grouped Term; MCC – Merkel Cell Carcinoma; PT: Preferred Terms; TEAE: Treatment emergent adverse event
Source: FDA Analysis

[a]Fatigue (GT) includes PT: asthenia, fatigue
[b]Pyrexia (GT) includes PT: pyrexia, hyperthermia, body temperature increased
[c]Edema (GT) includes PT: edema peripheral, edema, swelling, scrotal edema, edema genital, and face edema
[d]Musculoskeletal Pain (GT) includes PT: arthralgia, arthritis, pain in extremity, musculoskeletal stiffness, spinal pain, non-cardiac chest pain, back pain, bone pain, pain in extremity, neck pain, and myalgia
[e]Diarrhea (GT) includes PT: diarrhea, colitis
[f]Rash (GT) includes PT: rash, dermatitis, dermatitis bullous, rash erythematous, rash maculo-papular, rash papular, and rash pruritic
[g]Urinary Tract Infection (GT) includes PT: urinary tract infection, bacterial pyelonephritis, Escherichia urinary tract infection, cystitis
[h]Cough (GT) includes PT: cough, productive cough
[i]Dyspnea (GT) includes PT: dyspnea, dyspnea exertional
[j]Neuropathy peripheral (GT) includes PT: hypoesthesia, neuropathy peripheral, paresthesia, polyneuropathy, neuralgia

The Applicant's Position:

Based on FDA feedback, adverse reactions were identified based on safety results from the 65 participant Chemotherapy-Naïve MCC FAS (participants who received at least 1 dose of retifanlimab as of 15 OCT 2020) in Study 201. All participants received retifanlimab monotherapy 500 mg Q4W. As of the 21 JAN 2022 data cutoff date for this analysis, the median duration of retifanlimab exposure was 12.9 months (range: 1 day-24.0 months).

The adverse reactions identified for retifanlimab are based on the Sponsor's medical assessment of each individual TEAE where a causal relationship with the product is a reasonable possibility. The review consisted of the most common TEAEs, and irAEs, infusion-related reactions, ≥ Grade 3 TEAEs, serious TEAEs, fatal TEAEs, TEAEs leading to discontinuation or dose interruption (eg, dose delay), and TEAEs recorded as significant laboratory abnormalities, regardless of incidence. The following factors were considered when making decisions on whether a causal relationship to retifanlimab is plausible:

- Frequency of reporting
- Biological plausibility based on retifanlimab's mechanism of action and known effects of PD-(L)1 class
- Timing of the event relative to the time of retifanlimab exposure
- Evaluation of the clinical course, including medical interventions (eg, corticosteroids)
- Population under study, including comorbidities and prior/concomitant therapy

The adverse reactions reported with retifanlimab are listed below in Table 32. Select worsening laboratory values seen with retifanlimab treatment are listed in Table 33. The values were assessed as clinically relevant to healthcare practitioners and are potential symptoms of irAEs.

**Table 32: Adverse Drug Reactions in Participants With MCC Receiving Retifanlimab**

| System Organ Class/ Adverse Reaction | N = 65 | |
|---|---|---|
| | All Grades, n (%) | Grades 3-4, n (%) |
| General disorders and administration site conditions | | |
| Fatigue[a] | 25 (38.5) | 1 (1.5) |
| Pyrexia | 8 (12.3) | 0 (0.0) |
| Skin and subcutaneous tissue disorders | | |
| Pruritus | 16 (24.6) | 0 (0.0) |
| Rash[b] | 11 (16.9) | 1 (1.5) |
| Gastrointestinal disorders | | |
| Diarrhoea | 14 (21.5) | 0 (0.0) |
| Nausea | 8 (12.3) | 0 (0.0) |
| Constipation | 5 (7.7) | 0 (0.0) |
| Colitis | 2 (3.1) | 0 (0.0) |
| Pancreatitis | 1 (1.5) | 1 (1.5) |
| Musculoskeletal and connective tissue disorders | | |
| Arthralgia | 10 (15.4) | 1 (1.5) |
| Eosinophilic fasciitis | 1 (1.5) | 1 (1.5) |
| Polyarthritis | 1 (1.5) | 0 (0.0) |
| Respiratory, thoracic and mediastinal disorders | | |
| Cough | 8 (12.3) | 0 (0.0) |
| Pneumonitis[c] | 5 (7.7) | 2 (3.1) |
| Endocrine disorders | | |
| Hypothyroidism | 6 (9.2) | 0 (0.0) |
| Hyperthyroidism | 4 (6.2) | 0 (0.0) |
| Adrenal insufficiency | 2 (3.1) | 1 (1.5) |
| Autoimmune thyroiditis | 1 (1.5) | 0 (0.0) |
| Hypophysitis | 1 (1.5) | 1 (1.5) |
| Blood and lymphatic system disorders | | |
| Anaemia | 3 (4.6) | 1 (1.5) |
| Injury, poisoning, and procedural complications | | |
| Infusion-related reaction | 3 (4.6) | 1 (1.5) |
| Metabolism and nutrition disorders | | |
| Decreased appetite | 3 (4.6) | 0 (0.0) |
| Diabetic ketoacidosis | 1 (1.5) | 1 (1.5) |
| Nervous system disorders | | |
| Paraesthesia | 2 (3.1) | 0 (0.0) |
| Hepatobiliary disorders | | |
| Hepatitis | 1 (1.5) | 1 (1.5) |
| Renal and urinary disorders | | |
| Acute kidney injury | 1 (1.5) | 0 (0.0) |

Note: Graded according to CTCAE v5.0.

[a] Includes asthenia and fatigue.

[b] Includes dermatitis, dermatitis bullous, rash, rash erythematous, rash maculo-papular, rash papular, and rash pruritic.

[c] Includes interstitial lung disease, organising pneumonia, and pneumonitis.

Source: CSR Table 99.3.2.4.

**Table 33: Selected Treatment-Emergent Laboratory Abnormalities in Participants With MCC Receiving Retifanlimab**

| Laboratory Test | Retifanlimab 500 mg Q4W | |
|---|---|---|
| | All Grades, n (%) | Grades 3-4, n (%) |
| Increased alanine aminotransferase | 16 (25.8) | 3 (4.8) |
| Increased aspartate aminotransferase | 18 (29.0) | 2 (3.2) |
| Increased creatinine | 10 (16.1) | 0 (0.0) |
| Increased bilirubin | 8 (12.9) | 0 (0.0) |
| Increased thyroid-stimulating hormone[a] | 16 (27.1) | |
| Decreased thyroid-stimulating hormone[b] | 13 (22.0) | |

Note: The incidence is the incidence of the laboratory abnormality (not the incidence of the PT reported as a laboratory abnormality AE). Treatment-emergent consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality. The denominator varied from 59 to 62 participants with a baseline value and at least 1 post-treatment value.
[a] Participants with normal baseline TSH values and at least 1 on-treatment TSH value above the upper limit of normal.
[b] Participants with normal baseline TSH values and at least 1 on-treatment TSH value below the lower limit of normal.
Source: CSR Tables 3.3.2.4 and 3.3.3.5.

The FDA's Assessment:

FDA's approach to the primary safety analysis has been outlined in Section 8.2.1 and adverse reactions, regardless of causality, including relevant grouped preferred terms for fatigue, musculoskeletal pain, and rash with a frequency ≥10% are outlined in the table below and included in the retifanlimab USPI. The most common (≥2 patients) Grade 3 or 4 adverse reactions were musculoskeletal pain (GT) (N=3), pneumonitis (N=2), neutropenia (N=2), anemia (N=2), lipase increased (N=2), amylase increased (N=2), alanine aminotransferase increased (N=2), arrhythmia (N=2), and hyponatremia (N=2).

**Table 34: FDA Analysis of Common (≥ 10%) TEAEs in Patients Enrolled into PODIUM-201**

| Adverse Reaction | PODIUM-201 MCC N = 105 | |
|---|---|---|
| | Any Grade N (%) | Grades 3-4 N (%) |
| **General disorders and administration site conditions** | | |
| Fatigue[a] | 29 (28) | 1 (1) |
| Pyrexia | 11 (10) | 0 |
| **Musculoskeletal and connective tissue disorders** | | |
| Musculoskeletal pain[b] | 23 (22) | 3 (2.9) |
| **Skin and subcutaneous tissue disorders** | | |
| Pruritus | 19 (18) | 0 |
| Rash[c] | 12 (11) | 1 (1) |
| **Gastrointestinal disorders** | | |

| Adverse Reaction | PODIUM-201 MCC N = 105 | |
|---|---|---|
| | Any Grade N (%) | Grades 3-4 N (%) |
| Diarrhea | 16 (15) | 0 |
| Nausea | 11 (10) | 0 |

Abbreviations: MCC – Merkel Cell Carcinoma; TEAE: Treatment emergent adverse event
Source: FDA Analysis
[a]Fatigue (GT) includes PT: asthenia, fatigue
[b]Musculoskeletal pain (GT) includes PT: arthralgia, back pain, bone pain, pain in extremity, neck pain, and myalgia
[c]Rash (GT) includes PT: rash, dermatitis, dermatitis bullous, rash erythematous, rash maculo-papular, rash papular, and rash pruritic

FDA notes that the Applicant's Table 33 outlines only selected treatment-emergent laboratory abnormalities in patients included in PODIUM-201. The FDA analysis, and retifanlimab USPI, included all Grade 3 or 4 laboratory abnormalities that occurred in ≥1% of patients in PODIUM-201 (Table 35).

**Table 35: Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Patients in PODIUM-201**

| Laboratory Test | PODIUM-201 MCC N=105 | |
|---|---|---|
| | Any Grade (%)[a] | Grade 3-4 (%)[a] |
| **Hematology** | | |
| Decreased hemoglobin | 38 | 1.1 |
| Decreased lymphocytes | 29 | 10 |
| Decreased neutrophil | 13 | 3.3 |
| Decreased leukocytes | 12 | 1.1 |
| **Chemistry** | | |
| Increased lipase | 30 | 3.4 |
| Decreased sodium | 23 | 3.3 |
| Increased aspartate aminotransferase | 23 | 2.2 |
| Increased alanine aminotransferase | 21 | 3.3 |
| Increased alkaline phosphatase | 20 | 1.1 |
| Increased amylase | 19 | 1.2 |
| Decreased potassium | 9 | 1.1 |

| Laboratory Test | PODIUM-201 MCC N=105 | |
|---|---|---|
| | Any Grade (%)[a] | Grade 3-4 (%)[a] |
| Increased calcium | 8 | 1.1 |

Source: FDA analysis
[a]The denominator used to calculate the rate varied from 86 to 92 based on the number of patients with a baseline value and at least one post-treatment value.

## Laboratory Findings

Data:

Treatment-emergent worsening laboratory parameters are summarized in Table 36.

**Table 36: Treatment-Emergent Worsening of CTCAE-Graded Laboratory Parameters**

| Laboratory Parameter, n/N (%) | MCC (N = 105) Grade 3 or 4 | All Cancer 500 mg Q4W (N = 440) Grade 3 or 4 |
|---|---|---|
| **Hematology** | | |
| Lymphocytes (decreased) | 9/91 (9.9) | 42/406 (10.3) |
| Hemoglobin (decreased) | 1/92 (1.1) | 14/411 (3.4) |
| Neutrophils (decreased) | 3/91 (3.3) | 6/406 (1.5) |
| Leukocytes (decreased) | 1/91 (1.1) | 3/410 (0.7) |
| **Chemistry** | | |
| Magnesium (decreased) | 0/0 (0.0) | 4/113 (3.5) |
| ALT (increased) | 3/91 (3.3) | 11/412 (2.7) |
| Lipase (increased) | 3/89 (3.4) | 10/393 (2.5) |
| Triglycerides (increased)[a] | 0/64 (0.0) | 5/215 (2.3) |
| Potassium (decreased) | 1/91 (1.1) | 8/411 (1.9) |
| AST (increased) | 2/92 (2.2) | 8/413 (1.9) |
| Sodium (decreased) | 3/92 (3.3) | 7/412 (1.7) |
| Bilirubin (increased) | 0/91 (0.0) | 7/410 (1.7) |
| Creatinine (increased) | 0/92 (0.0) | 5/413 (1.2) |
| Albumin (decreased) | 0/91 (0.0) | 4/407 (1.0) |
| ALP (increased) | 1/90 (1.1) | 4/410 (1.0) |
| Cholesterol (increased)[a] | 0/65 (0.0) | 2/217 (0.9) |
| Magnesium (increased) | 0/0 (0.0) | 1/113 (0.9) |
| Amylase (increased) | 1/86 (1.2) | 3/369 (0.8) |
| Sodium (increased) | 0/92 (0.0) | 3/412 (0.7) |
| Calcium (increased) | 1/90 (1.1) | 2/399 (0.5) |
| Glucose (decreased) | 0/91 (0.0) | 2/408 (0.5) |
| Calcium (decreased) | 0/90 (0.0) | 1/399 (0.3) |
| Potassium (increased) | 0/91 (0.0) | 1/411 (0.2) |

Note: Worst CTCAE grade postbaseline. If baseline grade is missing, any postbaseline abnormality is considered worsening from baseline. Calcium is based on derived calcium corrected for albumin.
[a] Fasting was required for the lipid panel test in Studies 201, 202, and 203. Study 101 did not require cholesterol or triglycerides testing per protocol.
Source: ISS Tables ISS Table 3.3.3.4 and 3.3.3.5.

The Applicant's Position:

For clinical hematology parameters, changes from baseline and shifts in severity grades were variable and consistent with the disease under study. In both populations, treatment-emergent worsening of any CTCAE grade was observed most frequently for decreased hemoglobin and decreased lymphocytes. Treatment-emergent worsening to Grade 3 or higher worst postbaseline values was observed most frequently for decreased lymphocytes. The absence of clinically meaningful trends demonstrates that there is no increased risk for hematologic toxicity. This differentiates retifanlimab from chemotherapy.

For clinical chemistry parameters, changes from baseline and shifts in CTCAE severity grades were also variable and consistent with the diseases under study. Treatment-emergent worsening of any CTCAE grade was observed most frequently for decreased albumin in the All Cancer 500 mg Q4W Population and increased lipase in the MCC Population. Treatment-emergent worsening to Grade 3 or higher worst postbaseline values was infrequent; the chemistry parameters with worsening to Grade 3 or higher worst postbaseline values were decreased magnesium in the All Cancer 500 mg Q4W Population and increased lipase in the MCC Population. No participants met the laboratory-based criteria for Hy's law to warrant further clinical specialized assessment and/or adjudication. There is no evidence of retifanlimab-induced liver toxicity.

FDA agrees with the Applicant's analysis of Grade 3 or 4 treatment emergent laboratory-based abnormalities. There were no patients that met the criterial for potential Hy's law in the pooled safety population. When assessing the clinical relevance of a 10% incidence for Grade 3 or 4 lymphopenia, FDA conducted an analysis on to determine if the concomitant use of systemic corticosteroid use confounded the results. FDA confirmed that 4 of the 9 patients with Grade 3 or 4 worsening in lymphocytes had received systemic corticosteroids prior to the treatment-emergent laboratory abnormality.

FDA notes that 27 out of 89 patients (30%) in PODIUM-201 had any Grade increased lipase, and 3 out of 89 patients (3.4%) had Grade 3 or 4 increased lipase. In the pooled safety population, 10 out of 393 patients had Grade 3 or 4 increased lipase. FDA requested updated narratives for all patients with Grade 3 or higher increased lipase across the development program, these have been outlined in addition to FDA reviewer comments in Table 37. Following a review of the narratives, the risk for immune mediated pancreatitis does not appear elevated above what is known for the class.

**Table 37: Case Narratives of Grade 3 or Higher Lipase Elevation Within the Pooled Safety Population**

| Patient ID | Peak Lipase Value and Toxicity Grade | Patient Summary and FDA Reviewer Comments |
|---|---|---|
| Study INCMGA 0012-101 | | |
| (b) (6)<br>50 Years | 63 U/L (Day 168) | 50-year-old female with a diagnosis of metastatic breast cancer, had an incorrect ascertainment of Grade |

| Patient ID | Peak Lipase Value and Toxicity Grade | Patient Summary and FDA Reviewer Comments |
|---|---|---|
| Female | | 3 elevation in lipase based on normal range stated at 2.16 U/L. The normal ranges (8 – 80 U/L) was updated and the patient had no TEAEs reported.<br><br>*FDA Reviewer Comment: The patient had no laboratory evidence of lipase elevation, and no reports to suggest a clinical diagnosis of pancreatitis.* |
| (b) (6)<br>80 Years<br>Female | 1051 U/L (Day 533) | 80-year-old female with a diagnosis of MSI-H metastatic endometrial cancer who had normal lipase at baseline and received 16 retifanlimab infusions in total. On Day 505, she was noted to have Grade 3 elevation in lipase and amylase, with the concomitant Grade 1 TEAE of decreased appetite. On Day 533, she was noted to have asymptomatic Grade 3 elevation of LFT, leading to treatment interruption. The Applicant notes that the patient was treated with amoxicillin-clavulanic acid for a diagnosis of bronchitis (Day 519). She was hospitalized and treated with methylprednisone with improvement in liver function tests. The patient had no radiographic or clinical symptoms of pancreatitis. The patient's clinical course was further complicated with a diagnosis of septic spondylodiscitis (Day 550).<br><br>*FDA Reviewer Comments: The patient had no clinical evidence suggestive of a diagnosis of pancreatitis. The patient's LFT and lipase abnormalities responded to high-dose steroids. Her clinical course was subsequently complicated by culture positive septic spondylodiscitis, and she had stopped treatment due to the liver enzyme elevations.* |
| (b) (6)<br>58 years<br>Female | 5150 U/L (Day 106) | 58-year-old female with a diagnosis of metastatic MSI-H endometrial cancer who received 3 doses of retifanlimab prior to Grade 3 elevation of lipase. The patient's retifanlimab was interrupted on Day 58 and subsequently discontinued on Day 157. She had no reported TEAEs and received prednisone. The patient was reportedly asymptomatic and had an ultrasound assessment that excluded a diagnosis of pancreatitis. |

| Patient ID | Peak Lipase Value and Toxicity Grade | Patient Summary and FDA Reviewer Comments |
|---|---|---|
| | | *FDA Reviewer Comment: This patient had no clinical evidence of pancreatitis. Lipase elevation led to treatment discontinuation in this case and was included in the FDA analysis of immune-mediated adverse events.* |
| INCMGA 0012-201 (PODIUM-201) | | |
| (b) (6)<br>71 Years<br>Male | 1839 U/L (Day 254) | 71-year-old male with a diagnosis of metastatic MCC, with a known diagnosis of type II diabetes, received his last dose of retifanlimab on Day 225. He received an influenza vaccine (intramuscular) on Day 229. The patient subsequently complained of flu-like symptoms, nausea, and vomiting for 2 weeks. On Day 254, retifanlimab was interrupted due to elevated lipase. The patient was evaluated by gastroenterology with no evidence of pancreatitis. The patient was subsequently diagnosed with diabetic ketoacidosis (Day 284) requiring hospitalization and treatment with insulin. The patient had complete recovery of serum lipase and restarted treatment with retifanlimab on Day 309.<br><br>*FDA Reviewer Comment: FDA agrees with the Applicant's assessment that TEAEs of diabetic ketoacidosis, elevated serum lipase and serum amylase as related to retifanlimab. There was no clinical evidence suggestive of pancreatitis. Elevated serum lipase was included as a reason for treatment interruption in the retifanlimab USPI.* |
| (b) (6)<br>55 years<br>Male | 385 U/L (Day 29) | 55-year-old male with metastatic MCC, who had normal baseline lipase values and was hospitalized on Day 28 with CT evidence of pancreatitis. There was no radiographic evidence of gallstones, and the patient had no history of alcohol use. The patient discontinued treatment on Day 70.<br><br>*FDA Reviewer Comment: FDA disagrees with the Applicant's assessment that the TEAE of pancreatitis is not related to retifanlimab. Given the exclusion of alternative etiologies and temporal association, pancreatitis is possibly related to retifanlimab.* |

| Patient ID | Peak Lipase Value and Toxicity Grade | Patient Summary and FDA Reviewer Comments |
|---|---|---|
| | | *Pancreatitis has been added as the reason for permanent discontinuation to the retifanlimab USPI.* |
| (b) (6)<br>50 years<br>Female | 573 U/L (Day 197) | 50-year-old female with a diagnosis of metastatic MCC was noted to have Grade 3 elevation of lipase. He had complained of Grade 1 abdominal pain; however, no further intervention or investigations were reported. The patient had continued treatment with improvement in serum lipase levels. The patient subsequently discontinued treatment on Day 434 for hypophysitis.<br><br>*FDA Reviewer Comment: There is insufficient information to ascertain the etiology for the transient lipase elevation. Given that treatment was continued, with improvement in laboratory values and no deterioration of abdominal pain suggests an alternative etiology for lipase elevation.* |
| INCMGA 0012-202 | | |
| (b) (6)<br>44 Years<br>Female | 330 U/L (Day 85) | 44-year-old female with a diagnosis of metastatic MCC, with normal baseline lipase levels, experienced a Grade 3 elevation in lipase on Day 85. The patient received a total of four doses of retifanlimab and had evidence of disease progression prompting treatment discontinuation. No further lipase values or clinical follow up was performed.<br><br>*FDA Reviewer Comments: There were no symptoms suggestive of pancreatitis and the clinical course is complicated by evidence of disease progression. There is insufficient data to make a causality assessment.* |
| INCMGA 0012-203 | | |
| (b) (6)<br>83 Years<br>Male | 710 U/L (Day 139) | 83-year-old male with a diagnosis of metastatic urothelial cancer was admitted on Day 84 with Grade 3 elevation in creatinine. He was noted to have concomitant elevation in lipase (615 U/L) on the same day. There were no reported symptoms and no further diagnostic evaluations for pancreatitis. The patient was treated for acute kidney injury and discontinued treatment for elevated creatinine. No further lipase values are available after Day 139. |

| Patient ID | Peak Lipase Value and Toxicity Grade | Patient Summary and FDA Reviewer Comments |
|---|---|---|
| | | *FDA Reviewer Comment: There is insufficient data to make a causality assessment. The clinical course with acute kidney injury and site of disease confounds the lipase elevation, however there is no clear evidence of a concomitant clinical diagnosis of pancreatitis.* |
| (b) (6)<br>53 years<br>Male | 549 U/L (Day 60) | 53-year-old male with a diagnosis of metastatic renal cell cancer was identified with asymptomatic Grade 3 lipase elevation on Day 60. The patient continued treatment with complete resolution of lab abnormalities.<br><br>*FDA Reviewer Comment: There is no clinical evidence of pancreatitis.* |
| (b) (6)<br>60 years<br>Male | 528 U/L (Day 28) | 60-year-old male with a diagnosis of metastatic renal cell cancer was identified with asymptomatic Grade 3 lipase elevation. He had no admissions or evaluation for pancreatitis. He continued treatment with the lipase values returning to normal.<br><br>*FDA reviewer comment: There is no clinical evidence of pancreatitis.* |

Abbreviations: TEAE: Treatment Emergent Adverse Event, MSI-H: microsatellite instability-high; LFT: liver function test, MCC: Merkel cell cancer
Source: FDA analysis

**Vital Signs**

The Applicant's Position:

Vital signs measurements, including systolic blood pressure, diastolic blood pressure, pulse, respiration rate, and body temperature, were performed in all studies at screening and at Day 1 of each cycle at a minimum. Results demonstrate no meaningful effect of retifanlimab on vital signs parameters.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of vital signs submitted, with no clinically relevant changes or trends noted over time. FDA clarifies that two patients had recorded temperatures greater than 38.0C in PODIUM-201. Patient ID (b) (6) experienced a fever (Temp 38.9C) on an unscheduled visit on Study Day 111. This was recorded as a TEAE and led to drug interruption, which was included in the retifanlimab USPI. Patient ID (b) (6) had a localized infection noted on Day 50 and fever (Temp 38.2C) on Day 51, the retifanlimab dosing was not changed as a result of the fever.

**Electrocardiograms (ECGs) and QT**

The Applicant's Position:

As a monoclonal antibody, retifanlimab is not anticipated to cause QT prolongation. A thorough QT study was not performed, in accordance with ICH E14 Q&A (R3; 2015). A cardiac safety analysis showed that a large QT/QTc effect (> 20 milliseconds) can be excluded within the observed range of retifanlimab serum concentrations and, at the doses studied, retifanlimab did not have a relevant effect on cardiac conduction. Electrocardiograms were performed in each of the studies, and results available as of the respective data cutoff dates suggest no clinically relevant changes from baseline in the QTc interval and no meaningful effect of retifanlimab on ECG parameters.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. See FDA response in Section 6.2.1 for additional details.

**Immunogenicity**

The Applicant's Position:

In clinical studies of retifanlimab monotherapy, 11 of 640 participants (1.7%) were positive for treatment-emergent ADA to retifanlimab. There was no clinically significant impact on the PK profile of retifanlimab in these participants, and there was no apparent clinically meaningful impact of ADA on the incidence of infusion-related reactions or on the overall safety profile of retifanlimab.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. See FDA response in Section 6.3.1 for additional details.

### 8.2.5. Analysis of Submission-Specific Safety Issues

#### 8.2.5.1 Immune-related Adverse Events and Infusion-related Reactions

The Applicant's Position:

**Immune-related Adverse Events**

Immune-related events are anticipated with retifanlimab based on known class effects and mechanism of action, which enabled a predefined list of PTs to be analyzed across the retifanlimab development program. The analysis of irAEs was primarily based on the larger All Cancer 500 mg Q4W Population to sufficiently characterize rare irAEs. As anticipated, the most frequent irAE was hypothyroidism (9.5%), and the most frequent nonendocrine irAE was skin reactions (8.2%; Table 38). Most irAEs were Grade 1 or 2 in severity. The most frequent Grade 3 or higher irAE was hepatitis (2.5%). One participant had a fatal irAE (pneumonitis; PT of interstitial lung disease), which was assessed as not related to retifanlimab by the investigator and the Sponsor. Most irAEs were manageable according to established guidelines, based on the low incidence (4.5%) of irAEs leading to discontinuation of retifanlimab. The most frequent irAE leading to discontinuation of retifanlimab was hepatitis.

**Table 38: Immune-Related Adverse Events**

| | MCC (N = 105) | | All Cancer 500 mg Q4W (N = 440) | |
|---|---|---|---|---|
| **irAE, n (%)** | **All Grades** | **Grades ≥ 3** | **All Grades** | **Grades ≥ 3** |
| Participants with ≥ 1 irAE | 29 (27.6) | 10 (9.5) | 135 (30.7) | 37 (8.4) |
| **Endocrine irAEs** | | | | |
| Hypothyroidism | 9 (8.6) | 0 (0.0) | 42 (9.5) | 0 (0.0) |
| Hyperthyroidism | 5 (4.8) | 0 (0.0) | 24 (5.5) | 0 (0.0) |
| Adrenal insufficiency | 2 (1.9) | 1 (1.0) | 3 (0.7) | 2 (0.5) |
| Thyroiditis | 1 (1.0) | 0 (0.0) | 3 (0.7) | 0 (0.0) |
| Hypophysitis | 1 (1.0) | 0 (0.0) | 2 (0.5) | 0 (0.0) |
| Type 1 diabetes | 1 (1.0) | 1 (1.0) | 1 (0.2) | 1 (0.2) |
| **Nonendocrine irAEs** | | | | |
| Skin reactions | 6 (5.7) | 1 (1.0) | 36 (8.2) | 5 (1.1) |
| Hepatitis | 2 (1.9) | 1 (1.0) | 13 (3.0) | 11 (2.5) |
| Pneumonitis | 5 (4.8) | 2 (1.9) | 13 (3.0) | 5 (1.1) |
| Colitis | 2 (1.9) | 0 (0.0) | 7 (1.6) | 2 (0.5) |
| Nephritis | 0 (0.0) | 0 (0.0) | 6 (1.4) | 5 (1.1) |
| Myositis | 0 (0.0) | 0 (0.0) | 3 (0.7) | 1 (0.2) |
| Guillain-Barré Syndrome | 1 (1.0) | 1 (1.0) | 2 (0.5) | 1 (0.2) |
| Pancreatitis | 1 (1.0) | 1 (1.0) | 2 (0.5) | 2 (0.5) |
| Uveitis | 0 (0.0) | 0 (0.0) | 2 (0.5) | 0 (0.0) |
| **Other rare irAEs** | | | | |
| Musculoskeletal and connective tissue | 2 (1.9) | 1 (1.0) | 6 (1.4) | 2 (0.5) |
| Nervous system | 1 (1.0) | 1 (1.0) | 3 (0.7) | 1 (0.2) |
| Cardiac/vascular | 0 (0.0) | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| Hepatobiliary | 0 (0.0) | 0 (0.0) | 1 (0.2) | 1 (0.2) |
| Ocular | 0 (0.0) | 0 (0.0) | 1 (0.2) | 0 (0.0) |

Source: Module 2.7.4 Tables 22 and 23 and ISS Tables 3.2.2.3 and 3.2.6.3.

**Infusion-related Reactions**

Infusion-related reactions occurred in 25 participants (5.7%) in the All Cancer 500 mg Q4W Population, including 4 participants (3.8%) in the MCC Population. All infusion-related reactions were Grade 1 or 2 in severity with the exception of a single Grade 3 event in 1 participant (0.2%). Sponsor medical review determined this event was not an infusion-related reaction to retifanlimab based on the marked delay of onset (26 days following infusion). Infusion-related reactions led to retifanlimab infusion interruption and discontinuation in < 1% of participants (4/440 and 1/440 participants, respectively). Routine prophylaxis against infusion-related reactions is not required for retifanlimab.

The FDA's Assessment:

FDA agrees with the Applicant's cited incidence of irAEs and IRRs in PODIUM-201 and the pooled safety population. The majority of irAEs in the pooled safety database were either Grade 1 or 2 in severity. The common (≥1%) irAEs across the pooled safety population and the proportion of patients requiring systemic corticosteroids for each irAE is listed in Table 39. The incidence of irAE is consistent with other approved agents within this class and majority of non-endocrinopathy irAEs were managed with systemic corticosteroids.

**Table 39: Common (≥1%) irAE and Associated Systemic Corticosteroid Use Across the Pooled Safety Population**

| Immune-Related Adverse Event | Pooled Safety Population<br>Any Grade<br>N=440<br>N (%) | Proportion of patients with irAEs that Required Systemic Corticosteroids<br>N (%) |
|---|---|---|
| **Non-Endocrinopathy irAE** | | |
| Dermatitis | 36 (8) | 9 (25) |
| Hepatitis | 13 (3) | 11 (85) |
| Pneumonitis | 13 (3) | 10 (77) |
| Colitis | 7 (1.6) | 5 (71) |
| Nephritis | 7 (1.6) | 4 (57) |
| **Endocrinopathy irAE** | | |
| Hypothyroidism | 42 (10) | 1 (2.4) |
| Hyperthyroidism | 24 (6) | 3 (13) |

Abbreviation: irAE: immune-related adverse event
Source: FDA analysis

FDA disagrees with the Applicant's assessment that the cited fatal adverse event of pneumonitis was not related to retifanlimab. A summary of the patient narrative and FDA reviewer comment is listed in Table 40.

**Table 40: Patient Narrative of Fatal Interstitial Lung Disease**

| Patient ID | Patient Summary and FDA Reviewer Comments |
|---|---|
| Study INCMGA 0012-202 | |
| (b) (6)<br>76 Years<br>Male | 76-year-old male with a diagnosis of metastatic squamous cell cancer of the anal canal and a known diagnosis of cardiomyopathy, presented on Day 111 with a deterioration in his performance status. CT scan demonstrated a 'bilateral progressive interstitial pulmonary process' with a negative infective work-up. The patient was started on systemic corticosteroids. Retifanlimab was interrupted. The patient was readmitted on Day 139 with fever and altered mental status, systemic corticosteroids were continued with the addition of broad-spectrum antibiotics. Repeat CT imaging demonstrated 'worsening pulmonary infiltration' and the patient died on Day 147.<br><br>*FDA Reviewer Comment: FDA disagrees with the Applicant's assessment that the adverse event is attributable to underlying metastatic disease and concurrent pneumonia. Given the initial CT findings and the use of systemic corticosteroids, the fatal adverse event of 'interstitial lung disease' is possibly related to the use of retifanlimab.* (b) (4) |

Source: FDA Analysis

FDA adds that following the data cutoff date for safety in PODIUM-201 there was a reported case of Grade 4 biopsy-proven toxic epidermal necrolysis (TEN), which resulted in treatment discontinuation. The risks of TEN is known with this class of agent. There were no other reported cases within the development program, and the possible risks of TEN is included within the retifanlimab USPI.

FDA agrees with the Applicant's cited incidence of IRR in both PODIUM-201 and the pooled safety population. FDA clarifies that patients require monitoring for signs and symptoms of infusion-related reactions, and infusion prophylaxis should be guided by patients' prior medical history and systemic reaction to infusions.

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

The Applicant's Position:
Clinical outcome assessments were exploratory efficacy endpoints and are described in Section 8.1.2.

The FDA's Assessment:
FDA agrees with the Applicant's position. The analyses of PRO data were considered exploratory in nature and were not formally evaluated in PODIUM-201 because there was no pre-specified statistical testing procedure or alpha allocation for any PRO endpoints.

### 8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:
The possible effect of intrinsic factors, including demographic (age, sex, and race) and baseline characteristics (ECOG performance status, HIV status, renal impairment, and hepatic impairment) on the safety of retifanlimab were evaluated in the All Cancer 500 mg Q4W Population to provide a comprehensive risk assessment. Retifanlimab was generally well-tolerated in all participant subgroups with an acceptable safety profile that is consistent with the PD-(L)1 inhibitor class. These results align with the results of population PK analyses demonstrating no meaningful effect of demographic covariates on retifanlimab PK. Details on safety analyses by demographic subgroups are as follows.

***Age:*** In the All Cancer 500 mg Q4W Population, 59.3% were ≥ 65 years of age and 23.6% of participants were ≥ 75 years of age. Median durations of retifanlimab treatment for participants in the younger age subgroups were shorter than those of the older age subgroups. Overall, no clinically meaningful differences were observed in the frequency or severity of TEAEs or irAEs between participants < 65 years of age and those ≥ 65 years of age. Participants ≥ 75 years of age had higher frequencies of serious TEAEs, Grade 3 or higher TEAEs, and TEAEs leading to dose delay and discontinuation than participants who were < 75 years of age. There were few participants in the ≥ 85 years of age subgroup precluding meaningful comparisons.

***Sex:*** The All Cancer 500 mg Q4W Population was 43.2% male and 56.8% female. Median durations of retifanlimab treatment were similar in the 2 groups. Overall, the frequency and severity of TEAEs and irAEs was generally similar between male and female participants. A difference in irAEs in the All Cancer 500 mg Q4W Population is attributable to the higher incidence of hyperthyroidism and hypothyroidism in female participants (8.0% and 12.0%, respectively) than male participants (2.1% and 6.3%, respectively). There was no increase in the rate of serious, severe (≥ Grade 3), or fatal irAEs in female participants.

***Race:*** The All Cancer 500 mg Q4W Population was composed of 342 Caucasian participants (77.7%) and 98 non-Caucasian participants (22.3%). The median duration of retifanlimab treatment was similar for Caucasian participants and non-Caucasian participants. No clinically meaningful differences were observed in frequency or severity of TEAEs or irAEs.

The FDA's Assessment:
FDA generally agrees with the Applicant's assessment. FDA clarifies that there were insufficient patients in the pooled safety population with a prior diagnosis of HIV (N=10) or severe renal impairment (N=3) to allow for a comprehensive safety analysis in these subgroups. In the pooled safety population, patients with a baseline ECOG PS ≥1 had a higher incidence of SAEs (94/226 [42%] versus 55/214 [26%]), higher incidence of ≥ Grade 3 TEAEs (113/226 [50%] versus 70/214 [33%]), and fatal TEAEs (17/226 [8%] versus 6/214 [3%]) compared to patients with ECOG PS of 0 as expected in patients with a more favorable baseline performance status.

FDA notes that there is significant heterogeneity in the tumor types and prior treatment exposure in the pooled safety population, and the small sample size in the MCC population, which poses difficulties in ascertaining the differences in safety and tolerability in different subgroups exposed to retifanlimab.

FDA clarifies that due to the variation in collection of race and ethnicity in different regions, there are significant proportion of patients where race and ethnicity data is either unknown (11/440 [2.5%]) or not reported (63/440 [14%]), which prevents a comprehensive assessment of differences in safety by race and ethnicity.

The Applicant stated that the median durations of retifanlimab treatment for participants in the younger age subgroups were shorter than those of the older age subgroups. FDA does not agree with this statement.

### 8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**
The Applicant's Position: No human carcinogenicity studies were conducted.

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

**Human Reproduction and Pregnancy**
The Applicant's Position: Retifanlimab has not been studied in pregnant or lactating women.

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

**Pediatrics and Assessment of Effects on Growth**
The Applicant's Position: Not applicable.

The FDA's Assessment:
There were no pediatric patients enrolled in PODIUM-201. The Applicant was granted a full waiver for conducting pediatric studies, as the necessary studies are impossible or highly impracticable given the rarity of MCC in the pediatric population. In addition, a number of drugs in the same class have been evaluated in the pediatric population and have not demonstrated sufficient activity in patients with other tumor types to warrant further studies.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**
The Applicant's Position:
There are no human or animal data regarding overdose of retifanlimab. Treatment of overdose should consist of general supportive measures. The highest doses administered in clinical studies were 750 mg Q4W and 10 mg/kg Q2W. There is no known potential for abuse.

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

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**
The Applicant's Position:
Not applicable. Retifanlimab is a new molecular entity that is not approved in any region.

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

**Expectations on Safety in the Postmarket Setting**
The Applicant's Position:

Potential safety concerns beyond the risks observed in clinical studies of retifanlimab and described in product labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

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

### 8.2.11. Integrated Assessment of Safety

The Applicant's Position:
The primary evaluation of the safety of retifanlimab 500 mg Q4W is based on the 105 participants in the MCC Population. Safety data from the larger All Cancer 500 mg Q4W Population (N = 440) are supportive of the primary analysis and did not identify any potentially important risks that were not identified in the MCC Population. The safety database was sufficiently sized to thoroughly assess safety.

Overall, the safety data presented demonstrate that retifanlimab 500 mg Q4W is tolerable and has an acceptable safety profile that is predictable and manageable, with no unique immune-related toxicities. The majority of TEAEs in the MCC Population and the All Cancer 500 mg Q4W Population were Grade 1 or 2 in severity. Most of the frequent events were nonserious and did not lead to retifanlimab discontinuation. Treatment-emergent AEs leading to discontinuation occurred in 10.5% in the MCC Population and 10.7% in the All Cancer 500 mg Q4W Population, demonstrating the tolerability of retifanlimab. Treatment-related TEAEs leading to treatment discontinuation occurred in under 10% of participants in both populations. Results of subgroup analyses demonstrate that baseline characteristics do not affect the safety profile of retifanlimab. No clinically meaningful trends were observed in laboratory parameters.

The incidence and severity of class effects of irAEs were consistent with those of other PD-(L)1 inhibitors. The analysis of irAEs was primarily based on the larger All Cancer 500 mg Q4W Population to sufficiently characterize any rare irAEs. In the All Cancer 500 mg Q4W Population, irAEs occurred in 135 participants (30.7%) and Grade 3 or higher irAEs occurred in 37 participants (8.4%). As anticipated, the most frequent irAE was hypothyroidism (9.5%), and the most frequent nonendocrine irAE was skin reactions (8.2%). Most irAEs were Grade 1 or 2 in severity. The most frequent Grade 3 or higher irAE was hepatitis (2.5%). Overall, in terms of both frequency and severity, the profile of irAEs observed with retifanlimab appears to be consistent with published reports (Sise 2019, Wang 2017).Sise 2019, Wang 2017). One participant had a fatal irAE (pneumonitis), which was assessed as not related to retifanlimab by the investigator and the Sponsor. The low incidence of fatal irAEs is consistent with published data (Wang 2018). Most irAEs were manageable according to established guidelines (Brahmer 2021, Haanen 2017, NCCN 2021), based on the low incidence of irAEs leading to discontinuation of retifanlimab.

As with any therapeutic protein, retifanlimab may cause infusion-related reactions; however, routine preadministration prophylaxis is not required. Infusion-related reactions occurred in 25 participants (5.7%) in the All Cancer 500 mg Q4W Population, including 4 participants (3.8%) with MCC, 1 of whom had a Grade 3 infusion-related reaction that was managed with

treatment discontinuation. All other infusion-related reactions (All Cancer 500 mg Q4W Population) were Grade 1 or 2 and did not preclude subsequent dose administration. Notably, the incidence of infusion-related reactions for retifanlimab in participants with MCC is lower than the reported incidence for avelumab, which does require preadministration prophylaxis (3.8% vs 29.3%; D'Angelo 2021). The Q4W dose administration schedule for retifanlimab is also less burdensome than avelumab Q2W dose administration.

The FDA's Assessment:
FDA agrees that retifanlimab demonstrated an acceptable safety profile given the anti-tumor activity (generally) with manageable toxicities based on the safety data from 105 patients (including the 65 patients in the primary efficacy analysis) enrolled in PODIUM-201 and further supported by pooled safety data from 440 patients with varying tumor types that received the recommended therapeutic dose of retifanlimab (500 mg intravenously every 4 weeks). The most common adverse reactions (≥10%) in PODIUM-201 were fatigue, musculoskeletal pain, pruritus, diarrhea, rash, pyrexia, and nausea. The most common (≥2 patients) Grade 3 or 4 adverse reactions were musculoskeletal pain (3 patients), pneumonitis, neutropenia, anemia, lipase increased, amylase increased, alanine aminotransferase increased, arrhythmia, and hyponatremia (2 patients each).

FDA agrees that the pooled safety population was of a suitable size to assess the frequency of immune-related adverse events (irAEs). In the pooled safety population, the most common (≥2%) irAEs were hypothyroidism (10%), dermatitis (8%), hyperthyroidism (6%), hepatitis (3%), and pneumonitis (3%). The majority of patients with non-endocrine irAEs were treated with systemic corticosteroids, treatment interruptions, and discontinuations. Patients with endocrine irAEs were predominantly treated with hormone replacement therapy. FDA acknowledges that routine prophylaxis against IRR was not required in PODIUM-201, and there was one treatment discontinuation due to an IRR. FDA did not perform a systematic comparison between the rates of IRR in other development programs and that with retifanlimab. FDA disagrees with the use of selective comparisons across trials when assessing tolerability and convenience.

The cited frequency and severity of TEAEs and irAEs are consistent with the established safety profile seen with this class, with no current evidence to suggest a differential safety profile for retifanlimab.

# SUMMARY AND CONCLUSIONS

## 8.3. Statistical Issues

The FDA's Assessment:
No major statistical issues were identified that impacted the results or interpretation of the efficacy results from PODIUM-201. No inferential procedures were used to evaluate the single-arm study results. The efficacy evaluation was based on the magnitude of objective response rate and adequate duration of response.

## 8.4. Conclusions and Recommendations

The FDA's Assessment:

The results from PODIUM-201, a single-arm, open-label study, demonstrated a clinically meaningful response rate and durability of response in the intended population (n=65) with a safety profile (n=105) that is consistent with this class of drug. Due to the rarity of MCC and the small sample size enrolled, meaningful conclusions regarding subgroup analyses could not be made. Consistent with the demographics of MCC in the US, the majority of patients studied in PODIUM-201 were White; insufficient numbers of patients were studied to assess treatment effects across different racial/ethnic groups of patients. Confirmatory evidence of clinical benefit will be based on confirmation of response rate and duration of response data from 105 patients enrolled on PODIUM-201.

Based upon a favorable risk-benefit profile, the clinical and statistical reviewers recommend accelerated approval of retifanlimab for the following indication:

The treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC).

X X

Jiaxin Fan
Primary Statistical Reviewer

Joyce Cheng
Statistical Team Leader

X X

Vaibhav Kumar
Primary Clinical Reviewer

Leslie Doros
Clinical Team Leader

# 9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

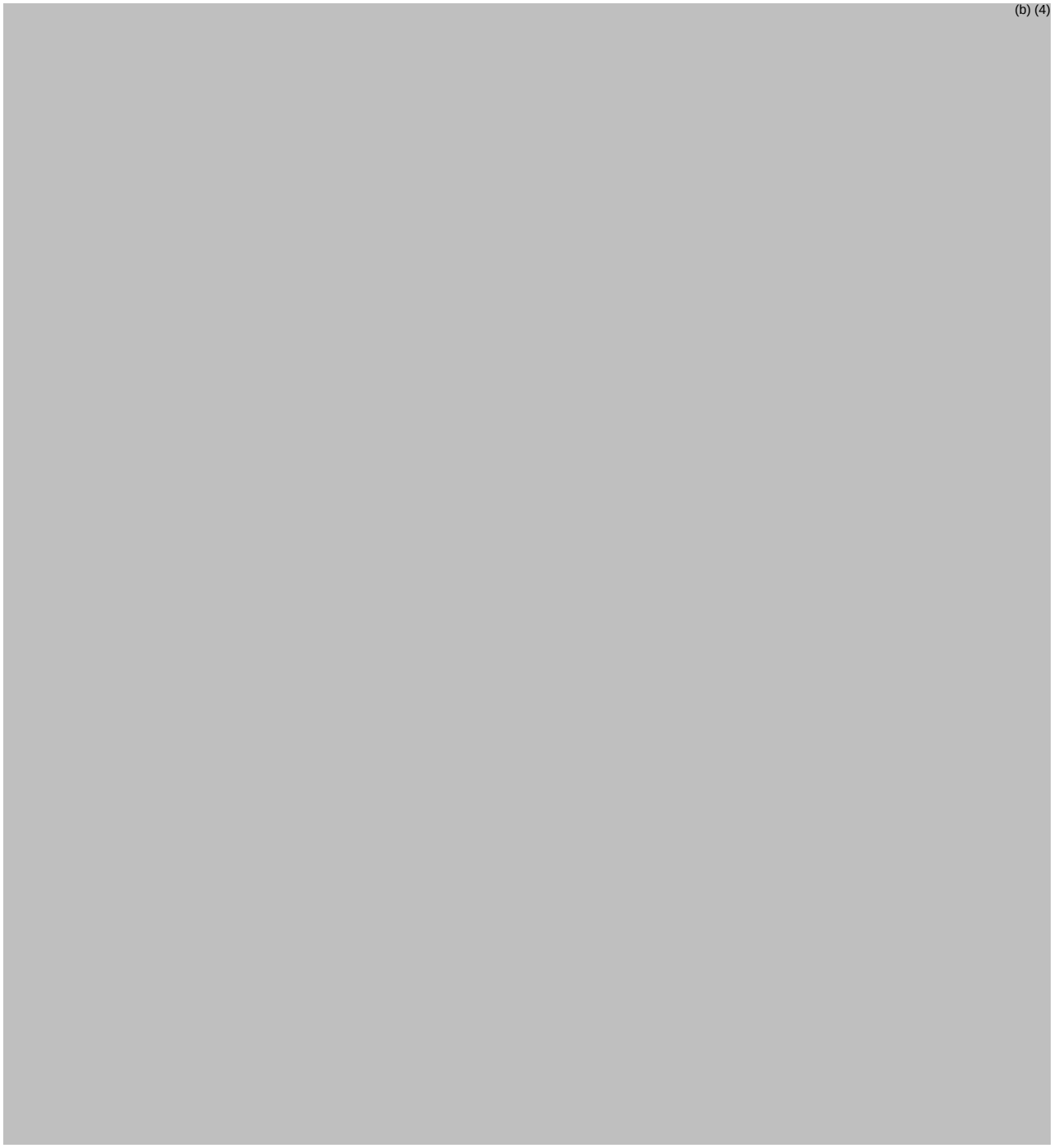
No advisory committee discussion were held for this BLA application. FDA has approved two drugs in the same class based on single-arm trials and no new issues regarding safety or efficacy were identified that would require discussion in an AC.

# 10 Pediatrics

The Applicant's Position:

Trials with safety or efficacy data pertaining to pediatric patients were not submitted with this BLA. The Sponsor requested a full waiver for all pediatric age groups from the requirements of PREA and FDARA.

(b) (4)



The FDA's Assessment:

(b) (4)

FDA issued a waiver of pediatric study requirement for this application because the necessary studies are impossible or highly impracticable due to the rarity of MCC in the pediatric population.

# 11 Labeling Recommendations

Data: The data provided in this BLA demonstrate the clinical benefit and safety of the use of retifanlimab for the treatment of adults and pediatric patients 12 years and older with metastatic or recurrent locally advanced MCC.

The Applicant's Position:
The proposed USPI is provided with this submission.

The FDA's Assessment: The proposed labeling submitted by the Applicant was revised to be consistent with current OOD labeling practices. The table below summarizes key changes.

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page


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

# 12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The safe use of retifanlimab can be adequately implemented in the postmarketing setting without issuing a REMS for this drug product. The product labeling for retifanlimab includes information on common and clinically significant adverse reactions that have been observed across the drug class, and trained oncologists have experience in the monitoring and management of these adverse reactions. Product labeling also includes dose modification and management guidelines for these events. Risk management based on labeling and routine pharmacovigilance is expected to ensure the safe use of retifanlimab.

# 13 Postmarketing Requirements and Commitment

The FDA's Assessment:
FDA issued the following post-marketing requirement:

Clinical PMR:

> 4412-1 Conduct a multicenter clinical trial intended to confirm the clinical benefit of retifanlimab in patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) who have not received prior systemic therapies for metastatic or recurrent locally advanced 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. Include an analysis of overall survival, when 70% of patients have died, or all patients have been followed for at least three years.

The proposed (Accelerated Approval) PMR will provide additional information regarding the durability of response following treatment with retifanlimab (in a larger population). This information will further characterize efficacy of retifanlimab and verify and describe the benefits (and provide additional safety data) intended to support an assessment for whether retifanlimab may receive regular approval.

| The following were evaluated and considered as part of FDA's review: | | Is a PMC/PMR needed? |
|---|---|---|
| □ | The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication. | _X_ Yes<br>__ No |
| □ | Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC? | __ Yes<br>_X_ No |
| □ | Other considerations (e.g.: PK/PD), if applicable: | __ Yes<br>_X_ No |

## 14 Division Director (DHOT) (NME ONLY)

X

# 15 Division Director (OCP)

X

# 16 Division Director (OB)

X

# 17 Division Director (Clinical)

I agree with the overall recommendations made by the review teams regarding the assessment of substantial evidence of effectiveness, risk/benefit, and the overall approvability of this application for this ultrarare malignancy. This approval will allow for the marketing of a third immune-checkpoint inhibitor in addition to two other drugs (avelumab and pembrolizumab) that have received accelerated approval for MCC. To support a future application for traditional approval, additional data to verify and describe the effect on response durability and longer-term safety will be obtained in the post-market setting as a PMR.

X

Steven Lemery

# 18 Office Director (or designated signatory authority)

*This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.*

X

Paul Kluetz

# 19 Appendices

## 19.1. References

The Applicant's References:

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## 19.2 Financial Discloser

The Applicant's Position:
All Investigators on Study 201, 101, 202 and 203 were assessed for significant equity or payments, proprietary interest and other compensation. None of the 971 Investigators had financial interests to disclose.

The FDA's Assessment:
FDA clarifies that the Applicant had submitted the list of all 971 Investigators and following a an information request, the Applicant confirmed that All investigators had submitted disclosure statements with no financial interests to disclose.

**Covered Clinical Study (Name and/or Number):* Studies 201, 101, 202, and 203**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 971 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in study: _____<br>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) 0 | | |
| Is an attachment provided with the | Yes ☐ | No ☐ (Request explanation |

| | | |
|---|---|---|
| reason: | | from Applicant) |

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

## 19.3 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

The nonclinical pharmacology/toxicology data to support this BLA was previously submitted under BLA 761209. No new information is provided in the current submission.

The FDA's Assessment:

See Section 5 for the FDA's assessment.

## 19.4 OCP Appendices (Technical documents supporting OCP recommendations)

### 19.4.1 Bioanalytical Review

Retifanlimab concentrations in human serum were quantified using validated enzyme-linked immunosorbent assay (ELISA) and Meso Scale Discovery-electrochemiluminescence (MSD-ECL) methods. The proposed pivotal clinical trial INCMGA 0012-201 used the MSD-ECL method. A summary of the bioanalytical method validation is shown below.

| | |
|---|---|
| **Bioanalytical method validation report name, amendments, and hyperlinks** | DMB-19.155, Validation of an Electrochemiluminescence Assay for the Quantitation of INCMGA00012 in Normal Human Serum |
| **Method description** | This was an MSD-ECL assay: This assay consisted of an ECL immunoassay, where recombinant human PD-1 was coated overnight onto an MSD standard plate (ECL capable). Retifanlimab was captured on the coated plate in the calibration standards, QC samples, controls, and other samples. After thorough washing of the wells to remove the unbound antibody, ruthenylated anti-retifanlimab (clone 4E3.1) was added to the wells so that the conjugate would bind to the captured retifanlimab. Excess unbound conjugate was removed by further washing of the wells followed by addition of MSD read buffer. The assay plate was then read using a MSD-ECL plate reader. The ECL signal generated relative to the amount of retifanlimab present in the calibration standards, QCs, controls, and other samples was tested. |
| **Materials used for standard calibration curve and concentration** | The reference material used for the standard calibration curve was retifanlimab interim reference standard (QC lab lot# QC15162) and was received from (b) (4) laboratory with concentration at 25.4 mg/mL. The validated assay range was initially tested at 200 to 10,000 ng/mL (using 100 ng/mL as the anchor point). During the validation, it was found that the method will be more robust if the assay was truncated to 200 ng/mL to 6000 ng/mL, with concentrations at 100, 7500, and 10,000 ng/mL to be set as anchor points. The calibration standard concentrations were determined to be 200, 500, 750, 1500, 3000, 5000, and 6000 ng/mL in human serum for routine use. |
| **Validated assay range** | The validated assay range was set at 200 ng/mL to 10000 ng/mL during validation and was truncated at 200 ng/mL to 10000 ng/mL for routine sample analysis use. |
| **Material used for QCs and concentration** | The reference material used for standard calibration curve was retifanlimab interim reference standard (QC lab lot# QC15162) and was received from (b) (4) laboratory with concentration at 25.4 mg/mL, and the QC sample concentrations were 200, 600, 2000, 7500, and 10000 ng/mL prepared in human serum in the validation. In routine use, the QC levels were at low (600 ng/mL), mid (2000 ng/mL), and high (4500 ng/mL) for routine use for the calibration range of 200 ng/mL to 6000 ng/mL. |
| **MRDs** | 25-fold |

| | | | |
|---|---|---|---|
| **Source and lot of reagents** | Pooled human serum was purchased from (b) (4) and was used in preparation calibration standards and QC samples in the validation.<br>The critical reagents are listed as the following:<br>Recombinant Human PD1/PDCD1 Protein, Lot Number: LC12JA2305, Source: (b) (4) (b) (4) Stored nominally at −20°C.<br>Retifanlimab, 4E3.1 Ru: Lot Number: SS#91171, Source: (b) (4) Stored nominally at −80°C.<br>Retifanlimab, 4E3.1 Ru: Lot Numbers: SS96143, SS114938, Source: (b) (4), Stored nominally at −80°C. | | |
| **Regression model and weighting** | The standard curve is obtained by fitting the experimental data from retifanlimab standards to a 4-PL fit with $1/Y^2$ weighting. | | |
| **Validation Parameters** | **Method Validation Summary** | | **Source Location** |
| **Standard calibration curve performance during accuracy and precision runs** | Number of standard calibrators from LLOQ of 200 ng/mL to ULOQ of 10000 ng/mL (excluding anchor point of 100 ng/mL) | 9 | DMB-19.155 Section 4.3.1 |
| | Number of standard calibrators from LLOQ of 200 ng/mL to ULOQ of 6000 ng/mL (excluding anchor points of 100, 7500, and 10000 ng/mL) | 7 | |
| | Cumulative accuracy (%RE) from LLOQ of 200 ng/mL to ULOQ of 10000 ng/mL (using 100 ng/mL as the anchor point) | −4.3% to 8.0% | DMB-19.155 Table 3 |
| | Cumulative precision (%CV) from LLOQ of 200 ng/mL to ULOQ of 10000 ng/mL (using 100 ng/mL as the anchor point) | 0.7% to 4.4% | |
| | Cumulative accuracy (%RE) from LLOQ of 200 ng/mL to ULOQ of 6000 ng/mL (using 100, 7500, and 10000 ng/mL as the anchor points) | −8.5% to 2.3% | DMB-19.155 Table 5 |
| | Cumulative precision (%CV) from LLOQ of 200 ng/mL to ULOQ of 6000 ng/mL (using 100, 7500, and 10000 ng/mL as the anchor points) | 1.0% to 5.1% | |
| **Performance of QCs during accuracy and precision runs** | Cumulative accuracy (%RE) of QCs for the calibration range of 200 ng/mL to 10000 ng/mL (using 100 ng/mL as the anchor point) | −3.3% to 10.1% | DMB-19.155 Table 10 |
| | Cumulative accuracy (%RE) of QCs for the calibration range of 200 ng/mL to 6000 ng/mL (using 100, 7500, and 10000 ng/mL as the anchor points) | −17.3% to −0.7% | DMB-19.155 Table 14 |

| Validation Parameters | Method Validation Summary | | Source Location |
|---|---|---|---|
| **Performance of QCs during accuracy and precision runs (continued)** | Interbatch %CV of QCs for the calibration range of 200 ng/mL to 10000 ng/mL (using 100 ng/mL as the anchor point) | 4.6% to 20.7% | DMB-19.155 Table 10 |
| | Interbatch %CV of QCs for the calibration range of 200 ng/mL to 6000 ng/mL (using 100, 7500, and 10000 ng/mL as the anchor points) | 4.9% to 15.2% | DMB-19.155 Table 14 |
| | Total Error of QCs for the calibration range of 200 ng/mL to 10000 ng/mL (using 100 ng/mL as the anchor point) | 7.4% to 30.8% | DMB-19.155 Table 11 |
| | Total Error of QCs for the calibration range of 200 ng/mL to 6000 ng/mL (using 100, 7500, and 10000 ng/mL as the anchor points) | 9.1% to 27.2% | DMB-19.155 Table 15 |
| **Selectivity and matrix effect** | The matrix effect was evaluated by spiking 10 individual lots of normal human serum in single replicate for each lot, at the blank (unspiked), LLOQ (200 ng/mL) and QCH (7500 ng/mL) concentrations initially. The acceptance criteria were as follows:<br>• Unspiked matrix must provide a response < LLOQ.<br>• The %RE of spiked samples must be ± 25.0 at the LLOQ, ± 20.0 at all other nominal concentrations for at least 80% of samples at each level.<br>The experiment failed to meet the acceptance criteria in the first attempt using the calibration range of 200 to 10,000 ng/mL. The experiment again failed on the repeat experiment. An investigation was initiated into the failure. The conclusion of the investigation was that the failure was not necessarily due to the assay not being selective, but rather that the calibration range may be too broad. After various troubleshooting experiments were conducted, the calibration range was truncated to a ULOQ of 6000 ng/mL. The selectivity experiment was thus repeated at the new QCH level of 4500 ng/mL, and this met the acceptance criteria. | | DMB-19.155 Section 4.6, Table 16, and Table 20 |
| **Interference and specificity** | Because there is no endogenous substance or coadministered medical agents in the planned clinical studies that might interfere with the accurate quantification of retifanlimab in human serum using this method, no interference and specificity test was conducted. The interference and specificity test will be added to the validation if required in the future. | | Not conducted |

| Validation Parameters | Method Validation Summary | Source Location |
|---|---|---|
| **Hemolysis effect** | The hemolysis effect was evaluated with spiked and unspiked (blank) samples. Hemolyzed serum samples were prepared at the LLOQ (200 ng/mL) and QCH (7500 ng/mL) in the validation. Acceptance criteria for the effect hemolyzed were as follows:<br>• Unspiked matrix must provide a response < LLOQ.<br>• The %RE of spiked samples must be ± 25% at the LLOQ, ± 20% at all other nominal concentrations for at least 80% of samples at each level.<br>The hemolysis of the spiked samples did not meet the acceptance criteria in the original attempt and in a repeat experiment attempted. However, after a new preparation of the hemolysis samples, the results from both the initial experiment and a confirmation experiment met the acceptance criteria. | DMB-19.155 Section 4.7, Table 24, and Table 25 |
| **Lipemic effect** | The lipemic effect was evaluated with spiked and unspiked (blank) samples. Lipemic serum samples were prepared at the LLOQ (200 ng/mL) and QCH (7500 ng/mL) in the first validation attempt. However, the lipemic effect did not meet the acceptance criteria in the original attempt and in a repeat experiment attempted. A new preparation of QC samples in lipemic serum were tested, and the results did not meet the predefined acceptance criteria, in addition, after the full investigation was complete and the calibration range truncated to 200 to 6000 ng/mL, the lipemic experiment was repeated at the new QCH level. It again failed to meet the acceptance criteria. The validation experiment for lipemic was thereby considered failed. Clinical samples identified as lipemic will either not be analyzed or analyzed for information only but the data will not be reported as numeric values in the concentration data table. | DMB-19.155 Section 4.7 and Table 26 through Table 31 |
| **Dilution linearity and hook effect** | Samples spiked with retifanlimab at 100 × ULOQ and diluted at a maximum of 1600-fold before analysis. The results met the acceptance criteria. Therefore, in this method, study samples may be diluted 1600-fold to extend the calibration range.<br>To test the hook effect of the assay, a high concentration stock solution was prepared at 100 × ULOQ undiluted and diluted at 10-, 100-, 200-, 400-, 800-, and 1600-fold to test the dilution linearity of the method. The following predefined acceptance criteria were met:<br>• The hook effect samples must be above the ULOQ.<br>• The samples diluted within the calibration range must be within %RE ± 20% of nominal with %CV of final concentrations ≤ 20%, and therefore, it is concluded that no hook effect occurs. | DMB-19.155 Section 4.8 and Table 32 |
| **Bench-top/process stability** | Retifanlimab at LQC level (600 ng/mL) and at HQC level (7500 ng/mL) in human serum stored at ambient temperature at both 21 hours before analysis. The results showed that retifanlimab in human serum is stable for at least 21 hours at ambient temperature. | DMB-19.155 Section 5.1 and Table 33 |

| Validation Parameters | Method Validation Summary | Source Location |
|---|---|---|
| **Freeze-thaw stability** | The samples of retifanlimab at LQC level (600 ng/mL) and at HQC level (4500 ng/mL) in human serum were subjected to 14 freeze-thaw cycles from −80°C prior analysis, and the results met the acceptance criteria. Therefore, retifanlimab in human serum is stable for at least 14 freeze-thaw cycles. | DMB-19.155 Section 12.1 and Table 40 |
| **Long-term storage** | Retifanlimab in human serum is verified to be stable for 664 days stored at −80°C and for 28 days at −20°C. Additional long-term storage stability tests at −80°C are ongoing. | DMB-19.155 Sections 12.2 and 12.3; Table 42 and Table 43 |
| **Parallelism** | Parallelism was not tested as retifanlimab is not an endogenous compound. In addition, mAb therapies, such as retifanlimab, are considered to be low risk for unknown interference by ADA, soluble ligands, etc which would only be identified via assessment of parallelism in incurred study samples. Further, demonstration of parallelism in a subset of incurred samples does not exclude the possibility of interference in another subset of samples. Given the low incidence of ADA, low levels of circulating soluble PD-1, and the observation that no significant alterations of PK profiles were observed for individual PK profiles, the Sponsor does not feel there is significant enough risk to require a parallelism assessment. | Not applicable |
| **Carryover** | Carryover was usually investigated in the chromatography-based assays, where the carryover is accessed from one injection to the next. This method is an LBA assay method and thus the carryover experiment was not conducted. | Not applicable |

Note: The section and table numbers in the above summary of bioanalytical method refer to the corresponding sections and tables in the bioanalytical method validation report (DMB-19.155), rather than the current review.

## 19.4.2 Population PK Analysis

### 19.4.2.1 Executive Summary

The FDA's Assessment:

Population PK analysis was conducted by the applicant and evaluated by the reviewer. The PK of retifanlimab was characterized by a two-compartment model with time-dependent reduction in clearance.

The population PK model described the observed data reasonably well. It was adequate to predict individual PK estimates for subsequent E-R analysis.

### 19.4.2.2 PPK Assessment Summary

The Applicant's Position:

| General Information | |
|---|---|
| Objectives of PPK Analysis | • To describe the PK of retifanlimab in patients across different tumor types enrolled across Studies 101, 104, 201, 202, and 203. |

| | | |
|---|---|---|
| | | • To identify predictors of exposure to the drug (demographics, laboratory values, disease status, and concomitant medications) and to identify subpopulations with altered PK.<br>• To estimate the IIV of retifanlimab PK.<br>• To predict a clinical dose for adolescent MCC patients. |
| Study Included | | Studies 101, 104, 201, 202, and 203. |
| Dose(s) Included | | Body weight–based dosing with Q2W, Q3W, and Q4W schedules at doses of 1 mg/kg, 3 mg/kg, or 10 mg/kg or flat dosing with 375 mg Q3W, 500 mg Q4W, or 750 mg Q4W |
| Population Included | | Cancer patients |
| Population Characteristics (Table 41) | General | The pooled population was 59.8% female, had a median age of 65 years (range: 18-94 years), and was primarily White/Caucasian (80.1%). The median body weight and BMI were 72.0 kg (range: 35.0-133 kg) and 26.1 kg/m$^2$ (range: 13.5 48.7 kg/m$^2$), respectively. |
| | Organ Impairment | Hepatic (NCI ODWG hepatic impairment category): 555 (87.5%) normal, 78 (12.3%) mild impairment, 1 (0.2%) unknown.<br>Renal (impairment classification by MDRD equation): 200 (31.5%) normal, 277 (43.7%) mild impairment, 142 (22.4%) moderate impairment, 4 (0.6%) severe impairment, 11 (1.7%) unknown. |
| | Pediatrics (if any) | No pediatric patients enrolled |
| No. of Patients, PK Samples, and BLQ | | In total, 7787 samples from 634 participants.<br>Pre-dose BLQ: 617 (7.9%)<br>Post-dose BLQ: imputed as half of the BLQ value and included in the analysis |
| Sampling Schedule | Rich Sampling | Studies 101 and 104 |
| | Sparse Sampling | Sparse samples were collected in Studies 201,202, and 203. Rich and sparse sampling approaches were used in Studies 101 and 104. |
| Covariates Evaluated | Static | Age, sex, ethnicity, race, albumin, AST, ALP, bilirubin, CrCl, renal function classification by MDRD equation, hepatic function classification by NCI standard, tumor type, DP produced by the P1 or P2 process, Infusion time 60 minutes vs 30 minutes and concomitant medications |
| | Time-varying | *Body weight, tumor burden and ECOG performance status* |

| **Final Model** | **Summary** | **Acceptability [FDA's comments]** |
|---|---|---|
| Software and Version | NONMEM, v7.5 | Yes |
| Model Structure | Two-compartment model with linear and time-varying clearance | Yes |
| Model Parameter Estimates | Table 42 | Yes |
| Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap) | All of the estimated fixed- and random-effect parameters were estimated with good precision. | Yes. High eta-shrinkage was observed for Vp and Imax, the estimates of covariate effect on these two parameters may not be reliable. However, the uncertainty in the effect of these covariates is not likely to impact post-hoc exposures used in the E-R analysis. |
| BLQ for Parameter Accuracy | Not applicable | Yes. Prior to first dose BLQ was excluded and post dose |

| | | |
|---|---|---|
| | | BLQ was imputed as half of the LLOQ. |
| GOF, VPC | Figure 1212,<br><br>Figure 1313 | Yes. No apparent bias was observed in the overall model fit. VPC showed that majority of the observations fell within the 90% prediction interval (PI), and median of the PI tracked the median of the observations. |
| Significant Covariates and Clinical Relevance | Figure 1414<br>CL:<br>- Positive factors: weight, tumor burden, ECOG status, NSCLC.<br>- Negative factors: female, albumin<br>Vc:<br>- Positive factors: body weight<br>Negative factors: female, albumin | Yes. None were likely to have clinically meaningful impact on exposure. |

(b) (4)

| **Labeling Language** | **Description** | **Acceptability [FDA's comments]** |
|---|---|---|
| 12.3 PK | PK characteristics and PK in specific populations | Yes |

**Table 41: Summary of Baseline Characteristics and Laboratory Values in the Dataset**

| | Retifanlimab Study Number | | | | | |
|---|---|---|---|---|---|---|
| **Participant Characteristic** | **101 (N = 311)** | **104 (N = 6)** | **201 (N = 102)** | **202 (N = 94)** | **203 (N = 121)** | **Pooled (N = 634)** |
| Number of PK samples | 6113 | 70 | 549 | 391 | 664 | 7787 |
| Average no. of PK samples | 19.7 | 11.7 | 5.4 | 4.2 | 5.5 | 12.3 |
| Dose, n (%) | | | | | | |
| 1 mg/kg | 3 (1.0) | 0 | 0 | 0 | 0 | 3 (0.5) |
| 3 mg/kg | 154 (49.5) | 0 | 0 | 0 | 0 | 154 (24.3) |
| 10 mg/kg | 14 (4.5) | 0 | 0 | 0 | 0 | 14 (2.2) |
| 375 mg | 15 (4.8) | 0 | 0 | 0 | 0 | 15 (2.4) |
| 500 mg | 110 (35.4) | 6 (100) | 102 (100) | 94 (100) | 121 (100) | 433 (68.3) |
| 750 mg | 15 (4.8) | 0 | 0 | 0 | 0 | 15 (2.4) |
| Dose frequency, n (%) | | | | | | |
| Q2W | 155 (49.8) | 0 | 0 | 0 | 0 | 155 (24.4) |
| Q3W | 15 (4.8) | 0 | 0 | 0 | 0 | 15 (2.4) |
| Q4W | 141 (45.3) | 6 (100) | 102 (100) | 94 (100) | 121 (100) | 464 (73.2) |
| Treatment, n (%) | | | | | | |
| 1 mg/kg Q2W | 3 (1.0) | 0 | 0 | 0 | 0 | 3 (0.5) |
| 3 mg/kg Q2W | 144 (46.3) | 0 | 0 | 0 | 0 | 144 (22.7) |
| 10 mg/kg Q2W | 8 (2.6) | 0 | 0 | 0 | 0 | 8 (1.3) |
| 3 mg/kg Q4W | 10 (3.2) | 0 | 0 | 0 | 0 | 10 (1.6) |

| Participant Characteristic | Retifanlimab Study Number | | | | | |
|---|---|---|---|---|---|---|
| | 101 (N = 311) | 104 (N = 6) | 201 (N = 102) | 202 (N = 94) | 203 (N = 121) | Pooled (N = 634) |
| 10 mg/kg Q4W | 6 (1.9) | 0 | 0 | 0 | 0 | 6 (0.9) |
| 375 mg Q3W | 15 (4.8) | 0 | 0 | 0 | 0 | 15 (2.4) |
| 500 mg Q4W | 110 (35.4) | 6 (100) | 102 (100) | 94 (100) | 121 (100) | 433 (68.3) |
| 750 mg Q4W | 15 (4.8) | 0 | 0 | 0 | 0 | 15 (2.4) |
| Infusion time (min), n (%) | | | | | | |
| 30 min | 0 | 0 | 0 | 0 | 121 (100) | 121 (19.1) |
| 60 min | 311 (100) | 6 (100) | 102 (100) | 94 (100) | 0 | 513 (80.9) |
| DP group, n (%) | | | | | | |
| P1 | 311 (100) | 6 (100) | 102 (100) | 94 (100) | 69 (57.0) | 582 (91.8) |
| P2 | 0 | 0 | 0 | 0 | 52 (43.0) | 52 (8.2) |
| Cancer type, n (%) | | | | | | |
| SCAC | 0 | 0 | 0 | 94 (100) | 0 | 94 (14.8) |
| MCC | 0 | 0 | 102 (100) | 0 | 0 | 102 (16.1) |
| NSCLC | 37 (11.9) | 0 | 0 | 0 | 23 (19.0) | 60 (9.5) |
| EC | 131 (42.1) | 3 (50.0) | 0 | 0 | 0 | 134 (21.1) |
| Other | 143 (46.0) | 3 (50.0) | 0 | 0 | 98 (81.0) | 244 (38.5) |
| HIV status, n (%) | | | | | | |
| Positive | 0 | 0 | 1 (1.0) | 9 (9.6) | 0 | 10 (1.6) |
| Negative/unknown | 311 (100) | 6 (100) | 101 (99.0) | 85 (90.4) | 121 (100) | 624 (98.4) |
| Age (years) | | | | | | |
| n | 311 | 6 | 102 | 94 | 121 | 634 |
| Mean (STD) | 59.9 (13.4) | 62.3 (9.46) | 70.4 (10.6) | 62.1 (11.4) | 68.3 (11.4) | 63.5 (13.0) |
| Median | 62.0 | 67.0 | 71.0 | 64.0 | 70.0 | 65.0 |
| Min, max | 18.0, 88.0 | 46.0, 71.0 | 38.0, 90.0 | 37.0, 94.0 | 38.0, 92.0 | 18.0, 94.0 |
| Weight (kg) | | | | | | |
| n | 311 | 6 | 102 | 94 | 121 | 634 |
| Mean (STD) | 72.7 (18.3) | 54.6 (9.05) | 83.0 (18.6) | 71.5 (16.4) | 73.3 (14.7) | 74.1 (17.8) |
| Median | 69.0 | 55.2 | 83.0 | 70.0 | 74.0 | 72.0 |
| Min, max | 35.0, 133 | 43.9, 67.2 | 48.8, 127 | 41.8, 110 | 36.0, 115 | 35.0, 133 |
| BMI ($kg/m^2$) | | | | | | |
| n | 311 | 6 | 102 | 94 | 121 | 634 |
| Mean (STD) | 26.9 (6.24) | 22.5 (4.51) | 28.7 (5.05) | 25.4 (4.96) | 26.0 (4.78) | 26.7 (5.69) |
| Median | 25.9 | 22.3 | 28.0 | 25.1 | 25.5 | 26.1 |
| Min, max | 13.5, 48.7 | 16.9, 29.5 | 18.7, 45.7 | 17.1, 43.7 | 16.2, 37.6 | 13.5, 48.7 |
| Sex, n (%) | | | | | | |
| Male | 73 (23.5) | 0 | 69 (67.6) | 33 (35.1) | 80 (66.1) | 255 (40.2) |
| Female | 238 (76.5) | 6 (100) | 33 (32.4) | 61 (64.9) | 41 (33.9) | 379 (59.8) |
| Race, n (%) | | | | | | |
| White/Caucasian | 245 (78.8) | 0 | 81 (79.4) | 72 (76.6) | 110 (90.9) | 508 (80.1) |
| Black/African American | 17 (5.5) | 0 | 0 | 1 (1.1) | 0 | 18 (2.8) |
| Asian | 15 (4.8) | 6 (100) | 1 (1.0) | 0 | 1 (0.8) | 23 (3.6) |
| Other | 33 (10.6) | 0 | 20 (19.6) | 15 (16.0) | 6 (5.0) | 74 (11.7) |
| Unknown | 1 (0.3) | 0 | 0 | 6 (6.4) | 4 (3.3) | 11 (1.7) |
| Ethnicity, n (%) | | | | | | |
| Hispanic or Latino | 17 (5.5) | 0 | 0 | 4 (4.3) | 5 (4.1) | 26 (4.1) |
| Not Hispanic or Latino | 249 (80.1) | 0 | 79 (77.5) | 49 (52.1) | 93 (76.9) | 470 (74.1) |
| Unknown | 45 (14.5) | 6 (100) | 23 (22.5) | 41 (43.6) | 23 (19.0) | 138 (21.8) |
| ECOG performance status, n (%) | | | | | | |
| 0 | 97 (31.2) | 5 (83.3) | 73 (71.6) | 39 (41.5) | 45 (37.2) | 259 (40.9) |
| 1 | 209 (67.2) | 1 (16.7) | 29 (28.4) | 55 (58.5) | 76 (62.8) | 370 (58.4) |

| Participant Characteristic | Retifanlimab Study Number | | | | | |
|---|---|---|---|---|---|---|
| | 101 (N = 311) | 104 (N = 6) | 201 (N = 102) | 202 (N = 94) | 203 (N = 121) | Pooled (N = 634) |
| 2 | 4 (1.3) | 0 | 0 | 0 | 0 | 4 (0.6) |
| Unknown | 1 (0.3) | 0 | 0 | 0 | 0 | 1 (0.2) |
| Tumor burden (sum of the target lesion diameters), mm | | | | | | |
| n | 311 | 6 | 102 | 94 | 120 | 633 |
| nmiss | 0 | 0 | 0 | 0 | 1 | 1 |
| Mean (STD) | 81.3 (58.8) | 59.0 (46.8) | 62.4 (49.8) | 73.1 (51.4) | 82.8 (60.6) | 77.1 (57.0) |
| Median | 62.0 | 41.5 | 51.0 | 58.0 | 68.0 | 60.0 |
| Min, max | 10.0, 315 | 15.0, 142 | 12.0, 236 | 14.0, 272 | 10.0, 360 | 10.0, 360 |
| ADA status, n (%) | | | | | | |
| Negative | 305 (98.1) | 6 (100) | 99 (97.1) | 85 (90.4) | 114 (94.2) | 609 (96.1) |
| Positive | 3 (1.0) | 0 | 2 (2.0) | 3 (3.2) | 1 (0.8) | 9 (1.4) |
| Unknown | 3 (1.0) | 0 | 1 (1.0) | 6 (6.4) | 6 (5.0) | 16 (2.5) |
| Corticosteroids, n (%) | | | | | | |
| Not used | 253 (81.4) | 5 (83.3) | 92 (90.2) | 80 (85.1) | 106 (87.6) | 536 (84.5) |
| Used | 58 (18.6) | 1 (16.7) | 10 (9.8) | 14 (14.9) | 15 (12.4) | 98 (15.5) |
| Serum albumin (g/L) | | | | | | |
| n | 311 | 6 | 102 | 94 | 121 | 634 |
| Mean (STD) | 38.3 (5.97) | 40.2 (2.64) | 40.4 (3.75) | 39.2 (5.10) | 40.6 (5.51) | 39.2 (5.51) |
| Median | 39.0 | 40.0 | 41.2 | 40.0 | 42.0 | 40.0 |
| Min, max | 20.9, 54.4 | 37.0, 44.0 | 28.0, 48.0 | 23.0, 48.0 | 26.0, 51.0 | 20.9, 54.4 |
| Serum ALP (U/L) | | | | | | |
| n | 311 | 6 | 102 | 94 | 121 | 634 |
| Mean (STD) | 121 (101) | 245 (90.0) | 80.3 (68.0) | 118 (91.8) | 116 (68.1) | 114 (90.8) |
| Median | 94.0 | 248 | 71.5 | 89.0 | 94.4 | 88.0 |
| Min, max | 33.0, 988 | 150, 336 | 36.0, 722 | 48.0, 596 | 36.0, 425 | 33.0, 988 |
| Serum AST (U/L) | | | | | | |
| n | 311 | 6 | 102 | 94 | 121 | 634 |
| Mean (STD) | 27.2 (19.2) | 21.7 (5.05) | 27.5 (15.4) | 28.9 (18.7) | 20.7 (10.9) | 26.2 (17.3) |
| Median | 22.0 | 22.0 | 22.0 | 24.0 | 18.0 | 21.0 |
| Min, max | 7.00, 200 | 15.0, 28.0 | 9.00, 87.0 | 8.00, 108 | 5.00, 80.0 | 5.00, 200 |
| Serum total bilirubin (µM) | | | | | | |
| n | 311 | 6 | 102 | 94 | 121 | 634 |
| Mean (STD) | 7.80 (4.29) | 9.69 (1.77) | 10.1 (4.60) | 7.42 (3.81) | 8.84 (4.28) | 8.33 (4.34) |
| Median | 7.00 | 10.3 | 9.25 | 6.92 | 8.00 | 7.52 |
| Min, max | 0.00, 30.8 | 6.84, 12.0 | 2.70, 30.7 | 2.00, 25.0 | 1.71, 24.6 | 0.00, 30.8 |
| Estimated ClCr (mL/min; Cockcroft-Gault) | | | | | | |
| n | 311 | 6 | 102 | 94 | 121 | 634 |
| Mean (STD) | 88.3 (38.2) | 65.5 (14.6) | 89.8 (34.8) | 88.4 (35.3) | 75.0 (30.8) | 85.8 (36.1) |
| Median | 81.1 | 64.6 | 83.7 | 82.3 | 68.0 | 79.5 |
| Min, max | 20.5, 243 | 51.8, 92.3 | 43.9, 205 | 30.2, 233 | 28.2, 195 | 20.5, 243 |
| Estimated GFR (mL/min/1.73 $m^2$; MDRD equation) | | | | | | |
| n | 310 | 6 | 102 | 88 | 117 | 623 |
| nmiss | 1 | 0 | 0 | 6 | 4 | 11 |
| Mean (STD) | 79.6 (27.9) | 78.2 (16.6) | 81.0 (20.9) | 83.9 (27.1) | 75.0 (27.2) | 79.5 (26.6) |
| Median | 77.5 | 76.5 | 81.0 | 80.5 | 74.0 | 78.0 |
| Min, max | 26.0, 203 | 62.0, 108 | 35.0, 153 | 29.0, 171 | 26.0, 169 | 26.0, 203 |
| NCI ODWG hepatic impairment category, n (%) | | | | | | |
| Normal | 273 (87.8) | 6 (100) | 88 (86.3) | 76 (80.9) | 112 (92.6) | 555 (87.5) |
| Mild | 38 (12.2) | 0 | 14 (13.7) | 17 (18.1) | 9 (7.4) | 78 (12.3) |
| Unknown | 0 | 0 | 0 | 1 (1.1) | 0 | 1 (0.2) |

| Participant Characteristic | Retifanlimab Study Number | | | | | |
|---|---|---|---|---|---|---|
| | 101 (N = 311) | 104 (N = 6) | 201 (N = 102) | 202 (N = 94) | 203 (N = 121) | Pooled (N = 634) |
| Renal impairment classification by MDRD equation, n (%) | | | | | | |
| Normal | 107 (34.4) | 1 (16.7) | 27 (26.5) | 35 (37.2) | 30 (24.8) | 200 (31.5) |
| Mild | 128 (41.2) | 5 (83.3) | 61 (59.8) | 35 (37.2) | 48 (39.7) | 277 (43.7) |
| Moderate | 73 (23.5) | 0 | 14 (13.7) | 17 (18.1) | 38 (31.4) | 142 (22.4) |
| Severe | 2 (0.6) | 0 | 0 | 1 (1.1) | 1 (0.8) | 4 (0.6) |
| Unknown | 1 (0.3) | 0 | 0 | 6 (6.4) | 4 (3.3) | 11 (1.7) |

## Table 42: Parameter Estimates and SE from Final Population PK Model

| Parameter | Population Mean | Final Parameter Estimate | | | Bootstrap | | |
|---|---|---|---|---|---|---|---|
| | | %RSE | 95% CI | IIV | Median | 95% CI | IIV |
| CL (L/h) | 0.0122 | 1.77 | 0.0118, 0.0126 | — | 0.0122 | 0.0117, 0.0126 | — |
| $V_c$ (L) | 3.76 | 1.37 | 3.66, 3.86 | — | 3.76 | 3.67, 3.86 | — |
| Q (L/h) | 0.0285 | 8.07 | 0.0240, 0.0330 | — | 0.0284 | 0.0236, 0.0330 | — |
| $V_p$ (L) | 2.64 | 3.37 | 2.47, 2.81 | — | 2.63 | 2.47, 2.83 | — |
| $I_{max}$ | −0.232 | 10.1 | −0.278, −0.186 | — | −0.232 | −0.294, −0.177 | — |
| $T_{50}$ (day) | 86.2 | 5.28 | 77.3, 95.1 | — | 86.4 | 78.2, 98.9 | — |
| Hill coefficient | 2.61 | 9.35 | 2.13, 3.09 | — | 2.63 | 1.99, 3.22 | — |
| Body weight (median = 72 kg) on $V_c$ | 0.401 | 8.88 | 0.331, 0.471 | — | 0.400 | 0.327, 0.472 | — |
| Body weight (median = 72 kg) on CL | 0.553 | 8.82 | 0.457, 0.649 | — | 0.553 | 0.459, 0.642 | — |
| Albumin (median = 40 g/L) on CL | −0.854 | 11.1 | −1.04, −0.668 | — | −0.858 | −1.03, −0.678 | — |
| Sex (female) on $V_c$ | −0.153 | 9.48 | −0.181, −0.125 | — | −0.153 | −0.182, −0.123 | — |
| Albumin (median = 40 g/L) on $V_c$ | −0.390 | 15.5 | −0.509, −0.271 | — | −0.393 | −0.522, −0.273 | — |
| Tumor burden (median tumor diameter = 60 mm) on CL | 0.0416 | 26.9 | 0.0196, 0.0636 | — | 0.0423 | 0.0188, 0.0651 | — |
| ECOG (> 0 vs = 0) on CL | 0.0534 | 24.3 | 0.0279, 0.0789 | — | 0.0541 | 0.0280, 0.0803 | — |
| Body weight (median = 72 kg) on $V_p$ | 0.470 | 25.1 | 0.239, 0.701 | — | 0.476 | 0.227, 0.702 | — |
| EC vs other on $I_{max}$ | 0.664 | 18.7 | 0.421, 0.907 | — | 0.655 | 0.328, 1.15 | — |
| NSCLC on CL | 0.165 | 31.8 | 0.0623, 0.268 | — | 0.165 | 0.0708, 0.277 | — |
| STD ($I_{max}$) | 0.106 | 16.2 | 0.0723, 0.140 | 0.326 | 0.106 | 0.0704, 0.148 | 0.326 |
| Correlated ($I_{max}$, CL) | −0.0511 | 18.4 | −0.0695, −0.0327 | −0.500 | −0.0512 | −0.0715, −0.0330 | −0.502 |
| IIV (CL) | 0.0984 | 8.58 | 0.0819, 0.115 | 31.4% | 0.0979 | 0.0831, 0.117 | 31.3% |
| Correlated ($I_{max}$, $V_c$) | 0.00 | — | — | 0 | 0 | — | |
| Correlated (CL, $V_c$) | 0.0192 | 14.1 | 0.0139, 0.0245 | 0.343 | 0.0193 | 0.0135, 0.0246 | 0.346 |
| IIV ($V_c$) | 0.0319 | 7.62 | 0.0271, 0.0367 | 17.9% | 0.0317 | 0.0268, 0.0367 | 17.8% |
| Correlated ($I_{max}$, $V_p$) | 0 | — | — | 0.00 | 0 | — | — |
| Correlated (CL, $V_p$) | 0 | — | — | 0.00 | 0 | — | — |
| Correlated ($V_c$, $V_p$) | 0.0178 | 30.0 | 0.00733, 0.0283 | 0.281 | 0.0177 | 0.00753, 0.0286 | 0.282 |
| IIV ($V_p$) | 0.126 | 20.3 | 0.0758, 0.176 | 35.5% | 0.124 | 0.0743, 0.180 | 35.3% |
| Residual error | 0.153 | 2.61 | 0.145, 0.161 | 15.3% | 0.153 | 0.146, 0.161 | 15.3% |
| Additive residual (ng/mL) | 1760 | 14.9 | 1250, 2270 | 1760 | 1730 | 1200, 2320 | 1730 |

MVOF = −16843.84; shrinkage for IIV (CL) = 10.1%; shrinkage for IIV ($V_c$) = 10.9; shrinkage for IIV ($V_p$) = 45.1%; shrinkage for IIV (Imax) = 30.6%. Covariate effect was parameterized using power function for continuous covariate WT, ALB, and tumor

burden normalized to median value (i.e., (COVi/COVref)^theta), or proportional shift for categorical covariate ECOG, cancer type, and sex (i.e., 1+theta).

APPEARS THIS WAY ON ORIGINAL

**Figure 1212: Goodness-of-fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED)**

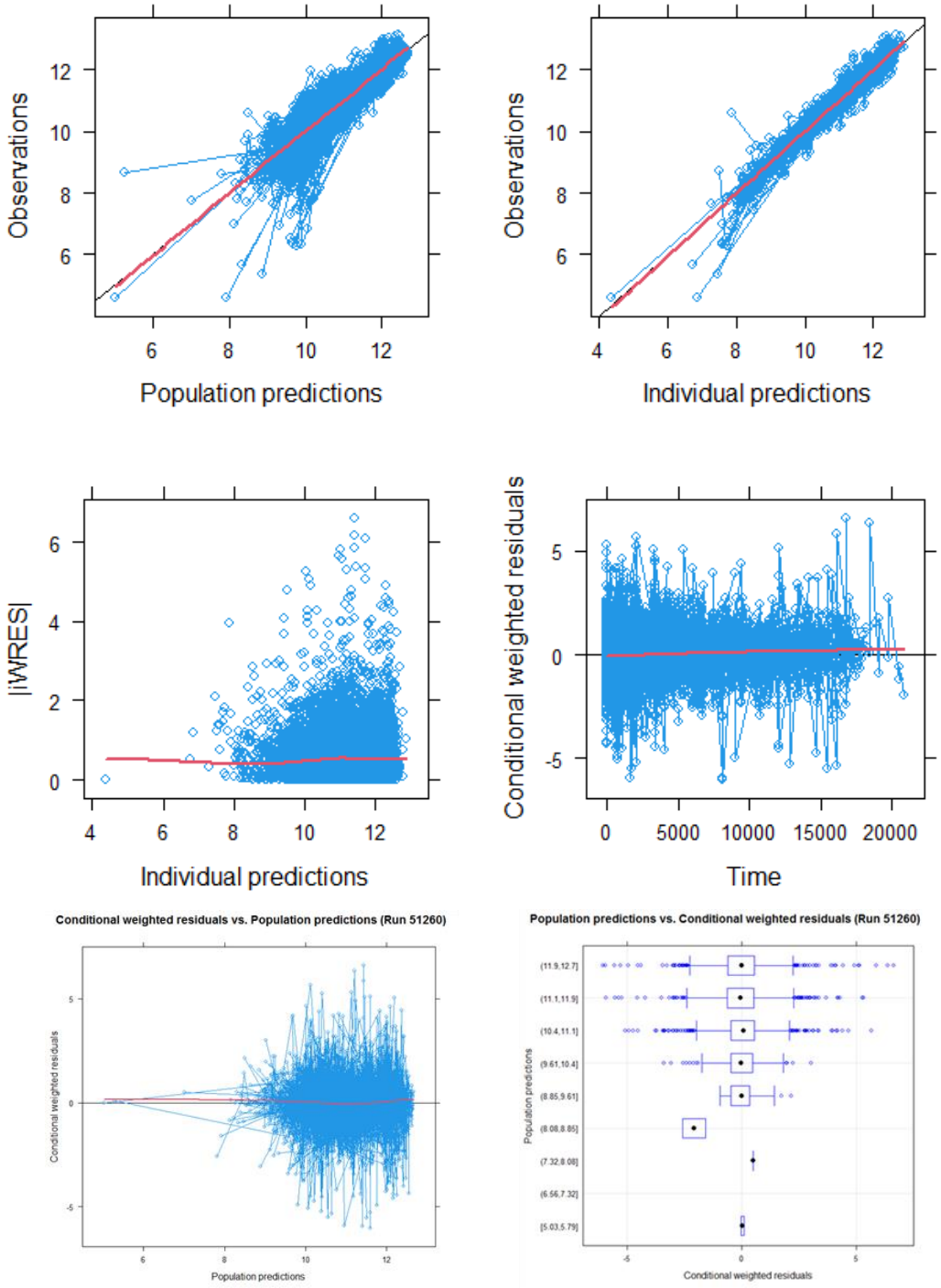


**Figure 1313: VPC of Final Population PK Model, Stratified by Dose**

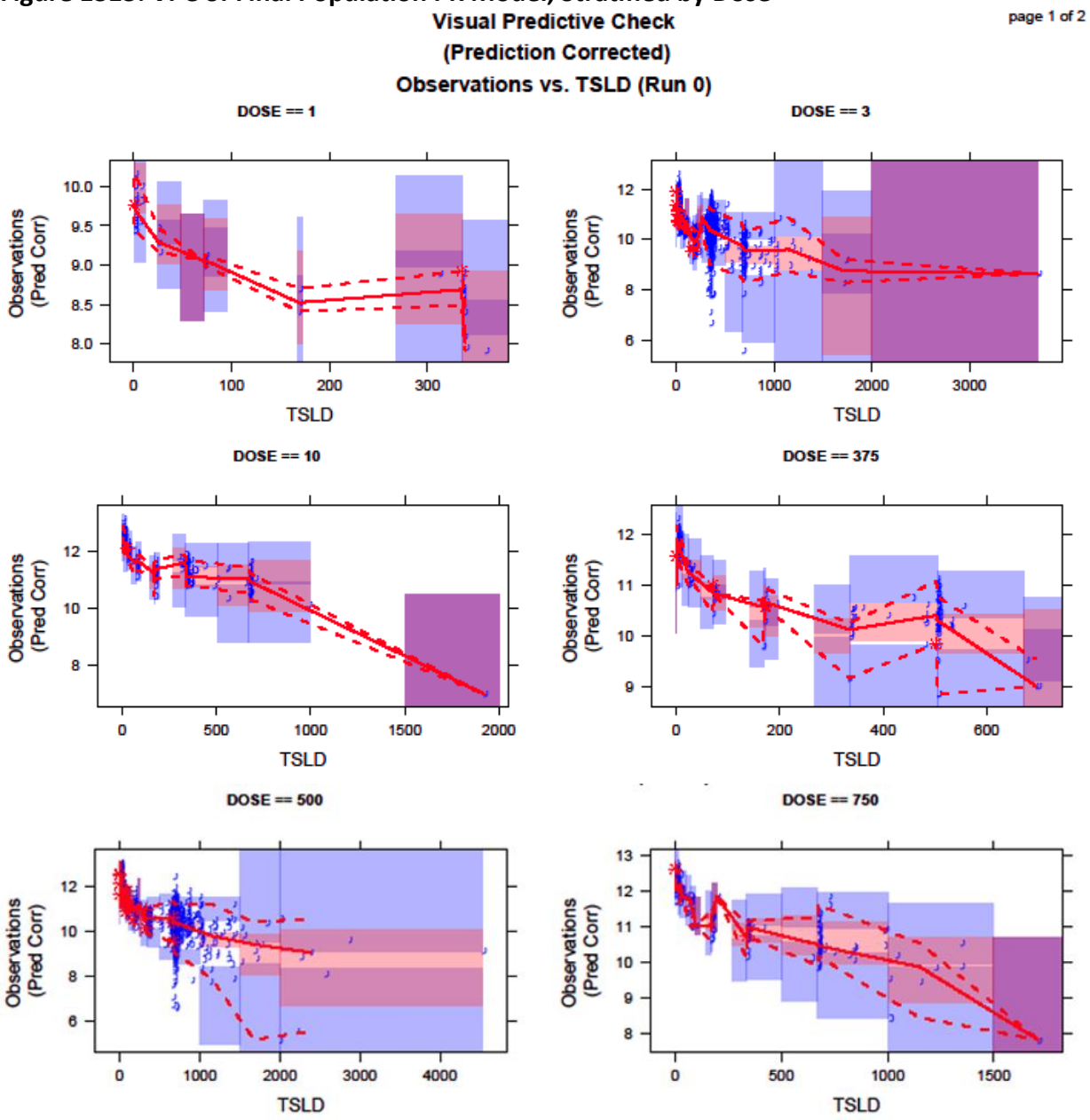
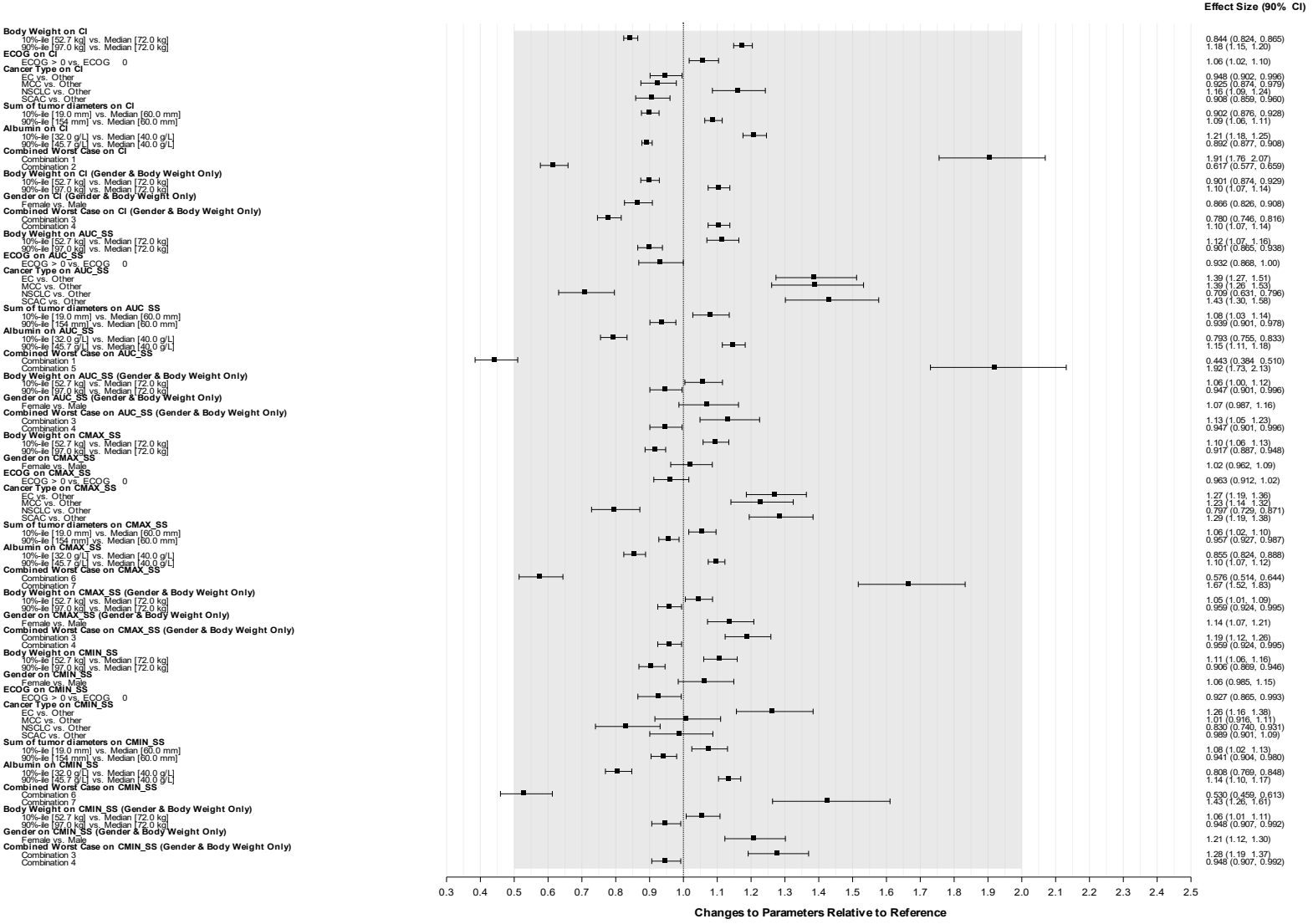


**Figure 1414: Impact of Significant Covariates on Exposure**



Note: Combination 1: albumin (10%-ile [32.0 g/L]) and sum of tumor diameters (90%-ile [154 mm]) and weight (90%-ile [97.0 kg]) and ECOG performance status > 0 and NSCLC versus albumin (median [40.0 g/L]) and sum of tumor diameters (median [60.0 mm]) and weight (median [72.0 kg]) and ECOG performance status = 0 and other. Combination 2: albumin (90%-ile [45.7 g/L]) and sum of tumor diameters (10%-ile [19.0 mm]) and weight (10%-ile [52.7 kg] and ECOG performance status =0 and SCAC versus albumin (median [40.0 g/L]) and sum of tumor diameters (median [60.0 mm]) and weight (median [72.0 kg]) and ECOG performance status > 0 and other. Combination 3: weight (10%-ile [52.7 kg]) and female versus weight (median [72.0 kg]) and male. Combination 4: weight (90%-ile [97.0 kg]) and male versus weight (median [72.0 kg]) and female. Combination 5: albumin (90%-ile [45.7 g/L]) and sum of tumor diameters (10%-ile [19.0 mm]) and weight (10%-ile [52.7 kg] and ECOG performance status = 0 and EC versus albumin (median [40.0 g/L]) and sum of tumor diameters (median [60.0 mm]) and weight (median [72.0 kg]) and ECOG performance status > 0 and other. Combination 6: albumin (10%-ile [32.0 g/L]) and sum of tumor diameters (90%-ile [154 mm]) and weight (90%-ile [97.0 kg]) and ECOG performance status > 0 and NSCLC and male versus albumin (median [40.0 g/L]) and sum of tumor diameters (median [60.0 mm]) and weight (median [72.0 kg]) and ECOG performance status = 0 and other and female.
Combination 7: albumin (90%-ile [45.7 g/L]) and sum of tumor diameters (10%-ile [19.0 mm]) and weight (10%-ile [52.7 kg]) and ECOG performance status = 0 and SCAC and female versus albumin (median [40.0 g/L]) and sum of tumor diameters (median [60.0 mm]) and weight (median [72.0 kg]) and ECOG performance status > 0 and other and male.

(b) (4)

#### 19.4.2.3 PPK Review Issues

No substantive issue.

### 19.4.3 Exposure-Response Analysis

#### 19.4.3.1 ER (efficacy) Executive Summary

The FDA's Assessment: The E-R analysis for efficacy is considered exploratory. Flat E-R relationships were generally observed for efficacy endpoints in chemotherapy-naïve participants with MCC.

#### 19.4.3.2 ER (efficacy) Assessment Summary

The Applicant's Position:

| General Information | |
|---|---|
| Goal of ER analysis | • To describe the relationship between retifanlimab exposure and the primary endpoint of ORR in chemotherapy-naïve MCC participants.<br>• To describe the relationship between retifanlimab exposure and DCR, DOR, PFS, and OS in chemotherapy-naïve MCC participants. |

| | | |
|---|---|---|
| Study Included | | Study 201 |
| Endpoint | | Primary: ORR; Secondary: DCR, DOR, PFS and OS |
| No. of Patients (total, and with individual PK) | | 65 |
| Population Characteristics (Table 43) | General | Age median (range) : 71.0 (44.0, 90.0)<br>Weight median (range): 77.1 (51.0, 127)<br>Sex: male, 42 (64.6%); female, 23 (35.4%)<br>Race: White, 51 (78.5%); Asian, 1 (1.5%); other, 13 (20%) |
| | Pediatrics (if any) | No pediatric patients enrolled |
| Dose(s) Included | | 500 mg Q4W |
| Exposure Metrics Explored (range) | | $AUC_1$, $C_{max1}$, $C_{min1}$, $AUC_{ss}$, $C_{max,ss}$, and $C_{min,ss}$ |
| Covariates Evaluated | | Age, sex, ethnicity, race, albumin, AST, ALP, bilirubin, CrCl, renal function classification by MDRD equation, hepatic function classification by NCI standard and corticosteroid use. |

| **Final Model Parameters** | **Summary** | **Acceptability [FDA's comments]** |
|---|---|---|
| Model Structure | Logistic regression model for ORR and DCR; a stratified log-rank test for time-to-event endpoints (DOR, PFS and OS) | Yes. The analysis is considered exploratory given a single dose. |
| Model Parameter Estimates | Not applicable | |
| Model Evaluation | Not applicable | |
| Covariates and Clinical Relevance | Not applicable | |
| Simulation for Specific Population | Not done | |
| Visualization of E-R relationships | Figure 1616 | Yes. CI of response variables across quantiles are highly overlapping. |
| Overall Clinical Relevance for ER | Flat E-R relationships were generally observed for efficacy endpoints in chemotherapy-naïve participants with MCC | Yes |

| **Labeling Language** | **Description** | **Acceptability [FDA's comments]** |
|---|---|---|
| 12.2 Pharmacodynamics | The exposure-response relationship and time course of pharmacodynamic response for safety and effectiveness of retifanlimab-dlwr have not been fully characterized. (b) (4) | Yes |

**Table 43: Summary of Baseline Characteristics and Laboratory Values in the Dataset**

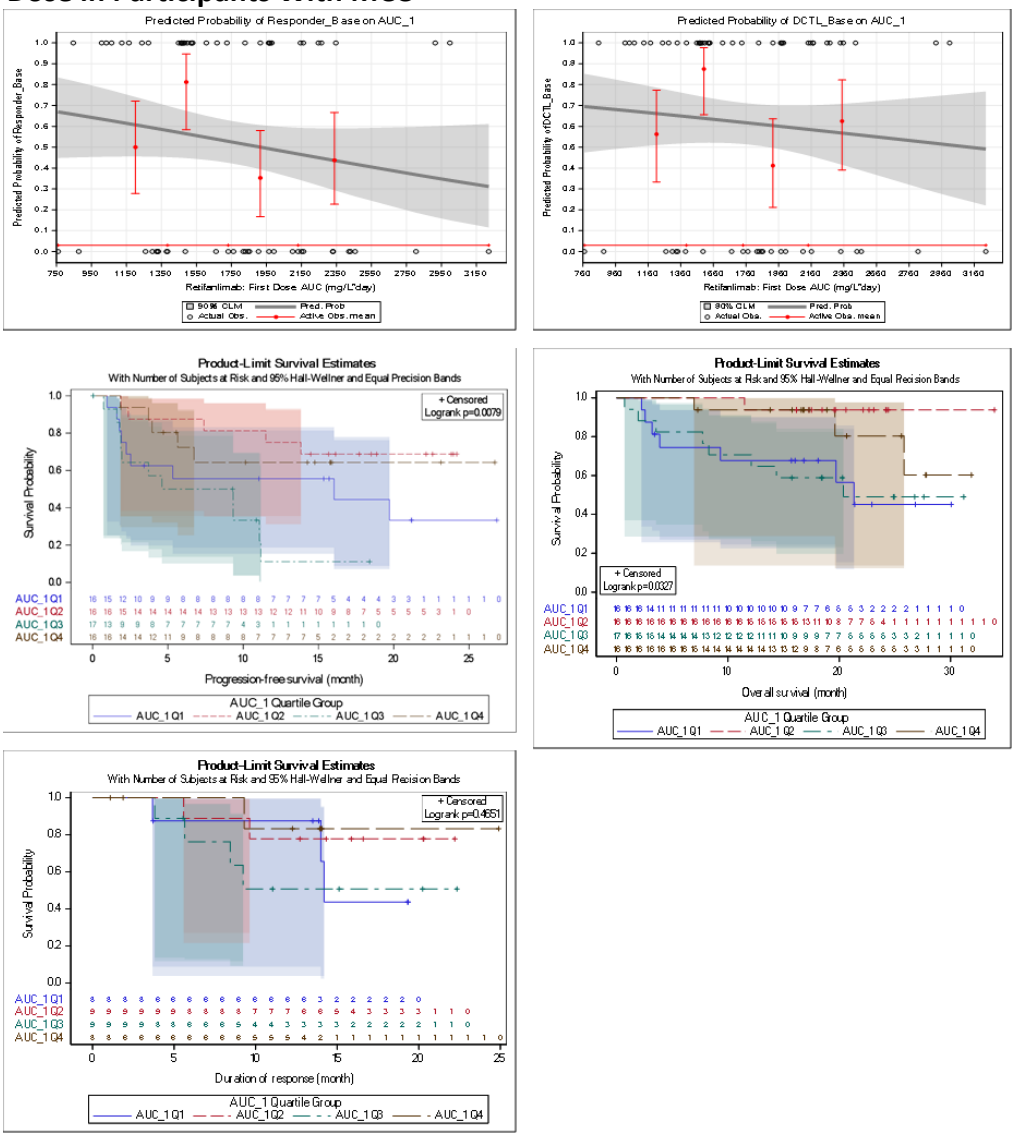
| Covariate | Overall (N = 65) |
|---|---|
| Age (years) | |
| Mean (STD) | 71.4 (10.26) |
| Median (min, max) | 71.0 (44.0, 90.0) |
| Baseline body weight (kg) | |
| Mean (STD) | 82.0 (18.6) |

| Covariate | Overall (N = 65) |
|---|---|
| Median (min, max) | 77.1 (51.0, 127) |
| Body mass index (kg/m$^2$) | |
| Mean (STD) | 28.71 (5.43) |
| Median (min, max) | 28.01 (20.4, 45.7) |
| Sex, n (%) | |
| Male | 42 (64.6) |
| Female | 23 (35.4) |
| HIV status, n (%) | |
| Positive | 1 (1.5) |
| Negative/unknown | 64 (98.5) |
| Corticosteroid use for AEs as permitted by protocol, n (%) | |
| Not used | 59 (90.8) |
| Used | 6 (9.2) |
| Baseline albumin (g/L) | |
| Mean (STD) | 40.6 (3.52) |
| Median (min, max) | 41.3 (33.0, 48.0) |
| Baseline ALP (U/L) | |
| Mean (STD) | 82.6 (82.9) |
| Median (min, max) | 73.0 (36.4, 722) |
| Baseline AST (U/L) | |
| Mean (STD) | 26.8 (14.2) |
| Median (min, max) | 23.0 (12.0, 87.0) |
| Baseline total bilirubin (µM) | |
| Mean (STD) | 10.2 (3.85) |
| Median (min, max) | 9.75 (2.70, 22.2) |
| Baseline eGFR (mL/min/1.73 m$^2$) | |
| Mean (STD) | 79.9 (20.2) |
| Median (min, max) | 79.0 (35.0, 134) |
| Hepatic impairment category, n (%) | |
| Normal | 59 (90.8) |
| Mild | 6 (9.2) |
| Renal impairment category, n (%) | |
| Normal | 18 (27.7) |
| Mild | 38 (58.5) |
| Moderate | 9 (13.8) |
| Race, n (%) | |
| White | 51 (78.5) |
| Asian | 1 (1.5) |
| Other[a] | 13 (20.0) |
| Ethnicity, n (%) | |
| Not Hispanic or Latino | 52 (80.0) |
| Not reported | 13 (20.0) |
| ECOG performance status, n (%) | |
| 0 | 48 (73.8) |
| 1 | 17 (26.2) |
| ADA status, n (%) | |
| Negative | 63 (96.9) |
| Positive | 1 (1.5) |

| Covariate | Overall (N = 65) |
|---|---|
| Unknown | 1 (1.5) |
| Sum of tumor diameters (mm), n (%) | |
| Mean (STD) | 60.3 (49.2) |
| Median (min, max) | 44.0 (12, 236) |

[a] Other includes participants from France, where information on race is not collected per regulatory requirements

**Figure 1616: Clinical efficacy endpoints Versus Retifanlimab First Dose AUC1 Following a 500 mg Q4W Dose in Participants With MCC**




## 19.4.3.3 ER (safety) Executive Summary

The FDA's Assessment: The E-R analysis for safety is considered exploratory. Flat E-R relationships were generally observed for safety endpoints in the All Cancer Population and the MCC Population.

### 19.4.3.4 ER (safety) Assessment Summary

The Applicant's Position:

| **General Information** | | |
|---|---|---|
| Goal of ER analysis | | To describe the relationship between retifanlimab exposure and safety endpoints in the MCC Population and All Cancer Population. |
| Study Included | | Studies 101, 104, 201, 202, and 203. |
| Population Included | | Cancer patients including MCC |
| Endpoint | | Major common AE/SAE, AE of interest |
| No. of Patients (total, and with individual PK) | | 634 |
| Population Characteristics (Table 43) | General | The pooled population was 59.8% female, had a median age of 65 years (range: 18-94 years), and was primarily White/Caucasian (80.1%). The median body weight and BMI were 72.0 kg (range: 35.0-133 kg) and 26.1 kg/$m^2$ (range: 13.5 48.7 kg/$m^2$), respectively. |
| | Organ impairment | Hepatic (NCI ODWG hepatic impairment category): 555 (87.5%) normal, 78 (12.3%) mild impairment, 1 (0.2%) unknown.<br>Renal (impairment classification by MDRD equation): 200 (31.5%) normal, 277 (43.7%) mild impairment, 142 (22.4%) moderate impairment, 4 (0.6%) severe impairment, 11 (1.7%) unknown. |
| | Pediatrics (if any) | No pediatric participants enrolled |
| | Geriatrics (if any) | Not generated. |
| Dose(s) Included | | Body weight–based dosing with Q2W, Q3W, and Q4W schedules at doses of 1 mg/kg, 3 mg/kg, or 10 mg/kg or flat dosing with 375 mg Q3W, 500 mg Q4W, or 750 mg Q4W |
| Exposure Metrics Explored (range) | | $AUC_1$, $C_{max1}$, $C_{min1}$, $AUC_{ss}$, $C_{max,ss}$, and $C_{min,ss}$ |
| Covariates Evaluated | | Age, sex, ethnicity, race, albumin, AST, ALP, bilirubin, CrCl, renal function classification by MDRD equation, hepatic function classification by NCI standard and corticosteroid use |

| **Final Model Parameters** | **Summary** | **Acceptability [FDA's comments]** |
|---|---|---|
| Model Structure | Logistic regression model | Yes. The analysis is considered exploratory given the long-term safety data are contributed by studies of a single dose. |
| Model Parameter Estimates | Table 44 | Yes. The slopes for exposures of significant E-R relationships are small. |
| Model Evaluation | Not applicable | |
| Covariates and Clinical Relevance | Not applicable | |
| Simulation for Specific Population | Not done | |
| Visualization of E-R relationships | Figure 1717, Figure 1818 | Yes. For immune/infusion related AEs (AESIs), the E-R appears flat. |

| | | |
|---|---|---|
| Overall Clinical Relevance for ER | Flat E-R relationships were generally observed for safety endpoints in the All Cancer Population and the MCC Population. | Yes |
| **Labeling Language** | **Description** | **Acceptability [FDA's comments]** |
| 12.2 Pharmacodynamics | The exposure-response relationship and time course of pharmacodynamic response for safety and effectiveness of retifanlimab-dlwr have not been fully characterized. | Yes |

**Table 44: Parameter Estimates from Final ER Model of TEAEs**

| TEAE | Population/N | Parameter | Estimate | P-Value | 95% CI (Profile Likelihood) |
|---|---|---|---|---|---|
| Anaemia | All Cancer/634 | Intercept | 4.8554 | <.0001 | 3.2320, 6.5623 |
| | | $C_{min,ss}$ | -0.0150 | 0.0129 | -0.0274, -0.00375 |
| | | Hemoglobin | -0.0526 | <.0001 | -0.0679, -0.0384 |
| | | OR for $C_{min,ss}$ (unit = 10 mg/L) | 0.861 | — | 0.761, 0.963 |
| | | OR for hemoglobin (unit = 1 g/L) | 0.949 | — | 0.934, 0.962 |
| Asthenia | All Cancer/634 | Intercept | -3.8450 | <.0001 | — |
| | | Age | 0.0376 | <.0001 | — |
| | | Race | -0.3277 | 0.0071 | — |
| Arthralgia | All Cancer/634 | Intercept | -4.6060 | <.0001 | — |
| | | Age | 0.0378 | 0.0008 | — |
| Pruritus | All Cancer/634 | Intercept | -2.7065 | <.0001 | -3.2967, -2.1513 |
| | | $AUC_{ss}$ | 0.000410 | 0.0007 | 0.000174, 0.000648 |
| | | OR for $AUC_{ss}$ (unit = 100 day*mg/L) | 1.042 | — | 1.018, 1.067 |

**Figure 1717: Probability of AESI Versus Retifanlimab Exposure in the MCC Population**

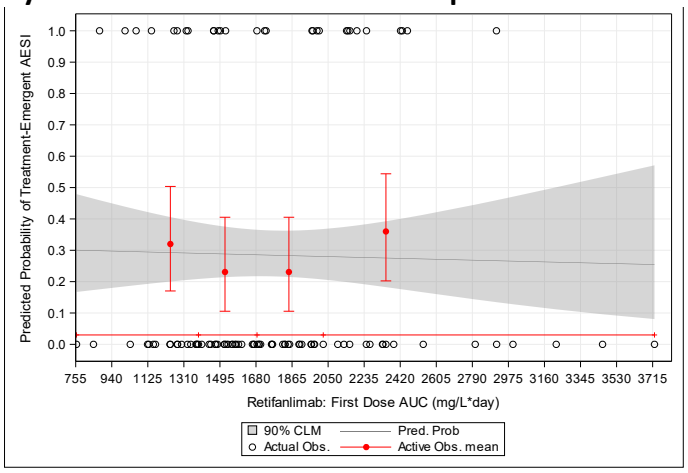
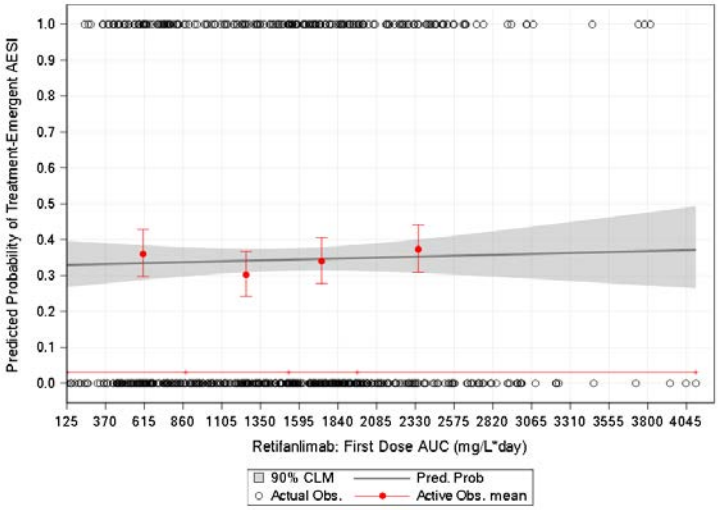


**Figure 1818: Probability of AESI Versus Retifanlimab Exposures in the All Cancer Population**




The FDA's Assessment: The exposure-response analyses showed apparent flat relationship for efficacy and safety endpoints. However, interpretation should be taken with caution because long-term safety data are mainly contributed by studies of a single dose level with narrow exposure range. Additional analyses with respect to TEAE and lab abnormalities were requested via IR. All but leukocyte decrease showed a positive E-R relationship with steady state Cmin in All Cancer population. The OR of leukocyte decrease is 1.263 with 10 mg/L increase in steady state Cmin, and 0.761 with a 1-GI/L increase in baseline leukocyte. This positive relationship was not present in MCC population and was not identified for Grade 2/Grade 3 above leukocyte decrease. Taken together, the exposure dependent leukocyte decrease was not considered clinically meaningful for MCC indication.

### 19.4.3.5 ER Review Issues

No substantive issues.

### 19.4.3.6 Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The E-R efficacy analyses were conducted on 65 chemotherapy-naïve participants with MCC. Clinical meaningful improvement in ORR, PFS, DOR, DCR and OS provides substantial evidence of efficacy for the recommended indication. Statistically significant relationships were not seen between any PK exposure and ORR, PFS, DOR, DCR, and OS.

The E-R safety analyses were conducted in both the All Cancer Population and the MCC Population. A flat E-R relationship was observed for AESIs (irAEs and infusion-related reactions), irAEs, and ≥ Grade 3 treatment-related TEAEs.
Clinical meaningful or statistically significant relationships were not identified between retifanlimab exposure and TEAEs with > 10% incidence rate. The safety profiles and exposure-safety relationships of retifanlimab were consistent with the known safety profiles and exposure-safety relationships of other PD-1 monoclonal

antibodies. The integration of E-R findings for both efficacy and safety provide a justification for the proposed dose of retifanlimab 500 mg Q4W as a 30-minute IV infusion for treatment of MCC.

The FDA's Assessment: The data used in E-R analyses are contributed by studies of a single dose. No alternative dose or dose modifications were indicated for the pivotal study. Therefore, E-R analyses is not conclusive and should be considered as exploratory only. The overall benefit-risk profile is determined mainly by clinical evaluation of the pivotal study.

## 19.5 Additional Safety Analyses Conducted by FDA

The categorization of adverse events of special interest (AESI) used in the primary safety analysis is listed in Table 45.

**Table 45: Adverse Events of Special Interest Grouped Terms**

| Preferred Terms for AESI (MedDRA v23.1a) | Grouped Terms | All Grades | Grade ≥ 3 | Grade ≥ 2 |
|---|---|---|---|---|
| **Preferred Terms for irAEs** | | | | |
| Acute interstitial pneumonitis | irAE of pneumonitis | Yes | | |
| Acute kidney injury | irAE of nephritis | | Yes | |
| Adrenal insufficiency | irAE of adrenal insufficiency | Yes | | |
| Adrenocortical insufficiency acute | irAE of adrenal insufficiency | Yes | | |
| Anal rash | irAE of skin reactions | | | Yes |
| Anti-glomerular basement membrane disease | irAE of vasculitis | Yes | | |
| Antineutrophil cytoplasmic antibody increased | irAE of vasculitis | Yes | | |
| Antineutrophil cytoplasmic antibody positive | irAE of vasculitis | Yes | | |
| Anti-neutrophil cytoplasmic antibody positive vasculitis | irAE of vasculitis | Yes | | |
| Arteritis | irAE of vasculitis | Yes | | |
| Arteritis coronary | irAE of vasculitis | Yes | | |
| Autoimmune blistering disease | irAE of skin reactions | Yes | | |
| Autoimmune cholangitis | irAE, other rare | Yes | | |
| Autoimmune colitis | irAE of colitis | Yes | | |
| Autoimmune encephalopathy | irAE of encephalitis | Yes | | |
| Autoimmune hepatitis | irAE of hepatitis | Yes | | |

| | | | | |
|---|---|---|---|---|
| Autoimmune lung disease | irAE of pneumonitis | Yes | | |
| Autoimmune myocarditis | irAE of myocarditis | Yes | | |
| Autoimmune nephritis | irAE of nephritis | Yes | | |
| Autoimmune pancreatitis | irAE of pancreatitis | Yes | | |
| Autoimmune thyroiditis | irAE of thyroiditis | Yes | | |
| Autoimmune thyroid disorder | irAE of thyroiditis | Yes | | |
| Autoimmune uveitis | irAE of uveitis | Yes | | |
| Axonal and demyelinating polyneuropathy | irAE of Guillain-Barre Syndrome | Yes | | |
| Axonal neuropathy | irAE of Guillain-Barre syndrome | Yes | | |
| Basedow's disease | irAE of hyperthyroidism | Yes | | |
| Behcet's syndrome | irAE of vasculitis | Yes | | |
| Capillaritis | irAE of vasculitis | Yes | | |
| Central nervous system inflammation | irAE, other rare | Yes | | |
| Central nervous system vasculitis | irAE of vasculitis | Yes | | |
| Cerebral arteritis | irAE of vasculitis | Yes | | |
| Cholangitis sclerosing | irAE of vasculitis | Yes | | |
| Chronic allograft nephropathy | irAE of transplant rejection/GVHD | Yes | | |
| Chronic graft versus host disease | irAE of transplant rejection/GVHD | Yes | | |
| Chronic graft versus host disease in intestine | irAE of transplant rejection/GVHD | Yes | | |
| Chronic graft versus host disease in liver | irAE of transplant rejection/GVHD | Yes | | |
| Chronic graft versus host disease in skin | irAE of transplant rejection/GVHD | Yes | | |
| Chronic inflammatory demyelinating polyradiculoneuropathy | irAE, other rare | Yes | | |
| Cogan's syndrome | irAE of vasculitis | Yes | | |
| Colitis | irAE of colitis | Yes | | |
| Colitis erosive | irAE of colitis | Yes | | |
| Colitis microscopic | irAE of colitis | Yes | | |
| Corneal graft rejection | irAE of transplant rejection/GVHD | Yes | | |
| Cryoglobulinaemia | irAE of vasculitis | Yes | | |
| Cutaneous sarcoidosis | irAE of sarcoidosis | Yes | | |
| Cutaneous vasculitis | irAE of vasculitis | Yes | | |
| Cyclitis | irAE of uveitis | Yes | | |

| | | | | |
|---|---|---|---|---|
| Cytokine storm | irAE, other rare | Yes | | |
| Demyelinating polyneuropathy | irAE of Guillain-Barre syndrome | Yes | | |
| Dermatitis | irAE of skin reactions | | | Yes |
| Dermatitis acneiform | irAE of skin reactions | | | Yes |
| Dermatitis bullous | irAE of skin reactions | Yes | | |
| Dermatitis exfoliative | irAE of skin reactions | Yes | | |
| Dermatitis exfoliative generalised | irAE of skin reactions | Yes | | |
| Dermatomyositis | irAE of myositis | Yes | | |
| Diabetic ketoacidosis | irAE of type 1 diabetes | Yes | | |
| Diabetic ketoacidotic hyperglycaemic coma | irAE of type 1 diabetes | Yes | | |
| Diabetic ketosis | irAE of type 1 diabetes | Yes | | |
| Diffuse vasculitis | irAE of vasculitis | Yes | | |
| Drug eruption | irAE of skin reactions | Yes | | |
| Drug Induced liver injury | irAE of hepatitis | Yes | | |
| Enanthema | irAE of skin reactions | | | Yes |
| Encephalitis | irAE of encephalitis | Yes | | |
| Encephalitis autoimmune | irAE of encephalitis | Yes | | |
| Enterocolitis | irAE of colitis | Yes | | |
| Enterocolitis hemorrhagic | irAE of colitis | Yes | | |
| Eosinophilic fasciitis | irAE, other rare | Yes | | |
| Eosinophilic granulomatosis with polyangiitis | irAE of vasculitis | Yes | | |
| Epidermal necrosis | irAE of skin reactions | Yes | | |
| Erythema multiforme | irAE of skin reactions | Yes | | |
| Euglycaemic diabetic ketoacidosis | irAE of type 1 diabetes | Yes | | |
| Exfoliative rash | irAE of skin reactions | Yes | | |
| Fulminant type 1 diabetes mellitus | irAE of type 1 diabetes | Yes | | |
| Giant cell arteritis | irAE of vasculitis | Yes | | |
| Glomerulonephritis | irAE of nephritis | Yes | | |
| Glomerulonephritis acute | irAE of nephritis | | | |
| Glomerulonephritis membranoproliferative | irAE of nephritis | Yes | | |
| Glomerulonephritis membranous | irAE of nephritis | Yes | | |
| Glomerulonephritis minimal lesion | irAE of nephritis | Yes | | |
| Glomerulonephritis proliferative | irAE of nephritis | Yes | | |

| | | | | |
|---|---|---|---|---|
| Glomerulonephritis rapidly progressive | irAE of nephritis | Yes | | |
| Graft versus host disease | irAE of transplant rejection/GVHD | Yes | | |
| Graft versus host disease in eye | irAE of transplant rejection/GVHD | Yes | | |
| Graft versus host disease in gastrointestinal tract | irAE of transplant rejection/GVHD | Yes | | |
| Graft versus host disease in liver | irAE of transplant rejection/GVHD | Yes | | |
| Graft versus host disease in lung | irAE of transplant rejection/GVHD | Yes | | |
| Graft versus host disease in skin | irAE of transplant rejection/GVHD | Yes | | |
| Granulomatosis with polyangiitis | irAE of vasculitis | Yes | | |
| Guillain-Barre syndrome | irAE of Guillain-Barre syndrome | Yes | | |
| Haemorrhagic vasculitis | irAE of vasculitis | Yes | | |
| Heart transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Heart-lung transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Hepatitis | irAE of hepatitis | Yes | | |
| Hepatitis acute | irAE of hepatitis | Yes | | |
| Hepatitis fulminant | irAE of hepatitis | Yes | | |
| Hypersensitivity myocarditis | irAE of myocarditis | Yes | | |
| Hyperthyroidism | irAE of hyperthyroidism | Yes | | |
| Hypophysitis | irAE of hypophysitis | Yes | | |
| Hypopituitarism | irAE of hypophysitis | Yes | | |
| Hypothyroidic goitre | irAE of hypothyroidism | Yes | | |
| Hypothyroidism | irAE of hypothyroidism | Yes | | |
| Idiopathic pneumonia syndrome | irAE of pneumonitis | Yes | | |
| Immune recovery uveitis | irAE of uveitis | Yes | | |
| Immune system disorder | irAE, other rare | Yes | | |
| Immune thrombocytopenia | irAE, other rare | Yes | | |
| Immune-mediated adverse reaction | irAE of transplant rejection/GVHD | Yes | | |
| Immune-mediated arthritis | irAE, other rare | Yes | | |
| Immune-mediated cholangitis | irAE, other rare | Yes | | |
| Immune-mediated cholestasis | irAE, other rare | Yes | | |
| Immune-mediated cytopenia | irAE, other rare | Yes | | |
| Immune-mediated dermatitis | irAE of skin reactions | | | Yes |

| | | | | |
|---|---|---|---|---|
| Immune-mediated encephalitis | irAE of encephalitis | Yes | | |
| Immune-mediated encephalopathy | irAE of encephalitis | Yes | | |
| Immune-mediated enterocolitis | irAE of colitis | Yes | | |
| Immune-mediated gastritis | irAE, other rare | Yes | | |
| Immune-mediated hepatic disorder | irAE of hepatitis | Yes | | |
| Immune-mediated hepatitis | irAE of hepatitis | Yes | | |
| Immune-mediated hyperthyroidism | irAE of hyperthyroidism | Yes | | |
| Immune-mediated hypothyroidism | irAE of hypothyroidism | Yes | | |
| Immune-mediated myocarditis | irAE of myocarditis | Yes | | |
| Immune-mediated myositis | irAE of myositis | Yes | | |
| Immune-mediated nephritis | irAE of nephritis | Yes | | |
| Immune-mediated pancreatitis | irAE of pancreatitis | Yes | | |
| Immune-mediated pneumonitis | irAE of pneumonitis | Yes | | |
| Immune-mediated renal disorder | irAE of nephritis | Yes | | |
| Immune-mediated thyroiditis | irAE of thyroiditis | Yes | | |
| Immune-mediated uveitis | irAE of uveitis | Yes | | |
| Interstitial lung disease | irAE of pneumonitis | Yes | | |
| Intestine transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Iridocyclitis | irAE of uveitis | Yes | | |
| Iritis | irAE of uveitis | Yes | | |
| Keratitis | irAE, other rare | Yes | | |
| Ketosis-prone diabetes mellitus | irAE of type 1 diabetes | Yes | | |
| Kidney transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Latent autoimmune diabetes in adults | irAE of type 1 diabetes | Yes | | |
| Limbic encephalitis | irAE of encephalitis | Yes | | |
| Liver and pancreas transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Liver transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Lung transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Lymphocytic hypophysitis | irAE of hypophysitis | Yes | | |
| MAGIC syndrome | irAE of vasculitis | Yes | | |
| Meningitis | irAE, other rare | Yes | | |
| Meningitis aseptic | irAE, other rare | Yes | | |

| | | | | |
|---|---|---|---|---|
| Meningitis eosinophilic | irAE, other rare | Yes | | |
| Meningitis noninfective | irAE, other rare | Yes | | |
| Mesangioproliferative glomerulonephritis | irAE of nephritis | Yes | | |
| Microscopic enteritis | irAE of colitis | Yes | | |
| Microscopic polyangiitis | irAE of vasculitis | Yes | | |
| Miller Fisher syndrome | irAE of Guillain-Barre syndrome | Yes | | |
| Multifocal motor neuropathy | irAE of Guillain-Barre syndrome | Yes | | |
| Multiple organ transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Myasthenia gravis | irAE of myasthenic syndrome | Yes | | |
| Myasthenia gravis crisis | irAE of myasthenic syndrome | Yes | | |
| Myasthenic syndrome | irAE of myasthenic syndrome | Yes | | |
| Myelitis | irAE, other rare | Yes | | |
| Myocarditis | irAE of myocarditis | Yes | | |
| Myopathy | irAE of myositis | Yes | | |
| Myositis | irAE of myositis | Yes | | |
| Myxodema | irAE of hypothyroidism | Yes | | |
| Myxodema coma | irAE of hypothyroidism | Yes | | |
| Necrotising myositis | irAE of myositis | Yes | | |
| Necrotizing colitis | irAE of colitis | Yes | | |
| Nephritis | irAE of nephritis | Yes | | |
| Nephritis haemorrhagic | irAE of nephritis | Yes | | |
| Nephrotic syndrome | irAE of nephritis | | Yes | |
| Nodular vasculitis | irAE of vasculitis | Yes | | |
| Non-infective encephalitis | irAE of encephalitis | Yes | | |
| Ocular myasthenia | irAE of myasthenic syndrome | Yes | | |
| Ocular sarcoidosis | irAE of sarcoidosis | Yes | | |
| Ocular vasculitis | irAE of vasculitis | Yes | | |
| Optic perineuritis | irAE, other rare | Yes | | |
| Palmar-plantar erythrodysaesthesia syndrome | irAE of skin reactions | | | Yes |
| Pancreas transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Pancreatitis | irAE of pancreatitis | Yes | | |
| Pancreatitis acute | irAE of pancreatitis | Yes | | |

| | | | | |
|---|---|---|---|---|
| Pancreatitis haemorrhagic | irAE of pancreatitis | Yes | | |
| Pancreatitis necrotising | irAE of pancreatitis | Yes | | |
| Paraneoplastic encephalomyelitis | irAE, other rare | Yes | | |
| Pemphigoid | irAE of skin reactions | Yes | | |
| Pemphigus | irAE of skin reactions | Yes | | |
| Penile rash | irAE of skin reactions | | | Yes |
| Pericarditis | irAE, other rare | Yes | | |
| Pneumonitis | irAE of pneumonitis | Yes | | |
| Polyarteritis nodosa | irAE of vasculitis | Yes | | |
| Polyarthritis | irAE, other rare | Yes | | |
| Polyglandular autoimmune syndrome type II | irAE, other rare | Yes | | |
| Polymyalgia rheumatic | irAE, other rare | Yes | | |
| Polymyositis | irAE of myositis | Yes | | |
| Polyneuropathy idiopathic progressive | irAE of Guillain-Barre syndrome | Yes | | |
| Pruritus | irAE of skin reactions | | | Yes |
| Pruritus genital | irAE of skin reactions | | | Yes |
| Pulmonary sarcoidosis | irAE of sarcoidosis | Yes | | |
| Pulmonary vasculitis | irAE of vasculitis | Yes | | |
| Radiculopathy | irAE, other rare | Yes | | |
| Rash | irAE of skin reactions | | | Yes |
| Rash erythematous | irAE of skin reactions | | | Yes |
| Rash macular | irAE of skin reactions | | | Yes |
| Rash maculo-papular | irAE of skin reactions | | | Yes |
| Rash pruritic | irAE of skin reactions | | | Yes |
| Rash pustular | irAE of skin reactions | | | Yes |
| Renal and pancreas transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Renal arteritis | irAE of vasculitis | Yes | | |
| Renal transplant failure | irAE of transplant rejection/GVHD | Yes | | |
| Renal vasculitis | irAE of vasculitis | Yes | | |
| Retinal vasculitis | irAE of vasculitis | Yes | | |
| Rheumatoid vasculitis | irAE of vasculitis | Yes | | |
| Sarcoidosis | irAE of sarcoidosis | Yes | | |
| Secondary adrenocortical insufficiency | irAE of adrenal insufficiency | Yes | | |
| Silent thyroiditis | irAE of thyroiditis | Yes | | |
| Sjogren's syndrome | irAE, other rare | Yes | | |
| Skin graft rejection | irAE of transplant rejection/GVHD | Yes | | |

| | | | | |
|---|---|---|---|---|
| Skin hypopigmentation | irAE of skin reactions | | | Yes |
| Skin necrosis | irAE of skin reactions | Yes | | |
| Solid organ transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Stevens-Johnson syndrome | irAE of skin reactions | Yes | | |
| Subacute inflammatory demyelinating polyneuropathy | irAE of Guillain-Barre syndrome | Yes | | |
| Subacute pancreatitis | irAE of pancreatitis | Yes | | |
| Systemic immune activation | irAE of transplant rejection/GVHD | Yes | | |
| Takayasu's arteritis | irAE of vasculitis | Yes | | |
| Thryroiditis acute | irAE of thyroiditis | Yes | | |
| Thyroid disorder | irAE of thyroiditis | Yes | | |
| Thyroiditis | irAE of thyroiditis | Yes | | |
| Thyrotoxic crisis | irAE of hyperthyroidism | Yes | | |
| Toxic epidermal necrolysis | irAE of skin reactions | Yes | | |
| Toxic skin eruption | irAE of skin reactions | Yes | | |
| Transplant rejection | irAE of transplant rejection/GVHD | Yes | | |
| Tubulointerstitial nephritis | irAE of nephritis | Yes | | |
| Type 1 diabetes mellitus | irAE of type 1 diabetes | Yes | | |
| Ulcerative keratitis | irAE, other rare | Yes | | |
| Uveitis | irAE of uveitis | Yes | | |
| Vascular purpura | irAE of vasculitis | Yes | | |
| Vasculitic rash | irAE of vasculitis | Yes | | |
| Vasculitis | irAE of vasculitis | Yes | | |
| Vasculitis gastrointestinal | irAE of vasculitis | Yes | | |
| Vasculitis necrotizing | irAE of vasculitis | Yes | | |
| Vitiligo | irAE of skin reactions | | | Yes |
| Vitritis | irAE of uveitis | Yes | | |
| Vogt-Koyanagi-Harada syndrome | irAE of uveitis | Yes | | |
| Vulvovaginal rash | irAE of skin reactions | | | Yes |
| **Preferred Terms for IRRs** | | | | |
| Anaphylactic reaction | Diagnosis of infusion reaction | Yes | | |
| Anaphylactoid reaction | Diagnosis of infusion reaction | Yes | | |
| Anaphylactic shock | Diagnosis of infusion reaction | Yes | | |
| Anaphylactoid shock | Diagnosis of infusion reaction | Yes | | |

| | | | | |
|---|---|---|---|---|
| Cytokine release syndrome | Diagnosis of infusion reaction | Yes | | |
| Drug hypersensitivity | Diagnosis of infusion reaction | Yes | | |
| Hypersensitivity | Diagnosis of infusion reaction | Yes | | |
| Infusion related hypersensitivity reaction | Diagnosis of infusion reaction | Yes | | |
| Infusion-related reaction | Diagnosis of infusion reaction | Yes | | |
| Serum sickness | Diagnosis of infusion reaction | Yes | | |
| Serum sickness-like reaction | Diagnosis of infusion reaction | Yes | | |
| Shock | Diagnosis of infusion reaction | Yes | | |
| Type I hypersensitivity | Diagnosis of infusion reaction | Yes | | |
| Allergic oedema | Symptom of potential infusion reaction | Yes | | |
| Angioedema | Symptom of potential infusion reaction | Yes | | |
| Blood pressure decreased | Symptom of potential infusion reaction | Yes | | |
| Bronchial oedema | Symptom of potential infusion reaction | Yes | | |
| Bronchospasm | Symptom of potential infusion reaction | Yes | | |
| Cardiac arrest | Symptom of potential infusion reaction | Yes | | |
| Cardio-respiratory arrest | Symptom of potential infusion reaction | Yes | | |
| Chest pain | Symptom of potential infusion reaction | Yes | | |
| Chills | Symptom of potential infusion reaction | Yes | | |
| Choking | Symptom of potential infusion reaction | Yes | | |
| Choking sensation | Symptom of potential infusion reaction | Yes | | |
| Circulatory collapse | Symptom of potential infusion reaction | Yes | | |
| Skin reactions | Symptom of potential infusion reaction | Yes | | |

| | | | | |
|---|---|---|---|---|
| Dyspnoea | Symptom of potential infusion reaction | Yes | | |
| Erythema | Symptom of potential infusion reaction | Yes | | |
| Flushing | Symptom of potential infusion reaction | Yes | | |
| Hyperhidrosis | Symptom of potential infusion reaction | Yes | | |
| Hypotension | Symptom of potential infusion reaction | Yes | | |
| Laryngeal oedema | Symptom of potential infusion reaction | Yes | | |
| Laryngospasm | Symptom of potential infusion reaction | Yes | | |
| Lip oedema | Symptom of potential infusion reaction | Yes | | |
| Lip swelling | Symptom of potential infusion reaction | Yes | | |
| Mouth swelling | Symptom of potential infusion reaction | Yes | | |
| Oedema | Symptom of potential infusion reaction | Yes | | |
| Oedema mouth | Symptom of potential infusion reaction | Yes | | |
| Oropharyngeal oedema | Symptom of potential infusion reaction | Yes | | |
| Oropharyngeal spasm | Symptom of potential infusion reaction | Yes | | |
| Oropharyngeal swelling | Symptom of potential infusion reaction | Yes | | |
| Pruritus | Symptom of potential infusion reaction | Yes | | |
| Pruritus allergic | Symptom of potential infusion reaction | Yes | | |
| Pyrexia | Symptom of potential infusion reaction | Yes | | |
| Rash | Symptom of potential infusion reaction | Yes | | |
| Rash erythematous | Symptom of potential infusion reaction | Yes | | |
| Rash pruritic | Symptom of potential infusion reaction | Yes | | |
| Respiratory arrest | Symptom of potential infusion reaction | Yes | | |

| | | | | |
|---|---|---|---|---|
| Respiratory distress | Symptom of potential infusion reaction | Yes | | |
| Respiratory failure | Symptom of potential infusion reaction | Yes | | |
| Shock symptom | Symptom of potential infusion reaction | Yes | | |
| Stridor | Symptom of potential infusion reaction | Yes | | |
| Swelling face | Symptom of potential infusion reaction | Yes | | |
| Swollen tongue | Symptom of potential infusion reaction | Yes | | |
| Tachycardia | Symptom of potential infusion reaction | Yes | | |
| Tachypnoea | Symptom of potential infusion reaction | Yes | | |
| Tongue oedema | Symptom of potential infusion reaction | Yes | | |
| Tracheal oedema | Symptom of potential infusion reaction | Yes | | |
| Tracheal obstruction | Symptom of potential infusion reaction | Yes | | |
| Upper airway obstruction | Symptom of potential infusion reaction | Yes | | |
| Urticaria | Symptom of potential infusion reaction | Yes | | |
| Urticaria papular | Symptom of potential infusion reaction | Yes | | |
| Wheezing | Symptom of potential infusion reaction | Yes | | |

Abbreviations: AESI: Adverse event of special interest; irAE: immune related adverse event; IRR: infusion related reaction

# Signatures BLA 761334

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTION(S) AUTHORED/ APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Nonclinical Reviewer/ Team Leader | Matthew Thompson, PhD, MPH | OOD/DHOT | Section: 5 | **Select one:** ☒ Authored ☒ Approved |
| | **Signature:** Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S Date: 2023.02.23 14:18:34 -05'00' | | | |
| Nonclinical Team Division Director | John Leighton, PhD | OOD/DHOT | Section: 5 | **Select one:** ☐ Authored ☒ Approved |
| | **Signature:** John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2023.02.23 10:46:22 -05'00' | | | |
| Clinical Pharmacology Reviewers | Yixuan Dong, PhD | OCP/DCPII | Section: 6 | **Select one:** ☒ Authored ☐ Approved |
| | **Signature:** Yixuan Dong -S Digitally signed by Yixuan Dong -S Date: 2023.02.23 14:30:14 -05'00' | | | |
| | Ye Xiong, PhD | OCP/DPM | Section: 19.4 | **Select one:** ☒ Authored ☐ Approved |
| | **Signature:** Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2023.02.23 14:41:05 -05'00' | | | |
| Clinical Pharmacology Team Leaders | Jason Moore, PharmD | OCP/DCPII | Section: 6 | **Select one:** ☒ Authored ☒ Approved |
| | **Signature:** Jason N. Moore Jr -S Digitally signed by Jason N. Moore Jr -S Date: 2023.02.23 14:34:11 -05'00' | | | |
| | Youwei Bi, PhD | OCP/DPM | Section: 19.4 | **Select one:** ☒ Authored ☒ Approved |
| | **Signature:** Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2023.02.23 16:17:42 -05'00' | | | |
| Clinical Pharmacology Division Director | Nam Atiqur (Atik) Rahman, PhD | OCP/DCPII | Sections: 6, 19.4 | **Select one:** ☐ Authored ☒ Approved |
| | **Signature:** Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2023.02.27 10:49:55 -05'00' | | | |

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTION(S) AUTHORED/ APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Clinical Reviewer | Vaibhav Kumar, MD, MS | OOD/DO3 | Sections: 1, 2, 3, 7, 8, 9, 10, 19 | **Select one:** ☒ Authored ☐ Approved |
| | **Signature:** Vaibhav Kumar -S Digitally signed by Vaibhav Kumar -S Date: 2023.02.24 09:07:07 -05'00' | | | |
| Clinical Team Leader | Leslie Doros, MD | OOD/DO3 | Authored Section: 1.3 Approved Sections: 1, 2, 3, 7, 8, 9, 10, 19 | **Select one:** ☒ Authored ☒ Approved |
| | **Signature:** Leslie Doros -S Digitally signed by Leslie Doros -S Date: 2023.02.24 09:19:08 -05'00' | | | |
| Statistical Reviewer | Jiaxin Fan, PhD | OB/DBV | Sections: 1, 8 | **Select one:** ☒ Authored ☐ Approved |
| | **Signature:** Jiaxin Fan -S (Affiliate) Digitally signed by Jiaxin Fan -S (Affiliate) Date: 2023.02.23 12:29:25 -05'00' | | | |
| Statistical Team Leader | Joyce Cheng, PhD | OB/DBV | Sections: 1, 8 | **Select one:** ☒ Authored ☒ Approved |
| | **Signature:** Joyce Cheng -S Digitally signed by Joyce Cheng -S Date: 2023.02.23 17:03:49 -05'00' | | | |
| Division Director (OB) | Shenghui Tang, PhD | OB/DBV | Sections: 1, 8 | **Select one:** ☐ Authored ☒ Approved |
| | **Signature:** Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2023.02.23 10:58:04 -05'00' | | | |
| Associate Director for Labeling (ADL) | Doris Auth, PharmD | OCE | Section: 11 | **Select one:** ☒ Authored ☒ Approved |
| | **Signature:** Doris Auth -S Digitally signed by Doris Auth -S Date: 2023.02.23 14:21:51 -05'00' | | | |
| Cross-Disciplinary Team Leader (CDTL) | Leslie Doros, MD | OOD/DO3 | Sections: All | **Select one:** ☐ Authored ☒ Approved |
| | **Signature:** Leslie Doros -S Digitally signed by Leslie Doros -S Date: 2023.02.24 10:01:49 -05'00' | | | |
| Division Director (Clinical) | Steven Lemery, MD, MHS | OOD/DO3 | Sections: All | **Select one:** ☐ Authored ☒ Approved |
| | **Signature:** *Signature will be included in Assessment Aid.* | | | |

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/s/

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LESLIE A DOROS
03/21/2023 11:20:41 AM

STEVEN J LEMERY
03/21/2023 02:54:52 PM

PAUL G KLUETZ
03/21/2023 03:42:15 PM