22 February 2024
EMA/122634/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zynyz

International non-proprietary name: retifanlimab

Procedure No. EMEA/H/C/006194/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ADA	antidrug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
COVID-19	corona virus disease 2019
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CXCL	chemokine (C-X-C motif) ligand
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DOR	duration of response
DP	drug product
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
Fc	fragment crystallizable
FDA	Food and Drug Administration

GVHD	graft-versus-host-disease
HIV	human immunodeficiency virus
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
IRR	infusion-related reaction
ISI	Integrated Summary of Immunogenicity
ISS	Integrated Summary of Safety
IV	intravenous(ly)
K-M	Kaplan-Meier
LPLV	last participant last visit
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MedDRA	Medical Dictionary for Regulatory Activities
MSD-ECL	Meso Scale Discovery electroluminescence
NCCN	National Comprehensive Cancer Network
NE	not estimable
NR	not reached
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
P1/2	process 1/2
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)
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
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
UV	ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Incyte Biosciences Distribution B.V. submitted on 27 February 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Zynyz, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 September 2022.

Zynyz was designated as an orphan medicinal product EU/3/22/2743 on 13 January 2023 in the following condition: treatment of Merkel cell carcinoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Zynyz as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/zynyz.

The applicant applied for the following indication:

Zynyz is indicated as monotherapy for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0014/2023 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active substance status

The applicant requested the active substance retifanlimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 February 2021	EMA/SA/0000046547	Joao de Oliveira and Minne Casteels

The advice pertained to the following clinical aspects:

- the design of the ongoing Phase 2 study, in patients with locally advanced or metastatic MCC (POD1UM-201), together with the anticipated efficacy data and proposed safety database to support a conditional marketing authorisation;
- the proposal to follow all patients in POD1UM-201 for collection of overall survival data (OS) for at least 2 years after enrolment, to provide confirmatory evidence to convert the conditional approval into a regular approval.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: Selma Arapovic Dzakula

The application was received by the EMA on	27 February 2023
The procedure started on	23 March 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 June 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 June 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 July 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	6 October 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 November 2023

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2023
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	14 December 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 January 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 February 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zynyz on	22 February 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	22 February 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication is in the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC).

2.1.2. Epidemiology and risk factors, screening tools/prevention

Merkel cell carcinoma is an aggressive, life-threatening, cutaneous malignancy with a poor outcome when advanced. The disease primarily affects old and/or immunosuppressed patients (Stockfleth. Cancers. 2023; Gauci et al. Eur J Cancer. 2022). Merkel cell carcinoma is a rare disease (<1% of all cutaneous malignancies; Gauci et al. Eur J Cancer. 2022). The approximate annual incidence is 0.13 per 100,000 persons in Europe (van der Zwan et al. Eur J Cancer. 2013). The annual incidence is increasing in multiple countries at a faster rate than other solid tumours (Fondain et al. J Eur Acad Dermatol Venereol. 2018; Fondain et al. J Eur Acad Dermatol Venereol. 2018; Zaar et al. J Eur Acad Dermatol Venereol. 2016). RARECARENet estimates 1172 new patients with MCC across Europe in 2013, for an estimated prevalence of 1.3 per 100,000 persons, or 6513 cases (RARECARENet 2022).

The annual incidence of MCC worldwide is ranging between 0.10 and 1.6 per 100,000 persons (Spada et al. J Immunother Cancer. 2022).

Risk factors for MCC include old age, UV exposure, white skin type, male sex, immunosuppression and MCPyV infection (Gauci et al. European Journal of Cancer. 2022). Hence, elderly, fair-skinned individuals with a history of chronic sun exposure have the highest risk of developing MCC (Dellambra et al. Biomedicines 2021, Gauci et al. European Journal of Cancer. 2022, Harms et al. Ann Surg Oncol. 2016, Paulson et al. J Am Acad Dermatol. 2018).

The 5-year survival rates are poor; 35% for those with nodal involvement and only 14% for metastatic disease (Harms et al. Ann Surg Oncol. 2016, Trinidad et al. J Clin Pathol. 2019).

2.1.3. Biologic features

Merkel cell carcinoma is an immunogenic tumour. Cell surface expression of PD-L1 by tumour cells and tumour infiltrating lymphocytes is present in approximately half of MCC tumour specimens (Lipson et al. Cancer Immunol Res. 2013). Approximately 80% of MCCs are associated with Merkel cell polyomavirus (MCPyV) infection. The MCPyV DNA integrates in the host cell genome, resulting in persistent expression of MCPyV T antigens (Feng et al. Science. 2008). Peripheral blood and tumours from most patients with MCPyV-positive MCC contain MCPyV-specific T cells (Lipson et al. Cancer Immunol Res. 2013). PD-1, as well as Tim-3, are frequently highly expressed on MCPyV-specific T cells and MCC-infiltrating lymphocytes (Afanasiev et al. Clin Cancer Res. 2013). 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 et al. Emerg Infect Dis. 2009, Harms et al. Cancer Res. 2015, Knepper et al. Clin Cancer Res. 2019, Wong et al. Cancer Res. 2015).

2.1.4. Clinical presentation and diagnosis

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 J Am Acad Dermatol. 2003, Albores-Saavedra et al. J Cutan Pathol.2010, Harms et al. Ann Surg Oncol. 2016, Hodgson J. Surg Oncol. 2005, Lemos et al. J Am Acad Dermatol. 2010, Sridharan et al. J Natl Compr Canc Netw. 2016). MCC metastasizes first to lymph nodes and spread is typically to lung, adrenal glands, pancreas, liver, brain, and bones (Dellambra et al. Biomedicines. 2021). Recurrence (reappearance or considerable progression of disease) is common (~40%) and often incurable (Bhatia et al. Curr Oncol Rep. 2011, McEvoy et al. JAMA Dermatol. 2022).

Diagnosis is based on incisional tumor biopsy. Merkel cell carcinoma generally consists of a solid nodular lesion in the dermis and subcutis. Immunohistochemistry is required for diagnosis, and MCC is characterized by expression of both epithelial markers, such as cytokeratin 20 with a characteristic paranuclear dot-like staining and also AE1/AE3 and CAM5.2, and by expression of neuroendocrine markers such as neuron-specific enolase, synaptophysin, CD56, and chromogranin A (more specific for MCC; Gauci et al. Eur J Cancer. 2022). Evidence for an associated MCPyV infection can be identified in the majority of patients (Lipson et al. Cancer Immunol Res. 2013).

2.1.5. Management

Surgery and/or radiation therapy are indicated and, potentially, curative for local-regional disease (Bhatia et al. Curr Oncol Rep. 2011).

Historically, metastatic MCC has been treated with chemotherapy regimens similar to those used for small cell lung cancer. Platinum-based chemotherapy provides high initial response rates that are of short duration. According to relevant publications, no survival advantage has ever been demonstrated for chemotherapy in this disease (Cassler et al. Curr Treat Options Oncol. 2016, Hughes et al. Curr Dermatol Rep. 2014, Lebbe et al. Eur J Cancer. 2015, NCCN 2017, Voog et al. Cancer. 1999). Management of patients with recurrent, locally advanced, unresectable MCC is also challenging (Becker et al. Oncotarget. 2017). Similar to distant metastatic disease, patients with recurrent, unresectable MCC require systemic therapy to achieve disease control.

Chemotherapy is also associated with risk of severe toxicity and toxic death, particularly among older patients.

Immunotherapy is a promising new approach to treatment of advanced/metastatic MCC. Updated results from a study with the PD-L1 inhibitor, avelumab, showed an ORR of 39.7% in chemotherapy-naive participants (D'Angelo et al. J Immunother Cancer. 2021) and 32% in participants with chemotherapy-refractory metastatic disease, most of which were durable (Kaufman et al. Lancet Oncol. 2016). Responses occurred in patients with both PD-L1-positive and negative tumours and were independent of Merkel cell polyomavirus status. Recently, updated results from a study of pembrolizumab, a PD-1 inhibitor, in participants with advanced MCC were published. In this Phase 2 trial, the objective response rate was 56% in participants with distant metastatic or recurrent, locoregional MCC not amenable to definitive surgery or radiation therapy (Nghiem et al. J Immunother Cancer. 2021). Bavencio (avelumab) has been granted marketing authorisation by the European Commission for the treatment of MCC (EMEA/H/C/004338/0000; EMEA/H/C/004338/II/0013). The FDA has granted approval to Bavencio (avelumab), Keytruda (pembrolizumab), and Zynyz (retifanlimab), for the treatment of MCC.

Anti-PD-(L)1 therapies are currently recommended as first-line treatment for locally advanced/metastatic MCC (Gauci et al. European Journal of Cancer. 2022).

While the prognosis has improved with the introduction of immunotherapy, an unmet medical need remains in the absence of curative therapies.

2.2. About the product

Retifanlimab is an immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with its ligands PD-L1 and PD-L2. Engagement of PD-1 with its ligands PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumour cells and/or other cells in the tumour microenvironment, results in inhibition of T-cell function such as proliferation, cytokine secretion and cytotoxic activity. Retifanlimab binds to the PD-1 receptor, blocks interaction with its ligands PD-L1 and PD-L2 and potentiates T-cell activity.

The applicant initially applied for the following indication:

Zynyz is indicated as monotherapy for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC).

The finally approved indication was:

Zynyz is indicated as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation therapy.

Treatment should be initiated and supervised by a physician experienced in the treatment of cancer.
The recommended dose is 500 mg retifanlimab every 4 weeks administered as an intravenous infusion over 30 minutes. Treatment should continue until disease progression or unacceptable toxicity for up to 2 years. Dose escalation or reduction of retifanlimab is not indicated.

Recommended dose modifications to manage immune related adverse reactions are provided in SmPC section 4.2.

2.3. Type of Application and aspects on development

Clinical program

The retifanlimab clinical studies in this application consist of one primary study and four supportive studies (contributing supportive safety and pharmacology data).

Based on the rare incidence of MCC, controlled studies against chemotherapy, other immunotherapies, or placebo were not considered feasible or appropriate.

Scientific advice

CHMP Scientific Advice has been provided for retifanlimab for the treatment of metastatic or locally advanced Merkel cell carcinoma (MCC) on 25/02/2021 (EMA/SA/0000046547).

The key points that were considered were that although a high response rate in a single-arm trial could be considered meaningful, a confirmed ORR $\geq$ 30% could not, on its own, support an efficacy claim and the Applicant would be expected to substantiate that the ORR results observed from the single arm trial are providing compelling evidence for efficacy, while supported by a duration of response (DoR) that is considered to represent a clinical benefit, given the target population.

Furthermore, the response should be large enough to clearly outweigh the possible bias associated with the lack of a concurrent control. The lack of unambiguously pre-specified rules triggering the primary analysis questions the credibility of results. Development of a detailed statistical analysis is acknowledged, but the study is ongoing and unblinded, and thus it cannot be excluded that analysis options are chosen in a data-driven way. The primary analysis should thus follow the protocol (the last version before start of the study) as close as possible, and any aspects that are not unambiguously defined should be justified. The impact of the repeated analyses (after 60 patients and after at least 100 patients) on the type I error rate and the bias of the estimates should be taken into consideration.

The safety data was considered sufficient to support a B/R evaluation.

The POD1UM-201 trial should show that retifanlimab induces durable objective responses in patients with metastatic or locally advanced MCC.

The Scientific Advice was predominantly sought on the appropriateness of the data package to support conditional marketing authorisation. As the Applicant decided to submit an application for standard marketing authorisation, the requirements for a CMA, like the major therapeutic advantage, are not currently relevant,

as the Applicant has submitted a request for standard marketing authorisation. Nevertheless, some points were still considered, such as that the data need to be assessed for comprehensiveness, regardless of type of application requested by the Applicant.

The FDA has granted accelerated approval to Zynyz (retifanlimab) on April 2023, for the treatment of MCC.

2.4. Quality aspects

2.4.1. Introduction

Retifanlimab, the active substance contained in Zynyz, is an anti-programmed cell death protein 1 (PD-1) immunoglobulin G4 (IgG4) humanised monoclonal antibody (MAb), produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture.

The finished product is presented as a concentrate for solution for infusion containing 25 mg of retifanlimab as active substance per 1 mL. One vial of 20 mL concentrate contains 500 mg of retifanlimab.

Other ingredients in the finished product are: sodium acetate trihydrate, acetic acid, sucrose, polysorbate 80, and water for injections.

Module 3 of this dossier was previously submitted in almost identical form (marketing authorisation application EMEA/H/C/005632 withdrawn in October 2021). The current dossier is based on the previous one and includes implemented responses to the previous Day 120 List of Questions (EMEA/H/C/005632) and other updates.

2.4.2. Active Substance

2.4.2.1. General information

Retifanlimab is a humanised hinge-stabilised IgG4, IgK MAb that recognises human PD-1 expressed on T cells (CD4+ and CD8+), B cells, NK cells, and myeloid-derived cells. It has a serine to proline mutation (S227P/S228P-Kabat) in human heavy chain (HC) CH2 region to greatly reduce or eliminate hinge inter-chain disulfide instability. Moreover, in order to remove an N-linked glycosylation site in CDR1, a single point mutation, N26S, was introduced into the variable region of the light chain (LC). C-terminal lysine (K) is eliminated from retifanlimab heavy chain DNA sequence to eliminate K-truncation as one of the post-translational modifications. Its light chain consists of 218 and its heavy chain of 445 amino acids, respectively, and it has a molecular weight of approximately 148 kDa.

2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

MacroGenics, 9704 Medical Center Drive, Rockville, MD 20850, United States is responsible for the manufacture of the active substance. All sites involved in the manufacture and control of the active substance operate in accordance with EU GMP.The manufacturing process consists of two main stages: cell culture and harvest and purification.

Retifanlimab is expressed using recombinant CHO cells that secrete the antibody into the culture medium. A single working cell bank (WCB) vial is thawed and expanded before inoculation into a production bioreactor. The unprocessed bulk containing retifanlimab is clarified The resulting harvested cell culture fluid is stored until the start of the purification process which includes a series of chromatography, viral inactivation and filtration steps.

The purification process consists of affinity chromatography, viral inactivation and neutralisation, depth filtration, cation exchange chromatography (CEX), anion exchange membrane chromatography, nanofiltration, UF/DF, bulk filtration and filling, and storage and transportation. The process steps, process parameters, operation ranges and controls have been laid down in sufficient detail.

No human- or animal-derived components were used in this process.

Control of materials

A two-tiered cell banking system consisting of MCB and WCB was established. Their preparation is described in the dossier. MCBs and WCBs are stored at multiple sites for safety purposes. All cell banks were tested for sterility, endogenous and adventitious agents and for identity. The characterisation and testing of the cell banks is considered comprehensive and in line with ICH Q5A and Q5D. The limit for *in vitro* cell age for production has been established in line with ICH Q5B. Genetic stability has been assessed satisfactorily.

According to an established supplier qualification program, appropriate measures (auditing, testing, and certification) are defined for each raw material supplier.

Media usage in the production of retifanlimab is described in sufficient detail together with their preparation holding times and in-process controls (IPCs).

Control of critical steps and intermediates

Critical process parameters (CPPs) and IPCs have been specified. The Applicant has also clearly stated Normal Operating Ranges (NORs) and Proven Acceptable Ranges (PARs) when applicable. These were validated during process characterisation and process verification (also referred to as process performance qualification (PPQ)) runs. PPQ runs were performed on three full scale batches in line with the recommendations in the guideline.

Process characterisation studies were based on failure modes and effects analysis (FMEA) risk assessment in line with the principles outlined in ICH Q8 (R2) in small scale with established and qualified small scale models.

Process validation

Validation of the retifanlimab manufacturing process was conducted using a lifecycle approach consisting of three stages:

- Process Design-in which the commercial process is defined based on the outcome of development and characterisation studies;

- Process Performance Qualification providing documented evidence that the process is capable of reproducible commercial manufacture;

- Ongoing Process Verification providing ongoing assurance that the commercial process remains in a validated state of control.

Overall, process validation is considered satisfactory.

Manufacturing process development

The retifanlimab manufacturing process was developed over two generations, M1 and M2.

The retifanlimab P1 finished product was a liquid formulation for intravenous application, stored at 5°C ± 3°C, at a target concentration of 25 mg/mL in acetate, sucrose, polysorbate 80, formulation buffer.

Active substance batches manufactured using M1 process have been used in the pivotal clinical study [INCMGA 0012-201].

Changes were made to the M1 manufacturing process in order to:

- Ensure clonality of the production cell line
- Utilise a working cell bank (WCB)
- Improve titre and increase scale to support late-stage clinical studies and eventual commercialisation of the process to meet supply demands.

This modified M1 process is designated M2. All changes between M1 and M2 process were related to optimising productivity and facility fit.

At the time M2 process-derived active substance was introduced into clinical studies, a comprehensive comparability study was performed which demonstrated that the M2 process produced material is comparable to M1 process produced material. Product purity was slightly improved in the M2 manufacturing process. As further substantiation of comparability, the three most recently manufactured batches of M1 and M2 were included in a side-by-side analysis with Reference Standard for the assessment of purity and potency.

Considerations discussed during a CHMP Scientific Advice, such as regarding comparability criteria, description of statistical and mathematical methodologies used and number and genealogy of batches, were taken into account in the comparability analysis.

Control Strategy

The approach taken to develop the retifanlimab manufacturing process and control strategy comprises the following steps:

- Definition of the quality target product profile (QTPP), forming the basis of design for development of the product;
- Identification, ranking, and characterisation of CQAs linking quality attributes to clinical safety and efficacy;
- Gathering of process understanding derived from (M1) and (M2) processes
- Process development risk assessments linking process parameters to CQAs;
- Establishment of a scale-down model (SDM) as basis for process characterisation studies;
- Process characterization to identify CPPs for each unit operation and to establish PARs in which all process parameters are to be controlled in order to maintain corresponding CQAs within appropriate ranges;
- Summary of process knowledge and process capability evaluation to derive justification of control elements per CQA;
- Definition of the retifanlimab control strategy;
- Confirmation of process by PPQ, demonstrating that the commercial process performs as expected in the commercial facility.

A list of potential CQAs was created and an impact scoring system was set up taking into account the potential effect on efficacy/potency, pharmacokinetics, immunogenicity and safety. An uncertainty factor was applied reflecting the relevance and quality of information used to assign the impact ranking (e.g. the availability of product specific data or the relevance of available literature references).

Process and pharmaceutical and safety related CQAs have been adequately defined.

NORs, PARs and the acceptance criteria for IPCs are substantiated by the studies performed.

The resulting control strategy consists of the control of raw materials, procedural controls, process design, CPPs, NORs and PARs, IPCs, and release and stability testing. This is comprehensively described.

Characterisation

Elucidation of structure

A comprehensive set of techniques was applied to evaluate relevant parameters such as primary, secondary, and higher order structures, heterogeneity aspects such as charge, size, and oxidised variants.

Oligosaccharide structure and distribution in retifanlimab is as expected for a typical monoclonal antibody produced by a CHO host cell line. Furthermore, potency aspects were investigated: functional potency (PD-1 blockade bioassay), Fc receptor binding (surface plasmon resonance) and potency (antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) assays). No ADCC and CDC activity mediated by retifanlimab were observed. Although Fc function is not required for retifanlimab biological function, detailed discussion of Fc bindings was provided.

Impurities

Process-related impurities include host cell proteins, host cell DNA, residual Protein A,. Product-related impurities/variants include fragments (low molecular weight species), dimers and aggregates (high molecular weight species).

Overall, characterisation of retifanlimab is considered satisfactory.

2.4.2.3. Specification

Specifications

Specifications for the active substance include control identity, purity and impurities, potency and other general tests.

Analytical procedures

Analytical procedures for release and stability testing of retifanlimab either comply with Ph. Eur. or in-house methods. Detailed method descriptions have been provided as well as respective validations.

Two methods are used to control potency:

- The PD-1 binding ELISA assay is a quantitative assay designed to measure the binding activity of retifanlimab to PD-1. The final reportable result (relative potency) is expressed as the binding activity of a test sample in percent compared to the reference standard.

The PD-1 blockade bioassay is a quantitative assay designed to measure the potency of retifanlimab to block the PD-1/PD-L1 interaction. The final reportable result (relative potency) is expressed as the activity of a test sample in percent compared to the reference standard.

In general, the descriptions of the analytical procedures are considered sufficient.

It is noted that the active substance and finished product are tested for endotoxin using the compendial Limulus Amebocyte lysate (LAL) test. The Applicant committed to evaluate the feasibility of transitioning to Ph. Eur. 2.6.32 Test for bacterial endotoxins using recombinant factor C. Based on the outcome of this evaluation, the Applicant will consider the development and validation of an assay based on recombinant Factor C. A bridging study between the current kinetic-chromogenic detection method and the recombinant Factor C endotoxin assay will then be performed. Statistical approaches were used for measuring the commercial process capability and evaluating the resulting product quality. The results from the statistical evaluation define the acceptance criteria for several of the quantitative product quality parameters.

The identification of retifanlimab currently relies on the bioactivity and the capillary isoelectric focusing (cIEF) result. This is considered sufficient.

Overall, the proposed specifications (acceptance criteria and corresponding analytical methods) are considered acceptable.

Reference standards

During development and manufacturing of retifanlimab, several reference standards have been used. Stability of the interim reference standard (IRS) is monitored as part of the annual requalification.

A working reference standard is prepared and was qualified against the primary reference standard. For future reference standards a protocol is provided. The selection of the proposed acceptance limits is clearly justified. Sufficient information is provided in the dossier. The Applicant has committed to update section primary reference standard (PRS) / working reference standard (WRS) qualification protocol in the event that the active substance specification is updated. The Applicant will qualify a new reference standard in such a way that the risk of a drift from the mean is reduced. Justification of the statistical approach and proposed acceptance ranges have been provided.

Batch analysis

Batch analyses results were provided for M1 and M2 processes.

Bridging studies were performed and demonstrate comparability between old and new analytical methods. Amended acceptance criteria were appropriately justified and described.

All results for the batches analysed comply with their predefined specifications and demonstrate appropriate batch-to-batch consistency.

Container closure

Retifanlimab active substance is stored at ≤ - 60^0C in bags . The system consists of a flexible bag with an integrative protective shell. The container closure system is sufficiently described; its suitability is sufficiently demonstrated by stability studies and data on extractable/leachables. No patient safety risk was observed for the bags in the extractables and leachables analysis.

2.4.2.4. Stability

The claimed shelf life and recommended storage conditions for retifanlimab active substance are 36 months at ≤ -60°C.

Stability studies for retifanlimab were conducted at the recommended storage condition of ≤ -60°C and at the accelerated storage temperature of 5 ± 3°C to assess the effect of these conditions on product quality. The three PPQ active substance batches also contain an arm at the stressed stability storage temperature of 25 ± 2°C. The testing was performed according to ICH Q5C and Q1A guidelines. Batches from the M1 process and batches at commercial scale (M2 process, were used for studying various storage conditions. In addition, different representative package materials were studied.

The stability plan was adequately designed and covered a sufficiently large time span at standard, accelerated and stressed conditions. All results reported for stability studies comply with the specifications and no trends could be observed.

The Applicant commits to continue the stability testing of the active substance as outlined in the stability plan presented.

The proposed active substance shelf life of 36 months when stored at ⩽ -60^{0}C is considered acceptable.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product

Retifanlimab finished product is a solution for intravenous infusion with a clear to slightly opalescent, colorless to pale yellow solution for intravenous infusion in a single-use 500 mg/vial (20 mL/vial) presentation. The primary packaging is a single-use 20 mL Type I glass vial closed with a chlorobutyl rubber stopper, an aluminum seal and plastic overseal. The concentration of the active ingredient is 25 mg/mL. An overfill of 0.6 mL is applied to ensure that 20.0 mL, corresponding to 500 mg, can be withdrawn from the vials. The composition of the finished medicinal product is provided in **Table 1** below.

Table 1: Composition of Retifanlimab finished product

Component	**Function**
Retifanlimab	Active ingredient
Sodium Acetate Trihydrate	Buffer component
Acetic acid	Buffer component
Sucrose	Stabiliser, osmolyte
Polysorbate 80	Stabiliser
Water for Injection	Solvent

Pharmaceutical development

The active substance and finished product have an identical formulation. The intended commercial formulation is the same as that used in clinical studies. The excipients are compendial and commonly used in parental medicinal products. The compatibility of the active substance with excipients is supported by the formulation study and stability data. There is no use of material of animal or human origin.

The commercial manufacturing process for retifanlimab was developed to meet the predefined criteria of the QTPP.

Retifanlimab active substance is stored frozen at ≤ -60°C, and then thawed to manufacture the finished product. The finished product is formulated at a nominal protein concentration of 25 mg/mL in sodium acetate, sucrose, and polysorbate 80. Manufacture of retifanlimab finished product involves thawing of frozen active substance, mixing, sterile filtration, vial filling, stoppering, and sealing. There is no dilution or compounding step involved for the manufacture of the finished product. The initial retifanlimab finished product manufacturing process (defined as P1) produced the to be marketed formation to supply the first non-clinical toxicity study as well as the clinical Phase I and Phase 2 studies. To support late phase clinical development and commercial readiness, a need for larger vial size (500 mg) was required, and the P2 process was implemented at Catalent. Subsequently, the P2 process was further optimised at Catalent resulting in P2-TPF, which is the finished product commercial manufacturing process. The active substance manufactured with M2 process (M2 AS) is used for both P2 and P2-TPF processes. Comparability studies show that the materials produced by the finished product manufacturing processes are comparable.

Finished product manufacturing steps that could impact CQAs were identified evaluated through characterisation studies. The control strategy that is in place to attenuate the risks associated to the CQAs is considered approvable.

Levels of potential leachables from the manufacturing process or container closure are very low and pose a low risk. Leachable studies currently cover up to 20 months of storage in the commercial primary packaging and reveal no issues.

Risk assessments for elemental impurities and nitrosamine contamination are included in the dossier. Elemental impurities pose a low risk whereas no risk of nitrosamine formation was identified.

The choice of materials for the container closure system are considered adequate to support the stability of the product, as demonstrated by extractables and leachables studies and supported by stability data. The container closure system’s ability to maintain the product’s quality during transport has also been demonstrated.

Retifanlimab finished product compatibility with different types of IV bags, in-line and add-on sterile filters are tested. The use of in-line or add-on filters as mandatory per the SmPC is considered adequately justified by the compatibility studies. The studies further demonstrate that the tested filters did not impact the product quality. Information in the SmPC including supported filter materials and infusion lines during administration and the shelf life after dilution are considered adequately supported by compatibility studies. The finished product formulation, including the excipient composition, is identical to the active substance. An overview of formulation developments studies is provided and includes selection of pH and formulation buffer, tonicity adjustor, surfactant and protein concentration. Selection of chosen formulation was additionally confirmed in stress studies (freeze-thaw, agitation, accelerated and stressed temperature). The results demonstrated that the developed retifanlimab finished product formulation is stable in the container closure system under long-term storage conditions. Based on the formulation development data, the finished product is formulated at 25 mg/mL retifanlimab in sodium acetate, sucrose and polysorbate 80. The robustness study was designed using a fractional factorial design of experiments (DoE) approach to evaluate formulation robustness to determine the impact of each formulation parameter on product quality and stability (CQAs). The study demonstrated that the proposed formulation is robust against variations in pH, excipient and protein concentration. Additional (extended) characterisation for sub-visible particles

demonstrated that analysing particles of ⩾ 10 µm and ⩾ 25 µm provides sufficient control of sub-visible particles and no on-going testing for ⩾ 2 µm particles will be performed, which is considered acceptable.

2.4.3.2. Manufacture of the product and process controls

Description of the manufacturing process

All sites involved in manufacture and control of the finished product operate in compliance with EU GMP.

The batch formula is provided for the validated range. Ph. Eur. monographs exist for all excipients. All analytical procedures used for retifanlimab excipient testing are compendial test methods and no validations are required.

The finished product manufacture is a straightforward thawing, mixing, filtration and aseptic filling process which has been described in sufficient detail. A flow diagram of the manufacturing process is provided. All mixing conditions, holding times, filtration steps and where relevant equipment have been clearly defined. All primary container parts are pre-sterilised and received ready to use.

Process validation

Control of critical process steps and intermediates of retifanlimab finished product manufacture is described through CPPs and IPCs. Proposed PARs and process limits for CPPs and acceptance criteria for IPCs are given for pooling, mixing, bioburden reduction filtration, sterile filtration, capping.

Process performance is qualified on three consecutive runs encompassing the proposed batch size. Process parameters, IPC-results and specification testing, and testing for within batch homogeneity is reported. Filter specifications and validation data are provided. Holding times are validated and clearly presented. Filled vials undergo 100% visual inspection for pre-defined defect categories. All specifications and pre-defined acceptance criteria for the manufacture of the PPQ batches were met. Aseptic filling is validated by media fills and shipping to respective distributors is validated by transport simulations.

Overall, the finished product manufacturing process is demonstrated to be adequately controlled.

2.4.3.3. Product specification

Specifications

The proposed commercial specifications for retifanlimab finished product include control of identity, purity and impurities, potency and other general tests. References to compendial methods are provided as well as unique method identification numbers for the in-house methods.

The predominant part of the finished product control tests and their release specifications are the same as applied for active substance control. Bioburden is replaced by sterility for finished medicinal product in accordance with Ph. Eur. monograph for monoclonal antibodies, and the acceptance criterion for protein concentration is slightly wider based on the target content of 25 mg/mL with a range around the target concentration and is considered acceptable. A statistical approach for setting criteria is described in the active substance module. Several quantitative product quality parameters and associated limits are not statistically derived. Rather, they are based on manufacturing experience during clinical development, supportive development studies (e.g. formulation robustness) as well as USP, Ph. Eur. and ICH guidelines. Identity is

confirmed with PD-1 blockade bioassay. Acceptance criteria for potency (PD-1 binding assay, PD-1 blockade bioassay) and purity are statistically derived. The finished product release and shelf life specifications are acceptable and the acceptance criteria have been adequately set.

Analytical procedures and reference standards

Except from the test for container closure integrity (CCI), the analytical methods used for release and stability testing of the finished product are either described in the active substance section of the dossier or are compendial methods. The approach to evaluating CCI is acceptable and the description is adequate. Volume in container, appearance and sub-visible particles are considered basic compendial test procedures which have been demonstrated to be suitable for use in finished product testing. Endotoxin and sterility testing are performed in accordance with the Ph. Eur. and have been verified with an acceptable approach.

The reference standard used for retifanlimab finished product is the same as the reference standard used for the active substance.

Batch analyses

Sufficient details on release tests and results of finished product batches have been provided including changes in analytical procedures during development. All release data meet the acceptance criteria and the lot to lot consistency is considered acceptable.

Characterisation of impurities

There are no new impurities introduced during manufacture of retifanlimab finished product. Risk assessments for elemental impurities and nitrosamine contamination are presented as part of the pharmaceutical development and demonstrate that impurities represent a low risk to product quality. This is acceptable. No specific control is considered necessary.

Container closure system

The container closure system (CCS) consists of a Type I glass vial closed with a chlorobutyl rubber stopper and an aluminum seal and plastic overseal. All components of the container closure are delivered ready-to-use from the manufacturer. Sterilisation is performed by the manufacturer. Schematic drawings, dimensions, release testing specifications and analytical certificates are provided for the components of the primary container. The suitability of the container closure system is supported by compatibility data included in the formulation studies together with the stability data for P2 and P2-TPF batches.

2.4.3.4. Stability of the product

An overview of the currently available finished product stability data is provided.The stability studies are performed according to ICH guidelines and described in sufficient detail. The studies are carried out with relevant container closure systems and the methods used are the same methods as referred in P.5. Stability protocol with time points together with testing panel are presented and considered sufficient and acceptable. Methods that are not considered as stability indicating are only analyzed at release. The currently proposed shelf life of 24 months for finished products stored at 5 ± 3°C is supported by real-time stability data from all primary stability finished product lots and can therefore be endorsed. A photostability study was performed in accordance with ICH guidance and shows that the finished product is sensitive to light exposure to which the original carton provides adequate protection. In-use stability studies cover the proposed use of retifanlimab finished product after dilution with normal saline 9 mg/mL (0.9%) solution or 5% glucose solutions in IV

bags, supporting the proposed hold times of IV bag preparations for up to 8 hours at room temperature (20 – 25°C) and 24 hours at 2 – 8°C from a physicochemical and microbial standpoint. The in-use stability studies performed support the concentration interval of diluted finished product referred in the product information between 1.4 to 10 mg/mL, as well as the proposed hold periods and conditions after preparation.

2.4.3.5. Adventitious agents

No human or animal-derived components or materials was used in the generation of host cell line, retifanlimab MCB, WCB. Retifanlimab active substance manufacturing process also does not use any raw materials containing human or animal-derived components.

MCB and WCB were tested for non-viral adventitious agents in compliance with ICH Q5A and results confirmed sterility for both the MCB and WCB.

During manufacture of retifanlimab active substance, unprocessed harvest bulk (pre-harvest) samples are routinely tested for mycoplasma and contamination control based on bioburden testing. Test results confirm that the bioburden is consistently low and no mycoplasma was detected.

Hence, raw materials used for retifanlimab active substance manufacturing process are not considered to pose a viral safety risk.

During manufacture of retifanlimab, unprocessed harvest bulk (pre harvest) samples are routinely tested for adventitious virus *in vitro* and minute virus of mice (MVM). Quantitation of retrovirus-like particles by Transmission Electron Microscopy (TEM) is also performed on the harvest sample to assess the potential viral load. Testing and results for viral adventitious agents in unprocessed bulk samples are presented and confirm that no adventitious viral agents were detected.

Viral clearance study

Virus clearance of the retifanlimab purification process was assessed using retifanlimab product-specific scaled-down models with four representative viruses (enveloped and non-enveloped, i.e. xenotropic murine leukaemia virus (XMuLV), pseudorabies (PRV), reovirus (Reo 3), MVM) in at least two orthogonal steps, in two independent experiments as defined in relevant regulatory and ICH guidance documents.

This study was designed to evaluate purification process steps

Detailed results are provided. An overall cumulative reduction factor for the retifanlimab active substance purification process was determined for each virus by summation of the reduction factors obtained for all selected steps to remove or inactivate virus.

Overall, viral and non-viral including TSE adventitious agents safety is considered sufficiently assured.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Module 3 of CTD of Zynyz is generally of good quality.

Active substance

The manufacturing process has been described in sufficient detail and information on quality and control of all raw and starting materials including the cell banks has been provided. The retifanlimab active substance manufacturing process was developed over two generations, M1 and M2, along with establishment of the

working cell bank. An extensive analytical comparability assessment has been performed between M1 and M2 manufacturing processes. The comparability approach and selection of the different analytical tools for comparability testing is appropriate. No major differences between active substance manufactured using the M2 process and M1 process were observed. Adequate characterisation has been presented using a broad set of analytical methods. Active substance specification ensure consistent quality of the active substance. Specifications include parameters commonly encountered for a monoclonal antibody. Description of in-house analytical methods and their validation are provided and considered acceptable. For reference standard, acceptable documentation is provided. Sufficient detail has been provided on the CCS for the active substance. Stability of the active substance has been demonstrated within the proposed shelf life of 36 months.

Finished product

The finished product is presented as a sterile, single dose solution for intravenous infusion in a 20 mL vial. The product is formulated using commonly used excipients. Sufficient details are provided detailing the pharmaceutical development of the product. Analytical comparability study performed between different processes demonstrated that the manufacturing changes did not impact the product quality. The manufacturing process (comprised of active substance receiving and storage, thawing, pooling and mixing, bioburden reduction filtration, sterile filtration and filling, stoppering and capping, visual inspection followed by secondary packaging) has been acceptably described and validated. Finished product specification ensure consistent quality of the finished product. Specifications include parameters commonly encountered for a monoclonal antibody. Description of in-house analytical methods is linked to active substance section. Summary of the transfer of methods is presented and considered acceptable. All presented batch release results are within stated acceptance criteria. Sufficient detail has been provided on the CCS for the finished product. Stability has been demonstrated within the proposed shelf life of 24 months.

The marketing authorisation application (MAA) is considered approvable from a quality point of view.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Zynyz is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the MAA for Zynyz is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended points for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

Retifanlimab is an anti-PD-1 antibody designed to target PD-1-expressing cells, in particular "exhausted" T cells, in order to sustain/restore their effector function by blocking inhibitory checkpoint interactions between PD-1 and its two ligands, PD-L1 and PD-L2. Retifanlimab contains a human IgG4 Fc region to limit effector function, while retaining FcRn binding to extend circulating half-life. Retifanlimab binds to both human and cynomolgus monkey PD-1. The primary non-clinical pharmacology program for retifanlimab was designed to characterize the biological activity and mechanism of action of retifanlimab. Pharmacology of PD-1 blockade was evaluated *in vitro* using primarily human peripheral blood mononuclear cells (PBMCs), cynomolgus monkey PBMCs and cells engineered for ectopic expression of human PD-1.
The non-clinical pharmacokinetics of retifanlimab were evaluated in cynomolgus monkeys as part of the single dose and repeat-dose toxicology studies. Anti-drug antibodies after retifanlimab dosing were assessed in repeat-dose toxicology studies.

The non-clinical toxicology program was conducted in compliance with Good Laboratory Practice (GLP) and in accordance with the recommendations provided in ICH S9 and ICH S6(R1) guidelines and was designed to support repeat-dose IV administration of retifanlimab in clinical trials in patients with advanced solid tumours. The safety of retifanlimab was evaluated exclusively in nonhuman primates, the only relevant and pharmacologically responsive model. The non-clinical toxicology package included single-dose and repeat-dose toxicology studies, as well as a tissue cross-reactivity study with human tissues. Reproductive and developmental toxicity studies have not been conducted with retifanlimab.

The pivotal 4- and 13-week repeat-dose toxicity studies, as well as the tissue cross-reactivity study, were performed in accordance with GLP as claimed by the Applicant.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro

1, IN VITRO-20.05: Retifanlimab Binding to PD-1 by SPR

Binding of retifanlimab to human and cynomolgus monkey PD-1 was evaluated by SPR technology. The SPR analysis measured the binding of human or cynomolgus monkey PD-1 protein at varying concentrations (0, 6.25, 12.5, 25, 50, and 100 nM) to retifanlimab captured on a F(ab')2 goat anti-human IgG Fc specific surface. Equilibrium dissociation constants (K_D) were determined by a global fit of binding curves to the Langmuir 1:1 binding model. The data are summarized in **Table 2**. The K_D values of retifanlimab for human PD-1 and cynomolgus monkey PD-1 are 0.6 and 3.6 nM, respectively. Retifanlimab has an approximate 6-fold higher binding affinity for human PD-1 than for cynomolgus monkey PD-1 due to a higher k_a and a lower k_d.

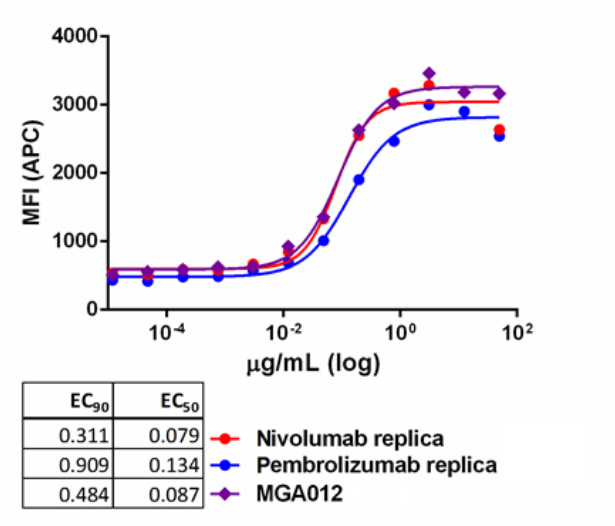
Table 2: Equilibrium Dissociation Constants (KD) for Binding of Human or Cynomolgus Monkey PD-1 Protein to Capture Retifanlimab

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

2, IN VITRO-20.06: Evaluation of Retifanlimab Binding to PD-1-expressing NS0 Cell Lines

To evaluate retifanlimab binding to ectopically expressed PD-1, NS0 cells were engineered to express the human PDCD1 gene (NS0/PDCD1 cells), and cell surface binding was determined by flow cytometry.

The representative experiment shown in figure 1 demonstrates that anti-PD-1 mAbs bind to NS0/PDCD1 cells in a dose-dependent manner. Specifically, retifanlimab binding to NS0/PDCD1 cells is comparable to the binding of the replicas of approved anti-PD-1 mAbs nivolumab and pembrolizumab. The mean EC_{50} averaged across 4 experiments for retifanlimab was 0.14 µg/mL, which is comparable to the EC_{50} values obtained for the replicas of nivolumab (0.16 µg/mL) and pembrolizumab (0.14 µg/mL).



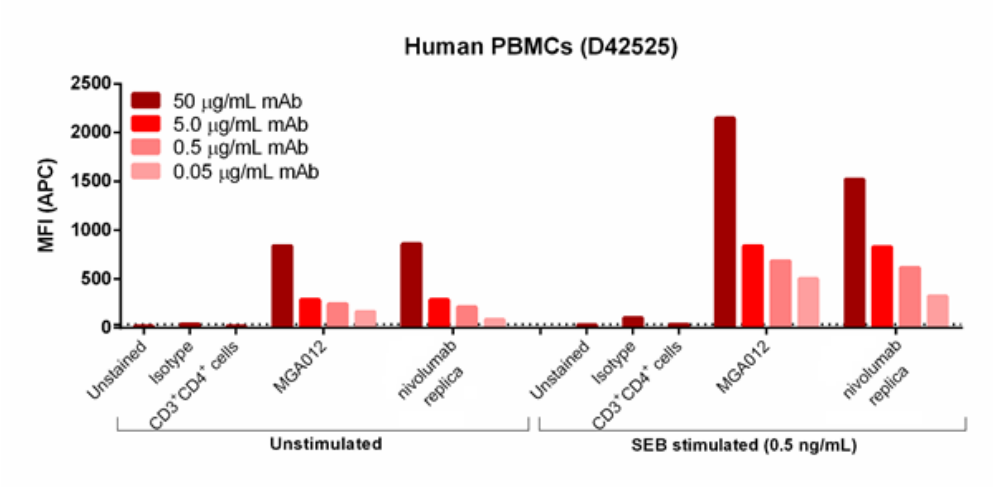
Dose-saturation curves of anti-PD-1 mAb binding to PD-1-expressing NS0 cells (NS0/PDCD1). Unlabeled anti-PD-1 mAbs, including nivolumab replica (red line), pembrolizumab replica (blue line), or retifanlimab (purple line), were prepared as 1:4 serial dilutions starting at 50 µg/mL and incubated with NS0/PDCD1 cells. Binding was then detected with a secondary goat anti-human Fc-APC conjugate. Data shown are plotted as mean fluorescence intensity MFI (APC) by anti-PD-1 mAb concentration on a semi-logarithmic plot. Representative data from 1 of 4 separate experiments.

Figure 1: Binding of Retifanlimab to PD-1-Expressing NS0 Cell Line (NS0/PDCD1)

3, IN VITRO-20.06: Retifanlimab Binding to Human T Cells Following Staphylococcal enterotoxin B-stimulation of Human PBMCs

Naïve T cells express relatively low levels of PD-1 on their surface, but enhanced expression has been observed following chronic viral infection, in tumor-infiltrating immune cells, or after SEB stimulation. The ability of retifanlimab to bind to native PD-1 expressed on T cells was evaluated by flow cytometry using human T cells that were stimulated for 48 hours in the presence of 0.5 ng/mL SEB or left unstimulated.

Unstimulated PBMCs expressed basal levels of PD-1 that were detected similarly by retifanlimab or nivolumab replica in a concentration-dependent manner (0.05-50.0 µg/mL) (**Figure 2**). Upon SEB stimulation, a 2 to 2.5-fold increase in PD-1 expression was detected on PBMCs. The increased PD-1 expression was also detected by the PD-1 mAbs in a concentration-dependent manner. Negative controls included unstained human PMBCs, isotype control stained PBMCs, and CD3+CD4+ gated cells alone with no anti-PD-1 mAbs. This dose-dependent binding to PD-1 was evident on both CD4+ and CD8+ T cells present within the unstimulated and SEB-stimulated PBMC populations (figure not shown).



10-fold serial dilutions of anti-PD-1 mAbs retifanlimab or nivolumab replica, on unstimulated or SEB-stimulated human PBMCs. Binding of 50.0 to 0.05 µg/mL of unlabeled anti-PD-1 mAbs was detected with a secondary goat anti-human Fc-APC conjugate. Data shown is plotted as grouped column graph as MFI (APC) by anti-PD-1 mAb concentration. Negative controls include unstained human PMBCs, isotype control stained PBMCs, and CD3+CD4+ gated cells alone with no anti-PD-1 mAbs.

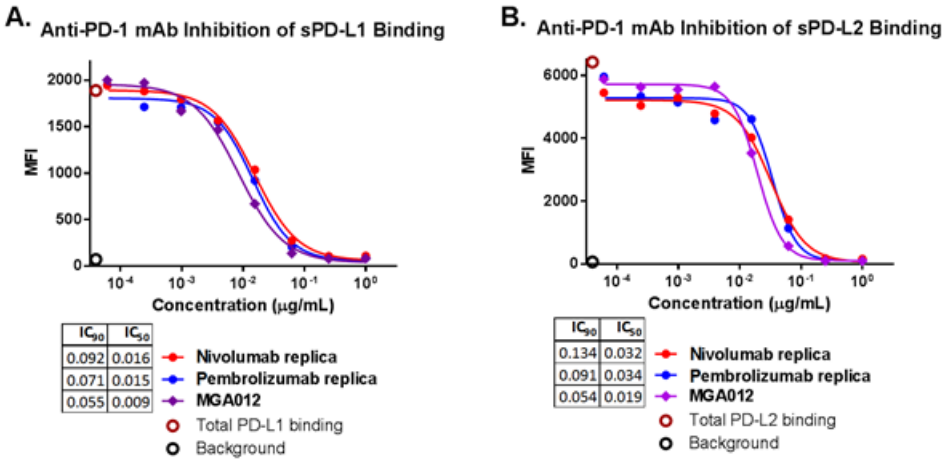
Figure 2: Binding of Retifanlimab to Unstimulated or SEB-stimulated Human PBMCs

4, IN VITRO-20.06: Retifanlimab Binding to SEB-stimulated Cynomolgus or Rhesus Monkey PBMCs

Retifanlimab was next evaluated for its ability to cross-react with non-human primate species by flow cytometry. Retifanlimab bound to both cynomolgus and rhesus monkey PBMCs following SEB stimulation. In contrast, isotype, unstained, or non-human primate CD45 stained cells that did not receive retifanlimab, showed little evidence of PD-1-specific binding and was comparable to retifanlimab binding observed in unstimulated cynomolgus or rhesus PBMCs.

5, IN VITRO-20.06: Retifanlimab Inhibition of Binding of Soluble PD-L1 or PD-L2 to PD-1-positive Cell Line

Retifanlimab was next evaluated for its ability to inhibit the interaction of PD-1 with its 2 corresponding ligands: PD-L1 and PD-L2. Specifically, a set of serially diluted anti-PD-1 mAbs were incubated with NS0/PDCD1 cells in the presence of soluble forms of human PD-L1 or PD-L2 and anti-PD-1 mAb binding was detected with a secondary-labeled goat anti-human Fc-APC conjugate. As shown in **Figure 3**, retifanlimab inhibited binding of soluble PD-L1 and PD-L2 to PD-1-expressing cells in a dose-dependent manner, which was comparable to the inhibition observed with the nivolumab and pembrolizumab replicas. With respect to the inhibition of sPD-L1, the mean half-maximal inhibitory concentration (IC50) of anti-PD-1 mAbs across 3 experiments were as follows: 0.010 µg/mL (retifanlimab), 0.016 µg/mL (nivolumab replica), and 0.014 µg/mL (pembrolizumab replica). With respect to the inhibition of sPD-L2, the mean IC50 of anti-PD-1 mAbs across 3 experiments were as follows: 0.021 µg/mL (retifanlimab), 0.028 µg/mL (nivolumab replica), and 0.028 µg/mL (pembrolizumab replica). Taken together, retifanlimab is capable of inhibiting the binding of sPD-L1 and sPD-L2 to PD-1-expressing (NS0/PDCD1) cells at similar concentrations as the replicas.



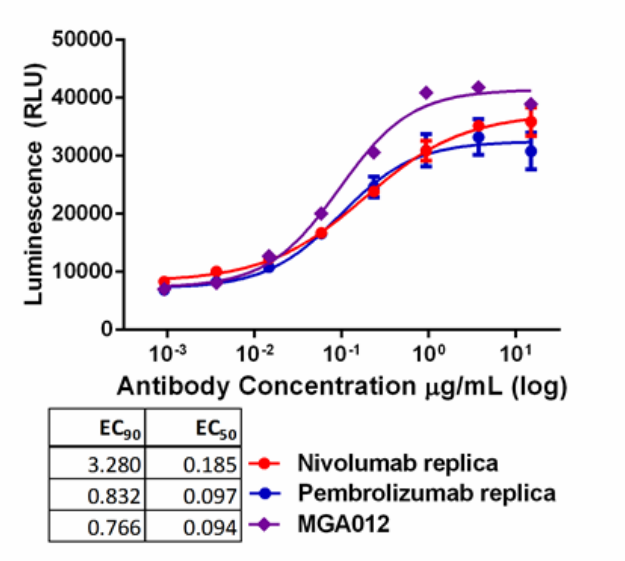
Representative dose-inhibition curves of anti-PD-1 mAbs blocking soluble PD-L1 (sPD-L1) (A) or sPD-L2 (B) binding to PD-1-expressing NS0 cells (NS0/PDCD1). Unlabeled anti-PD-1 mAbs, including nivolumab replica (red line), pembrolizumab replica (blue line), or retifanlimab (purple line), were prepared in 1:4 serial dilutions (starting at 10 µg/mL) and incubated with NS0/PDCD1 cells containing 0.1 µg of sPD-L1 or sPD-L2. Total sPD-L1 or sPD-L2 binding (open red circles) and background (open black circle) is shown as positive and negative ligand binding controls. Anti-PD-1 mAb binding was detected with a secondary-labeled goat anti-human Fc-APC conjugate. Data shown are plotted as MFI (APC) by anti-PD-1 mAb concentration. Representative data from 1 of three separate experiments.

Figure 3: Retifanlimab-mediated Inhibition of Soluble PD-L1 or PD-L2 Binding to a PD-1-positive Cell Line (NS0/PDCD1)

6, IN VITRO-20.06: Retifanlimab Inhibition of PD-1/PD-L1 Signaling Within a Reporter Assay System

Retifanlimab was evaluated for the ability to directly inhibit the PD-1/PD-L1 inhibitory axis through the use of a co-culture reporter assay system designed to assess PD-1/PD-L1 therapeutic antibodies for immunotherapy development. In this assay system, the functional intervention of PD-1/PD-L1 mediated blockade of NFAT signaling mediated by TCR stimulation is determined in the context of the co-culture of 2 cell lines: (1) a CD3-positive Jurkat reporter cell line engineered to constitutively express PD-1 and a luciferase reporter gene under the control of NFAT promoter triggered by a TCR activation and (2) a CHO-stimulator line that stably expresses PD-L1 and a TCR activator (anti-CD3). When co-cultured, NFAT signaling (despite TCR engagement) is strongly inhibited by the PD-1/PD-L1 interaction present between the Jurkat and CHO/PD-L1 cell lines. In the presence of blocking anti-PD-1 or anti-PD-L1 mAbs, this inhibitory axis is repressed in a dose-dependent manner allowing increased NFAT signaling that is measured optically through the transcription of a luciferase reporter gene.

As shown in **Figure 4**, retifanlimab, nivolumab replica, and pembrolizumab replica comparably block the PD-1/PD-L1 inhibitory axis and increase luciferase expression in a dose-dependent manner. With regards to increasing luciferase expression, the mean EC50 of anti-PD-1 mAbs averaged across 3 experiments were as follows: 0.090 µg/mL (retifanlimab), 0.171 µg/mL (nivolumab replica), and 0.103 µg/mL (pembrolizumab replica).

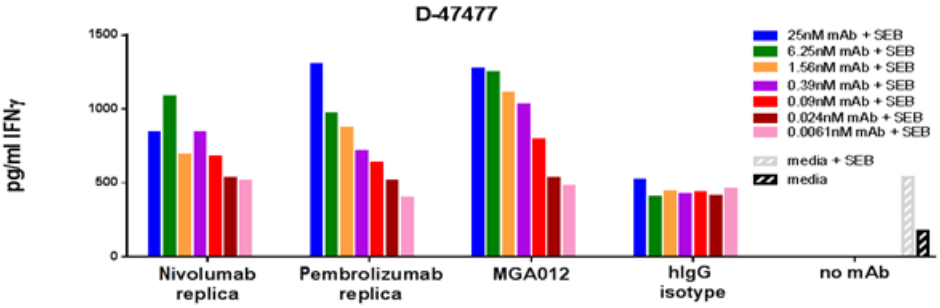


Representative evaluation of anti-PD-1 mAbs to enhance luciferase expression by releasing the inhibitory PD-1/PD-L1 axis within a co-culture reporter assay system (Promega). Unlabeled anti-PD-1 mAbs, including nivolumab replica (red line), pembrolizumab replica (blue line), or retifanlimab (purple line), were prepared as 1:5 serial dilutions (starting at 20 nM) and incubated in co-culture with Jurkat reporter cells expressing PD-1 and CD3/TCR (NFAT-luc2/PD-1 Jurkat cells) and CHO stimulator cells expressing PD-L1 and a TCR activator (CHO-PD-L1 cells). 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. The optical density of each well in duplicate is read at 450 nm with luminescence relative light unit (RLU) as the readout. The data were plotted as mean RLU against concentration and fitted using a log (agonist) vs. response–variable slope (four parameter) function. Representative data from 1 of 3 separate experiments.

Figure 4: Retifanlimab-mediated Reversal of PD-1/PD-L1 Inhibitory Signaling as Measured by Luciferase Gene Expression in a Co-culture Reporter Assay System

7, IN VITRO-20.06: Evaluation of Retifanlimab to Enhance IFN-γ Secretion Following SEB Stimulation of Human PBMCs

Retifanlimab was evaluated functionally with regard to the ability to enhance the secretion of cytokines such as IFN-γ following stimulation of human PBMCs by SEB.

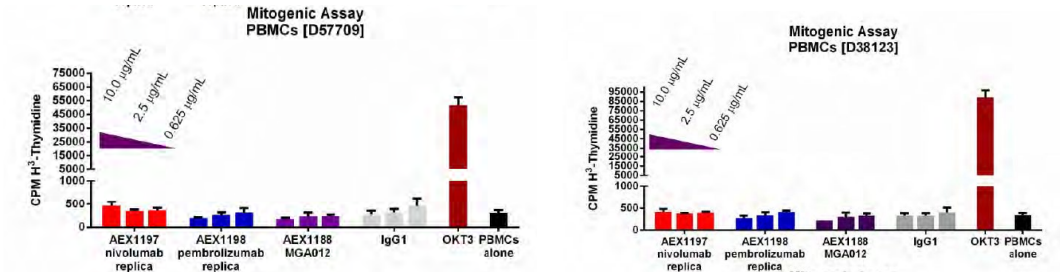


Secretion of IFN-γ from SEB-stimulated human PBMCs (showing 1 representative donor of 8). Human PBMCs were stimulated for 2 days, washed twice, and restimulated with 0.5 ng/mL SEB in the presence or absence of anti-PD-1 mAbs: retifanlimab, nivolumab replica, pembrolizumab replica. Human PBMCs either cultured alone in media or restimulated with SEB alone or SEB incubated with human IgG isotype control served to establish basal levels of IFN-γ secretion. The secretion of IFN-γ was determined by ELISA. The optical density of each well was read at 450 nm with luminescence relative light unit (RLU) as the readout and converted by standard curve linear regression to a concentration (pg/mL).

Figure 5: Evaluation of Retifanlimab to Enhance IFN-γ Signaling Following SEB Stimulation of Human PBMCs

8, IN VITRO-20.06: Evaluation of Intrinsic Mitogenicity of retifanlimab Following Culture of Human PBMCs

To confirm the lack of intrinsic mitogenicity of MGA012 on resting PBMCs, the anti-PD-1 mAbs: retifanlimab, the AEX1197 nivolumab replica, or the AEX1198 pembrolizumab replica were incubated with human PBMCs for 2 days and their proliferative potential was determined using the 3H-thymidine incorporation assay. As shown in the figure below with two donor PBMCs, none of the tested antibodies induced PBMCs to proliferate following two days of culture. The level of proliferation was consistent to the negative controls observed with culture of PBMCs alone or in the presence of human IgG1 isotype. In contrast, agonist CD3 stimulation through anti-CD3 mAb (OKT3 clone) induced robust proliferation.



MGA012 (purple), AEX1197 (nivolumab replica) (red), or AEX1198 (pembrolizumab replica) (blue) were incubated at 10.0, 2.5, or 0.625 µg/mL. Human PBMCs alone (black), or incubated with IgG1 isotype control (grey) or anti-CD3 [OKT3 clone] (maroon) were used as negative controls and a positive control, respectively. Radioactive incorporation was then detected as counts per minute (CPM) on Packard TopCount NXT microplate scintillation and luminescence counter (PerkinElmer).

Figure 6: Evaluation of intrinsic mitogenicity of anti-PD-1 mAbs

In vivo

Retifanlimab cross reacts with PD-1 from cynomolgus and rhesus monkeys, but not with PD-1 from non-primate species. Thus, in vivo studies were limited to cynomolgus monkeys with retifanlimab delivered by IV infusion. These studies in monkeys included the evaluation of a pharmacodynamic endpoint – retifanlimab binding to peripheral T cells by flow cytometry; these binding data are summarized in the sections for the single-dose PK study, the repeat-dose pilot toxicology study, and the 4-week repeat-dose GLP toxicology study.

2.5.2.2. Secondary pharmacodynamic studies

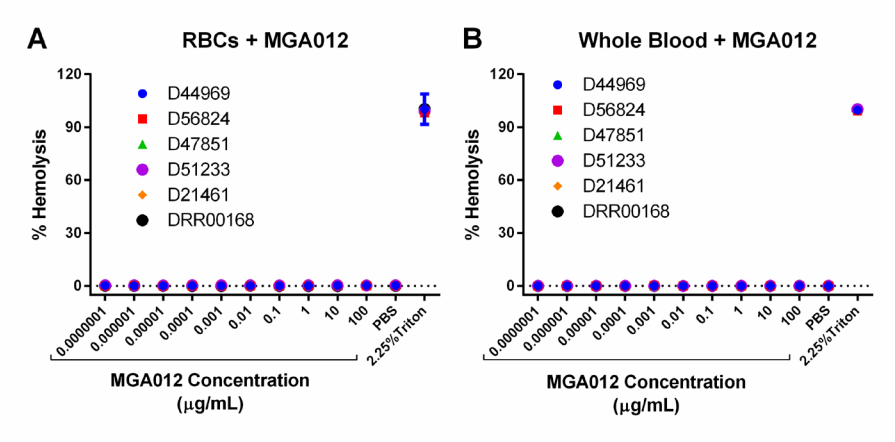
To support IV administration in humans, the hemocompatibility of retifanlimab was tested using purified human RBCs or whole blood. The ability of retifanlimab to mediate ADCC and CDC activity was evaluated in vitro. The intrinsic mitogenicity of retifanlimab was evaluated in PBMCs in vitro. Finally, a series of in vitro studies were conducted to evaluate cytokine production following retifanlimab treatment of human PBMCs alone, using both soluble as well as wet and dry-coated methods, and cytokine release was evaluated in vivo following administration of retifanlimab to cynomolgus monkeys.

A tissue cross-reactivity study to evaluate the potential cross-reactivity of retifanlimab in normal human tissues was conducted (see toxicology section).

1, IN VITRO-20.07: Evaluation of Retifanlimab Blood Compatibility

To evaluate the hemocompatibility of retifanlimab, purified human RBCs or whole blood from 6 independent healthy human donors were incubated with retifanlimab (up to 100 µg/mL) and tested for haemolysis. The use of purified RBCs avoids any potential interference from human plasma in the assay read-out, while whole blood accounts for the potential effects of other cell types present in the blood.

No hemolytic activity was observed with retifanlimab at any concentration tested in any of the purified RBC or whole blood samples evaluated (Figure 7). In contrast, treatment with the positive control (2.25% Triton X-100) decmonstrated nearly complete (> 94%) hemolysis in all samples.



Percent haemolysis evaluated in purified human RBCs (~1.5 × 108 cells/well) (A) or whole blood (B) from 6 independent human donors treated with the indicated concentrations of retifanlimab or 2.25% Triton X 100 (positive control) for 2 hours at 37°C.

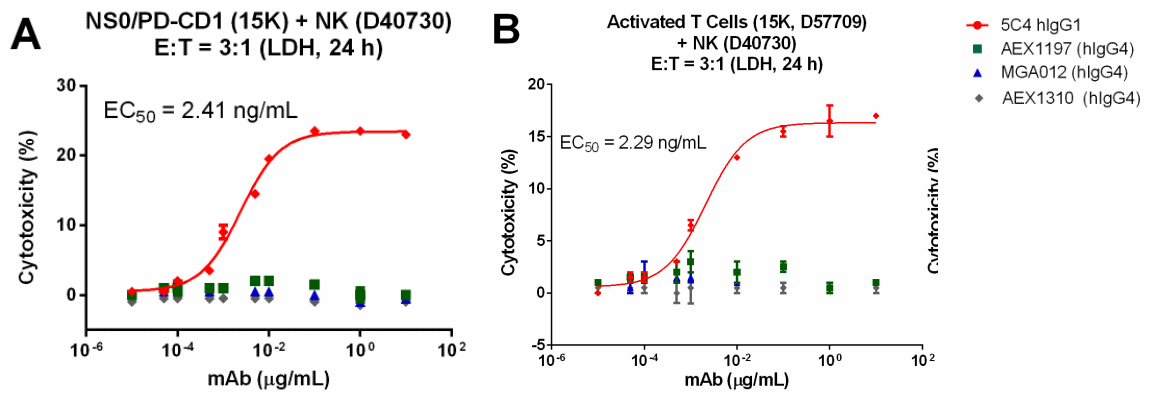
Figure 7: No Haemolysis with Retifanlimab in Purified RBCs or Whole Blood.

2, IN VITRO-20.08: Evaluation of Antibody-dependent Cellular Cytotoxicity (ADCC) or Complement-dependent Cytotoxicity (CDC)

The ability of retifanlimab to mediate ADCC activity was evaluated with a PD-1-positive target cell line (NS0/PDCD1) or activated human primary T cells from 3 independent human donors as target cells using purified human NK cells as effector cells at an E:T cell ratio of 3:1. This ratio reflects the effective NK cell-to-target cell ratio in standard cytotoxicity assays performed with PBMCs at a final E:T cell ratio of 30:1.

ADCC data from the LDH assay using NS0/PDCD1 cells are shown in Figure 8A. Similarly, ADCC data from the LDH assay using activated human primary T cells as target cells and NK cells as effectors from 3 independent donors, including 2 of the same donors used in the assays with NS0/PDCD 1 target cells, are shown in Figure 8B.

B. No retifanlimab-mediated cytolytic activity was observed against NS0/PDCD1 cells or activated human primary T cells at concentrations up to 10 µg/mL (the highest concentration evaluated). Likewise, no cytolytic activity was observed with the nivolumab replica or irrelevant control antibody (palivizumab replica, an anti-RSV antibody). In contrast, 5C4 hIgG1, the anti-PD 1 control mAb with a wild-type human IgG1 Fc domain, demonstrated concentration-dependent ADCC activity against NS0/PDCD1 cells and against activated human primary T cells with EC50 values ranging between 0.17-2.41 ng/mL for NS0/PDCD 1 cells and 2.29-12.74 ng/mL for activated human primary T cells.

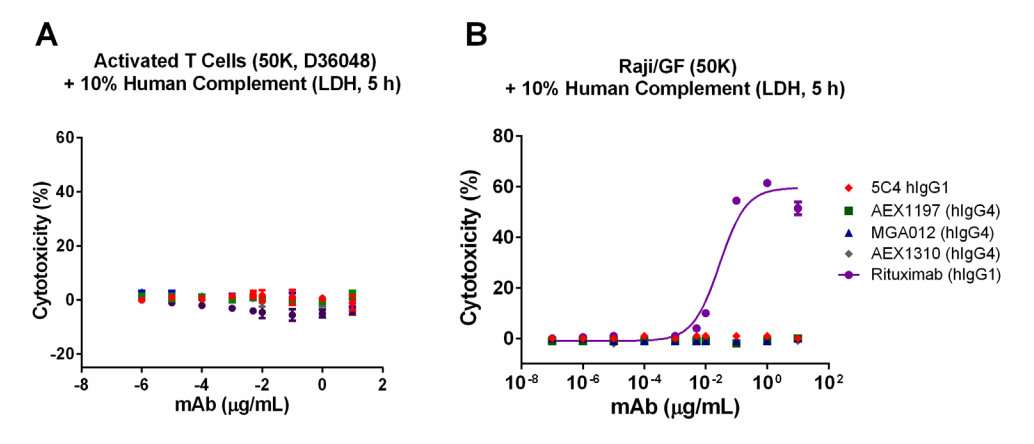


The ability of retifanlimab to mediate ADCC was evaluated using NS0/PDCD1 (Panels A) or activated primary human T cells (Panel B) as target cells and purified human NK cells as effector cells at an E:T cell ratio of 3:1. Retifanlimab activity was compared to anti-PD-1 mAbs, 5C4 hIgG1 and the AEX1197 nivolumab replica with human IgG1 and IgG4 Fc domains, respectively, as well as the AEX1310 palivizumab replica with a human IgG4 Fc domain (irrelevant control antibody). Purified NK cells from 3 independent healthy donors were utilized and data from 1 representative donor for each target cell type are shown. The percent cytotoxicity shown in Panels A and B was calculated from measured LDH release from NS0/PDCD1 and activated primary human T cells target cells, respectively, following 24 hour incubation.

Figure 8: No ADCC Activity Mediated by Retifanlimab in NS0/PDCD1 (PD-1-Expressing Cells) or Activated Primary Human T cells Target Cells.

The ability of retifanlimab to mediate CDC activity was evaluated with PD 1-postive activated human primary T cells using 10% human serum as a source of complement. No retifanlimab-mediated CDC activity was detected across the retifanlimab concentrations evaluated (up to 10 µg/mL) with PD 1-positive activated human primary T cells (see Figure 9A). The 10% human serum complement concentration was chosen based on assay optimization conducted using varying percentages of human serum complement to measure rituximab cytotoxicity against lymphoma target cells and is consistent with the concentration ranges used by others for rituximab-based CDC assays.

As a positive control, the ability of rituximab (hIgG1) to mediate CDC activity in Raji/GF cells (human Burkitt's lymphoma cell line) was confirmed using the same assay format (see Figure 9B). Lack of CDC activity mediated by retifanlimab is based on the inability of the IgG4 Fc to bind C1q, and as reported previously in the context of the anti-PD 1 nivolumab bearing the same IgG4 Fc domain as retifanlimab. These data suggest that there is no CDC activity mediated by the IgG4 Fc domain in retifanlimab.

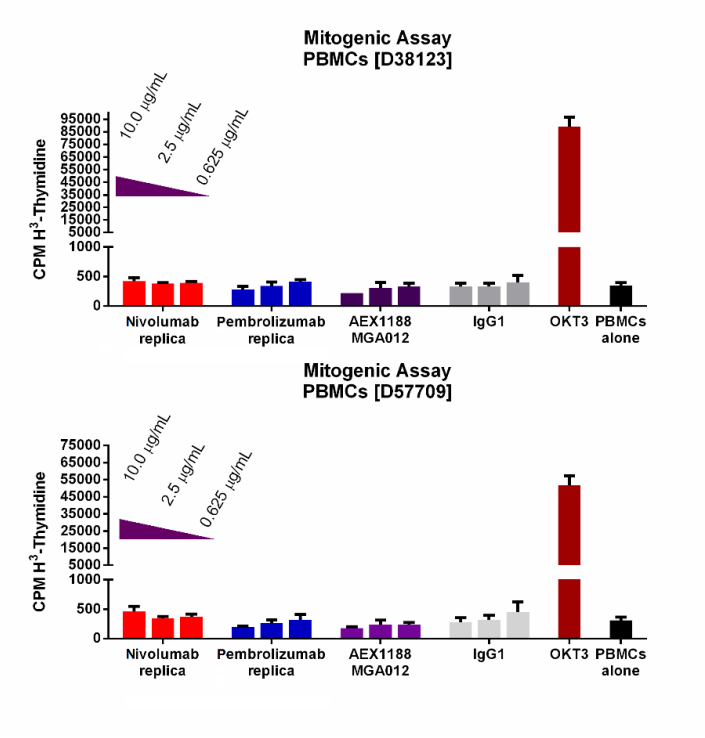


The ability of retifanlimab to mediate CDC was evaluated on activated primary human T cell target cells following 5-hour incubation in the LDH assay. Retifanlimab activity was compared to anti-PD-1 mAbs, 5C4 hIgG1 and the nivolumab replica (AEX1197) with human IgG1 and IgG4 Fc domains, respectively, as well as the palivizumab replica (AEX1310) with a human IgG4 Fc domain (irrelevant control antibody) and rituxumab (anti-CD20 IgG1 antibody). Human serum complement was utilized at 10% concentration. Data are shown for 1 of 2 independent studies.

Figure 9: **No CDC Activity Mediated by Retifanlimab in Activated Primary Human T cells Target Cells**

3, IN VITRO -20.06: Evaluation of Intrinsic Mitogenicity of Retifanlimab Following Culture of Human PBMCs

To confirm the lack of intrinsic mitogenicity of retifanlimab on resting PBMCs, the anti-PD 1 mAbs: retifanlimab, nivolumab replica, or pembrolizumab replica were incubated with human PBMCs for 2 days and their proliferative potential was determined using the 3H-thymidine incorporation assay (IN VITRO-20.06). As shown in Figure 10 with 2 donor PBMCs, none of the tested antibodies induced PBMCs to proliferate following 2 days of culture. The level of proliferation was consistent to the negative controls observed with culture of PBMCs alone or in the presence of human IgG1 isotype. In contrast, agonist CD3 stimulation through anti-CD3 mAb (OKT3 clone) induced robust proliferation.



Evaluation of intrinsic mitogenicity of anti-PD 1 mAbs. Retifanlimab (purple), nivolumab replica (red), or pembrolizumab replica (blue) were incubated at 10.0, 2.5, or 0.625 µg/mL. Human PBMCs alone (black), or incubated with IgG1 isotype control (grey) or anti-CD3 [OKT3 clone] (maroon) were used as negative controls and a positive control, respectively. Radioactive incorporation was then detected as counts per minute (CPM) on Packard TopCount NXT microplate scintillation and luminescence counter (PerkinElmer).

Figure 10: **Evaluation of Intrinsic Mitogenicity of Retifanlimab.**

In Vitro Cytokine Release

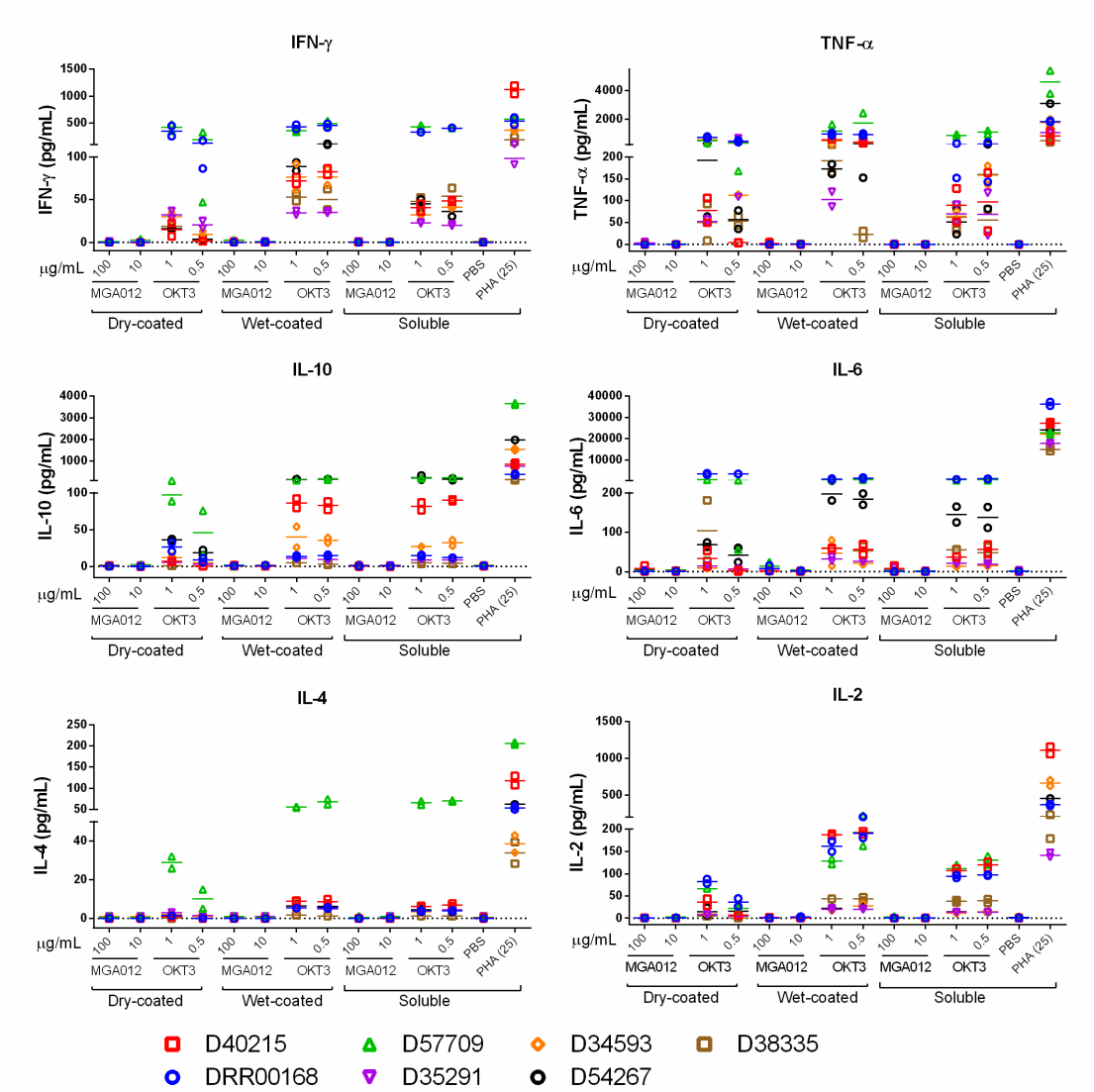
4, IN VITRO-20.09: Evaluation of Cytokine Production from Human PBMCs by Soluble or Immobilized retifanlimab

In vitro cytokine production following treatment with retifanlimab was tested using human PBMCs under different conditions whereby retifanlimab was presented as either soluble or immobilized onto assay plates by wet- or dry-coating. Assay positive controls included the anti-CD3 mAb, OKT3, and the T-cell mitogen, phytohaemagglutinin (PHA). Culture supernatants were harvested and the levels of six cytokines (IFN-γ, IL-2, IL-4, IL-6, IL-10, and TNF-α) determined using the BD™ Cytometric Bead Array Human Th1/Th2 Cytokine Kit, according to the manufacturer's instructions.

Peripheral blood mononuclear cells from 7 independent healthy human donors were incubated with increasing concentrations of soluble or plate-immobilized (ie, wet- or dry-coated) retifanlimab (100 and 10 µg/mL) for 24 hours and the accumulated levels of IFN γ, IL 2, IL 4, IL 6, IL 10, and TNF α in culture supernatants were determined. The mean level for each individual cytokine detected across the 7 donors following treatment with retifanlimab under the 3 assay conditions evaluated in parallel is presented in Figure 11. Phytohemagglutinin (soluble form only) and OKT3-induced cytokine release confirmed the PBMC response for each donor in each assay.

Upon exposure of PBMCs to retifanlimab concentrations of 10 µg/mL and 100 µg/mL (ie, 10-200 times higher than the positive control antibody OKT3), no cytokine production was observed with all three conditions of retifanlimab presentation. Also, no cytokine release was observed when PBMCs were exposed to retifanlimab

concentrations below 1 µg/mL. The level of individual cytokines observed across seven independent human PBMC donors with 100 µg/mL or 10 µg/mL retifanlimab under these three conditions evaluated in parallel assays is presented in Figure 11.



Cytokine concentrations measured in the culture supernatants of normal human donor PBMCs (n = 7) following 24 hours incubation in plates with dry-coated retifanlimab, wet-coated retifanlimab, or soluble retifanlimab. The OKT3 control was also dry- and wet-coated onto assay plates, as well as tested in soluble format. The PHA control was only evaluated in soluble format. Symbols show duplicate values for each individual donor with the respective horizontal line indicating the mean value for the duplicate samples. Note different y-axis scales for each cytokine.

Figure 11: Mean Cytokine Induction in Normal Human PBMCs by Soluble or Immobilized Retifanlimab

In Vivo Cytokine Release

Cytokine release following administration of retifanlimab to cynomolgus monkeys was also evaluated as part of: (1) a single dose PK study with selected toxicological endpoints (T15 06 12), (2) a repeat dose pilot toxicology study (T15-08-05), and (3) a 13-week toxicity study (T18-02-10).

5, Study T15 06 12: single dose PK study with selected toxicological endpoints

A single-dose PK study with selected toxicological endpoints was conducted in cynomolgus monkeys. In this study, retifanlimab was compared to 2 other anti-PD 1 IgG4κ mAbs: pembrolizumab (MK-3475) and nivolumab replica. Each antibody was administered at 10 mg/kg by 1-hour IV infusion to 2 monkeys (1M, 1F) and animals were monitored for 65 days, at which time they were returned to the colony.

No cytokines (IFN γ, IL 2, IL 4, IL 5, IL 6, IL 10, and TNF α) were induced in serum samples of cynomolgus monkeys treated with retifanlimab or nivolumab replica, except for elevations in IL 5 following pembrolizumab administration.

6, Study T15-08-05: repeat dose pilot toxicology study

Retifanlimab or Vehicle was administered as a 1 hour IV infusion once weekly for 3 weeks. Two animals (1M, 1F) received vehicle and 4 animals (2M, 2F) received retifanlimab at doses of 1 or 100 mg/kg making a total of eight animals that received retifanlimab.

Infusion of retifanlimab did not result in notable changes in serum levels of IFN γ, IL-2, IL-4, IL 5, IL-10, or TNF-α. Small (< 100 pg/mL) and transient increases in IL-6 levels were observed at 3 and 6 hours following infusion, which returned to or near baseline levels within 24 hours of infusion; however, these changes were not considered related to retifanlimab as similar increases in IL-6 were observed following infusion of vehicle control. One animal treated with 100 mg/kg retifanlimab had an isolated transient increase in IL-6 up to 1946 pg/mL at 3 hours post-infusion on Day 1, but IL-6 levels returned to near baseline (8 pg/mL) by 6 hours post-infusion; minimal (<10 pg/mL) IL-6 increases were observed following subsequent infusions on Days 8 and 15 in this animal. There were no notable clinical observations in this animal during the study.

7, Study T18-02-10: 13-week toxicity study

Cynomolgus monkeys (5/sex/group) were administered retifanlimab once weekly by IV infusion over 30 minutes at doses of 0, 5, 20, or 100 mg/kg for 13 weeks. Blood samples were collected for cytokine analysis pre-dose and 1, 4, and 24 hours post-dose on Days 1 and 85. The majority of cytokine/chemokine levels were BLQ at all timepoints for all groups.

Measurable levels of IL-6 were occasionally observed post-dose in a few animals across groups (including control animals) without a dose response; a relationship to retifanlimab, at least in part, could not be ruled out.

Higher IL-12 levels were observed for in 1 female administered 10 mg/kg on Day 1(4 and 24 hours post-dose) and Day 86 (24 hours post-dose). Although IL-12 was detected in this animal only after dosing, this was considered unlikely related to retifanlimab due to occurrence in a single low dose animal.

2.5.2.3. Safety pharmacology programme

No dedicated safety pharmacology studies have been performed with retifanlimab. Evaluation of safety pharmacology endpoints were included in toxicology and/or pharmacodynamic studies, in accordance with ICH S6(R1) (2011) and ICH S7A (2000) guidelines for biotechnology-derived products.

Parameters evaluated in the 4-week GLP toxicology study (T19-01-03) performed in cynomolgus monkeys contributing to the safety pharmacology core battery assessment of the CNS, cardiovascular system, and respiratory system included neurological examinations (general attitude, behaviour, motor function, cranial nerves, proprioception and postural reactions, and spinal nerves) and body temperature; evaluation of blood pressure, heart rate, electrocardiograms, and respiration rate; as well as clinical observations and gross and

histologic examination. No retifanlimab-related findings suggestive of adverse effects on the CNS, cardiovascular, or respiratory systems were noted at any dose level evaluated (10-150 mg/kg).

In addition, the evaluation of cytokine production in vitro and in vivo also informed the safety pharmacology evaluation for retifanlimab.

2.5.2.4. Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies have been performed, as non-clinical pharmacology studies were conducted to support the use of retifanlimab as monotherapy.

2.5.3. Pharmacokinetics

The PK of retifanlimab were evaluated in cynomolgus monkeys as part of the single dose and repeat dose toxicology studies. Anti-drug antibodies after retifanlimab dosing were assessed in repeat dose toxicology studies in cynomolgus monkeys. A limited drug distribution study was performed on a select set of tissues harvested from the 3-week non-GLP repeat dose study in cynomolgus monkeys.

A summary of toxicology studies performed in cynomolgus monkeys with TK evaluation and the determined mean PK parameters are provided in Table 3.

Table 3: Study Design and Mean PK parameters a of Toxicology Studies Conducted for Retifanlimab in Cynomolgus Monkeys with TK Evaluation

Type of Study	Single Dose	3-week Repeat Dose	4-week Repeat Dose[b]	13-week Repeat Dose[b]
Testing facility	Charles River Laboratories, Inc			SNBL USA, Ltd
Study number	T15-06-12	T15-08-05	T19-01-03	T18-02-10
Lot number	P753.043	826.002	805.173	120617001
Dose (mg/kg)	10	1, 100	10, 40, 150	5, 20, 100
Regimen	Single dose	Once weekly × 3 doses	Once weekly × 4 doses	Once weekly × 13 doses
Dosing Route	1 hr IV infusion	1 hr IV infusion	1 hr IV infusion	30 min IV infusion

Type of Study	Single Dose	3-week Repeat Dose	4-week Repeat Dose[b]	13-week Repeat Dose[b]
Animal number	2 (1M/1F)	8 (2M/2F per dose)	30 (5M/5F per dose)	30 (5M/5F per dose)
CL (mL/h/kg)	0.345	0.262 ± 0.06	0.213 ± 0.02	0.259 ± 0.03
V_{ss} (mL/kg)	85.8	54.2 ± 7.8	68.4 ± 2.9	70.5 ± 3.3
$t_{1/2}$,term (h)	68.6	155 ± 29	242 ± 21	209 ± 22
MRT (h)	261	216 ± 43	335 ± 31	288 ± 30
BA and TK report number	DMB-20.46	DMB-20.47	DMB-20.48 DMB-20.49	DMB-18.151 DMB-18.152 DMB-18.146

[a] Mean (±SD if N>2) PK parameters calculated from NCA
[b] report contains a GLP compliance statement
M: male; F: female

Methods of analysis

A (non-validated) ELISA was used to quantitate retifanlimab levels in monkey serum in the non-GLP single dose and 3 week studies. The method used for non-GLP studies was a non-validated, fit for purpose method. The LLOQ of the method was set at 9.775 ng/mL initially for the single dose study (T15-06-12 (20077288)). However, in the 3-week repeated dose study (T15-08-05 (20079545)), in order to ensure a complete PK profile, the assay LLOQ was lowered to 4.875 ng/mL.

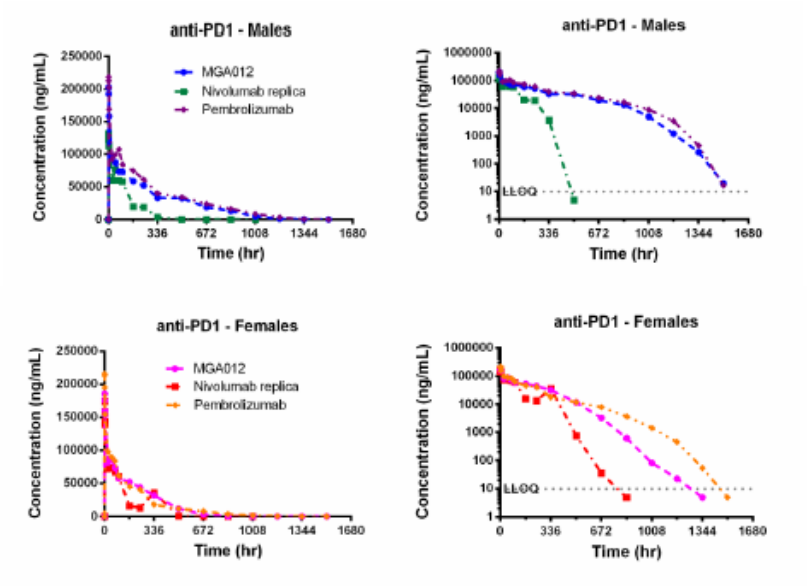
For the pivotal 4 week and 13 week studies, a validated ELISA was used to quantitate retifanlimab levels in monkey serum. For the detection of antibodies against retifanlimab in serum, a screening assay and a confirmatory assay were used, based on a qualified bridging ELISA method. ADA methods were not validated in accordance with GLP.

Single-Dose Pharmacokinetics

The PK of retifanlimab were determined in male cynomolgus monkeys after a single dose at 10 mg/kg via 1-hr IV infusion (DMB-20.46). For comparison purposes, 2 other anti-PD-1 mAbs, AEX1197 (nivolumab replica constructed based on the published sequence) and MK-3475 (authentic pembrolizumab [Keytruda; Merck], were included in the same study. Blood samples were collected for determination of serum TK for all three anti-PD-1 mAbs. ADA was not evaluated in this study.

Serum concentration-time profiles by sex of retifanlimab, nivolumab replica, and authentic pembrolizumab in monkeys are illustrated in Figure 12.

Pharmacokinetic parameters of retifanlimab in monkeys after single dose are summarized in Table 4. The mean CL_{pred} was 0.345 mL/h/kg, which is substantially lower than the GFR in cynomolgus monkeys (~125 mL/h/kg), indicating minimal renal clearance. The mean CL_{pred} for retifanlimab was similar to authentic pembrolizumab but approximately 2.2 times lower than nivolumab replica. The mean $V_{ss, pred}$ was 85.8 mL/kg, which is about twice the plasma space (~45 mL/kg), but less than the extracellular space (~200 mL/kg) of cynomolgus monkeys.



Serum concentration-time profiles in animals receiving 10 mg/kg retifanlimab (MGA012), nivolumab replica , or authentic pembrolizumab administered by IV infusion over 1 hour. Panels on the left are on a linear y-scale, panels on the right are on a logarithmic y-scale.

Figure 12: **Serum Concentration-time Profiles for Anti-PD-1 mAbs After Single 1-hour IV Infusion at 10 mg/kg**

Table 4: Anti-PD-1 mAbs PK Parameters in Monkeys Following Single 1-hour IV infusion of 10 mg/kg

Test Article	Retifanlimab (MGA012)			Nivolumab replica			Pembrolizumab		
Animal ID	M	F	Mean	M	F	Mean	M	F	Mean
T_{max} (h)	1.3	1.3	**1.3**	1.0	1.0	**1.0**	1.3	1.3	**1.3**
$C_{max,obs}$ (µg/mL)	203	185	**194**	132	174	**153**	218	216	**217**
AUC_{last}(h·µg/mL	36237	24208	**30222**	11806	14914	**13360**	43555	24367	**33961**
$AUC_{inf,pred}$(h·µg/mL)	36240	24208	**30224**	11807	14914	**13360**	43557	24368	**33963**

Test Article	Retifanlimab (MGA012)			Nivolumab replica			Pembrolizumab		
Cl_{pred}(mL/h/kg)	0.276	0.413	**0.345**	0.847	0.670	**0.759**	0.230	0.410	**0.320**
$V_{ss,pred}$ (mL/kg)	89.0	82.6	**85.8**	85.6	96.6	**91.1**	78.2	91.9	**85.1**
$t_{1/2,term}$ (h)	64.2	73.1	**68.6**	26.9	39.2	**33.0**	55.7	60.8	**58.3**
$MRT_{inf,pred}$ (h)	322.5	200.0	**261.2**	101.1	144.0	**122.6**	340.6	224.0	**282.3**

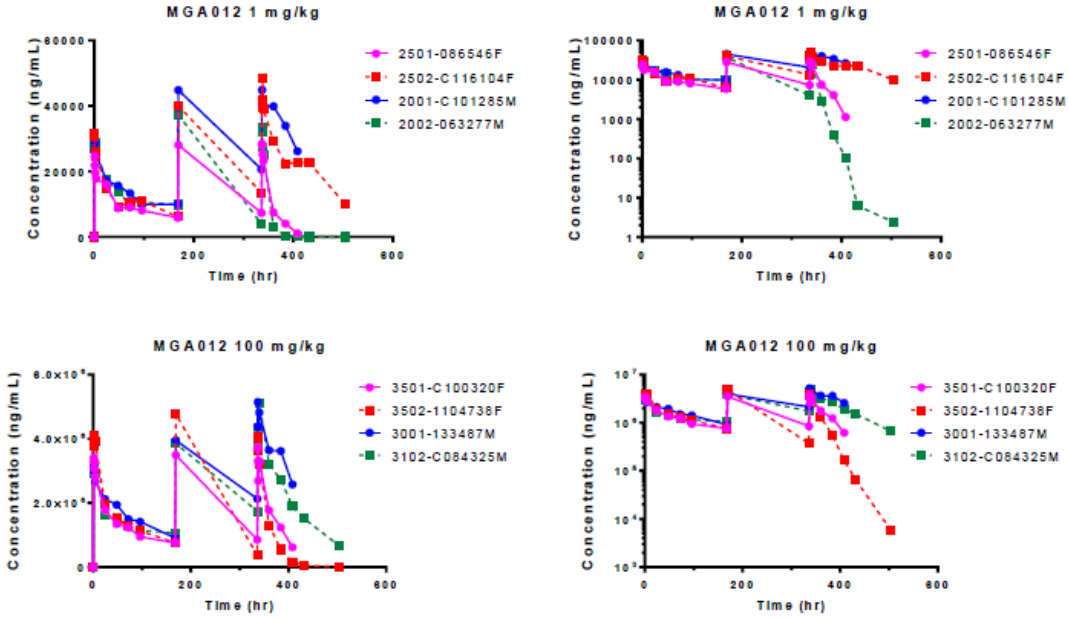
Repeat-dose Pharmacokinetics

Toxicokinetics in Repeat-dose - non-GLP Toxicology Study

A multiple-dose non GLP TK study was conducted in cynomolgus monkeys for retifanlimab according to Study protocol T15-08-05 (DMB-20.47). Two groups of monkeys (N=2/sex/dose) were given weekly doses of 1 or 100 mg/kg of retifanlimab via 1-hr IV infusion for three weeks.

Blood samples were collected for determination of serum retifanlimab TK. Anti-drug antibodies were also assessed for all animals treated with retifanlimab. Serum concentration-time profiles are illustrated in Figure 13. From visual inspection of the PK profiles, the slope of the curves after the third dose dropped more sharply than after the first dose for Animals 2002, 2501, 3501, and 3502, indicating the possible emergence of ADA at later cycles. Therefore, ADA was evaluated for all animals treated with retifanlimab.

Non-compartmental analysis was performed for Week 1 data from all animals since they were not impacted by ADA. However, data from the 4 animals that showed aberrant PK profiles were not included in the two-compartmental analysis since the clearance may not be constant over time in these animals. TK parameters from NCA and two-compartmental analysis are shown in Table 5 and Table 6, respectively. Mean clearance of retifanlimab at 1 mg/kg was similar to that at 100 mg/kg (0.22 vs. 0.21 mL/h/kg for males and 0.34 vs. 0.28 mL/h/kg for females by NCA; 0.17 vs 0.20 mL/h/kg by two-compartment analysis), suggesting PK is linear from 1 mg/kg to 100 mg/kg. Consequently, the sex averaged mean Cmax and AUC values for retifanlimab increased proportionally with dose from 1 mg/kg to 100 mg/kg. Mean Vss of retifanlimab by either NCA or two-compartment modeling ranged from 47 to 67 mL/kg, independent of dose and animal sex. Mean MRT values of retifanlimab were 170 to 256 hours (7.1 to 10.7 days) and 281 to 437 hours (11.7 to 18.2 days) from NCA and two-compartment modeling, respectively.



Panels on the left are on a linear y-scale, panels on the right are on a logarithmic y-scale. Male and female animals are labeled with the suffix "M" and "F", respectively.

Figure 13: Serum Concentration-time Profiles for Retifanlimab After Weekly IV Infusion at 1 or 100 mg/kg for 3 weeks

Table 5: Mean TK Parameters in Cynomolgus Monkeys (2M+2F) Following 1-hour IV Infusion of 1 or 100 mg/kg Retifanlimab by Noncompartmental Analysis of Week 1 Data

Dose (mg/kg)	1		100	
Sex	Male	Female	Male	Female
N	2	2	2	2
T_{max} (h)	1.13	1.13	1.13	1.13
$C_{max,obs}$ (µg/mL)	30.2	28.1	3118	3755
AUC_{last} (h•µg/mL)	2208	1741	248622	226322
$AUC_{inf,pred}$ (h•µg/mL)	4554	2923	496216	359856
CL_{pred} (mL/h/kg)	0.220	0.342	0.207	0.279
$V_{ss,pred}$ (mL/kg)	56.1	64.4	48.8	47.4
$t_{1/2,term}$ (h)	182.0	134.8	176.6	125.5
$MRT_{inf,pred}$ (h)	255.7	188.3	249.4	169.8

Table 6: Mean TK Parameters in Cynomolgus Monkeys Following 1-hour IV Infusion of 1 or 100 mg/kg Retifanlimab by Two-compartmental Analysis of All Data That Were Not Impacted by ADA

Dose (mg/kg)	1	100
N	2 (1M/1F)	2 M
$C_{max,pre}$ (µg/mL)	29.4	3055
$AUC_{inf,pred}$ (h•µg/mL)	6487	548303
CL (mL/h/kg)	0.172	0.196
CL_{D2} (mL/h/kg)	0.965	0.495
V_1 (mL/kg)	33.6	32.4
V_2 (mL/kg)	33.3	18.1
Vss (mL/kg)	66.9	50.5
$t_{1/2,\alpha}$ (h)	13.9	16.7
$t_{1/2,\beta}$ (h)	318	206
MRT (h)	437	281

Toxicokinetics in 4-Week Repeat-dose GLP Toxicology Study

A 4-week GLP TK study was conducted in cynomolgus monkeys for retifanlimab according to Study protocol T19-01-03 (DMB-20.49). Male and female monkeys (5/sex/dose) were given retifanlimab at 10, 40, or 150 mg/kg by 1 hour IV infusion once weekly for 4 weeks. Blood samples were collected on Week 1 (after first dose) and Week 4 for determination of serum retifanlimab TK. Predose and EOI blood samples were also collected at Week 2 and Week 3 to determine serum retifanlimab concentrations. The presence or absence of ADA in serum samples was assessed for animals with evidence of altered TK profiles.

Decreased retifanlimab concentrations at Week 2 to Week 4 were observed in 14 out of 30 animals (7/10, 4/10, and 3/10 animals in the 10, 40, and 150 mg/kg dose groups, respectively). Seven of the 14 animals (4/7, 2/4, and 1/3 animals in the 10, 40, and 150 mg/kg dose groups, respectively) with evidence of altered TK profiles were confirmed positive for ADA against retifanlimab. For the 7 animals with evidence of altered

TK profiles that were not confirmed positive for ADA, the corresponding retifanlimab trough concentrations were above the drug tolerance level of the ADA, thus it was assumed that these animals formed ADA but was undetected due to the interference from the high retifanlimab serum concentrations. Accordingly, when a trough retifanlimab concentration was lower than the preceding trough concentration, data from this time forward were not included in TK analysis.

The TK parameters were averaged across male and female monkeys since there is minimal sex differences in the pharmacokinetics of retifanlimab according to PK parameters in individual monkeys, see Table 7 and Table 8.

Retifanlimab pharmacokinetics are linear across the tested dose range of 10 to 150 mg/kg. Based on NCA analysis of Cycle 1 data (before the emergence of ADA), the mean values across all three dose groups for CL, Vss, and the MRT are 0.21 mL/h/kg, 68 mL/kg and 335 hours (around 14 days), respectively (see Table 3). From two-compartment modeling of data across all cycles for the 3 dose groups, mean values were 0.22 mL/h/kg for clearance, 72.3 mL/kg for steady-state volume of distribution (38.5 mL/kg for V1, and 33.8 mL/kg for V2), and 329 hours for MRT.

Table 7: Toxicokinetic Parameters (Mean ± SD) in Cynomolgus Monkeys (5M+5F) Following 1-hour IV Infusion of 10, 40 or 150 mg/kg Retifanlimab by Noncompartmental Analysis of Week 1 Data

Parameter	10 mg/kg (Group 2)	40 mg/kg (Group 3)	150 mg/kg (Group 4)
N	10	10	10
$C_{max.obs}$ (µg/mL)	251 ± 24.7	1140 ± 223	4114 ± 464
t_{max} (h)	1.2 ± 0.4	1.3 ± 0.5	1.2 ± 0.4
$AUC_{0\text{-}168h}$ (h*µg/mL)	18997±2347	82108±7813	305355±23166
$t_{½\ term}$ (h)	241 ± 54	264 ± 50	222 ± 28
$AUC_{inf,pred}$ (h*µg/mL)	47328 ± 11280	214350 ± 33558	696573 ± 79695
CL_{pred} (mL/h/kg)	0.229 ± 0.087	0.191 ± 0.028	0.218 ± 0.026
$V_{ss,pred}$ (mL/kg)	71.2 ± 5.7	68.4 ± 7.5	65.5 ± 4.9
$MRT_{inf,pred}$ (h)	334 ± 77	366 ± 71	304 ± 40

Table 8: Toxicokinetic Parameters (Mean ± SD) in Cynomolgus Monkeys Following 1-hour IV Infusion of 10, 40 or 150 mg/kg Retifanlimab by Two-compartmental Analysis of All Data which were not impacted by ADA

Parameter	10 mg/kg QW	40 mg/kg QW	150 mg/kg QW
	(Group 2)	(Group 3)	(Group 4)
N	10	10	10
$C_{max, pred}$ (µg/mL)	240 ± 20	1078 ± 130	3938 ± 306
t_{max} (h)	1	1	1
$AUC_{inf,pred}$ (h*µg/mL)	47310 ± 16970	205723 ± 65215	745681 ± 134493
CL (mL/h/kg)	0.236 ± 0.09	0.210 ± 0.06	0.210 ± 0.04
CL_{d2} (mL/h/kg)	1.11± 0.40	1.64 ± 1.02	0.94 ± 0.97
V_1 (mL/kg)	41.2 ± 3.3	36.7 ± 4.2	37.7 ± 2.7

Parameter	10 mg/kg QW	40 mg/kg QW	150 mg/kg QW
V_2 (mL/kg)	29.8 ± 7.7	30.2 ± 8.7	41.4 ± 16.9
$V_{ss,pred}$ (mL/kg)	71.0 ± 8.9	66.8 ± 11.9	79.1 ± 17.7
$t_{½\ term}$ (h)	242 ± 92	254 ± 112	311 ± 123
$MRT_{inf,pred}$ (h)	336 ± 129	353 ± 155	399 ± 129

Toxicokinetics in 13-Week Repeat-dose GLP Toxicology Study

A 3-month GLP TK study was conducted in cynomolgus monkeys for retifanlimab according to Incyte protocol T18-02-10 (DMB-18.146). Male and female monkeys were given retifanlimab at 5, 20, or 100 mg/kg by 30 min IV infusion once weekly for 13 weeks. Blood samples were collected at Week 1 (after first dosing), Week 4, and Week 13 for determination of serum retifanlimab TK. Anti-drug antibodies were also assessed for all animals.

After IV dosing of retifanlimab at 5, 20, and 100 mg/kg in both male and female monkeys, sex differences were not observed in the TK of retifanlimab. Retifanlimab exhibited linear TK across the tested dose range. For Week 1 TK parameters from all groups combined, mean clearance and steady-state volume of distribution were 0.259 mL/h/kg and 70.5 mL/kg, respectively. Mean terminal half-life value was 209 hours, or ~9 days, and mean residence time (MRT) was 288 hours, or ~12 days. The AUC0-167.5h values after the fourth dosing in comparison to AUCinf,pred values after the first dosing suggested ~92% steady state was reached after the fourth weekly dosing.

Immunogenicity (ADA) was observed for 10/30 (33%) animals, including 8/10 animals in Group 2, 2/10 animals in Group 3, and 0/10 animals in Group 4. Evidence of decreased retifanlimab serum concentrations following repeated doses of retifanlimab was observed in 8/10, 3/10, and 1/10 animals in the 5, 20, and 100 mg/kg dose groups, respectively. The presence of ADA against retifanlimab was confirmed in 8/8, 2/3, and 0/1 of the animals in the 5, 20, and 100 mg/kg dose groups, respectively. For the 2 animals with aberrant TK profiles but without a positive ADA response, the corresponding retifanlimab trough concentrations were above the drug tolerance level of the ADA.

Distribution

Mean Vss determined by NCA from all studies ranged from 54.2-85.8 mL/kg (see Table 3). These values were about 1-2 fold of the plasma space (~45 mL/kg).

A limited drug distribution study was performed on a select set of tissues harvested from cynomolgus monkeys treated with retifanlimab (1 or 100 mg/kg administered IV once weekly for 3 weeks, Study T15-08-05) using an IHC-based approach (DMB-20.45). Tissues examined included mandibular lymph node, mesenteric lymph node, muscle, colon, thymus, spleen, and tonsil. Same tissues harvested from vehicle control-treated monkeys were stained with a murine anti-PD-1 IgG1 mAb (MG13.78) to obtain tissue cross-reactivity information.

Immunohistochemistry analyses under optimal conditions using a murine anti-PD-1 IgG1 mAb (MG13.78, the precursor antibody to retifanlimab, which has the same epitope specificity as retifanlimab) revealed MG13.78 mainly bound to lymphocytes in germinal centers of lymph node, spleen, and tonsil, as well as in medullary of spleen. The staining was also observed in rare lymphocytes of colon. No staining was observed in parenchymal elements of the test tissues.

The staining pattern of tissues from monkeys treated with retifanlimab revealed evident distribution of retifanlimab in intravascular fluid and perivascular interstitium. Retifanlimab was also present in the membrane and cytoplasm of lymphocytes in lymphoid organs such as lymph node, spleen, tonsil, and thymus, which is consistent with PD-1 expression in these tissues. The degree of retifanlimab detected on lymphocytes was directly correlated with the dose level and inversely correlated with the time interval between last treatment administration and organ harvest. The higher the dose and the shorter the time interval, the more intense was the staining intensity. No binding of retifanlimab was evident in skeletal muscle or colon.

Table 9: Summary of Serum Retifanlimab Toxicokinetics (Mean ± SD) Following Weekly Intravenous Administrations of Retifanlimab for 13 Weeks in Male and Female Cynomolgus 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

Sex	Week	Parameter	5 mg/kg QW (Group 2)	20 mg/kg QW (Group 3)	100 mg/kg QW (Group 4)
	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

Sex	Week	Parameter	5 mg/kg QW (Group 2)	20 mg/kg QW (Group 3)	100 mg/kg QW (Group 4)
	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

Note: Not all subjects have calculable TK at Week 4 and Week 13

Metabolism

Retifanlimab is an anti-PD-1 IgG4κ mAb. The metabolism of immunoglobulins is generally thought to be through elimination by cellular catabolism following nonspecific uptake by pinocytosis or receptor-mediated endocytosis. No specific studies to evaluate the metabolism of retifanlimab have been conducted.

Excretion

The clearance of retifanlimab in cynomolgus monkeys from different studies ranged 0.213 to 0.345 mL/h/kg, which is significantly lower than the GFR in cynomolgus monkeys (~125 mL/h/kg). No specific studies to evaluate the excretion of retifanlimab have been conducted.

Pharmacokinetic drug interactions

No PK drug interaction studies with retifanlimab have been performed.

Other pharmacokinetic studies

No other PK studies with retifanlimab have been performed.

2.5.4. Toxicology

The non-clinical toxicology program for retifanlimab was conducted in accordance with ICH S9 (2010), and ICH S6(R1) (2011) guidelines.

The principal repeat-dose toxicology studies to support the application are a 4-week repeat-dose GLP study with a 10-week recovery period (T19-01-03), and a 13-week repeat-dose GLP study (T18-02-10).

2.5.4.1. Single dose toxicity

The tolerability, PK and PD of retifanlimab was compared to MK-3475 (pembrolizumab [Keytruda®; Merck]) and AEX1197 (an anti-PD-1 antibody constructed based on the published sequence for nivolumab [Opdivo®; Bristol-Myers Squibb]; hereafter referred to as the nivolumab replica) following a single IV infusion (1 hour) to cynomolgus monkeys (1/sex) at 10 mg/kg.

All 3 antibodies were tolerated with no test article-related clinical signs, changes in body weight, food consumption, or immune cells (as evaluated by immunophenotyping). Retifanlimab and the nivolumab replica were not associated with any changes in cytokines, whereas elevations in IL-5 were observed following pembrolizumab administration. Retifanlimab and pembrolizumab demonstrated prolonged binding to PD-1 on the surface of CD4+ and CD8+ T cells (≥80% maintained for 28 days or more), whereas the nivolumab replica exhibited less prolonged binding (≥80% maintained for 21 days or less). For each of the anti-PD-1 antibodies, the T-cell PD-1 binding data correlated with their serum concentrations. The serum concentration-time profiles for retifanlimab and pembrolizumab appeared generally comparable, while C was lower and clearance was faster in animals treated with the nivolumab replica.

Table 10: Single dose toxicity studies with retifanlimab in cynomolgus monkeys

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
T15-06-12	Cynomolgus monkey/1M 1F	10 mg/kg IV over 1 hour 9 weeks recovery	NA/10 mg/kg	None

2.5.4.2. Repeat dose toxicity

Pivotal repeat-dose toxicity studies with retifanlimab in cynomolgus monkeys include a 4-week study (doses: 0, 10, 40, or 150 mg/kg) with a 10-week recovery period (T19-01-03) and a 13 week study (doses: 0, 5, 20, 100 mg/kg; T18 02-10). In both studies, retifanlimab was administered once weekly by IV infusion (1 hour infusion in 4-week study, 30 minute infusion in 13-week study).

In both studies there were no observed adverse clinical signs, or effects on body weight, food consumption, ophthalmology or electrocardiograms. There were no effects in neurological and respiratory evaluations in the 4-week study.

There were no definitive retifanlimab-related changes in cytokines in the 13-week study (not evaluated in the 4-week study). The majority of cytokine/chemokine levels were below the limit of quantitation at all time points. However, measurable levels of IL-6 were occasionally observed postdose in a few animals (including control animals) without a dose response. Transient increases in IL-6 levels following infusion, which returned to at or near baseline levels within 24 hours, were also observed in a single animal administered 100 mg/kg/dose in a preliminary range-finding study (T15-08-05).

In both studies, variable transient reductions in lymphocytes were observed on Day 2 (following the first infusion). In the 4-week study, transient reductions also occurred following subsequent infusions in some animals. These findings correlated with flow cytometry evaluation of immune cell populations (immunophenotyping) in the 4-week study which showed a transient dose-independent, decline in total leukocytes, T cells, B cells, and NK cells at 23 hours post-infusion which generally recovered by 72 hours post-infusion. The greatest magnitude of change was observed following the first infusion.

In the 13-week study, minimally to moderately increased fibrinogen occurred on Day 2 in retifanlimab-treated groups, which may have been a nonspecific response to a foreign protein.

T cell occupancy was evaluated in the 4-week study by detecting cell-bound retifanlimab on CD4+ and CD8+ T cells with an anti-human IgG4 antibody. Maximal retifanlimab binding to PD-1+/CD4+ and PD-1+/CD8+ cells was observed during the dosing phase at all doses. In recovery animals without evidence of ADA, retifanlimab binding to PD-1+/CD4+ and PD 1+/CD8+ T cells was maintained throughout the 10 week recovery period and correlated with serum concentrations.

In the 4-week study, retifanlimab-related microscopic changes were noted at the IV administration site and consisted of minimal multifocal perivascular mononuclear cell infiltrates within the superficial dermis (males at ≥40 mg/kg; females at ≥10 mg/kg).

In a preliminary 3-week range-finding study (doses 0, 1, 100 mg/kg; 2 animals/sex; T15-08-05), increases in spleen weight and a dose-dependent mild to moderate lymphohistiocytic infiltrate of the red pulp were evident in animals receiving retifanlimab. Similar findings were not observed in longer-term pivotal studies at similar or higher doses.

In both the 4- and 13-week studies, decreased retifanlimab serum concentrations following repeated dosing were observed in animals in all dose groups, with greater frequency at lower doses. This correlated with the presence of ADA, which was confirmed in most of these animals.

Toxicokinetic analysis in the 13-week study demonstrated dose proportional exposure. The estimated half-life was approximately 8 days. There were no apparent sex differences in the exposure or disposition.

Transient decreases in lymphocyte populations and increases in fibrinogen were observed which were most pronounced after the first infusion. Following administration for 13 weeks, the NOAEL was considered to be 100 mg/kg per dose, the highest dose evaluated (sex combined mean Cmax of 4.88 mg/mL and AUC of 237 h•mg/mL).

Table 11: Repeat-dose toxicity studies

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg)	Major findings
T15-08-05 (non-GLP)	Cynomolgus monkeys/ 1M 1F (veh) 2M, 2F	0, 1, 100 mg/kg IV 1hr infusion	3 weeks, no recovery	100 mg/kg	**Microscopy** ≥1: dose-dependent increase in lymphohistiocytic infiltrate of red pulp of spleen **Organ weight** ≥1: increased relative spleen weight **Cytokines** =100F: ↑IL-6
T19-01-03 (GLP)	Cynomolgus monkeys/ 3M 3F main study, 2M 2F recovery study	0, 10, 40, 150 mg/kg IV 1hr infusion	4 weeks, 10 weeks recovery	150 mg/kg	**Microscopy** ≥10(F), ≥40(M): mononuclear cell infiltration IV site ≥10: mononuclear/mixed cell infiltration in multiple organs **Flow cytometry** ≥10: ↓ leukocytes, T cells, B cells, NK cells **Haematology** =10, 40 (M), ≥40(F): ↓lymphocytes =150 (M): ↑large unstained cells
T18-02-10 (GLP)	Cynomolgus monkeys/ 5M 5F	0, 5, 20, 100 mg/kg IV 30 min. infusion	13 weeks, no recovery	100 mg/kg	**Microscopy** ≥5F, =20, 100M: mononuclear cell infiltration IV site ≥5: mononuclear/ macrophage cell infiltration in multiple organs **Haematology** ≥5(M), =5(F): ↓lymphocytes **Coagulation** ≥5:↑fibrinogen **Cytokines** ≥5M, =5, 100F: ↑IL-6 **Flow cytometry** =100F: ↓monocytes

- **Toxicokinetics**

Study ID	NOAEL (mg/kg)	Animal $AUC_{0\text{-}168t}$ (mg.h/ml)	Exposure Multiple AUC
3 week rep dose (T15-08-05)	100	237	20
4 week rep dose (T19-01-03)	150	305	26
13 week rep dose (T18-02-10)	100	237	20
human*		11.82	

*MRHD is 500 mg retifanlimab every 4 weeks (70 kg). AUC is estimated by POP-PK analysis.

2.5.4.3. Genotoxicity

No genotoxicity studies were performed with retifanlimab.

2.5.4.4. Carcinogenicity

Carcinogenicity studies with retifanlimab have not been conducted.

2.5.4.5. Reproductive and developmental toxicity

Standard fertility and early embryonic development, embryofetal development and pre- and postnatal development studies have not been conducted with retifanlimab as not required for advanced cancer therapeutics (ICH S9 2009).

Scientific literature suggests that the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the foetus during pregnancy. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the foetus and to result in an increase in foetal loss; As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, foetal exposure to retifanlimab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

Based on these reports, potential risks associated with administration of retifanlimab during pregnancy include increased rates of abortion and stillbirth (data not shown).

2.5.4.6. Toxicokinetic data

Anti-retifanlimab antibodies were measured in some of the animals in all studies. Based on the provided TK data and the NOAELs of the pivotal studies, the exposure multiples were calculated. Data from all animals (including animals with suspected or proven ADA's) were included for a worst-case calculation.

Table 12: Exposure multiples based on TK data and NOAELs from three pivotal studies

Study ID	**NOAEL (mg/kg)**	**Animal $AUC_{0\text{-}168t}$ (mg.h/ml)**	**Exposure Multiple AUC**
3 week rep dose (T15-08-05)	100	237	20
4 week rep dose (T19-01-03)	150	305	26
13 week rep dose (T18-02-10)	100	237	20
human*		11.82	

*MRHD is 500 mg retifanlimab every 4 weeks (70 kg). AUC is estimated by POP-PK analysis.

2.5.4.7. Local Tolerance

Local tolerance was not evaluated in a separate study, but local tolerance endpoints were integrated in two pivotal repeat dose studies with retifanlimab, in accordance with ICH S6(R1) (2011) and ICH M3(R2) (2009) guidelines.
At the end of the dosing phase in the 4-week GLP toxicology study (T19-01-03), retifanlimab-related microscopic changes were noted at the IV administration site and consisted of minimal multifocal perivascular mononuclear cell infiltrates within the superficial dermis (males at ≥40 mg/kg; females at ≥10 mg/kg). Minimal mononuclear or mixed cell infiltration at the injection site was observed in the 13-week study although this finding was also observed in control males (T18-02-10). At the end of the recovery phase, there were no retifanlimab-related microscopic changes noted.

2.5.4.8. Other toxicity studies

Antigenicity

When administered in 3-, 4- and 13-week repeat-dose toxicity studies, the presence of ADAs was confirmed in 37.5%, 23% and 33% of the animals, respectively. In general, the incidence of ADA responses was highest in the lower-dose groups.

Tissue Cross-Reactivity

The objective of study T16-02-22 was to determine the potential cross-reactivity of retifanlimab with cryosections of a broad panel of human tissues. Biotinylated retifanlimab (MGA012-Bio) was applied to cryosections of normal human tissues (3 donors per tissue, where available) at two concentrations (2.5 and 0.25 µg/mL), followed by a two-step indirect IHC staining method. Specific staining with MGA012-Bio was observed in both plasma membrane and cytoplasm elements of mononuclear cells (lymphocytes) in several tissues including colon, esophagus, small intestine, kidney, lung (BALT), lymph node, prostate, spleen, thymus, tonsil, ureter, cervix, and uterus.

Retifanlimab-stained lymphocytes were most often observed in germinal centers in lymphoid organs (lymph node, spleen, and tonsil), except thymus which was primarily in medulla, and submucosal lymphoid aggregates in several human tissues including colon, esophagus, small intestine, kidney, ureter, cervix, uterus and lung (BALT) as well as tissues where lymphocytes were present including kidney and prostate.

2.5.5. Ecotoxicity/environmental risk assessment

According to the Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00 corr 2, 01 June 2006), retifanlimab, as a protein, is exempt from the preparation of an Environmental risk Assessment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The mode of action of retifanlimab was supported by in vitro studies. No in vivo models were presented to demonstrate proof of concept. These are not considered needed based on the experience with PD-1

inhibitors. However, it could be imagined that in vitro efficacy studies on specific tumours would have been informative with regard to the proof of concept of retifanlimab.

Regarding CDC activity, it should be noted that there was no positive control that mediated CDC activity in activated primary T cells, which would have allowed for a direct comparison with retifanlimab. In Raji/GF cells (human Burkitt's lymphoma cell line) rituximab (hIgG1) was used as a positive control, mediating CDC activity, whereas retifanlimab did not. Combined, these data indicate that retifanlimab has no ability to activate CDC activity.

Regarding the assessment of safety pharmacology, these were incorporated in the 4-week GLP repeat dose toxicity study.

Pharmacokinetics

A (non-validated) fit for purpose ELISA method was used to quantitate retifanlimab levels in monkey's serum in the non-GLP single dose and 3-week studies. The LLOQ of the assay differs for the single dose and 3 week study (9.775 ng/ml versus 4.875 ng/ml). In study 20077288 the calibration standard at 4.875 ng/mL was only used as an anchor point but was not included in the regression, whereas it was used in study 20079545 which explains the lower LLOQ in the second study.

It is acknowledged that immunogenicity assessments in animals are generally limited in their ability to predict the incidence of human immune responses to a therapeutic protein product. Nevertheless, the determination of clearing and/or neutralizing ADA's is essential to correctly interpret the results of a non-clinical study. Therefore, in principle, the (bio)analytical methods (including ADA analysis) used in the pivotal toxicokinetic studies should be adequately validated and qualification only is not considered sufficient. However, since the TK data are in line with the ADA results (in general a decrease in exposure in ADA-positive animals), the issue was not further pursued.

Toxicology

No genotoxicity or carcinogenicity studies with retifanlimab have not been conducted, according to ICH S6(R1) (2011) and ICH S9 (2009) guidelines.

The safety of retifanlimab was evaluated in a preliminary 3-week study, and in pivotal 4-week and 13-week repeat-dose studies. All studies used cynomolgus monkeys as a pharmacologically relevant species. Across the studies, animals were given weekly doses ranging between 1 and 150 mg/kg (150 mg/kg corresponds to 26-fold the proposed MRHD exposure) administered via IV infusion. Retifanlimab was generally well tolerated. The observed retifanlimab-related findings may be linked to its pharmacological action on the immune system and were not severe. Several animals among all dose groups developed ADAs, resulting in decreased exposure. Taking into account the totality of the data, sufficient exposure was maintained to adequately interpret the toxicology studies.

No standard fertility and early embryonic development, embryofetal development and pre- and postnatal development studies were conducted with retifanlimab. This is in accordance with guidelines (ICH S9, 2009) for advanced cancer therapeutics. Based on the mechanism of action and literature on murine models of pregnancy, retifanlimab is anticipated to disrupt the maintenance of a normal pregnancy or may alter immunologic phenotypes following fetal exposure. Hence, it is agreed that the conduct of embryofetal development studies in cynomolgus monkeys would likely not be informative. Subsequently, the use of retifanlimab is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception, and as specifically reflected in the SmPC section 4.6, there is insufficient information

on the excretion of retifanlimab in animal milk. Human IgGs are known to be excreted in breast milk during the first few days after birth; which decreases to low concentrations soon afterwards; consequently a risk to the breast-fed infant cannot be excluded during this short period. For this specific period, a decision should be made whether to discontinue/abstain from retifanlimab therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman. Afterwards, retifanlimab could be used during breast-feeding if clinically needed.

2.5.7. Conclusion on the non-clinical aspects

In conclusion, the non-clinical studies (pharmacology, pharmacokinetics and toxicology) submitted for the marketing authorisation application for retifanlimab were considered acceptable for the assessment of non-clinical aspects. The lack of carcinogenicity, genotoxicity, reproductive and developmental studies were adequately justified. Based on cynomolgus monkey studies, there was no clinically relevant toxicity. From a non-clinical point of view market approval for Zynyz can be granted.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 13: Tabular overview of all clinical studies included in the submission

Study Identifier (Type of Study) Location of Study Report or Safety Data Registry Numbers	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, and Route of Administration	Number of Participants Exposed to Retifanlimab[a]	Diagnosis of Participants	Estimated Duration of Treatment	Study Status; Type of Report (Data Cutoff Date for ISS)	Countries Involved[b]
INCMGA 0012-101 (Efficacy, safety, tolerability, PK); 5.3.3.2 NCT03059823; EudraCT 2017-000865-63; CTR20200310	Safety and tolerability	Phase 1, open-label, multiregional, dose-escalation, and cohort-expansion study	Retifanlimab 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, 10 mg/kg Q4W, 500 mg Q4W, 750 mg Q4W, 375 mg Q3W; all IV over 60 minutes	315	Advanced solid tumors	Up to 2 years	Ongoing; Interim (06 JUL 2021)	Australia, Belgium, Bulgaria, China, Finland, France, Germany, Italy, Lithuania, Latvia, New Zealand, Poland, Spain, UK, Ukraine, US

Study Identifier (Type of Study) Location of Study Report or Safety Data Registry Numbers	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, and Route of Administration	Number of Participants Exposed to Retifanlimab[a]	Diagnosis of Participants	Estimated Duration of Treatment	Study Status; Type of Report (Data Cutoff Date for ISS)	Countries Involved[b]
INCMGA 0012-104[c] (Efficacy, safety, tolerability, PK); 5.3.3.2 NCT03910530 JapicCTI-194882	Safety and tolerability	Phase 1b, open-label, multicenter study	Retifanlimab 500 mg Q4W IV over 60 minutes	Retifanlimab monotherapy: 6	Japanese participants with advanced solid tumors	Up to 2 years	Ongoing[d], enrollment complete; Interim (05 MAR 2021)	Japan
INCMGA 0012-201 (Efficacy, safety, PK); 5.3.5.2 NCT03599713 EudraCT 2018-001627-39	Efficacy (ORR)	Phase 2, open-label, multiregional study	Retifanlimab 500 mg Q4W IV over 60 minutes	105[e]	Metastatic or recurrent locally advanced MCC	Up to 2 years	Ongoing, enrollment complete; Interim (16 JUN 2021)[f]	Canada, Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, Switzerland, UK, US
INCMGA 0012-202[g] (Efficacy, safety, PK); 5.3.5.2 NCT03597295; EudraCT 2018-002070-51	Efficacy (ORR)	Phase 2, open-label, single-arm, multiregional study	Retifanlimab 500 mg Q4W IV over 60 minutes	94	Locally advanced or metastatic SCAC	Up to 2 years	Ongoing[d], enrollment complete; Interim (15 MAR 2021)	Belgium, Denmark, France, Germany, Italy, Norway, Spain, UK, US
INCMGA 0012-203 (Efficacy, safety, PK); 5.3.5.2 NCT03679767; EudraCT 2018-002941-12	Efficacy (ORR)	Phase 2, open-label, multiregional study	Retifanlimab 500 mg Q4W IV over 30 minutes	121	Metastatic or locally advanced NSCLC, UC, melanoma, or RCC	Up to 2 years	Ongoing[d], enrollment complete; Interim (15 APR 2021)	Austria, France, Hungary, Italy, Poland, Romania, Spain, US

[a] Number of participants exposed to retifanlimab as of the data cutoff date.
[b] Countries with sites that enrolled participants.
[c] INCMGA 0012-104 also includes participants who receive INCB001158 (arginase inhibitor) monotherapy or in combination with retifanlimab. As of the data cutoff date, there have been no serious TEAEs in participants who received retifanlimab in combination with INCB001158.
[d] This study achieved LPLV after the data cutoff date.
[e] In Study INCMGA 0012-201, 105 participants were exposed to retifanlimab as of the data cutoff date of 16 JUN 2021; this includes both participants who are chemotherapy-naïve (N = 99) and participants who were previously treated with platinum-based chemotherapy (N = 6).
[f] Data for the MCC and All Cancer Populations used a data cutoff date of 16 JUN 2021.
The data cutoff date was 10 MAR 2023 for the exposure-efficacy analysis (MCC Population, N = 100).
[g] INCMGA 0012-202 CSR was written based on a data cutoff date of 08 JUN 2020; updated safety data as of 15 MAR 2021 are included in the ISS.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Pharmacokinetics of retifanlimab were studied in patients with MCC and patients with different types of cancer. Patients received 1-10 mg/kg (Q2W or Q4W) retifanlimab as well as flat doses of 375 mg (Q3W), 500 mg (Q4W), and 750 mg (Q4W). Non-compartmental analysis was used to analyse the pharmacokinetics after the first dose in studies INCMGA 0012-101 and INCMGA 0012-104. A population pharmacokinetic model was developed based on cancer patients from all 5 studies (see Table 13).

Study INCMGA 0012-201 was submitted to specifically support the marketing application of retifanlimab for patients with MCC using the 500 mg dose every four weeks (Q4W) regimen.

In studies INCMGA 0012-101 and INCMGA 0012-104, both rich and sparse PK sampling were performed. 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 studies INCMGA 0012-201, INCMGA 0012-202, and INCMGA 0012-203, only sparse PK samples were collected and no NCA was performed.

Development of antibodies against retifanlimab was measured in all 5 studies.

Analytical methods and bioanalysis: The bioanalytical methods used for the determination of retifanlimab concentrations in human serum used 2 types of assay platforms, ELISA and MSD-ECL. Part of the samples in study INCMGA 0012-101 were analysed using a first-generation ELISA method. The other samples were analysed using second generation ELISA and MSD-ECL. The assays were validated.

The analysis of anti-drug antibodies (ADAs) was performed by a three-tiered approach: a screening assay, a confirmatory assay, and a titration assay. The analyses were performed using ELISA. The assays were adequately validated.

A method for the detection of neutralizing ADAs (NAb) in human serum was developed and validated. Serum samples from participants in studies with confirmed positive ADA were tested for NAb. Participant samples from all 5 clinical studies were included for immunogenicity analysis and ADA sampling strategies. A total of 25 human serum samples from 20 participants (including 1 sample from a nonassessable participant) were tested as ADA positive (out of 4431 samples from 640 participants), among which 20 samples were analysed for neutralizing anti-retifanlimab antibodies. At the sample level, 8 out of 20 were detected as positive NAb samples; at the participant level, 4 tested as NAb positive.

Pharmacokinetic analysis and statistics: Standard pharmacokinetic methods and descriptive statistics have been used for non-compartmental analysis in studies INCMGA 0012-101 and INCMGA 0012-104. In the other studies, no pharmacokinetics analyses were performed. Descriptive summaries (mean, SD, %CV) of concentrations at each scheduled timepoint, and the determined or calculated PK parameters were presented.

Population PK analysis: A population pharmacokinetic model was developed based on data from all 5 studies. The population PK analysis population was defined as all participants who received at least 1 dose of retifanlimab and provided at least 1 evaluable post-dose sample for serum PK analysis. A total of 7787 serum retifanlimab concentration records from 634 participants were included in the population PK analysis, including 102 patients with MCC (549 serum retifanlimab concentration records). The majority of participants

(91.0%) in the population PK dataset were dosed at 3 mg/kg Q2W or 500 mg Q4W. Population PK modelling was performed using non-linear mixed effects models. The base and final model demonstrated successful minimisation. The model has been used to characterise within- and between-subject variability in the pharmacokinetics of retifanlimab, and investigate the influence of covariates on the pharmacokinetics of retifanlimab. The model is thus not used for any extrapolations.

Goodness of fit was assessed using diagnostic plots (plots of observed vs predicted data, residual and WRES plots), precision of the parameter estimates as measured by the percent standard error of the mean and changes in the estimates of inter-individual variability (IIV) and residual variability (RV). The accuracy and robustness of the final population PK model was investigated using bootstrap and a visual predictive check method (based on 1000 simulations).

Logarithm-transformed serum retifanlimab concentrations were used as dependent variables. Two-compartment models with first-order linear elimination, with first-order linear plus nonlinear elimination (Michaelis-Menten equation), and with first-order linear elimination plus time-varying CL were tested as base structural models. The variables listed in Table 14 were considered as covariates in the population PK analysis.

Table 14: Participant Demographics, Clinical Laboratory Values, Disease-Related Evaluations, and Other Variables Available for Use as Covariates in the Population Pharmacokinetic Analysis (DMB-22.133.1)

Category	Variable Name
Demographics	Age
	Body weight[a]
	Sex
	Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
	Race (White/Caucasian, Black/African American, Asian, other[b])
Clinical laboratory values	Albumin
	AST
	ALP
	Bilirubin
	ClCr (by MDRD/Cockcroft-Gault equation)
Disease-related evaluations	Renal function classification by MDRD equation[c]
	Hepatic function classification by NCI standard[d]
	Tumor type
	Tumor burden (sum of target lesion diameters based on ICR)[a]
	ECOG performance status[a]
Other variables	DP produced by the P1 process or P2 process (P2 will be used in commercialization)
	Infusion time 60 minutes vs 30 minutes (30 minutes is the proposed infusion time)
	Concomitant medications (eg, corticosteroids used for irAE management)[a]

[a] Time-variate covariate, but baseline values are time-independent covariates.
[b] Other races include those reported as Maori, Eurasian, Ecuadorian, Italian, Portuguese, not reported/recorded/collected/applicable at French, Italian, and Norwegian sites, unknown, Caucasian with Italian and Spanish heritage, and chose not to provide.
[c] Creatinine clearance was calculated based on the MDRD formula and classified based on regulatory guidelines (EMA 2015, FDA 2020).
[d] Hepatic impairment categories were as follows: normal = bilirubin ≤ ULN and AST ≤ ULN; mild = bilirubin ≤ ULN and AST > ULN or ULN < bilirubin ≤ 1.5 × ULN; moderate = 1.5 × ULN < bilirubin ≤ 3 × ULN; severe = bilirubin > 3 × ULN.

The serum concentrations for retifanlimab were best characterized with a 2-compartment model with first-order elimination plus time-varying CL from the central compartment (to capture increasing trough values over time). Parameters were estimated with sufficiently low RSE (1.37 – 31.8%). Standard goodness-of-fit plots indicated no relevant bias. Statistically significant covariates were baseline body weight (on CL, V_c, and V_p), serum albumin (on CL and V_c), sex (on V_c), tumour burden (on CL), ECOG performance status (on CL), and cancer type (on CL and I_{max}).

Model results

Base model

Time-dependent CL terms (I_{max}, T_{50}, Hill coefficient) were included in the base and final population PK model in order to capture the increasing trough concentrations observed in studies INCMGA 0012-101 and INCMGA 0012-104 beyond 200 days of treatment. IIV was estimated on Imax, CL, Vc and Vp. Correlation for IIVs of CL, V_c, V_p, and I_{max} was added to the base model. A combined additive and proportional residual variability model was used, but later reduced to additive only (in log scale).

Covariate model

Bodyweight (at baseline) on Vc, Vp and CL, Albumin on CL and Vc, Sex on Vc, Tumor burden on CL, ECOG performance status on CL, and tumor type (NSCLC) on CL significantly improved model fit in the forward selection process. None of the covariates have been determined to be insignificant covariates by backward elimination.

Final model

In the final model results (table below), all of the fixed- and random-effect parameters were estimated with reasonable precision.

Table 15: Parameter Estimates and Standard Errors From the Retifanlimab Final Population Pharmacokinetic Model (DMB-22.133.1)

		Final Parameter Estimate			Bootstrap		
Parameter	**Population Mean**	**%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 performance status (> 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

Parameter	Population Mean	Final Parameter Estimate			Bootstrap		
		%RSE	95% CI	IIV	Median	95% CI	IIV
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 (I_{max}) = 30.6%.

Goodness-of-Fit plots for the final population PK model are shown in Figure 14**.**

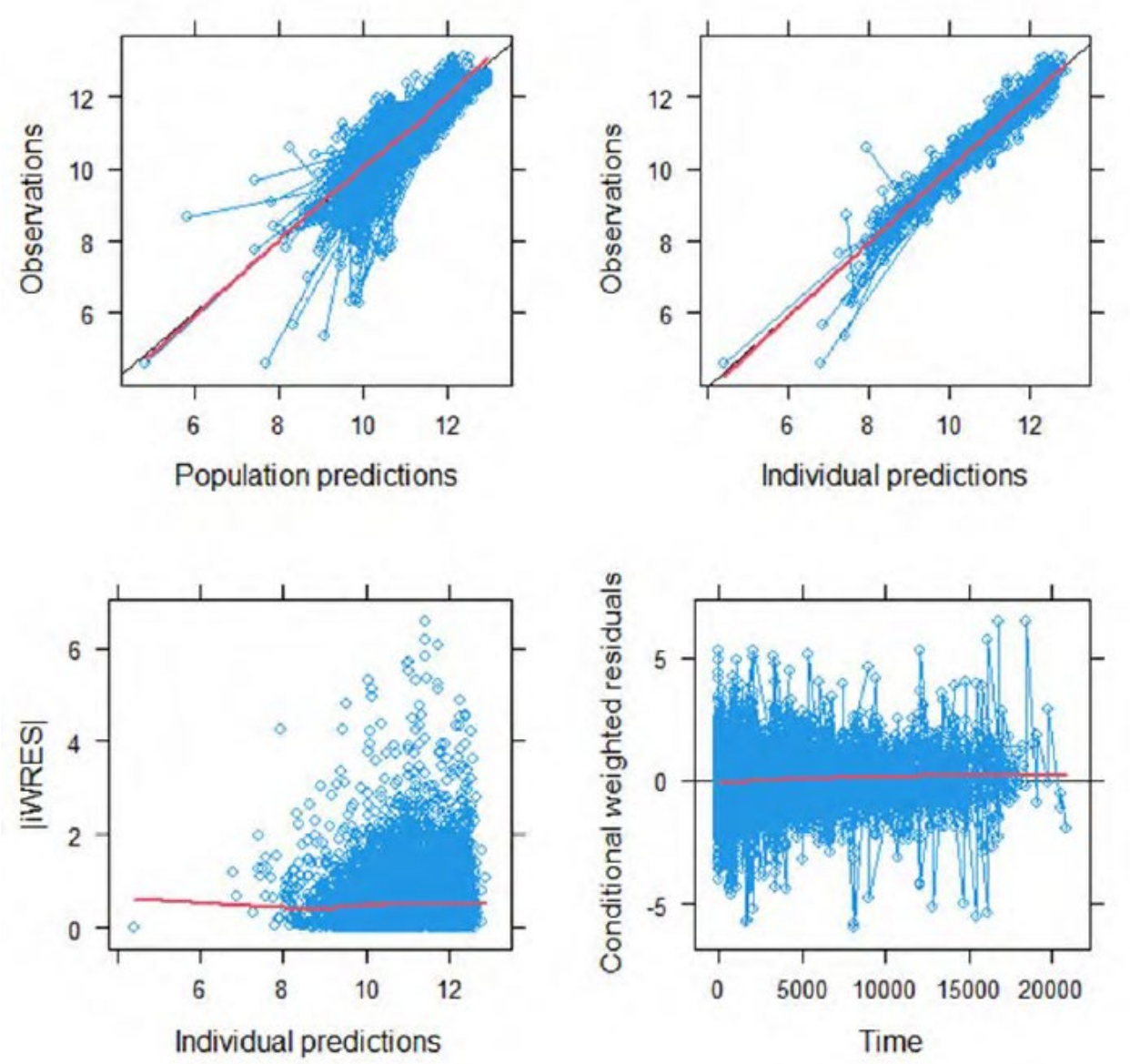
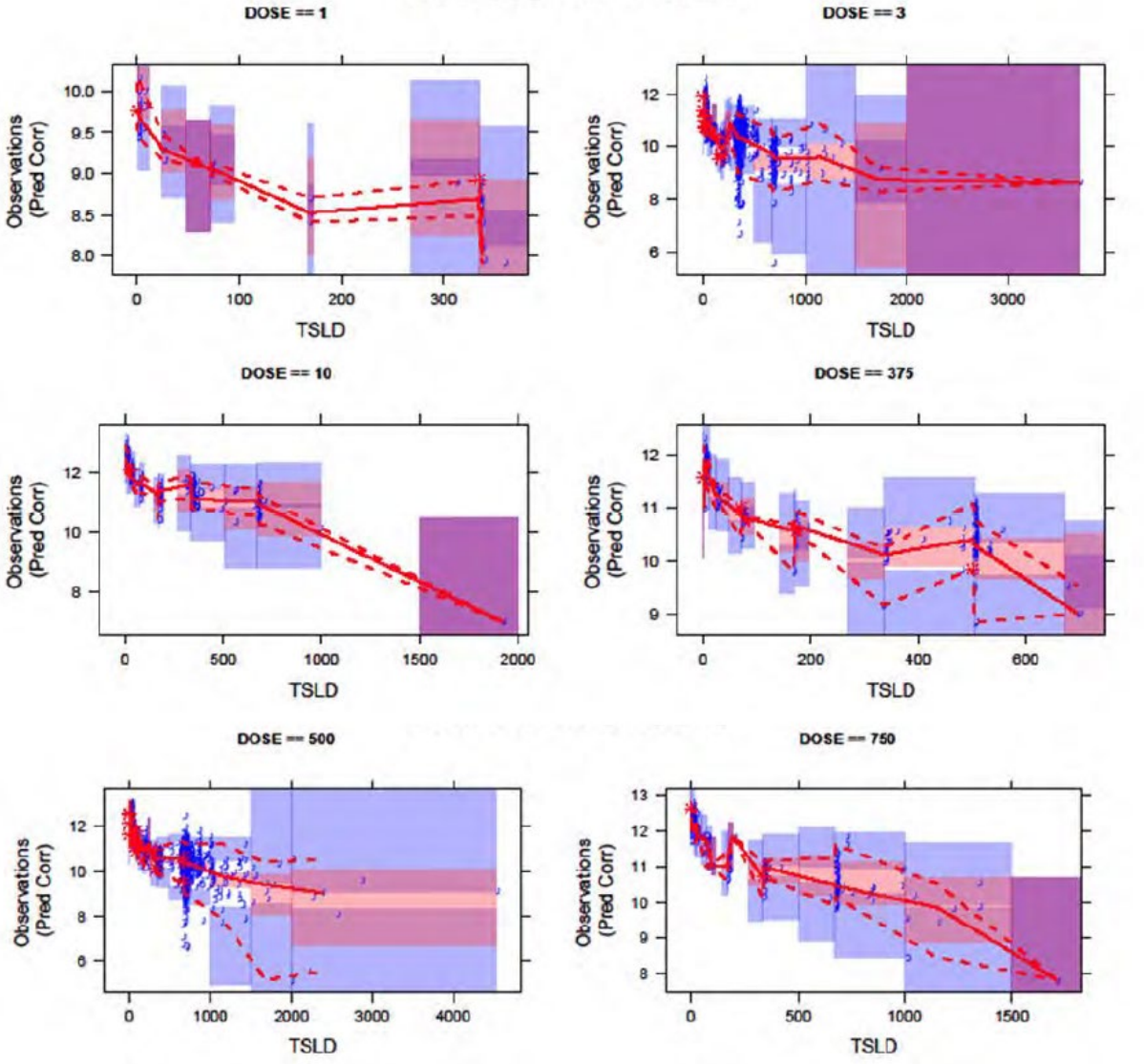


Figure 14: Goodness-of-Fit Plots for the Base Population Pharmacokinetic Model (study DMB-22.133.1)

The visual predictive check of the final population PK model is shown in Figure 15.



p5 = fifth percentile, p95 = 95th percentile, PI = prediction interval.
Note: The dots are observed data points, and the red lines are the observed p5, median, and p95. The red areas are the 95% PI of the simulated median, and the purple areas are the 95% PI of the simulated p5 and p95.

Figure 15: Visual Predictive Check of the Final Population Pharmacokinetic stratified by Dose (study DMB-22.133.1); TSLD = time since last dose

The impact of continuous covariate effects on retifanlimab CL, V_c and V_p is shown in Table 16.

Table 16: Impact of Continuous Covariate Effects on Retifanlimab CL, Vc, and Vp (DMB-22.133.1)

Covariates	Fifth Percentile	Median	95th Percentile
Albumin (g/L)	28.9	40	47
CL with albumin	0.0161	0.0122	0.0106
CL variation with albumin (%)	32.0	0	−12.9
V_c with albumin	4.27	3.76	3.53
V_c variation with albumin (%)	13.5	0	−6.10
Body weight range (kg)	49.0	72.0	107
CL with body weight (L/h)	0.00986	0.0122	0.0152
CL variation with body weight (%)	−19.2	0	24.2
V_c with body weight (L/h)	3.22	3.76	4.40
V_c variation with body weight (%)	−14.3	0	17.0
V_p with body weight (L/h)	2.20	2.64	3.17
V_p variation with body weight (%)	−16.5	0	20.3
Tumor burden (mm)	16.0	60.0	190
CL with tumor burden	0.0115	0.0122	0.0128
CL variation with tumor burden (%)	−5.35	0	4.91

Exposure-response modelling: E-R (efficacy and safety) analyses were performed in patients with MCC (for safety, also in other cancers, with a total of 634 patients, of which 102 with MCC). The relationship between estimated retifanlimab exposure and clinical endpoints was investigated using either binary logistic regression (analysis of ORR and DCR) or Kaplan-Meier analysis (analysis of DOR, PFS, and OS). A stepwise logistic regression was used to evaluate the E-R safety relationships. Investigated exposure variables were AUC, C_{max} and C_{min} after first dose and at steady state. No statistically significant relationships between exposure variables and clinical outcomes could be established for patients with MCC (below figures). For efficacy, 100 patients were included in the analyses that only used one dose. No extensive non-linear pharmacokinetic behaviour was observed. The relationship between retifanlimab serum concentrations and ΔQTcF was investigated using a nonlinear mixed effects model (see further below).

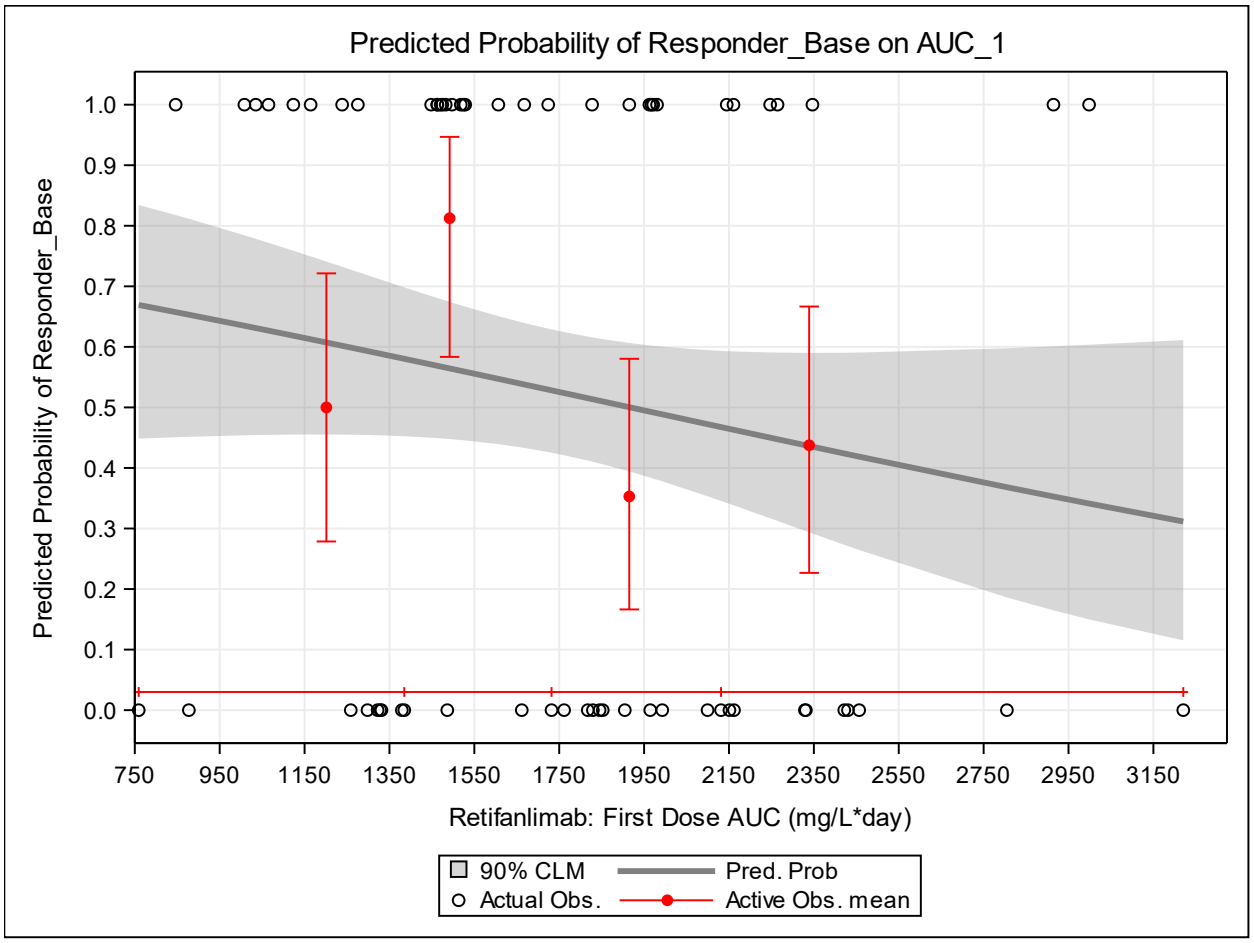


Figure 16: Probability of Objective Response Rate Versus Retifanlimab First-Dose AUC_1 Following a 500 mg Q4W Dose in Participants With MCC

Note: The red crosses represent the first (759-1380 day*mg/L), second (1380-1730 day*mg/L), third (1730-2130 day*mg/L), and fourth (2130-3220 day*mg/L) quartiles of retifanlimab AUC_1.

Note: The black solid line and gray shaded areas represent logistic model-predicted relationship and 95% CI. Quartile borders of AUC_1 quartiles are displayed at the bottom. Quartile-wise ORR (red dots) and 95% Clopper-Pearson CIs (red vertical lines) are overlaid for information. Black circles on the top and bottom represent actual observations used for regression.

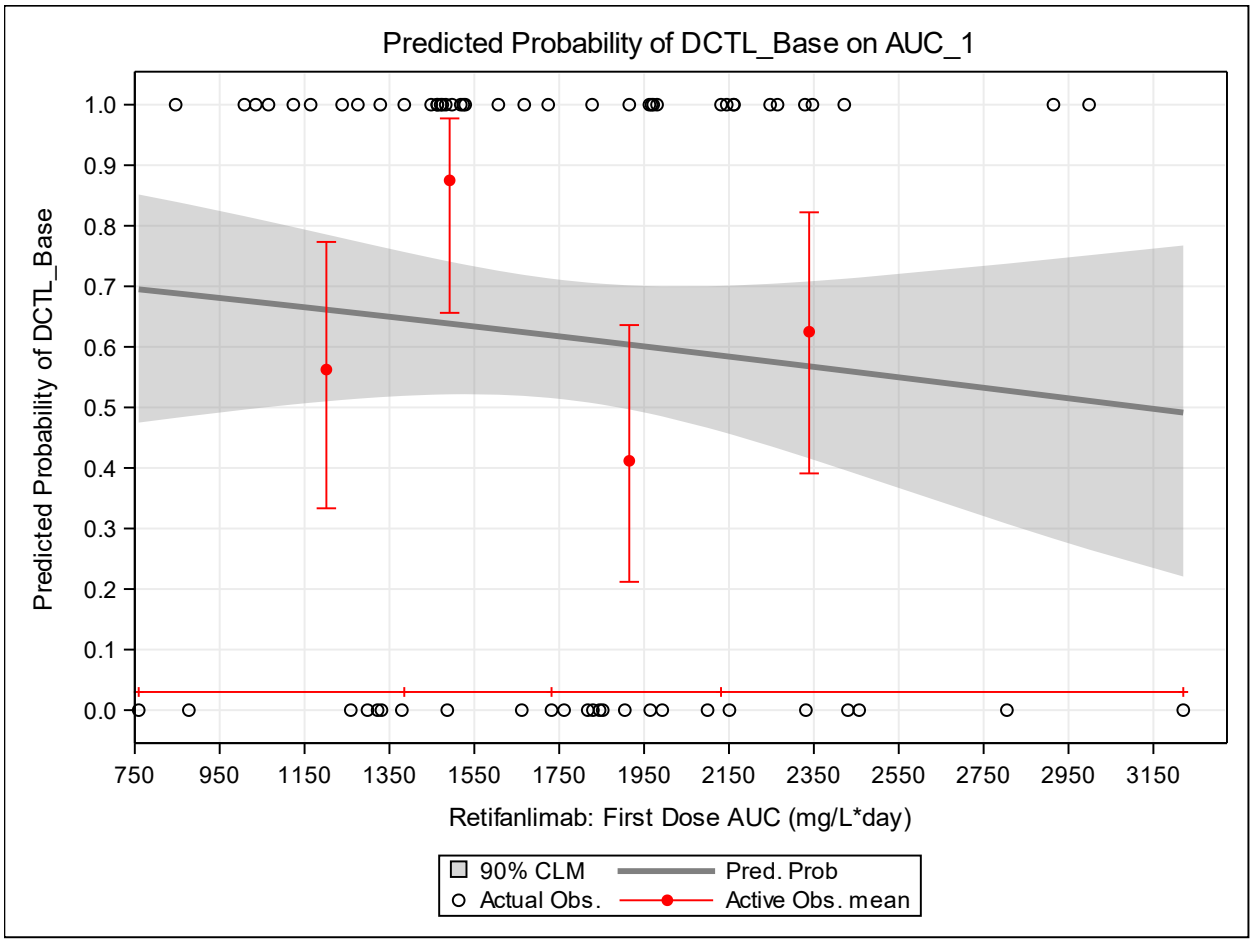


Figure 17: Probability of Disease Control Rate Versus Retifanlimab First-Dose AUC_1 Following a 500 mg Q4W Dose in Participants With MCC

Note: The red crosses represent the first (759-1380 day*mg/L), second (1380-1730 day*mg/L), third (1730-2130 day*mg/L), and fourth (2130-3220 day*mg/L) quartiles of retifanlimab AUC_1.

Note: The black solid line and gray shaded areas represent logistic model-predicted relationship and 95% CI. Quartile borders of AUC_1 quartiles are displayed at the bottom. Quartile-wise ORR (red dots) and 95% Clopper-Pearson CIs (red vertical lines) are overlaid for information. Black circles on the top and bottom represent actual observations used for regression.

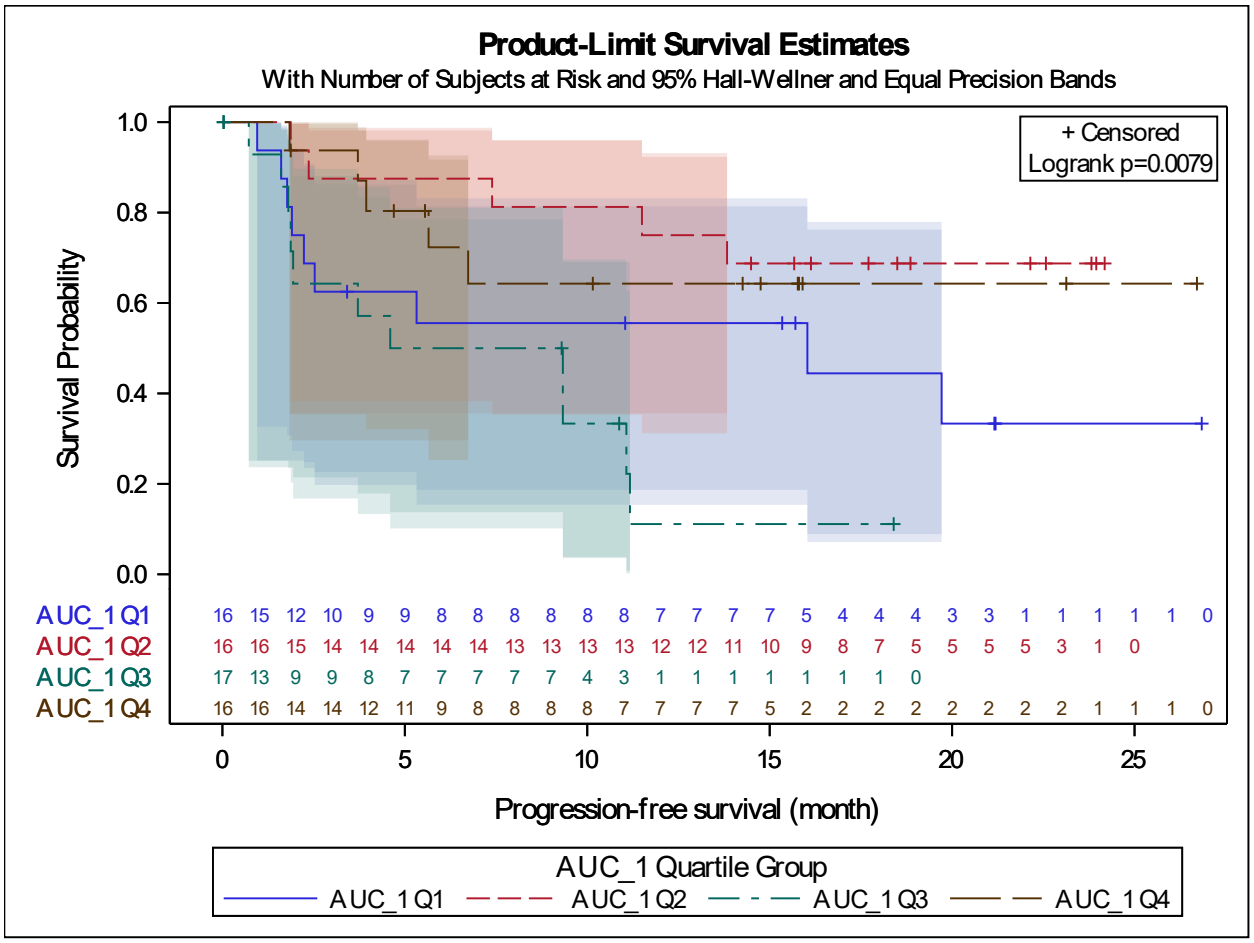


Figure 18: Progression-Free Survival Versus Retifanlimab AUC_1 Following a 500 mg Q4W Dose

Note: The first (759-1380 day*mg/L), second (1380-1730 day*mg/L), third (1730-2130 day*mg/L), and fourth (2130-3220 day*mg/L) quartiles of retifanlimab AUC_1.

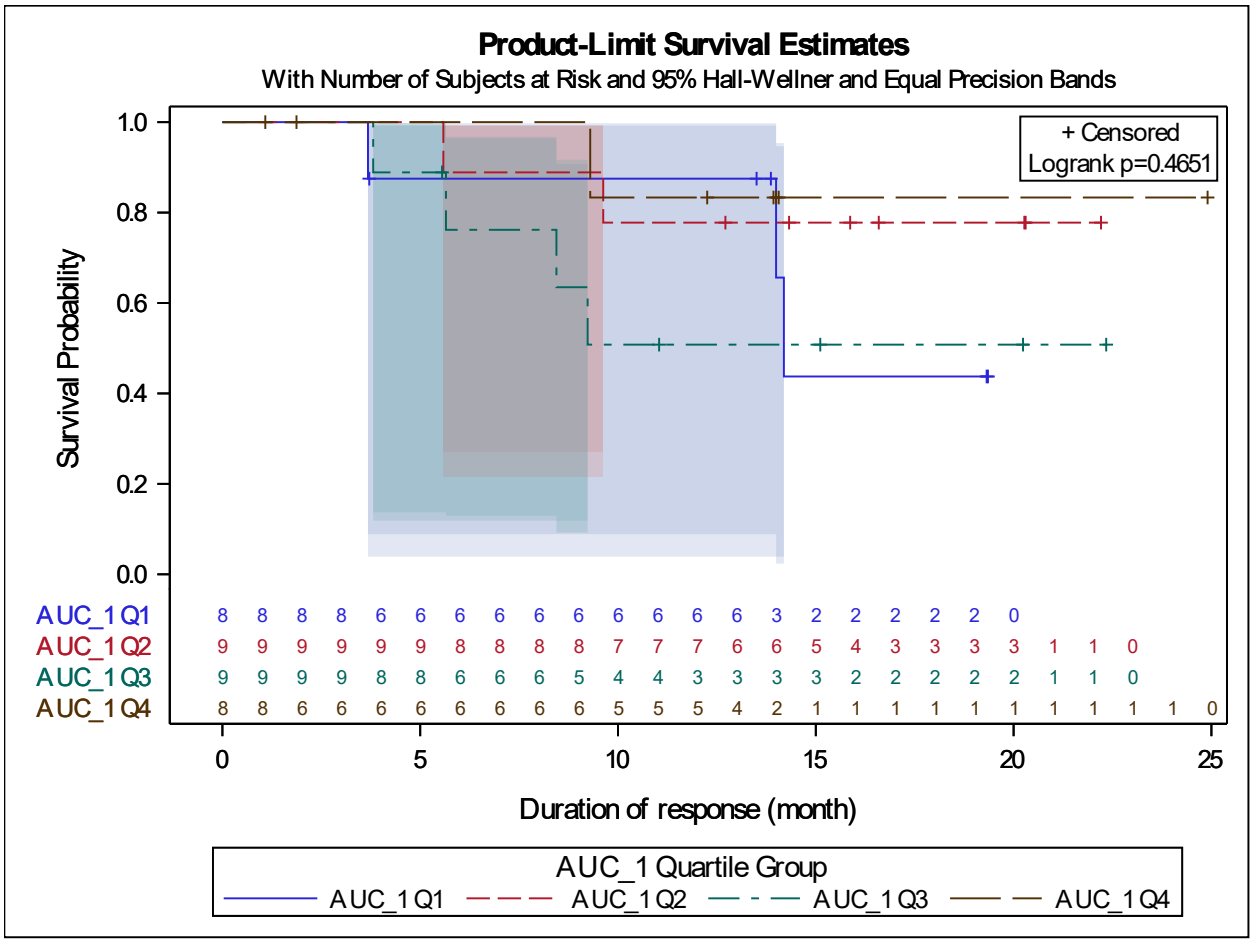


Figure 19: Duration of Response Versus Retifanlimab AUC_1 Following a 500 mg Q4W Dose

Note: The first (759-1380 day*mg/L), second (1380-1730 day*mg/L), third (1730-2130 day*mg/L), and fourth (2130-3220 day*mg/L) quartiles of retifanlimab AUC_1.

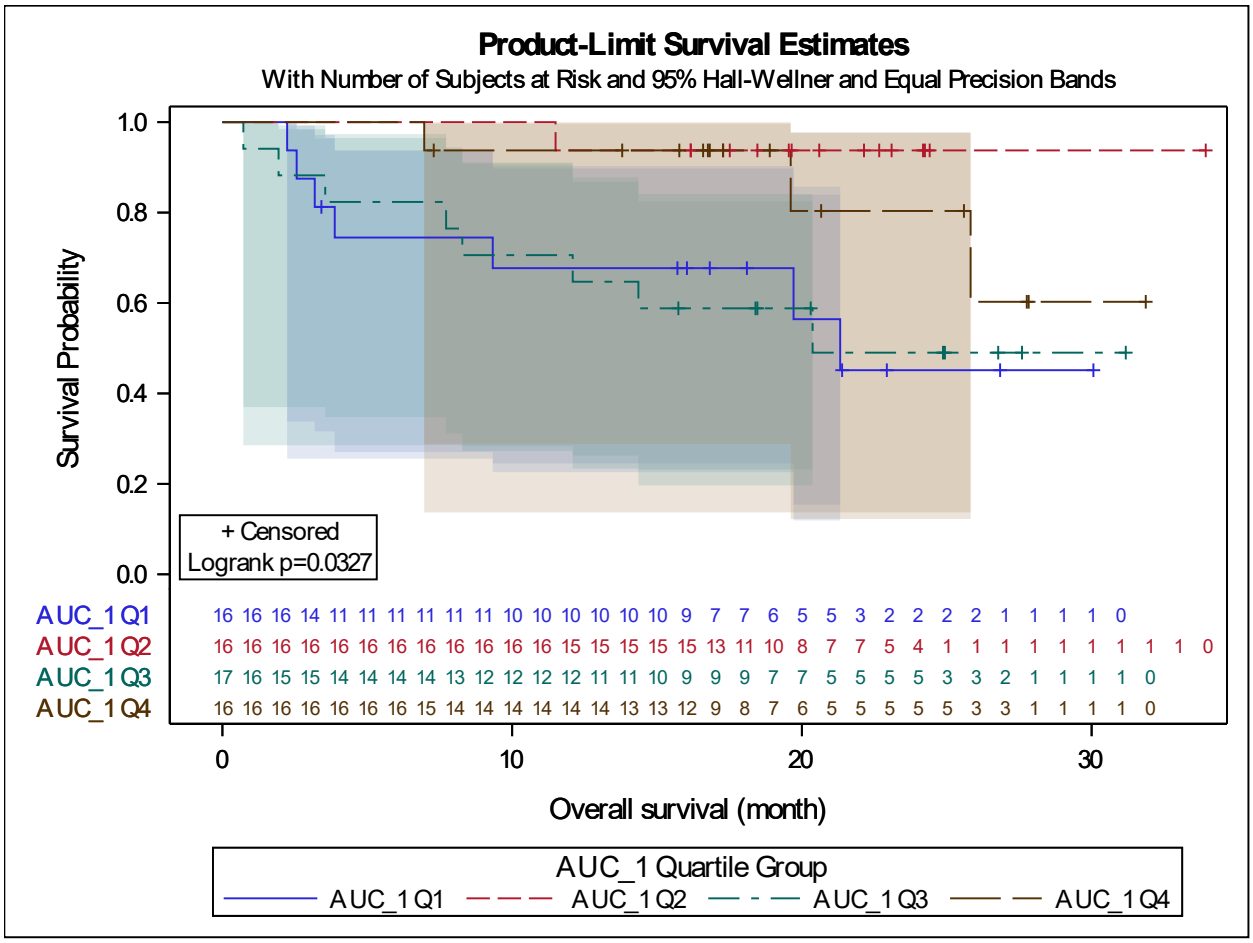


Figure 20: Overall Survival Versus Retifanlimab AUC_1 Following a 500 mg Q4W Dose

Note: The first (759-1380 day*mg/L), second (1380-1730 day*mg/L), third (1730 2130 day*mg/L), and fourth (2130-3220 day*mg/L) quartiles of retifanlimab AUC_1.

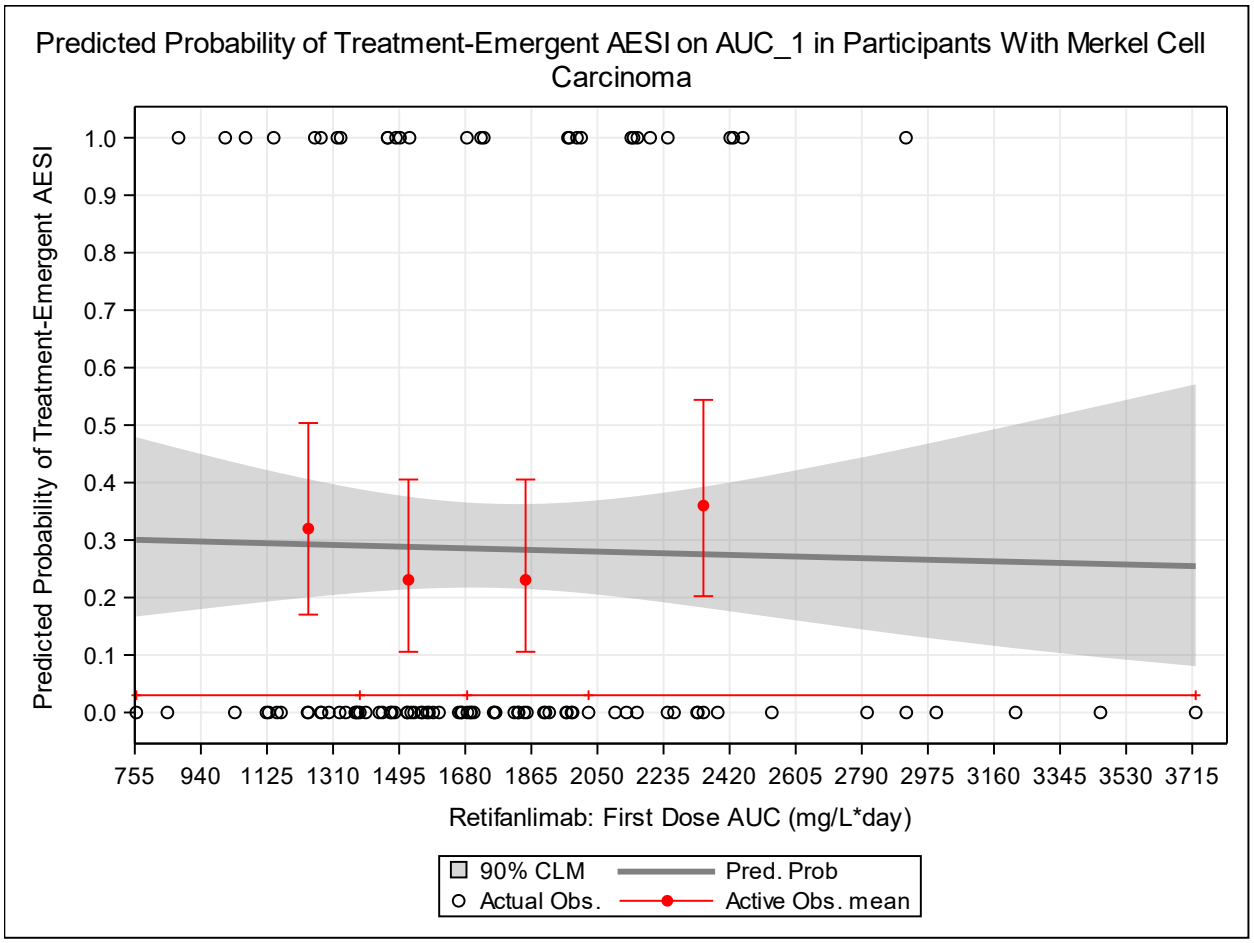


Figure 21: Probability of Adverse Events of Special Interest Versus Retifanlimab Exposure Following Retifanlimab 500 mg Q4W in the Merkel Cell Cancer Population

Note: The red crosses represent the first (759-1380 day*mg/L), second (1380-1690 day*mg/L), third (1690-2030 day*mg/L), and fourth (2030-3720 day*mg/L) quartiles of retifanlimab AUC_1.

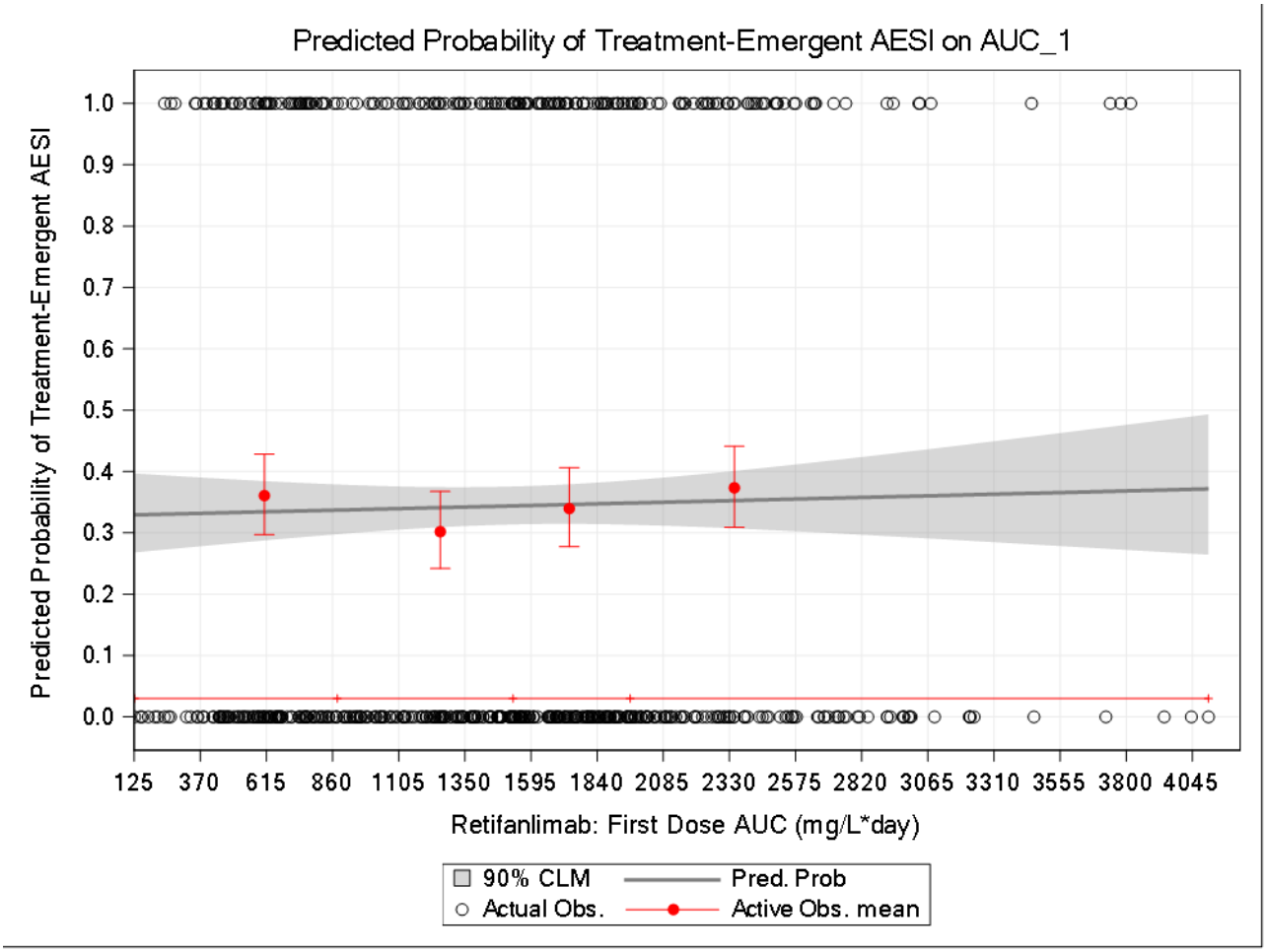


Figure 22: Probability of Adverse Events of Special Interest Versus Retifanlimab Exposures Following Different Doses of Retifanlimab in the All Cancer Population

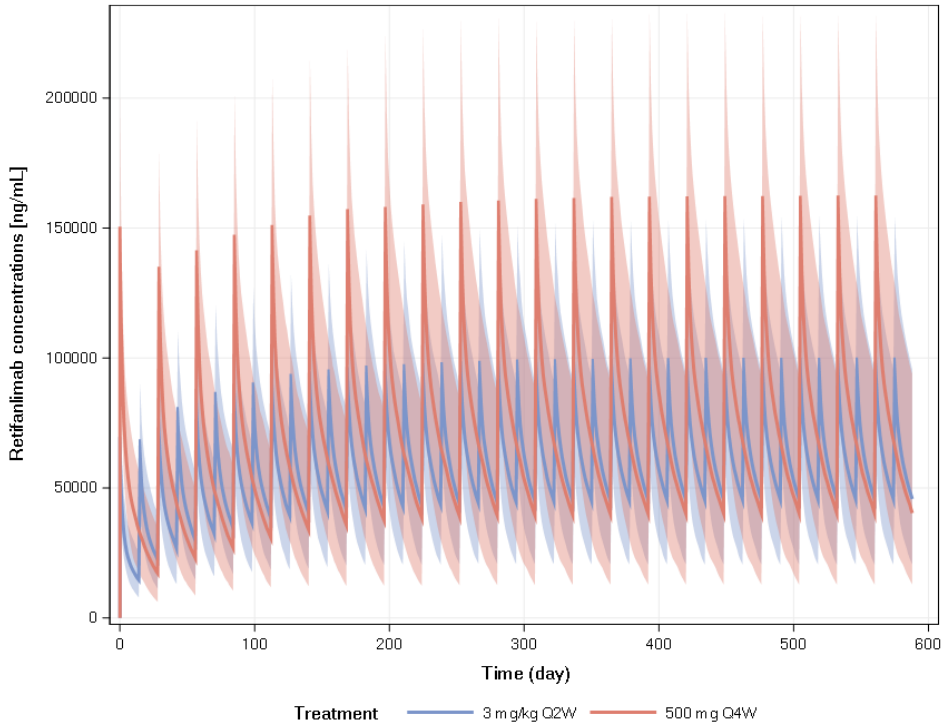
Note: The red crosses represent the first (127-877 day·mg/L), second (877-1530 day·mg/L), third (1530-1960 day·mg/L), and fourth (1960-4110 day·mg/L) quartiles of retifanlimab AUC_1.

Absorption

Retifanlimab is dosed via the IV route and therefore completely bioavailable and no specific studies examining bioavailability have been carried out. After a single intravenous dose, serum retifanlimab concentrations attained peak values at the end of infusion and subsequently exhibited a biexponential decay.

Retifanlimab was studied using a bodyweight-based dosing and fixed-dose regimen. A fixed-dose regimen is proposed. A comparison between the population PK model simulated-PK profile for the 3 mg/kg Q2W dosing regimen and the proposed 500 mg Q4W dosing regimen was conducted (Figure 23). At 500 mg Q4W, the geometric mean retifanlimab concentrations (CV%) at steady state ranged between a C_{min} of 38.0 mg/L (66.8%) and a C_{max} of 188 mg/L (25.7%) and steady state was achieved after approximately 308 days. Comparable PK profiles were also observed for 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 131% and 13.9% higher than that of the 3 mg/kg Q2W dose; the mean $C_{min,ss}$ and $C_{max,ss}$ were 16.3% lower and 69.4% higher than those after 3 mg/kg Q2W dosing.



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.

Figure 23: Comparison of Model-Simulated Pharmacokinetic Profiles Following 500 mg Q4W Versus 3 mg/kg Q2W Retifanlimab (DMB-22.133.1)

The proposed administration of retifanlimab is over a 30 minute infusion. In the clinical studies an infusion duration of 30 minutes and a 60 minute infusion were tested. The population pharmacokinetic analyses did not identify infusion time as relevant covariate (60 minutes versus 30 minutes).

Bioequivalence: During clinical development two different manufacturing processes have been used: process P1 and process P2. The commercial drug product P2-TPF is the same as the drug product produced via process P2, with the only difference being the filling process. The change of the production process was evaluated in study INCMGA 0012-203. Subjects received retifanlimab 500 mg Q4W by a 30 minute infusion; part of the subjects received the P1 DP, and part of the subjects received the P2 DP. Results from study INCMGA 0012-203 showed comparable pharmacokinetics after the first dose between the P1 and P2 DP. EOI and pre-dose trough concentrations were not completely comparable when comparing the specific cycles. The DP manufacturing process was not identified to be a significant predictor for PK parameter variabilities in the population PK analysis. No relevant difference in the pharmacokinetics of retifanlimab between the P1 DP and the P2 DP were identified.

Distribution

Based on the population PK analysis, consistent with a limited extravascular distribution and the lack of expected protein binding, the geometric mean V_{ss} of retifanlimab is 6.1 L (20.2% CV), within the range of the

volumes of serum and extracellular water. In study INCMGA 0012-101, V_z calculated by NCA was 4.7 – 7.6 L. The results of the population pharmacokinetic analysis and non-compartmental analysis consistently estimated the overall volume of distribution at approximately 6 L.

Serum albumin was a significant covariate in the population pharmacokinetic model. Simulations indicated a 32% higher clearance in typical patients with albumin levels of 28 g/L and a -12.9% lower clearance in typical patients with albumin levels of 47 g/L compared to typical patients with albumin levels of 40 g/L.

Elimination

No excretion studies were performed as retifanlimab is an antibody expected to be catabolised through protein degradation processes.
A geometric mean clearance of 0.314 (36% CV) L/day, without accounting for the time-varying part of the clearance, with a half-life of 14.6 (31.5% CV) and 18.7 (28.7% CV) days, after first-dose and at steady-state, respectively, were estimated in the population pharmacokinetic analyses.

Metabolism

Retifanlimab is catabolized through protein degradation processes. As retifanlimab is not subject of metabolism by CYP450 enzymes no classical studies regarding metabolism were performed.

Genetic polymorphism

The pharmacokinetics of retifanlimab are expected to be dependent on the target (PD-1). Participants' blood or tumour tissue samples were not analysed for genetic polymorphisms for PD-1 as it was not a defined protocol exploratory objective to explore the relationships between tumour and host factors and clinical outcomes.

Dose proportionality and time dependencies

Single dose

Rich PK samples were collected after the first infusion in Study INCMGA 0012-101. Therefore, non-compartmental analysis was performed to calculate the PK parameters in different dose groups (1 mg/kg, 3 mg/kg, 10 mg/kg, 375 mg, 500 mg, and 750 mg) following the first infusion in study INCMGA 0012-101. PK parameters are shown in table 17. Dose proportionality of retifanlimab serum exposure was evaluated using a power function regression. Figure 24 and 25 show the relationship between dose and C_{max} and AUC_{∞} after the first dose. For the body weight-based dose group, actual doses were used in the analysis.

Results showed that the exponent, β, of the power function (or equivalently the slope of the log-transformed equation) for C_{max} = 1.08 was not statistically significantly different from 1 (90% CI: 1.00, 1.15), and the β value of AUC_{∞} was estimated as 1.28 (90% CI: 1.19, 1.36).

An approximately linear relationship was observed for retifanlimab exposures between 1 mg/kg to 10 mg/kg and flat doses (375 mg, 500 mg, and 750 mg) were also within the range.

Table 17: Summary of Pharmacokinetic Parameters of Retifanlimab From Study INCMGA 0012-101

Dose		N	First Dose							Steady State	
			C_{max} (mg/L)	T_{max} (h)	$t_{1/2}$ (day)	AUC_t (day·mg/L)	AUC_∞ (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
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.

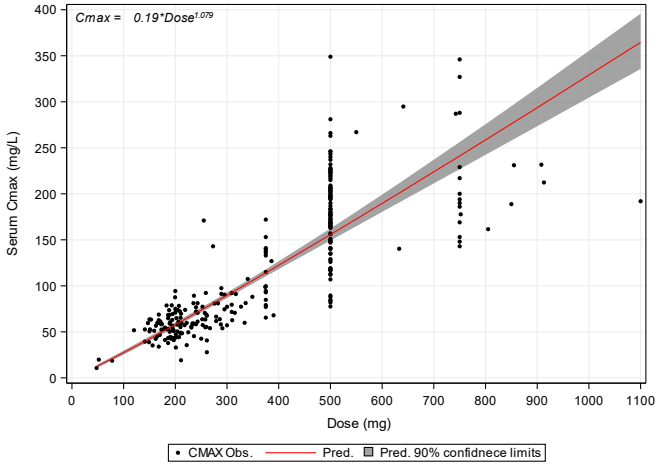


Figure 24: Relationship of Dose and First-Dose Retifanlimab Cmax in Individual Participants Receiving Different Dosing Regimens

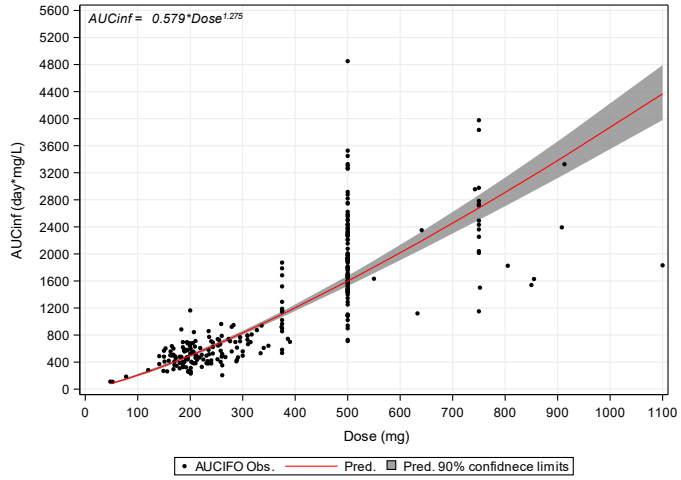


Figure 25: Relationship of Dose and First-Dose Retifanlimab AUC∞ in Individual Participants Receiving Different Dosing Regimens

Summary statistics of AUC, C_{max} and C_{min} after the first dose, as estimated in the population PK analysis, are shown in Table 18.

Table 18: Estimated summary statistics of first-dose PK parameters based on population PK analysis (DMB-22.133.1)

Study Parameter	Statistic	1 mg/kg Q2W	3 mg/kg Q2W	3 mg/kg Q4W	10 mg/kg Q2W	10 mg/kg Q4W	375 mg Q3W	500 mg Q4W	750 mg Q4W	Overall (Pooled)
AUC_1 (day*mg/L)	n	3	144	10	8	6	15	433	15	NA
	Mean (STD)	153 (25.4)	634 (228)	715 (225)	2150 (583)	2670 (417)	1200 (398)	1780 (570)	2580 (860)	NA
	Median	154	612	709	2180	2580	1210	1720	2500	NA
	Min, max	127, 177	148, 1600	383, 1020	1320, 2980	2250, 3240	604, 1840	607, 4100	1060, 4040	NA
	Q1,Q3	127, 177	473, 768	552, 913	1680, 2590	2320, 3080	907, 1520	1410, 2060	2150, 3090	NA
	Geometric mean (CV)	151 (17.1)	592 (40.2)	681 (34.7)	2080 (28.6)	2650 (15.5)	1140 (36.3)	1690 (33.8)	2430 (39.4)	NA
C_{max1} (mg/L)	n	3	144	10	8	6	15	433	15	NA
	Mean (STD)	16.0 (3.95)	59.8 (14.4)	67.8 (10.6)	197 (49.5)	237 (43.9)	112 (26.1)	152 (33.1)	200 (47.5)	NA
	Median	17.7	58.1	63.7	192	221	119	150	190	NA
	Min, max	11.4, 18.8	31.6, 109	53.8, 82.3	129, 292	203, 316	67.1, 152	76.8, 271	138, 285	NA
	Q1,Q3	11.4, 18.8	49.1, 69.1	60.0, 78.8	165, 219	204, 255	92.5, 137	129, 175	172, 253	NA
	Geometric mean (CV)	15.6 (27.5)	58.2 (24.1)	67.0 (15.7)	191 (25.1)	234 (17.4)	109 (25.0)	149 (22.3)	195 (23.9)	NA
C_{min1} (mg/L)	n	3	144	10	8	6	15	433	15	NA
	Mean (STD)	3.54 (0.574)	13.6 (4.49)	7.59 (3.44)	47.1 (13.5)	29.8 (7.44)	18.6 (7.00)	20.2 (7.98)	28.9 (11.4)	NA
	Median	3.59	13.3	7.34	45.5	26.9	18.8	19.8	27.4	NA
	Min, max	2.95, 4.10	1.85, 26.8	1.86, 12.1	27.5, 69.4	21.5, 40.8	6.66, 30.1	1.72, 48.6	7.40, 46.4	NA
	Q1,Q3	2.95, 4.10	10.6, 16.8	5.76, 10.7	38.4, 56.2	25.7, 37.0	14.3, 23.9	15.3, 24.8	23.0, 36.4	NA
	Geometric mean (CV)	3.51 (16.6)	12.7 (42.2)	6.67 (64.3)	45.4 (30.0)	29.1 (24.5)	17.2 (45.0)	18.3 (53.1)	26.2 (54.4)	NA

Multiple dose

Summary statistics of AUC, C_{max} and C_{min} at steady state, as estimated in the population PK analysis, are shown in **Table 19**.

Table 19: Estimated summary statistics of Steady-State PK parameters based on population PK analysis (DMB-22.133.1)

Study Parameter	Statistic	1 mg/kg Q2W	3 mg/kg Q2W	3 mg/kg Q4W	10 mg/kg Q2W	10 mg/kg Q4W	375 mg Q3W	500 mg Q4W	750 mg Q4W	Overall (Pooled)
AUC_{ss} (day*mg/L)	n	3	144	10	8	6	15	433	15	NA
	Mean (STD)	196 (50.4)	857 (312)	903 (215)	2680 (595)	3340 (472)	1480 (495)	2300 (742)	2970 (889)	NA
	Median	206	800	949	2670	3370	1330	2180	2660	NA
	Min, max	142, 241	182, 2010	597, 1130	1890, 3500	2750, 3990	780, 2570	788, 5990	1660, 4380	NA
	Q1,Q3	142, 241	654, 1010	668, 1110	2190, 3160	2880, 3690	1100, 1770	1770, 2710	2340, 3840	NA
	Geometric mean (CV)	192 (27.8)	803 (38.1)	877 (26.1)	2620 (23.3)	3310 (14.4)	1410 (33.0)	2190 (32.4)	2840 (31.5)	NA
$C_{max,ss}$ (mg/L)	n	3	144	10	8	6	15	433	15	NA
	Mean (STD)	25.2 (6.38)	103 (30.1)	84.0 (12.5)	329 (74.0)	298 (49.2)	154 (41.5)	198 (46.2)	258 (61.4)	NA
	Median	27.4	97.2	82.2	312	272	149	195	251	NA
	Min, max	18.0, 30.2	42.4, 205	67.8, 102	229, 443	260, 384	86.2, 230	89.7, 353	164, 376	NA
	Q1,Q3	18.0, 30.2	80.6, 123	72.6, 96.6	276, 392	270, 332	129, 189	164, 230	201, 300	NA
	Geometric mean (CV)	24.6 (28.0)	98.7 (29.7)	83.1 (14.8)	322 (22.8)	295 (15.6)	148 (28.1)	193 (24.1)	252 (24.2)	NA
$C_{min,ss}$ (mg/L)	n	3	144	10	8	6	15	433	15	NA
	Mean (STD)	9.22 (2.46)	43.1 (19.2)	16.2 (6.72)	133 (35.8)	61.6 (13.8)	41.9 (18.4)	45.7 (21.6)	58.1 (25.3)	NA
	Median	9.70	40.1	17.7	136	67.5	37.4	41.7	56.3	NA
	Min, max	6.55, 11.4	3.41, 118	5.85, 24.8	75.7, 187	38.7, 76.4	19.1, 87.6	4.97, 151	24.7, 101	NA
	Q1,Q3	6.55, 11.4	30.8, 52.9	9.47, 21.8	108, 155	51.4, 67.9	27.2, 51.5	29.7, 56.4	30.6, 86.6	NA
	Geometric mean (CV)	8.98 (29.1)	39.0 (50.5)	14.6 (55.7)	128 (29.7)	60.1 (25.6)	38.6 (43.0)	41.0 (50.8)	52.8 (49.4)	NA

Trough concentrations in study INCMGA 0012-101 are shown in the below figure.

Accumulation in concentration was observed from Cycle 2 to Cycle 5, and the C_{trough} values appeared to reach steady state at or before Cycle 6.

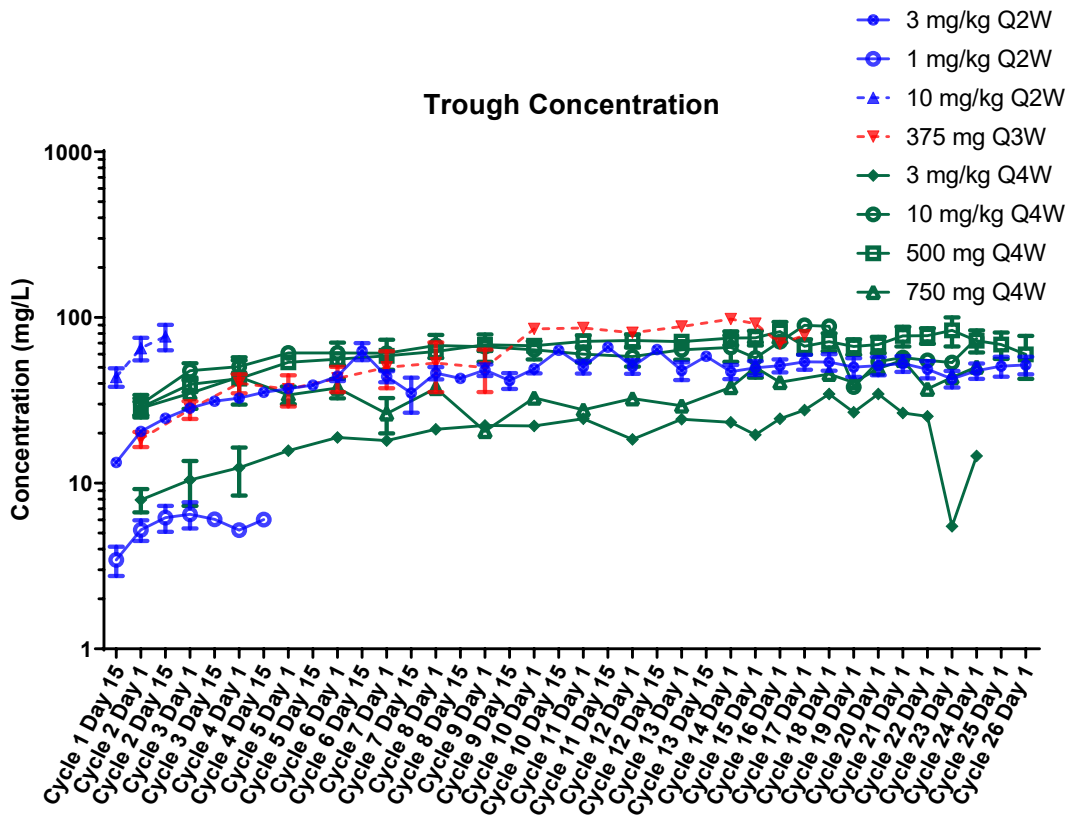


Figure 26: Trough Concentration (Mean ± SE) Profile of Retifanlimab for Different Treatment Regimens From Study INCMGA 0012-101

Intra- and inter-individual variability

Inter-individual variability in studies INCMGA 0012-101 and INCMGA 0012-104 is shown in **Table 20** (Cmax, AUC_{inf}, CL and V_z after first dose).

Table 20: Between subject variability (%CV based on geometric mean) in pharmacokinetic parameters

Study	Dose	N	Cmax (mg/L)	Ctrough (mg/L)	AUCinf (day· mg/L)	CL (L/day)	Vz (L)
INCMGA 0012-101	1 mg/kg Q2W	3	34.6%	NA	30.6%	6.62%	16.9%
	3 mg/kg Q2W[a]	131	31.0%	59.8%	34.2%	32.3%	27.7%
	3 mg/kg Q4W	9	21.4%	NA	34.9%	32.0%	41.6%
	10 mg/kg Q2W	7	27.0%	NA	29.9%	30.9%	30.6%
	10 mg/kg Q4W	5	17.4%	NA	25.8%	53.9%	49.7%
	375 mg Q3W[b]	15	30.4%	31.5%	39.2%	39.2%	25.0%
	500 mg Q4W[c]	97	37.8%	68.8%	35.2%	35.2%	33.0%
	750 mg Q4W[d]	13	29.5%	25.7%	31.8%	31.8%	27.3%
INCMGA 0012-104	500 mg Q4W	6	8.6%	25.7%	27.2%	27.2%	7.7%

[a] n = 46 for steady state.
[b] n = 4 for steady state.
[c] n = 57 for steady state.
[d] n = 3 for steady state.

In the population PK analysis, based on summarising empirical Bayesian estimates of the population, inter-individual variability of CL, after first dose, was estimated to be 36.0%, and at steady state, 33.6%. Inter-individual variability of V_{ss} was estimated to be 20.2%. Residual variability was best described using an additive model in the log-domain: After back-transforming, this would result in ±1760 ng/mL (or 0.153 in log-domain).

Inter-individual variability as measured in the more richly sampled studies INCMGA 0012-101 and INCMGA 0012-104 was mostly low to moderate (C_{max}: 8.6 – 37.8%, $AUC_{0\text{-}inf}$: 25.8 – 39.2%). Higher values were found for C_{trough} at 3 mg/kg Q2W and 500 mg Q4W in study INCMGA 0012-101 (59.8 – 68.8%) and for CL and V_z at 10 mg/kg Q4W (53.9% and 49.7%, respectively).

Intra-individual variability was not calculated in the studies, but residual variability in the population PK analysis was low.

Pharmacokinetics in target population

All studied subjects were cancer patients, but only in study INCMGA 0012-201 sparse pharmacokinetic samples in patients with advanced or metastatic MCC patients (n=102) were collected. The influence of population type was investigated in the population pharmacokinetic analysis.

In the population PK analysis, estimated CL and V_c of patients with Merkel cell carcinoma, were not significantly different from other cancer types. Participants with NSCLC (n = 60) tended to have approximately 16.5% higher CL than participants with other cancer types. Participants with Endometrial

Carcinoma (EC) (n = 134) tended to have approximately 66.4% higher I_{max} than participants with other cancer types.

In addition to patient type, also ECOG performance status on CL and tumour burden (>60 mm lesion: yes/no) on CL were significant covariates in the population pharmacokinetic model. In total 259 (40.9%), 370 (58.4%), 4 (0.6%) and 1 (0.2%) of the patients had a ECOG performance status of 0, 1, 2, and unknown, respectively. The median tumour burden was 60 mm (ranging from: 10 – 360, mean ± SD: 77.1 ± 57.0 mm).

The estimated effect size for ECOG performance status 0 versus 1 was 1.05 [90% CI: 1.02 – 1.10]. For tumour burden, comparing the observed 10^{th} percentile (19.0 mm) and 90^{th} percentile (154.0 mm) versus the median (60.0 mm) resulted in an effect size of 0.90 [90% CI: 0.88 – 0.93] and 1.09 [90% CI: 1.05 – 1.11], respectively.

The pharmacokinetics are influenced by the type of cancer, for patients with NSCLC had 16.5% higher clearance compared to the other cancer populations (i.e. EC, MCC, SCAC and others). For patients with EC I_{max} increased by 66.4%. Also, tumour burden and ECOG status had a significant impact on CL in the total cancer population. There was no statistically significant effect of cancer type, when comparing MCC to other cancers, on CL and I_{max}.

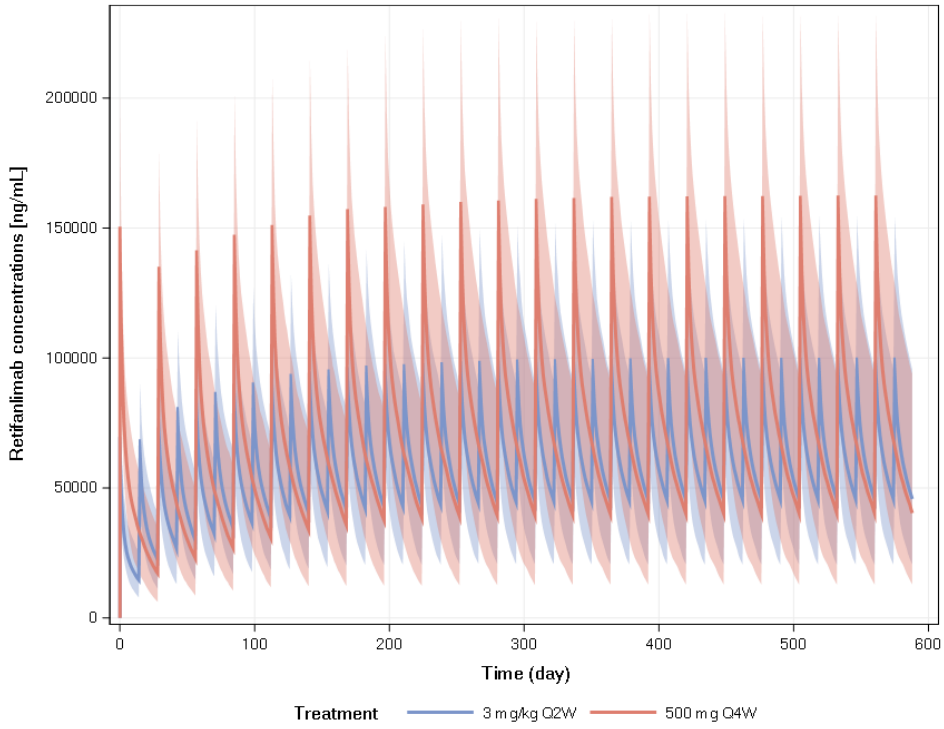
Special populations

Dedicated studies in special populations were not performed. Special populations were investigated with population PK analysis.

Weight

The median (range) weight of participants (n = 634) included in the population PK analysis of retifanlimab was 72 kg (35.0-133 kg). Baseline body weight was identified as a predictor for CL, V_c, and V_p. Higher body weight was associated with higher CL, V_c, and V_p. However, the magnitude of impact of body weight on CL, AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$, if any, was less than 18% in either the 10^{th} percentile (52.7 kg) or 90^{th} percentile (97.0 kg) of body weight with regard to the median body weight of 72 kg.

Retifanlimab was studied using a bodyweight-based dosing and fixed-dose regimen. A comparison between the population PK model simulated-PK profile for the 3 mg/kg Q2W dosing regimen and the proposed 500 mg Q4W dosing regimen was conducted (see Figure 27).



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.

Figure 27: Comparison of Model-Simulated Pharmacokinetic Profiles Following 500 mg Q4W Versus 3 mg/kg Q2W Retifanlimab (DMB-22.133.1)

Results showed that at 500 mg Q4W, the geometric mean retifanlimab concentrations (CV%) at steady state ranged between a C_{min} of 38.0 mg/L (66.8%) and a C_{max} of 188 mg/L (25.7%) and steady state was achieved after approximately 308 days. Comparable PK profiles were also observed for 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 131% and 13.9% higher than that of the 3 mg/kg Q2W dose; the mean $C_{min,ss}$ and $C_{max,ss}$ were 16.3% lower and 69.4% higher than those after 3 mg/kg Q2W dosing (see **Table 21**).

Table 21: Comparison of Model-Simulated Retifanlimab Exposures of 500 mg Q4W Versus Retifanlimab 3 mg/kg Q2W Exposures at Population Level and Body Weight–Stratified Subgroups (DMB-22.133.1)

Parameters	C_{min1} (mg/L)			C_{max1} (mg/L)			$C_{min,ss}$ (mg/L)			$C_{max,ss}$ (mg/L)			$AUC_{0\text{-}28d,ss}$ (day*mg/L)		
	3 mg/kg Q2W	500 mg Q4W	% Change	3 mg/kg Q2W	500 mg Q4W	% Change	3 mg/kg Q2W	500 mg Q4W	% Change	3 mg/kg Q2W	500 mg Q4W	% Change	3 mg/kg Q2W	500 mg Q4W	% Change
Median	14.7	17.2	17.0%	63.2	144	128%	45.8	40.4	−11.8%	109	188	72.5%	1790	2160	20.7%
(95% quantiles)	(7.95, 25.0)	(6.28, 34.8)	—	(43.6, 92.6)	(100, 207)	—	(20.6, 95.4)	(12.9, 93.8)	—	(72.3, 174)	(125, 289)	—	(1020, 3310)	(1110, 3870)	—
Geometric mean	14.4	16.4	13.9%	62.9	145	131%	45.4	38.0	−16.3%	111	188	69.4%	1820	2090	14.8%
CV%	35.4	56.4	—	23.2	23.1	—	50.5	66.8	—	27.3	25.7	—	37.8	39.4	—
Body weight subgroups (mean)															
35 kg, 61.35 kg	13.0	22.4	72.3%	55.2	171	210%	43.8	55.2	26.0%	98.9	226	129%	1670	2680	60.5%
61.35 kg, 72 kg	14.5	18.9	30.3%	62.5	153	145%	49.1	44.2	−9.98%	112	197	75.9%	1880	2250	19.7%
72 kg, 85.5 kg	15.6	17.7	13.5%	66.2	142	115%	52.2	43.9	−15.9%	118	186	57.6%	2010	2190	8.96%
85.5 kg, 132.8 kg	17.8	15.4	−13.5%	74.5	130	74.5%	57.1	36.5	−36.1%	132	167	26.5%	2230	1880	−15.7%

Box plots showing the effect of body weight (by quantiles) on first-dose and steady-state PK of the 500 mg Q4W dose are presented in Figure 28.

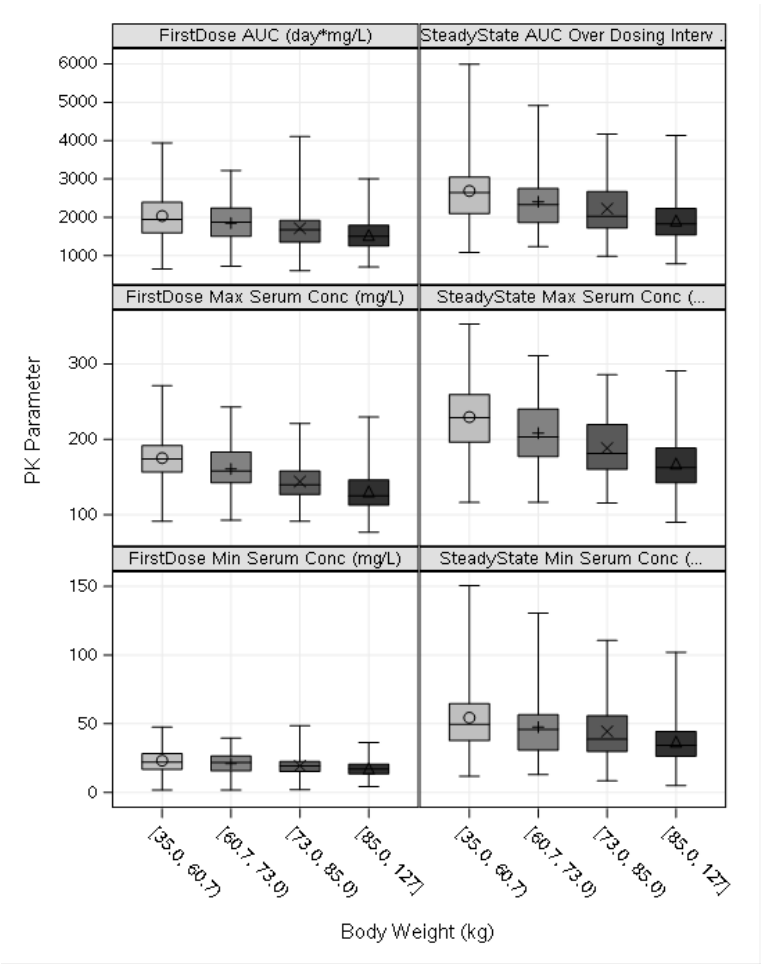


Figure 28: Box plots of the Estimated Retifanlimab Pharmacokinetic Parameters Versus Body Weight With 500 mg Q4W Dose

The effects of bodyweight were estimated to be mild in the relatively narrow bodyweight range included in the studies.

The effect of age, gender, race, renal impairment and hepatic impairment on retifanlimab PK was evaluated in the population PK analysis.

Gender: The effect of sex on retifanlimab PK was evaluated in the population PK analysis. Of the total 634 participants included in the population PK analysis of retifanlimab, 59.8% were female. Sex was found to be the significant predictor for Vc. The typical retifanlimab Vc was estimated at 3.76 L for male participants with body weight of 72 kg and was 15.3% lower in female participants. Sex was not identified as a significant covariate on CL.

Race: In the population PK analysis, there were 508 White/Caucasian participants (80.1%), 18 Black/African American participants (2.8%), and 23 Asian participants (3.6%), and race was not identified as a significant predictor for CL. Post hoc Bayesian estimated CLs showed that non-White participants had similar CL to White participants (geometric mean ratio of CL = 0.997; 90% CI: 0.952, 1.04.

With respect to ethnicity, a slightly higher CL (~23%) in Hispanic participants was estimated than that in non-Hispanic participants. However, only 26 out of 634 participants were Hispanic.

Renal impairment: Mild (n = 277, 43.7%) and moderate (n = 142, 22.4%) renal impairment, as classified by the MDRD equation had no effect on clearance. Data in patients with severe renal impairment are limited (n = 4, 0.6%) and there are no data for patients with end-stage renal disease. Eleven (11) patients with unknown renal impairment were included in the population PK analysis. The comparisons of post hoc Bayesian estimated CL values between participants with renal impairment and participants with normal renal function showed that the geometric mean ratio and 90% CI of CL for mild renal impairment versus normal renal function and moderate renal impairment versus normal renal function was 0.954 (0.914, 0.996) and 0.925 (0.880, 0.971), respectively.

Hepatic impairment: There are limited data on the effect of hepatic impairment. The majority of the participants (> 99%) included in the clinical studies for population PK analysis had normal hepatic function or mild hepatic impairment, as classified by the NCI ODWG classification system. Patients with moderate and severe hepatic impairment were not included in the population PK analysis. One (1) patient with unknown hepatic impairment was included. Mild (n = 78, 12.3%) hepatic impairment was not found to be a statistically significant predictor for CL in the population PK analysis. The comparisons of post hoc Bayesian estimated CLs between hepatic impairment and normal function showed that the geometric mean ratio and 90% CI of CL for mild hepatic impairment versus normal hepatic function was 1.00 (0.947, 1.06). Mild hepatic impairment had no effect on clearance.

No dedicated PK studies examining the effect of impaired renal and hepatic function on retifanlimab PK have been carried out.

Immunogenicity: Immunogenicity analysis included participant samples from each of the 5 clinical studies. The serum retifanlimab concentration-time profiles of ADA-positive versus ADA-negative participants by study and cancer type were compared. Samples for assessing ADAs were collected from each participant at baseline as well as at multiple visits prior to retifanlimab infusions. A total of 4431 ADA samples from 640 participants were collected for analysisA total of 25 samples (0.5% of the total number of samples) from 19 participants (3.0% from total participants (642) tested positive for antidrug antibodies (ADAs) of which 11 participants (1.7%) tested positive for treatment emerged ADAs. Only 1 participant was repeatedly ADA-positive. Patients (n=8) that had non-treatment-emergent pre-existing ADAs were not positive after the

treatment initiation. Neutralizing ADAs were present in 4 (0.6%) participants (8 samples) across all studies, of which 2 MCC patients (6 samples from the study INCMGA 0012-201).

Elderly: The effect of age on retifanlimab PK was evaluated in the Population PK analysis. The median age of participants (n = 634) included in the population PK analysis of retifanlimab was 64 years (range: 18.0-94.0 years). Age was not determined to be a significant predictor of PK variability in the final population PK model.

Table 22: number of elderly patients included in the clinical trials

PK Trials	**Age 65-74 (Older subjects number /total number)**	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
INCMGA 0012-101 (N = 311)	92 (29.6)	26 (8.4)	6 (1.9)
INCMGA 0012-104 (N = 6)	4 (66.7)	0	0
INCMGA 0012-201 (N = 102)	38 (37.3)	29 (28.4)	8 (7.8)
INCMGA 0012-202 (N = 94)	36 (38.3)	9 (9.6)	1 (1.1)
INCMGA 0012-203 (N = 121)	40 (33.1)	29 (24.0)	8 (6.6)

Pharmacokinetic interaction studies

Dedicated DDI studies of retifanlimab have not been performed.

Pharmacokinetics using human biomaterials

The applicant did not submit pharmacokinetic studies using biomaterials.

2.6.2.2. Pharmacodynamics

Mechanism of action

Retifanlimab is a fully humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with its ligands PD-L1 and PD-L2. Engagement of PD-1 with its ligands PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumour cells and/or other cells in the tumour microenvironment, results in inhibition of T cell function such as proliferation, cytokine secretion, and cytotoxic activity. Retifanlimab potentiates T cell responses, including antitumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Primary and secondary pharmacology

Pharmacodynamics correlates were investigated in study **INCMGA 0012-101**. The design of the dose-

response study is described in section 2.6.5.

Primary pharmacology

Receptor Occupancy on T Cells by Retifanlimab

Retifanlimab receptor occupancy of PD-1 on CD8 and CD4 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 labelled 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 was collected at various timepoints after dosing. In the first method, receptor occupancy was measured as percent of maximal binding over time from individual patients. Receptor occupancy was determined by the percentage of retifanlimab-positive CD8 cells (detected with an anti-IgG4Fc antibody) at the time following retifanlimab infusion divided by the percentage of retifanlimab-positive CD8 cells at the same time 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 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.

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 (Figure 29). 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 patients receiving flat doses of retifanlimab (500 mg Q4W [n=15] and 750 mg Q4W [n=15]) also demonstrated full occupancy in both dosing cohorts (**Figure 30**). Specifically, average receptor occupancy for both CD4+ and CD8+ T cells was above 90% at all time points assessed.

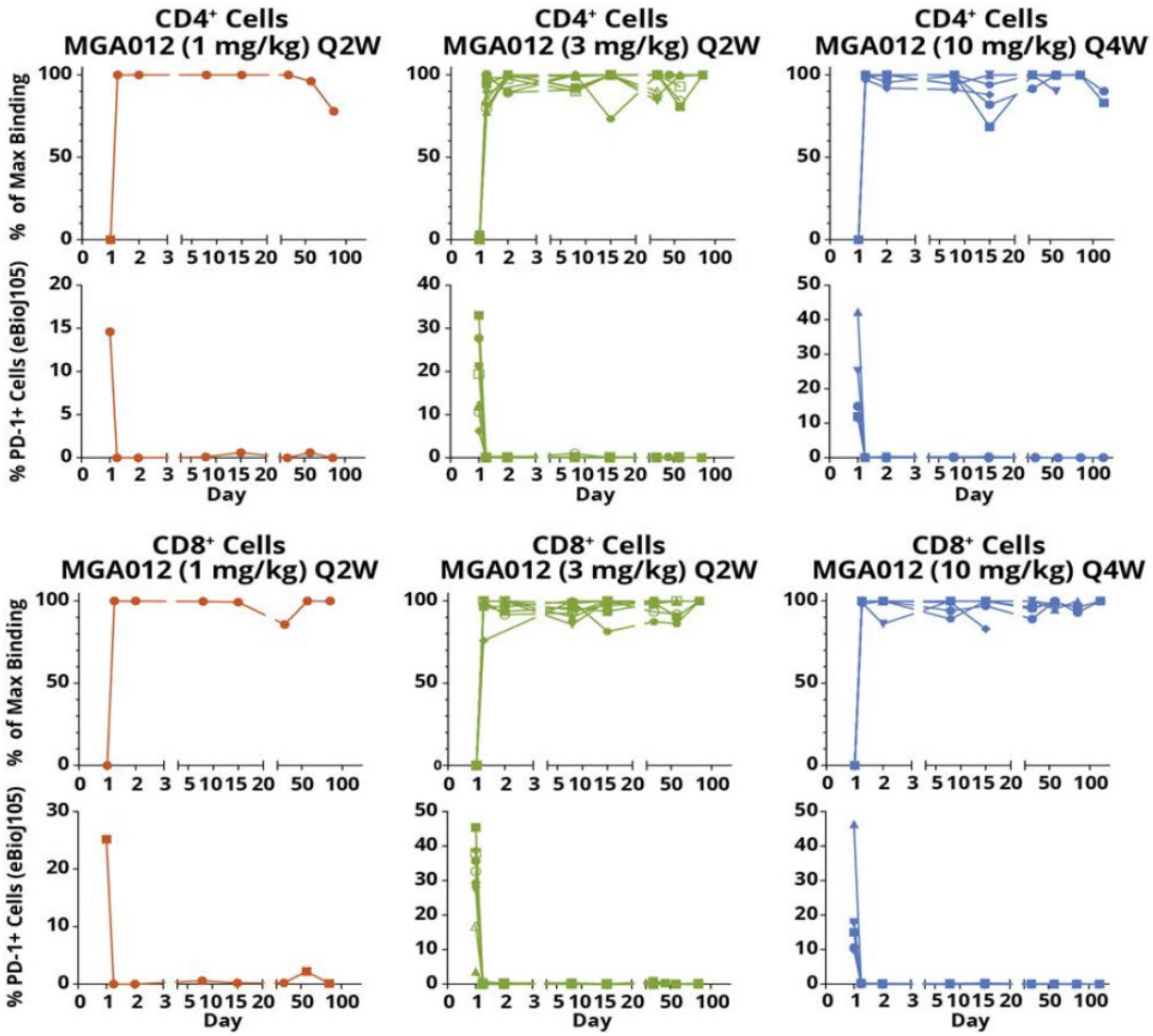


Figure 29: PD-1 T-Cell Receptor Occupancy in CD4- and CD8-Expressing Cells Following Dosing With retifanlimab

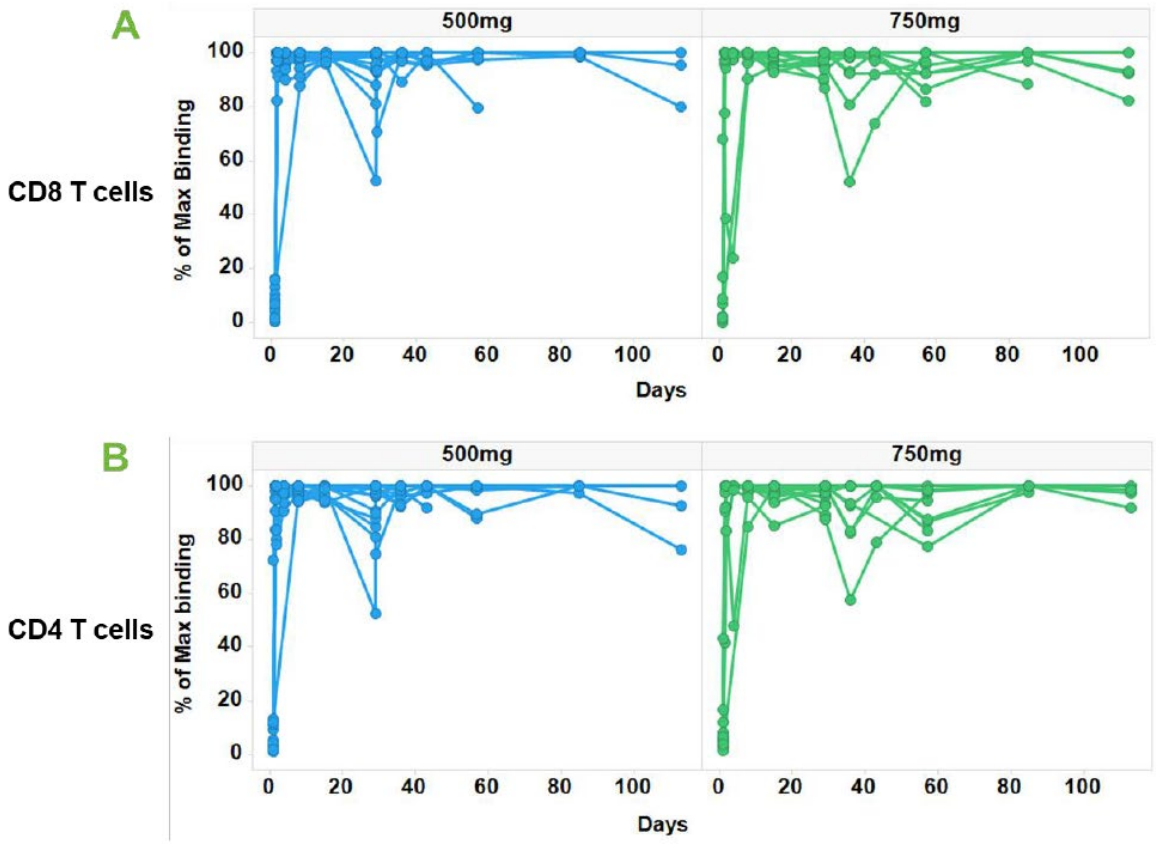
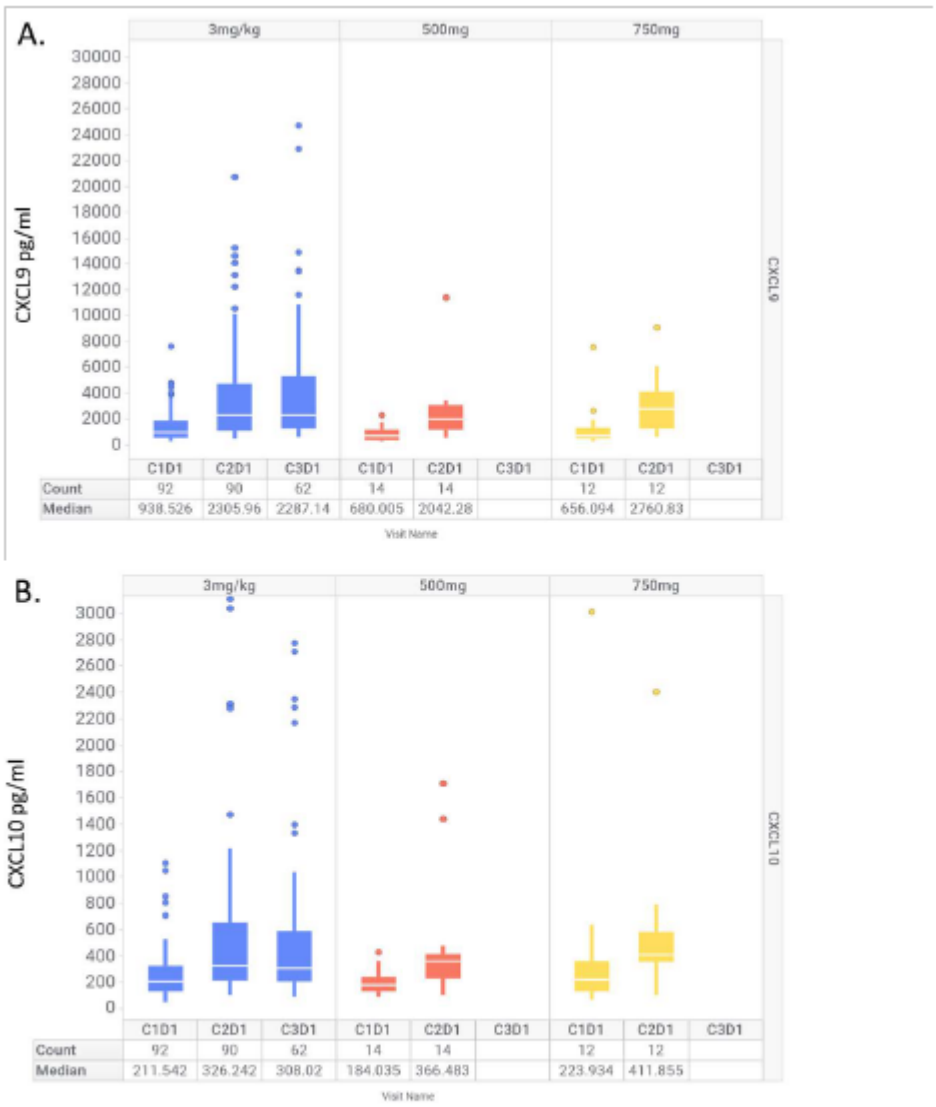


Figure 30: PD-1 Receptor Occupancy Following Dosing in the Flat-Dosing Cohorts

IFN-Inducible Plasma Cytokines

An array of serum proteins and metabolites, including cytokines, chemokines, and the tryptophan metabolite kynurenine, rapidly increased in patients dosed with retifanlimab. The IFNγ-inducible chemokines CXCL9 and CXCL10 were among the highest upregulated serum proteins identified as induced by retifanlimab administration, peaking at Cycle 2 Day 1 but remaining elevated through Cycle 3 Day 1. Regardless of the clinical outcomes and the tumour type, an increase in the level of CXCL9 and CXCL10 was observed following infusion with retifanlimab (Figure 31). The levels of CXCL9 and CXCL10 were measured by immunoassays in serum samples collected at baseline (Cycle 1 Day 1 pre-treatment) and on treatment (Cycle 2 Day 1 and Cycle 3 Day 1) in patients enrolled in the tumour-specific cohorts at 3 mg/kg Q2W and flat-dosing cohorts (Cycle 1 Day 1 and Cycle 2 Day 1 only).



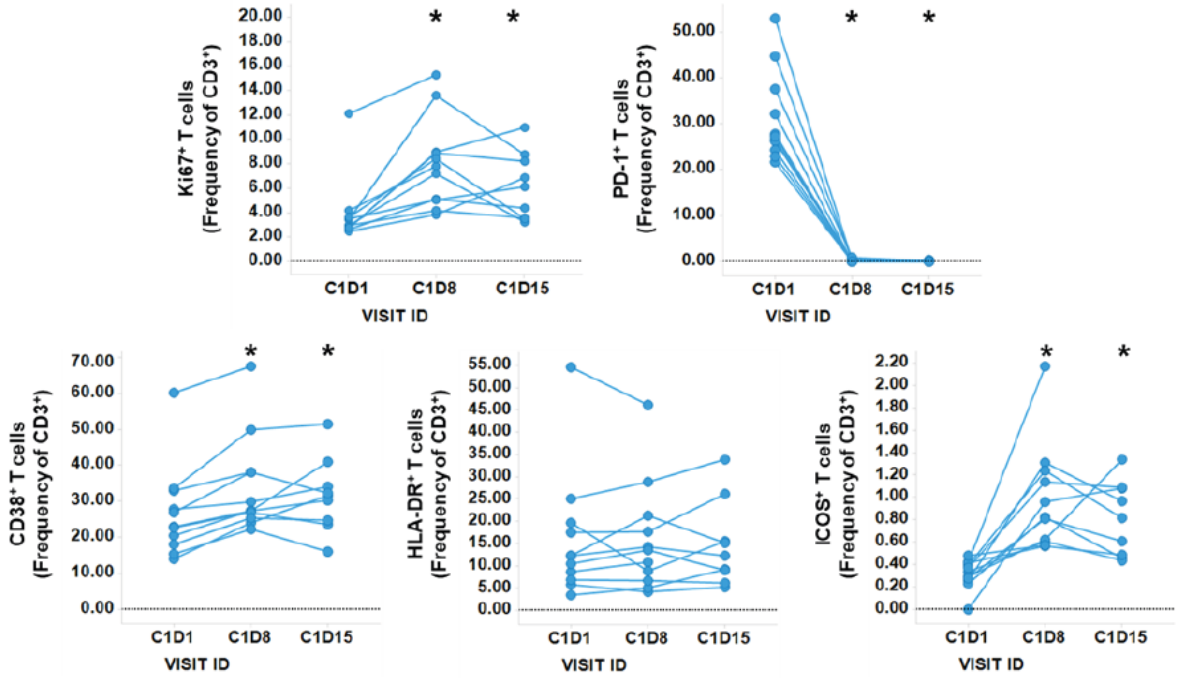
CxDx = Cycle x Day x.
Note: Levels of CXCL9 (A) and CXCL10 (B) were measured by immunoassays in serum samples collected at baseline (C1D1 pretreatment) and on treatment (C2D1 and C3D1) in participants in the tumor-specific (3 mg/kg) and flat-dosing cohorts.
Source: TRS-20.15, Figure 5 and data on file.

Figure 31: Levels of CXCL9 and CXCL10 in Tumour-Specific (3 mg/kg Q2W) and Flat-Dosing Cohorts

Effects of Retifanlimab Treatment on Peripheral T-Cell Activation

Circulating immune cell phenotyping was analysed using flow cytometry. Whole blood was collected at various timepoints following treatment with retifanlimab and shipped overnight for analysis. Staining for CD45, CD3, CD4, CD8, PD1, CD38, HLA-DR, ICOS, and Ki67 was performed. Cells were first gated on single cells, then on CD45+ cells (leukocytes), and then on CD3+ cells (T cells). Frequency of each marker at Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15 was depicted for 11 participants enrolled in the 375 mg Q3W cohort (*$p < 0.05$ by Wilcoxon matched pairs test; each timepoint was compared with Cycle 1 Day 1). A

transient increase in the frequency of proliferating T cells and activated T cells was observed in participants receiving retifanlimab (Figure 32). This effect seems to peak 8 days following the first infusion and to decrease to baseline subsequently.



CxDx = Cycle x Day x.
Note: Whole blood was collected following treatment with retifanlimab. Frequency of each marker at C1D1, C1D8, and C1D15 is depicted for 11 participants enrolled in the 375 mg Q3W cohort (*p < 0.05 by Wilcoxon matched pairs test; each timepoint was compared with C1D1).
Source: TRS-20.15, Figure 7.

Figure 32: Increases in Activated T Cells After Infusion of Retifanlimab

Ex Vivo Restimulated CD8+ and CD4+ T Cells

Additionally, following ex vivo restimulation, T cells isolated from peripheral blood mononuclear cells demonstrated an increased capacity to secrete cytokines (Figure 33). Ex vivo restimulated CD8 and CD4 T cells secrete higher levels of IFNγ post INCMGA00012 treatment. These assays were only conducted on Day 8, when both proliferating and activated T cells appear to peak, but no later assessment was conducted to determine whether or not this enhanced ability to produce interferon declines over time.

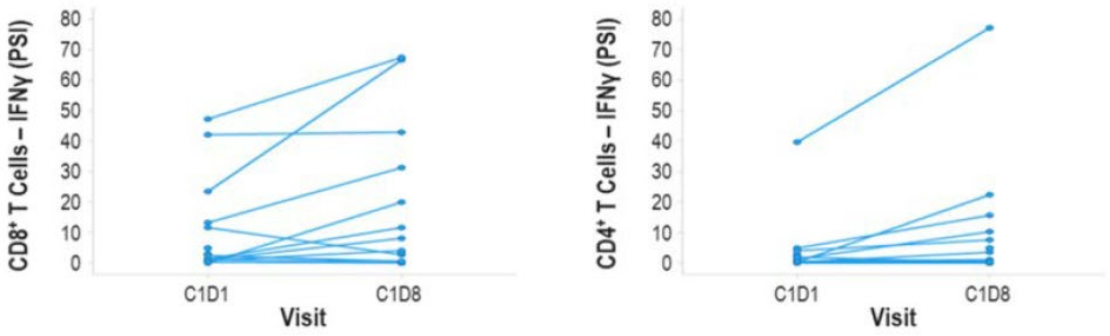
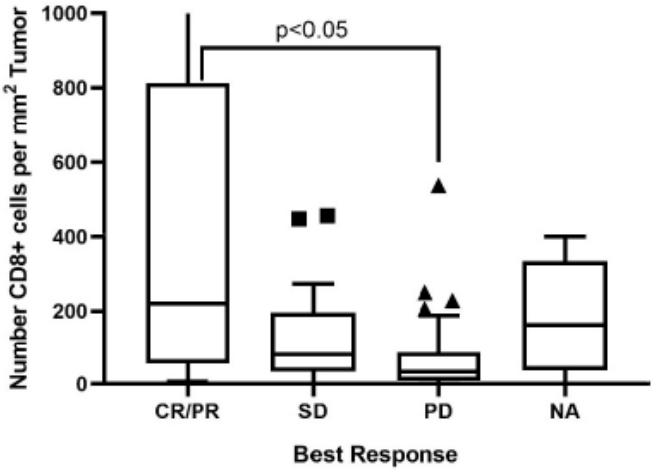


Figure 33: Ex Vivo Restimulated CD8+ and CD4+ T Cells Secrete Higher Level of IFNγ Post INCMGA00012 Treatment

Immune Correlates of Response Within the Tumours

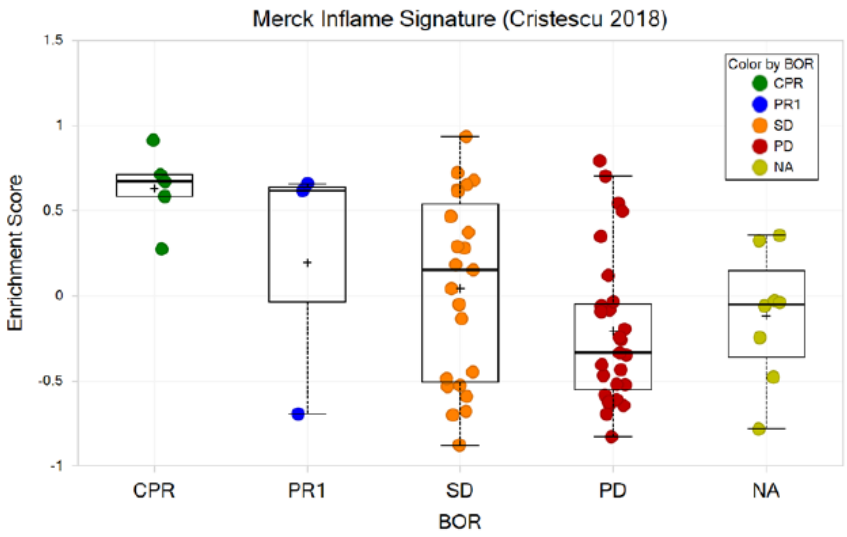
To evaluate immune correlates within the tumour, baseline biopsies from patients enrolled in Cohorts A, B, C, and D (biomarker-unselected endometrial cancer, cervical cancer, soft tissue sarcoma, and NSCLC, respectively) were analysed for T-cell infiltration by multiplex IHC for CD3, CD8, FoxP3, and PanCK/S100. The density of T cells was quantified per mm2 of tumour tissue (tumour tissue was identified as the PanCK/S100-positive area). CD8+ infiltration is shown in Figure 34. These data indicate that higher T-cell infiltration, as determined by measurement of CD8+ cells, at baseline is associated with subsequent clinical response to retifanlimab.



Note: Multiplex IHC quantification of CD8+ T-cell infiltration into tumor regions. $p < 0.05$ by Wilcoxon matched pairs test comparing each response strata to each other.

Figure 34: CD8+ T-Cell Infiltration Is Associated With Clinical Response

RNA extracted from formalin-fixed, paraffin-embedded tissue sections of baseline tumour samples was analysed for expression of an inflamed gene signature by RNAseq. Tumour inflammation gene signatures are gene expression profiles that are generally reflective of the presence or absence of immune cells, as well as immune activation, in the tumour microenvironment (Cristescu et al 2018). From this analysis (Figure 35), as observed with other anti–PD-1 therapies, the presence of an inflamed signature (Ayers et al 2017) was shown to be positively associated with a response to treatment with retifanlimab.



BOR = best objective response; CPR = confirmed partial response; PR1 = unconfirmed partial response; NA = response data not available.
Note: Baseline biopsies from participants enrolled in Cohorts A, B, C, and D (biomarker-unselected endometrial cancer, cervical cancer, soft tissue sarcoma, and NSCLC) were analyzed by RNAseq and the enrichment score for the inflamed signature derived by gene set enrichment analysis.
Source: TRS-20.15, Figure 11 and data on file.

Figure 35: Inflamed Signature in Tumour Is Associated With Tumour Response After Retifanlimab Administration

Secondary pharmacology

In Study INCMGA 0012-101, 12-lead ECGs (triplicate through Amendment 6 and single thereafter) were performed during the treatment period at screening, Cycle 1 Day 1, and, depending on dose regimen, at a minimum on Day 1 of every third cycle. In this study, retifanlimab was studied as a monotherapy in escalating doses of 1 mg/kg every 2 weeks (Q2W), 3 mg/kg Q2W (or Q4W), and 10 mg/kg Q2W (or Q4W) in weight-based dosing and doses of 375 mg every 3 weeks, 500 mg Q4W, and 750 mg Q4W in flat dosing in participants with advanced malignancies.

The categorical analysis did not reveal dose dependence in the incidences of outliers in heart rate (HR), QTcF intervals, PR intervals, and QRS intervals. The least squares mean (LSM) of change from baseline (Δ) HR were all within ± 10 beats/min with respect to the nominal timepoints for all dose groups. The LSM ΔQTcF from the central tendency analysis were between −17.1 and 6.85 milliseconds (ms) across dose groups. The highest upper limit of 90% CIs of the LSM ΔQTcF was 13.1 ms in the dose group of 10 mg/kg Q2W at the preinfusion timepoint, which is below 20 ms, the threshold of large QT effects for an oncology drug. The LSM

of ΔPR and ΔQRS were small, suggesting that retifanlimab at the studied doses did not have a relevant effect on heart rate or cardiac conduction (Table 23).

Table 23: Categorical Analysis of QTcF or ΔQTcF by Dose Group (Overall)

	Category	1 mg/kg Q2W	3 mg/kg Q2W	10 mg/kg Q2W	3 mg/kg Q4W	10 mg/kg Q4W	375 mg Q3W	500 mg Q4W	750 mg Q4W	All Doses
QTcF interval										
No. of participants	QTcF total	3	140	8	10	6	15	48	15	245
	QTcF ≤ 450 ms	3 (100)	124 (88.6)	8 (100)	9 (90.0)	4 (66.7)	13 (86.7)	45 (93.8)	15 (100)	221 (90.2)
	QTcF > 450 and ≤ 480 ms	0	12 (8.6)	0	1 (10.0)	2 (33.3)	1 (6.7)	2 (4.2)	0	18 (7.3)
	QTcF > 480 and ≤ 500 ms	0	3 (2.1)	0	0	0	0	1 (2.1)	0	4 (1.6)
	QTcF > 500 ms	0	1 (0.7)	0	0	0	1 (6.7)	0	0	2 (0.8)
No. of observations	QTcF total	22	1963	49	106	106	136	259	128	2769
	QTcF ≤ 450 ms	22 (100)	1865 (95.0)	49 (100)	105 (99.1)	99 (93.4)	122 (89.7)	248 (95.8)	128 (100)	2638 (95.3)
	QTcF > 450 and ≤ 480 ms	0	65 (3.3)	0	1 (0.9)	7 (6.6)	9 (6.6)	10 (3.9)	0	92 (3.3)
	QTcF > 480 and ≤ 500 ms	0	16 (0.8)	0	0	0	4 (2.9)	1 (0.4)	0	21 (0.8)
	QTcF > 500 ms	0	17 (0.9)	0	0	0	1 (0.7)	0	0	18 (0.7)
ΔQTcF										
No. of participants	ΔQTcF total	3	140	8	10	6	15	48	15	245
	ΔQTcF ≤ 30 ms	3 (100)	121 (86.4)	8 (100)	10 (100)	6 (100)	14 (93.3)	43 (89.6)	15 (100)	220 (89.8)
	ΔQTcF > 30 and ≤ 60 ms	0	18 (12.9)	0	0	0	1 (6.7)	5 (10.4)	0	24 (9.8)
	ΔQTcF > 60 ms	0	1 (0.7)	0	0	0	0	0	0	1 (0.4)
No. of observations	ΔQTcF total	22	1963	49	106	106	136	259	128	2769
	ΔQTcF ≤ 30 ms	22 (100)	1921 (97.9)	49 (100)	106 (100)	106 (100)	135 (99.3)	252 (97.3)	128 (100)	2719 (98.2)
	ΔQTcF > 30 and ≤ 60 ms	0	41 (2.1)	0	0	0	1 (0.7)	7 (2.7)	0	49 (1.8)
	ΔQTcF > 60 ms	0	1 (0.1)	0	0	0	0	0	0	1 (0.0)

Note: Values are presented as count or count (%), in which the frequency (%) was calculated with respect to the total count of the match parameters within each column.

Table 24: Categorical Analysis of HR, PR, and QRS by Dose Group (Overall)

	Category	1 mg/kg Q2W	3 mg/kg Q2W	10 mg/kg Q2W	3 mg/kg Q4W	10 mg/kg Q4W	375 mg Q3W	500 mg Q4W	750 mg Q4W	All Doses
HR										
No. of participants	HR total	3	140	8	10	6	15	48	15	245
	HR ≤ 100 beats/min	3 (100)	100 (71.4)	7 (87.5)	7 (70.0)	3 (50.0)	13 (86.7)	43 (89.6)	13 (86.7)	189 (77.1)
	HR > 100 beats/min	0	40 (28.6)	1 (12.5)	3 (30.0)	3 (50.0)	2 (13.3)	5 (10.4)	2 (13.3)	56 (22.9)
No. of observations	HR total	22	1963	49	106	106	136	259	128	2769
	HR ≤ 100 beats/min	22 (100)	1849 (94.2)	48 (98.0)	103 (97.2)	103 (97.2)	134 (98.5)	253 (97.7)	126 (98.4)	2638 (95.3)
	HR > 100 beats/min	0	114 (5.8)	1 (2.0)	3 (2.8)	3 (2.8)	2 (1.5)	6 (2.3)	2 (1.6)	131 (4.7)
PR interval										
No. of participants	PR total	3	140	8	9	6	15	48	15	244
	PR ≤ 200 ms	2 (66.7)	127 (90.7)	6 (75.0)	8 (88.9)	6 (100)	12 (80.0)	41 (85.4)	12 (80.0)	214 (87.7)
	200 ms < PR ≤ 220 ms	0	3 (2.1)	1 (12.5)	0	0	1 (6.7)	5 (10.4)	3 (20.0)	13 (5.3)
	PR > 220 ms	1 (33.3)	10 (7.1)	1 (12.5)	1 (11.1)	0	2 (13.3)	2 (4.2)	0	17 (7.0)
No. of observations	PR total	22	1961	49	100	106	136	258	128	2760
	PR ≤ 200 ms	14 (63.6)	1821 (92.9)	44 (89.8)	91 (91.0)	106 (100)	117 (86.0)	240 (93.0)	117 (91.4)	2550 (92.4)
	200 ms < PR ≤ 220 ms	3 (13.6)	34 (1.7)	4 (8.2)	3 (3.0)	0	7 (5.1)	15 (5.8)	11 (8.6)	77 (2.8)
	PR > 220 ms	5 (22.7)	106 (5.4)	1 (2.0)	6 (6.0)	0	12 (8.8)	3 (1.2)	0	133 (4.8)
QRS interval										
No. of participants	QRS total	3	140	8	10	6	15	48	15	245
	QRS ≤ 100 ms	3 (100)	103 (73.6)	5 (62.5)	6 (60.0)	3 (50.0)	10 (66.7)	37 (77.1)	12 (80.0)	179 (73.1)
	QRS ms < PR ≤ 110 ms	0	27 (19.3)	3 (37.5)	3 (30.0)	1 (16.7)	2 (13.3)	8 (16.7)	3 (20.0)	47 (19.2)
	QRS > 110 ms	0	10 (7.1)	0	1 (10.0)	2 (33.3)	3 (20.0)	3 (6.3)	0	19 (7.8)

Note: Values are presented as count or count (%), in which the frequency (%) was calculated with respect to the total count of the match parameters within each column.

In the concentration-ΔQTcF analysis, a prespecified linear mixed effects model was determined to be an insufficient fit for the data. A nonlinear mixed effects model of maximum effect (Emax) family was used to establish the relationship between serum retifanlimab concentrations and ΔQTcF. The Emax model estimated the maximum effect at 12.5 ms (95% CI: 9.96, 15.0), with a concentration required for an individual to experience 50% of the maximum effect of 51.3 mg/L (95% CI: 13.4, 89.2). Using this concentration-ΔQTcF Emax model, the QT effect (ΔQTcF) was predicted to be −2.02 ms (90% CI: −3.05, −0.988) at 15.9 mg/L

(34.6% geometric coefficient of variation [GCV]), the observed peak concentration after the first infusion of retifanlimab at 1 mg/kg (the lowest dose level); 4.47 ms (90% CI: 3.33, 5.62) at 159 mg/L (35.0% GCV) after a 500 mg flat dose, which is the clinical therapeutic dose; and 5.49 ms (90% CI: 4.08, 6.90) at 264 mg/L (7.02% GCV), the geometric mean of steady-state maximum serum concentration observed in the dose group of 750 mg Q4W (Figure 36).

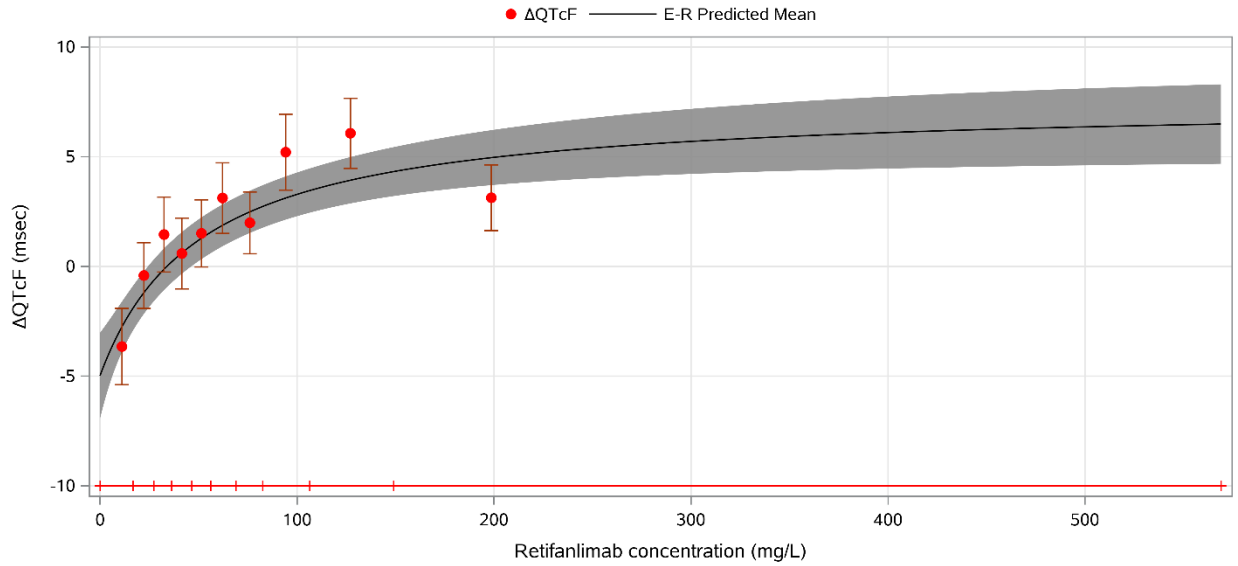


Figure 36: Concentration-ΔQTcF E_{max} Model Predicted ΔQTcF Interval (90% CI) at Observed Geometric Mean Peak Retifanlimab Concentrations

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics (PK) of retifanlimab were characterised using a population pharmacokinetics analysis with concentration data collected from 634 patients with various cancers who received retifanlimab doses of 1, 3, 10 mg/kg every 2 weeks, 375 mg every 3 weeks, or 3 mg/kg, 10 mg/kg, 500 mg and 750 mg every 4 weeks. The AUC was dose proportional in the studied dose range. The geometric mean (CV%) of C_{max} and AUC at steady state for the recommended 500 mg every 4 weeks dose were 193 mg/L (24.1%) and 2190 day*mg/L (32.4%).

Dose-proportionality was concluded after single dose, but the fit of the power model was poor and biased by the influence of bodyweight. Dose-proportionality was not evaluated at steady state, because rich sampling was only performed after the first dose. Dose was not evaluated in the population pharmacokinetic model as a covariate. No trends with dose were observed in the ETA for CL versus dose plots. Therefore, dose proportionality for AUC can be concluded in the studied dose range (1, 3, 10 mg/kg every 2 weeks, 375 mg every 3 weeks, or 3 mg/kg, 10 mg/kg, 500 mg and 750 mg every 4 weeks). Minor trends between the ETAs for the volumes of distributions and dose were observed. Geometric mean accumulation ratios varied between 1.5 and 2.4. The population pharmacokinetic model included a time-varying clearance parameter to account for an increase in C_{trough} over time. The time-varying clearance was described using a Sigmoid-type equation. As a result, C_{trough} is increasing over time, as also observed with other PD-(L)1 inhibitors (Centanni et al., 2019) and considered associated with improvement in disease status and the corresponding decrease

in the rate of cancer-related cachexia (cachexia is known to cause rapid degradation of proteins). Increased trough concentrations may also be caused by decreased target-mediated drug disposition (TMDD) due to decreased tumour burden (Centanni et al., 2019). Nonetheless, the effect for a typical individual appears limited as I_{max} was approximately -0.23. A rough approximation of the influence of time on CL is 80%. Therefore, clearance seems to decrease by about 20% over time. The clinical impact of this is negligible, considering low accumulation of retifanlimab and no evidence indicating a connection between exposure and safety.

The geometric mean value (CV%) for volume of distribution at steady state is 6.1 L (20.2%). This volume of distribution estimate slightly exceeds blood volume and was lower than extracellular fluid volume, which suggests that retifanlimab distributes to some extent outside of the vascular compartment.

The metabolic route of retifanlimab has not been characterised. Retifanlimab is expected to be catabolised through protein degradation processes and no metabolic drug-drug interactions are expected, and no formal pharmacokinetic drug interaction studies have been conducted. Retifanlimab is not expected to be a victim or perpetrator of drug-drug interactions involving drug transporters or CYP enzymes. The use of systemic corticosteroids or immunosuppressants before starting retifanlimab, except for physiological doses of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of retifanlimab. However, systemic corticosteroids or other immunosuppressants can be used after starting retifanlimab to treat immune-related adverse reactions (see SmPC section 4.5).

A geometric mean (CV%) clearance of 0.314 L/day (36%), without accounting for the time-varying part of the clearance, with a half-life of 14.6 days (31.5%) and 18.7 days (28.7%), after first-dose and at steady-state, respectively, were estimated in the population pharmacokinetic analyses.

The following factors are not expected to have clinically important effects on the pharmacokinetics of retifanlimab: age (range: 18 to 94 years), weight (35 to 133 kg), sex, race, or tumour burden.

The pharmacokinetics are influenced by the type of cancer, but the effect size can be expected to be mild for patients with NSCLC (only 16.5% higher clearance) compared to the other cancer populations (i.e. EC, MCC, SCAC and others). The effect size can be expected to be moderate for patients with EC as I_{max} increased by 66.4%, indicating that the decrease in CL over time is more pronounced. Also, tumour burden and ECOG status had a significant impact on CL in the total cancer population. There was no statistically significant effect of cancer type, when comparing MCC to other cancers, on CL and I_{max}.

Overall, the most pronounced impact on the pharmacokinetics of retifanlimab can be expected from bodyweight and tumour-related variables. The effects of bodyweight were estimated to be mild this is most likely caused by the relatively narrow bodyweight range included in the studies. Therefore, the influence of bodyweight can be expected to be more pronounced in the general population. Volume of distribution was however low, so distribution in adipose tissue is not expected. Furthermore, also the effects of tumour-related variables were mild and are presumably linked to PD-1 expression. The magnitude of impact of body weight on CL, AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$, if any, was less than 18% in either the 10^{th} percentile (52.7 kg) or 90^{th} percentile (97.0 kg) of body weight with regard to the median body weight of 72 kg which are not considered of clinical significance. All in all, no clinically relevant effects on the pharmacokinetics are to be expected. No dose adjustment for body weight is recommended.

No dedicated PK studies examining the effect of impaired renal and hepatic function on retifanlimab PK have been carried out. From a pharmacokinetic point of view, no relevant effect of impaired renal and hepatic

function on retifanlimab PK is expected. The effect of renal impairment on the clearance of retifanlimab was evaluated by population pharmacokinetic analyses in patients with mild (n = 277) or moderate (n = 142) renal impairment (eGFR between 89 and 30 mL/min/1.73m^2; n = 419) compared to patients with normal renal function (eGFR ≥ 90 mL/min/1.73m^2; n = 200). No clinically important differences were found in the clearance of retifanlimab. No dose adjustment is needed for patients with mild or moderate renal impairment. There are limited data in patients with severe renal impairment (n = 4, lowest eGFR 26.0 mL/min/1.73m^2). Retifanlimab has not been studied in patients with end-stage renal disease and therefore no dosing recommendation can be made (see SmPC 4.2).

The effect of hepatic impairment on the clearance of retifanlimab was evaluated by population pharmacokinetic analyses in patients with mild (n = 78; TB > ULN to 1.5 ULN or AST > ULN) hepatic impairment compared to patients with normal (n = 555; TB and AST ≤ ULN) hepatic function. No clinically important differences were found in the clearance of retifanlimab. No dose adjustment is needed for patients with mild hepatic impairment. There are limited data in patients with moderate (n = 1; TB between 1.5 and 3.0 times ULN and any AST) hepatic impairment. Retifanlimab has not been studied in patients with severe (TB between 3.0 and 10 times ULN and any AST) hepatic impairment and therefore no dosing recommendations can be made (see SmPC 4.2).

Although the proportion of participants being signed as inconclusive in the immunogenicity analysis was unacceptably high (30.6% (186 out of 607 assessable participants)) in the pooled all cancer population and 79.0% (79 out of 100 assessable participants) in the MCC population, the Applicant elaborated that inconclusive patients were in fact missing their matched serum retifanlimab concentrations. Since all of the observed pre-infusion concentrations or follow-up concentrations were below drug-tolerance level for ADA (1000 mg/L), the possibility of the retifanlimab trough concentration potentially leading to false negative results during ADA analysis was deemed as minimal. Based on the visual inspection of the concentration-time profiles of ADA-positive participants it can be concluded that they are generally within those of ADA-negative participants. Given the low number of ADA and NAb positive patients, the possibility of ADAs affecting retifanlimab PK seems to be minimal.

IgG antibodies 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 *et al*. 2017, FDA 2020). It is unlikely that retifanlimab would be a victim of PK DDI (EMA 2012, FDA 2020). Corticosteroids were used in the studies to treat some immune-related AEs (by 98 subjects), so the coadministration of corticosteroids was explored as a time-independent predictor for PK variability in the population PK model. Corticosteroid coadministration was not identified as a significant predictor for PK parameter variabilities.

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

Age was not determined to be a significant predictor of PK variability in the final population PK model. Therefore, no dose adjustment was warranted based on age.

Pharmacodynamics

The mechanism of action of anti-PD-1 therapies is known; that is, targeting PD-1-expressing cells, including T cells, and restoring their effector function by blocking checkpoint inhibitory interactions between PD-1 and its ligands, PD-L1 and PD-L2. These therapies have shown to be effective in several tumour types.

Primary pharmacology

Limited data were available regarding receptor occupancy results. Nonetheless, target engagement and (almost) full receptor occupancy was observed on PD-1 expressing CD4+ and CD8+ cells across all dose levels investigated.

Other PD results (not included in this report), such as those concerning the effect of retifanlimab on serum proteins and T-cell activation, indicate that retifanlimab is biologically active at the doses investigated in the expansion phase of the dose-finding study. In line with literature, the clinical response was associated with T-cell infiltration and presence of an inflamed signature in the tumour.

Secondary pharmacology

The relationship between retifanlimab serum concentrations and ΔQTcF was investigated using a non-linear mixed effects model of E_{max} family. A large QT/QTc effect (>20 ms) 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 (i.e., the PR and QRS intervals).

Exposure-response simulation

E-R (efficacy and safety) analyses were performed in patients with MCC (for safety, also in other cancers, with a total of 634 patients, of which 102 with MCC). No statistically significant relationships between exposure variables and clinical outcomes could be established for patients with MCC by the Applicant. It should be noted that the used methodology only provides a rough and presumably biased approximation of this relationship and does not account for changes over time and competing events, which are likely to happen in this population. Additionally, for efficacy, 100 patients were included in the analyses, but these patients only used one dose. This will prohibit any conclusions on dose-exposure-response. For the total cancer population, some correlations were found for safety, but these were not considered to be relevant. No extensive non-linear pharmacokinetic behaviour is however observed. Therefore, it is assumed that the target is saturated over the treatment interval. The lack of demonstrating an exposure-response relationship does not have consequences for this procedure, but could have consequences for future extrapolation exercises.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of retifanlimab have mainly been characterised using a population PK model, which is considered acceptable. Age (range: 18 to 94 years), weight (35 to 133 kg), sex, race, or tumour burden are not expected to have clinically important effects on the pharmacokinetics of retifanlimab, and dose adjustment is not needed. No dose adjustment is needed for patients with mild or moderate renal impairment, and for patients with mild hepatic impairment.

In terms of PD, there is target engagement and (almost) full receptor occupancy across all tested dose levels. Moreover, additional PD results indicate that retifanlimab is biologically active at the doses investigated. These results support the 500 mg Q4W dose regimen.

Retifanlimab at the studied doses up to 10 mg/kg Q2W or 750 mg Q4W did not have a relevant effect on cardiac conduction (i.e., the PR and QRS intervals).

No statistically significant relationships between exposure variables and clinical outcomes could be established by the Applicant for patients with MCC.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics of INCMGA00012 in Patients with Advanced Solid Tumours (POD1UM-101)

This is an ongoing study evaluating retifanlimab in patients with advanced solid tumours. Approximately 322 patients overall are planned for enrolment. The study consists of 2 phases, a Dose Escalation Phase (which has been completed) followed by a Cohort Expansion Phase.

The goal of dose escalation was to characterize the safety and tolerability of retifanlimab and to define the MTD based on the frequency of occurrence of DLTs in each cohort. A conventional 3 + 3 design was used. The initial dose regimen of retifanlimab was 1 mg/kg Q2W. The dose was then escalated to 3 mg/kg and 10 mg/kg Q2W or Q4W (**Figure 37**).

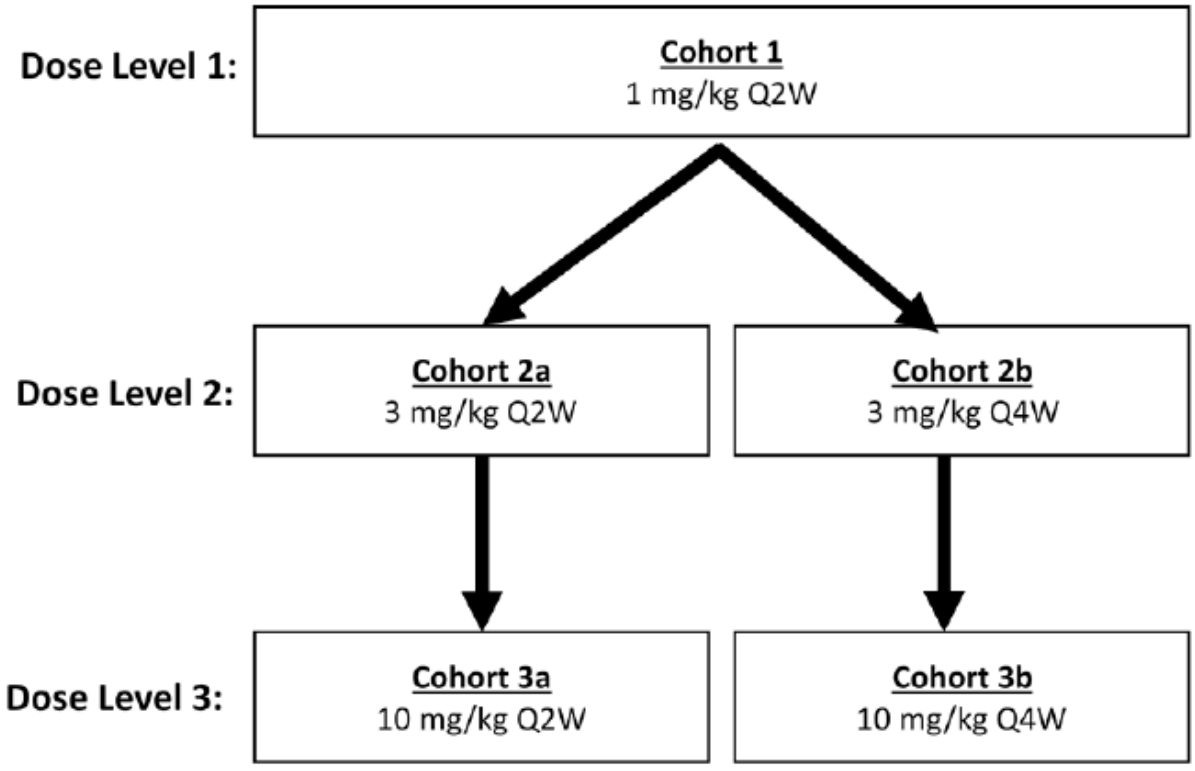


Figure 37: Dose Escalation Schema and Retifanlimab Regimens

The goals of the cohort expansion phase were to further characterize safety, PK, PD, and immunogenicity of weight-based and flat-dose retifanlimab regimens and to evaluate antitumor activity in patients with biomarker-unselected endometrial cancer, cervical cancer, soft tissue sarcoma NSCLC, and MSI-H/dMMR endometrial cancer (Table 25). Enrolment is complete in all cohorts with the exception of the MSI-H/dMMR endometrial cancer cohorts (i.e., Cohorts H and I).

Table 25: Expansion Cohorts

Cohort	Tumor Type	Retifanlimab Regimen
A	Biomarker-unselected endometrial cancer	3 mg/kg Q2W
B	Cervical cancer	3 mg/kg Q2W
C	Soft tissue sarcoma	3 mg/kg Q2W
D	NSCLC	3 mg/kg Q2W
E	Tumor-agnostic	500 mg Q4W
F	Tumor-agnostic	750 mg Q4W
G	Tumor-agnostic	375 mg Q3W
H	MSI-H/dMMR endometrial cancer	500 mg Q4W
I	MSI-H/dMMR endometrial cancer (China only)	500 mg Q4W

- **Methods**

Treatment

The study treatment is outlined in **Table 21**.

Table 26: Study Treatment Administered

Study Treatment Name	Retifanlimab
Dosage Formulation	Liquid formulation
Dosage Level	1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, 10 mg/kg Q4W, 500 mg Q4W, 750 mg Q4W, 375 mg Q3W
Route of Administration	IV
Administration Instructions	Administered IV over 60 minutes (± 15 minutes)
Packaging and Labeling	Retifanlimab is provided in a 25 mg/mL vial. Each vial is labeled as required per country requirement.
Current/Former Names	INCMGA00012, MGA012

First-in-human dose selection

The initial dose proposed for retifanlimab was selected using the FDA guidance on maximum recommended starting dose (MRSD) for first-in-human clinical Trials. A traditional toxicology-based approach was taken in

which the NOAEL determined in the repeat-dose GLP toxicology study of INCMGA00012 was converted to a human equivalent dose using appropriate and recommended scaling factors and then applying safety factors.

The NOAEL in the repeat dose GLP toxicology study of retifanlimab was determined to be 150 mg/kg, the highest dose tested in cynomolgus monkeys. The human equivalent dose of the NOAEL dose in monkeys, based on a body surface area conversion factor of 0.32 was calculated as 48 mg/kg (i.e., 150 mg/kg x 0.32). To this, a 10-fold safety factor was applied as well as an additional 6-fold factor to account for the 6-fold lower affinity of INCMGA00012 for cynomolgus PD-1 compared to human PD-1, resulting in a total applied safety factor of 60 and an estimated MRSD of 0.8 mg/kg. Because of high systemic exposure multiples and the conservative calculation incorporating a 6-fold difference for affinity between species, 1 mg/kg was considered as the MRSD.

Flat dose rationale

These doses were selected based on the safety profile, PK, and PD from the ongoing study.

Modeling and simulations of the PK data of retifanlimab were performed on 10 patients treated with 3 or 10 mg/kg Q4W schedule who had PK profiles characterized up to 672 hours. The mean BW of these patients was 87.7 kg with a range from 50.0 to 109.8 kg. Based on the mean BW, the top dose of 10 mg/kg Q2W corresponds to a flat dose of 877 mg Q2W, and in a 4-week interval, the total dose administered is 1754 mg (877 mg x 2). Thus, the 500 and 750 mg Q4W doses result in total exposures that are approximately 3.5- and 2.3-fold lower than the total exposures associated with the top dose investigated in Study INCMGA 0012-101 (10 mg/kg Q2W), providing adequate safety margins.

Objectives

Primary objective

The primary objective of this study is to characterize the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD), or maximum administered dose (MAD; if no MTD is defined), of retifanlimab in patients who have relapsed/refractory, unresectable locally advanced or metastatic solid tumours.

Secondary objectives

The secondary objectives of this study are:

- To characterize the PK and immunogenicity of retifanlimab for a variety of dose schedules.
- To investigate the preliminary anti-tumour activity of retifanlimab by ORR, DOR, PFS, and OS.

- **Results**

Outcomes and estimates

Primary objective (safety and tolerability)

All patients in dose escalation had at least 1 treatment-emergent adverse event (TEAE). No DLTs occurred during the DLT evaluation period, and an MTD was not reached. No clinically meaningful dose-related trends in the incidence or severity of TEAEs were observed (Table 27).

Table 27: Overall Summary of TEAEs: Dose Escalation (Safety Population)

Participants (n [%]) With:	Retifanlimab Dose Regimen					Total (N = 37)
	Q2W			Q4W		
	1 mg/kg (N = 3)	3 mg/kg (N = 10)	10 mg/kg (N = 8)	3 mg/kg (N = 10)	10 mg/kg (N = 6)	
TEAE	3 (100.0)	10 (100.0)	8 (100.0)	10 (100.0)	6 (100.0)	37 (100.0)
Treatment-related TEAE	2 (66.7)	9 (90.0)	5 (62.5)	5 (50.0)	5 (83.3)	26 (70.3)
Serious TEAE	2 (66.7)	3 (30.0)	1 (12.5)	4 (40.0)	3 (50.0)	13 (35.1)
≥ Grade 3 TEAE	2 (66.7)	8 (80.0)	4 (50.0)	7 (70.0)	6 (100.0)	27 (73.0)
Fatal TEAE	0	0	0	0	0	0
Serious treatment-related TEAE	0	1 (10.0)	0	0	0	1 (2.7)
≥ Grade 3 treatment-related TEAE	0	4 (40.0)	0	0	0	4 (10.8)
Study drug dose delay due to TEAE[a]	2 (66.7)	2 (20.0)	1 (12.5)	2 (20.0)	1 (16.7)	8 (21.6)
Permanent discontinuation of retifanlimab due to TEAE	0	0	0	0	0	0

[a] Treatment-emergent AEs leading to dose delay and infusion interruptions are captured as drug interruption and referred to as "dose delays" throughout this CSR.

Source: Table 3.2.1.1.

Secondary objective (anti-tumour activity; dose escalation & cohort expansion)

In the dose escalation phase, the investigator-assessed ORR according to RECIST v1.1 was 8.1% (95% CI: 1.7, 21.9), with confirmed partial responses observed in 3 patients. Cancer types of the objective responders were MSS endometrial cancer (retifanlimab 3 mg/kg Q2W), NSCLC (retifanlimab 3 mg/kg Q4W), and MSI-H colorectal cancer (retifanlimab 10 mg/kg Q4W). Durations of confirmed response were 7.7 months, 3.7 months, and 20.3 months (ongoing response, censored at last valid assessment date prior to the data cut-off date), respectively.

2.6.5.2. Main study

INCMGA 0012-201: A Phase 2, open-label, single-arm, multicenter study designed to assess the clinical activity and safety of retifanlimab in participants with advanced or metastatic MCC Study of Retifanlimab (POD1UM-201)

Methods

- **Study Participants**

Inclusion criteria

Patients were eligible to be included in the study only if all of the following criteria applied:

1. Signed informed consent.
2. Men and women, aged 18 or older (or as applicable per local country requirements).
3. Diagnosis of MCC with distant metastatic disease or recurrent, advanced locoregional disease not amenable to surgery or radiation.
4. ECOG performance status of 0 to 1.

5. Measurable disease according to RECIST v1.1. Tumour lesions that are located in a previously irradiated area or in an area subjected to other locoregional therapy should only be selected as target lesions if progression has been demonstrated in such lesions.
6. Availability of tumour tissue (fresh or archival) for central pathology review.
7. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 6 months after the last dose of study treatment and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Women of childbearing potential must have a negative serum pregnancy test at screening and before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 120 days after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. Women of nonchildbearing potential (i.e., surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age) are eligible.

Exclusion criteria

Patients were excluded from the study if any of the following criteria applied:

1. Prior systemic therapy for MCC, including chemotherapy and prior PD-1– or PD-L1–directed therapy.
2. Treatment with anticancer drugs or participation in another interventional clinical study within 21 days before the first administration of study drug.
3. Patient has not recovered to ≤ Grade 1 or baseline from toxic effects of prior therapy (with the exceptions for anaemia not requiring transfusion support and any grade of alopecia) and/or complications from prior surgical intervention within 7 days before starting study treatment.
4. Radiation therapy administered within 2 weeks of first dose of study treatment or radiation therapy to the thoracic region that is > 30 Gy within 6 months of the first dose of study treatment.
5. Known CNS metastases and/or carcinomatous meningitis.
   Note: Patients with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS oedema, and have not required steroids for at least 14 days before the first dose of study drug.
6. Any known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 3 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ

of the cervix, or other non-invasive or indolent malignancy, or cancers from which the participant has been disease-free for > 1 year, after treatment with curative intent.

7. Patients with laboratory values at screening defined in Table 28.

Table 28: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
A	Platelets	$< 100 \times 10^9$/L
B	Hemoglobin	< 9 g/dL
C	ANC	$< 1.5 \times 10^9$/L
Hepatic		
D	ALT	> 2.5 × ULN OR > 5 × ULN for participants with liver metastases
E	AST	> 2.5 × ULN OR > 5 × ULN for participants with liver metastases
F	Bilirubin/total bilirubin	≥ 1.5 × ULN unless conjugated bilirubin is ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds the ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin.
Renal		
G	Calculated creatinine clearance	< 30 mL/min
Coagulation		
H	INR or PT	> 1.5 × ULN
I	aPTT	> 1.5 × ULN

8. Evidence of interstitial lung disease or active, non-infectious pneumonitis.
9. Patients with impaired cardiac function or clinically significant cardiac disease:
    a. New York Heart Association Class III or IV cardiac disease, including pre-existing clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy.
    b. Unstable angina pectoris ≤ 6 months before study participation.
    c. Acute myocardial infarction ≤ 6 months before study participation.
    d. Other clinically significant heart disease (i.e., uncontrolled ≥ Grade 3 hypertension, history of labile hypertension, or poor compliance with an antihypertensive regimen). Must have recovered (to baseline or ≤ Grade 1) from toxicity associated with prior treatment.
10. Active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids.
11. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment.
12. Known active hepatitis A, B, or C or active infections requiring systemic antibiotics.
13. Has received a live vaccine within 28 days of planned start of study therapy.
    Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps,

rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live-attenuated vaccines and are not allowed.

14. Current use of prohibited medication.
15. Known hypersensitivity to another monoclonal antibody, which cannot be controlled with standard measures (e.g., antihistamines and corticosteroids).
16. Patient lacks the ability or is unlikely, in the opinion of the investigator, to comply with the Protocol requirements.
17. Patient who is pregnant or breastfeeding
18. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug/treatment and attending required study visits; pose a significant risk to the patient; or interfere with interpretation of study data.
19. History of organ transplant, including allogeneic stem cell transplantation.
20. Known allergy or hypersensitivity to any component of the study drug formulation.
21. Patients who are known to be HIV-positive, unless all of the following criteria are met:
    a. CD4+ count ≥ 300 µL.
    b. Undetectable viral load.
    c. Receiving highly active antiretroviral therapy.

Locations and setting

Patients were enrolled and treated at 34 study centres in Italy, France, the United States, Poland, Canada, Switzerland, Hungary, the Czech Republic, Germany, Spain, and the United Kingdom.

Treatments

The study treatment is outlined in Table 29.

Table 29: Study Treatment Administered

Study Treatment Name	Retifanlimab
Dosage Formulation	Liquid formulation
Unit Dose Strength/Dosage Level	500 mg Q4W
Route of Administration	IV
Administration Instructions	Administered over 60 minutes (+ 15 minutes)
Packaging and Labeling	Retifanlimab is provided in a 250 mg/10 mL vial (25 mg/mL). Each vial is labeled as required per country requirement.
Storage	Upright under refrigeration at 2°C-8°C (36°F-46°F) protected from light.
Current/Former Names or Aliases	INCMGA00012, MGA012

Dose modifications

Dose interruptions of retifanlimab were allowed for adverse events (AEs) as outlined in the protocol. No dose reductions or other modifications of retifanlimab were allowed for the management of toxicities for individual patients. Doses of retifanlimab may have been delayed up to 12 weeks for toxicity management.

Before the start of each treatment cycle, the patient must have met the treatment continuation criteria before administration of retifanlimab. If the criteria were not met at the beginning of a treatment cycle, retifanlimab infusion may have been delayed up to 12 weeks to allow for resolution of any abnormal laboratory results or AEs. Patients should have been withdrawn from the active treatment portion of the study if re-treatment criteria were not met within 12 weeks of the scheduled start of a cycle. Upon resolution, patients may have resumed treatment if no medical condition or other circumstance existed that, in the opinion of the investigator, would make the patient unsuitable for further participation in the study. If retifanlimab must have been discontinued due to unacceptable toxicity, then the patient should have been withdrawn from active treatment and enter the follow-up period of the study.

Prior and Concomitant Therapy

The incidence of infusion-related reactions with retifanlimab was low, and premedication prophylaxis (acetaminophen/paracetamol and a histamine blocker) was recommended only for patients who have had prior clinically significant reactions to infusion of a protein product.

Permanent Discontinuation of Study Drug Due to Toxicity

The occurrence of unacceptable toxicity not caused by the underlying disease required that the study treatment was permanently discontinued. Unacceptable toxicity were defined as follows:

- Occurrence of an AE that is related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the patient's ability to continue study-specific procedures or is considered to not be in the patient's best interest.
- Persistent AE requiring a delay of therapy for more than 12 weeks.
- Any AE defined in the dose modifications management guidelines requiring the study treatment be discontinued.

Treatment After the End of the Study

Once a patient discontinued study treatment, no further treatment was provided in the study. Patients who discontinued were eligible to enter the follow-up period to be evaluated for safety and survival. Any patients entering the follow-up period for any reason other than progressive disease were continued to be evaluated for disease status according to the scheduled assessments.

Objectives

Primary objective

To determine the efficacy of retifanlimab in terms of the objective response rate (ORR) in chemotherapy-naïve patients with advanced/metastatic MCC.

Secondary objectives

- To determine the duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) in the chemotherapy-naïve population with advanced/metastatic MCC treated with retifanlimab.
- To evaluate the safety of retifanlimab in patients with advanced/metastatic MCC.
- To determine the PK of retifanlimab administered to patients with advanced/metastatic MCC.

Exploratory objectives

- To assess efficacy of retifanlimab according to Immune Response Evaluation Criteria in Solid Tumors (iRECIST).
- To evaluate the relationship between baseline biomarkers and clinical activity.
- To assess the immunogenicity of retifanlimab in patients with advanced/metastatic MCC.
- Assessment of health-related quality of life of retifanlimab in patients with advanced/metastatic MCC.
- To assess impact of retifanlimab on HIV control.
- To determine the efficacy of retifanlimab in terms of the ORR, DOR, DCR, PFS, Tumour Size Change Over Time and OS in the full study population (chemotherapy-naïve and chemotherapy-refractory) with advanced/metastatic MCC.

Hypothesis

Not applicable.

Outcomes/endpoints

Primary endpoint

ORR, defined as the percentage of patients having an objective response (complete response [CR] or partial response [PR]), according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1), as determined by independent central radiographic review (ICR) in chemotherapy-naïve patients with advanced/metastatic MCC.

Secondary endpoints

- DOR, defined as the time from an initial objective response (CR or PR, which is confirmed subsequently) according to RECIST v1.1 until disease progression, or death due to any cause, as determined by ICR.
- DCR, defined as the proportion of patients with either an objective response or SD lasting at least 6 months.
- PFS, defined as the time from the start of therapy until disease progression, or death due to any cause, as determined by the ICR.
- 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 patients with advanced/metastatic MCC, including C_{max}, t_{max}, C_{min}, and AUC_t, was summarised.

Exploratory endpoints

- Efficacy parameters such as ORR and DCR evaluated according to iRECIST using investigator response assessments.
- Blood or tumour analytes, immune cell profile, and other relevant marker levels from baseline and correlation with treatment outcomes.
- Immunogenicity, defined as the occurrence of specific ADA to retifanlimab.
- Evaluations include changes in EQ-5D and FACT-M scores during the treatment period and correlations of the HR-PRO scores to tumour responses.
- HIV viral load and CD4+ cell counts monitored in patients who are known to be HIV-positive.
- ORR, defined as the percentage of patients having an objective response (CR or PR), according to RECIST v1.1, as determined by ICR (chemotherapy-naïve and chemotherapy-refractory patients).
- DOR, defined as the time from an initial objective response (CR or PR) according to RECIST v1.1 until disease progression, or death due to any cause, as determined by ICR (chemotherapy-naïve and chemotherapy-refractory patients).
- DCR, defined as the proportion of patients with either an objective response or SD lasting at least 6 months (chemotherapy-naïve and chemotherapy-refractory patients).
- PFS, defined as the time from the start of therapy until disease progression, or death due to any cause, as determined by the ICR (chemotherapy-naïve and chemotherapy-refractory patients).
- OS, defined as the time from the start of therapy until death due to any cause (chemotherapy-naïve and chemotherapy-refractory patients).
- Tumour Size Change Over Time, is defined as the sum of diameters of target lesions.

Sample size

A pilot study of avelumab in patients with chemotherapy-naive metastatic MCC showed a confirmed ORR of 39.7% with lower 95% CI of 30.7% (D'Angelo et al 2019). A pilot study of pembrolizumab in the same population showed an ORR of 56% with lower 95% CI of 35% (Nghiem et al 2016, Nghiem et al 2019).

Based on the results from studies of avelumab and pembrolizumab, the Applicant considered it reasonable to target a response rate of approximately 48%.

Approximately 60 chemotherapy-naïve patients were to be enrolled for the primary analysis. Based on a target ORR of 48% and a sample size of approximately 60, the study would be over 80% power to exclude the lower 95% confidence limit of 30% with $\alpha = 0.025$ (1-sided) in the chemotherapy-naive population.

Approximately 100 chemotherapy-naive patients were to be enrolled for the final analysis. This sample size ensured that half of the 95% CI would have been approximately 10% for an ORR ranging from 40% to 60%. This sample size also ensured 99% power to detect any AE with an underlying event rate as low as 0.5%.

Randomisation and blinding (masking)

This wasan open-label, single-arm study.

Statistical methods

Analysis Populations

Full analysis set

The FAS included all patients enrolled in the study who received at least 1 dose of study drug and were included in the primary analysis (i.e., approximately 60 chemotherapy-I patients and chemotherapy-refractory patients). The FAS was used for the summary of demographics, baseline characteristics, participant disposition, and efficacy. Note: This analysis population was to be used in the CSR reporting the primary analyses. The primary analysis of ORR was to be based on the chemotherapy-I subset of the FAS.

Efficacy Evaluable Population

The efficacy evaluable population includes all patients from the FAS with a centrally confirmed diagnosis of MCC who have measurable disease at baseline according to RECISTv1.1.

Safety Evaluable Population

The safety evaluable population included all enrolled patients who received at least 1 dose of study drug. The safety evaluable population was used to support the safety analysis at the primary analysis and to support all analyses, including efficacy at the final analysis.

Hypothesis

There was no formal hypothesis testing in this study. The study was designed to exclude an ORR of 30% or lower, based on the lower limited of the estimated 95% CI. Response rate as well as the associated 95% CI were to be provided.

Primary analysis

Objective response rate

The primary endpoint of the study is ORR in chemotherapy-naive patients, defined as the percentage of patients with confirmed CR or PR at any postbaseline visit before first PD or new anticancer therapy, according to RECIST v1.1 (Eisenhauer et al 2009) as determined by an ICR. The primary analysis of ORR will be performed at least 6 months after the last patient in the FAS is enrolled in the study. Patients who do not have sufficient baseline data to ascertain response will be included in the denominators in the calculation of ORR. The primary analysis of ORR will be based on the chemotherapy-naive subset of the FAS. Objective response rate and its exact 95% CI will be presented. In addition, ORR by investigator assessment will be provided as sensitivity analysis for the primary endpoint. The analysis will be repeated using the efficacy evaluable population as supportive analysis.

Secondary analyses

Duration of response

Duration of response is defined as the time from first documented response (CR or PR, which is confirmed subsequently) to the time of first documented disease progression or death due to any cause. If a patient does not have an event before data cut-off or new anticancer therapy, DOR will be censored at the date of the last adequate tumour assessment before data cut-off or new anticancer therapy following the same algorithm as censoring of PFS (Table 30). Duration of response will be analysed in chemotherapy-naive patients at least 6 months after the last patient in the FAS is enrolled in the study. The Kaplan-Meier estimate of the distribution function will be constructed for DOR. The estimated median along with 95% CIs will be reported. A swimmer plot for DOR may be generated. Analysis of DOR will be according to RECIST v1.1 as determined by ICR in the FAS. In addition, DOR assessed by investigator may be provided. The percentage of patients with confirmed response that lasts for 6 months from Kaplan-Meier estimate (6-month DOR estimate) will be estimated and provided as durable response rate (DRR).

Disease control rate

Disease control rate is defined as the proportion of patients with an overall response (CR and PR) or SD lasting at least 6 months per RECIST v1.1, according to the ICR. The DCR will be assessed in chemotherapy-naive patients using the FAS, and the exact 95% CI will be reported.

Progression-free survival

Progression-free survival is defined as the time from the first dose of study treatment to the date of the first documented progression per RECIST v1.1 according to ICR or death due to any cause. Progression-free survival will be analysed by the Kaplan-Meier method, including estimated median with 95% CIs and Kaplan-Meier estimated probabilities at several timepoints. If patients have no observed death or disease progression before data cut-off or new anticancer therapy, the patients will be treated as censored at their last adequate tumour assessment before cut-off or new anticancer therapy according to Table 30, which is based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). Date of death will be determined using the Death Report, Survival Follow-Up, Subject Status, and other datasets collected in the eCRFs. Progression-free survival will be assessed for chemotherapy-naïve patients in the FAS.

Table 30: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
Incomplete or no baseline tumor assessments	Censored	First Dose Date
No valid postbaseline response assessments in the absence of death prior to first scheduled tumor assessment	Censored	First Dose Date
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE or missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE or missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE or missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE or missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or documented progression immediately after missing 2 or more consecutive scheduled tumor assessment	Censored	Date of last valid radiologic assessment (not NE or missing) prior to missed assessments

Overall survival

Overall survival is defined as the time from first dose of study treatment to the date of death due to any cause. Date of death will be determined using the Death Report, Survival Follow-Up, and Subject Status eCRFs. Patients who are lost to follow-up or still alive at the time of analysis will be censored at the last known alive date. The last known alive date is defined as the later of the last study visit and the date the patient was last known alive from the Survival Follow-Up, Subject Status, or other datasets collected in the eCRFs. Kaplan-Meier curves, medians, and 95% CIs of the medians will be presented for OS. Overall survival will be assessed for chemotherapy-naïve patients using the FAS

Tumour Size Change Over Time

Tumour size is defined as the sum of diameters of target lesions. The best percentage change from baseline, defined as the largest decrease in tumour size for each patient, will be summarized descriptively. In addition, the best percentage change may be presented by a waterfall plot. The analysis will be performed in all patients in the FAS with a baseline tumour size available. Tumour size change over time may be assessed for chemotherapy-naïve patients.

Per RECIST v1.1, target lesions considered "too small to measure" will be assigned a default value of 5 mm for purposes of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm for this analysis. In the event a target lesion is unaccounted for in a particular postbaseline timepoint (i.e., assessment missing or NE), then the overall sum of diameters for target lesions will not be evaluable for that timepoint.

Subgroup analysis

Subgroup analyses will be performed on the following based on the patient's baseline status:

- 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% or missing, ≥ 1%
- Merkel cell polyomavirus status determined by central pathology review: positive, negative/equivocal/missing

Subgroup analyses will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered if there are too few patients in some subgroups.

Efficacy analyses in subgroups will generally be exploratory and are intended to explore the intrinsic consistency of any treatment effects found overall.

Subgroup analyses of the primary endpoint (ORR) will be performed on the FAS by presenting the point estimates in the subgroup with the exact 95% CIs. Summary tables and forest plots may be presented.

Safety analyses

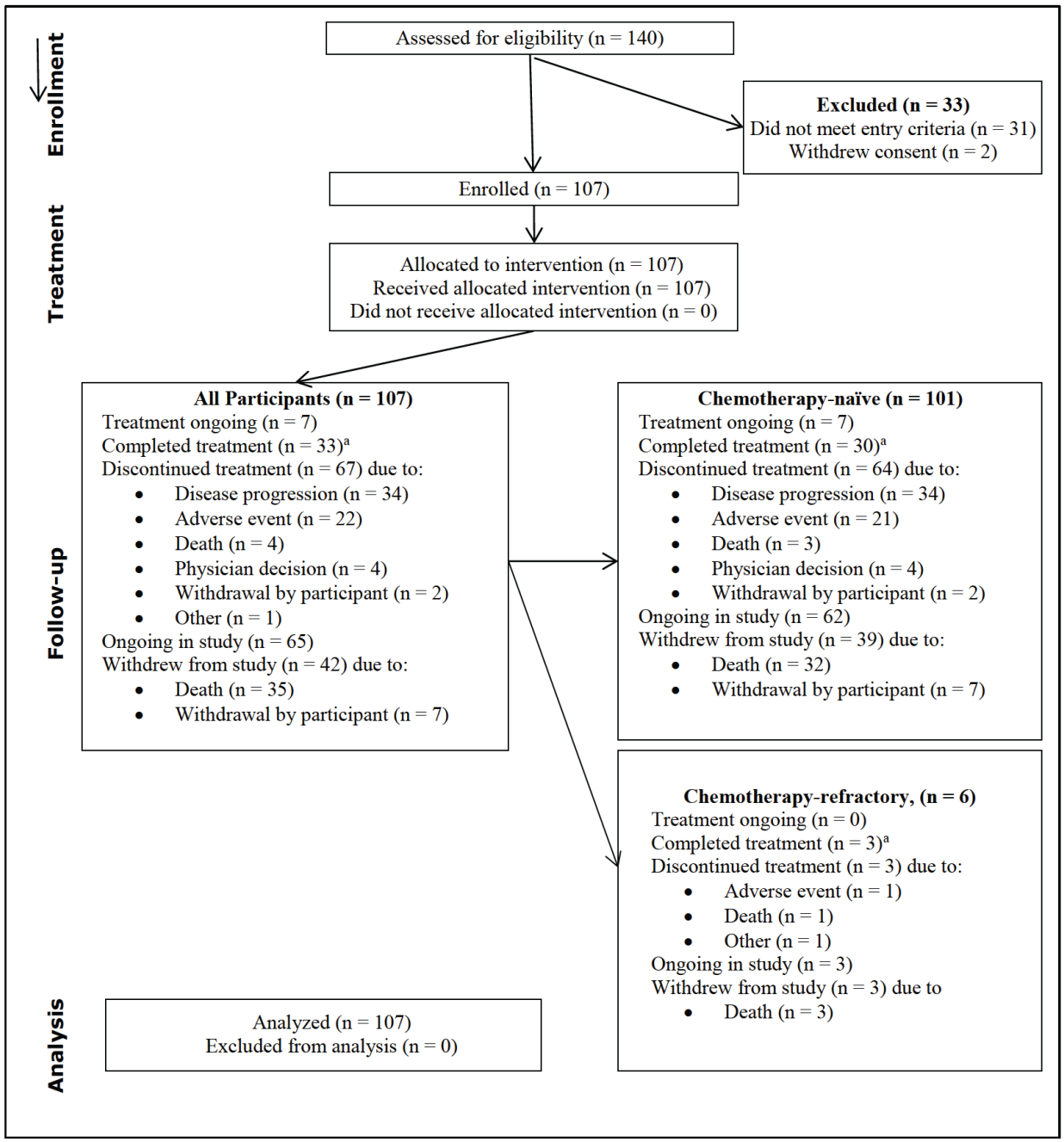
The clinical safety data (e.g., vital signs, ECGs, laboratory tests, and AEs) are summarized using descriptive statistics (e.g., mean, frequency) using the safety evaluable population

A TEAE was defined as either an AE reported for the first time or a worsening of a pre-existing event after the first dose of study drug until 90 days after the last dose of study drug. An AE with onset after starting a new anticancer therapy was not summarized as a TEAE.

Results

Participant flow

Figure 38 shows the participant flow. A tabular presentation of disposition is presented in Table 31.



[a] Completed Protocol-specified treatment period or had treatment discontinued at the discretion of the investigator following at least 6 months of therapy with confirmed CR, as allowed per Protocol discontinuation criteria.
Source: Table 1.1.1, Table 1.1.2.1, and Listing 2.1.1.

Figure 38: Participant flow

Table 31: Summary of Participant Disposition (Safety Evaluable Population)

Variable, n (%)	Chemotherapy-Naive (N = 101)	Total (N = 107)
Participants treated	101 (100.0)	107 (100.0)
Participants with ongoing treatment	7 (6.9)	7 (6.5)
Participants who completed treatment[a]	30 (29.7)	33 (30.8)
Participants who discontinued treatment	64 (63.4)	67 (62.6)
Primary reason:		
Disease progression – clinical progression	8 (7.9)	8 (7.5)
Disease progression – radiographic progression	26 (25.7)	26 (24.3)
AE	21 (20.8)	22 (20.6)
Death	3 (3.0)	4 (3.7)
Physician decision	4 (4.0)	4 (3.7)
Withdrawal by participant	2 (2.0)	2 (1.9)
Other	0 (0.0)	1 (0.9)
Participants ongoing in study	62 (61.4)	65 (60.7)
Participants who withdrew from study	39 (38.6)	42 (39.3)
Primary reason:		
Death	32 (31.7)	35 (32.7)
Withdrawal by participant	7 (6.9)	7 (6.5)

[a] Participants who received 2 years of treatment or who were treated for at least 6 months and achieved a confirmed CR.
Source: INCMGA 0012-201 CSR Table 1.1.2.1.

Recruitment

The first patient was dosed on 25 Feb 2019.

Enrolment is complete and the study is ongoing.

As of the latest data cut-off date for the INCMGA 0012-201 CSR (10 Mar 2023), the median duration of survival follow-up was 24.0 months (range: 0.7-48.1 months).

Conduct of the study

Protocol deviations

A summary of protocol deviations is provided in Table 32.

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.

Six participants in the safety evaluable population had Protocol deviations that were considered clinically important.

Table 32: Summary of Protocol Deviations

Deviation Categories	Chemo-naive advanced (N=10)	Chemo-naive metastatic (N=91)	Chemo-naive total (N=101)	Chemo-refractory (N=6)	Total (N=107)
ADVERSE EVENT	0 (0.0)	4 (4.4)	4 (4.0)	0 (0.0)	4 (3.7)
ENTRY CRITERIA	2 (20.0)	4 (4.4)	6 (5.9)	0 (0.0)	6 (5.6)
INFORMED CONSENT	3 (30.0)	19 (20.9)	22 (21.8)	0 (0.0)	22 (20.6)
NON COMPLIANCE WITH STUDY PROCEDURE - MISSED ASSESSMENT	10 (100.0)	83 (91.2)	93 (92.1)	5 (83.3)	98 (91.6)
NON COMPLIANCE WITH STUDY PROCEDURE - OUT OF WINDOW ASSESSMENT	7 (70.0)	54 (59.3)	61 (60.4)	3 (50.0)	64 (59.8)
NON COMPLIANCE WITH STUDY TREATMENT	4 (40.0)	23 (25.3)	27 (26.7)	1 (16.7)	28 (26.2)
OTHER	3 (30.0)	32 (35.2)	35 (34.7)	1 (16.7)	36 (33.6)

Protocol amendments

The INCMGA 0012-201 Protocol was amended 7 times. A summary of amendments is provided in **Table 33**.

Table 33: Summary of INCMGA 0012-201 Protocol Amendments

Protocol Amendment	Date	Primary Reason for Amendment
1	27 JUN 2018	• Addressed comments received from the US FDA. • Limited the assessment of the primary endpoint of ORR to the chemotherapy-naive study population. The ORR in the full study population, composed of both chemotherapy-naive and chemotherapy-refractory participants, was assessed as a secondary endpoint. • Added and/or revised multiple secondary endpoints to specify that the analysis would be performed on the chemotherapy-naïve population and the full study population, composed of both chemotherapy-naive and chemotherapy-refractory participants. • Revised assumptions and sample size in accordance with literature estimates for ORR in both the primary efficacy population (chemotherapy-naive) and the full study population. The final sample size also reflected allowance for attrition during the course of the study. Statistical analyses were updated to align with the revised primary and secondary efficacy endpoints. • Revised the futility analysis to be based on responses in the chemotherapy-naïve population. The number of participants assessable for response needed for the analysis was updated from 25 to 20.
2	04 OCT 2018	• Addressed comments from the European Competent Authorities. • Added an independent data monitoring committee. • Updated inclusion and exclusion criteria as follows: - The duration of contraception for females was changed to 120 days after the last dose of study treatment. - Participants who had received a live virus vaccine within 28 days of the start of study therapy were excluded. - Participants with a history of organ transplant, including allogeneic stem cell transplantation, were excluded. - Participants with a known allergy or hypersensitivity to any component of the study drug formulation were excluded. • Clarified that study treatment must be discontinued for any ⩾ Grade 3 IRR. • Added guidance for the management of immune-mediated myocarditis. • Clarified that disease status was evaluated by ICR.
3	05 DEC 2018	• Addressed comments from Health Canada. • Allowed inclusion of participants with well-controlled HIV. • Adjusted the ALT and AST exclusionary laboratory values to allow for the possibility of participants with liver metastases to have enrolled if their ALT or AST values were ⩽ 5 × ULN.

		• Removed the requirement for premedication prophylaxis before the first dose of retifanlimab. • Added language that allows participants to discontinue study treatment if they achieve a confirmed CR and have received at least 6 months of study treatment.
4	16 AUG 2019	• Expanded the eligibility criteria to include participants with recurrent locoregional advanced disease in addition to participants with distant metastatic MCC. • Added language to specify that the FAS includes all participants who received a dose of study drug (this was updated from those participants who had centrally confirmed diagnosis of MCC).
5	09 APR 2020	• Clarified the definition of target lesions for participants who had progression in areas previously treated with locoregional therapy. • Adjusted the study design and eligibility criteria to exclude participants who had received prior systemic therapy for treatment of MCC due to the changed treatment landscape with the availability of anti–PD-(L)1 therapies.
6	22 OCT 2020	• Increased the sample size of the study to 100 chemotherapy-naive participants to allow a more robust characterization of durability of response and OS, as recommended by the FDA. • Clarified that the study will end once 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. • Updated the statistical section to clarify how the populations will be analyzed for the primary and final analyses. • Provided the outcome of the futility analysis.
7	16 DEC 2021	• Updated the irAE management guidelines to reflect updated published guidance.

Baseline data

Demographic Characteristics

Patients age ranged from 38 to 90 years in the safety evaluable population, with a median age of 71.0 years. Most patients (68.2%) were male (Table 34). Eighty-four patients (78.5%) were White/Caucasian, 1 patient (0.9%) was Asian, and race in the remaining 22 patients (20.6%) was not reported. Eighty-one patients (75.7%) were not Hispanic or Latino, 1 patient (0.9%) was Hispanic or Latino, and ethnicity in the remaining 25 patients (23.4%) was not reported.

Table 34: Summary of Demographic Characteristics (Safety Evaluable Population)

Variable	Chemotherapy-Naïve		Total
	FAS (N = 65)	Total (N = 101)	(N = 107)
Age (years)			
Mean	71.4	71.1	70.7
STD	10.26	10.45	10.54
Median	71.0	71.0	71.0
Minimum, maximum	44, 90	38, 90	38, 90
Age group, n (%)			
< 65 years	14 (21.5)	24 (23.8)	27 (25.2)
≥ 65 years	51 (78.5)	77 (76.2)	80 (74.8)
< 75 years	41 (63.1)	62 (61.4)	67 (62.6)
≥ 75 years	24 (36.9)	39 (38.6)	40 (37.4)
Sex, n (%)			
Male	42 (64.6)	68 (67.3)	73 (68.2)
Female	23 (35.4)	33 (32.7)	34 (31.8)
Race, n (%)			
White/Caucasian	51 (78.5)	78 (77.2)	84 (78.5)
Asian	1 (1.5)	1 (1.0)	1 (0.9)
Other[a]	13 (20.0)	22 (21.8)	22 (20.6)
Ethnicity, n (%)			
Hispanic or Latino	0 (0.0)	1 (1.0)	1 (0.9)
Not Hispanic or Latino	52 (80.0)	75 (74.3)	81 (75.7)
Not reported	13 (20.0)	25 (24.8)	25 (23.4)
ECOG performance status, n (%)			
0	48 (73.8)	74 (73.3)	77 (72.0)
1	17 (26.2)	27 (26.7)	30 (28.0)
HIV infection, n (%)			
Positive	1 (1.5)	1 (1.0)	1 (0.9)
Negative/unknown	64 (98.5)	100 (99.0)	106 (99.1)

[a] Other includes participants from France, where information on race is not collected per regulatory requirements.
Source: Tables 1.2.1.1, 1.2.1.2, 1.3.1.1, and 1.3.1.2 and Listing 2.4.1.

Disease Characteristics

The baseline disease characteristics observed for the safety evaluable population were as anticipated based on the Protocol eligibility criteria. The majority of patients (97 [90.7%]) had metastatic disease at study entry as assessed by investigators, and 39 patients (36.4%) had visceral metastases (Table 35). Merkel cell polyomavirus status by central laboratory testing was positive in a majority of patients (78 out of the 102 patients for whom test results were available). The PD-L1 CPS was ≥1% in 88 out of the 101 patients for whom test results were available. All participants had Stage 3 (3/3A/3B; 10 participants [9.3%]) or Stage 4 disease (97 participants [90.7%]) at study entry.

Table 35: Summary of Cancer History and Baseline Disease Characteristics (Safety Evaluable Population)

Variable	Chemotherapy-Naïve		Total (N = 107)
	FAS (N = 65)	Total (N = 101)	
Time since initial diagnosis, months			
Mean	12.78	10.86	11.18
STD	14.727	13.441	13.401
Median	8.94	4.67	5.45
Minimum, maximum	0.2, 64.0	0.2, 64.0	0.2, 64.0
Liver metastasis, n (%)			
Yes	6 (9.2)	9 (8.9)	11 (10.3)
No	59 (90.8)	92 (91.1)	96 (89.7)
MCPyV status by central laboratory, n (%)			
Positive	46 (70.8)	73 (72.3)	78 (72.9)
Negative	15 (23.1)	20 (19.8)	21 (19.6)
Equivocal	1 (1.5)	3 (3.0)	3 (2.8)
Not evaluable	0 (0.0)	1 (1.0)	1 (0.9)
Missing	3 (4.6)	4 (4.0)	4 (3.7)
PD-L1 CPS, n (%)			
< 1%	9 (13.8)	12 (11.9)	13 (12.1)
≥ 1%	52 (80.0)	83 (82.2)	88 (82.2)
Missing	4 (6.2)	6 (5.9)	6 (5.6)
Centrally confirmed diagnosis of MCC, n (%)			
Yes	60 (92.3)	92 (91.1)	98 (91.6)
No	1 (1.5)	1 (1.0)	1 (0.9)
Equivocal	1 (1.5)	3 (3.0)	3 (2.8)
Not evaluable	0 (0.0)	1 (1.0)	1 (0.9)
Missing	3 (4.6)	4 (4.0)	4 (3.7)
Visceral metastases at baseline per ICR, n (%)[a]			
Present	25 (38.5)	36 (35.6)	39 (36.4)
Absent	40 (61.5)	65 (64.4)	68 (63.6)

[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: Tables 1.3.1.1 and 1.3.1.2.

Prior Anticancer Therapies

Of the 107 patients, 101 patients were chemotherapy-naïve and 6 patients were chemotherapy refractory. No patients had received prior immunotherapy. All patients in the chemotherapy-refractory group had received chemotherapy with a platinum compound in combination with etoposide. Three patients had a best response of PR, 2 patients had an unknown response, and 1 patient had a best response of SD.

Forty of the 107 patients (37.4%) in the safety evaluable population and 25 patients (38.5%) in the chemotherapy-naïve FAS had received prior radiotherapy.

A majority of patients (74 patients [69.2%]) in the safety evaluable population had a prior surgery/procedure for MCC. Forty-seven patients (72.3%) in the chemotherapy-naïve FAS had a prior surgery/procedure for MCC.

Subsequent anti-cancer therapy

Thirty-seven of the 107 patients (34.6%) in the safety evaluable population received anticancer therapy subsequent to retifanlimab, including 17 patients (15.9%) who received a PD-(L)1 inhibitor. Responses to poststudy therapy (as assessed by the investigator) were seen in 13 patients. There is no information available on durability of these responses.

Numbers analysed

A total of 107 patients were enrolled (completed screening) in the study.

All 107 enrolled patients received at least 1 dose of study drug as of 10 Mar 2023 and were included in the safety evaluable population. Of the 107 patients, 101 patients were chemotherapy-naïve and 6 patients were chemotherapy refractory (Table 36). Sixty-five chemotherapy-naïve patients were enrolled in the study prior to 15 Oct 2020, received at least 1 dose of retifanlimab. The first 65 chemotherapy-naïve patients based on enrolment date were included in the full analysis set (FAS), which was used for the primary analysis of efficacy. An additional 6 patients with chemotherapy-refractory disease were also enrolled prior to this date.

Sixty patients from the chemotherapy-naïve FAS had a centrally confirmed diagnosis of MCC and measurable disease at baseline according to RECIST v1.1 and were included in the efficacy evaluable population.

Table 36: Analysis Populations (Screened Patients)

Variable, n (%)	Chemotherapy-Naïve Advanced (N = 10)	Chemotherapy-Naïve Metastatic (N = 91)	Chemotherapy-Naïve Total (N = 101)	Chemotherapy-Refractory (N = 6)	Total (N = 140)
Participants screened	—	—	—	—	140 (100.0)
Screen failures	—	—	—	—	33 (23.6)
Enrolled participants	10 (100.0)	91 (100.0)	101 (100.0)	6 (100.0)	107 (76.4)
Safety evaluable population	10 (100.0)	91 (100.0)	101 (100.0)	6 (100.0)	107 (76.4)
Full analysis set	8 (80.0)	57 (62.6)	65 (64.4)	6 (100.0)	71 (50.7)
Efficacy evaluable	7 (70.0)	53 (58.2)	60 (59.4)	6 (100.0)	66 (47.1)

Source: Table 1.1.1.

Outcomes and estimation

The protocol-specified primary analysis of efficacy was performed with a 15 Oct 2020 enrolment cut-off date to allow for at least 60 chemotherapy-naïve patients to be followed for at least 6 months after confirmed response. Results of the analysis had a data cut-off date of 21 Jan 2022.

Following the initial data cut-off, additional chemotherapy-naïve patients were enrolled in order to increase robustness of the study results. Updated results of the subsequent analysis were based on a clinical data cut-off date of 10 Mar 2023 for all 101 chemotherapy-naïve patients.

For the primary endpoint, results from both the primary and subsequent analysis are included in the report. For the secondary endpoints, only updated results are shown.

Primary and Secondary endpoints

Objective Response Rate Based on ICR According to RECIST v1.1 – primary analysis (data cut-off date 21 Jan 2022)

The ORR was 52.3% (95% CI: 39.5, 64.9) based on confirmed tumour responses (Table 37). Best overall response was CR in 12 patients (18.5%) and PR in 22 patients (33.8%).

Table 37: Summary of Best Overall Response Based on ICR According to RECIST v1.1 (Full Analysis Set)

Variable	Chemotherapy-Naïve Advanced (N = 8)	Chemotherapy-Naïve Metastatic (N = 57)	Chemotherapy-Naïve Total (N = 65)
BOR[a], n (%)			
CR	3 (37.5)	9 (15.8)	12 (18.5)
PR	2 (25.0)	20 (35.1)	22 (33.8)
SD	3 (37.5)	10 (17.5)	13 (20.0)
PD	0 (0.0)	12 (21.1)	12 (18.5)
Not evaluable	0 (0.0)	6 (10.5)	6 (9.2)
Objective Response[b], n (%)	5 (62.5)	29 (50.9)	34 (52.3)
95% CI[c] for ORR	24.5, 91.5	37.3, 64.4	39.5, 64.9
DCR[d], n (%)	7 (87.5)	33 (57.9)	40 (61.5)
95% CI[c] for DCR	47.3, 99.7	44.1, 70.9	48.6, 73.3

[a] The BOR was defined as the best confirmed response in the order of CR > PR > SD (≥ 7 weeks after start of treatment and non-CR/non-PD) > PD > not evaluable recorded until the first PD or start of new anticancer therapy.
[b] A participant was considered as an objective responder if the participant had a confirmed overall response of CR or PR at any postbaseline visit until the first PD or start of new anticancer therapy.
[c] Confidence intervals were calculated based on the exact method for binomial distributions.
[d] Disease control rate 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.

Objective Response Rate Based on ICR According to RECIST v1.1 – updated analysis (data cut-off date: 10 Mar 2023)

The ORR was 53.5% (95% CI: 43.3, 63.5) based on confirmed tumour responses (Table 38). Best overall response was CR in 17 patients (16.8%) and PR in 37 patients (36.6%).

Table 38: Summary of Best Overall Response Based on ICR According to RECIST v1.1 (Chemotherapy-Naïve, Safety Evaluable Population)

Variable	Chemotherapy-Naïve Advanced (N = 10)	Chemotherapy-Naïve Metastatic (N = 91)	Chemotherapy-Naïve Total (N = 101)
BOR[a], n (%)			
CR	3 (30.0)	14 (15.4)	17 (16.8)
PR	3 (30.0)	34 (37.4)	37 (36.6)
SD	3 (30.0)	13 (14.3)	16 (15.8)
PD	1 (10.0)	20 (22.0)	21 (20.8)
Missing	0 (0.0)	10 (11.0)	10 (9.9)
Objective Response[b], n (%)	6 (60.0)	48 (52.7)	54 (53.5)
95% CI[c] for ORR	26.2, 87.8	42.0, 63.3	43.3, 63.5
DCR[d], n (%)	8 (80.0)	52 (57.1)	60 (59.4)
95% CI[c] for DCR	44.4, 97.5	46.3, 67.5	49.2, 69.1

[a] The BOR was defined as the best confirmed response in the order of CR > PR > SD (≥ 7 weeks after start of treatment and non-CR/non-PD) > PD > not evaluable recorded until the first PD or start of new anticancer therapy.
[b] A participant was considered as an objective responder if the participant had a confirmed overall response of CR or PR at any postbaseline visit until the first PD or start of new anticancer therapy.
[c] Confidence intervals were calculated based on the exact method for binomial distributions.
[d] Disease control rate 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.
Source: Tables 2.1.1 and 2.2.2.

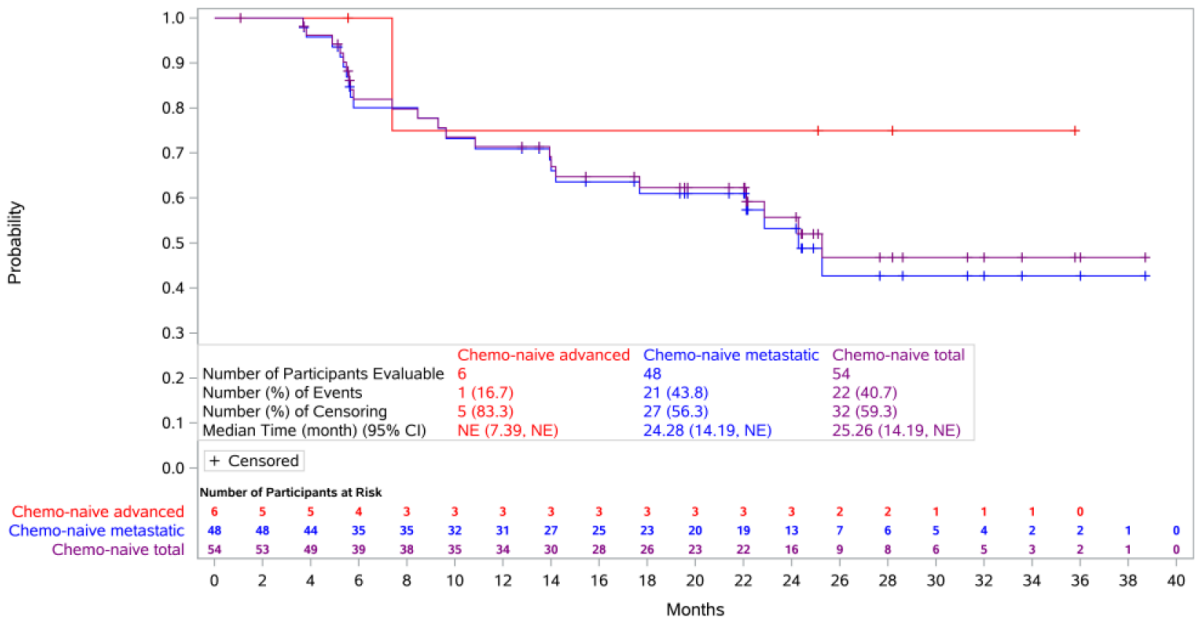
Duration of Response Based on ICR According to RECIST v1.1 – updated analysis (data cut-off date: 10 Mar 2023)

Median DOR based on Kaplan-Meier analysis was 25.26 months (95% CI: 14.19, NE), with a median follow-up time of 17.6 months (range: 1.1-38.7 months). The duration of observed responses ranged from 1.1 to 38.7+ months (see Table 39 and Figure 39). Based on landmark analysis, 39 of 54 responses (72.2%) were ⩾ 6 months and 34 (63.0%) were ⩾ 12 months (see Table 39).

Table 39: Summary of Duration of Response Based on ICR According to RECIST v1.1 (Chemotherapy-Naïve, Safety Evaluable Population)

Variable	Chemotherapy-Naïve Advanced (N = 10)	Chemotherapy-Naïve Metastatic (N = 91)	Chemotherapy-Naïve Total (N = 101)
Number (%) of participants who had response[a]	6 (60.0)	48 (52.7)	54 (53.5)
Number (%) of participants with events[b]	1 (16.7)	21 (43.8)	22 (40.7)
Disease progression	1 (16.7)	19 (39.6)	20 (37.0)
Death	0 (0.0)	2 (4.2)	2 (3.7)
Number (%) of participants censored	5 (83.3)	27 (56.3)	32 (59.3)
DOR (months) (95% CI)[c]			
25th	NR (7.39, NE)	9.63 (5.49, 17.68)	9.63 (5.59, 17.68)
50th	NR (7.39, NE)	24.28 (14.19, NE)	25.26 (14.19, NE)
75th	NR (7.39, NE)	NR (25.26, NE)	NR (NE, NE)
Event-free probability estimates (95% CI)[d]			
Month 6	1.00 (1.00, 1.00)	0.80 (0.65, 0.89)	0.82 (0.68, 0.90)
Month 12	0.75 (0.13, 0.96)	0.71 (0.55, 0.82)	0.71 (0.57, 0.82)
Month 18	0.75 (0.13, 0.96)	0.61 (0.45,0.74)	0.62 (0.47,0.74)
Month 24	0.75 (0.13, 0.96)	0.53 (0.36,0.68)	0.56 (0.39,0.69)
Month 36	NR (NE, NE)	0.43 (0.24, 0.60)	0.47 (0.29, 0.63)
Median follow-up time (months)	16.2	17.6	17.6
Minimum, maximum	1.1, 35.8	3.7, 38.7	1.1, 38.7
Duration of response range (months)	1.1, 35.8+	3.7, 38.7+	1.1, 38.7+
DRR, % (95% CI)[e]	60.0 (29.6, 90.4)	42.2 (32.0, 52.5)	43.8 (34.0, 53.6)
Participants with DOR ≥ 6 months, n (%)[f]	4 (66.7)	35 (72.9)	39 (72.2)
Participants with DOR ≥ 12 months, n (%)[f]	3 (50.0)	31 (64.6)	34 (63.0)
Participants with DOR ≥ 18 months, n (%)[f]	3 (50.0)	23 (47.9)	26 (48.1)
Participants with DOR ≥ 24 months, n (%)[f]	3 (50.0)	13 (27.1)	16 (29.6)

NE = not estimable; NR = not reached.
Note: + indicates ongoing response.
Note: The number of months was calculated as the number of days divided by 30.4375.
[a] Participants who had confirmed CR or PR prior to PD or start of new anticancer therapy.
[b] Denominator is total number of responders.
[c] The 95% CI was calculated using the Brookmeyer and Crowley's method (1982) and Klein and Moeschberger's method (1997) with log-log transformation.
[d] The 95% CI was calculated using Greenwood's formula to estimate the standard error.
[e] The 6-month DRR was estimated as the product of the ORR and the Kaplan-Meier estimate of 6-month DOR. An asymptotic 95% CI for the DRR was obtained by applying the standard formula for the variance of a product of independent random variables.
[f] Landmark analysis.
Source: Table 2.2.1 and Listing 2.6.4.



Note: Number of participants evaluable represents confirmed responders per RECIST v1.1.
Source: Figure 4.1.1.

Figure 39: Kaplan-Meier Estimates of Duration of Response Based on ICR According to RECIST v1.1 (Chemotherapy-Naïve, Safety Evaluable Population)

At the time of the data cut-off (10 Mar 2023), 32 of 54 (59.3%) responders from the chemotherapy-naive patients in the safety evaluable population (N = 101) in INCMGA 0012-201 were censored. Among those censored, reasons for censoring were ongoing (24 patients, 44.4%), start of new anticancer treatment (6 patients, 11.1%), and study completion or discontinuation (2 patients, 3.7%).

Only 3 patients had ongoing assessments after the start of new anticancer therapy.

If considering new anticancer medicine to be an event, the median DOR based on Kaplan-Meier analysis was 22.87 months (95% CI: 14.00, NE), with a median follow-up time of 17.6 months (range: 2.9-38.7 months).

If both investigator- and ICR-based progressions are considered to be events, the median DOR based on Kaplan-Meier analysis was 22.11 months (95% CI: 10.84, NE), with a median follow-up time of 14.8 months (range: 1 day to 38.7 months).

Disease Control Rate Based on ICR – updated analysis (data cut-off date: 10 Mar 2023)

The DCR, defined as the proportion of patients with either an objective response or SD lasting at least 6 months, was 59.4% (95% CI: 49.2, 69.1) based on ICR.

Progression-Free Survival Based on ICR According to RECIST v1.1– updated analysis (data cut-off date: 10 Mar 2023)

Median PFS was 12.65 months (95% CI: 7.33, 24.87; see Table 40 and Figure 40), with a median follow-up time of 9.0 months. The PFS rates at Months 6 and 12 were 0.64 (95% CI: 0.54, 0.73) and 0.51 (95% CI: 0.40, 0.60), respectively.

Of the 101 patients, 57 patients (56.4%) had events and 44 (43.6%) were censored. Among those with events, 48 patients had disease progression and 9 patients died. Among those censored, reasons for censor

were ongoing in the study (27 patients), start of new anticancer treatment (7 patients), death or progression after ≥ 2 missed assessments (5 patients), study completion or discontinuation (3 patients), and no valid postbaseline response assessments (2 patients).

Table 40: Summary of Progression-Free Survival Based on ICR According to RECIST v1.1 (Chemotherapy-Naïve, Safety Evaluable Population)

Variable	Chemotherapy-Naïve Advanced (N = 10)	Chemotherapy-Naïve Metastatic (N = 91)	Chemotherapy-Naïve Total (N = 101)
Number (%) of participants with events	2 (20.0)	55 (60.4)	57 (56.4)
Disease progression	2 (20.0)	46 (50.5)	48 (47.5)
Death	0 (0.0)	9 (9.9)	9 (8.9)
Number (%) of participants censored	8 (80.0)	36 (39.6)	44 (43.6)
Median PFS (months) (95% CI)[a]	NR (1.84, NE)	11.17 (6.57, 23.95)	12.65 (7.33, 24.87)
Month 3 PFS rate (95% CI)	0.90 (0.47, 0.99)	0.71 (0.60, 0.79)	0.73 (0.63, 0.81)
Month 6 PFS rate (95% CI)	0.90 (0.47, 0.99)	0.62 (0.50, 0.71)	0.64 (0.54, 0.73)
Month 9 PFS rate (95% CI)	0.90 (0.47, 0.99)	0.54 (0.43, 0.64)	0.58 (0.47, 0.67)
Month 12 PFS rate (95% CI)	0.77 (0.34, 0.94)	0.48 (0.37, 0.58)	0.51 (0.40, 0.60)
Follow-up time (months)			
Median	19.4	7.4	9.0
Minimum, maximum	1.8, 37.6	0.0, 40.5	0.0, 40.5

NE = not estimable; NR = not reached.
Note: According to RECIST v1.1, PFS was defined as the length of time from initial infusion of study drug until the earliest date of disease progression, determined by ICR, or death due to any cause, if occurring sooner than progression.
Note: The number of months was calculated as the number of days divided by 30.4375.
[a] Median PFS time was estimated using the Kaplan-Meier method. The CI for median PFS time was calculated using the method of Brookmeyer and Crowley (1982).
Source: Table 2.2.3.

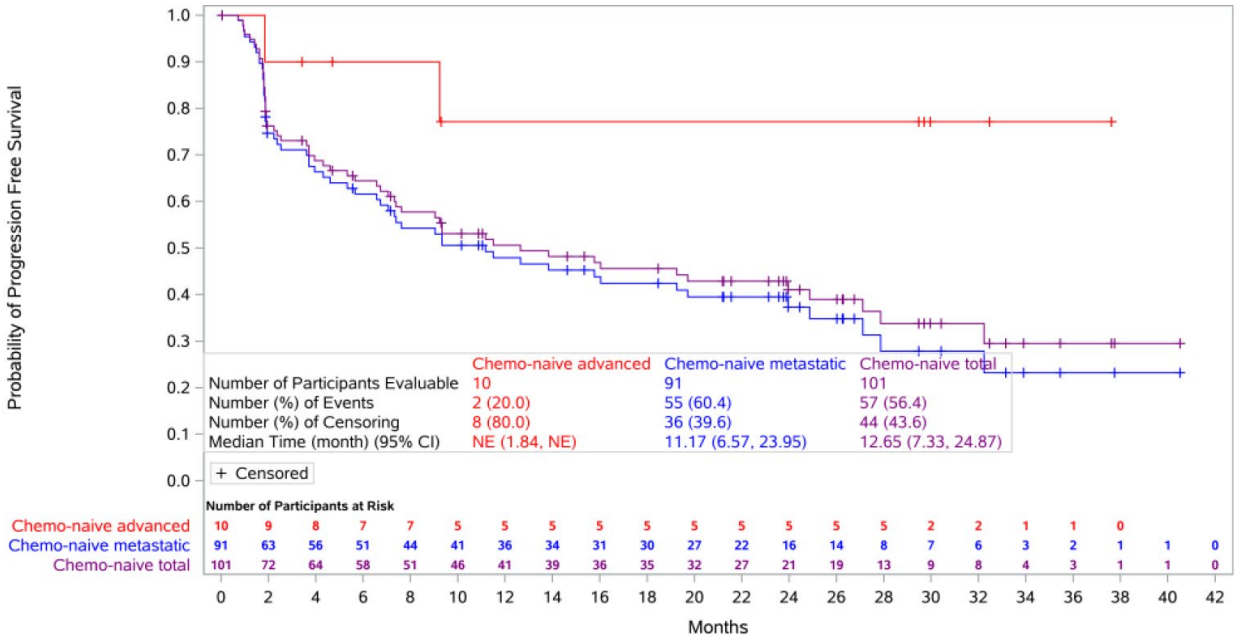


Figure 40: Kaplan-Meier Estimates of Progression-Free Survival Based on ICR According to RECIST v1.1 (Chemotherapy-Naïve, Safety Evaluable Population)

Overall Survival - updated analysis (data cut-off date: 10 Mar 2023)

As of the data cut-off, 33 patients (32.7%) had died and 68 patients (67.3%) were alive and censored for OS at the last date known alive. Median OS had not been reached based on Kaplan-Meier analysis (see **Table 41** and Figure 41), with a median follow-up of 24.0 months (range: 0.7-48.1 months). The OS rates at Months 6, 12, 24, 36, and 48 were 0.88 (95% CI: 0.80, 0.93), 0.79 (95% CI: 0.69, 0.86), 0.68 (95% CI: 0.58, 0.76), 0.65 (95% CI: 0.54, 0.74), and 0.65 (95% CI: 0.54, 0.74), respectively, based on Kaplan-Meier analysis.

An apparent plateau in survival is observed beginning after approximately 2 years of observation (Figure 41).

Table 41: Summary of Overall Survival (Chemotherapy-Naïve, Safety Evaluable Population)

Variable	Chemotherapy-Naïve Advanced (N = 10)	Chemotherapy-Naïve Metastatic (N = 91)	Chemotherapy-Naïve Total (N = 101)
Number (%) of participants with:			
Death	1 (10.0)	32 (35.2)	33 (32.7)
Censoring	9 (90.0)	59 (64.8)	68 (67.3)
Median OS (months) (95% CI)[a]	NR (17.08, NE)	NR (NE, NE)	NR (NE, NE)
Month 6 OS rate (95% CI)	1.00 (1.00, 1.00)	0.87 (0.78, 0.92)	0.88 (0.80, 0.93)
Month 12 OS rate (95% CI)	1.00 (1.00, 1.00)	0.76 (0.66, 0.84)	0.79 (0.69, 0.86)
Month 18 OS rate (95% CI)	0.89 (0.43, 0.98)	0.73 (0.63, 0.81)	0.75 (0.65, 0.82)
Month 24 OS rate (95% CI)	0.89 (0.43, 0.98)	0.66 (0.55, 0.75)	0.68 (0.58, 0.76)
Month 36 OS rate (95% CI)	0.89 (0.43, 0.98)	0.62 (0.51,0.72)	0.65 (0.54,0.74)
Month 48 OS rate (95% CI)	NR (NE, NE)	0.62 (0.51,0.72)	0.65 (0.54,0.74)
Follow-up time (months)			
Median	29.6	22.8	24.0
Minimum, maximum	3.4, 37.6	0.7, 48.1	0.7, 48.1

NE = not estimable; NR = not reached.
Note: Months were calculated as the number of days divided by 30.4375.
Note: Overall survival was defined as the time in months between the first dose date (Day 1) and the date of death due to any cause.
[a] Median OS time was estimated using the Kaplan-Meier method. The CI for median OS time was calculated using the method of Brookmeyer and Crowley (1982).
Source: Table 2.2.4.

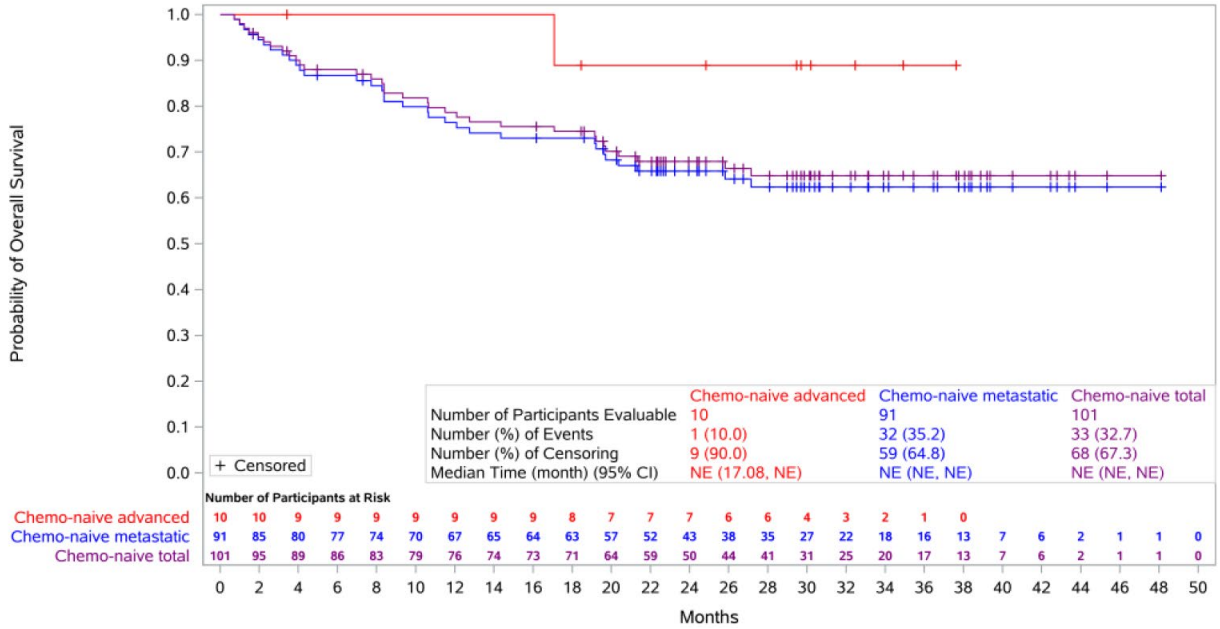
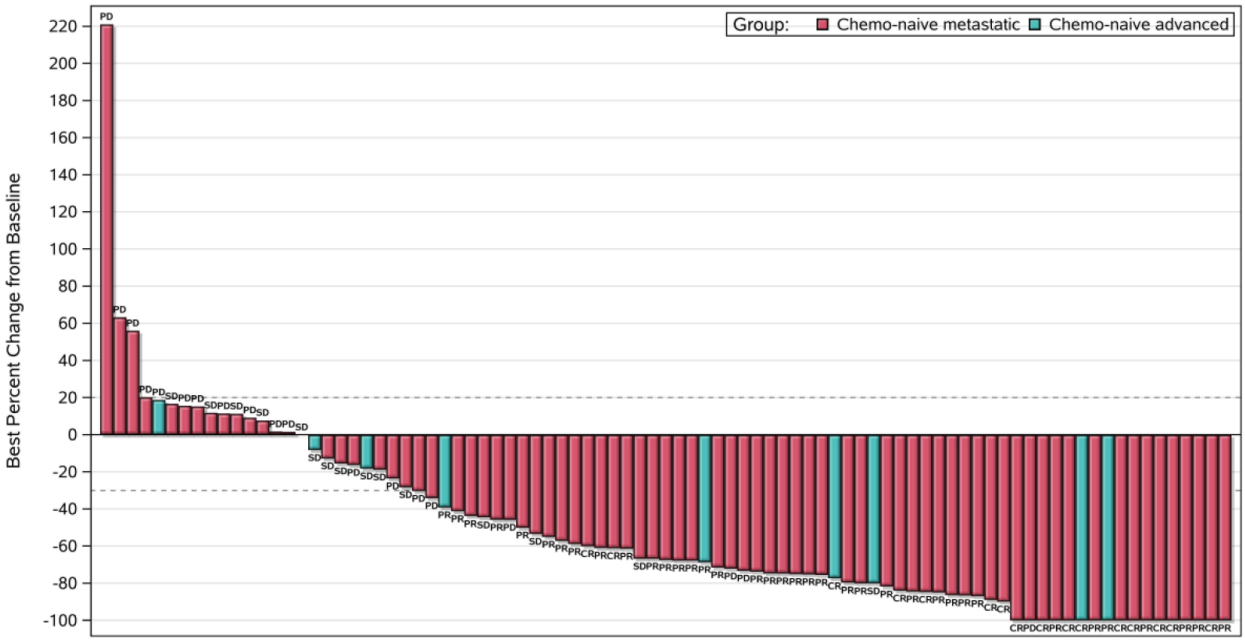


Figure 41: Kaplan-Meier Estimates of Overall Survival (Chemotherapy-Naïve, Safety Evaluable Population)

Exploratory endpoints

Reduction in Tumour Size Based on ICR - updated analysis (data cut-off date: 10 Mar 2023)

Nearly all patients had some reduction in tumour burden (**Figure 42**).

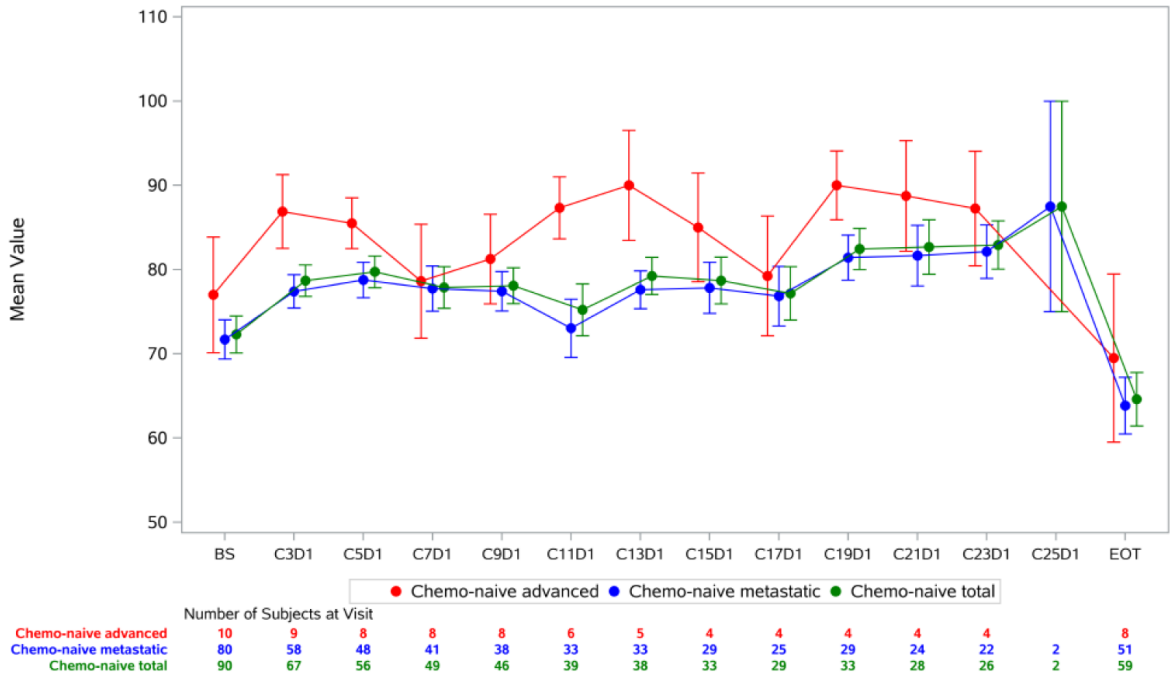


Note: Upper limit of dotted line indicates a criterion for PD (≥ 20% increase in sum of target lesion diameters) and lower limit indicates a criterion for PR (≥ 30% decrease in sum of target lesion diameters). Complete response without a 100% decrease in sum of target lesions was due to lymph nodes involved. Confirmed BOR is provided for each participant in the figure. The best percentage change in sum of target lesions was prior to new anticancer therapy. A total of 101 chemotherapy-naïve participants were enrolled in the study, but 14 participants had missing baseline or postbaseline target lesion assessments.
Source: Figure 4.3.2.1.

Figure 42: Waterfall Plot of Best Percentage Change in Sum of Target Lesion Diameters From Baseline Based on ICR (Chemotherapy-Naïve, Safety Evaluable Population)

Patient-Reported Outcomes - updated analysis (data cut-off date: 10 Mar 2023)

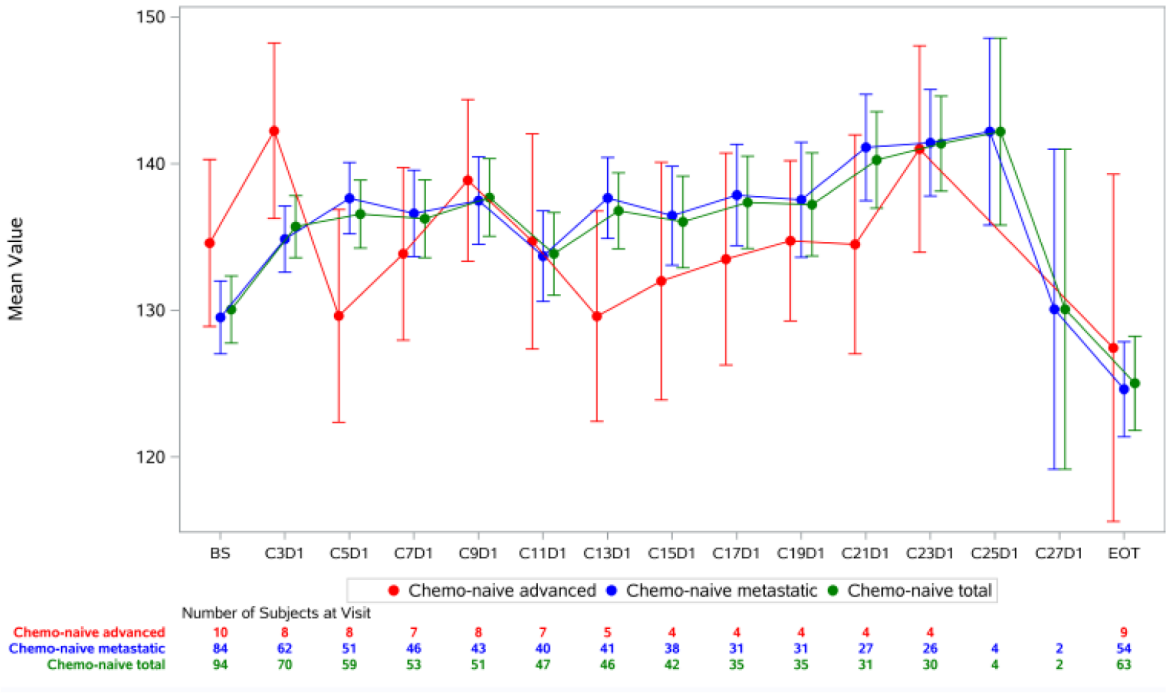
Mean and median EQ-5D-5L scores were relatively stable during the treatment period (Figure 43).



Note: Higher scores indicate self-rated better health state.
Note: EOT may occur any time on study.
Source: Figure 4.7.1.

Figure 43: Mean and Standard Error of EQ-5D-5L Score (Chemotherapy-Naïve, Safety Evaluable Population)

Mean and median FACT-M total score were relatively stable over time (Figure 44).



Note: Score range: 0-172.
Note: Higher scores indicate better health-related quality of life.
Note: EOT may occur any time on study.
Source: Figure 4.7.2.

Figure 44: Mean and Standard Error of FACT-M Total Score (Chemotherapy-Naïve, Safety Evaluable Population)

Ancillary analyses

Objective Response Rate in Subgroups - updated analysis (data cut-off date: 10 Mar 2023)

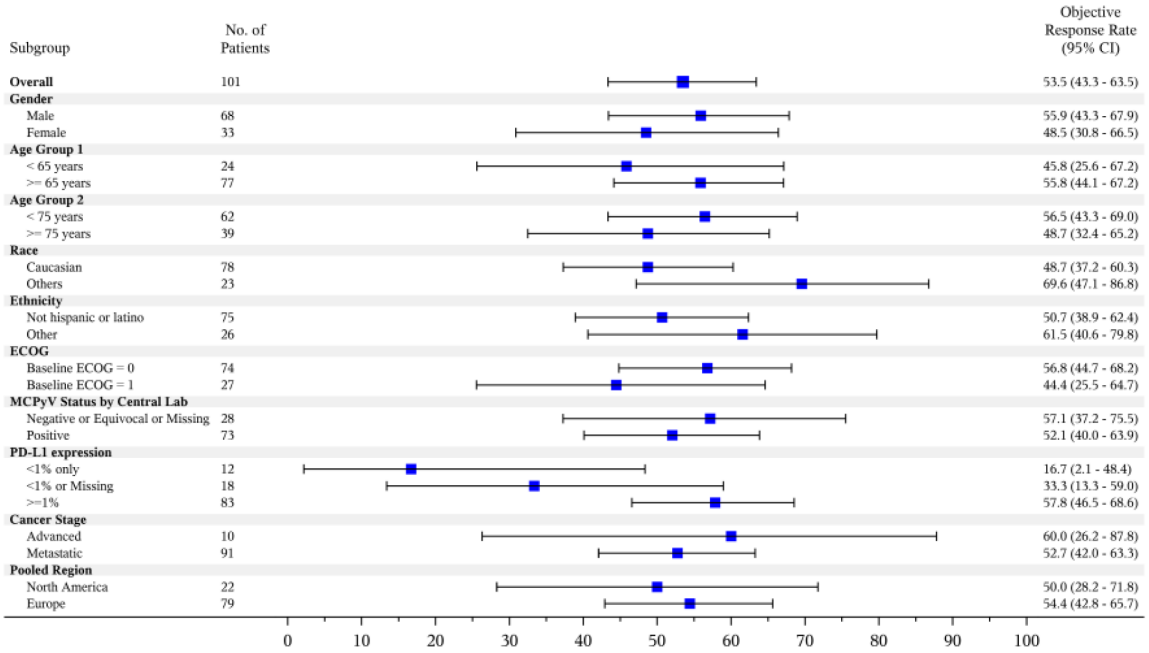
Pre-planned exploratory subgroup analyses of ORR were performed on sex, age, race, ethnicity, ECOG performance status, PD-L1 status, MCPyV status, geographic region, and cancer stage. Clinical activity was observed regardless of PD-L1 or MCPyV status. Table below summarises the objective response rates by tumour PD-L1 expression and MCPyV status of chemotherapy-naïve MCC patients with central biomarker results in the POD1UM-201 study.

Table 42: Objective response rates by tumour PD-L1 expression and MCPyV status

	Zynyz **Objective response rates (95% CI)** **N = 101**
PD-L1 expression[a] at cut-off of ⩾ 1%	
Positive (n=83)	57.8% (46.5, 68.6)
Negative or missing (n=18)	33.3% (13.3, 59.0)
MCPyV status	
Positive (n=73)	52.1% (40, 63.9)
Negative, equivocal, or missing (n=28)	57.1% (37.2, 75.5)

MCPyV = Merkel cell polyomavirus.
[a] PD-L1 expression was determined by IHC using Combined Positive Score (CPS) interpretation.

Responses were seen in all subgroups of interest, including the elderly, who are most at risk for MCC (Figure 45).



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

Figure 45: Objective Response Rates Based on ICR According to RECIST v1.1 by Subgroup (Chemotherapy-Naïve, Safety Evaluable Population)

Efficacy Results Based on Investigator Assessment - updated analysis (data cut-off date: 10 Mar 2023)

The ORR based on investigator assessment according to RECIST v1.1 was 59.4% (95% CI: 49.2, 69.1) and by iRECIST, 61.4% (95% CI: 51.2, 70.9). Best overall responses were CR and PR in 21 patients (20.8%) and 39 patients (38.6%), respectively, and iCR and iPR in 22 patients (21.8%) and 40 participants (39.6%), respectively.

Investigator-assessed median DOR according to RECIST v1.1 was 34.86 months (range:

25.30 months, NE).

Investigator-assessed median PFS according to RECIST v1.1 was 14.36 months (95% CI: 7.39, 31.18).

2.6.5.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 43: Summary of efficacy for trial INCMGA00012

Title: A Phase 2 Study of INCMGA00012 in Patients With Metastatic Merkel Cell Carcinoma (POD1UM-201)			
Study identifier	EudraCT 2018-001627-39; NCT03599713		
Design	Open-label, single-arm, multiregional, Phase 2 study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Up to 2 years of treatment not applicable not applicable
Hypothesis	Exploratory: There is no formal hypothesis testing in this study. The study was designed to exclude an ORR of 30% or lower, based on the lower limited of the estimated 95% CI.		
Treatments group	retifanlimab arm		Retifanlimab 500 mg Q4W intravenously over 60 minutes. Participation for an individual patient includes 28 days for screening, up to 2 years of treatment, and survival follow-up., 107 patients were enrolled (safety population).
Endpoints and definitions	Primary endpoint	ORR, determined by independent central radiographic review	The percentage of patients having an objective response (complete response [CR] or partial response [PR]), according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
	Secondary	DOR, determined by independent central radiographic review	The time from an initial objective response (CR or PR) according to RECIST v1.1 until disease progression, or death due to any cause
	Secondary	PFS	The time from the start of therapy until disease progression, or death due to any cause
	Secondary	OS	The time from the start of therapy until death due to any cause
Database lock	21 Jan 2022; 10 Mar 2023 (updated results)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	other: full analysis set (all patients enrolled in the study who received at least 1 dose of study drug and includes the first 60 chemotherapy-I patients)		
Descriptive statistics and estimate variability	Treatment group	Retifanlimab	
	Number of subjects	n=65	
	Objective Response (CR+PR), percentage	52.3% (95% CI: 39.5, 64.9) • CR=18.5% • PR=33.8%	
Effect estimate per comparison	Not applicable		
Analysis description	**Secondary analysis**		

Descriptive statistics and estimate variability	Treatment group	Retifanlimab
	Median DOR, months	Not reached (95% CI: 14.00, NE)
	Median PFS, months	16.0 months (95% CI: 9.33, NE)
	Median OS, (months)	Not reached (95% CI: NE, NE)
Updated Results and Analysis		
Analysis description	**Updated analysis**	
Descriptive statistics and estimate variability	Treatment group	Retifanlimab
	Number of subjects	n=101
	ORR (CR+PR), percentage	53.5% (95% CI: 43.3, 63.5)
	Median DOR, months	25.26 months (95% CI: 14.19, NE)
	Median PFS, months	12.65 months (95% CI: 7.33, 24.87)
	Median OS, months	Not reached (95% CI: NE, NE)

2.6.5.4. Clinical studies in special populations

Table 44: The number of older participants (chemotherapy-naïve) in Study INCMGA 0012-201

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Non-Controlled trials	38/101	30/101	9/101

2.6.5.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.7. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

The **dose escalation** study (INCMGA 0012-101) was conducted in patients with relapsed/refractory, unresectable locally advanced or metastatic solid tumours not including MCC. It consisted of the Dose Escalation Phase (which has been completed and included starting dose of 1 mg/kg, 3 mg/kg, and 10 mg/kg) followed by a Cohort Expansion Phase (500 mg Q4W, 750 mg Q4W and 375 mg Q3W).

Recent studies recommend the use of flat dosing over body size–based dosing in clinical trials, as both approaches performed similarly in reducing variability in drug exposure, with flat dosing being superior for some mAbs (Bai et al. Clin Pharmacokinet. 2012; Wang et al. Clin Pharmacol. 2009). Furthermore, flat dosing offers the advantages of convenience, compliance, cost effectiveness, and safety due to less risk of dosing errors (Bai et al. Clin Pharmacokinet. 2012). Since the degree of the impact of body weight (BW) on the PK of retifanlimab in humans has not been delineated and since it is unknown whether body size-based dosing would influence inter-subject variability in drug exposure, the study design additionally explored a flat dosing scheme. This approach allowed for the evaluation of the PK/PD parameters corresponding to patients treated at flat doses.

The rationale behind the choice of 500 mg and 750 mg flat dose is understood and supported. The proposed flat dose regimen of 500 mg Q4W was based on modelling of clinical PK data from the dose-escalation part of study INCMGA 0012-101 and benchmarking to pembrolizumab. The 500 mg Q4W dose had similar PK properties to 3 mg/kg dosing, and had ~77% probability for steady state trough plasma concentration $\geqslant$ 10 mg/L. Based on these observations, 500 mg Q4W was chosen as the dosing regimen for further development in the MCC indication. The selection of the weight based dose of 3 mg/kg from the dose escalation is supported due to the small number of patients (n=3) in the lowest investigated dose of 1 mg/kg and slightly better safety profile for the 3 mg/kg dose compared to 10 mg/kg.

At this moment, there is one medical product authorised for the treatment of MCC; Bavencio (avelumab). Anti-PD-(L)1 therapies are the recommended first-line therapy for locally advanced or metastatic MCC (Gauci et al. European Journal of Cancer. 2022). Before the authorisation of Bavencio, chemotherapy (e.g., chemotherapy with a platinum component in combination with etoposide) was recommended as first-line therapy (Chan et al. Journal for ImmunoTherapy of Cancer. 2018). MCC is chemosensitive – "tumour regressions in ~60% of cases", but responses are generally of short duration (Iyer et al. Cancer Med. 2016; Nghiem et al. J Immunother Cancer. 2021).

A methodology of engaging with patient organisations at the start of evaluation of new MAAs has been agreed by CHMP (for more details see the dedidcated process and FAQs document). In this context feedback from patient organisation regarding Zynyz (retifanlimab) provided some information on aspects that are of particular importance to patients/carers. Efficiency of treatment to cure them and acceptable quality of life during and after treatment as top priorities for patients when discussing treatment options. For patients still working or with family obligations, of equal importance is that the treatment does not impact their physical, mental and psychological functions, which includes also side effects that make them uncomfortable in social gatherings, whereas elder patients tend to accept more stoically treatment side effects.

Design and conduct of clinical studies

The **pivotal study** supporting this marketing authorisation application (MAA) is INCMGA 0012-201 (POD1UM-201), an ongoing, open-label, single-arm, multiregional, Phase 2 study in chemotherapy-naïve patients with advanced Merkel cell carcinoma (MCC). The data cut-off for the primary efficacy analysis was 21 Jan 2022. Following the initial data cut-off, additional chemotherapy-naïve patients were enrolled in order to increase robustness of the study results (data cut-off date of 10 Mar 2023).

There are situations where a single-arm design is justifiable (e.g., RCTs not feasible, predictable course of the disease, large treatment effects; EMA/CHMP/205/95 Rev.6). Considering the rarity of the disease (Harms et al. Nature Reviews Clinical Oncology. 2018; Stockfleth. Cancers. 2023; Becker et al. Nat Rev Dis Primer.

2017) and the regulatory precedent (EMEA/H/C/004338/0000; EMEA/H/C/004338/II/0013), a pivotal study with a single arm design is acceptable. The challenges associated with conducting a RCT in MCC have already been acknowledged by the CHMP during another procedure (EMEA/H/C/004338/0000). Furthermore, it is described in the European consensus-based guideline that the rarity of the disease precludes robust clinical trials (Gauci et al. European Journal of Cancer. 2022).

The **inclusion and exclusion criteria** of the study are acceptable/appropriate considering the experimental setting, the target population, and the potential risks. At large, eligibility criteria were comparable to those used in study EMR100070-00; the clinical trial investigating avelumab in Merkel cell carcinoma (EMEA/H/C/004338/0000).

Immunosuppressed patients have a higher risk of developing MCC (Coggshall et al. J Am Acad Dermatol. 2018); thus are an important – albeit relatively small – subgroup. Yet, these patients were generally excluded from participation, with the exception of patients with controlled HIV infections. The effort of the Applicant to include HIV-positive patients is acknowledged, but only one HIV-positive patient was enrolled in the study. Even though immunosuppressed patients are more often excluded from clinical trials investigating immunotherapy (Tapia Rico G, et al. Cancer Treat Rev. 2020), the benefit-risk balance in this subgroup remains to an extent uncertain. A subsection on "Patients excluded from the clinical programme" is included in section 4.4 of the SmPC. In these patients excluded from the clinical trials the benefit-risk should be assessed at the individual level.

The **dosage** of retifanlimab in the pivotal study was 500 mg every four weeks. Justification was provided by the Applicant, although it should be noted that the approach for dose finding – i.e., determining an MTD – may not have been optimal for this type of therapy. Pharmacodynamic results, however, show near-complete receptor occupancy across investigated doses. Importantly, retifanlimab showed compelling anti-tumour activity in the main study; thus, in retrospect, the dose is active in the target population.

Treatment duration was up to 2 years. This is acknowledged, although, based on the available data, it cannot be determined whether this is also the optimal treatment duration.

Objective response rate as **primary endpoint** is appropriate for single-arm trials. Anti-tumour activity observed in the trial can directly be linked to the activity of the study drug and, thereby, interpretable without a control arm. It should, however, be noted that (complete) spontaneous regression has been reported, occasionally (Gauci et al. European Journal of Cancer. 2022

Objective assessment of disease status was evaluated according to RECIST v1.1 by an independent central review committee (ICR). This is supported, since INCMGA 0012-201 is open-label study and independent central review limits assessment bias.

Secondary endpoints are acceptable. For single-arm trials, duration of response (DoR) as secondary endpoint is of particular interest, as it adds to the relevance of the primary endpoint (i.e., to determine whether the responses evoked by retifanlimab are durable). However, it should be noted that time-to-event endpoints are difficult to interpret without a control arm.

Immunogenicity and biomarkers related endpoints are exploratory. Employment of iRECIST criteria is endorsed because of specificities of immunotherapeutics.

Sample size of approximately 60 patients gives a 80% power to exclude the lower 95% CI of 30% was made based on the avelumab approved in MCC, which showed a confirmed ORR of 39.7% with lower 95% CI

of 30.7% in chemotherapy-naïve patients. The estimated value for the target ORR was based on prior findings with other anti-PD-1/PD-L1 therapies, which is a reasonable approach.

Statistical methods, described in the SAP state that "Protocol-specified analysis was performed with a 15 OCT 2020 enrolment cut-off date to allow for at least 60 chemotherapy-naïve participants to be followed for at least 6 months after the first response assessment". The timing of the primary analysis appears ambiguous, but the protocol was followed.

Subgroup analyses were based on patient's baseline status and groups were pre-specified. The analyses were, however, exploratory.

The censoring rules for DOR and PFS may result in informative censoring. Additional analyses were provided for which 'starting a new anti-cancer therapy' was considered an event, and investigator and independent assessments were combined, both representing composite estimand strategies, and while more conservative, are likely to present a more realistic estimate of the treatment effect. For both of these, the estimated median DOR is of around 22 months, which is still considered to be a clinically meaningful DOR for the patients who had a BOR of CR or PR in this population.

The overall incidence of protocol deviations was high (98.5% in chemotherapy-naïve FAS; 93.5% in total population), mostly driven by missed or out of window assessments. There were six patients identified by the Applicant that had a clinically important protocol deviation. These deviations are not expected to have a major impact on the study results or the interpretation thereof.

In general, the **protocol amendments** are acceptable, but some need to be highlighted. Amendment 5 was implemented to exclude patients who had received prior systemic therapy for treatment of MCC; thereby restricting the study population to chemotherapy-naïve subset patients. The reason for this amendment, i.e., the changing landscape and slow enrolment, is understood. Amendment 6 was implemented so that additional patients were enrolled for more robust characterization of durability of response and OS.Sample size determination for the primary analysis, the retifanlimab target ORR and the to be excluded lower bound of the 95% CI were updated. This was based on external data (i.e., updated avelumab data and pembrolizumab data), and therefore acceptable.

Efficacy data and additional analyses

Patients were predominantly enrolled from sites within the European Union. Thus, the European population is adequately represented in the pivotal trial.

A total of 33 patients were not enrolled as a result of screen failures. The majority of screen failures was due to poor performance status or unmeasurable disease (i.e., inclusion criterion 4 and 5, respectively). Few were due to patients having previously-untreated locally advanced disease; thereby, not meeting inclusion criterion 3. Five patients were excluded from the efficacy evaluable population, as MCC could not be centrally confirmed in these patients.

The **demographic characteristics** generally reflect the target population. The majority of patients enrolled in the trial were male, white, and not Hispanic or Latino, which is consistent with real-world evidence (Levy et al. J Immunother Cancer. 2020; Bhatia et al. J Immunother Cancer. 2022;Averbuch et al. Cancer Medicine. 2023). The median age of the study population is numerically lower than described in literature (Gauci et al. European Journal of Cancer. 2022) or reported for other studies (EMEA/H/C/004338/II/0013). Patients with

locally advanced disease were allowed in the study, but only a minority of patients had locally advanced disease (10 patients [9.3%]).

With regard to the **disease characteristics**,most tumours were Merkel cell polyomavirus (MCPyV)-positive. Merkel cell polyomavirus is a risk factor for MCC, and the virus is often present in this type of tumour (Gauci et al. European Journal of Cancer. 2022). Most patients had PD-L1-positive tumours, which is relevant considering the mechanism of action of retifanlimab. In the second round, the Applicant provided results for ORR by PD-L1 TPS. Even though results across assays can be difficult to interpret as different clones were used, the percentage of patients with PD-L1 positive tumours based on TPS assessment was comparable between studies INCMGA 0012-201 and EMR100070-003 (18.8% vs. 18.1%, respectively, EMEA/H/C/004338/II/0013). The Applicant also clarified that a validated assay using clone 22C3 was used to determine PD-L1 expression. Immunocompromised patients were generally excluded from the study, except for the one patient that had a controlled HIV infection. This patient achieved a confirmed PR on retifanlimab and did not have any irAEs reported, opportunistic infections, or loss of HIV control. In general, immunocompromised patients were generally excluded. Limited data from patients with medical history conditions which could potentially cause immunosuppression did not allow to draw any specific conclusion. Lack of information in subgroups that were excluded from participation has been described in section 4.4. of the SmPC.

Among the patients who received anticancer therapy subsequent to retifanlimab, a few received subsequent avelumab/pembrolizumab, but no information was available on whether these patients responded to another checkpoint inhibitor.

Retifanlimab shows promising anti-tumour activity in patients with advanced/metastatic MCC, as evident by the primary and (key) secondary outcomes. The **ORR** was high (52.3% [95% CI: 39.5, 64.9]) and median **DOR** not reached (61.8% of the responses were ≥ 12 months). The primary objective of the study was met (i.e., the lower limit of the 95% CI exceeded 30%). Updated results (data cut-off date of 10 Mar 2023) were consistent with earlier findings. The ORR remained high (53.5% [95% CI: 43.3, 63.5]) and response was durable (25.3 months [95% CI: 14.2, NE]). Results from other studies strengthen the relevance of PD-(L)1 inhibitors in MCC, although the limitations associated with cross-study comparisons should be taken into account. The studies investigating avelumab and pembrolizumab in MCC showed an ORR of 39.7 (95% CI: 30.7–49.2) and 56% (95%CI: 41.3-70.0), respectively (EMEA/H/C/004338/II/0013; Nghiem et al. JCO. 2019). The median DoR was 18.2 months (95% CI: 11.3-not estimable) for avelumab (EMEA/H/C/004338/II/0013). Hence, results are considered credible (i.e., class effects in MCC; biological rationale).

Objective response rate in the 60 chemotherapy-naïve patients with centrally confirmed MCC and measurable disease was consistent with the primary analysis. This supports the internal validity. There were small numerical differences between ICR-assessed and **investigator-assessed ORR,** mainly due to some additional partial responses based on investigator assessment. As investigators may overestimate responses in open-label studies, ORR by ICR is considered most reliable.

PFS and **OS** results are difficult to interpret without a control arm. Nevertheless, PFS results are encouraging, with median PFS 12.7 months (95% CI: 7.3, 24.9). Overall survival data were immature, as 46 patients (70.8%) were censored at the data cut-off date. Updated OS data were provided during the procedure but are still immature with 68 patients (67.3%) alive and censored for OS. Survival outcomes are difficult to interpret in the context of a single-arm trial, but the survival curve appears to flatten over time – indicative of a plateau. The Applicant will provide updated OS results in the final INCMGA 0012-201 CSR

(PAM-REC). Important to note is that retifanlimab and avelumab both target the PD-1/PD-L1 pathway/axis; thus, it is considered not likely that retifanlimab will show a detrimental effect on important endpoints, such as overall survival, compared to the current standard of care.

Responses were seen in all **subgroups** of interest, including the elderly, those with positive and negative MCPyV status, and PD-L1 expressing and non-expressing tumours, and cancer stage. Regarding the latter, only few patients with locally advanced disease were enrolled in the study. Still, results show consistent treatment effect between patients with advanced and metastatic cancer. Important to note is that patients with locally advanced inoperable tumours are in need of systemic treatment therapy and clinical practice guidelines also recommend immunotherapy specifically for these patients (Gauci et al. European Journal of Cancer. 2022). Zynyz would be the first approved treatment in this subpopulation. In the initial data cut-off, differences in treatment effects were observed for the subgroups "Age Group 2 (< 75 years vs ≥ 75 years)" and "PD-L1 expression". In the updated data package, the treatment effect for ORR was consistent across age subgroups, which is reassuring. For PD-L1 by CPS subgroups, the difference in treatment effect remained, however, no definitive conclusions can be made due to imprecise estimates and overlapping confidence intervals.

Note that in the pivotal trial supporting the authorisation of avelumab "the PD-L1 positive tumours subgroup achieved overall better ORR and DRR compared to PD-L1 negative tumour, with a trend toward improved outcome with higher cut-off positivity" (EMEA/H/C/004338/0000). This was also observed for retifanlimab in the updated results for ORR by PD-L1 tumour proportion score (TPS), as TPS was also used in study JAVELIN Merkel 200 (i.e., the pivotal study for avelumab in MCC). Objective response rate by TPS was numerically higher in the PD-L1 positive subgroup compared to the PD-L1-negative subgroup (84.2% [95% CI: 60.4, 96.6] vs. 46.1% [95% CI: 34.5, 57.9], respectively). Besides the pre-planned subgroups, post-hoc subgroups, such as results per combined PD-L1 expression and MCV status categories at baseline showed ORR > 40%, but ORR was numerically higher in the PD-L1-positive subgroups, and highest in combined PD-L1-positive and MCPyV positive subgroup.

The risk of lack of efficacy in patients with ADAs treated with retifanlimab was considered during the procedure. It was suggested that potential immunogenicity and the risk for the lack of efficacy due to ADA formation is not considered to have an impact on B/R of retifanlimab. Clinically, no apparent impact of ADAs on PK, efficacy or safety was observed. Moreover, the numbers presented show a low number of ADA-positive participants across studies, with even lower number of participants with neutralizing ADAs. Yet, no cross-study comparison or analysis was conducted by the Applicant. **Contextualization** of results would generally be expected for single-arm trials (EMA/CHMP/205/95 Rev.6), preferably by a properly matched comparison on individual patient data. However, given the understanding of the mechanisms of action and consistency in treatment effects it is deemed plausible that the clinical outcomes will be comparable between retifanlimab and avelumab (i.e., the current standard of care). Yet, cross-study comparisons are generally biased by imbalances in both known and unknown baseline factors and should be interpreted with caution.

Initially, the wording of the **indication** was not acceptable as the claimed indication did not adequately reflect the study population. Specifically, the indication was line-independent, while the study population predominately consisted of patients who did not receive prior systemic therapy. Moreover, the indication was not restricted to patients in need of systemic treatment. The indication was revised to include "first-line" and "not amenable to curative surgery or radiation therapy" to the wording of the indication, thereby accurately reflecting the study population.

As highlighted in scientific advice, a discussion on the **comprehensiveness** of the data is inevitable. Important to highlight is that Bavencio received MA for the treatment of MCC based on data from 204 patients (116 treatment-naïve patients). This regulatory precedent is also relevant for the assessment of comprehensiveness. With the latest data update and the "first-line" indication, it is considered that the criteria for comprehensiveness are met (see section 4.7.3).

2.6.7. Conclusions on the clinical efficacy

Retifanlimab shows promising antitumour activity that likely translates into meaningful benefit. The treatment effects observed in the pivotal trial are consistent with those estimated for other anti-PD-(L)1 therapies in MCC. The ORR was high (53.5% [95% CI: 43.3, 63.5]) and response was durable (25.3 months [95% CI: 14.2, NE]), and PFS results are encouraging. Responses were seen in all subgroups of interest, including the elderly, those with positive and negative MCPyV status, and PD-L1 expressing and non-expressing tumours, and cancer stage. Regarding the latter, only few patients with locally advanced disease were enrolled in the study. Still, results show consistent treatment effect between patients with advanced and metastatic cancer. Taking into account the intrinsic limitations of single arm studies, the rarity of the disease and the challenges to compare the results with data from external controls, the currently available data are deemed to substantiate the efficacy of retifanlimab in the first line treatment of adult patients with metastatic or recurrent locally advanced MCC not amenable to curative surgery or radiation therapy.

2.6.8. Clinical safety

The safety of retifanlimab monotherapy was evaluated in the 5 clinical studies detailed in **Table 13**.

Data from these 5 clinical studies were pooled for the safety analyses (DCO 21 January 2022). An updated safety analysis was provided with a later data cut-off (DCO 10 March 2023) of the ongoing studies, where the median (range) durations of safety follow-up for the MCC and All Cancer 500 mg Q4W populations were 12.06 months (0.3-27.0 months) and 7.59 months (0.3-30.0 months), respectively. The All Cancer Population (N = 653) includes all participants with solid tumours who received at least 1 dose of retifanlimab as monotherapy. Four hundred and fifty-two of these participants (including all participants with MCC) received retifanlimab at the proposed dose of 500 mg Q4W (referred to as the "All Cancer 500 mg Q4W Population"). This is considered the main population for the analysis of clinical safety. The All Cancer 500 mg Q4W Population is inclusive of the following populations:

- MCC Population (N = 107), which includes all participants with MCC who received at least 1 dose of retifanlimab 500 mg Q4W monotherapy. All participants in the MCC Population were enrolled in Study INCMGA 0012-201.
- Non-MCC 500 mg Q4W Population (N = 345), which includes all participants with solid tumours.

Baseline characteristics for the MCC population are described in the efficacy part.

In the All Cancer 500mg Q4W population, the most common types of cancer were MCC (23.7%), endometrial cancer (EC, 24.8%), and squamous carcinoma of the anal canal (SCAC, 20.8%; see Table 45). One hundred six participants (23.5%) had liver metastases. Most participants had an ECOG performance status at baseline of 0 (48.5%) or 1 (50.9%). Similar to the MCC Population, renal function in the All Cancer 500 mg Q4W Population was distributed across normal renal function (35.4%), mild renal impairment (37.2%), and moderate renal impairment (26.8%). No patients with end-stage-renal disease were treated. The majority of

participants (87.4%) had normal hepatic function. Ten participants (2.2%) were known to be HIV-positive at baseline 265 participants (58.6%) had received prior systemic therapy, 230 participants (50.9%) received prior radiotherapy, and 11 participants (2.4%) received prior immunotherapy. Median age was 67.0 years (range: 36-94 years), 42.5% of participants were male, and 57.5% of participants were female. Among the participants with a reported race and/or ethnicity, most participants were white. (Table 45).

Table 45: Baseline patient and disease characteristics

Variable, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Cancer type by most common in All Cancer 500 mg Q4W Population			
EC	0 (0.0)	112 (32.5)	112 (24.8)
MCC	107 (100.0)	0 (0.0)	107 (23.7)
SCAC	0 (0.0)	94 (27.2)	94 (20.8)
Melanoma	0 (0.0)	35 (10.1)	35 (7.7)
Renal cell carcinoma	0 (0.0)	34 (9.9)	34 (7.5)
Bladder cancer	0 (0.0)	29 (8.4)	29 (6.4)
NSCLC	0 (0.0)	23 (6.7)	23 (5.1)
Colorectal cancer	0 (0.0)	6 (1.7)	6 (1.3)
Breast cancer	0 (0.0)	4 (1.2)	4 (0.9)
Other	0 (0.0)	3 (0.9)	3 (0.7)
Sarcoma	0 (0.0)	2 (0.6)	2 (0.4)
Hepatocellular carcinoma	0 (0.0)	1 (0.3)	1 (0.2)
Lung cancer	0 (0.0)	1 (0.3)	1 (0.2)
Ovarian cancer	0 (0.0)	1 (0.3)	1 (0.2)
Liver metastases			
Yes	11 (10.3)	95 (27.5)	106 (23.5)
No	96 (89.7)	250 (72.5)	346 (76.5)
ECOG status			
0	77 (72.0)	142 (41.2)	219 (48.5)
1	30 (28.0)	200 (58.0)	230 (50.9)
2	0 (0.0)	2 (0.6)	2 (0.4)
Missing	0 (0.0)	1 (0.3)	1 (0.2)
Creatinine clearance[a]			
≥ 90 mL/min (normal renal function)	41 (38.3)	119 (34.5)	160 (35.4)
≥ 60 to < 90 mL/min (mild renal impairment)	41 (38.3)	127 (36.8)	168 (37.2)
≥ 30 to < 60 mL/min (moderate renal impairment)	25 (23.4)	96 (27.8)	121 (26.8)
≥ 15 to < 30 mL/min (severe renal impairment not requiring dialysis)[b]	0 (0.0)	3 (0.9)	3 (0.7)
Hepatic impairment[c]			
Normal	92 (86.0)	303 (87.8)	395 (87.4)
Mild/moderate	15 (14.0)	41 (11.9)	56 (12.4)
Severe	0 (0.0)	0 (0.0)	0 (0.0)

Variable, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Missing	0 (0.0)	1 (0.3)	1 (0.2)
HIV status			
Positive	1 (0.9)	9 (2.6)	10 (2.2)
Negative/unknown	106 (99.1)	336 (97.4)	442 (97.8)
Participants with any prior systemic therapy	6 (5.6)	259 (75.1)	265 (58.6)
Participants with prior radiotherapy	40 (37.4)	190 (55.1)	230 (50.9)
Participants with prior surgery/procedure	74 (69.2)	247 (71.6)	321 (71.0)

[a] Creatinine clearance is calculated based on Cockcroft-Gault formula: [(140 − age [years]) × (weight in kg) × (0.85 if female)] / (72 × serum creatinine [mg/dL]).
[b] No participants with end-stage renal disease (ie, < 15 mL/min GFR not on dialysis or requiring dialysis) were included.
[c] Hepatic impairment categories: normal = bilirubin ≤ ULN and AST ≤ ULN; mild = bilirubin ≤ ULN and AST > ULN or ULN < bilirubin ≤ 1.5 × ULN; moderate = 1.5 × ULN < bilirubin ≤ 3 × ULN; severe: bilirubin > 3 × ULN.
Source: ISS Tables 1.2.1 and 1.3.

2.6.8.1. Patient exposure

Sixteen participants in the MCC Population completed the maximum 2 year treatment period or had treatment discontinued at the discretion of the investigator (following at least 6 months of therapy with confirmed response).

Table 46: Summary of patient disposition

Variable, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Participants treated	107 (100.0)	345 (100.0)	452 (100.0)
Participants who completed treatment	16 (15.0)	48 (13.9)	64 (14.2)
Participants with ongoing treatment	26 (24.3)	22 (6.4)	48 (10.6)
Participants who discontinued treatment	65 (60.7)	275 (79.7)	340 (75.2)
Primary reason for treatment discontinuation:			
AE	22 (20.6)	44 (12.8)	66 (14.6)
Death	4 (3.7)	11 (3.2)	15 (3.3)
Lost to follow-up	0 (0.0)	2 (0.6)	2 (0.4)
Physician decision	3 (2.8)	3 (0.9)	6 (1.3)
Progressive disease – clinical progression	9 (8.4)	67 (19.4)	76 (16.8)
Progressive disease – radiographic progression	24 (22.4)	132 (38.3)	156 (34.5)
Withdrawal by participant	2 (1.9)	10 (2.9)	12 (2.7)
Other	1 (0.9)	6 (1.7)	7 (1.5)
Participants ongoing on study	68 (63.6)	64 (18.6)	132 (29.2)
Participants who completed study	0 (0.0)	9 (2.6)	9 (2.0)
Participants who withdrew from study	39 (36.4)	272 (78.8)	311 (68.8)
Primary reason for study withdrawal:			

Death	32 (29.9)	179 (51.9)	211 (46.7)
Lost to follow-up	0 (0.0)	13 (3.8)	13 (2.9)
Withdrawal by participant	7 (6.5)	3 (0.9)	10 (2.2)
Progressive disease	0 (0.0)	1 (0.3)	1 (0.2)
Other	0 (0.0)	76 (22.0)	76 (16.8)

All Cancer 500 mg Q4W Population

The median duration of retifanlimab treatment was 5.4 months (range: 1-27.0 months; see Table 47). As of the data cut-off date (12 March 2023), 212 participants (46.9%) had received retifanlimab for >6 months, 144 participants (31.9%) had received retifanlimab for >12 months, and 99 participants (21.9%) had received retifanlimab for >18 months. Relative dose intensity was 100% in the 452 participants in the All Cancer 500 mg Q4W Population. At the time of the data cutoff dates for the individual studies, the median duration of safety follow-up in the All Cancer 500 mg Q4W Population was 7.59 months (0.3-30.0 months).

MCC Population

In the MCC Population, the median duration of retifanlimab treatment was 10.3 months (range: 1 day-24.1 months; see Table 47). As of the data cut-off date, 66 participants (61.7%) had received retifanlimab for >6 months, 49 participants (45.8%) had received retifanlimab for >12 months, and 27 participants (25.2%) had received retifanlimab for >18 months.

Table 47: Summary of Retifanlimab exposure

Variable	**MCC 500 mg Q4W (N = 107)**	**Non-MCC 500 mg Q4W (N = 345)**	**All Cancer 500 mg Q4W (N = 452)**
Total PYs[a]	95.6	236.3	331.9
Total number of infusions[b]			
Mean (STD)	12.1 (8.93)	9.5 (8.67)	10.1 (8.79)
Median	12.0	6.0	6.0
Min, max	1, 27	1, 27	1, 27
Duration of treatment (months)[c]			
Mean (STD)	10.7 (8.54)	8.2 (8.23)	8.8 (8.36)
Median	10.3	4.6	5.4
Min (day), max (months)	1, 24.1	1, 27.0	1, 27.0
Dose intensity (mg/day)[d]			
Mean (STD)	17.22 (1.210)	17.31 (1.166)	17.29 (1.175)
Median	17.86	17.86	17.86
Min, max	11.3, 18.2	8.2, 18.9	8.2, 18.9
Participants treated, n (%)			
≤ 1 month	21 (19.6)	68 (19.7)	89 (19.7)
> 1 to ≤ 3 months	10 (9.3)	77 (22.3)	87 (19.2)
> 3 to ≤ 6 months	10 (9.3)	54 (15.7)	64 (14.2)
> 6 to ≤ 9 months	7 (6.5)	27 (7.8)	34 (7.5)

Variable	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
> 9 to ≤ 12 months	10 (9.3)	24 (7.0)	34 (7.5)
> 12 to ≤ 15 months	15 (14.0)	14 (4.1)	29 (6.4)
> 15 to ≤ 18 months	7 (6.5)	9 (2.6)	16 (3.5)
> 18 to ≤ 21 months	6 (5.6)	18 (5.2)	24 (5.3)
> 21 to ≤ 24 months	17 (15.9)	52 (15.1)	69 (15.3)
> 24 months[e]	4 (3.7)	2 (0.6)	6 (1.3)

Note: The number of month(s) was calculated as the number of day(s) divided by 30.4375.

[a] Total PYs was calculated as sum of duration of treatment (days) of all the participants in each group divided by 365.25.
[b] Total number of infusions: total number of infusions per participant with a nonzero dose of retifanlimab.
[c] Duration of treatment (months) = (date of last dose of retifanlimab − date of first dose + 1) / 30.4375.
[d] Dose intensity (mg/day) = total dose administered (mg) / (duration of treatment [days] + cycle length − 1).
[e] Participants received a maximum of 2 years of retifanlimab treatment, including dose delays.

2.6.8.2. Adverse events

Table 48: Summary of treatment emergent adverse events

Participants (n [%]) With a:	MCC 500 mg Q4W (N = 107) PYs = 95.6	Non-MCC 500 mg Q4W (N = 345) PYs = 236.3	All Cancer 500 mg Q4W (N = 452) PYs = 331.9
TEAE	96 (89.7)	331 (95.9)	427 (94.5)
Treatment-related TEAE	72 (67.3)	229 (66.4)	301 (66.6)
Serious TEAE	28 (26.2)	137 (39.7)	165 (36.5)
Grade 3 or higher TEAE	34 (31.8)	168 (48.7)	202 (44.7)
Fatal TEAE	4 (3.7)	21 (6.1)	25 (5.5)
Serious treatment-related TEAE	13 (12.1)	20 (5.8)	33 (7.3)
Grade 3 or higher treatment-related TEAE	18 (16.8)	45 (13.0)	63 (13.9)
Dose interruption due to TEAE[a]	40 (37.4)	104 (30.1)	144 (31.9)
Infusion interruption due to TEAE	3 (2.8)	2 (0.6)	5 (1.1)
Dose delayed due to TEAE	38 (35.5)	102 (29.6)	140 (31.0)
Discontinuation of study drug due to TEAE	22 (20.6)	44 (12.8)	66 (14.6)
Discontinuation of study drug due to treatment-related TEAE	16 (15.0)	22 (6.4)	38 (8.4)

a TEAEs leading to dose interruption include TEAEs leading to infusion interruption and TEAEs leading to dose delay.

Common adverse events

Table 49: Summary of common (≥ 5% of participants in the all cancer 500 mg Q4W population) TEAEs by System Organ Class and Preferred Term

MedDRA SOC MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107) PYs = 95.6	Non-MCC 500 mg Q4W (N = 345) PYs = 236.3	All Cancer 500 mg Q4W (N = 452) PYs = 331.9
Gastrointestinal disorders	48 (44.9)	184 (53.3)	232 (51.3)
Diarrhoea	19 (17.8)	65 (18.8)	84 (18.6)
Constipation	12 (11.2)	48 (13.9)	60 (13.3)
Nausea	13 (12.1)	47 (13.6)	60 (13.3)
Abdominal pain	5 (4.7)	34 (9.9)	39 (8.6)
Vomiting	6 (5.6)	33 (9.6)	39 (8.6)
General disorders and administration site conditions	50 (46.7)	180 (52.2)	230 (50.9)
Asthenia	24 (22.4)	78 (22.6)	102 (22.6)
Fatigue	13 (12.1)	53 (15.4)	66 (14.6)
Pyrexia	13 (12.1)	46 (13.3)	59 (13.1)
Oedema peripheral	4 (3.7)	26 (7.5)	30 (6.6)
Infections and infestations	37 (34.6)	150 (43.5)	187 (41.4)
Urinary tract infection	8 (7.5)	48 (13.9)	56 (12.4)
Skin and subcutaneous tissue disorders	47 (43.9)	118 (34.2)	165 (36.5)
Pruritus	22 (20.6)	50 (14.5)	72 (15.9)
Rash	7 (6.5)	38 (11.0)	45 (10.0)
Dry skin	5 (4.7)	18 (5.2)	23 (5.1)
Musculoskeletal and connective tissue disorders	43 (40.2)	116 (33.6)	159 (35.2)
Arthralgia	17 (15.9)	43 (12.5)	60 (13.3)
Back pain	7 (6.5)	32 (9.3)	39 (8.6)
Metabolism and nutrition disorders	22 (20.6)	126 (36.5)	148 (32.7)
Decreased appetite	6 (5.6)	51 (14.8)	57 (12.6)
Hypokalaemia	3 (2.8)	22 (6.4)	25 (5.5)
Investigations	33 (30.8)	104 (30.1)	137 (30.3)
Alanine aminotransferase increased	8 (7.5)	17 (4.9)	25 (5.5)
Aspartate aminotransferase increased	7 (6.5)	18 (5.2)	25 (5.5)
Respiratory, thoracic and mediastinal disorders	21 (19.6)	92 (26.7)	113 (25.0)
Cough	9 (8.4)	33 (9.6)	42 (9.3)
Dyspnoea	6 (5.6)	31 (9.0)	37 (8.2)
Nervous system disorders	18 (16.8)	85 (24.6)	103 (22.8)
Headache	5 (4.7)	24 (7.0)	29 (6.4)
Blood and lymphatic system disorders	13 (12.1)	85 (24.6)	98 (21.7)
Anaemia	5 (4.7)	64 (18.6)	69 (15.3)
Endocrine disorders	17 (15.9)	51 (14.8)	68 (15.0)
Hypothyroidism	10 (9.3)	34 (9.9)	44 (9.7)
Hyperthyroidism	6 (5.6)	19 (5.5)	25 (5.5)
Renal and urinary disorders	9 (8.4)	59 (17.1)	68 (15.0)
Vascular disorders	16 (15.0)	42 (12.2)	58 (12.8)

MedDRA SOC MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107) PYs = 95.6	Non-MCC 500 mg Q4W (N = 345) PYs = 236.3	All Cancer 500 mg Q4W (N = 452) PYs = 331.9
Psychiatric disorders	10 (9.3)	40 (11.6)	50 (11.1)
Insomnia	6 (5.6)	17 (4.9)	23 (5.1)
Injury, poisoning and procedural complications	14 (13.1)	31 (9.0)	45 (10.0)
Reproductive system and breast disorders	10 (9.3)	29 (8.4)	39 (8.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (11.2)	25 (7.2)	37 (8.2)
Eye disorders	8 (7.5)	22 (6.4)	30 (6.6)
Cardiac disorders	10 (9.3)	13 (3.8)	23 (5.1)

Note: Total PYs was calculated as sum of duration of treatment (days) of all participants in each group divided by 365.25.

Treatment-related adverse events

Treatment-related TEAEs occurred in 72 participants (67.3%) in the MCC Population and in 301 participants (66.6%) in the All Cancer 500 mg Q4W Population.

The most common treatment-related AEs were pruritus (15 and 13.1%) and asthenia (14 and 11.3%) in the MCC and All Cancer populations, respectively, in line with the most common treatment-emergent adverse events (Table 45).

Table 50: Common Treatment-Related TEAEs (≥ 2% of Participants in the All Cancer 500 mg Q4W Population) by MedDRA Preferred Term

MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Pruritus	16 (15.0)	43 (12.5)	59 (13.1)
Asthenia	15 (14.0)	36 (10.4)	51 (11.3)
Diarrhoea	10 (9.3)	32 (9.3)	42 (9.3)
Fatigue	9 (8.4)	33 (9.6)	42 (9.3)
Hypothyroidism	8 (7.5)	26 (7.5)	34 (7.5)
Rash	6 (5.6)	27 (7.8)	33 (7.3)
Arthralgia	7 (6.5)	23 (6.7)	30 (6.6)
Hyperthyroidism	5 (4.7)	16 (4.6)	21 (4.6)
Nausea	6 (5.6)	15 (4.3)	21 (4.6)
Alanine aminotransferase increased	5 (4.7)	12 (3.5)	17 (3.8)
Decreased appetite	3 (2.8)	14 (4.1)	17 (3.8)
Myalgia	6 (5.6)	11 (3.2)	17 (3.8)
Pyrexia	4 (3.7)	13 (3.8)	17 (3.8)
Dry skin	3 (2.8)	11 (3.2)	14 (3.1)
Anaemia	0 (0.0)	13 (3.8)	13 (2.9)
Aspartate aminotransferase increased	3 (2.8)	10 (2.9)	13 (2.9)
Vomiting	4 (3.7)	9 (2.6)	13 (2.9)
Lipase increased	7 (6.5)	5 (1.4)	12 (2.7)
Dry mouth	4 (3.7)	7 (2.0)	11 (2.4)

MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Amylase increased	5 (4.7)	5 (1.4)	10 (2.2)
Constipation	4 (3.7)	6 (1.7)	10 (2.2)

Adverse reactions (below) were identified based on safety results of retifanlimab 500 mg Q4W in 452 participants with advanced solid malignancies, including 107 participants with metastatic or recurrent locally advanced MCC. Median duration of treatment in these 452 evaluated participants was 5.4 months (range: 1 day-27.0 months). The adverse reactions identified for retifanlimab are based on the sponsor's medical assessment of each individual TEAE when a causal relationship with the product was a reasonable possibility. The review consisted of all TEAEs, including irAEs, IRRs, ≥ Grade 3 TEAEs, serious TEAEs, fatal TEAEs, TEAEs leading to discontinuation or dose interruption (eg, dose delay), and laboratory abnormalities, regardless of incidence.

Table 51: Adverse Reactions in Participants in the All Cancer 500 mg Q4W Population (N = 452)

System Organ Class	Adverse Reaction	
	Frequency of All Grades	Frequency of Grades 3-4
Blood and lymphatic system disorders	**Very common** Anaemia[a]	**Common** Anaemia[a]
Endocrine disorders	**Common** Hypothyroidism Hyperthyroidism **Uncommon** Adrenal insufficiency Thyroiditis[b] Hypophysitis	**Uncommon** Adrenal insufficiency Hypophysitis
Metabolism and nutrition disorders	**Very common** Decreased appetite **Uncommon** Diabetic ketoacidosis	**Uncommon** Decreased appetite Diabetic ketoacidosis
Nervous system disorders	**Common** Paraesthesia **Uncommon** Polyneuropathy[c] Radiculopathy Vocal cord paralysis	**Uncommon** Polyneuropathy[c] Radiculopathy
Eye disorders	**Uncommon** Uveitis[d] Keratitis	**Uncommon** Uveitis[d]
Cardiac disorders	**Uncommon** Pericarditis Myocarditis	**Uncommon** Myocarditis
Respiratory, thoracic and mediastinal disorders	**Common** Pneumonitis[e]	**Uncommon** Pneumonitis[e]

System Organ Class	Adverse Reaction	
	Frequency of All Grades	**Frequency of Grades 3-4**
Gastrointestinal disorders	**Very common** Diarrhoea Nausea Constipation **Common** Colitis[f] **Uncommon** Pancreatitis	**Uncommon** Diarrhoea Pancreatitis Colitis[f]
Hepatobiliary disorders	**Common** Hepatocellular injury Hepatitis[g] **Uncommon** Hyperbilirubinaemia Cholangitis	**Uncommon** Hepatitis[g] Hepatocellular injury Cholangitis Hyperbilirubinaemia
Skin and subcutaneous skin disorders	**Very common** Rash[h] Pruritus	**Common** Rash[h]
Musculoskeletal and connective tissue disorders	**Very common** Arthralgia **Uncommon** Arthritis[i] Myositis Eosinophilic fasciitis Polymyalgia rheumatica	**Uncommon** Arthralgia Arthritis[i] Myositis Eosinophilic fasciitis
Renal and urinary disorders	**Common** Acute kidney injury Renal failure **Uncommon** Tubulointerstitial nephritis	**Uncommon** Acute kidney injury Tubulointerstitial nephritis
General disorders and administration site conditions	**Very common** Fatigue[j] Pyrexia	**Common** Fatigue[j] **Uncommon** Pyrexia
Investigations	**Common** Transaminases increased[k] Blood creatinine increased Amylase increased Lipase increased Blood bilirubin increased Blood thyroid-stimulating hormone increased **Uncommon** Blood thyroid-stimulating hormone decreased	**Common** Transaminases increased[k] **Uncommon** Blood bilirubin increased Lipase increased Blood creatinine increased Amylase increased
Injury, poisoning and procedural complications	**Common** Infusion-related reaction[l]	**Uncommon** Infusion-related reaction[l]

[a] Includes anaemia, iron deficiency anaemia, anaemia of malignant disease, and anaemia vitamin B12 deficiency.
[b] Includes thyroiditis and autoimmune thyroiditis.
[c] Includes polyneuropathy and demyelinating polyneuropathy.
[d] Includes uveitis and iritis.

[e] Includes pneumonitis, interstitial lung disease, organising pneumonia, and lung infiltration.
[f] Includes colitis and immune-mediated enterocolitis.
[g] Includes hepatitis and autoimmune hepatitis.
[h] Includes rash, rash maculo-papular, rash erythematous, rash pruritic, dermatitis, psoriasis, rash macular, rash papular, lichenoid keratosis, rash pustular, dermatitis bullous, palmar-plantar erythrodyseasthesia syndrome, toxic epidermal necrolysis, and toxic skin eruption.
[i] Includes arthritis and polyarthritis.
[j] Includes asthenia and fatigue.
[k] Includes transaminases increased, alanine aminotransferase increased, and aspartate aminotransferase increased.
[l] Includes drug hypersensitivity and infusion-related reaction.

Grade 3 or higher adverse events

All Cancer 500 mg Q4W Population

Grade 3 or higher TEAEs are summarized in Table 52. In the All Cancer 500 mg Q4W Population, TEAEs of maximum severity Grade 3, Grade 4, and Grade 5 occurred in 34.1%, 5.1%, and 5.5% of participants, respectively.

MCC population

Grade 3 or higher TEAEs occurred in 34 participants (31.8%) in the MCC Population. The most common Grade 3 or higher TEAEs were lipase increased and COVID 19 (3 patients; 2.8% each). Treatment-related Grade 3 or higher TEAEs occurred in 18 participants (16.8%).

Table 52: Common (≥ 1% of participants in the All Cancer 500 mg Q4W Population) Grade 3 or higher TEAEs by MedDRA Preferred Term

MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Anaemia	2 (1.9)	26 (7.5)	28 (6.2)
Pneumonia	2 (1.9)	7 (2.0)	9 (2.0)
Asthenia	2 (1.9)	6 (1.7)	8 (1.8)
Hyponatraemia	2 (1.9)	6 (1.7)	8 (1.8)
Dyspnoea	1 (0.9)	6 (1.7)	7 (1.5)
Hyperglycaemia	1 (0.9)	6 (1.7)	7 (1.5)
Hypertension	1 (0.9)	6 (1.7)	7 (1.5)
Sepsis	1 (0.9)	6 (1.7)	7 (1.5)
Abdominal pain	0 (0.0)	6 (1.7)	6 (1.3)
Alanine aminotransferase increased	2 (1.9)	4 (1.2)	6 (1.3)
Blood alkaline phosphatase increased	0 (0.0)	6 (1.7)	6 (1.3)
Pelvic pain	0 (0.0)	6 (1.7)	6 (1.3)
Urinary tract infection	1 (0.9)	5 (1.4)	6 (1.3)
Fatigue	0 (0.0)	5 (1.4)	5 (1.1)
General physical health deterioration	0 (0.0)	5 (1.4)	5 (1.1)
Hypercalcaemia	0 (0.0)	5 (1.4)	5 (1.1)
Pleural effusion	1 (0.9)	4 (1.2)	5 (1.1)

Table 53: Common (≥ 2 participants in the All Cancer 500 mg Q4W Population) treatment-related Grade 3 or higher TEAEs by MedDRA Preferred Term

MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Anaemia	0 (0.0)	4 (1.2)	4 (0.9)
Alanine aminotransferase increased	1 (0.9)	2 (0.6)	3 (0.7)
Amylase increased	2 (1.9)	1 (0.3)	3 (0.7)
Hepatitis	1 (0.9)	2 (0.6)	3 (0.7)
Lipase increased	2 (1.9)	1 (0.3)	3 (0.7)
Adrenal insufficiency	1 (0.9)	1 (0.3)	2 (0.4)
Diarrhoea	0 (0.0)	2 (0.6)	2 (0.4)
Fatigue	0 (0.0)	2 (0.6)	2 (0.4)
Hepatocellular injury	0 (0.0)	2 (0.6)	2 (0.4)
Hyperglycaemia	1 (0.9)	1 (0.3)	2 (0.4)
Hyponatraemia	1 (0.9)	1 (0.3)	2 (0.4)
Lymphopenia	0 (0.0)	2 (0.6)	2 (0.4)
Pancreatitis	1 (0.9)	1 (0.3)	2 (0.4)
Pneumonitis	0 (0.0)	2 (0.6)	2 (0.4)
Rash	0 (0.0)	2 (0.6)	2 (0.4)

Adverse events of special interest

Immune-related AEs (irAEs) and infusion-related reactions (IRRs) were analysed as AEs of special interest (AESI):

- **Immune-related AEs:** Predefined preferred terms were grouped into AESI categories and used to identify irAEs independent of investigator's assessment of causality.
- **Infusion-related reactions:** Predefined preferred terms were grouped into AESI categories, and used to identify infusion-related reactions independent of investigator's assessment of causality. Diagnosis of infusion-related reactions that occurred any time during the treatment period or symptoms potentially associated with infusion-related reactions that occurred within 1 day of infusion and resolved within 2 days from onset were captured as infusion-related reactions.

Immune-related adverse events

Most irAEs were Grade 1 or 2 in severity. In the All Cancer 500 mg Q4W Population, irAEs were Grade 3 in 38 participants (8.4%) and Grade 4 in 6 participants (1.3%).

No fatal irAEs occurred in the MCC Population, and 1 fatal irAE (PT: interstitial lung disease) occurred in the All Cancer 500 mg Q4W Population.

Table 56 summarizes the time to first onset of irAEs for each irAE group term. Median, minimum, and maximum are summarized from observed event date of time to first onset of the irAE.

Table 54: Overall summary of immune-related adverse events

Participants (n [%]) With a:	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
irAE	42 (39.3)	114 (33.0)	156 (34.5)
Serious irAE	12 (11.2)	19 (5.5)	31 (6.9)
Grade 3 or higher irAE	13 (12.1)	32 (9.3)	45 (10.0)
Fatal irAE	0 (0.0)	1 (0.3)	1 (0.2)
Dose delayed due to irAE	14 (13.1)	25 (7.2)	39 (8.6)
Discontinuation of study drug due to irAE	12 (11.2)	18 (5.2)	30 (6.6)

Table 55: Immune-related adverse events by Group Term

	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
irAE, n (%)	All Grades	Grades ≥ 3	All Grades	Grades ≥ 3	All Grades	Grades ≥ 3
Endocrine irAEs						
Hypothyroidism[a]	11 (10.3)	0 (0.0)	35 (10.1)	0 (0.0)	46 (10.2)	0 (0.0)
Hyperthyroidism[b]	6 (5.6)	0 (0.0)	20 (5.8)	0 (0.0)	26 (5.8)	0 (0.0)
Adrenal insufficiency	3 (2.8)	1 (0.9)	1 (0.3)	1 (0.3)	4 (0.9)	2 (0.4)
Hypophysitis	2 (1.9)	1 (0.9)	1 (0.3)	0 (0.0)	3 (0.7)	1 (0.2)
Thyroiditis[c]	1 (0.9)	0 (0.0)	2 (0.6)	0 (0.0)	3 (0.7)	0 (0.0)
Type 1 diabetes[d]	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Nonendocrine irAEs						
Skin reactions[e]	10 (9.3)	2 (1.9)	33 (9.6)	4 (1.2)	43 (9.5)	6 (1.3)
Hepatitis[f]	4 (3.7)	2 (1.9)	12 (3.5)	10 (2.9)	16 (3.5)	12 (2.7)
Pneumonitis[g]	5 (4.7)	2 (1.9)	9 (2.6)	3 (0.9)	14 (3.1)	5 (1.1)
Colitis[h]	5 (4.7)	0 (0.0)	7 (2.0)	3 (0.9)	12 (2.7)	3 (0.7)
Nephritis[i]	1 (0.9)	0 (0.0)	8 (2.3)	7 (2.0)	9 (2.0)	7 (1.5)
Pancreatitis	1 (0.9)	1 (0.9)	1 (0.3)	1 (0.3)	2 (0.4)	2 (0.4)
Other rare irAEs						
Musculoskeletal and connective tissue[j]	2 (1.9)	1 (0.9)	4 (1.2)	1 (0.3)	6 (1.3)	2 (0.4)
Guillain-Barré syndrome (immune-related neuropathy)[k]	1 (0.9)	1 (0.9)	2 (0.6)	0 (0.0)	3 (0.7)	1 (0.2)
Myositis	0 (0.0)	0 (0.0)	3 (0.9)	1 (0.3)	3 (0.7)	1 (0.2)
Uveitis[l]	0 (0.0)	0 (0.0)	3 (0.9)	1 (0.3)	3 (0.7)	1 (0.2)
Nervous system[m]	1 (0.9)	1 (0.9)	1 (0.3)	0 (0.0)	2 (0.4)	1 (0.2)
Cardiac/vascular[n]	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Hepatobiliary[o]	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)
Myocarditis	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)

irAE, n (%)	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
	All Grades	Grades ≥ 3	All Grades	Grades ≥ 3	All Grades	Grades ≥ 3
Ocular[p]	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)

[a] Hypothyroidism includes the PTs of blood TSH increased and hypothyroidism.

[b] Hyperthyroidism includes the PTs of blood TSH decreased and hyperthyroidism.

[c] Thyroiditis includes the PTs of autoimmune thyroiditis and thyroiditis.

[d] Type 1 diabetes includes the PT of diabetic ketoacidosis.

[e] Skin reactions includes the PTs of dermatitis, dermatitis bullous, lichenoid keratosis, palmar-plantar erythrodysesthesia syndrome, pruritus, psoriasis, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, and toxic skin eruption.

[f] Hepatitis includes the PTs of ALT increased, AST increased, autoimmune hepatitis, blood bilirubin increased, hepatitis, hepatocellular injury, hyperbilirubinemia, and transaminases increased.

[g] Pneumonitis includes the PTs of interstitial lung disease, organizing pneumonia, and pneumonitis.

[h] Colitis includes the PTs of colitis, diarrhea, and immune-mediated enterocolitis.

[i] Nephritis includes the PTs of acute kidney injury, blood creatinine increased, and renal failure.

[k] Guillain-Barré syndrome includes the PTs of demyelinating polyneuropathy and polyneuropathy.

[l] Uveitis includes the PTs of iritis and uveitis.

[j] Musculoskeletal and connective tissue irAEs include the PTs of arthritis, eosinophilic fasciitis, polyarthritis, and polymyalgia rheumatica.

[m] Nervous system irAEs include the PTs of paresthesia, radiculopathy, and vocal cord paralysis.

[n] Cardiac/vascular irAEs include the PT of pericarditis.

[o] Hepatobiliary irAEs include the PT of cholangitis.

[p] Ocular irAEs include the PT of keratitis.

Table 56: Time to first onset of observed irAEs (All Cancer 500 mg Q4W Population)

irAE by Group Term	Events, n (%) N = 452	Median Time to Onset in Days (min, max)
Endocrine irAEs		
Hypothyroidism	46 (10.2)	88.0 (1, 505)
Hyperthyroidism	26 (5.8)	55.5 (8, 575)
Adrenal insufficiency	4 (0.9)	220.5 (146, 275)
Thyroiditis	3 (0.7)	252.0 (63, 306)
Hypophysitis	3 (0.7)	308.0 (266, 377)
Type 1 diabetes	1 (0.2)	284.0 (284, 284)
Nonendocrine irAEs		
Skin reactions	43 (9.5)	86.0 (2, 589)
Hepatitis	16 (3.5)	70.5 (8, 580)
Pneumonitis	14 (3.1)	100.0 (43, 673)
Colitis	12 (2.7)	165.5 (11, 749)
Nephritis	9 (2.0)	176.0 (15, 515)
Pancreatitis	2 (0.4)	128.5 (29, 228)
Other rare irAEs		
Musculoskeletal and connective tissue	6 (1.3)	60.0 (31, 181)
Guillain-Barre Syndrome (immune-related neuropathy)	3 (0.7)	51.0 (10, 338)
Myositis	3 (0.7)	173.0 (51, 391)
Uveitis	3 (0.7)	188.0 (35, 622)
Nervous system	2 (0.4)	34.0 (20, 48)
Cardiac/vascular	1 (0.2)	275.0 (275, 275)
Hepatobiliary	1 (0.2)	49.0 (49, 49)
Myocarditis	1 (0.2)	690.0 (690, 690)
Ocular	1 (0.2)	142.0 (142, 142)

Immune-related endocrinopathies

Table 57: Immune-related endocrinopathies (All Cancer 500 mg Q4W Population)

Grouped Term	All Grades, n (%) (N = 452)	Grade 3 or Higher, n (%)	Serious, n (%)	Use of Endocrine Treatment		Time to Onset (days), Median (Min, Max)	Resolved, n (%)	Time to Resolution (days), Median (Min, Max)
				Thyroid, n (%)	Insulin, n (%)			
Endocrinopathies	**69 (15.3)**	**4 (0.9)**	**4 (0.9)**	**48 (69.6)**	**1 (1.4)**	**84.0 (1, 575)**	**23 (33.3)**	**57.0 (2, 309)**
Hypothyroidism[a]	46 (10.2)	0 (0.0)	0 (0.0)	36 (78.3)	0 (0.0)	88.0 (1, 505)	15 (32.6)	56.0 (2, 224)
Hyperthyroidism[b]	26 (5.8)	0 (0.0)	0 (0.0)	13 (50.0)	0 (0.0)	55.5 (8, 575)	16 (61.5)	74.0 (15, 295)
Adrenal insufficiency	4 (0.9)	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	220.5 (146, 275)	1 (25.0)	12.0 (12, 12)
Thyroiditis[c]	3 (0.7)	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	252.0 (63, 306)	1 (33.3)	29.0 (29, 29)
Hypophysitis	3 (0.7)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	308.0 (266, 377)	1 (33.3)	6.0 (6, 6)
Type 1 diabetes[d]	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	1 (100.0)	284.0 (284, 284)	1 (100.0)	6.0 (6, 6)

[a] Hypothyroidism includes the PTs of blood TSH increased and hypothyroidism.

[b] Hyperthyroidism includes the PTs of blood TSH decreased and hyperthyroidism.

[c] Thyroiditis includes the PTs of autoimmune thyroiditis and thyroiditis.

[d] Type 1 diabetes includes the PT of diabetic ketoacidosis.

Most events were grade 1 or 2, and, depending on the type of AEs and taking into account the small absolute number of cases, 33-100% of the events resolved, most with endocrine treatments. Hypophysitis led to discontinuation of retifanlimab treatment in a single patient.

Immune-related skin reactions

Table 58: Immune-related skin reactions (All Cancer 500 mg Q4W Population)

Grouped Term	All Grades, n (%) (N = 452)	Grade 3 or Higher, n (%)	Serious, n (%)	Use of Treatment		Time to Onset (days), Median (min, max)[b]	Resolved, n (%)[a]	Time to Resolution (days), Median (min, max)[c]
				Topical Steroid, n (%)[a]	Systemic Steroid, n (%)[a]			
Skin reactions	43 (9.5)	6 (1.3)	1 (0.2)	24 (55.8)	14 (32.6)	86.0 (2, 589)	31 (72.1)	37.0 (3, 470)

Note: The grouped term of skin reactions includes the PTs of dermatitis, dermatitis bullous, lichenoid keratosis, palmar-plantar erythrodysaesthesia syndrome, pruritus, psoriasis, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic epidermal necrolysis, and toxic skin eruption.

a Denominator is the number of participants with a skin reaction.

[b] Median, minimum, and maximum are summarized from observed event data of time to first onset of skin reaction.

[c] Median, minimum, and maximum are summarized from date of first onset to last resolution of skin reaction.

Immune-related skin reactions occurred in 9.5% of patients in the All Cancer 500mg Q4W population. Most skin reactions were grade 1 or 2 and resolved with a median time to resolution of 37 days (Table 58). The proportion of patients that needed systemic corticosteroid treatment for a skin reaction was 32.6% (14/43

patients), including 8 patients that needed high-dose systemic corticosteroids. There were three patients that discontinued retifanlimab treatment due to an immune-related skin reaction (0.7%).

Immune-related hepatitis

Immune-related hepatitis occurred in 3.5% of patients (n=16), was mainly grade 2 or 3 in severity (0.9% and 2.4%and was treated with systemic corticosteroids in most patients (81.3%). It resolved in about half of the cases (n=9/16) but also led to discontinuation of retifanlimab treatment in 7/16 patients (1.5% of the total All Cancer 500mg Q4W population).

The median onset time of observed hepatitis was 70.5 days (range: 8-580 days). Among the 16 participants with hepatitis, the 13 participants (84.6%) receiving systemic corticosteroids included 12 participants (75%) who received high dose systemic corticosteroids, and 1 participant (6.3%) who received another immunosuppressant (mycophenolate mofetil). Hepatitis resolved in 9 participants (56.3%), with a median time to resolution of 22 days (range: 6-104 days).

Immune-related pneumonitis

Immune-related pneumonitis occurred in 14 participants (3.1%) in the All Cancer 500mg Q4W population. It was mostly treated with systemic corticosteroids (71.4%) and resolved in 11/14 participants (78.6%). Treatment with retifanlimab had to be discontinued due to pneumonitis in 1 case, which was fatal.

The fatal case of interstitial lung disease in the All Cancer 500mg Q4W population concerned a 76-year old patient with SCAC, treated in Study INCMGA 0012-202. Upon an updated causality assessment, the pneumonitis was considered an immune-related adverse event related to study treatment.

The median onset time of observed pneumonitis was 100.0 days (range: 43-399 days). Among the 14 participants with pneumonitis, 10 participants (71.4%) received systemic corticosteroids, including 7 participants (50%) who received high dose systemic corticosteroids, and no participants received other immunosuppressants. Pneumonitis resolved in 11 participants (78.6%), with a median time to resolution of 37.0 days (range: 9-104 days).

Immune-related colitis

In the All Cancer 500 mg Q4W Population, immune-related colitis (PTs: colitis, diarrhea, and enterocolitis) occurred in 12 participants (2.7%). Colitis was maximum severity Grade 1 in 4 participants (0.9%), Grade 2 in5 participants (1.1%), Grade 3 in 2 participant (0.4%), and Grade 4 in 1 participant (0.2%). Three participants (0.7%) had serious colitis. Colitis led to dose delay in 6 participants (1.3%). Four participants (0.9%) had an event that led to discontinuation of retifanlimab.

The median onset time of observed colitis was 165.5 days (range 11-749 days). Among the 12 participants with colitis, 9 participants (75%) received systemic corticosteroids, including 5 participants (41.7%) who received high dose systemic corticosteroids, and 1 participant (8.3%) received other immunosuppressants (infliximab). Colitis resolved in 8 participants (66.7%), with a median time to resolution of 83.5 days (range: 15-675 days).

Immune-related nephritis

In the All Cancer 500 mg Q4W Population, immune-related nephritis occurred in 9 participants (2%). One of these events occurred in the MCC population. Nephritis was maximum severity Grade 2 in 2 participants (0.4%), Grade 3 in 5 participants (1.1%), and Grade 4 in 2 participants (0.4%). Five participants ((1.1%)

had serious nephritis. Nephritis led to dose delay in 3 participants ((0.7%). Five participants (1.1%) had events that led to discontinuation of retifanlimab.

The median onset time of nephritis was 176.0 days (range: 15-515 days). Among the 9 participants with nephritis, 6 participants (66.7%) received systemic corticosteroids, including 4 participants (44.4%) who received high dose systemic corticosteroids, and no participants received other immunosuppressants. Nephritis resolved in 4 participants (44.4%), with a median time to resolution of 22.5 days (range: 9-136 days).

Immune-related myositis

In the All Cancer 500 mg Q4W Population, immune-related myositis occurred in 3 participants (0.7%). None of these events occurred in the MCC population. Myositis was maximum severity Grade 2 in 2 participants (0.4%) and Grade 3 in 1 participant (0.2%). One participant (0.2%) had serious myositis. Myositis led to dose delay in 2 participants (0.5%). One participant (0.2%) had an event that led to discontinuation of retifanlimab.

The median onset time of myositis was 173.0 days (range: 51-391 days). Among the 3 participants with myositis, all received high dose systemic corticosteroids, and no participants received other immunosuppressants. Myositis resolved in 1 participant (33.3%), with a time to resolution of 13 days.

Guillain-Barré syndrome

In the All Cancer 500 mg Q4W Population, Guillain-Barré syndrome (PTs: demyelinating polyneuropathy and polyneuropathy) occurred in 3 participants (0.7%), of which one event was in a patient with MCC. Guillain Barré syndrome was maximum severity Grade 1 in 2 participants (0.4%) and Grade 3 in 1 participant (0.2%). One participant (0.2%) had serious Guillain Barré syndrome. No events led to dose delay. One participant (0.2%) had an event that led to discontinuation of retifanlimab.

The median onset time of Guillain-Barré syndrome was 51 days (range: 10-338days). Among the 3 participants with Guillain-Barré syndrome, 1 participant (50.0%) received high dose systemic corticosteroids, and no participants received other immunosuppressants. Guillain-Barré syndrome resolved in 1 participant (33%), with a time to resolution of 13 days.

Immune-related pancreatitis

In the All Cancer 500 mg Q4W Population, immune-related pancreatitis of maximum severity Grade 3 occurred in 2 participants (0.4%), of which one event was in a patient with MCC. One participant (0.2%) had serious pancreatitis. No pancreatitis events led to dose delay. One participant (0.2%) had an event that led to discontinuation of retifanlimab.

The median onset time of observed pancreatitis was 128.5 days (range: 29-228 days). Among the 2 participants with pancreatitis, 1 participant (50.0%) received high dose systemic corticosteroids, and no participants received other immunosuppressants. Pancreatitis resolved in 1 participant (50.0%), with a time to resolution of 54 days.

Immune-related uveitis

In the All Cancer 500 mg Q4W Population, uveitis (PTs: iritis and uveitis) maximum severity Grade 2 occurred in 3 participants (0.7%). None of these events occurred in the MCC population. One participant had serious uveitis that led to dose delay. Two participants (0.4%) had an event that led to discontinuation of retifanlimab. The median onset time of observed uveitis was 188 days (range: 35-622 days). All three

participants with uveitis received ophthalmic corticosteroids; no participants received systemic corticosteroids or other immunosuppressants. Uveitis resolved in 2 participants (66.7%), with a median time to resolution of 43.5 days.

Other, rare immune-related adverse events

Other, rare immune-related adverse events occurred in the All Cancer 500 mg Q4W Population as follows (see Table 55): polyarthritis in 3 participants (0.7%; one Grade 1 and two Grade 2 events), arthritis in 1 participant (0.2%; a Grade 3 serious TEAE), eosinophilic fasciitis in 1 participant (0.2%; a Grade 3 serious TEAE), polymyalgia rheumatica in 1 participant (0.2%; Grade 2), immune-related nervous system events occurred in 2 participants (0.4%, 1 radiculopathy and 1 vocal cord paralysis), one participant had an immune-related myocarditis (a serious grade 4 event, which did not resolve with high-dose corticosteroids), a grade 2 pericarditis occurred in 1 participant (0.2%), a serious TEAE of Grade 3 cholangitis occurred in 1 participant (0.2%), and there was one nonserious TEAE of Grade 2 keratitis.

Infusion-related reactions

Infusion-related reactions included diagnosis of infusion-related reactions, symptoms potentially associated with infusion-related reactions, and AEs assessed by the investigator as an infusion related reaction.

Infusion-related reactions occurred in 28 participants (6.2%) in the All Cancer 500 mg Q4W Population, including 5 participants (4.7%) in the MCC Population (see Table 59). In the All Cancer 500 mg Q4W Population, infusion-related reactions led to retifanlimab infusion interruptions in 5 participants (1.1%) and to retifanlimab discontinuation in 2 participants (0.4%). Infusion-related reactions are presented by group term and PT in Table 60.

Table 59: Overall summary of infusion-related reactions

Participants (n [%]) With a:	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Infusion-related reaction	5 (4.7)[a]	23 (6.7)[b]	28 (6.2)[a,]
Treatment-related infusion-related reaction	5 (4.7)	16 (4.6)	21 (4.6)
Serious infusion-related reaction	2 (1.9)	1 (0.3)	3 (0.7)
Grade ≥ 3 infusion-related reaction	2 (1.9)	0 (0.0)	2 (0.4)
Fatal infusion-related reaction	0 (0.0)	0 (0.0)	0 (0.0)
Serious treatment-related infusion-related reaction	2 (1.9)	1 (0.3)	3 (0.7)
Grade ≥ 3 treatment-related infusion-related reaction	2 (1.9)	0 (0.0)	2 (0.4)
Dose interruption due to infusion-related reaction	2 (1.9)	3 (0.9)	5 (1.1)
Infusion interruption due to infusion-related reaction	2 (1.9)	2 (0.6)	4 (0.9)
Dose delayed due to infusion-related reaction	0 (0.0)	1 (0.3)	1 (0.2)
Discontinuation of study drug due to infusion-related reaction	2 (1.9)	0 (0.0)	2 (0.4)
Discontinuation of study drug due to treatment-related infusion-related reaction	2 (1.9)	0 (0.0)	2 (0.4)

Note: In Study INCMGA 0012-101, TEAEs leading to dose delay and infusion interruption were captured as 'drug interruption' and are summarized as 'dose delay.'

Note: Infusion-related reactions include AEs indicating diagnosis of infusion-related reaction that occurred during the treatment period, symptoms of infusion-related reaction that occurred within 1 day of infusion and resolved within 2 days from AE onset, and investigator-assessed infusion-related reactions.

One participant in the Non-MCC 500 mg Q4W Population had an infusion-related reaction to acetyl L-carnitine, which is captured here as an infusion-related reaction.

Table 60: Summary of infusion-related reactions by Group Term and Preferred Term

Group Term Preferred Term, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Participants with any infusion-related reaction	5 (4.7)[a]	23 (6.7)[b]	28 (6.2)[a,]
Diagnosis of infusion reaction	4 (3.7)	7 (2.0)	11 (2.4)
Drug hypersensitivity	1 (0.9)	2 (0.6)	3 (0.7)
Infusion related reaction	3 (2.8)	5 (1.4)	8 (1.8)
Investigator assessed infusion reaction	1 (0.9)	1 (0.3)	2 (0.4)
Pneumonitis	1 (0.9)	0 (0.0)	1 (0.2)
Rash	0 (0.0)	1 (0.3)	1 (0.2)
Symptom of potential infusion reaction	1 (0.9)	16 (4.6)	17 (3.8)
Chest pain	0 (0.0)	1 (0.3)	1 (0.2)
Chills	0 (0.0)	2 (0.6)	2 (0.4)
Dyspnoea	0 (0.0)	1 (0.3)	1 (0.2)
Erythema	0 (0.0)	1 (0.3)	1 (0.2)
Pruritus	0 (0.0)	6 (1.7)	6 (1.3)
Pyrexia	0 (0.0)	6 (1.7)	6 (1.3)
Rash pruritic	1 (0.9)	0 (0.0)	1 (0.2)

Note: Infusion-related reactions include AEs indicating diagnosis of infusion-related reaction that occurred during the treatment period, symptoms of infusion-related reaction that occurred within 1 day of infusion and resolved within 2 days from AE onset, and investigator-assessed infusion-related reactions. Participants were counted once under each group term and PT.

One participant in the Non-MCC 500 mg Q4W Population had an infusion-related reaction to acetyl L-carnitine, which is captured here as an infusion-related reaction.

In the All Cancer 500 mg Q4W Population, infusion-related reactions (IRR) occurred in 28 participants (6.2%). All infusion-related reactions were Grade 1 or 2 in severity with the exception of the following Grade 3 events in 2 participants (0.4%):

- Participant 202001 in Study INCMGA 0012-201 received 2 infusions of retifanlimab 500 mg Q4W without premedication prophylaxis. Following the second infusion administered on Day 28, the participant had 3 delayed TEAEs that the investigator designated as infusion reactions. On Day 36, a Grade 1 TEAE with a PT of infusion-related reaction was reported and on Day 39 was considered resolved. On Day 43, a Grade 2 TEAE with a PT of pneumonitis was reported and on Day 51 was considered resolved. On Day 54, a Grade 3 TEAE with a PT of infusion-related reaction with symptoms of swollen tongue, impaired breathing, and visual impairment was reported; on the same day, the TEAE was considered resolved following treatment with corticosteroids. The study drug was discontinued due to this event. Sponsor medical review of the Grade 3 infusion related reaction determined this event not to be a true infusion-related reaction to retifanlimab based on the duration of the interval from the last retifanlimab infusion on Day 28 and the onset of the reported infusion-related reaction on Day 54.

- Participant 302011 in Study INCMGA 0012 201 had an infusion-related reaction (PT: drug hypersensitivity) during the 14th retifanlimab infusion on Day 365. The participant had not received pre-infusion prophylaxis for this infusion or any prior infusion, and this was the first infusion-related reaction. After 75% of the infusion was completed, the participant had an allergic reaction (rash, cough, and hypertension). The infusion was interrupted, the participant was hospitalized and treated with paracetamol and dexchlorpheniramine maleate, and blood pressure rapidly returned to normal. On the same day as onset, the infusion-related reaction resolved. Retifanlimab was discontinued on Day 414 due to Grade 2 infusion-related reactions (PT: drug hypersensitivity) during the 2 subsequent infusions.

Three participants in the All Cancer 500 mg Q4W Population (0.7%) had serious infusion-related reactions that were considered related to retifanlimab by the investigator: Participants 202001 and 302011 in Study INCMGA 0012-201 (above) and the following participant:

- Participant 006001 in Study INCMGA 0012-203 received 4 infusions of retifanlimab 500 mg Q4W. The participant had NSCLC at baseline and a medical history that included chronic cough, pneumonia, and vocal cord paralysis. The serious Grade 1 infusion related reaction started on Day 1 following the first infusion, despite premedication with paracetamol and diphenhydramine hydrochloride. The event resolved on Day 2. Treatment medications for the infusion-related reaction included methylprednisolone sodium succinate 125 mg IV once and sodium chloride 1000 mL IV once. Piperacillin/tazobactam 4.5 g IV was administered 1 time for possible infection. Retifanlimab administration continued unchanged, and the participant received 3 additional premedicated infusions without recurrence of an infusion related reaction before discontinuing study treatment on Day 118 due to radiographic disease progression.

In the All Cancer 500 mg Q4W Population, time from the most recent retifanlimab infusion to the onset of the infusion-related reaction ranged from 0 to 1 day with the exception of Participant 202001 in Study INCMGA 0012-201 (see summary of this case above). Three participants had drug hypersensitivity to treatments other than retifanlimab (amoxicillin, ciflox, and acetyl L-carnitine), which were captured as infusion-related reactions and are not included in this range. Median time to resolution was 3.0 days (range: 1-97 days) for infusion reactions.

In study INCMGA 0012-203 (n=121 patients included in the All Cancer 500mg Q4W population), retifanlimab was given in a 30-minute infusion, and in the other 4 studies it was given as a 60-minute infusion. The incidence and severity of infusion-related reactions in participants receiving retifanlimab as a 30-minute infusion in Study INCMGA 0012-203 were generally similar to that for a 60-minute infusion (8/121 participants (6.6%) and 20/331 participants (6.0%), respectively).

Of note, 1 of the participants with an IRR after a 30-minute infusion had drug hypersensitivity to acetyl L-carnitine, and 2 participants with an IRR after a 60-minute infusion had drug hypersensitivity to other treatments (ciflox and amoxicillin). For completeness, these participants are included in Table 61.

Table 61: Summary of safety for Retifanlimab 30-minute and 60-minute infusions in the All cancer 500 mg Q4W Population

Participants (n [%]) With a:	30-Minute Infusion (N = 121)	60-Minute Infusion (N = 331)
Infusion-related reaction overall	8 (6.6)	20 (6.0)
Infusion-related reaction during/after first infusion	3 (2.5)	9 (2.7)
Infusion-related reaction during/after first 3 infusions	7 (5.8)	16 (4.8)
Hypersensitivity[a]	1 (0.8)	2 (0.6)
Anaphylactic reaction[b]	0 (0.0)	0 (0.0)
irAE	36 (29.8)	120 (36.3)
Grade 3 or higher irAE	10 (8.3)	35 (10.6)
TEAE	113 (93.4)	314 (94.9)
Grade 3 or higher TEAE	57 (47.1)	145 (43.8)
TEAE leading to discontinuation	19 (15.7)	47 (14.2)

Note: Infusion-related reactions include AEs indicating diagnosis of infusion-related reaction that occurred during the treatment period, symptoms of infusion-related reaction that occurred within 1 day of infusion and resolved within 2 days from AE onset, and investigator-assessed infusion-related reactions.

[a] Includes the PT of drug hypersensitivity. Of note, the PTs of drug hypersensitivity, hypersensitivity, infusion-related hypersensitivity reaction, and Type I hypersensitivity were included in the group term of Diagnosis of Infusion Reaction, which is part of the overall infusion-related reaction frequency.

[b] The PTs of anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock were included in the group term of Diagnosis of Infusion Reaction, which is part of the overall infusion-related reaction frequency.

Long-term adverse effects

At the updated data cutoff dates for the individual studies, the median duration of safety follow-up in the All Cancer 500 mg Q4W Population was 7.6 months (range: 8 days-30 months).

Time to first event onset was analyzed for irAEs based on observed events. The median time to first onset for irAEs in the All Cancer 500 mg Q4W Population ranged from 34 days (immune related nervous system event [paresthesia]) to 690.0 days (myocarditis), consistent with published literature (Haanen et al 2017). Immune-related AEs with first onset > 12 months of initiating retifanlimab treatment were reported in 20 participants (4.4%) in the All Cancer 500 mg Q4W Population and included colitis (4 participants, 0.9%), hyperthyroidism, pneumonitis and skin reactions (3 participants [0.7%] each) and hepatitis and hypothyroidism (2 participants [0.4%] each), and hypophysitis, myocarditis, myositis, nephritis and uveitis (1 participant [0.2%] each). Five of these events were serious, 5 were Grade 3, one was Grade 4. Seven led to retifanlimab discontinuation, and 14 resolved. Details for each first event are provided in Table 62.

Table 62: Immune-related adverse events with first onset > 12 months of initiating Retifanlimab treatment in the All Cancer 500 mg Q4W Population

Study Age/Sex	Group Term (PT)	Worst Grade	Serious (Y/N)	Concomitant Medication for irAEs	Action Taken With the Study Drug Retifanlimab Administration Resumed	Onset Duration
MCC Population						
INCMGA 0012-201	Pneumonitis (pneumonitis)	2	Y	Systemic corticosteroids, including high-dose systemic corticosteroids	Drug interrupted Day 407	Day 368 5 days
INCMGA 0012-201	Nephritis (tubulointerstitial nephritis)	2	N	Systemic corticosteroids, including high-dose systemic corticosteroids	Drug withdrawn NA	Day 515 136 days
INCMGA 0012-201	Hepatitis (hepatitis)	3	Y	None	Drug withdrawn NA	Day 580 87 days
INCMGA 0012-201	Colitis (diarrhoea)	2	N	Systemic corticosteroids	Drug withdrawn NA	Day 406 115 days
INCMGA 0012-201	Hypophysitis (hypophysitis)	3	N	Systemic corticosteroids	Drug withdrawn NA	Day 377 Ongoing
INCMGA 0012-201	Pneumonitis (pneumonitis)	1	N	None	Drug interrupted Day 449	Day 399 47 days
INCMGA 0012-201	Colitis (diarrhoea)	1	N	Systemic corticosteroids	No change NA	Day 731 15 days
INCMGA 0012-201	Hypothyroidism (hypothyroidism)	1	N	None	No change NA	Day 480 30 days
INCMGA 0012-201	Skin reactions (pruritus)	2	N	Systemic corticosteroids	No change NA	Day 589 Ongoing
INCMGA 0012-201	Hypothyroidism (hypothyroidism)	1	N	Endocrine therapy (thyroid)	No change NA	Day 505 Ongoing
All Cancer 500 mg Q4W Population						
INCMGA 0012-101	Hepatitis (hepatitis)	3	Y	Systemic corticosteroids, including high-dose systemic corticosteroids	Drug withdrawn NA	Day 533 10 days
INCMGA 0012-101	Hyperthyroidism (hyperthyroidism)	1	N	Endocrine therapy (thyroid)	Drug interrupted Day 556	Day 502 Ongoing
INCMGA 0012-101	Hyperthyroidism (hyperthyroidism)	2	N	None	No change NA	Day 391 85 days
	Pneumonitis (lung infiltration)	1	N	None	Drug interrupted Day 701	Day 673 28 days
INCMGA 0012-101	Hyperthyroidism (hyperthyroidism)	2	N	None	No change NA	Day 575 42 days
INCMGA 0012-101	Uveitis (uveitis)	3	Y	Ophthalmic corticosteroids	Drug withdrawn NA	Day 622 58 days
INCMGA 0012-104	Myocarditis (myocarditis)	4	Y	Systemic corticosteroids, including high-dose systemic corticosteroids	Drug interrupted NA[a]	Day 690 Ongoing (resolving)

Study Age/Sex	Group Term (PT)	Worst Grade	Serious (Y/N)	Concomitant Medication for irAEs	Action Taken With the Study Drug Retifanlimab Administration Resumed	Onset Duration
INCMGA 0012-203	Myositis (myositis)	2	N	Systemic corticosteroids, including high-dose systemic corticosteroids	Drug interrupted Day 414	Day 391 Ongoing
INCMGA 0012-203	Skin reactions (rash macular)	2	N	Topical and systemic corticosteroids	No change NA	Day 550 25 days
INCMGA 0012-203	Skin reactions (rash)	2	N	None	Drug interrupted Day 506	Day 488 47 days
	Colitis (diarrhoea)	3	N	Systemic corticosteroids	Drug withdrawn NA	Day 565 Ongoing
INCMGA 0012-203	Colitis (colitis)	1	N	None	NA: onset 34 days after last retifanlimab dose	Day 749 Ongoing

[a]The participant completed the Protocol-specified treatment period on Day 661.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

All Cancer 500 mg Q4W Population

Serious TEAEs occurred in 165 participants (36.5%) in the All Cancer 500 mg Q4W Population. The most frequent (>1%) serious TEAEs were urinary tract infection (2.4%), pneumonia (2.2%), anaemia (1.5%) and abdominal pain, asthenia and sepsis (1.3% each).

Treatment-related serious TEAEs are summarized in Table 63. Treatment-related serious TEAEs occurred in 33 participants (7.3%) in the All Cancer 500 mg Q4W Population. The most frequent treatment-related serious TEAE were hepatitis and pneumonitis in 3 patients each (0.7%).

MCC population

Serious TEAEs occurred in 28 participants (26.2%) in the MCC Population. The most frequent (>1%) serious TEAEs were asthenia and COVID 19 (2.8 each %), and urinary tract infection, pneumonitis, atrial fibrillation, and bone pain (1.9% each).

Treatment-related serious TEAEs occurred in 13 participants (12.1%) in the MCC Population (see Table 63).

Table 63: Treatment-related Serious TEAEs by MedDRA Preferred Term

MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Hepatitis	1 (0.9)	2 (0.6)	3 (0.7)
Pneumonitis	1 (0.9)	2 (0.6)	3 (0.7)
Adrenal insufficiency	1 (0.9)	1 (0.3)	2 (0.4)
Hepatocellular injury	0 (0.0)	2 (0.6)	2 (0.4)
Infusion-related reaction	1 (0.9)	1 (0.3)	2 (0.4)
Abdominal pain	0 (0.0)	1 (0.3)	1 (0.2)

MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Acute kidney injury	0 (0.0)	1 (0.3)	1 (0.2)
Amylase increased	1 (0.9)	0 (0.0)	1 (0.2)
Arthritis	0 (0.0)	1 (0.3)	1 (0.2)
Autoimmune hepatitis	0 (0.0)	1 (0.3)	1 (0.2)
Colitis	1 (0.9)	0 (0.0)	1 (0.2)
Concomitant disease progression	1 (0.9)	0 (0.0)	1 (0.2)
Demyelinating polyneuropathy[a]	1 (0.9)	0 (0.0)	1 (0.2)
Diabetic ketoacidosis	1 (0.9)	0 (0.0)	1 (0.2)
Diarrhoea	0 (0.0)	1 (0.3)	1 (0.2)
Drug hypersensitivity	1 (0.9)	0 (0.0)	1 (0.2)
Eosinophilic fasciitis	1 (0.9)	0 (0.0)	1 (0.2)
Extrapyramidal disorder	0 (0.0)	1 (0.3)	1 (0.2)
Gastric haemorrhage	1 (0.9)	0 (0.0)	1 (0.2)
Herpes zoster	0 (0.0)	1 (0.3)	1 (0.2)
Hyperbilirubinaemia	0 (0.0)	1 (0.3)	1 (0.2)
Hypophysitis	0 (0.0)	1 (0.3)	1 (0.2)
Immune-mediated enterocolitis	0 (0.0)	1 (0.3)	1 (0.2)

Deaths

Table 64: Summary of deaths

Variable, n (%)	MCC Population (N = 107)	All Cancer 500 mg Q4W Population (N = 452)
Participants treated	107 (100)	452 (100)
Participants who died	33 (30.8)	213 (47.1)
Primary reason		
Disease progression	28 (26.2)	172 (38.1)
AE	0 (0.0)	6 (1.3)
Other	4 (3.7)	33 (7.3)
Unknown	1 (0.9)	2 (0.4)
Participants with death records on treatment	13 (12.1)	83 (18.4)
Primary reason		
Disease progression	8 (7.5)	56 (12.4)
AE	0 (0.0)	4 (0.9)
Other	4 (3.7)	22 (4.9)
Unknown	1 (0.9)	1 (0.2)

Note: There were differences in the eCRF design between studies used in the pooled analysis. There was not an option for "AE" or "Unknown" in the eCRF for several studies, and deaths due to AEs or unknown causes were entered as "Other." Refer to ISS Listing 2.6 for a description of the "Other" reasons.

Table 65: Summary of fatal TEAEs by MedDRA SOC and PT

MedDRA SOC MedDRA PT, n (%)	MCC Population (N = 107)	All Cancer 500 mg Q4W Population (N = 452)
Number (%) of participants with any fatal TEAE	4 (3.7)	25 (5.5)
Cardiac disorders	0 (0.0)	1 (0.2)
Right ventricular failure	0 (0.0)	1 (0.2)
Gastrointestinal disorders	0 (0.0)	1 (0.2)
Large intestinal stenosis	0 (0.0)	1 (0.2)
General disorders and administration site conditions	2 (1.9)	4 (0.9)
Asthenia	1 (0.9)	1 (0.2)
Concomitant disease progression	1 (0.9)	1 (0.2)
Death	0 (0.0)	1 (0.2)
General physical health deterioration	0 (0.0)	1 (0.2)
Infections and infestations	1 (0.9)	7 (1.5)

COVID-19	1 (0.9)	1 (0.2)
COVID-19 pneumonia	0 (0.0)	1 (0.2)
Pelvic infection	0 (0.0)	1 (0.2)
Peritonitis	0 (0.0)	1 (0.2)
Pneumocystis jirovecii pneumonia	0 (0.0)	1 (0.2)
Sepsis	0 (0.0)	1 (0.2)
Septic shock	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.2)
Femur fracture	0 (0.0)	1 (0.2)
Metabolism and nutrition disorders	0 (0.0)	1 (0.2)
Hypercalcaemia	0 (0.0)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	4 (0.9)
Lymphangiosis carcinomatosa	0 (0.0)	1 (0.2)
Pancreatic carcinoma	0 (0.0)	1 (0.2)
Tumour embolism	0 (0.0)	1 (0.2)
Tumour hyperprogression	0 (0.0)	1 (0.2)
Nervous system disorders	0 (0.0)	1 (0.2)
Cerebrovascular accident	0 (0.0)	1 (0.2)
Renal and urinary disorders	0 (0.0)	1 (0.2)
Renal failure	0 (0.0)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (0.9)	3 (0.7)
Acute respiratory failure	1 (0.9)	1 (0.2)
Interstitial lung disease	0 (0.0)	1 (0.2)
Pleural effusion	0 (0.0)	1 (0.2)
Vascular disorders	0 (0.0)	1 (0.2)
Haemorrhage	0 (0.0)	1 (0.2)

Fatal TEAEs occurred in 25 participants (5.5%) in the All Cancer 500 mg Q4W Population (see Table 65), of which 4 occurred in the MCC population. Three fatal AEs were assessed to be related to retifanlimab according to the investigator:

- a patient in the SCAC population with lymphangiosis carcinomatosa, which was considered to be a possible manifestation of treatment-induced hyperprogression by the investigator. At baseline the patient had pulmonary metastases and 1 week before study treatment she was diagnosed with a pulmonary infection. On Day 11 of the study a CT scan made because of symptoms of dizziness, decline general condition, anorexia, and dyspnoea showed lymphangiosis carcinomatosa. The patient refused further evaluation and died on Day 38.
- a patient with MCC who was also diagnosed 4 years earlier with CLL, which was stable and required no treatment. On the day of the third treatment with retifanlimab, the patient was hospitalized

because of progressive pancytopenia due to progression of CLL. Treatment with retifanlimab was discontinued and the patient died on day 97 due to progressive disease, either MCC or CLL.

- an event of tumour hyperprogression was considered by the investigator to be possibly related to retifanlimab due to rapid progression of the underlying disease (EC). An autopsy was not performed.

2.6.8.4. Laboratory findings

Laboratory data were classified according to NCI CTCAE v5.0 for all the included studies.

Haematology

In the clinical studies of retifanlimab, clinical haematology evaluations were performed at screening and/or Cycle 1 Day 1 and then Day 1 of every subsequent cycle at a minimum. A summary of treatment-emergent worsening haematology parameters is presented in Table 66.

Table 66: Treatment-emergent worsening of CTCAE-graded haematology parameters

Laboratory Parameter, n/N (%)	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hemoglobin (decreased)	42/101 (41.6)	1/101 (1.0)	134/331 (40.5)	15/331 (4.5)	176/432 (40.7)	16/432 (3.7)
Lymphocytes (decreased)	31/100 (31.0)	11/100 (11.0)	124/326 (38.0)	34/326 (10.4)	155/426 (36.4)	45/426 (10.6)
Leukocytes (decreased)	13/100 (13.0)	1/100 (1.0)	55/330 (16.7)	3/330 (0.9)	68/430 (15.8)	4/430 (0.9)
Neutrophils (decreased)	14/100 (14.0)	3/100 (3.0)	33/327 (10.1)	3/327 (0.9)	47/427 (11.0)	6/427 (1.4)
Platelets (decreased)	18/100 (18.0)	0/100 (0.0)	23/330 (7.0)	0/330 (0.0)	41/430 (9.5)	0/430 (0.0)
Hemoglobin (increased)	2/101 (2.0)	0/101 (0.0)	7/331 (2.1)	0/331 (0.0)	9/432 (2.1)	0/432 (0.0)
Lymphocytes (increased)	2/100 (2.0)	0/100 (0.0)	3/326 (0.9)	0/326 (0.0)	5/426 (1.2)	0/426 (0.0)
Leukocytes (increased)	0/100 (0.0)	0/100 (0.0)	0/330 (0.0)	0/330 (0.0)	0/430 (0.0)	0/430 (0.0)

Note: Worst CTCAE grade postbaseline. If baseline grade is missing, any postbaseline abnormality (Grade 1-4) is considered worsening from baseline.
Note: Denominator is total number of participants with both baseline and postbaseline assessments within each parameter.

Clinical chemistry

In the clinical studies of retifanlimab, clinical chemistry evaluations were performed at screening and/or Cycle 1 Day 1, Day 1 of every subsequent cycle, and EOT at a minimum. A summary of treatment-emergent worsening clinical chemistry parameters is presented in Table 67.

Grade 1 and 2 amylase and lipase elevations are by definition asymptomatic per CTCAE criteria. There were 12 participants in the All Cancer 500 mg Q4W Population with a Grade 3 elevation in amylase and/or lipase. The reported frequency of pancreatitis in the All Cancer 500mg Q4W population was only 0.4% (2 patients). There were no signs of pancreatitis in the other patients with an increased amylase or lipase.

Table 67: Treatment-emergent worsening of CTCAE-graded chemistry parameters

Laboratory Parameter, n/N (%)	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
AST (increased)	28/101 (27.7)	3/101 (3.0)	101/333 (30.3)	6/333 (1.8)	129/434 (29.7)	9/434 (2.1)
Albumin (decreased)	23/100 (23.0)	0/100 (0.0)	103/327 (31.5)	5/327 (1.5)	126/427 (29.5)	5/427 (1.2)
Magnesium (decreased)	0/0 (0.0)	0/0 (0.0)	36/123 (29.3)	5/123 (4.1)	36/123 (29.3)	5/123 (4.1)
Sodium (decreased)	26/101 (25.7)	3/101 (3.0)	97/330 (29.4)	4/330 (1.2)	123/431 (28.5)	7/431 (1.6)
ALP (increased)	21/99 (21.2)	2/99 (2.0)	93/331 (28.1)	5/331 (1.5)	114/430 (26.5)	7/430 (1.6)
Cholesterol (increased)[a]	19/77 (24.7)	0/77 (0.0)	41/152 (27.0)	2/152 (1.3)	60/229 (26.2)	2/229 (0.9)
Lipase (increased)	37/98 (37.8)	5/98 (5.1)	70/314 (22.3)	7/314 (2.2)	107/412 (26.0)	12/412 (2.9)
Urate (increased)	25/96 (26.0)	NA	75/298 (25.2)	NA	100/394 (25.4)	NA
ALT (increased)	26/100 (26.0)	4/100 (4.0)	81/333 (24.3)	8/333 (2.4)	107/433 (24.7)	12/433 (2.8)
Creatinine (increased)	22/101 (21.8)	0/101 (0.0)	85/332 (25.6)	6/332 (1.8)	107/433 (24.7)	6/433 (1.4)
Triglycerides (increased)[a]	14/76 (18.4)	0/76 (0.0)	41/151 (27.2)	4/151 (2.6)	55/227 (24.2)	4/227 (1.8)
Lactate dehydrogenase (increased)	19/99 (19.2)	NA	51/201 (25.4)	NA	70/300 (23.3)	NA
Derived calcium corrected for albumin (increased)	10/99 (10.1)	1/99 (1.0)	84/319 (26.3)	1/319 (0.3)	94/418 (22.5)	2/418 (0.5)
Amylase (increased)	22/96 (22.9)	1/96 (1.0)	64/293 (21.8)	3/293 (1.0)	86/389 (22.1)	4/389 (1.0)
Potassium (increased)	21/100 (21.0)	1/100 (1.0)	63/330 (19.1)	2/330 (0.6)	84/430 (19.5)	3/430 (0.7)
Potassium (decreased)	15/100 (15.0)	2/100 (2.0)	47/330 (14.2)	8/330 (2.4)	62/430 (14.4)	10/430 (2.3)
Bilirubin (increased)	14/100 (14.0)	0/100 (0.0)	39/331 (11.8)	8/331 (2.4)	53/431 (12.3)	8/431 (1.9)
Derived calcium corrected for albumin (decreased)	13/99 (13.1)	1/99 (1.0)	30/319 (9.4)	1/319 (0.3)	43/418 (10.3)	2/418 (0.5)
Glucose (decreased)	6/100 (6.0)	0/100 (0.0)	36/327 (11.0)	3/327 (0.9)	42/427 (9.8)	3/427 (0.7)
Magnesium (increased)	0/0 (0.0)	0/0 (0.0)	7/123 (5.7)	0/123 (0.0)	7/123 (5.7)	0/123 (0.0)
Sodium (increased)	2/101 (2.0)	0/101 (0.0)	15/330 (4.5)	3/330 (0.9)	17/431 (3.9)	3/431 (0.7)

Note: Denominator is total number of participants with both baseline and postbaseline assessments within each parameter.
Note: Worst CTCAE grade postbaseline. If baseline grade is missing, any postbaseline abnormality (Grade 1-4) is considered worsening from baseline. NA indicates CTCAE Grade 3 or 4 is not applicable to the parameter.
[a] Fasting was required for the lipid panel test in Studies INCMGA 0012-201, INCMGA 0012-202, and INCMGA 0012-203. Study INCMGA 0012-101 did not require cholesterol or triglycerides testing per Protocol.

Other laboratory test results

Thyroid parameters

In all clinical studies, thyroid parameters were assessed serially given the relative frequency of clinical and subclinical abnormalities seen with the PD-(L)1 inhibitor class. Specifically, testing was done at screening and/or Cycle 1 Day 1; at a minimum on Day 1 of every subsequent cycle in Studies INCMGA 0012-101, INCMGA 0012-104, and INCMGA 0012-201; or on Day 1 of every third cycle in Studies INCMGA 0012-202 and INCMGA 0012-203; and at EOT.

Table 68: Summary of Thyroid-Stimulating Hormone values on-study

Variable, n (%)	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
	Baseline	On-Treatment	Baseline	On-Treatment	Baseline	On-Treatment
TSH > ULN	5 (4.8)	27 (25.2)	36 (10.4)	85 (24.6)	41 (9.1)	112 (24.8)
TSH > 3 × ULN	0 (0.0)	12 (11.2)	6 (1.7)	38 (11.0)	6 (1.3)	50 (11.1)
TSH > 10 × ULN	0 (0.0)	3 (2.8)	3 (0.9)	23 (6.7)	3 (0.7)	26 (5.8)
TSH < LLN	2 (1.9)	23 (21.5)	20 (5.8)	60 (17.4)	22 (4.9)	83 (18.4)
TSH > ULN and TSH < LLN	NA	10 (9.3)	NA	20 (5.8)	NA	30 (6.6)
Normal	98 (91.6)	57 (53.3)	286 (82.9)	156 (45.2)	384 (85.0)	213 (47.1)
Missing	2 (1.9)	10 (9.3)	3 (0.9)	64 (18.6)	5 (1.1)	74 (16.4)

Coagulation parameters

Coagulation panels were performed at a minimum at screening and at follow-up. Treatment emergent worsening of coagulation parameters among the participants with available data in the safety evaluable population in Study INCMGA 0012-201 (MCC population) are shown in Table 69.

Table 69: Treatment-emergent worsening of coagulation laboratory abnormalities (Safety Evaluable Population Study INCMGA 0012-201)

Parameter, n (%)	Total N = 107				
	n	Any Grade	Grade 1	Grade 2	Grade 3
Activated partial thromboplastin time (increased)	43	3 (7.0)	1 (2.3)	2 (4.7)	0 (0.0)
Partial thromboplastin time (increased)	22	2 (9.1)	1 (4.5)	1 (4.5)	0 (0.0)
Prothrombin intl. normalized ratio (increased)	73	4 (5.5)	3 (4.1)	1 (1.4)	0 (0.0)

Vital signs

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.

In Study INCMGA 0012-201, among the 107 participants with MCC in the safety evaluable population, 18 participants had alert vital sign values (value outside the normal range and > 25% change from baseline; see Table 70).

Table 70: Summary of alert vital signs at any time on study in Study INCMGA 0012-201

Variable, n	Chemotherapy-Naïve		Total (N = 107)
	FAS (N = 65)	Total (N = 101)	
Systolic blood pressure	4	8	9
Diastolic blood pressure	2	2	2
Pulse rate	4	5	5
Respiratory rate	2	4	4

Electrocardiograms

The All Cancer 500 mg Q4W Population included 1 participant with a Grade 1 TEAE of ECG T-wave inversion that was an isolated finding of no clinical significance that occurred concurrently with hypothyroidism.

As retifanlimab is a monoclonal antibody, a thorough QT-study was not performed, in accordance with ICH E14 Q&A (R3; 2015). A cardiac safety analysis was performed using 12-lead ECG data from participants treated with retifanlimab at doses up to 10 mg/kg Q2W and 750 mg Q4W in Study INCMGA 0012-101. 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 (i.e., the PR and QRS intervals).

Electrocardiograms were performed in each of the studies, and results available as of the respective data cut-off dates suggest no clinically relevant changes from baseline in the QTc interval and no meaningful effect of retifanlimab on ECG parameters.

In Study INCMGA 0012-201, 12-lead ECGs were performed at screening, Cycle 1 Day 1, and Day 1 of every third cycle. Among the 107 participants in the safety evaluable population, most participants had normal ECG values at all timepoints assessed. Changes were generally small, and no clinically meaningful trends were observed. At any time on study, of the 51 participants with QTcF values during the study, 5 participants (9.8%) had a measured QTcF value ≥ 480 milliseconds, 2 participants (3.9%) had a measured QTcF value ≥ 500 milliseconds, 8 participants (15.7%) had a QTcF change from baseline of ≥ 30 milliseconds, and 3 participants (5.9%) had a QTcF change from baseline of ≥ 60 milliseconds. Eight participants had alert ECG values (value outside the normal range and > 25% [> 30% for QRS] change from baseline):

- Two participants had alert PR values (244-280 milliseconds; 33.3%-42.9% increase from baseline).
- Four participants had alert QRS interval values (43-192 milliseconds; 48.8% decrease to 67.0% increase from baseline).
- Two participants had alert QTcF interval values (477-535 milliseconds; 30.2% 51.4% increase from baseline).

One participant had an alert QT value (509 milliseconds; 57.6% increase from baseline).

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Demographic characteristics

Age

The All Cancer 500 mg Q4W Population was composed of 188 participants (41.6%) who were < 65 years of age and 264 participants (58.4%) who were ≥ 65 years of age; 347 participants (76.8%) were < 75 years of age and 105 participants (23.2%) were ≥ 75 years of age (see Table 71). 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 who were ≥ 75 years of age had higher frequencies of serious TEAEs, Grade 3 or higher TEAEs, fatal TEAEs, and TEAEs leading to dose delay and discontinuation than participants who were < 75 years of age (see Table 71).

No clinically meaningful differences were observed in frequency or severity of infusion-related reactions between age subgroups.

Subgroup analyses comparing the < 85 years of age subgroup to the ≥ 85 years of age subgroup for TEAEs, irAEs, and infusion-related reactions were also performed. However, there were very few participants in the ≥ 85 years of age subgroup for the All Cancer 500 mg Q4W Population (4.9%), precluding meaningful comparisons of these subgroups.

Table 71: Safety subgroup analyses by age

Variable	MCC 500 mg Q4W (N = 107)				Non-MCC 500 mg Q4W (N = 345)				All Cancer 500 mg Q4W (N = 452)			
	< 65 Years (N = 27)	≥ 65 Years (N = 80)	< 75 Years (N = 67)	≥ 75 Years (N = 40)	< 65 Years (N = 161)	≥ 65 Years (N = 184)	< 75 Years (N = 280)	≥ 75 Years (N = 65)	< 65 Years (N = 188)	≥ 65 Years (N = 264)	< 75 Years (N = 347)	≥ 75 Years (N = 105)
Median duration of retifanlimab treatment (min, max), days	197.0 (1, 733)	348.5 (1, 731)	309.0 (1, 733)	324.0 (1, 731)	113.0 (1, 736)	154.5 (1, 823)	113.5 (1, 823)	197.0 (1, 729)	116.0 (1, 736)	197.0 (1, 823)	141.0 (1, 823)	202.0 (1, 731)
Participants (n [%]) with TEAEs:												
Any TEAE	22 (81.5)	74 (92.5)	59 (88.1)	37 (92.5)	154 (95.7)	177 (96.2)	267 (95.4)	64 (98.5)	176 (93.6)	251 (95.1)	326 (93.9)	101 (96.2)
Treatment-related TEAE	17 (63.0)	55 (68.8)	47 (70.1)	25 (62.5)	104 (64.6)	125 (67.9)	182 (65.0)	47 (72.3)	121 (64.4)	180 (68.2)	229 (66.0)	72 (68.6)
Serious TEAE	5 (18.5)	23 (28.8)	16 (23.9)	12 (30.0)	62 (38.5)	75 (40.8)	103 (36.8)	34 (52.3)	67 (35.6)	98 (37.1)	119 (34.3)	46 (43.8)
≥ Grade 3 TEAE	8 (29.6)	26 (32.5)	22 (32.8)	12 (30.0)	75 (46.6)	93 (50.5)	130 (46.4)	38 (58.5)	83 (44.1)	119 (45.1)	152 (43.8)	50 (47.6)
Fatal TEAE	0 (0.0)	4 (5.0)	1 (1.5)	3 (7.5)	10 (6.2)	11 (6.0)	16 (5.7)	5 (7.7)	10 (5.3)	15 (5.7)	17 (4.9)	8 (7.6)
Serious treatment-related TEAE	4 (14.8)	9 (11.3)	9 (13.4)	4 (10.0)	7 (4.3)	13 (7.1)	10 (3.6)	10 (15.4)	11 (5.9)	22 (8.3)	19 (5.5)	14 (13.3)
≥ Grade 3 treatment-related TEAE	5 (18.5)	13 (16.3)	14 (20.9)	4 (10.0)	21 (13.0)	24 (13.0)	31 (11.1)	14 (21.5)	26 (13.8)	37 (14.0)	45 (13.0)	18 (17.1)
TEAE leading to dose interruption	5 (18.5)	35 (43.8)	23 (34.3)	17 (42.5)	45 (28.0)	59 (32.1)	79 (28.2)	25 (38.5)	50 (26.6)	94 (35.6)	102 (29.4)	42 (40.0)
TEAE leading to infusion interruption	2 (7.4)	1 (1.3)	2 (3.0)	1 (2.5)	1 (0.6)	1 (0.5)	2 (0.7)	0 (0.0)	3 (1.6)	2 (0.8)	4 (1.2)	1 (1.0)
TEAE leading to dose delay[a]	4 (14.8)	34 (42.5)	22 (32.8)	16 (40.0)	44 (27.3)	58 (31.5)	77 (27.5)	25 (38.5)	48 (25.5)	92 (34.8)	99 (28.5)	41 (39.0)
TEAE leading to discontinuation	5 (18.5)	17 (21.3)	11 (16.4)	11 (27.5)	16 (9.9)	28 (15.2)	28 (10.0)	16 (24.6)	21 (11.2)	45 (17.0)	39 (11.2)	27 (25.7)
Treatment-related TEAE leading to discontinuation	5 (18.5)	11 (13.8)	9 (13.4)	7 (17.5)	8 (5.0)	14 (7.6)	12 (4.3)	10 (15.4)	13 (6.9)	25 (9.5)	21 (6.1)	17 (16.2)
Participants (n [%]) with irAEs:[b]												
Any irAE	9 (33.3)	33 (41.3)	28 (41.8)	14 (35.0)	51 (31.7)	63 (34.2)	90 (32.1)	24 (36.9)	60 (31.9)	96 (36.4)	118 (34.0)	38 (36.2)
Serious irAE	4 (14.8)	8 (10.0)	9 (13.4)	3 (7.5)	7 (4.3)	12 (6.5)	10 (3.6)	9 (13.8)	11 (5.9)	20 (7.6)	19 (5.5)	12 (11.4)
≥ Grade 3 irAE	4 (14.8)	9 (11.3)	10 (14.9)	3 (7.5)	15 (9.3)	17 (9.2)	23 (8.2)	9 (13.8)	19 (10.1)	26 (9.8)	33 (9.5)	12 (11.4)
Fatal irAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.4)	0 (0.0)	1 (1.0)
irAE leading to dose interruption	0 (0.0)	14 (17.5)	10 (14.9)	4 (10.0)	9 (5.6)	16 (8.7)	18 (6.4)	7 (10.8)	9 (4.8)	30 (11.4)	28 (8.1)	11 (10.5)
irAE leading to dose delay	0 (0.0)	14 (17.5)	10 (14.9)	4 (10.0)	9 (5.6)	16 (8.7)	18 (6.4)	7 (10.8)	9 (4.8)	30 (11.4)	28 (8.1)	11 (10.5)
irAE leading to discontinuation	4 (14.8)	8 (10.0)	7 (10.4)	5 (12.5)	7 (4.3)	11 (6.0)	11 (3.9)	7 (10.8)	11 (5.9)	19 (7.2)	18 (5.2)	12 (11.4)

[a] In Study INCMGA 0012-101, TEAEs leading to dose delay and infusion interruption were captured as 'drug interruption' and are summarized as 'dose delay'.

[b] Immune-related AEs were identified using predefined PTs regardless of investigator's assessment of causality.

Table 72: TEAEs by age group (All Cancer 500 mg Q4W Population)

MedDRA Terms Age	Age < 65 number (percentage) N = 188	Age 65-74 number (percentage) N = 159	Age 75-84 number (percentage) N = 83	Age 85+ number (percentage) N = 22
Total AEs	176 (93.6)	150 (94.3)	80 (96.4)	21 (95.5)
Serious AEs – Total	67 (35.6)	52 (32.7)	34 (41.0)	12 (54.5)
- Fatal	10 (5.3)	7 (4.4)	6 (7.2)	2 (9.1)
- Hospitalization/prolong existing hospitalization	66 (35.1)	50 (31.4)	31 (37.3)	11 (50.0)
- Life-threatening	9 (4.8)	3 (1.9)	0 (0.0)	0 (0.0)
- Disability/incapacity	4 (2.1)	1 (0.6)	0 (0.0)	0 (0.0)
- Other (medically significant)	11 (5.9)	9 (5.7)	4 (4.8)	2 (9.1)
AE leading to drop-out	21 (11.2)	18 (11.3)	19 (22.9)	8 (36.4)
Psychiatric disorders (SOC)	23 (12.2)	14 (8.8)	12 (14.5)	1 (4.5)
Nervous system disorders (SOC)	43 (22.9)	36 (22.6)	20 (24.1)	4 (18.2)
Accidents and injuries (SMQ)	7 (3.7)	14 (8.8)	11 (13.3)	2 (9.1)
Cardiac disorders (SOC)	7 (3.7)	10 (6.3)	5 (6.0)	1 (4.5)
Vascular disorders (SOC)	24 (12.8)	21 (13.2)	10 (12.0)	3 (13.6)
Cerebrovascular disorders[a]	1 (0.5)	3 (1.9)	1 (1.2)	0 (0.0)
Infections and infestations (SOC)	75 (39.9)	64 (40.3)	39 (47.0)	9 (40.9)
Anticholinergic syndrome (PT)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quality of life decreased (PT)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[b]	9 (4.8)	15 (9.4)	11 (13.3)	1 (4.5)

[a] SMQ of central nervous system vascular disorders.

[b] Combined PTs of ankle fracture, ataxia, dizziness, dizziness postural, fall, femoral neck fracture, femur fracture, hand fracture, humerus fracture, loss of consciousness, lumbar vertebral fracture, orthostatic hypotension, radius fracture, spinal compression fracture, spinal fracture, syncope, traumatic fracture, upper limb fracture, vertigo positional, wrist fracture.

Sex

The All Cancer 500 mg Q4W Population was composed of 192 male (42.5%) and 260 female (57.5%) participants. Median durations of retifanlimab treatment were similar for male and female participants. Overall, the frequency and severity of TEAEs and irAEs was generally similar between male and female participants (see Table 73). The difference in irAEs between male and female participants in the All Cancer 500 mg Q4W Population is attributable to the higher incidence of hyperthyroidism and hypothyroidism in female participants (8.1% and 12.3%, respectively) than male participants (2.6% and 7.3%, respectively). There was no increase, however, in the rate of serious, severe (⩾ Grade 3), or fatal irAEs in female participants treated with retifanlimab.

No clinically meaningful differences were observed in frequency or severity of infusion-related reactions between sex subgroups.

Table 73: Safety subgroup analyses by sex

Variable	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
	Male (N = 73)	Female (N = 34)	Male (N = 119)	Female (N = 226)	Male (N = 192)	Female (N = 260)
Median duration of retifanlimab treatment (min, max), days	369.0 (1, 733)	207.5 (1, 731)	114.0 (1, 736)	141.5 (1, 823)	174.0 (1, 736)	145.0 (1, 823)
Participants (n [%]) with TEAEs:						
Any TEAE	65 (89.0)	31 (91.2)	110 (92.4)	221 (97.8)	175 (91.1)	252 (96.9)
Treatment-related TEAE	48 (65.8)	24 (70.6)	68 (57.1)	161 (71.2)	116 (60.4)	185 (71.2)
Serious TEAE	20 (27.4)	8 (23.5)	44 (37.0)	93 (41.2)	64 (33.3)	101 (38.8)
≥ Grade 3 TEAE	25 (34.2)	9 (26.5)	53 (44.5)	115 (50.9)	78 (40.6)	124 (47.7)
Fatal TEAE	2 (2.7)	2 (5.9)	10 (8.4)	11 (4.9)	12 (6.3)	13 (5.0)
Serious treatment-related TEAE	9 (12.3)	4 (11.8)	7 (5.9)	13 (5.8)	16 (8.3)	17 (6.5)
≥ Grade 3 treatment-related TEAE	13 (17.8)	5 (14.7)	12 (10.1)	33 (14.6)	25 (13.0)	38 (14.6)
TEAE leading to dose interruption	29 (39.7)	11 (32.4)	28 (23.5)	76 (33.6)	57 (29.7)	87 (33.5)
TEAE leading to infusion interruption	1 (1.4)	2 (5.9)	0 (0.0)	2 (0.9)	1 (0.5)	4 (1.5)
TEAE leading to dose delay[a]	28 (38.4)	10 (29.4)	28 (23.5)	74 (32.7)	56 (29.2)	84 (32.3)
TEAE leading to discontinuation	14 (19.2)	8 (23.5)	13 (10.9)	31 (13.7)	27 (14.1)	39 (15.0)
Treatment-related TEAE leading to discontinuation	10 (13.7)	6 (17.6)	6 (5.0)	16 (7.1)	16 (8.3)	22 (8.5)
Participants (n [%]) with irAEs:[b]						
Any irAE	26 (35.6)	16 (47.1)	30 (25.2)	84 (37.2)	56 (29.2)	100 (38.5)
Serious irAE	9 (12.3)	3 (8.8)	6 (5.0)	13 (5.8)	15 (7.8)	16 (6.2)
≥ Grade 3 irAE	9 (12.3)	4 (11.8)	9 (7.6)	23 (10.2)	18 (9.4)	27 (10.4)
Fatal irAE	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)
irAE leading to dose interruption	11 (15.1)	3 (8.8)	5 (4.2)	20 (8.8)	16 (8.3)	23 (8.8)
irAE leading to dose delay	11 (15.1)	3 (8.8)	5 (4.2)	20 (8.8)	16 (8.3)	23 (8.8)
irAE leading to discontinuation	7 (9.6)	5 (14.7)	4 (3.4)	14 (6.2)	11 (5.7)	19 (7.3)

[a] In Study INCMGA 0012-101, TEAEs leading to dose delay and infusion interruption were captured as 'drug interruption' and are summarized as 'dose delay.'
[b] Immune-related AEs were identified using predefined PTs regardless of investigator's assessment of causality.

Race

The All Cancer 500 mg Q4W Population was composed of 343 Caucasian participants (75.9%), 109 non Caucasian participants (24.1% including those with race "unknown," i.e., due to local privacy regulations). The median duration of retifanlimab treatment was similar for Caucasian participants and non-Caucasian participants (see Table 74). Generally, no clinically meaningful differences were observed in frequency or severity of TEAEs or irAEs between race subgroups.

No clinically meaningful differences were observed in frequency or severity of infusion-related reactions between race subgroups.

Table 74: Safety subgroup analyses by race

Variable	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
	Caucasian (N = 84)	Other[a] (N = 23)	Caucasian (N = 259)	Other[a] (N = 86)	Caucasian (N = 343)	Other[a] (N = 109)
Median duration of retifanlimab treatment (min, max), days	293.5 (1, 733)	369.0 (29, 729)	139.0 (1, 823)	143.0 (1, 729)	162.0 (1, 823)	167.0 (1, 729)
Participants (n [%]) with TEAEs:						
Any TEAE	74 (88.1)	22 (95.7)	246 (95.0)	85 (98.8)	320 (93.3)	107 (98.2)
Treatment-related TEAE	51 (60.7)	21 (91.3)	168 (64.9)	61 (70.9)	219 (63.8)	82 (75.2)
Serious TEAE	19 (22.6)	9 (39.1)	100 (38.6)	37 (43.0)	119 (34.7)	46 (42.2)
≥ Grade 3 TEAE	26 (31.0)	8 (34.8)	126 (48.6)	42 (48.8)	152 (44.3)	50 (45.9)
Fatal TEAE	2 (2.4)	2 (8.7)	19 (7.3)	2 (2.3)	21 (6.1)	4 (3.7)
Serious treatment-related TEAE	7 (8.3)	6 (26.1)	14 (5.4)	6 (7.0)	21 (6.1)	12 (11.0)
≥ Grade 3 treatment-related TEAE	13 (15.5)	5 (21.7)	37 (14.3)	8 (9.3)	50 (14.6)	13 (11.9)
TEAE leading to dose interruption	31 (36.9)	9 (39.1)	79 (30.5)	25 (29.1)	110 (32.1)	34 (31.2)
TEAE leading to infusion interruption	1 (1.2)	2 (8.7)	1 (0.4)	1 (1.2)	2 (0.6)	3 (2.8)
TEAE leading to dose delay[b]	30 (35.7)	8 (34.8)	78 (30.1)	24 (27.9)	108 (31.5)	32 (29.4)
TEAE leading to discontinuation	14 (16.7)	8 (34.8)	38 (14.7)	6 (7.0)	52 (15.2)	14 (12.8)
Treatment-related TEAE leading to discontinuation	9 (10.7)	7 (30.4)	19 (7.3)	3 (3.5)	28 (8.2)	10 (9.2)
Participants (n [%]) with irAEs:[c]						
Any irAE	34 (40.5)	8 (34.8)	85 (32.8)	29 (33.7)	119 (34.7)	37 (33.9)
Serious irAE	8 (9.5)	4 (17.4)	14 (5.4)	5 (5.8)	22 (6.4)	9 (8.3)
≥ Grade 3 irAE	10 (11.9)	3 (13.0)	27 (10.4)	5 (5.8)	37 (10.8)	8 (7.3)
Fatal irAE	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
irAE leading to dose interruption	13 (15.5)	1 (4.3)	20 (7.7)	5 (5.8)	33 (9.6)	6 (5.5)
irAE leading to dose delay	13 (15.5)	1 (4.3)	20 (7.7)	5 (5.8)	33 (9.6)	6 (5.5)
irAE leading to discontinuation	8 (9.5)	4 (17.4)	16 (6.2)	2 (2.3)	24 (7.0)	6 (5.5)

[a] Other includes all races except White/Caucasian and those participants of whom race is not known/not reported.
[b] In Study INCMGA 0012-101, TEAEs leading to dose delay and infusion interruption were captured as 'drug interruption' and are summarized as 'dose delay.'
[c] Immune-related AEs were identified using predefined PTs regardless of investigator's assessment of causality.

Baseline characteristics

ECOG performance status

The All Cancer 500 mg Q4W Population was composed of 219 participants (48.5%) with a baseline ECOG performance status of 0 and 233 participants (51.5%) with a baseline ECOG performance status of ⩾ 1, including 230 participants with performance status of 1, 2 participants with a performance status of 2, and 1 participant with missing performance status.

No clinically meaningful differences were observed in frequency or severity of infusion-related reactions between ECOG performance status subgroups.

Table 75: Safety subgroup analyses by baseline ECOG Performance Status

Variable	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
	ECOG PS 0 (N = 77)	ECOG PS ≥ 1 (N = 30)	ECOG PS 0 (N = 142)	ECOG PS ≥ 1 (N = 203)	ECOG PS 0 (N = 219)	ECOG PS ≥ 1 (N = 233)
Median duration of retifanlimab treatment (min, max), days	336.0 (1, 731)	169.0 (1, 733)	154.5 (1, 823)	114.0 (1, 736)	197.0 (1, 823)	115.0 (1, 736)
Participants (n [%]) with TEAEs:						
Any TEAE	70 (90.9)	26 (86.7)	139 (97.9)	192 (94.6)	209 (95.4)	218 (93.6)
Treatment-related TEAE	59 (76.6)	13 (43.3)	103 (72.5)	126 (62.1)	162 (74.0)	139 (59.7)
Serious TEAE	19 (24.7)	9 (30.0)	47 (33.1)	90 (44.3)	66 (30.1)	99 (42.5)
≥ Grade 3 TEAE	26 (33.8)	8 (26.7)	57 (40.1)	111 (54.7)	83 (37.9)	119 (51.1)
Fatal TEAE	1 (1.3)	3 (10.0)	6 (4.2)	15 (7.4)	7 (3.2)	18 (7.7)
Serious treatment-related TEAE	12 (15.6)	1 (3.3)	8 (5.6)	12 (5.9)	20 (9.1)	13 (5.6)
≥ Grade 3 treatment-related TEAE	16 (20.8)	2 (6.7)	18 (12.7)	27 (13.3)	34 (15.5)	29 (12.4)
TEAE leading to dose interruption	30 (39.0)	10 (33.3)	39 (27.5)	65 (32.0)	69 (31.5)	75 (32.2)
TEAE leading to infusion interruption	3 (3.9)	0 (0.0)	1 (0.7)	1 (0.5)	4 (1.8)	1 (0.4)
TEAE leading to dose delay[a]	28 (36.4)	10 (33.3)	38 (26.8)	64 (31.5)	66 (30.1)	74 (31.8)
TEAE leading to discontinuation	17 (22.1)	5 (16.7)	18 (12.7)	26 (12.8)	35 (16.0)	31 (13.3)
Treatment-related TEAE leading to discontinuation	14 (18.2)	2 (6.7)	9 (6.3)	13 (6.4)	23 (10.5)	15 (6.4)
Participants (n [%]) with irAEs:[b]						
Any irAE	36 (46.8)	6 (20.0)	57 (40.1)	57 (28.1)	93 (42.5)	63 (27.0)
Serious irAE	10 (13.0)	2 (6.7)	8 (5.6)	11 (5.4)	18 (8.2)	13 (5.6)
≥ Grade 3 irAE	11 (14.3)	2 (6.7)	14 (9.9)	18 (8.9)	25 (11.4)	20 (8.6)
Fatal irAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.4)
irAE leading to dose interruption	12 (15.6)	2 (6.7)	13 (9.2)	12 (5.9)	25 (11.4)	14 (6.0)
irAE leading to dose delay	12 (15.6)	2 (6.7)	13 (9.2)	12 (5.9)	25 (11.4)	14 (6.0)
irAE leading to discontinuation	10 (13.0)	2 (6.7)	7 (4.9)	11 (5.4)	17 (7.8)	13 (5.6)

[a] In Study INCMGA 0012-101, TEAEs leading to dose delay and infusion interruption were captured as 'drug interruption' and are summarized as 'dose delay.'
[b] Immune-related AEs were identified using predefined PTs regardless of investigator's assessment of causality.

Renal impairment

No participants had end stage renal disease (i.e., < 15 mL/min GFR not on dialysis or requiring dialysis). Overall, no clinically meaningful differences were observed in frequency or severity of TEAEs or irAEs.

No clinically meaningful differences were observed in frequency or severity of infusion-related reactions in participants with mild or moderate renal impairment. The number of participants with severe renal impairment or end-stage renal disease was insufficient to allow comparisons.

Table 76: Safety subgroup analyses by renal impairment category at baseline

Variable	MCC 500 mg Q4W (N = 107)				Non-MCC 500 mg Q4W (N = 345)				All Cancer 500 mg Q4W (N = 452)			
	Normal (N = 41)	Mild (N = 41)	Moderate (N = 25)	Severe (N = 0)	Normal (N = 119)	Mild (N = 127)	Moderate (N = 96)	Severe (N = 3)	Normal (N = 160)	Mild (N = 168)	Moderate (N = 121)	Severe (N = 3)
Median duration of retifanlimab treatment (min, max), days	332.0 (1, 731)	336.0 (1, 733)	218.0 (1, 704)	NA	113.0 (1, 823)	142.0 (1, 727)	160.5 (1, 736)	92.0 (29, 147)	169.0 (1, 823)	146.5 (1, 733)	169.0 (1, 736)	92.0 (29, 147)
Participants (n [%]) with TEAEs:												
Any TEAE	36 (87.8)	37 (90.2)	23 (92.0)	NA	114 (95.8)	123 (96.9)	91 (94.8)	3 (100.0)	150 (93.8)	160 (95.2)	114 (94.2)	3 (100.0)
Treatment-related TEAE	28 (68.3)	31 (75.6)	13 (52.0)	NA	74 (62.2)	84 (66.1)	69 (71.9)	2 (66.7)	102 (63.8)	115 (68.5)	82 (67.8)	2 (66.7)
Serious TEAE	10 (24.4)	7 (17.1)	11 (44.0)	NA	44 (37.0)	47 (37.0)	45 (46.9)	1 (33.3)	54 (33.8)	54 (32.1)	56 (46.3)	1 (33.3)
≥ Grade 3 TEAE	16 (39.0)	8 (19.5)	10 (40.0)	NA	57 (47.9)	53 (41.7)	57 (59.4)	1 (33.3)	73 (45.6)	61 (36.3)	67 (55.4)	1 (33.3)
Fatal TEAE	0 (0.0)	0 (0.0)	4 (16.0)	NA	8 (6.7)	6 (4.7)	7 (7.3)	0 (0.0)	8 (5.0)	6 (3.6)	11 (9.1)	0 (0.0)
Serious treatment-related TEAE	5 (12.2)	3 (7.3)	5 (20.0)	NA	4 (3.4)	3 (2.4)	12 (12.5)	1 (33.3)	9 (5.6)	6 (3.6)	17 (14.0)	1 (33.3)
≥ Grade 3 treatment-related TEAE	9 (22.0)	4 (9.8)	5 (20.0)	NA	14 (11.8)	8 (6.3)	23 (24.0)	0 (0.0)	23 (14.4)	12 (7.1)	28 (23.1)	0 (0.0)
TEAE leading to dose interruption	13 (31.7)	18 (43.9)	9 (36.0)	NA	35 (29.4)	29 (22.8)	39 (40.6)	1 (33.3)	48 (30.0)	47 (28.0)	48 (39.7)	1 (33.3)
TEAE leading to infusion interruption	1 (2.4)	1 (2.4)	1 (4.0)	NA	0 (0.0)	1 (0.8)	1 (1.0)	0 (0.0)	1 (0.6)	2 (1.2)	2 (1.7)	0 (0.0)
TEAE leading to dose delay[a]	12 (29.3)	18 (43.9)	8 (32.0)	NA	35 (29.4)	28 (22.0)	38 (39.6)	1 (33.3)	47 (29.4)	46 (27.4)	46 (38.0)	1 (33.3)
TEAE leading to discontinuation	6 (14.6)	6 (14.6)	10 (40.0)	NA	8 (6.7)	18 (14.2)	18 (18.8)	0 (0.0)	14 (8.8)	24 (14.3)	28 (23.1)	0 (0.0)
Treatment-related TEAE leading to discontinuation	5 (12.2)	6 (14.6)	5 (20.0)	NA	3 (2.5)	8 (6.3)	11 (11.5)	0 (0.0)	8 (5.0)	14 (8.3)	16 (13.2)	0 (0.0)
Participants (n [%]) with irAEs:[b]												
Any irAE	17 (41.5)	17 (41.5)	8 (32.0)	NA	40 (33.6)	38 (29.9)	36 (37.5)	0 (0.0)	57 (35.6)	55 (32.7)	44 (36.4)	0 (0.0)
Serious irAE	5 (12.2)	4 (9.8)	3 (12.0)	NA	6 (5.0)	2 (1.6)	11 (11.5)	0 (0.0)	11 (6.9)	6 (3.6)	14 (11.6)	0 (0.0)
≥ Grade 3 irAE	6 (14.6)	5 (12.2)	2 (8.0)	NA	12 (10.1)	8 (6.3)	12 (12.5)	0 (0.0)	18 (11.3)	13 (7.7)	14 (11.6)	0 (0.0)
Fatal irAE	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
irAE leading to dose interruption	7 (17.1)	4 (9.8)	3 (12.0)	NA	9 (7.6)	7 (5.5)	9 (9.4)	0 (0.0)	16 (10.0)	11 (6.5)	12 (9.9)	0 (0.0)
irAE leading to dose delay	7 (17.1)	4 (9.8)	3 (12.0)	NA	9 (7.6)	7 (5.5)	9 (9.4)	0 (0.0)	16 (10.0)	11 (6.5)	12 (9.9)	0 (0.0)
irAE leading to discontinuation	4 (9.8)	6 (14.6)	2 (8.0)	NA	4 (3.4)	6 (4.7)	8 (8.3)	0 (0.0)	8 (5.0)	12 (7.1)	10 (8.3)	0 (0.0)

Note: Normal renal function = creatinine clearance at baseline ≥ 90 mL/min (normal GFR). Mild renal impairment = creatinine clearance at baseline ≥ 60 to < 90 mL/min (mild decrease in GFR). Moderate renal impairment = creatinine clearance at baseline ≥ 30 to < 60 mL/min (moderate decrease in GFR). Severe renal impairment = creatinine clearance at baseline ≥ 15 to < 30 mL/min (severe decrease in GFR not requiring dialysis).

In Study INCMGA 0012-101, TEAEs leading to dose delay and infusion interruption were captured as 'drug interruption' and are summarized as 'dose delay.'

[b] Immune-related AEs were identified using predefined PTs regardless of investigator's assessment of causality.

Hepatic impairment

None of the participants had moderate or severe hepatic impairment, and 1 participant (0.2%) had a missing hepatic impairment status at baseline. The median duration of retifanlimab treatment was longer for participants with normal hepatic function (169.0 days) than participants with mild hepatic impairment (58.0 days; see Table 77). Overall, no clinically meaningful differences were observed in frequency or severity of TEAEs, irAEs, or infusion related reactions in participants with normal hepatic function and those with mild hepatic impairment.

Table 77: Safety subgroup analyses by hepatic impairment category at baseline

	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
Variable	**Normal (N = 92)**	**Mild Impairment (N = 15)**	**Normal (N = 303)**	**Mild Impairment (N = 42)**	**Normal (N = 395)**	**Mild Impairment (N = 57)**
Median duration of retifanlimab treatment (min, max), days	337.5 (1, 733)	30.0 (1, 505)	141.0 (1, 823)	85.0 (1, 730)	169.0 (1, 823)	64.0 (1, 730)
Participants (n [%]) with TEAEs:						
Any TEAE	85 (92.4)	11 (73.3)	291 (96.0)	40 (95.2)	376 (95.2)	51 (89.5)
Treatment-related TEAE	66 (71.7)	6 (40.0)	203 (67.0)	26 (61.9)	269 (68.1)	32 (56.1)
Serious TEAE	24 (26.1)	4 (26.7)	121 (39.9)	16 (38.1)	145 (36.7)	20 (35.1)
≥ Grade 3 TEAE	29 (31.5)	5 (33.3)	150 (49.5)	18 (42.9)	179 (45.3)	23 (40.4)
Fatal TEAE	1 (1.1)	3 (20.0)	19 (6.3)	2 (4.8)	20 (5.1)	5 (8.8)
Serious treatment-related TEAE	11 (12.0)	2 (13.3)	17 (5.6)	3 (7.1)	28 (7.1)	5 (8.8)
≥ Grade 3 treatment-related TEAE	15 (16.3)	3 (20.0)	42 (13.9)	3 (7.1)	57 (14.4)	6 (10.5)
TEAE leading to dose interruption	39 (42.4)	1 (6.7)	91 (30.0)	13 (31.0)	130 (32.9)	14 (24.6)
TEAE leading to infusion interruption	3 (3.3)	0 (0.0)	1 (0.3)	1 (2.4)	4 (1.0)	1 (1.8)
TEAE leading to dose delay[a]	37 (40.2)	1 (6.7)	90 (29.7)	12 (28.6)	127 (32.2)	13 (22.8)
TEAE leading to discontinuation	17 (18.5)	5 (33.3)	39 (12.9)	5 (11.9)	56 (14.2)	10 (17.5)
Treatment-related TEAE leading to discontinuation	13 (14.1)	3 (20.0)	20 (6.6)	2 (4.8)	33 (8.4)	5 (8.8)
Participants (n [%]) with irAEs:[b]						
Any irAE	38 (41.3)	4 (26.7)	100 (33.0)	14 (33.3)	138 (34.9)	18 (31.6)
Serious irAE	11 (12.0)	1 (6.7)	17 (5.6)	2 (4.8)	28 (7.1)	3 (5.3)
≥ Grade 3 irAE	12 (13.0)	1 (6.7)	28 (9.2)	4 (9.5)	40 (10.1)	5 (8.8)
Fatal irAE	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
irAE leading to dose interruption	14 (15.2)	0 (0.0)	22 (7.3)	3 (7.1)	36 (9.1)	3 (5.3)
irAE leading to dose delay	14 (15.2)	0 (0.0)	22 (7.3)	3 (7.1)	36 (9.1)	3 (5.3)
irAE leading to discontinuation	10 (10.9)	2 (13.3)	16 (5.3)	2 (4.8)	26 (6.6)	4 (7.0)

Note: Hepatic impairment categories are based on NCI Organ Dysfunction Working Group. Normal = bilirubin ≤ ULN and AST ≤ ULN; Mild = bilirubin ≤ ULN and AST > ULN or ULN < bilirubin ≤ 1.5 × ULN; Moderate = 1.5 × ULN < bilirubin ≤ 3 × ULN; Severe = bilirubin > 3 × ULN.

Note: One participant in the non-MCC 500 mg Q4W Population with missing baseline hepatic assessments was pooled with the 'Mild/Moderate' group.

[a] In Study INCMGA 0012-101, TEAEs leading to dose delay and infusion interruption were captured as 'drug interruption' and are summarized as 'dose delay.'
[b] Immune-related AEs were identified using predefined PTs regardless of investigator's assessment of causality.

HIV status

The All Cancer 500 mg Q4W Population was composed of 10 participants (2.2%) who were HIV positive and controlled on antiretroviral therapy per the Study protocols. The median duration of retifanlimab treatment was similar in the HIV-positive population (155.0 days) and the non-HIV population (164.5days). Overall, no clinically meaningful differences were observed in frequency or severity of TEAEs or irAEs between the 2 groups (see Table 78). No HIV-positive participant had a fatal TEAE.

While HIV viral load testing has become the primary method to gauge the effect of antiretroviral therapy, CD4+ cell count remains the best indication of immune status and potential for HIV opportunistic infections, and correlations occur between CD4+ cell count and risk of death, life expectancy, and adherence to HIV treatment (Ford et al 2017). For the participants who were known to be HIV-positive at baseline in the All Cancer 500 mg Q4W Population, there were no consistent trends in CD4+ counts compared with baseline while receiving retifanlimab, and viral load measurements did not exceed the threshold levels associated with treatment failure of antiretroviral therapy, defined as 2 consecutive viral loads > 1000 copies/mL (WHO 2016; see Figure 46). No opportunistic infections were reported. Participants were permitted to continue their antiretroviral therapy per the Study protocols.

None of the HIV-positive participants had an infusion-related reaction.

Table 78: Safety subgroup analyses by HIV status

	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
Variable	**HIV-Positive (N = 1)**	**Non-HIV (N = 106)**	**HIV-Positive (N = 9)**	**Non-HIV (N = 336)**	**HIV-Positive (N = 10)**	**Non-HIV (N = 442)**
Median duration of retifanlimab treatment (min, max), days	169.0 (169, 169)	322.0 (1, 733)	141.0 (1, 495)	141.0 (1, 823)	155.0 (1, 495)	164.5 (1, 823)
Participants (n [%]) with TEAEs:						
Any TEAE	1 (100.0)	95 (89.6)	8 (88.9)	323 (96.1)	9 (90.0)	418 (94.6)
Treatment-related TEAE	0 (0.0)	72 (67.9)	5 (55.6)	224 (66.7)	5 (50.0)	296 (67.0)
Serious TEAE	0 (0.0)	28 (26.4)	4 (44.4)	133 (39.6)	4 (40.0)	161 (36.4)
≥ Grade 3 TEAE	0 (0.0)	34 (32.1)	4 (44.4)	164 (48.8)	4 (40.0)	198 (44.8)
Fatal TEAE	0 (0.0)	4 (3.8)	0 (0.0)	21 (6.3)	0 (0.0)	25 (5.7)
Serious treatment-related TEAE	0 (0.0)	13 (12.3)	1 (11.1)	19 (5.7)	1 (10.0)	32 (7.2)
≥ Grade 3 treatment-related TEAE	0 (0.0)	18 (17.0)	1 (11.1)	44 (13.1)	1 (10.0)	62 14.0)
TEAE leading to dose interruption	0 (0.0)	40 (37.7)	0 (0.0)	104 (31.0)	0 (0.0)	144 (32.6)
TEAE leading to infusion interruption	0 (0.0)	3 (2.8)	0 (0.0)	2 (0.6)	0 (0.0)	5 (1.1)
TEAE leading to dose delay[a]	0 (0.0)	38 (35.8)	0 (0.0)	102 (30.4)	0 (0.0)	140 (31.7)
TEAE leading to discontinuation	0 (0.0)	22 (20.8)	2 (22.2)	42 (12.5)	2 (20.0)	64 (14.5)
Treatment-related TEAE leading to discontinuation	0 (0.0)	16 (15.1)	1 (11.1)	21 (6.3)	1 (10.0)	37 (8.4)
Participants (n [%]) with irAEs:						
Any irAE	0 (0.0)	42 (39.6)	1 (11.1)	113 (33.6)	1 (10.0)	155 (35.1)
Serious irAE	0 (0.0)	12 (11.3)	1 (11.1)	18 (5.4)	1 (10.0)	30 (6.8)
≥ Grade 3 irAE	0 (0.0)	13 (12.3)	1 (11.1)	31 (9.2)	1 (10.0)	44 (10.0)
Fatal irAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
irAE leading to dose interruption	0 (0.0)	14 (13.2)	0 (0.0)	25 (7.4)	0 (0.0)	39 (8.8)
irAE leading to infusion interruption	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Variable	MCC 500 mg Q4W (N = 107)		Non-MCC 500 mg Q4W (N = 345)		All Cancer 500 mg Q4W (N = 452)	
	HIV-Positive (N = 1)	Non-HIV (N = 106)	HIV-Positive (N = 9)	Non-HIV (N = 336)	HIV-Positive (N = 10)	Non-HIV (N = 442)
irAE leading to dose delay	0 (0.0)	14 (13.2)	0 (0.0)	25 (7.4)	0 (0.0)	39 (8.8)
irAE leading to discontinuation	0 (0.0)	12 (11.3)	1 (11.1)	17 (5.1)	1 (10.0)	29 (6.6)

[a] In Study INCMGA 0012-101, TEAEs leading to dose delay and infusion interruption were captured as 'drug interruption' and are summarized as 'dose delay.'

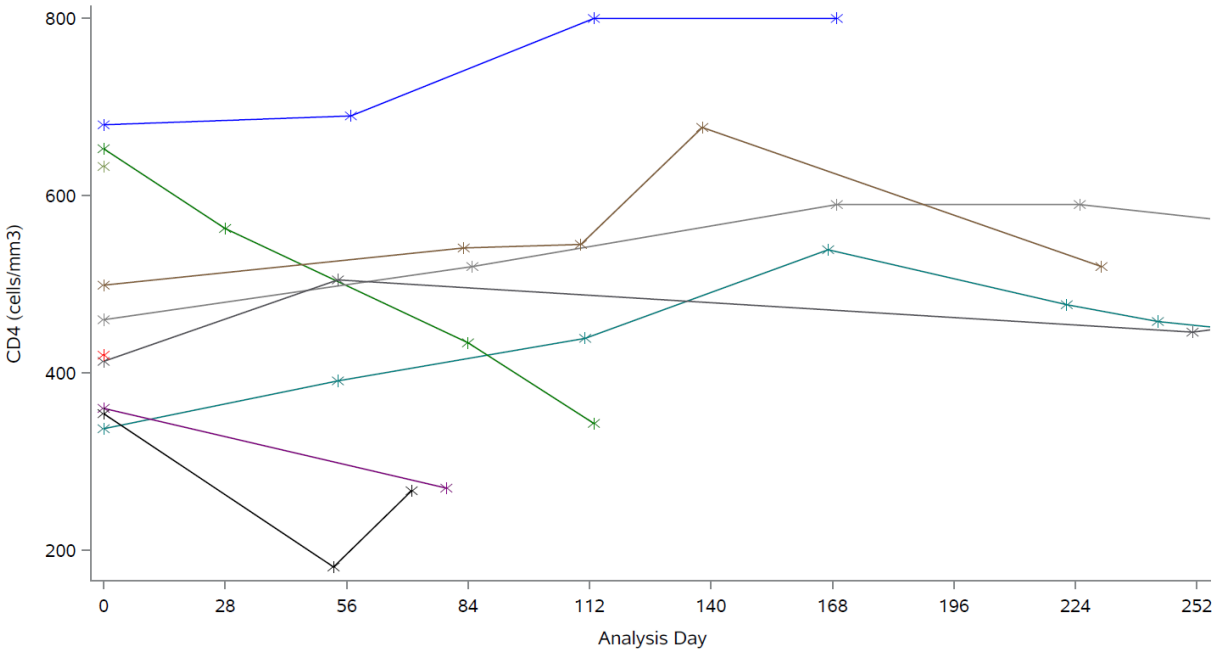


Figure 46: CD4+ Counts Over Time for HIV-Positive Participants in the All Cancer 500 mg Q4W Population

2.6.8.7. Immunological events

ADA and nAb results

As of the data cut-off date of each study, 4689 human serum samples from 642 evaluable participants were analysed for anti-retifanlimab antibodies. At the sample level, 25 (0.5%) positive ADA samples were detected. Nine (0.2%) were baseline positive and 16 (0.3%) were postbaseline positive (see Table 79). All were from 3 mg/kg or 500 mg dose levels. No postbaseline positive samples were observed in Studies INCMGA 0012-104 and INCMGA 0012-202.

At the participant level, an assessable participant was defined as a participant treated with retifanlimab and with at least 1 post-dose sample with a reportable ADA result. Excluding the inconclusive participants based on DTL, the total number of negative and positive participants was 421, including 19 ADA-positive participants (see Table 80). Eight of the 19 ADA-positive participants had non-treatment-emergent ADA with only baseline positive ADAs, and 11 (1.7%) of them had treatment-emergent ADA. Out of these 11 treatment-emergent positive participants, 1 participant with persistent positive ADA was observed.

Among the 11 treatment-emergent positive participants, 6 participants were from Study INCMGA 0012-101, 3 participants were from Study INCMGA 0012-201, and 2 participants were from Study INCMGA 0012-203.

None of the treatment-emergent positive participants were from Study INCMGA 0012-104 or 0012-202. Of those who were ADA positive, nAbs were detected in only 4 participants (0.6% of the total). Among the 4 nAb-positive participants, 2 participants each were from Studies INCMGA 0012-101 and INCMGA 0012-201 with 500 mg Q4W.

Table 79: Summary of clinical sample results in confirmatory nAb assay by treatment (pooled analysis of studies INCMGA 0012-101, INCMGA 0012-104, INCMGA 0012-201, INCMGA 0012-202, and INCMGA 0012-203)

		Retifanlimab Dose Regimen							
ADA Status	All Treatments	1 mg/kg Q2W	3 mg/kg Q2W	3 mg/kg Q4W	10 mg/kg Q2W	10 mg/kg Q4W	375 mg Q3W	500 mg Q4W	750 mg Q4W
Total number of samples	4689	16	1489	54	31	56	103	2843	97
Missing	4 (0.1%)	0	0	0	0	0	0	4 (0.1%)	0
Negative	4660 (99.4%)	16 (100%)	1484 (99.7%)	53 (98.1%)	31 (100%)	56 (100%)	103 (100%)	2820 (99.2%)	97 (100%)
Positive	25 (0.5%)	0	5 (0.3%)	1 (1.9%)	0	0	0	19 (0.7%)	0
Baseline positive	9 (0.2%)	0	3 (0.2%)	0	0	0	0	6 (0.2%)	0
Postbaseline positive	16 (0.3%)	0	2 (0.1%)	1 (1.9%)	0	0	0	13 (0.5%)	0
Neutralizing ADA Positive	8 (0.2%)	0	0	0	0	0	0	8 (0.3%)	0

Table 80: Summary of participant immunogenicity results (pooled analysis of studies INCMGA 0012-101, INCMGA 0012-104, INCMGA 0012-201, INCMGA 0012-202, and INCMGA 0012-203) by dose regimen

		Retifanlimab Dose Regimen							
ADA Status	All Dose Regimens	1 mg/kg Q2W	3 mg/kg Q2W	3 mg/kg Q4W	10 mg/kg Q2W	10 mg/kg Q4W	375 mg Q3W	500 mg Q4W	750 mg Q4W
Evaluable participants	642	3	144	10	8	6	15	441	15
Assessable participants	607 (94.5%)	3 (100%)	137 (95.1%)	9 (90.0%)	8 (100%)	6 (100%)	15 (100%)	414 (93.9%)	15 (100%)
Inconclusive participants	186 (29.0%)	0	2 (1.4%)	0	0	0	0	184 (41.7%)	0
Negative participants	402 (62.6%)	3 (100%)	130 (90.3%)	8 (80.0%)	8 (100%)	6 (100%)	15 (100%)	217 (49.2%)	15 (100%)
Positive participants	19 (3.0%)	0	5 (3.5%)	1 (10.0%)	0	0	0	13 (2.9%)	0
Nontreatment-emergent positive participants	8 (1.2%)	0	3 (2.1%)	0	0	0	0	5 (1.1%)	0
Treatment-emergent positive participants	11 (1.7%)	0	2 (1.4%)	1 (10.0%)	0	0	0	8 (1.8%)	0
Persistent treatment-emergent positive participants	1 (0.2%)	0	0	0	0	0	0	1 (0.2%)	0
Neutralizing ADA-positive participants	4 (0.6%)	0	0	0	0	0	0	4 (0.9%)	0

Note:
Evaluable participants: participant with a negative ADA status or a positive ADA status (exclude missing ADA visits)
Assessable participants: participant treated with retifanlimab and with at least 1 post-treatment sample with reportable ADA result
Inconclusive participants: participant with all the pretreatment and post-treatment samples negative AND the concentration of retifanlimab in the last postdose sample above DTL OR with missing last postdose sample matched concentration
Negative participants: participant with all pretreatment and postdose samples negative AND the concentration of retifanlimab in the last postdose sample below the DTL
Positive participant: participant with at least 1 pretreatment or postdose sample positive in the confirmatory assay for antibodies against retifanlimab
Nontreatment-emergent positive participants: participant with pretreatment sample positive and postdose sample negative in the confirmatory assay OR pretreatment and postdose sample positive in the confirmatory assay with a postdose titer< 2-fold of baseline
Treatment-emergent positive participants: participant with negative pretreatment samples and at least 1 postdose sample positive in the confirmatory assay OR pretreatment and postdose sample positive in the confirmatory assay with an increase in titer ≥ 2 fold of baseline OR no predose ADA records
Persistent treatment-emergent positive participants: participant with more than 1 treatment-emergent positive ADA.

Relationship of ADA and nAb status to efficacy

Among the 11 treatment-emergent positive participants, 3 participants were from Study INCMGA 0012-201. Due to the low number of ADA-positive participants, only an individual descriptive assessment of the ADA status on clinical efficacy was performed.

Of the 65 chemotherapy-naïve participants from Study INCMGA 0012-201 with MCC, 2 participants had treatment-emergent ADAs; 1 was persistent, and 1 of these participants was identified as nAb positive. Given that both ADA-positive participants had either a best overall response by ICR of partial response or stable disease, efficacy does not appear to be impacted by immunogenicity in these participants.

Relationship of ADA and nAb status to safety

Due to the low number of treatment-emergent ADA-positive participants, an individual descriptive assessment of the ADA status and NAb status on clinical safety was performed for the 11 participants with post-baseline treatment-emergent ADA-positive samples (see Table 81).

Table 81: Safety profile in participants with treatment-emergent ADA

Study INCMGA 0012-X/ Participant	Retifanlimab Dose/ No. of Infusions	ADA/NAb Results	IRRs[a]
Primary Efficacy MCC Population			
201/501-001 (ICR-assessed PR with 13.5 month DOR)	500 mg Q4W/15	+ (persistent)/+	0
201/501-005 (ICR-assessed SD for 2+ years)	500 mg Q4W/24	+/-	0
All Cancer Population			
101/FI001-0001	500 mg Q4W/2	+/+	1 IRR (G2)
101/FR003-0001	500 mg Q4W/5	+/-	0
101/IT002-0009	500 mg Q4W/1	+/nt	0
101/US002-0006	3 mg/kg Q4W/2	+/nt	1 IRR (G2)
101/UA005-0006	3 mg/kg Q2W/52	+/nt	0
101/PL004-0009	3 mg/kg Q2W/2	+/-	0
201/301-004	500 mg Q4W/2	+/+	0
203/301-002	500 mg Q4W/21	+/nt	0
203/302-010	500 mg Q4W/15	+/nt	0

ICR = independent central radiographic review; NT = not tested.
[a] Infusion-related reactions are described in ISS SAP Section 5.1.2.
Source: Appendix B, ISS Listings 2.1.1 and 2.7.6, and INCMGA 0012-101 Interim CSR 2 Listing 2.6.9.1.

There was no apparent clinically meaningful impact of ADA and NAb on the incidence of hypersensitivity/IRRs or on the overall safety profile.

2.6.8.8. Safety related to drug-drug interactions and other interactions

No dedicated drug-drug interactions studies have been performed. Please refer to the section on interactions in the pharmacokinetics section.

2.6.8.9. Discontinuation due to adverse events

AEs leading to infusion interruption

Treatment-emergent AEs leading to infusion interruption occurred in 5 participants (1.1%) in the All Cancer 500 mg Q4W Population (see table 48). Of these, 3 TEAEs were infusion-related reactions and are discussed in the section on AESIs. One participant had another TEAE leading to infusion interruption (extravasation [MCC]).

AEs leading to dose delay

Treatment delays of up to 12 weeks were allowed for treatment-related toxicity. Treatment emergent AEs leading to dose delay are summarized in Table 82.

Table 82: Summary of common (≥ 2 participants in the All Cancer 500 mg Q4W Population) TEAEs leading to dose delay by MedDRA Preferred Term

MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
COVID-19	5 (4.7)	4 (1.2)	9 (2.0)
Diarrhoea	1 (0.9)	8 (2.3)	9 (2.0)
Pyrexia	3 (2.8)	5 (1.4)	8 (1.8)
Alanine aminotransferase increased	6 (5.6)	1 (0.3)	7 (1.5)
Lipase increased	4 (3.7)	3 (0.9)	7 (1.5)
Rash	2 (1.9)	5 (1.4)	7 (1.5)
Arthralgia	2 (1.9)	4 (1.2)	6 (1.3)
Blood creatinine increased	1 (0.9)	5 (1.4)	6 (1.3)
Pneumonia	1 (0.9)	5 (1.4)	6 (1.3)
Amylase increased	4 (3.7)	1 (0.3)	5 (1.1)
Aspartate aminotransferase increased	3 (2.8)	2 (0.6)	5 (1.1)
Urinary tract infection	1 (0.9)	4 (1.2)	5 (1.1)
Abdominal pain	1 (0.9)	3 (0.9)	4 (0.9)
Anaemia	0 (0.0)	4 (1.2)	4 (0.9)
Blood alkaline phosphatase increased	2 (1.9)	1 (0.3)	3 (0.7)
Cough	1 (0.9)	2 (0.6)	3 (0.7)
Hepatocellular injury	0 (0.0)	3 (0.9)	3 (0.7)
Herpes zoster	2 (1.9)	1 (0.3)	3 (0.7)
Myalgia	1 (0.9)	2 (0.6)	3 (0.7)
Pneumonitis	2 (1.9)	1 (0.3)	3 (0.7)
Sepsis	1 (0.9)	2 (0.6)	3 (0.7)
Acute kidney injury	1 (0.9)	1 (0.3)	2 (0.4)
Asthenia	2 (1.9)	0 (0.0)	2 (0.4)
Cardiac failure	1 (0.9)	1 (0.3)	2 (0.4)
Colitis	2 (1.9)	0 (0.0)	2 (0.4)
Colonic fistula	0 (0.0)	2 (0.6)	2 (0.4)
COVID-19 pneumonia	0 (0.0)	2 (0.6)	2 (0.4)
Cystitis	0 (0.0)	2 (0.6)	2 (0.4)
Decreased appetite	1 (0.9)	1 (0.3)	2 (0.4)
Eosinophilia	2 (1.9)	0 (0.0)	2 (0.4)
Erysipelas	0 (0.0)	2 (0.6)	2 (0.4)
Haematuria	0 (0.0)	2 (0.6)	2 (0.4)
Hyperglycaemia	1 (0.9)	1 (0.3)	2 (0.4)

MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Hyperthyroidism	1 (0.9)	1 (0.3)	2 (0.4)
Hypothyroidism	0 (0.0)	2 (0.6)	2 (0.4)
Influenza	0 (0.0)	2 (0.6)	2 (0.4)
Intestinal obstruction	0 (0.0)	2 (0.6)	2 (0.4)
Myositis	0 (0.0)	2 (0.6)	2 (0.4)
Pharyngitis	0 (0.0)	2 (0.6)	2 (0.4)
Respiratory tract infection	0 (0.0)	2 (0.6)	2 (0.4)
Vaginal discharge	0 (0.0)	2 (0.6)	2 (0.4)

AEs leading to study drug discontinuation

AEs leading to retifanlimab discontinuation were observed in 14.6% of the All Cancer 500mg Q4W Population (8.4% treatment-related) and in 20.6% of the MCC Population (15% treatment-related), see Table 48. By PT, the most frequent (⩾ 2 participants [0.5%]) TEAE leading to retifanlimab discontinuation were diarrhoea and hepatitis (0.7% each; see Table 83). By PT, no treatment-related TEAEs led to retifanlimab discontinuation in more than 1 participant with MCC.

Table 83: Summary of treatment-related TEAEs leading to retifanlimab discontinuation by MedDRA Preferred Term

MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Diarrhoea	1 (0.9)	2 (0.6)	3 (0.7)
Hepatitis	1 (0.9)	2 (0.6)	3 (0.7)
Tubulointerstitial nephritis	1 (0.9)	1 (0.3)	2 (0.4)
Acute kidney injury	0 (0.0)	1 (0.3)	1 (0.2)
Autoimmune hepatitis	0 (0.0)	1 (0.3)	1 (0.2)
Azotaemia	0 (0.0)	1 (0.3)	1 (0.2)
Blood creatinine increased	0 (0.0)	1 (0.3)	1 (0.2)
Colitis	1 (0.9)	0 (0.0)	1 (0.2)
Concomitant disease progression	1 (0.9)	0 (0.0)	1 (0.2)
Demyelinating polyneuropathy[a]	1 (0.9)	0 (0.0)	1 (0.2)
Drug hypersensitivity	1 (0.9)	0 (0.0)	1 (0.2)
Dry mouth	0 (0.0)	1 (0.3)	1 (0.2)
Dry skin	0 (0.0)	1 (0.3)	1 (0.2)
Eosinophilic fasciitis	1 (0.9)	0 (0.0)	1 (0.2)
Hepatocellular injury	0 (0.0)	1 (0.3)	1 (0.2)
Hypophysitis	1 (0.9)	0 (0.0)	1 (0.2)
Immune-mediated enterocolitis	0 (0.0)	1 (0.3)	1 (0.2)
Infusion related reaction	1 (0.9)	0 (0.0)	1 (0.2)
Iritis	0 (0.0)	1 (0.3)	1 (0.2)

MedDRA PT, n (%)	MCC 500 mg Q4W (N = 107)	Non-MCC 500 mg Q4W (N = 345)	All Cancer 500 mg Q4W (N = 452)
Lung disorder	1 (0.9)	0 (0.0)	1 (0.2)
Myositis	0 (0.0)	1 (0.3)	1 (0.2)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0)	1 (0.3)	1 (0.2)
Pancreatitis	1 (0.9)	0 (0.0)	1 (0.2)
Pneumonia	0 (0.0)	1 (0.3)	1 (0.2)
Pneumonitis	0 (0.0)	1 (0.3)	1 (0.2)
Polyarthritis	1 (0.9)	0 (0.0)	1 (0.2)
Polymyalgia rheumatica	0 (0.0)	1 (0.3)	1 (0.2)
Radiculopathy	1 (0.9)	0 (0.0)	1 (0.2)
Rash	0 (0.0)	1 (0.3)	1 (0.2)
Renal failure	0 (0.0)	1 (0.3)	1 (0.2)
Toxic epidermal necrolysis	1 (0.9)	0 (0.0)	1 (0.2)
Transaminases increased	1 (0.9)	0 (0.0)	1 (0.2)
Uveitis	0 (0.0)	1 (0.3)	1 (0.2)

Verbatim term is acute inflammatory demyelinating polyneuropathy.

2.6.8.10. Post marketing experience

Recently, the FDA approved retifanlimab for treatment of MCC, but as the approval date was very recent (22-03-2023) no post-marketing data has been provided.

2.6.9. Discussion on clinical safety

The main population for the analysis of clinical safety is the 'All Cancer 500mg Q4W population', which includes all 452 patients that were treated with at least one dose of retifanlimab in the proposed dose, regardless of tumour type, in five uncontrolled clinical studies. Although it is acknowledged that there is heterogeneity in this population with regards to baseline disease characteristics and previous treatments, the mechanism of action of anti-PD(L)1 inhibitors is well known and the related toxicity profile of immune-related adverse events is not considered to be dependent of the underlying disease or previous treatments. The pooled population includes more patients, and this allows for a higher chance of detection of rare adverse events. The All Cancer 500mg Q4W population is considered large enough to provide an integrated analysis of safety of retifanlimab, but it is noted that less common toxicities might be missed in a safety population of this size, and the estimated frequencies of less common AEs are less precise. The five included studies were uncontrolled, which makes it more difficult to assess the treatment-relatedness of adverse events for this new product. On the other hand, context is provided by the known safety profile of other PD-(L)1-inhibitors with the same mechanism of action that are registered for other indications, and the PD-L1 inhibitor avelumab that is authorised in the proposed indication of advanced MCC. All 107 patients with MCC that are included in the All Cancer 500mg Q4W population were treated in the study INCMGA-0012-201 (PODIUM-201), which is the pivotal study for the current application.

Median duration of treatment with retifanlimab is short, with 5.4 months (and 10.3 months in the 107 patients with MCC). An updated safety analysis with longer follow-up was provided during the procedure,

including data from 144 patients treated beyond 12 months (31.9%; including 49 patients with MCC). Sixteen participants in the MCC Population completed the maximum 2 year treatment period or had treatment discontinued at the discretion of the investigator (following at least 6 months of therapy with confirmed response). At the time of the updated data cutoff dates for the individual studies, the median duration of safety follow-up in the All Cancer 500 mg Q4W Population was 7.59 months (0.3-30.0 months). Duration of exposure is considered rather limited and long-term safety has been included as a safety concern in the RMP.

The most common cancer types of patients treated with retifanlimab at the proposed dose were MCC (the target indication), endometrial carcinoma and anal carcinoma. All participants were fit with an ECOG-PS of 0 or 1, and the percentage of patients with an ECOG-PS of 0 was higher in the MCC population (72% versus 48.5% for all tumour types). No patients with end-stage renal disease, and only 3 patients with severe renal impairment (creatinine clearance ⩾15 to <30 mL/min) were treated with retifanlimab. Furthermore, patients with moderate hepatic impairment were not included in the All Cancer 500mg Q4W population, and patients with severe hepatic impairment were excluded from the clinical studies. This is adequately reflected in section 4.2 of the SmPC. In the All Cancer 500mg Q4W population, most patients (58.6%) had received prior systemic therapy, but this was mainly driven by the patients with other tumour types than MCC (75.1% prior systemic therapy). Only 6 patients with MCC were previously treated with platinum-based chemotherapy. Median age of the patients with MCC was 71 years, and most were male. This is reflective of clinical practice, where MCC predominantly affects older, male adults with light skin types.

The overall incidence of treatment-emergent adverse events (TEAEs, 94.5%; percentages for the All Cancer 500mg Q4W population), treatment-related AEs (66.6%), serious TEAEs (36.5%), ≥ grade 3 TEAEs (44.7%) and fatal TEAEs (5.5%) was somewhat lower in the patients with MCC compared to the larger population of patients regardless of tumour type. This could be due to the fact that the MCC patients had a better performance score and were less heavily pre-treated with systemic therapy. On the other hand, treatment-related AEs that were serious, ≥ grade 3 or AEs that led to treatment modifications were comparable for the MCC patients and the All Cancer 500mg Q4W population.

The most common AEs were comparable for the MCC population and the population treated with retifanlimab regardless of tumour type. The types of AEs are compatible with the underlying disease(s) of advanced cancer (fatigue, asthenia, anaemia, nausea) or the mechanism-of-action of immunotherapy (rash, pruritus, arthralgia, hypothyroidism).

The most common ADRs listed in section 4.8 of the SmPC are fatigue (35.4%) and rash (18.8%). These are considered important to patients, which is reflected by the following input from patient representatives (see also Efficacy discussion for further details):

'Among the most common cancer treatment side effects, patients are rating generalized tiredness as debilitating since it impacts on their ability to function and to have a social life, also itching and rash as not socially acceptable and making them uncomfortable in social gatherings. They are not ready to accept continuous nausea and diarrhoea during the treatment but only as a reaction of their body only during the first days of treatment.'

The most common treatment-related AEs were pruritus (15 and 13.1%) and asthenia (14 and 11.3%) in the MCC and All Cancer populations, respectively, in line with the most common treatment-emergent adverse events. Treatment-related AEs of grade 3 or higher occurred in low frequencies per AE, and most are consistent with the known immune-related AEs that are associated with PD(L)1-inhibitors.

The most frequent treatment-related serious TEAE were hepatitis and pneumonitis in three patients each (0.7%) in the All Cancer 500mg Q4W population. Treatment-related serious TEAEs occurred in a somewhat higher frequency in the MCC population compared to the larger population regardless of tumour type. This could be related to the longer median treatment duration in the MCC patients (10.3 versus 5.4 months). All treatment related serious TEAEs occurred in a single patient each in the MCC population and most are known immune-related adverse events of PD(L)1-inhibitors.

Three fatal AEs were assessed to be related to retifanlimab according to the investigator. This concerned a patient in the SCAC population with lymphangiosis carcinomatosa, which was considered to be a possible manifestation of treatment-induced hyperprogression by the investigator. According to the Applicant the event was not related to retifanlimab as there were confounding factors such as lung infection and a minimal diagnostic work-up. Although it is agreed that other factors may have played a role, it cannot be excluded that the treatment with retifanlimab was (partly) causative. The second case concerns a patient with MCC who was also diagnosed four years earlier with CLL, which was stable and required no treatment. On the day of the third treatment with retifanlimab, the patient was hospitalized because of progressive pancytopenia due to progression of CLL. Treatment with retifanlimab was discontinued and the patient died on day 97 due to progressive disease, either MCC or CLL. Also in this case, it cannot be excluded that the treatment with retifanlimab was causative of the progression of the CLL, that was stable and did not require treatment before treatment with retifanlimab was initiated. The third case of an adverse event associated with an outcome of death that was considered possibly related to retifanlimab treatment by the investigator, but not by the Sponsor, concerns a case of hyperprogression of the underlying disease (endometrial carcinoma) shortly after start of retifanlimab treatment. The causality assessment is difficult in this case, in the absence of any information on the rate of progression prior to study enrolment.

All three fatal events that were assessed as treatment-related by the investigator were considered not related to retifanlimab by the sponsor. For all three cases, the causality assessment is limited by lack of crucial information, therefore it is still possible that these three events were related to retifanlimab treatment.

Two cases of TEAEs associated with an outcome of death in the All Cancer 500mg Q4W population (renal failure and acute respiratory failure) that needed further clarification because they could have been immune-related AEs, were considered not-related to treatment with retifanlimab by the investigator or sponsor. It is agreed that alternative causes were more likely to have led to death than immune-related (i.e., treatment-related) adverse events. One case of fatal interstitial lung disease was considered related to treatment upon an updated assessment and is as such reported in 4.8 of the SmPC as the only fatal treatment-related adverse event (immune related pneumonitis grade 5) in the All Cancer 500mg Q4W population.

Based on the established safety profile of the PD-(L)1 inhibitor class, immune-related AEs (irAEs) and infusion-related reactions (IRR) were considered adverse events of special interest for retifanlimab and included as important safety concerns in the RMP.

Immune related endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and diabetic ketoacidosis have been reported in patients receiving retifanlimab. Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and for cortisol, as indicated based on symptoms and/or falling thyroid stimulating hormone (see sections 4.2, 4.4 and 4.8 of the SmPC).

Immune-related skin reactions occurred in 9.5% of patients in the All Cancer 500mg Q4W population. Most skin reactions were grade 1 or 2 and resolved with a median time to resolution of 37 days. The proportion of patients that needed systemic corticosteroid treatment for a skin reaction was fairly high (32.6%, 14/43

patients), including 8 patients that needed high-dose systemic corticosteroids. There were three patients that discontinued retifanlimab treatment due to an immune-related skin reaction (0.7%).

Immune-related hepatitis occurred in 3.5% of patients (n=16), was mainly grade 2 or 3 in severity (0.9% and 2.4% and was treated with systemic corticosteroids in most patients (81.3%). It resolved in about half of the cases (n=9/16) but also led to discontinuation of retifanlimab treatment in 7/16 patients (1.5% of the total All Cancer 500mg Q4W population).

Immune-related pneumonitis occurred in 14 participants (3.1%). Treatment with retifanlimab had to be discontinued due to pneumonitis in 1 case, which was fatal. Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Patients should be managed with retifanlimab treatment modifications and corticosteroids (see sections 4.2, 4.4 and 4.8 of the SmPC).

Other immune-related adverse events that occurred in more than one patient in the All Cancer 500mg Q4W population were colitis (2.7%), nephritis (2.0%), myositis (0.7%), Guillain-Barré syndrome (0.7%), uveitis (0.7%), polyarthritis (0.7%) and pancreatitis (0.4%). With the exception of uveitis, most of these immune-related AEs required treatment with systemic corticosteroids. Retifanlimab treatment was discontinued in five patients with nephritis, four patients with colitis, 2 patients with myositis or uveitis, and in one patient each for, Guillain-Barré syndrome and pancreatitis.

Infusion-related reactions (IRR) occurred in 28 participants (6.2%) in the All Cancer 500mg Q4W population. As with any therapeutic protein, retifanlimab can cause infusion related reactions, some of which may be severe. Patients should be monitored for signs and symptoms of infusion related reactions. Retifanlimab treatment should be interrupted or the rate of infusion slowed or treatment should be permanently discontinued based on severity of reaction and the response to treatment. Premedication with an antipyretic and/or an antihistamine should be considered for patients who have had previous clinically significant reactions to infusions of therapeutic proteins (see sections 4.2, 4.4 and 4.8 of the SmPC).

Treatment had to be interrupted, delayed or discontinued due to an adverse event in 31.9%, 31.0% and 14.6% of patients in the All Cancer 500mg Q4W population. Retifanlimab was discontinued due to a treatment-related AE in 8.4% of patients. Dose reductions of retifanlimab were not allowed. Dose delays due to an AE occurred in similar frequencies in the All Cancer 500mg Q4W Population (31.0%) and the MCC Population (35.5%). The type of AEs that were most frequently reported to lead to a dose delay in the All Cancer 500mg Q4W population were COVID-19, diarrhoea, pyrexia, ALT increased, lipase increased and rash. In the MCC population, these were ALT increased, COVID-19, and lipase increased and amylase increased. Doses may have been delayed up to 12 weeks for toxicity management with acceptable treatment delays of > 12 weeks for logistical reasons. There were no patients with treatment delays of > 12 weeks who continued with the treatment. AEs leading to retifanlimab discontinuation were observed in 14.6% of the All Cancer 500mg Q4W Population (8.4% treatment-related) and in 20.6% of the MCC Population (15% treatment-related). The higher discontinuation rate due to (treatment-related) AEs in the MCC population can be explained by the longer treatment duration compared to the All Cancer 500mg Q4W. Treatment-related AEs leading to discontinuations were most frequently reported due to diarrhea and hepatitis (in 2 patients each, 0.7%). In the MCC Population treatment-related AEs leading to discontinuation occurred in single cases.

In general, haematology and clinical chemistry laboratory values did not show any unexpected clinically meaningful changes. At the start of retifanlimab treatment, the majority of patients had a low haemoglobin, a substantial fraction had decreased white blood cell counts and small number of patients had low platelet

counts. This was largely comparable between the patients with all tumour types and the MCC patients. During treatment, lowering of haemoglobin (40.7%, percentages for the All Cancer 500mg Q4W population) and lymphocytes (36.4%) were the most frequent haematology parameter events in both populations. Most events were of grade 1 or 2. Treatment-emergent worsening of chemistry parameters was observed most frequently for increased AST (29.7%), decreased albumin (29.5%), decreased magnesium (29.3%), decreased sodium (28.5%) and increased cholesterol (26.2%). Other frequently reported changes were ALT increased (24.7%), and lipase increased (26.0%). An increase in amylase was also frequently observed (22.1%). The reported frequency of pancreatitis in the All Cancer 500mg Q4W population was only 0.5% (2 patients). The other cases of increased lipase or amylase were asymptomatic. There was one patient with an immune-related pancreatitis that was serious, and retifanlimab treatment was discontinued because of the treatment-related AE. There were no cases of drug-induced liver injury (DILI). Based on the reported ECG findings it appears that retifanlimab does not induce clinically relevant changes from baseline in the QTc interval and has no meaningful effect on ECG parameters. It is expected that monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not deemed necessary.

General warnings relevant to PD-1 inhibitors have been reflected in section 4.4 of the SmPC. More specifically, solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with retifanlimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with retifanlimab versus the risk of possible organ rejection should be considered in these patients. In addition, fatal and other serious complications can occur in patients who receive allogeneic haematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1–blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GvHD), acute GvHD, chronic GvHD, hepatic veno-occlusive disease after reduced intensity conditioning and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. Patients should be closely followed for evidence of transplant-related complications and prompt intervention may be required. The benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT should be considered.

The Applicant investigated the safety profile in subgroups based on several intrinsic demographic and baseline characteristics.

Age - Frequencies of (severe) AEs or irAEs were comparable between the subgroups younger or older than 65 years. Participants who were ⩾ 75 years of age had higher frequencies of serious TEAEs, Grade 3 or higher TEAEs, fatal TEAEs, and TEAEs leading to dose delay and discontinuation than participants who were < 75 years of age. Frequency or severity of infusion-related reactions did not differ between age subgroups.

Gender - Female patients had a ~14% higher incidence of treatment-related AEs and ~10% higher incidence of irAEs compared to males; the incidence of ≥Grade 3 (ir)AEs was comparable in the All Cancer 500 mg Q4W Population. According to the Applicant, the difference in irAEs may be attributable to the higher frequency of thyroid-related endocrine irAEs in female patients.

Race - Frequency or severity of TEAEs or irAEs were in general comparable between subgroups based on race. The category 'non-Caucasian' includes also patients with no race reported and the results should therefore be interpreted with caution. This and also differences in the size of the subgroups are acknowledged. Overall, there are no safety signals in the subgroups by race.

ECOG status - As expected, the numbers of serious, ≥Grade 3 and fatal AEs were higher in patients with ECOG-PS ≥1 vs ECOG-PS 0 and median treatment duration was shorter in patients with worse performance

status. Patients with ECOG-PS of 2 or higher were formally excluded from the clinical studies (although 2 patients with ECOG-PS of 2 were included), and it might be expected that tolerability will be worse in that subgroup. In section 5.1 of the SmPC it is described that all patients had an ECOG performance score (PS) of 0 or 1. It is stated in the SmPC that patients with an ECOG-PS of ≥2 were excluded.

Renal impairment - In the All Cancer 500 mg Q4W Population, 35.4% had at baseline a normal renal function, 37.2% had mild renal impairment, 26.8% with moderate renal impairment, and 0.7% had a severe renal impairment. No patient had end stage renal disease. Overall, no clinically meaningful differences were observed in frequency or severity of TEAEs or irAEs, although the subgroup with severe renal impairment is considered too small to draw conclusions. This is reflected in section 4.2 of the SmPC.

Hepatic impairment - The All Cancer 500 mg Q4W Population consisted of 87.4% with normal hepatic function, and 12.6% with mild hepatic impairment at baseline. When comparing the patients with normal and mild hepatic impairment, no clinically meaningful differences were observed in frequency or severity of TEAEs, irAEs, or infusion related reactions. None of the participants had moderate or severe hepatic impairment. It is currently stated in section 4.2 of the SmPC that there is insufficient data in patients with moderate hepatic impairment to give a dosing recommendation, and no data in patients with severe hepatic impairment.

HIV status - In the All Cancer 500 mg Q4W Population, 10 HIV-positive patients were included. During retifanlimab treatment none of the patients developed 2 consecutive viral loads of > 1000 copies/mL and CD4+ counts were relatively stable. It is however noted that one patient shows CD4-decrease till below 500 and is still declining. As this concerns a single patient, this issue is not further pursued. Interpretation of the HIV-positive subgroup is hampered by the small sample size, but no safety signals emerged regarding the frequencies of (ir)AEs.

The Applicant only performed subgroup analyses for intrinsic factors and not for extrinsic factors such as region or number of prior lines of systemic therapy. As the study MCC Population was very homogeneous for number of prior lines of therapy and region (study was performed in EU and USA only), subgroup analyses for extrinsic factors was not further pursued. There are no data on the use of retifanlimab in pregnant women, lactating women (see SmPC 4.6), or patients younger than 18 years of age (see SmPC 4.2).

In the All Cancer Population 640 patients were assessable for immunogenicity of whom 214 had inconclusive results. Of the remaining 426 patients, 19 were ADA positive during the study. Eight of 19 ADA-positive patients had nontreatment-emergent ADA with only baseline positive ADAs, and 11 of them had treatment-emergent ADAs. Out of these 11 treatment-emergent positive patients, one patient with persistent positive ADAs was observed. Of those who were ADA positive, nAbs were detected in 4 participants (0.6% of the total). In study INCMGA 0012-201 in patients with MCC, 2 participants had treatment-emergent ADAs: 1 was persistent, and 1 of these participants was identified as nAb positive. Given that both ADA-positive participants had either a best overall response by ICR of partial response or stable disease, efficacy does not appear to be impacted by immunogenicity in these participants. Regarding safety, there were no new safety concerns in the patients that were treatment-emergent ADA positive.

In study INCMGA 0012-203 (n=121 patients included in the All Cancer 500mg Q4W population), retifanlimab was given in a 30-minute infusion, and in the other 4 studies it was given as a 60-minute infusion. The Applicant uses the similar frequencies of IRRs as clinical safety support for the 30 minute infusion time. Based on PK assessments, simulated Cmax after the first dose and at steady state showed no relevant difference after an infusion of 30 or 60 minutes (see 2.6.2).

The Applicant has provided a summary of safety data with respect to infusion-related reactions comparing the most studied 60-minute infusion time with the proposed 30-minute infusion time in the patients from the 500mg Q4W population. From a PK-perspective, the shorter infusion time can be supported. Looking at the safety comparison, the incidence of infusion-related reactions, irAEs and TEAEs appears comparable between the two groups. From a safety perspective, the shorter infusion time of 30 minutes can therefore also be accepted.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The frequencies and types of AEs are reflective of the known safety profile of PD-(L)1 inhibitory treatment and no new safety issues were identified. Toxicity in clinical practice might be higher given that the studied MCC population was a selected, relatively fit population. Furthermore, the safety data comes from open-label, uncontrolled studies hampering the causality assessment and thereby the overall interpretation. In addition, (duration of) exposure is limited and long-term safety has been included as a safety concern in the RMP. Considering the clinical setting, it can be concluded that the safety of retifanlimab in the agreed indication appears to be acceptable and manageable. The safety risks associated with immune related adverse reactions are managed through additional risk minimisation activities implemented in the form of patient card focused on signs and symptoms of immune-related adverse reactions and the best course of action to be taken by the patient and relevant healthcare professional (reflected in the RMP, SmPC section 4.2 and Annex IID).

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 84: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Immune-Mediated Adverse Reactions Infusion-Related Reactions
Important potential risks	None
Missing information	Long term safety

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities

2.7.3. Risk minimisation measures

Table 85: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immune-mediated adverse reactions	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Legal status Additional risk minimisation measures: Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Infusion-related reactions	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety	Routine risk minimisation measures: Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 22 March 2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group accepted the request to use minimum particulars on the vial label.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zynyz (retifanlimab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Zynyz is indicated as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation therapy.

3.1.2. Available therapies and unmet medical need

For patients with advanced or metastatic MCC that are not candidates for curative therapy, only few treatment options exist. Specifically for recurrent locally advanced MCC there are currently no approved therapies. The recommended first-line therapy in Europe is immunotherapy (Gauci et al. European Journal of Cancer. 2022); more specifically, anti-PD-(L)1 therapies, with avelumab being the only medicinal product authorised (EMEA/H/C/004338/0000;EMEA/H/C/004338/II/0013) in the metastatic setting. When immunotherapy is contraindicated, chemotherapy can be considered (Gauci et al. European Journal of Cancer. 2022).

Before the introduction of immunotherapy, the most commonly used first-line therapy was platinum-based chemotherapy ± etoposide, resulting in high response rates (60-70%; (EMEA/H/C/004338/0000), but poor duration of response (≤8 months; Nghiem et al. Future Oncol. 2017)

It is described in literature that the outcomes in patients with metastatic MCC are poor (i.e., 5-year survival of 13.5%; Stachyra et al. Int J Mol Sci. 2021). The prognosis has likely improved with the introduction of immunotherapy, but an unmet medical need remains in the absence of curative therapies. Retifanlimab can be considered a valuable addition to the treatment armamentarium for advanced MCC. No products are currently approved for recurrent locally advanced MCC.

3.1.3. Main clinical studies

The pivotal study supporting this marketing authorisation application is INCMGA 0012-201 (POD1UM-201, NCT03599713), an ongoing, open-label, single-arm, multiregional, Phase 2 study of retifanlimab in patients with metastatic or recurrent locally advanced MCC. Patients received retifanlimab 500 mg every 4 weeks until disease progression or unacceptable toxicity for a maximum of 2 years. The primary efficacy population was the Chemotherapy-Naïve MCC full analysis set (FAS), which included all patients enrolled in the study who received at least 1 dose of study drug as of 15 October 2020 (n=101).

The main population for the analysis of clinical safety is the 'All Cancer 500mg Q4W population', which includes all 452 patients that were treated with at least one dose of retifanlimab in the proposed dose of 500 mg Q4W, regardless of tumour type, in five uncontrolled clinical studies.

3.2. Favourable effects

The ORR based on ICR assessment was 52.3% (34/65; 95% CI: 39.5, 64.9); with a best overall response of CR in 12 patients (18.5%) and PR in 22 patients (33.8%) (DCO 21 January 2022).

Updated ORR was 53.5% (95% CI: 43.3, 63.5) (DCO 10 March 2023).

The ORR based on investigator assessment was 61.5% (95% CI: 48.6, 73.3) (DCO 10 March 2023).

The ORR based on ICR in chemotherapy-naïve patients with centrally confirmed MCC and measurable disease was 51.7% (31/60; 95% CI: 38.4, 64.8) (DCO 10 March 2023).

Responses were seen in all pre-defined subgroups.

Median DoR was not reached (95% CI: 14.0, NE). Based on landmark analysis, 26 of 34 responses (76.5%) were ≥ 6 months and 21 (61.8%) were ≥ 12 months (DCO 21 January 2022).

Updated mDoR was 25.3 months (95% CI: 14.2, NE) (DCO 10 March 2023).

3.3. Uncertainties and limitations about favourable effects

Study INCMGA 0012-201 is a single-arm trial and design techniques to avoid/minimize bias, such as randomisation and blinding, were not implemented. The study design is, however, acceptable, because MCC is a rare disease.

ORR is a surrogate endpoint and not a direct measure of clinical benefit. Still, a large treatment effect on ORR, in combination with long DoR, may be expected to translate into meaningful clinical benefit.

Immunosuppressed patients were excluded from participation in the trial, except for patients with controlled HIV infection. The lack of information on the use of retifanlimab in this subset of patients is reflected in section 4.4 of the SmPC.

3.4. Unfavourable effects

AEs occurred in 94.5% in the All Cancer 500mg Q4W population (66.6% treatment-related) and in 89.7% of the MCC population (67.3% treatment-related). The most common TEAEs were asthenia (22.6%), diarrhoea (18.6%), and pruritus (15.9%).

Grade ≥3 or higher AEs occurred in 44.7% in the All Cancer 500mg Q4W population (13.9% treatment-related) and in 31.8% of the MCC population (16.8% treatment-related). The most common Grade 3 or higher TEAE was anaemia (6.2%), which was considered treatment related in 4 patients (0.9%). The most common treatment-related Grade 3 or higher TEAEs in the MCC-population were amylase and lipase increased (1.9% each).

Serious AEs occurred in 36.5% in the All Cancer 500mg Q4W population (7.3% treatment-related) and in 26.2% of the MCC population (12.1% treatment-related). The most frequent treatment-related serious TEAE were hepatitis and pneumonitis in 3 patients each (0.7%).

There were 25 deaths due to an AE (5.5%) in the All Cancer 500mg Q4W population and 43 (3.7%) in the MCC population. Three fatal AEs were assessed to be possibly related to retifanlimab by the investigator but

not by the sponsor: treatment-induced hyperprogression (n=2) and progression of CLL. There was one fatal case of interstitial lung disease confirmed to be treatment-related.

AEs leading to retifanlimab discontinuation were observed in 14.6% of the All Cancer 500mg Q4W Population (8.4% treatment-related) and in 20.6% of the MCC Population (15% treatment-related).

Adverse events of special interest include immune-related AEs (34.5% any grade), most frequently hypothyroidism (10.2%) and immune-related skin reactions (9.5%); and infusion-related reactions (6.2% any grade).

Other immune-related AEs were pneumonitis (3.1%), hepatitis (3.5%), colitis (2.7%), nephritis (2.0%), myositis (0.7%), Guillain-Barré syndrome (0.7%), uveitis (0.7%) and pancreatitis (0.4%). With the exception of uveitis, most of these immune-related AEs required treatment with systemic corticosteroids.

Participants who were ≥ 75 years of age had higher frequencies of serious TEAEs, Grade 3 or higher TEAEs, fatal TEAEs, and TEAEs leading to dose delay and discontinuation than participants who were < 75 years of age.

Treatment had to be interrupted, delayed or discontinued due to an adverse event in 31.9%, 31.0% and 14.6% of patients in the All Cancer 500mg Q4W population. Retifanlimab was discontinued due to a treatment-related AE in 8.4% of patients.

3.5. Uncertainties and limitations about unfavourable effects

The five included studies were uncontrolled, which hampers the causality assessment of adverse events.

Certain subgroups (patients with ECOG-PS of 2 or higher, severe renal impairment or end-stage renal disease and moderate or severe hepatic impairment) were not (sufficiently) studied and the lack of data are reflected in section 4.4 of the SmPC.

There is no data on the use of retifanlimab in pregnant women, lactating women, or patients younger than 18 years of age. This information is reflected in the SmPC.

Due to the limited duration of safety follow-up, long-term safety data is lacking (see RMP).

3.6. Effects Table

Table 86: Effects Table for Zynyz for the treatment of MCC (data cut-off: 21.01.2022).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	The percentage of patients having an objective response (CR or PR).	%	53.5% (95% CI: 43.3, 63.5)	NA	Uncertainties: POD1UM-201 is a single-arm trial ORR is a surrogate endpoint and therefore not a direct measure of clinical benefit Strength: 17 patients (16.8%) had a CR	Table 38
DOR (median)	The time from an initial objective response until disease progression, or death due to any cause.	Months	25.3 months (95% CI: 14.2, NE)	NA	Uncertainties: Time-to-event endpoints difficult to interpret without control arm Data maturity was 40.7%	Table 39; Figure 39
Unfavourable Effects						
			MCC 500mg Q4W population (n=107)	**All Cancer 500mg Q4W population (n=452)**		
SAEs	All causality (drug-related)	%	26.2 (12.1)	36.5 (7.3)		Table 48
Grade ≥3 AEs	All causality (drug-related)	%	31.8 (16.8)	44.7 (13.9)		Table 48
Deaths	Due to AE (drug-related)	%	3.7 (0.9)	5.5 (0.2)		Table 48
Discontinuations	Due to AE (drug-related)	%	20.6 (15)	14.6 (8.4)		Table 48

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
AESI	Immune-related AEs	%	39.3	34.5		Table 54
	IRR		4.7	6.2		

Abbreviations: CR= complete response, DOR= duration of response, NA= not applicable, NR= not reached, ORR=objective response rate, PR = partial response
Notes: (1) data from study INCMGA 0012-201 (POD1UM-201)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

As MCC is a rare disease, a pivotal single-arm trial for authorisation purposes can be considered acceptable. Besides, treatment of MCC is mostly based on retrospective or small prospective studies. The methodological weaknesses associated with single-arm trials should, however, be taken into account when assessing the study results. Outcomes need to be reliable and compelling, and there should be sufficient evidence to assume that any detriment on important endpoints compared to the standard of care can be ruled out.

The anti-tumour activity of retifanlimab, as observed in study POD1UM-201, is clinically meaningful. Approximately half of the patients in the FAS either had a complete (16.8%) or partial response (36.6%). Moreover, the responses appear durable, considering that the median DOR based on Kaplan-Meier analysis was 25.3 months (95% CI: 14.2, NE). Overall survival outcomes are difficult to interpret in the context of a single-arm trial, but the survival curve appears to flatten over time – indicative of a plateau. The results of the pivotal trial are considered credible.

It is described in literature that MCC is immunosensitive, resulting from viral infection or UV exposure (Gauci et al. European Journal of Cancer. 2022). Hence, there is a clear rationale for the use of immunotherapy in MCC. The benefit of checkpoint inhibitors for the treatment of MCC has already been shown in studies investigating avelumab (EMEA/H/C/004338/II/0013). There is also potential activity with pembrolizumab (Nghiem et al. JCO. 2019). The treatment effects of retifanlimab are comparable to that estimated for other PD-(L)1 inhibitors. Importantly, immune checkpoint inhibitors are already the recommended first-line therapy in MCC in the European consensus guideline (Gauci et al. European Journal of Cancer. 2022). Retifanlimab is therefore considered a valid first-line treatment option in patients with advanced MCC.

Regarding safety, the most important toxicities are immune-related adverse effects and infusion-related reactions. Most common are endocrinopathies, which can usually be managed with endocrine replacement therapy, and skin reactions. Less frequent, but more severe, immune-related AEs are pneumonitis, hepatitis and colitis, which often require systemic corticosteroids. The safety profile of retifanlimab appears comparable to what is known from other PD-(L)1 inhibitors and can be considered acceptable as fatal treatment-related AEs are rare and treatment was rarely discontinued due to a treatment-related AE.

3.7.2. Balance of benefits and risks

The treatment effects of retifanlimab on ORR and DoR are compelling and expected to translate into

meaningful benefit. Considering the rarity of the disease and the regulatory precedent, a pivotal study with a single arm design is acceptable.

The safety profile of retifanlimab appears comparable to what is known from other PD(L)1-inhibitors, and can be considered acceptable as fatal treatment-related AEs are rare and treatment was rarely discontinued due to a treatment-related AE.

Considering the above it can be concluded that the benefit-risk balance is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Merkel cell carcinoma is a rare disease. The methodological weaknesses associated with single-arm trials are, of course, to be taken into consideration when assessing the data (e.g., use of surrogate endpoints, lack of comparator, risk of biases, *et cetera*). Results from the main study are meaningful (i.e., high rate of durable responses) and credible (i.e., class effects in MCC; pharmacological rationale). These findings add to the available evidence that support the use of immune checkpoint inhibitors in MCC (D'Angelo et al. J Immunother Cancer. 2021; Nghiem et al. JCO. 2019). Note that anti-PD-(L)1 therapies are currently recommended as first-line therapy for locally advanced or metastatic MCC in the European consensus guideline (Gauci et al. European Journal of Cancer. 2022).

Important to note is that the regulatory bar has been set with the approval of avelumab. This approval also changed the treatment landscape in MCC. When comparing Study INCMGA 0012-201 (Zynyz) with Study EMR100070-003 (Bavencio; EMEA/H/C/004338/II/0013), a difference in the size of the study population is observed. However, Study EMR100070-003 included both treatment-naïve (part B of the study) and previously-treated patients (part A of the study), resulting in the approval of a line-independent indication. After the first round, the Applicant no longer sought a line-independent indication for Zynyz. Efficacy of Zynyz in chemotherapy-naïve patients in the first-line setting has been substantiated to the same extent as for avelumab.

The data can be considered sufficiently comprehensive in the sought indication, because:

- the benefit/risk of Zynyz is characterized to a similar extent as for Bavencio in the first-line setting;
- external evidence (i.e., class-effect) support study findings and leverage the size of the data package.

Based on the above, the clinical data are considered sufficient for a standard marketing authorisation.

3.8. Conclusions

The overall benefit/risk balance of Zynyz is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zynyz is favourable in the following indication(s):

Zynyz is indicated as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

As the 1st PSUR has a data lock point within 6 months after the Commission Decision the marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Zynyz in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The purpose of the educational programme is to minimise the risk of immune-related adverse reactions and optimise the risk-benefit balance of Zynyz. The aim of this tool is to ensure that information regarding the patient's treatment with Zynyz and its important risks of immune-related adverse reactions are held by the patient at all times and reaches the relevant healthcare professionals as appropriate. The information on the patient card is focused on signs and symptoms of immune-related adverse reactions and the best course of action to be taken by the patient and relevant healthcare professional.

The MAH shall ensure that in each Member State where Zynyz is marketed, all healthcare professionals who are expected to prescribe Zynyz have access to/are provided with the following educational materials:

- Package leaflet
- Patient card

The **patient card** shall contain the following key messages:

- A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Zynyz
- That Zynyz treatment may increase the risk of immune-related adverse reactions
- Signs or symptoms of the safety concern and when to seek attention from a healthcare professional
- Contact details of their Zynyz prescriber

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that retifanlimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).