Amsterdam, 24 June 2021
EMA/CHMP/621679/2021
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Zynyz

International non-proprietary name: retifanlimab

Procedure No. EMEA/H/C/005632/0000

Note

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

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Table of Contents

List of abbreviations

ACB	accession cell bank
ADA	antidrug antibodies
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AESI	adverse event of special interest
AEX	anion exchange chromatography
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
AUC_{0-t}	area under the curve from time 0 to t
BALT	bronchus associated lymphoid tissue
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CDC	complement-dependent cytotoxicity
CE-LDS	reduced capillary gel electrophoresis – lithium dodecyl sulfate
CEX	cation exchange chromatography
CHO	Chinese Hamster Ovary cells
CI	confidence interval
cIEF	capillary isoelectric focusing
CL	clearance
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration over the dose interval
CNS	central nervous system
CPP	critical process parameter
CPV	continued process verification
CQA	critical quality attribute
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	threshold cycle
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CV	coefficient of variation
CXCL10	chemokine (C-X-C motif) ligand 10
CXCL9	chemokine (C-X-C motif) ligand 9
DCO	data cutoff
DCR	disease control rate
DDI	drug-drug interactions

DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DP	drug product
DS	drug substance
DTL	drug tolerance level
EC_{50}	effective concentration at 50% of maximal activity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOI	end of infusion
EOP	end of production
EOPCB	end of production cell bank
EOT	end of treatment
EOTV	end of treatment visit
ExGEN	extended generation
Fc	fragment crystallizable
FDA	Food and Drug Administration
FMEA	Failure Mode Effects Analysis
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HC	heavy chain
HCCF	harvested cell culture fluid
HCP	host cell protein
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HMW	high molecular weight species
HPV	human papilloma virus
IC_{50}	mean half-maximal inhibitory concentration
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICR	independent central review
IFN-γ	interferon gamma
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IIV	interindividual variability
IL	interleukin
IPC	in process controls
irAE	immune-related adverse event
iRECIST	modified RECIST v1.1 for immune-based therapeutics

ISS	Integrated Summary of Safety
IV	intravenous(ly)
kDA	kilodalton
KPP	key process parameter
LAL	Limulus amebocyte lysate
LC	light chain
LC-MS	liquid chromatography–mass spectrometry
LIVCA	limit of *in vitro* cell age
LLOQ	lower limit of quantification
LOD	limit of detection
mAb	monoclonal antibody
max	maximum
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MMR	mismatch repair
MRT	mean residence time
MSD-ECL	Meso Scale Discovery Electrochemiluminescence
MSI	microsatellite instability
MTD	maximum tolerated dose
MVM	Murine Minute Virus
MVOF	minimum value of objective function
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not estimable
nKPP	non-key process parameter
NOAEL	no-observed-adverse-effect level
NOR	normal operating range
ORR	objective response rate
OS	overall survival
PAR	proven acceptable range
PBMC	peripheral blood mononuclear cell
PC	process characterisation
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death receptor-ligand 1
PD-L2	programmed death receptor-ligand 2
PDT	population doubling time
PFS	progression-free survival
pI	isoelectric point
PK	pharmacokinetic
PO	oral
PPES	palmar-plantar erythrodysaesthesia syndrome
PPQ	process performance qualification
PQR	product quality review

PR	partial response
PTM	post-translational modifications
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QA	quality attributes
QC	quality control
qPCR	quantitative polymerase chain reaction
QT	QT interval in electrocardiogram tracings
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
QTTP	quality target product profile
RBC	red blood cell
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RS	reference standard
SAE	serious adverse event
SCAC	squamous carcinoma of the anal canal
SD	stable disease
SEB	staphylococcal enterotoxin B
SE-HPLC	size exclusion high-performance liquid chromatography
SmPC	summary of product characteristics
STD	standard deviation
TEAE	treatment-emergent adverse event
TEM	transmission electron microscopy
TFF	tangential flow filtration
TK	toxicokinetics
T_{max}	time to maximum concentration
TNF	tumour necrosis factor
Tregs	regulatory T cells
UF/DF	ultrafiltration/diafiltration
ULN	upper limit of normal
ULOQ	upper limit of quantification
Vc	Central volume of distribution
V_D	volume of distribution
Vp	peripheral volume of distribution
VL	variable region of the light chain
V_{ss}	volume of distribution at steady state
WCB	working cell bank
WFI	water for injection
WRES	weighted residuals
WHO	World Health Organization

1. Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Zynyz, an orphan medicinal product, in the treatment of adult patients with locally advanced or metastatic squamous carcinoma of the anal canal (SCAC) who have progressed on or who are intolerant of platinum-based chemotherapy is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

- Insufficient evidence to support the NAS claim
- It is unclear whether the reported ORR upon retifanlimab treatment can be expected to translate into clinical meaningful benefit in terms of time-dependent endpoints, i.e. PFS and OS.
- The proposed indication is not acceptable as it is broader than the study population treated in the single pivotal study.
- The application for a conditional marketing authorisation has not been sufficiently justified.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

A request for GMP inspection is not required.

GCP inspection(s)

No GCP inspection has been performed and is not required at this point.

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. However insufficient evidence has been presented and a MO has been raised.

Similarity with authorised orphan medicinal products

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products, because there are no authorised orphan medicinal products for the condition 'treatment of anal cancer'.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication is:

Retifanlimab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic squamous carcinoma of the anal canal (SCAC) who have progressed on or who are intolerant of platinum based chemotherapy.

2.1.2. Epidemiology and risk factors

Anal cancer is a rare disease and accounts for 3% of all gastro-intestinal malignancies (Rao et al., J Clin Oncol, 2020). The large majority of anal cancers concern squamous cell carcinomas of the anal canal (SCAC; 85-95%). The incidence is somewhat higher in women and is increasing. In Europe, approximately 2000 males and 2300 females are diagnosed with anal carcinoma every year (Glynne-Jones et al., Ann Oncol, 2014). For both sexes, 5-year prevalence in Europe is 40,826 (The Global Cancer Observatory, 2020). Five-year survival has changed little in the last two decades, with 5-year survival rates varying between 66% (Central Europe) and 44% Eastern Europe (Glynne-Jones et al., Ann Oncol, 2014). Lymph node involvement at diagnosis is observed in 30%–40% of cases while systemic spread is uncommon with distant extra-pelvic metastases recorded in 5%–8% at onset. While most patients with SCAC have localised disease at the time of initial diagnosis, systemic metastases will develop in approximately 10% to 25% of patients, and the 5-year OS rate for these patients is only 15% to 20% (Eng, Cancer Invest, 2006; Ghosn et al., World J Gastroenterol, 2015).

2.1.3. Biologic features

SCAC is strongly associated with human papillomavirus (HPV) infection which represents the causative agent in 80%–85% of patients (usually from HPV16 or HPV18 subtypes in Europe). Anal intercourse and a high lifetime number of sexual partners increase the risk of persistent HPV infection in men and women. Other important risk factors include human immunodeficiency virus (HIV) infection and the use of immunosuppressants. Cigarette smoking may also be important in the modulation/persistence of HPV infection and, hence, outcomes of treatment (Glynne-Jones et al., Ann Oncol, 2014).

Anal cancer may arise from a precursor dysplastic lesion—AIN —also known as anal squamous intra-epithelial lesions. Progression from AIN to invasive malignancy is uncommon in immunocompetent patients, but appears more likely in immunosuppressed patients, and is influenced by HIV seropositivity, low CD4 count and serotype of HPV infection. HPV-associated tumours usually retain wild-type P53, and this explains why patients with HPV-associated tumours respond well to concurrent chemoradiotherapy (Glynne-Jones et al., Ann Oncol, 2014).

The literature is indicating that approximately two-thirds of SCAC patients have PD-L1 positive tumours, and that there is no correlation between HPV infection status and PD-L1 expression (Wesseley et al 2020). Further, it is indicated through retrospective analyses that PD-L1 is an independent prognostic marker in SCAC for survival. At the present, no conclusion can be drawn whether or not PD-L1 expression is linked to response to immune checkpoint blockade.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Most patients with SCAC present with localised disease, with the most frequent presenting symptom being rectal bleeding in approximately 45% of patients (Ryan et al., N Eng J Med, 2000; Glynne-Jones et al., Ann Oncol, 2014). Approximately 30% of patients also experience anal pain and sensation of rectal mass (Ryan et al., N Eng J Med, 2000). Rarely patients present with inguinal lymphadenopathy. The diagnosis of anal cancer is made on biopsy-proven histology. Imaging should include magnetic resonance imaging (MRI) of the pelvis or, if not available, endo-anal ultrasound (EUS). Distant metastases can be assessed with computed tomography (CT) of the thorax and abdomen. Positron emission tomography (PET)/CT with [18F]fluorodeoxyglucose (FDG–PET/CT) has a high sensitivity in identifying involved lymph nodes, as the majority of anal carcinomas are FDG-avid (Glynne-Jones et al., Ann Oncol, 2014).

Prognostic factors for worse survival in anal cancer include male sex, positive lymph nodes - particularly positive inguinal lymph nodes - and primary tumour size >5 cm. Even in the context of HIV, patients with anal cancer who smoke also appear to have a worse OS than non-smokers (Glynne-Jones et al., Ann Oncol, 2014).

Before the widespread use of highly active antiretroviral therapy (HAART), HIV-positive patients were considered to have enhanced toxicity from chemoradiation (CRT), but more recent evidence suggests similar outcomes in HIV-positive patients treated with HAART in terms of complete response and survival to HIV-negative patients (Wexler et al., Dis Colon Rectum, 2008; Fraunholz et al,, Radiother Oncol, 2011).

Localised SCAC treated with primary chemoradiotherapy has a 5-year disease-free survival rate of approximately 60% (Flam et al., J Clin Oncol, 1996; Bartelink et al., J Clin Oncol, 2017; Ajani et al., JAMA, 2008).

Approximately 10%–20% of patients suffer distant relapse. The most common sites of metastatic spread are to the para-aortic nodes, liver, lungs and skin, which usually appear relatively late and in the context of local persistence or recurrence of disease following treatment. The prognosis in this group is poor with only 10% of patients with distant metastases surviving 2 years or more (Glynne-Jones et al., Ann Oncol, 2014).

2.1.5. Management

The primary aim of treatment of local or locoregional disease is to achieve cure with locoregional control and preservation of anal function, with the best possible quality of life. Combinations of 5-fluorouracil (5-FU)-based CRT and other cytotoxic agents [mainly mitomycin C (MMC)] have been established as the standard of care, leading to complete regression in 80%–90% of patients, with locoregional failures of ~15%-30% (Glynne-Jones et al., Ann Oncol, 2014). For some patients with local failure, salvage surgery is feasible (Renehan et al., Br J Surg, 2005).

Otherwise fit patients with symptomatic metastatic or recurrent disease not amenable to surgery should be considered for chemotherapy, usually with a combination of cisplatin and 5-FU. Activity is also reported for carboplatin, doxorubicin, taxanes and irinotecan ± cetuximab—or combinations of these agents (Glynne-Jones et al., Ann Oncol, 2014). The recent Phase 2 InterAACT study randomised 91 patients with advanced anal cancer to first line chemotherapy with cisplatin + 5-FU or carboplatin + weekly paclitaxel. Median PFS was 5.7 months for cisplatin + 5-FU compared with 8.1 months for carboplatin + paclitaxel. Median OS was 12.3 months for cisplatin + 5-FU compared with 20 months for carboplatin plus paclitaxel (HR 2.00; p= 0.014) (Rao et al., J Clin Oncol, 2020).

There is no established systemic therapy for patients with locally advanced or metastatic cancer whose disease has progressed on initial systemic treatment. Most guidelines, including the ESMO guideline, do not include specific recommendations for therapy following first-line platinum chemotherapy. Therefore, there remains a significant unmet medical need for these patients.

2.2. About the product

Mode of action

Retifanlimab is a humanised, hinge-stabilised, IgG4κ monoclonal antibody that recognises human PD-1 and contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1-expressing cells, including T cells, and restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

Pharmacological classification

Retifanlimab belongs to the pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, monoclonal antibodies. The ATC code is not yet specified.

Claimed indication and recommendation for use

The proposed indication is:

Retifanlimab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic squamous carcinoma of the anal canal (SCAC) who have progressed on or who are intolerant of platinum based chemotherapy.

Retifanlimab is formulated as concentrate for solution for infusion. The recommended dose is 500 mg retifanlimab every 4 weeks (Q4W) administered as an intravenous infusion over 30 minutes.

Special pharmaceutical aspects

Not applicable.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development plan in support of the current application consists of five ongoing clinical studies: two phase 1 studies (INCMGA 0012-101, INCMGA 0012-104) and three phase 2 studies (INCMGA 0012-201, INCMGA 0012-202, INCMGA 0012-203).

The single study considered to be key to the proposed indication is study INCMGA 0012-202 (PODIUM-202), an ongoing single arm, phase 2, multicentre, open-label study of retifanlimab monotherapy in patients with locally advanced or metastatic SCAC who progressed on or were intolerant to platinum-based chemotherapy.

One phase 3 study in locally advanced or metastatic SCAC is ongoing, in an earlier line of treatment (INCMGA 0012-303; PODIUM-303). This randomised study compares retifanlimab added to first line chemotherapy with placebo added to chemotherapy. PODIUM-303 is proposed as specific obligation as the confirmatory study for the current CMA application.

Specific CHMP guidelines relevant for the current application:

- Guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/205/95 Rev.5, 22 September 2017.

- Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004. EMA/CHMP/509951/2006, Rev.1, 25 February 2016.

Scientific advice

On 30 January 2020 the applicant Incyte Biosciences Distribution B.V. received CHMP scientific advice for their product INCMGA00012 (Retifanlimab) [EMEA/H/SA/4152/3/2019/II].

2.4. General comments on compliance with GMP, GLP, GCP

The applicant has stated that the studies were conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s).

No need for a GCP inspection was identified.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

  The applicant plans to confirm the B/R of retifanlimab in previously treated SCAC as observed in Study INCMGA 0012-202 with the confirmatory Study INCMGA 0012-303, which is currently ongoing. This PODIUM-303 study is a randomised double-blind study comparing first-line treatment with chemotherapy+placebo to chemotherapy+retifanlimab. The clinical study report based on the primary endpoint of PFS is planned for December 2024. OS is a key secondary endpoint. Crossover to retifanlimab monotherapy for subjects treated in the control arm of the study is allowed in PODIUM-303. This study will provide some additional information on the B/R for retifanlimab in the platinum-refractory setting because participants experiencing confirmed progression on the placebo control arm will be allowed to cross over. The confirmatory study design will also provide extra data on the relative efficacy of retifanlimab in locally advanced versus metastatic disease because this is a stratification factor for PODIUM-303.
- Unmet medical needs will be addressed.

  While most patients with SCAC have localised disease at the time of initial diagnosis, systemic metastases will develop in approximately 10% to 25% of patients, and the 5-year OS rate for these patients is only 15% to 20%. Patients with locally recurrent disease or distant disease frequently experience pain, sacral involvement, symptomatic bulky necrotic lymphadenopathy, and destructive anal canal involvement as a result of local tumour effects. After progression on first-

line chemotherapy, patients with locally advanced or metastatic SCAC may be treated with various chemotherapies, none of which are approved or have demonstrated substantial or consistent clinically meaningful benefit in rigorous studies. Response rates reported are 26.4% for 5-FU and mitomycin combination chemotherapy (ORR in 19 patients; Saint et al. 2019) and 11.6% for pembrolizumab (ORR in 112 patients; Marabelle et al. 2020).

The applicant concludes that locally advanced or metastatic SCAC that has progressed on platinum-based chemotherapy or in patients who are intolerant of platinum-based chemotherapy is a serious and life-threatening disease for which there is a significant unmet need for new therapies. There are no agents approved in this setting, and success with chemotherapy is limited and not rigorously studied.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The applicant states that in view of the level of evidence available from the Phase 2 study PODIUM-202, the favourable benefit-risk profile and the high unmet medical need in patients for whom there is currently no effective therapy, the immediate availability of retifanlimab via a conditional marketing authorisation clearly outweighs the risk inherent to the fact that randomised data confirming clinical benefit is not available yet.

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.

Orphan designation

Retifanlimab was designated as an orphan medicinal product EU/3/20/2343 on 19 Oct 2020 in the following condition: treatment of anal cancer.

Similarity with orphan medicinal products

There are no authorised orphan medicinal products for the condition 'treatment of anal cancer'.

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision [P/0336/2020] on the granting of a (product-specific) waiver for all subsets of the paediatric population for the treatment of squamous carcinoma of the anal canal, on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in adult populations.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as concentrate for solution for intravenous infusion containing 25 mg of retifanlimab as active substance per 1 mL.

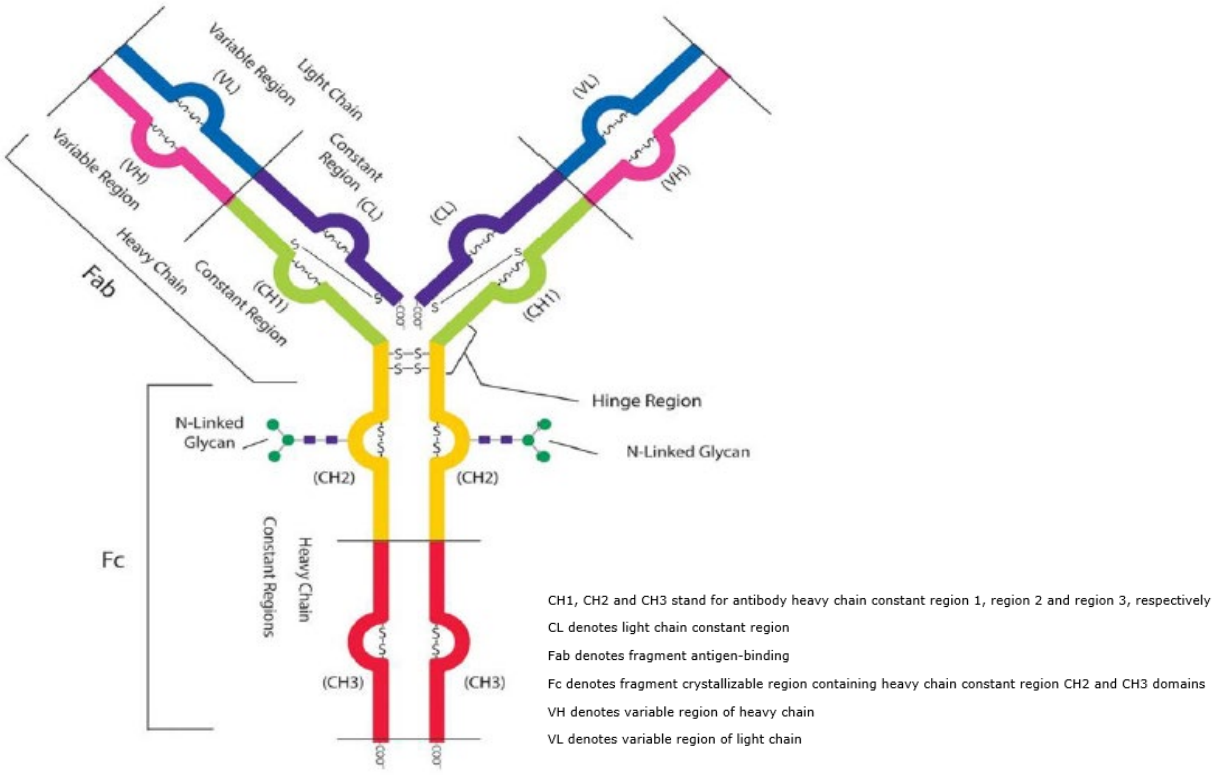
Retifanlimab is a humanised hinge-stabilised IgG4, IgK monoclonal antibody (mAb) that recognises human PD-1 expressed by T and B cells. PD-1 (programmed cell death protein 1) is an important checkpoint protein in immuno-oncology that helps the immune system to regulate and eliminate tumours.

Other ingredients in the finished product are sodium acetate trihydrate, acetic acid, sucrose, Polysorbate 80, and water for injection. The product is available as 20 mL of concentrate in a 20 mL Type I clear glass vial, with a FluroTec coated butyl rubber stopper and an aluminum seal with a flip-off cap, containing 500 mg retifanlimab.

3.1.2. Active Substance

General Information

The Drug Substance (DS) is retifanlimab, a humanised hinge-stabilised IgG4, IgK monoclonal antibody (mAb) that recognises human PD-1 expressed by T and B cells. It has a point mutation in human heavy chain 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, was introduced into the variable region of the light chain. 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.



The applicant requested retifanlimab to be considered a new active substance in itself since there is no other product containing retifanlimab as an active substance authorised in the European Union. However, retifanlimab is not the first PD-1 checkpoint inhibitor and as a result more confirmation is sought. The applicant is requested to confirm that the amino acid sequence and primary structure of retifanlimab differ from structurally similar compounds including PD-1 inhibitors already authorised as a medicinal product in the European Union (MO). Otherwise, NAS could be claimed on 3rd indent if it

can be demonstrated that retifanlimab significantly differs in properties with regard to safety and efficacy from a structurally similar substance contained in a medicinal product previously authorised in the EU.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The documentation provided supports that the DS is manufactured and tested in a GMP environment. However, for one site, which has been previously inspected by US FDA, proof of GMP compliance should be included in the dossier (OC).

The manufacturing process consists of two main stages, i.e. cell culture and harvest and purification.

Retifanlimab is expressed using recombinant Chinese Hamster Ovary (CHO) cells that secrete the antibody into the culture medium. A single working cell bank (WCB) vial is thawed and expanded in shake flasks, rocking and stirred tank bioreactors before inoculation into a production bioreactor.

The purification process consists of protein A affinity chromatography, low pH 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.

Questions have been raised for the maximum number of cycles the resin may be used for Protein A affinity chromatography and CEX chromatography (OC).

The process steps, process parameters, operation ranges and controls have been laid down in sufficient detail but critical process parameters (CPPs, defined as process parameters whose variability has an impact on a Critical Quality Attribute) are lacking for a number of important manufacturing steps such as protein A chromatography, depth filtration, CEX chromatography, anion exchange membrane chromatography and UF/DF. The applicant has been asked to define appropriate CPPs for these parameters (OC).

Oligosaccharide structures of retifanlimab were comprised mainly of the complex biantennary type with core fucosylation where G0F is the dominating glycoform. The oligosaccharide structure is as expected from an antibody produced in the CHO cell line and monosaccharide composition analysis confirmed that GlcNac is the dominant species. The monosaccharide values for GlcNAc, GalNAc, Gal, Man and Fuc are given, however monosaccharide values for sialic acid content is missing and should be provided (OC).

Source, History and Generation of the Cell Substrate

Retifanlimab is manufactured using a recombinant CHO cell line.

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

Cell Bank System

A two-tiered cell banking system consisting of Master Cell Bank and a Working Cell Bank (WCB, 335 vials) was established. 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 (C).

Genetic stability has been assessed satisfactorily but no information has been provided for the N-Glycan analysis that is part of this assessment. This information is requested (OC).

According to an established supplier qualification programme, appropriate measures (auditing, testing, and certification) are defined for each raw material supplier. The compendial raw materials and reagents comply with their respective monographs. The non-compendial materials are accepted on the basis of the in-house acceptance specifications. The in-house specifications can be agreed upon since it has been shown that the DS produced with these raw materials exhibits a consistent quality that meets pre-specified and significant product criteria.

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

Critical process parameters and in process controls have been specified. As remarked earlier, a question has been raised on the definition and number of CPPs for several process steps in the downstream process. Criticality is based on impact (severity), not on the residual risk after the implementation of the control strategy. Consequently, even if a critical parameter is adequately controlled, it will still be a critical parameter: the risk is lower but criticality is the same. As a result, the applicant is requested to revise their approach of CPPs based on the CQAs defined (OC).

The applicant has also clearly stated NORs (Normal Operating Ranges) and PARs (Proven Acceptable Ranges) when applicable. These were validated during Process Characterisation and PPQ runs. PPQ runs were performed on three full scale batches in line with the recommendations in the guideline. However, the PPQ batch used for the validation of the LIVCA at commercial scale is incorrectly named. This should be corrected in the dossier (OC).

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

Testing for adventitious viruses, Mycoplasma and Murine Minute Virus are described sufficiently. However, the applicant is asked to demonstrate specificity of the Mycoplasma test used in line with Ph.Eur. 2.6.7 recommendations (OC) and to clarify a typing error for the LOD for Murine Minute Virus (OC). In addition, the volume (1 mL) tested for contamination control should be clarified or modified to comply with Ph. Eur. 2.6.12 (OC).

The DS is stored frozen at either DS long term storage site or at DP manufacturing site.

Manufacturing process development

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

DS batches manufactured using M1 process have been used in the pivotal clinical study [INCMGA 0012-202 Squamous Cell Anal Cancer cells (SCAC) Study].

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

- Ensure clonality of the production cell line
- Utilize 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.

At the time M2 process derived DS 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. However, only three batches of M1 and three batches of M2 were included in this analysis and to avoid cherry picking, the applicant is requested to compare all M1 lots and M2 lots with Reference Standard lot for the assessment of purity and potency or sufficiently justify the selection of the batches introduced in the side-by-side analysis (OC).

Considerations discussed during the Scientific Advice meeting of 25 June 2020, such as regarding comparability criteria, description of statistical and mathematical methodologies used and number and genealogy of batches, were adopted in the comparability analysis.

Control Strategy (CS)

The approach taken to develop the retifanlimab DS 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 andM2 processes
- Process development risk assessments linking process parameters to CQAs
- Establishment of a scale-down model (SDM) as basis for process characterisation (PC) studies
- Process characterisation (PC) to identify CPPs for each unit operation and to establish proven acceptable ranges (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 process performance qualification (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, PK, 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).

For product related CQAs of retifanlimab the applicant designated hypothetical or rare QAs as 'low abundance QAs'. However, low abundance is not a relevant parameter for criticality assessment and the applicant is requested to rephrase this denomination into a term in line with ICH Q9 and to quantify 'low abundance' (OC). In addition, the number of CQAs is very low and excludes aspects such as misfolded proteins. The applicant is requested to clarify why so few product related quality attributes were designated as CQA and to demonstrate the effect of the removal of 'low abundance' as a contributing factor on CQAs that are currently deemed non-critical (OC).

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

As a result of redefining CQAs the identified CPPs could be impacted. Regardless of this effect, a question has already been raised on the identification of CPPs (OC) since criticality is based on impact (severity) and not on the residual risk after the implementation of the control strategy.

NORS, PARs and the acceptance criteria for in process controls 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, in process controls, and release and stability testing. This is

comprehensively described but no definite conclusion can be reached yet since questions have been raised and the control strategy may need to be modified.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The specification for release and stability of retifanlimab drug substance (DS) includes identity, purity and impurities, potency and other general tests.

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

In general, the descriptions suffice. However, additional information is required for the process specific ELISA kit used for the determination of residual CHO cell protein. The applicant is requested to demonstrate that most of the representative HCP species of the intended manufacturing process are present (in line with PhEur 2.6.34). It also needs to be specified what is meant by "CHO HCP Antigen Standard Stock" and how, where and when this was produced. For system suitability the applicant is requested to incorporate dilutional linearity into the SST criteria (OC).

It is noted that the DS and DP are tested for endotoxin using the compendial LAL test based on the Limulus Amebocyte lysate. The applicant is informed that the Ph. Eur recently adopted general text 2.6.32 on recombinant Factor C for Endotoxin control.

The validation document for PD-1 binding assay is missing and has been requested (OC). A PD-1 binding ELISA and a cell-based blocking assay has been used to monitor biological activity in both release and stability of DS and DP. FcRn binding conditions were provided in the method description. The rationale for studying FcRn binding at these conditions should be justified (OC).

The absence of a test for major glycosylation forms in the release specification should be justified (OC).

In addition, reference to in-house test method numbers are missing and should be included in the specifications table (OC).

The method description for determination of protein concentration is only briefly described and it is not clear what the procedure is with regards to dilution of samples and the use of BSA. The applicant is asked to clarify. Further, the applicant is asked to justify the use of the theoretical extinction coefficient and not the experimentally determined extinction coefficient when calculating the concentration. The experimentally determined extinction coefficient in the dossier should be clarified (OC).

In the method description of the polysorbate 80 assay, the number of points and the concentrations used for the polysorbate 80 standard curve is lacking and should be included (OC).

For residual CHO cell protein, an explanation is required regarding the HCPs used for spiking and how they were made (OC). In addition, the suitability should be assessed by demonstrating the coverage (OC).

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. DS release data from retifanlimab DS batches from the M1 process and thecommercial M2 process were used for this evaluation.

In general, this approach can be accepted and the acceptance criteria derived are substantiated by batches manufactured and used in studies. However, a specification for potency in PD-1 binding assay is considered too wide (OC). Similarly, the proposed specification for the PD-1 Blockade Bioassay is considered too wide (OC). The applicant is expected to align the DS acceptance criteria for potency by PD-1 binding ELISA and potency by PD-1 Blockade Bioassay with narrowed DP specifications (OC).

The applicant should strengthen the identification of retifanlimab in the DS by introducing identification criteria based on relevant structural properties. The applicant should implement a test which is able to unequivocally establish identity of retifanlimab, e.g. peptide map or other (combination of) highly specific methods (OC).

Reference standards

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

While most results are quite consistent over de period analysed both reference standards demonstrate an apparent drop in PD-1 binding (potency) EC50. An explanation is requested (OC). In addition, the applicant is requested to explain in case of a potency decrease of these standards how this affects the nominal activity of 100% assigned to the PRS which was qualified against one of these RS (OC).

A working reference standard is prepared and will be qualified against the primary reference standard. applicant is asked to update the status hereof (OC). For future reference standards a protocol is provided. The selection of the proposed acceptance limits should be clearly justified (OC).

The applicant is also requested to qualify a new RS in such a way that the risk of a drift from the mean is reduced. The SA requires justification of the statistical approach and proposed acceptance ranges. Currently, this information could not be located in the CTD and applicant is requested to provide this (OC).

Batch analysis

Batch analyses results were provided for M1 and and M2 processes.

Some analytical methods were adapted during development, 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 drug substance (DS) is stored frozen 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.

Stability

Stability studies for retifanlimab DS were conducted at the recommended storage condition and at the accelerated storage temperature to assess the effect of these conditions on product quality. The batches also contain an arm at the stressed stability storage temperature. The testing was performed

according to ICH Harmonized Tripartite Guidelines, Stability Testing of Biotechnological/Biological Products (Q5C) and Stability Testing of New Drug Substances and Products (Q1A).

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 DS as outlined in the stability plan presented.

Based on the presented data, the claimed shelf-life cannot be assigned at this time. Thus, in order to get acceptance for the proposed shelf-life, additional long-term stability data for commercial should be provided during the ongoing procedure (OC).

For dossier completeness, stability data (page 1 of 2) for one M1-produced batch is missing in the S.7.3 Stability data section and the applicant is asked to correct this discrepancy (OC).

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

Retifanlimab drug product (DP) is a solution for intravenous infusion with a clear to slightly opalescent, colorless to pale yellow solution. The drug product comprises the following ingredients: retifanlimab DS (active ingredient), sodium acetate trihydrate (buffering agent), acetic acid (buffering agent), sucrose (stabilizer, osmolyte), polysorbate 80 (stabilizer), and water for injections (solvent). The primary packaging is a single-use 20 mL Type I glass vial closed with a chlorobutyl rubber stopper, an aluminium seal and plastic overseal. The concentration of the active ingredient is 25 mg/mL. An overfill is applied to ensure that 20.0 mL, corresponding to 500 mg, can be withdrawn from the vials.

Pharmaceutical development

The commercial manufacturing process for retifanlimab was developed to meet the predefined criteria of the quality target product profile (QTPP, not reproduced here). The QTPP is a prospective summary of the quality characteristics to ensure the quality, safety, and efficacy of the drug product applied to the patient. The conditions as recommended in the SmPC are considered sufficiently covered by the development studies.

Retifanlimab DS is stored frozen, and then thawed to manufacture the DP. The DS and DP is formulated at a nominal protein concentration of 25 mg/mL in sodium acetate, sucrose, and polysorbate 80, pH 5.1. Manufacture of retifanlimab DP involves thawing of frozen DS, mixing, sterile filtration, vial filling, stoppering, and sealing. There is no dilution or compounding step involved for the manufacture of DP from DS.

The initial retifanlimab DP manufacturing process (defined as P1) produced the to be marketed formation presented as 10 mL in a 10 mL vial and was used 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. Subsequently, the P2 process was further optimised resulting in P2-TPF, which is the DP commercial manufacturing process. The DS manufactured with M2 process (M2 DS) is used for both P2 and P2-TPF processes. Comparability studies show that the materials produced by the DP manufacturing processes are comparable.

DP manufacturing steps that could impact CQA's were identified evaluated through characterisation studies. The control strategy that is in place to attenuate the risks associated to the CQA's 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.

Retifanlimab DP compatibility with different types of IV bags, in-line and add-on sterile filters are tested. It is noted that the results of infusion solutions in normal saline had elevated subvisible particles at pre-infusion time point and inclusion of in-line filter infusion sets were applied to reduce subvisible particulates to be in accordance with acceptance criteria of USP <788>. As a general principle, products should be designed in such a way that they do not need the use of an inline filter to assure their microbial and physical purity upon administration. The responsibility of ensuring sufficient quality of the product should not be given to the user by recommending filtering of the product prior to administration. The applicant should justify why filter is not considered mandatory and only recommended as stated in SmPC section 4.2 and 6.6 (OC).

Manufacture of the product and process controls

Manufacture

The facilities responsible for DP manufacture, testing, packaging, and release are GMP compliant.

The DP manufacture is a straightforward thawing, mixing, filtration and aseptic filling process which has been described in sufficient detail. All mixing conditions, holding times, filtration steps and where relevant equipment have been clearly defined. Where applicable Normal operating ranges (NOR) for process parameters are stated which are within the proposed proven acceptable ranges (PAR). All primary container parts are pre-sterilised and received ready to use.

Process controls and validation / verification

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. The applicant is requested to clarify one discrepancy where the validated time from start to end of sterile filtration is set in a table whereas a maximum hold time of is stated in the text (OC). Filled vials undergo 100% visual inspection for predefined 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 DP manufacturing process is demonstrated to be well controlled.

Product specification, analytical procedures, batch analysis

Specifications

The proposed commercial specifications for retifanlimab DP includes identity, purity and impurity, potency and other general tests.

The predominant part of the DP control tests and their release specifications are the same as applied for DS control. The following issues are identified concerning the DP release and shelf life specifications:

- The applicant is requested to tighten the shelf life value for purity to a value that is better reflected by observed changed during long-term stability (OC).
- In general, the statistical approach for setting acceptance criteria is not endorsed and should be revised (OC).
- The specification for potency in PD-1 binding assay is considered too wide (OC). Similarly, the proposed specification for the PD-1 Blockade Bioassay is considered too wide (OC). The applicant is requested to tighten these ranges in line with the statistical approach and/or batches used in clinical studies and assay variability (OC).
- The acceptance criteria for specific purity parameters should also be revised to reflect the presented batch data (OC).
- The acceptance criterion for polysorbate 80 is considered wide and should be revised to reflect the presented batch data (OC).
- To ensure that the levels of polysorbate 80 remain stable over the proposed shelf-life a test for polysorbate 80 should be considered included in the shelf life specification of the drug product (OC).

Analytical procedures and reference standards

Analytical procedures for the release testing of retifanlimab DP are partially identical for drug substance and drug product. The description of analytical methods and validation of DP specific methods is sufficiently detailed and raise no concerns.

The reference standard used for retifanlimab DP is the same as the reference standard used for drug substance.

Batch analyses

Sufficient details on release tests and results of DP batches have been provided including changes in analytical procedures during development. Batch-to-batch consistency is adequately demonstrated.

Characterisation of impurities

There are no new impurities introduced during manufacture of retifanlimab DP. 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.

Container closure system

The container closure system (CCS) consists of a Type I glass vial closed with a chlorobutyl rubber stopper and an aluminium seal and plastic overseal. Schematic drawings, dimensions, and release testing specifications are provided for the components of the primary container. The components are sterilised by the suppliers and received ready to use, however the information is not considered sufficient. For both vial and stopper, additional information should be laid down in the CTD as detailed in the LoQ (OC).

Stability of the product

The stability studies are performed according to ICH guidelines and described in sufficient detail. Data from P2 and P2-TPF manufactured batches are used for primary stability whereas P1 manufactured batches are used as supportive data, this is considered approvable. The currently available stability data demonstrate a robust stability of retifanlimab DP.

The proposed shelf life is 36 months for drug products stored at 5 ± 3°C. This period is covered by just 2 batches from supportive lots but not by any of the primary stability batches. The applicant is requested to propose a new shelf life period that is supported by at least three representative batches (OC).

A photostability study show that the DP is sensitive to light exposure to which the original carton provides adequate protection.

In-use stability studies cover the proposed use of retifanlimab DP after dilution with normal saline or 5% dextrose solutions in IV bags. The results support the proposed hold times of IV bag preparations for up to 6 hours at room temperature (20 – 25°C) and 24 hours at 2 – 8°C.

For a more comprehensive presentation of the data, the applicant could also include graphical figures trending the data for the stability indicating parameters as minimum. Sampling points OOS shall be noted in the tables (OC).

Adventitious agents

Retifanlimab is expressed using recombinant Chinese Hamster Ovary (CHO) cells that secrete the antibody into the culture medium. Apart from the producing cells the Retifanlimab DS and DP manufacturing processes does not use any materials containing human or animal-derived components. No materials of human or animal origin was used in the derivation of the master cell banks MCB and working cell bank WCB. Therefore, there is no risk of TSE contamination.

The MCB and WCB used for production of retifanlimab were extensively tested for various types of viruses per ICH Q5A. All results met the pre-defined acceptance criteria for absence of viruses.

During manufacture of retifanlimab, unprocessed harvest bulk (pre harvest) samples are routinely tested for adventitious virus *in vitro* and MVM. Results for 6 batches, including 3 PPQ batches, have been provided.

Four viruses were selected for virus clearance studies (XMuLV, PRV, Reo3, MVM) and their selection was sufficiently justified. DNA-(enveloped and non-enveloped) and RNA-(enveloped and non-enveloped) single and double-stranded viruses were selected.

More than two orthogonal techniques were combined with various reduction mechanisms which is in line with the GL. When individual virus reduction techniques were combined, considerable reduction was achieved for all tested viruses. Based on the studies performed and the data provided, this conclusion is justified satisfactorily.

GMO

Not applicable.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The overall quality standard of the Module 3 Quality dossier presented in support of this application for Zynyz is high. The development, manufacture and testing of DS And DP, are adequately described. A major objection has been raised with respect to insufficient evidence to support the NAS claim. Furthermore a few other concerns have been raised which needs to be addressed by the applicant. These deficiencies are described in detail in the assessment report and are reflected in the LoQ.

3.2. Non clinical aspects

3.2.1. Pharmacology

Primary pharmacodynamics

The nonclinical pharmacology programme for retifanlimab was designed to characterize the binding affinity and biological activity of retifanlimab *in vitro*. Anti-PD-1 monoclonal antibody (mAb) replicas for nivolumab and pembrolizumab were utilised as reference molecules. The replicas were generated based on the published amino acid sequences of the antibodies, but contain the same hinge-stabilised human IgG4κ Fc domain as retifanlimab.

Retifanlimab binding kinetics and affinity to human and cynomolgus monkey PD 1 was characterised using surface plasmon resonance. With equilibrium dissociation constants of 0.6 nM and 3.6 nM respectively, retifanlimab has a ~6-fold higher binding affinity for human PD-1 than for cynomolgus monkey PD-1, due to a higher association rate constant and a lower dissociation rate constant.

Retifanlimab bound to engineered human PD-1-expressing (NS0/PDCD1) cells in a dose-dependent manner, with comparable binding and EC50 (0.14 µg/mL) as nivolumab and pembrolizumab. Dose-dependent binding of retifanlimab to PD-1 was detected on unstimulated human PBMCs, including CD4+ and CD8+ T cells. The binding was 2- to 2.5-fold higher when stimulated with Staphylococcal enterotoxin B (SEB) to induce expression of PD-1 on T cells. In contrast, in cynomolgus and rhesus monkeys, retifanlimab bound to PBMCs solely following SEB stimulation, what can be reasoned by induction of PD-1 expression solely following SEB stimulation. Nevertheless, this does suggest that Cynomolgus would be a pharmacologically responsive species in repeat dose toxicity studies.

Retifanlimab dose-dependently inhibited binding of PD-1 positive cells to PD-1 ligands, soluble PD-L1 and PD-L2, with IC50 values (0.010 µg/mL and 0.021 µg/mL) at similar concentrations as the replicas.

Through the use of a co-culture reporter assay system, it was demonstrated that retifanlimab was able to repress the PD-1/PD-L1 inhibitory axis in a dose-dependent manner comparably to the nivolumab and pembrolizumab replicas, with an EC50 of 0.090 µg/mL.

Retifanlimab was able to activate T-cell responses, as demonstrated by an enhanced secretion of IFN-γ by human PBMCs following stimulation with SEB. All donor PBMCs showed enhanced IFN-γ secretion following anti-PD-1 mAb incubation compared to human IgG isotype control. For most donors, retifanlimab induced enhanced or comparable IFN-γ release to the nivolumab and pembrolizumab replicas. The majority of cells that expressed PD-1 following SEB stimulation were CD3+ T cells, however, expression of PD-1 was also detected on a subset of CD19+ B cells and CD56+ natural killer (NK) cells.

Overall, the *in vitro* primary pharmacology of retifanlimab has been adequately addressed. The mode of action is supported by *in vitro* studies from which the potential effects on tumour tissue can be extrapolated.

No *in vivo* primary pharmacodynamics studies were conducted, since retifanlimab does not cross react with PD-1 from nonhuman primate species. *In vivo* studies with retifanlimab addressing pharmacology were limited to the evaluation of retifanlimab binding to peripheral T cells in cynomolgus monkeys, as part of a single-dose PK study, a preliminary 3-week repeat-dose study, and a pivotal 4-week repeat-dose study.
From these studies it was apparent that retifanlimab exhibited prolonged pharmacodynamic activity in cynomolgus monkeys as demonstrated by its extended binding to PD-1 on the surface of T cells during the treatment phase of the 3-week study and treatment- and recovery phase of the 4-week study at all doses tested in animals that not developed ADAs. In these monkeys, retifanlimab bound to PD-1+/CD4+ and PD-1+/CD8+ cells with saturated binding and correlating with serum concentrations.

Secondary pharmacodynamics

To support IV administration in humans, the hemocompatibility of retifanlimab was tested with purified RBCs or whole blood from six healthy human donors. No hemolysis was observed in either RBCs or whole blood following treatment with retifanlimab.

Retifanlimab did not induce ADCC or CDC *in vitro*. In contrast, 5C4 hIgG1, and rituximab (hIgG1) were used as positive controls and induced robust ADCC and CDC in these assays, respectively.

The intrinsic mitogenicity of retifanlimab was evaluated in resting human donor PBMCs. Similar as the nivolumab and pembrolizumab replicas and human IgG1 isotype, retifanlimab did not induce proliferation in PBMCs.

Retifanlimab did not induce cytokine release *in vitro*. In contrast, the positive control, an anti-CD3+ antibody, strongly induced cytokine release.

In vivo cytokine release was evaluated in cynomolgus monkeys as part of a single dose PK study, a 3-week repeat dose pilot toxicity study and a 13-week toxicity study.

In the single dose PK study, no cytokines were induced in serum samples of monkeys treated with 10 mg/kg retifanlimab.

In the 3-week study, infusion of retifanlimab did not result in increased levels in the majority of the cytokines. One monkey dosed with 100 mg/kg had a transient elevation in IL-6 (1946 pg/mL), but without a corresponding clinical effect.

In the 13-week study, measurable levels of IL-6 were observed in a few animals across groups (including control animals). The applicant could not rule out a relationship to retifanlimab since the largest increases were observed in the high dose group, but a clear dose-response relationship with retifanlimab was not evident. Higher IL-12 levels were observed in one female dosed with 5 mg/kg which was considered unlikely related to retifanlimab due to occurrence in a single (low dose) animal.

Safety pharmacology

The safety pharmacology of retifanlimab was integrated in a 4-week pivotal repeat-dose study. This is supported by ICH guidelines S6(R1), and S9, which do not require separate safety pharmacology studies for biotechnology-derived products.

No untoward effects were identified that would pose a risk to the CNS, respiratory system or cardiovascular system.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed by the applicant. As retifanlimab is currently indicated to be used as a monotherapy, the absence of preclinical PD drug interaction studies

with retifanlimab is endorsed for this MAA. If the applicant wishes to combine retifanlimab with other medicines in the future, PD drug interaction studies may be required.

3.2.2. 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.

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. According to the applicant, the LLOQ differs for the single dose and 3 week study (9.775 ng/ml versus 4.875 ng/ml). This should be explained, considering that an LLOQ is normally assay specific and not study specific (OC).

For the pivotal 4 week and 13 week studies, a validated ELISA was used to quantitate retifanlimab levels in monkey serum. Although some in-study validation data is provided, the full validation report could not be located. According to the applicant, the lower and upper limits of quantitation (LLOQ and ULOQ) were 0.391 ng/mL and 25 ng/mL, however, due to the missing validation report this could not be checked (OC).

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. Moreover, also for the ADA assays, no validation data are provided. In the overview it is stated that the assay limit of detection was ≤ 0.1, ≤ 0.25, and ≤ 0.5 µg/mL in the presence of retifanlimab at 1, 2, and 4 µg/mL respectively. However, except for a mentioned tolerance level of 1 µg/mL in the 13 week study and 4 µg/mL in the 4 week study, no reports could be located that substantiate this (OC).

It is also noted that the levels of retifanlimab in serum in the repeated dose toxicity studies were well above the drug tolerance levels in several animals and may therefore have interfered with the assay sensitivity for ADA detection (see also 3.2).

It is also noted that the levels of retifanlimab in serum in the repeated dose toxicity studies were well above the drug tolerance levels in several animals and may therefore have interfered with the assay sensitivity for ADA detection (see also 3.2).

Absorption

A single dose pharmacokinetic study was performed in Cynomolgus monkeys (1 male and 1 female), with IV doses of 10 mg/kg bw. Since only one dose level was used, dose proportionality could not be evaluated . Retifanlimab showed a multiphasic decline, with a faster decline at terminal phases, which might be explained by development of ADAs or TMDD. The (predicted) steady state volume of distribution is low (86 mL/kg), which is in line with what is expected from antibodies. (Predicted) clearance was low (0.35 mL/h/kg), suggesting minimal clearance. Terminal elimination half-life (T1/2) was 69 hours. The mean MRT for retifanlimab is 261 hours. No clear gender differences were observed, although clearance tended to be more rapid in the female than in the male animal (less than a factor 2 difference). In general, PK parameters of retifanlimab were comparable to those of other anti-PD-1 mAbs.

A multiple-dose 3-week non GLP TK study, a 4-week GLP TK study and a 13-week GLP TK study were performed at dose levels of 1-150 mg/kg bw, administered by IV infusion (1h).

In all 3 repeated dose studies, based on the PK profiles, several animals were expected to have developed ADAs. This was confirmed in most animals of the lower dose groups but in few animals of the higher dose groups. In the animals in which the ADA profile was not confirmed in the ADA assay, retifanlimab serum concentrations were above the drug intolerance level. ADAs were first detected on Day 15.

Non-compartmental (first dose only) as well as two-compartmental TK analysis were performed (last week of dosing). In the two-compartmental analysis, data from animals that were expected to have developed ADAs were excluded.

After repeated exposure, systemic exposure of retifanlimab (Cmax and AUC) increased in a dose proportional manner over the dose range of 1 to 150 mg/kg. Steady state is reached after the 4th or 5th weekly dose. There were no apparent gender differences in exposure.

In the pivotal 13 week study, the mean terminal elimination half-life (t1/2) of retifanlimab ranged from 167-227 h after the first dose and became shorter after repeated dosing, probably due to the development of ADAs. Accumulation ratios were low in this study (1.8-2.3 for AUC0-167.5 at week 4 and 1.2-2.0 at week 13). The AUC0-167.5h values after the fourth dosing in comparison to AUCinf,pred values after the first dosing suggested a ~92% steady state was reached after the fourth weekly dosing.

Distribution

Consistent with the known biodistribution of monoclonal antibodies, retifanlimab has a low volume of distribution (54-86 ml/kg), suggesting a distribution to plasma and extravascular fluid. A limited drug distribution study with retifanlimab (1 or 100 mg/kg administered IV once weekly for 3 weeks) in monkeys indeed showed that retifanlimab mainly distributed 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.

Foetal exposure has not been investigated. However, considering that retifanlimab is an IgG4κ antibody it is expected that it will be transferred over the placenta.

Excretion to milk has not been investigated.

Metabolism

No metabolism studies with retifanlimab were conducted in animals. The absence of metabolism studies is in accordance with ICH S6(R1) and is agreed with.

Excretion

As retifanlimab is a monoclonal antibody, no renal excretion is anticipated due to its molecular size Therefore, no specific studies to measure excretion of retifanlimab were conducted. The absence of excretion studies in accordance with ICH S6(R1) and is agreed with.

Pharmacokinetic drug interactions

Drug-drug interaction at the PK level is highly unlikely for this type of product since biotechnology-derived substances do not metabolize via CYP P450 enzymes. The absence of PK drug interaction studies with retifanlimab is endorsed.

3.2.3. Toxicology

Single dose toxicity

A single 10 mg/kg IV-dose of retifanlimab administered to cynomolgus monkeys did not result in any test-article related effects of retifanlimab.

Retifanlimab demonstrated extended binding to PD-1 on the surface of CD4+ and CD8+ T cells, comparable to pembrolizumab, with an PD-1 occupancy percentage of ≥80% for 28 days or more. In contrast, the nivolumab replica exhibited less prolonged binding.

Repeat-dose toxicity

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 model. Across the studies, animals were given weekly doses ranging between 1 and 150 mg/kg, which was administered via IV infusion. Retifanlimab was generally well tolerated in all repeat-dose studies. All animals survived until scheduled necropsy. There were no major observations in clinical observations, food consumption, body weight, ophthalmology, serum chemistry, urinalysis, gross pathology and organ weight that were attributed to retifanlimab.

In all repeat-dose studies, several animals across dose groups developed ADAs. ADAs were more frequently detected in animals of the lower dose groups. In animals of the higher dose group suspected of ADA development, high concentrations of retifanlimab in serum may have interfered with ADA assessment. However, these animals were still sufficiently exposed to retifanlimab. At all doses tested, retifanlimab bound with maximum saturation to PD-1 expressing T-cells in animals that did not develop ADAs. Data from all animals (including animals with suspected or proven ADAs) were included for a worst-case calculation of exposure multiples. The exposure multiples were at least 20 times the MHRD. Thus, sufficient exposure was maintained to adequately interpret the toxicology studies.

In the non-pivotal 3-week study, the NOAEL was 100 mg/kg, the highest dose tested, corresponding to an exposure multiple of 20 based on the MHRD. A retifanlimab-related, but dose-independent increase in relative spleen weights was seen in animals dosed with 1 and 100 mg/kg. Related to this, a dose-dependent mild to moderate lymphohistiocytic cellular infiltrate of the red pulp was observed in the spleen. These findings were not observed in the pivotal studies. Other results were generally comparable as the pivotal studies, which are discussed in detail below.

In the 4-week study, the NOAEL was 150 mg/kg, the highest dose tested, corresponding to an exposure multiple of 26 compared to the MHRD. Safety pharmacology parameters including respiratory rate, blood pressure, heart rate, body temperature and neurologic examinations revealed no notable retifanlimab-related findings. ECG parameters were also reported not to show any retifanlimab-related findings but were not included in the study report. For completeness of the non-clinical dossier, the applicant is requested to provide the tables with ECG study data (see OC).

Retifanlimab-treated animals (doses of 10 mg/kg and higher) had multifocal perivascular mononuclear cell infiltrates at the administration site, limited to minimal severity but with a dose-related incidence in the number of animals. Following recovery, minimal infiltrates were only noted in two animals. A higher incidence of mononuclear or mixed-cell infiltration was seen in the brain, heart, urinary bladder, kidney, liver, gastrointestinal (GI) tract, spinal cord, trachea, lung and thyroid gland in retifanlimab-treated animals and in some control animals. There was no clear dose-response correlation for all observations and the infiltrates may be related to immune-activation of retifanlimab. Less microscopic changes, of minimal severity, were noted at the end of the recovery.

A dose-independent, transient decline in circulating immune cell populations, including total leukocytes, T cells, B cells, and NK cells, was observed in animals dosed with ≥10 mg/kg. In line, lymphocyte counts were transiently decreased following the first dose in males at 10 and 40 mg/kg and females at ≥40 mg/kg. Retifanlimab-related increases in large unstained cells were observed in

males dosed with 150 mg/kg solely around the fourth dosing day, hence likely to be a nonspecific effect.

In the 13-week study, the NOAEL was 100 mg/kg, the highest dose tested, corresponding to an exposure multiple of 20 compared to the MHRD. Dose-independent multifocal perivascular mononuclear cell infiltrates were noted at the administration site, limited to minimal severity. In females this was observed at doses of ≥5 mg/kg, in males it occurred in controls and at doses of ≥20 mg/kg.

A retifanlimab-related higher incidence of mononuclear, macrophage or mixed-cell infiltration was seen in the brain, lungs, skeletal muscle, uterus, GI tract, mammary gland and thyroid gland, mainly limited to minimal severity. There was no clear dose-response correlation for all observations and the infiltrates may be related to immune-activation of retifanlimab. It should be noted that the 13-week study was not followed by a recovery period.

Minimal to moderate increases in fibrinogen occurred in animals administered ≥5 mg/kg. This effect was not dose-responsive, and is probably a nonspecific response to a foreign protein. No notable findings on coagulation were seen in the 4-week study.

The majority of cytokine levels (IL-1β, IL-2, IL-4, IL-8, IL-10, IFN-γ, and TNF-α) were below the limit of quantitation throughout the study for all groups. Measurable IL-6 levels were observed in a few animals across all groups including controls. The applicant could not rule out a relationship to retifanlimab since the largest increases were observed in the high dose group, but a clear dose-response relationship with retifanlimab was not evident.

In contrast to the 4-week study, in the 13-week study no test article-related changes were found in T cells, B cells or NK cells. A slight decrease in monocyte counts in females given 100 mg/kg was observed, but this finding is not likely to be test-article related due to a lack of changes in monocyte counts in the hematology data in both pivotal studies. Similar as in the 4-week study, a transient retifanlimab-related decrease in lymphocytes was observed in males given ≥5 mg/kg following the first dose. The lymphocyte count was also mildly decreased in one female given 5 mg/kg consistent with the clinical condition of the animal, although a test article-related contribution could not be excluded.

Overall, no clinically relevant toxicity was observed with retifanlimab when administered once weekly to cynomolgus monkeys by IV infusion, at dose levels ranging from 1 to 150 mg/kg.

Toxicokinetics

Serum concentrations increased dose proportionally in the repeated dose toxicity studies with retifanlimab. Anti-retifanlimab antibodies were measured in some of the animals in all studies (see pharmacokinetics chapter 3.2). However, despite the high incidence of ADA development at the lower dose levels in the repeated dose toxicity studies, ADA formation did not prevent an adequate assessment of the safety of retifanlimab. The applicant has not provided calculations of exposure multiples. Based on the provided TK data and the NOAELs of the pivotal studies, the assessor has calculated the exposure multiples. Data from all animals (including animals with suspected or proven ADA's) were included for a worst case calculation. Exposure multiples based on AUC0-last varied from 20-26. It can therefore be concluded that adequate exposure was maintained to evaluate safety in the toxicologic studies.

Interspecies comparison

The pharmacokinetics of retifanlimab were studied primarily in rats and monkeys. Following repeated IV administration, exposure of retifanlimab (Cmax and AUC) increased in a dose proportional manner over the dose range of 1 to 150 mg/kg in monkeys and 1-10 mg/kg in humans. Accumulation ratios in the 13 week study were low (<3). In humans, dosed every four weeks (Q4W), steady state was

achieved after approximately 11 months. In monkeys, which were dosed weekly, steady state is reached after the 4th or 5th dose. Predicted plasma clearance is low in monkeys (0.345 mL/h/kg) and in humans (0.305 L/d after the first dose and decreasing to 0.229 L/day at steady state), indicating minimal clearance. Volume of distribution in monkeys is low (54-86 ml/kg), consistent with a distribution to serum and extravascular fluid. In humans, Vdss is 99.8 ml/kg for a 65 kg weighing adult. As expected for a monoclonal IgG antibody, elimination of retifanlimab was slow, with elimination half-life ranging from 7.0-9.5 days in monkeys. Retifanlimab showed a multiphasic decline, with a faster decline at terminal phases (presumably due to ADA development). In humans a terminal elimination half-life of 18.4 days was found. No gender differences were observed in the pharmacokinetics of retifanlimab.

Genotoxicity

No genotoxicity studies were performed for retifanlimab in line with ICH S6(R1). This is agreed, since retifanlimab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity studies were conducted for retifanlimab. This is in accordance with ICH S1A, S6(R1) and S9.

Reproductive and developmental toxicity

No standard fertility and early embryonic development, embryofetal development and pre- and postnatal development studies have been conducted with retifanlimab. This is in accordance with guidelines (ICH S9, 2009) for advanced cancer therapeutics. In addition, based on the mechanism of action and literature on murine models of pregnancy, retifanlimab is anticipated to disrupt the maintenance of a normal pregnancy. Similarly, administration of the PD-1 antagonist nivolumab to pregnant cynomolgus monkeys increased the risk of abortion and neonatal mortality. Furthermore, from literature it is known that fetal exposure to retifanlimab may alter immunologic phenotypes or increase the risk of developing immune-related diseases. Thus, conduct of embryofetal development studies in cynomolgus monkeys would likely not be informative. This is agreed. Subsequently, the use of retifanlimab is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception, as reflected in the SmPC.

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. This is in accordance with ICH S6(R1) (2011) and ICH M3(R2) (2009) guidelines.

In both studies, microscopic changes were noted at the administration site and consisted of minimal multifocal perivascular mononuclear cell infiltrates within the superficial dermis. In the 4-week study, this occurred with a dose-related incidence in the number of animals, whereas in the 13-week study the infiltrates were not dose-related. Following recovery in the 4-week study, minimal infiltrates were only noted in two animals. Infiltrates were of minimal severity, also in the highest dose tested (150 mg/kg, corresponding to 26-fold the proposed MRHD exposure) and are most likely related to injection of a foreign protein. Hence, retifanlimab is not expected to cause issues with local tolerance.

Other toxicity studies

No dedicated studies were conducted to investigate antigenicity. The potential for retifanlimab to cause ADA responses was investigated in repeat-dose toxicity/toxicokinetics studies. Anti-retifanlimab antibodies were measured in some of the animals in all studies (see pharmacokinetics chapter 3.2).

Overall, sufficient exposure was maintained throughout the repeated-dose toxicity studies to allow for an adequate assessment of the safety of retifanlimab.

No dedicated studies were conducted to investigate immunotoxicity. The potential for retifanlimab to influence the immune system was investigated in single- and repeat-dose toxicity studies that evaluated immunophenotyping.

No studies on dependence, metabolites or impurities were conducted with retifanlimab. This is agreed.

Tissue cross-reactivity of retifanlimab was evaluated in human tissues. Retifanlimab staining was limited to plasma membrane and cytoplasmic elements of lymphocytes, 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, ureter, cervix, uterus, and lung (BALT) as well as tissues where lymphocytes were present including kidney and prostate. No unexpected tissue staining was observed with retifanlimab based on literature reports of PD-1 expression on T cells in lymphocytes in follicles of lymphoid organs.

3.2.4. Ecotoxicity/environmental risk assessment

Retifanlimab is comprised of naturally occurring amino acids, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, according to the Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00 corr 2, 01 June 2006), retifanlimab is exempt from the preparation of an Environmental risk Assessment. This justification is adequate.

3.2.5. 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.

Pharmacokinetics

In the (not validated) ELISA that was used to quantitate retifanlimab levels in monkey serum in the non-GLP single dose and 3 week studies, the LLOQ differs for the single dose and 3 week study (9.775 ng/ml versus 4.875 ng/ml). This should be explained, considering that an LLOQ is normally assay specific and not study specific (OC).

The full validation report (R1-MTV-15-007/RPT-18-064?) of the ELISA that was used for quantification of retifanlimab levels in monkey serum in the pivotal 4 and 13 week studies could not be located. Also for the ADA assays, no validation data are provided. The relevant validation reports should be provided (OC).

Toxicology

The applicant has not clarified if the test item batches used in the different toxicology studies are comparable to the batches used in a clinical setting. The comparability between the nonclinical batches and with batches used in clinical trials should therefore be discussed and clarified by the applicant (OC).

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 related 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, embryofoetal 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 foetal exposure. Hence, it is agreed that the conduct of embryofoetal 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, as reflected in the SmPC.

3.2.6. Conclusion on non-clinical aspects

In conclusion, the non-clinical studies (pharmacology, pharmacokinetics and toxicology), submitted for the conditional 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 conditional market approval for Zynyz can be granted provided that the posed non-clinical questions are sufficiently addressed.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Study ID	Population	Number of subjects in population PK analysis	Dosing regimen	PK sampling
INCMGA 0012-101	Patients with relapsed/ refractory, unresectable locally advanced or metastatic solid tumours	249	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 IV over 60 minutes	**Q2W body weight–based dose** Cycle 1 Day 1: predose, EOI, 6 h and Day 2, Day 4, Day 8 after infusion Cycle 1 Day 15: predose, EOI Cycle 2 and beyond: Day 1 predose, EOI and Day 15 predose, EOI EOTV **Q4W body weight–based dose** Cycle 1: predose, EOI, 6 h and Day 2, Day 4, Day 8, and Day 15 after infusion

				Cycle 2 and beyond: Day 1 predose, EOI and Day 15 any time EOTV **Q4W flat dose** Cycle 1: predose, EOI, 6 h and Day 2, Day 4, Day 8, and Day 15 after infusion Cycle 2 and beyond: Day 1 predose, EOI EOTV **Q3W flat dose** Cycle 1: Predose, EOI, 6 h and Day 2, Day 4, Day 8, and Day 15 after infusion Cycle 2: Day 1 predose, EOI and Day 8 and Day 15 after infusion Cycle 3 and beyond: Day 1 predose, EOI EOTV
INCMGA 0012-104	Patients with advanced or metastatic solid tumors; Japanese participants	6	500 mg Q4W IV over 60 minutes	Monotherapy Cycle 1 Day 1: predose, EOI, 6 h and Day 2, Day 8, and Day 15 after infusion Cycle 2 and beyond: Day 1 predose (every cycle until Cycle 8 and every 4 cycles after Cycle 8) and EOI (only Cycles 2 and 6)
INCMGA 0012-201	Patients with advanced or metastatic Merkel Cell carcinoma	40	500 mg Q4W IV over 60 minutes	Cycle 1 Day 1 and Cycle 6 Day 1: predose and 10 min and 4 h after infusion Cycles 2, 4, and 7 Day 1: predose
INCMGA 0012-202	Patients with advanced or metastatic SCAC	92	500 mg Q4W IV over 60 minutes	Cycle 1 Day 1 and Cycle 6 Day 1: predose and 10 min and 4 h after infusion Cycles 2, 4, and 7 Day 1: predose
INCMGA 0012-203	Patients with advanced or metastatic NSCLC, UC, RCC, and melanoma	119	500 mg Q4W IV over 30 minutes	Cycle 1 Day 1: predose and 10 min and 4 h after infusion Cycles 2, 4, and 6 Day 1: predose and 10 min after infusion EOTV or 28 day safety follow-up visit Cycle 4 Day 1 post-infusion (added in Protocol Amendment 2)

3.3.1. Pharmacokinetics

Retifanlimab is a humanised, hinge-stabilised, IgG4κ monoclonal antibody that recognises human PD-1 and contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1–expressing cells, including T cells, and restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

Zynyz is formulated as concentrate for solution for infusion. The recommended dose is 500 mg retifanlimab every 4 weeks (Q4W) administered as an intravenous infusion over 30 minutes.

Pharmacokinetics of retifanlimab were studied in cancer patients. Non-compartmental analysis was used to analyse the pharmacokinetics after the first dose in studies INCMGA 0012-101, -104 and -203. A population pharmacokinetic model was developed based on cancer patients from all studies.

Development of antibodies against retifanlimab was measured in all studies.

Analytical methods: The bioanalytical methods used for the determination of retifanlimab concentrations in human serum used 2 types of assay platforms, ELISA and MSD-ECL. Some samples in study INCMGA 0012-101 were analysed . using a first generation ELISA method. The other samples were analysed at Syneos Health using second generation ELISA and MSD-ECL. The validation of the ELISA reported to be performed in accordance with GLP. In the validation of the ELISA and the MSD-ECL assays no GLP was claimed. The assays were in general adequately validated, except for carryover and parallelism, which were not investigated. Cross validation was performed in study INCMGA 0012-101 between the results obtained by ELISA and MSD-ECL . The investigation of long-term stability is reported to be ongoing.

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. Also for these analyses, no GLP was claimed for the validations performed. The assays were in general adequately validated. The investigation of long-term stability is reported to be ongoing. No analyses were performed for neutralizing ADAs. A method for the detection of neutralizing antibodies to retifanlimab is still under development.

Population PK analysis: Population PK modelling was performed using nonlinear mixed effect models. The serum concentrations for retifanlimab were best characterised with a 2-compartment model with first order elimination + time varying CL from the central compartment. The time varying CL component was used to describe the decline of CL over time which was observed. Statistically significant covariates were albumin, tumour burden, ECOG performance, gender and cancer type on CL and body weight, gender, albumin and tumour burden on Vc. The variation for these parameters was however within the interindividual variability range and these covariates were considered not clinically significant.

Table 1. Parameter Estimates and standard errors from the retifanlimab final popPK model

Parameter	Population Mean	Final Parameter Estimates		Bootstrap Estimates	
		%RSE	95% CI	Median	95% CI
CL(L/h)	0.0127	2.83	0.0120, 0.0134	0.0127	0.120, 0.134
V_c (L)	3.87	1.62	3.75, 3.99	3.87	3.74, 3.99
Q (L/h)	0.0241	10.9	0.0190, 0.0292	0.0241	0.020, 0.030
Vp (L)	2.85	4.49	2.60, 3.10	2.84	2.61, 3.10
I_{max}	-0.285	17.7	-0.384, -0.186	-0.286	-0.381, -0.191
T_{50} (day)	111	9.10	91.2, 131	111	93.4, 135.3
Hill	3.44	19.2	2.15, 4.73	3.40	2.39, 5.46
Albumin (median = 40 g/L) on CL	-0.823	14.6	-1.06, -0.588	-0.834	-1.09, -0.58
Tumor burden (Median tumor diameter = 62 mm) on CL	0.108	27.8	0.0492, 0.167	0.108	0.051, 0.172
ECOG (>0 vs =0) on CL	0.0718	35.2	0.0222, 0.121	0.0719	0.0253, 0.122
NSCLC on CL	0.143	43.4	0.0213, 0.265	0.144	0.0328, 0.285
Sex (Female) on CL	-0.144	20.6	-0.202, -0.0860	-0.146	-0.199, -0.0838
Body weight (median = 71.4 kg) on V_c	0.280	15.3	0.196, 0.364	0.279	0.192, 0.358
Sex (Female) on V_c	-0.156	11.7	-0.192, -0.120	-0.156	-0.192, -0.120
Albumin (median = 40 g/L) on V_c	-0.322	24.2	-0.475, -0.169	-0.320	-0.488, -0.173
Tumor burden (Median tumor diameter = 62 mm) on V_c	0.0319	38.6	0.00779, 0.0560	0.0316	0.00666, 0.0557
IIV (CL)	31.8%	8.58%		31.6%	
Correlation (CL, V_c/V_p)	0.323	17.9%			
IIV (V_c/V_p)	17.4%	9.87%		17.4%	
Residual variability	0.171	2.90	0.161, 0.181	0.170	0.159, 0.180

Minimum value of the objective function: -11887.576.
Shrinkage for IIV (CL): 7.42%; Shrinkage for IIV (V_c/V_p): 13.2%.

The IIV for Q and Imax was tested and fixed due to high shrinkages. The IIV for Vc was shared by Vp, and the correlation for IIV (CL) and IIV (Vc/Vp) was added. No IIV on T50 and Hill coefficient was estimated.
970 of 1000 bootstrap runs converged successfully.

Absorption: Retifanlimab is dosed via the IV route and therefore completely bioavailable. After a single dose, serum retifanlimab concentrations attained median peak values at approximately 1.2 hours and subsequently exhibited a biexponential decay.

Cmax after the first dose and at steady state showed no relevant difference after an infusion duration of 30 or 60 minutes.

Bioequivalence: For initial clinical studies, drug product (DP) was manufactured at 250 mg/10 mL using the P1 process . A new presentation (500 mg/20 mL) was manufactured, the P2 process. Drug product produced by process P2 is planned for commercialisation. P1 and P2 were compared in study INCMGA 0012-203. Cmax, Tmax and AUCt appear comparable between subjects treated with P1 and those treated with P2 after single dose administration.

Immunogenicity: Only a low number of subjects were positive for ADAs, since there were only 4 subjects with treatment-emergent samples, with one positive sample per subject. ADAs were therefore not persistent. There were also 5 subjects and 6 samples positive already at baseline. No analyses for neutralizing antibodies were performed because the neutralizing antibody assay is still under development.

Distribution: Apparent volume of distribution in study INCMGA 0012-101 was 5.50 L (range 4.70-7.59 L). Estimated Vss based on the population PK analysis was 6.49 L. Volume of distribution slightly exceeded plasma volume and was lower than extracellular fluid volume, suggesting that retifanlimab

distributes to some extent outside of the vascular compartment; this is consistent with the distribution seen for other mAbs.

Elimination: No excretion studies were performed which is agreed, because retifanlimab is an antibody which is degraded to small peptides and amino acids. Estimated steady state clearance was 0.30 L/day. Elimination half-life is 18.4 days.

Metabolism: Retifanlimab is catabolised through protein degradation processes; thus, metabolism does not contribute to its clearance.

Dose and time dependency: Dose-proportionality was shown after single dose. Dose-proportionality was not evaluated at steady state, because rich sampling was performed only after the first dose. Dose was not a covariate in the population PK analysis, supporting dose proportionality also at steady-state.

Accumulation ratio was 1.6, 1.5, and 1.3 for the Q2W, Q3W, and Q4W dose regimens. Trough concentrations increase over time, which is a known phenomenon for PD-L1 compounds, and is thought to be caused by improved disease status with corresponding decreases in the rate of degradation of proteins and decreased target-mediated drug disposition. Steady state was achieved after approximately 336 days.

Intra- and inter-individual variability: Interindividual variability as measured in studies INCMGA 0012-101 and INCMGA 0012-104 was mostly low to moderate (6.62 – 42.0%). Higher values were found for Ctrough at 3 mg/kg Q2W and 500 mg Q4W (51.8 – 59.8%) and for CL and Vz at 10 mg/kg Q4W (53.9% and 49.7% respectively). In the population PK analysis, interindividual variability of CL was estimated as 31.8% and for Vc/Vp it was 17.4%.

Intra-individual variability was not calculated in the studies, but residual variability in the population PK analysis was low (17.4%).

Pharmacokinetics in the target population: All studied subjects were cancer patients. In the population PK analysis, estimated CL and Vc of patients with SCAC (n=92) were not significantly different from patients with Merkel cell carcinoma, endometrial cancer and other cancer types. Only in subjects with NSCLC, estimated CL was 14.3% higher compared to subjects with other cancer types.

Special populations: No dose adjustment is needed for gender, body weight and older subjects. For race, there are insufficient data to conclude on a need for dose adjustment. No dose adjustment is needed for mild and moderate renal impairment. Subjects with severe renal impairment have not been studied. No dose adjustment is needed for mild hepatic impairment. Subjects with moderate and severe hepatic impairment have not been studied. Zynyz is not indicated in children. A waiver has been granted for all subsets of the paediatric population (0 to 18 years of age) in the condition of treatment of squamous carcinoma of the anal canal (SCAC) based on the ground that the disease for which Zynyz is intended does not occur in the paediatric population. Results from a limited number of subjects treated with anti-HIV agents (n=10) suggest no relevant influence of HIV status on CL.

Interactions: Retifanlimab is an IgG4 monoclonal antibody, which is likely eliminated by non-specific catabolism in the reticuloendothelial system. The enzymes involved are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of retifanlimab. Based on the population PK analysis, the pharmacokinetics of retifanlimab seemed not to be affected by the concomitant use of corticosteroids or anti-HIV treatment. Since the information on the concomitant treatment was limited and also the number of subjects with HIV was limited, this analysis is considered exploratory only. Nevertheless, no effect was anticipated since retifanlimab is an antibody.

Retifanlimab is known to increase some proinflammatory cytokine levels. Some cytokines are known to down-regulate cytochrome P450, which may affect metabolism of other drugs used concomitantly. This

is a class effect of PD-1/PD-L1 antibodies. PD-1/PD-L1 antibodies have been used in combination with chemotherapeutic agents.

3.3.2. Pharmacodynamics

In this section pharmacodynamic correlates with retifanlimab will be discussed, followed by ECG findings with retifanlimab treatment and exposure-response efficacy and safety results. Immunogenicity results will be discussed in the pharmacokinetics and safety parts.

Mechanism of action

Retifanlimab is a humanised, hinge-stabilised, IgG4κ monoclonal antibody that recognises human PD-1, and contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1-expressing cells, including T cells, and restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

Primary pharmacology

Pharmacodynamic results from study INCMGA 0012-101 demonstrate full PD-1 receptor occupancy on PD-1 expressing CD4+ and CD8+ cells at different weight based and flat dosing of retifanlimab. An array of serum proteins and metabolites, including cytokines, chemokines, and the tryptophan metabolite kynurenine, rapidly increased after retifanlimab treatment. The IFNγ-inducible chemokines CXCL9 and CXCL10 were among the highest upregulated serum proteins. In addition, a transient increase in the frequency of proliferating and activated T cells was observed, with a peak 8 days following the first retifanlimab infusion. Moreover, analysis of baseline tumour samples indicated that clinical response to retifanlimab was associated with T-cell infiltration and the presence of an inflamed RNA signature in the tumour.

Secondary pharmacology

In study INCMGA 0012-101, clinical ECG exposure-response (i.e., concentration–heart rate corrected QT interval [C-QTc]) analyses were performed with the dataset containing dose levels of 1 mg/kg Q2W (n=3), 3 mg/kg Q4W (n=10), 3 mg/kg Q2W (n=140), 10 mg/kg Q4W (n=6), 10 mg/kg Q2W (n=8), 375 mg Q3W (n=15), 500 mg Q4W (n=148), and 750 mg Q4W (n=15). The relationship between retifanlimab serum concentrations and ΔQTcF was investigated using a nonlinear 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). Please refer to the safety section for more information on ECG findings in different clinical studies.

Exposure-efficacy analyses

Data from study INCMGA 0012-202 show a flat relationship between AUC after the first dose and ORR and PFS. The relationship with the other investigated PK parameters was not shown. This is however not a problem because AUC correlates well with Cmax and Ctrough.

Exposure-safety analyses

No statistically significant correlation was identified between retifanlimab exposure and the most frequent TEAEs with the exception of the correlation between C_{min1} and anaemia in the E-R safety population of the All Cancer Population and between $C_{max,ss}$ and pruritus for the E-R safety population of the SCAC Population. When age and baseline haemoglobin were included in the logistic regression model for

anaemia, this correlation was no longer apparent. In addition, the applicant argues that because $C_{max,ss}$ was a significant covariate for pruritus only in the SCAC population and not in the All Cancer Population, the effect in the SCAC Population was likely a chance finding. Furthermore, $C_{min,ss}$ was observed to be correlated with asthaenia in the pooled population with a shallow negative slope and thus was considered as not clinically relevant by the applicant. No statistically significant correlation was identified for any retifanlimab exposures and irAEs.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

The bioanalytical methods used for the determination of retifanlimab concentrations in human serum used 2 types of assay platforms, ELISA and MSD-ECL. Some 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 validation of the ELISA at is reported to be performed in accordance with GLP. In the validation of the ELISA and the MSD-ECL assays however, no GLP was claimed. The applicant should explain whether the validations were performed in compliance with GLP and if not, in what aspects relevant deviations from GLP could have occurred (**OC**). The assays were in general adequately validated, except for carryover and parallelism, which were not investigated. This should be clarified (**OC**). Cross validation was performed in study INCMGA 0012-101 between the results obtained by ELISA and MSD-ECL and between ELISA . Concerns have been raised with regards to the inclusion of a centrifugation step only for samples where debris was visible (**OC**), and a confirmation that no samples have been analysed with coated plates that have been stored is requested. (**OC**) Furthermore, although acceptable validation reports from each site have been submitted, a cross-validation with the purpose to directly compare results, should be provided. (**OC**) The ECL method has been demonstrated to be precise and accurate over the concentration range studied and considered reliable and robust, and found suitable for the analyses of retifanlimab in human serum, except for analysis of lipemic samples. According to the applicant, validation of the lipemic selectivity has been reported as failed, and clinical study samples identified as lipemic will not be reported as valid values. It is unclear how this is reported in the result tables from the clinical studies, which should be clarified. (**OC**) The investigation of long-term stability is reported to be ongoing. This should still be provided (**OC**).

Also for the ADA analyses, no GLP was claimed for the validations performed . This should be clarified (**OC**). The assays were in general adequately validated. The investigation of long-term stability is reported to be ongoing. This should still be provided (**OC**).

In the population PK modelling, excluded records due to pharmacometrician's decisions (in total 107 records) should be further specified (**OC**). The SmPC should be updated with PK parameter values obtained from the final model instead of summary statistics based on Empirical Bayes estimates as these latter values are subject to shrinkage and will not adequately account for imbalances in individual data contribution (**SmPC**). Furthermore, a clarification regarding the model building process and the inclusion of time-varying terms as well as covariates, has been requested (**OC**).

In study INCMGA 0012-203, bioequivalence was compared between drug products P1 and P2. No statistical analysis was performed to compare P1 and P2. Cmax, Tmax and AUCt appear comparable between subjects treated with P1 and those treated with P2 after single dose administration. However, the comparison was based on only few time points. Even though the population PK analysis, in which the P2 group was compared to all other subjects from all studies, indicates that the two products are comparable, statistical analysis should be provided of the data after the first dose to support the comparability in study INCMGA 0012-203 (**OC**).

An integrated summary of immunogenicity (ISI) has been submitted according the Immunogenicity guideline (EMEA/CHMP/BMWP/14327/2006 Rev 1). However, the report is lacking important issues and several inconsistencies have been detected. The applicant has modified the molecular structure of retinfanlimab to potentially become less immunogenic, as well as using humanised IgG4, also decreasing the immunogenic potential. Comparability studies on batches used in clinical studies *versus* commercial batches have been adequately performed, demonstrating that commercial batches can be considered representative of batches used in the clinical trials. The ADA assay was first developed and validated prior to method transfer . Although validations of the assays have been provided for both sites, a cross-validation with the purpose to directly compare results, cannot be found, and should be provided (**OC**). Furthermore, a description of eventual attempts on optimising the DT assay especially for the 5.00 ng/mL and 25 ng/mL ADA level is requested (**OC**). Only a low number of subjects were positive for ADAs, since there were only 4 subjects with treatment-emergent samples, with one positive sample per subject. ADAs were therefore not persistent. However, a total of 72 subjects were reported as inconclusive, which is quite a high number. This may in part be due to retifanlimab levels being above the DTL to detect ADAs at certain timepoint. Also, 229 samples from study INCMGA 0012-101 were analysed . For these samples, the DTL was 6 µg/mL. In this study, there were only very few samples with trough values of retifanlimab ≤ 6 µg/mL. It can thus be concluded that in these 229 samples, ADAs could not have been analysed reliably. The applicant should discuss whether or not the number of subjects with ADAs may have been significantly higher due to the 72 subjects indicated as inconclusive and the samples analysed with DTL of 6 µg/mL (**OC**). According to the EMA Guideline on Immunogenicity Assessment of Therapeutic Proteins, EMEA/CHMP/BMWP/14327/2006 Rev 1, the applicant should have included a validated assay to detect neutralising antibodies in the dossier, but this is currently lacking. It is noted, however, that the applicant has such an assay under development. This should be finalised within the ongoing procedure, or otherwise properly justified. The applicant is asked to provide a status update, including timelines involved. The applicant should also submit available data on neutralising activity for ADAs from patients that have tested positive, both pre-existing ADAs and treatment-emergent (**OC**).

Available data indicate that ~1% of patients treated with retifanlimab may experience reduced exposure due to the formation of ADAs, which could potentially translate into a lack of efficacy (**SmPC**). Although no treatment emergent ADAs were detected in the target population, the number of SCAC patients investigated is limited and the length of treatment with retifanlimab relatively short. Hence, the possibility of reduced exposure due to ADA-formation in the target population cannot be completely ruled out, although the perceived risk is low at this stage. Several concerns are however identified with respect to method performance within the validated parameters, the available ADA data set (ADA sampling schedule, inconclusive ADA status, missing samples) and lack of results on neutralising activity that confer uncertainty to the assessment of immunogenicity results (**OCs**). Long-term data are not available. Overall, there are not enough data to conclude on any impact of ADAs on clinical efficacy. It is doubted that retifanlimab follows a linear pharmacokinetic behavior for the following reasons. (i) the pharmacokinetic results for study INCMGA 0012-101and study DMB-20.61.1 indicate a dose disproportional change in exposure as well as a decrease in CL by dose, and (ii) the pharmacological nature of the compound suggest that it follows a target-mediated drug disposition (TMDD), which might affects the pharmacokinetics (and consequently the pharmacodynamics) as well. The applicant might provide plots showing dose-normalised mean concentration-time profiles and discuss whether TMMD models were investigated to assess the pharmacokinetic behavior (**OC**).

The main pharmacokinetic evaluation has been based on a population-based PK approach. As no dedicated PK studies have been performed, dose recommendations in special populations and pharmacokinetic information provided in the SmPC rely on popPK model results only and the popPK model is thus considered to be of medium to high regulatory impact.

The final dataset consisted of 5545 serum retifanlimab concentrations from 506 patients with different solid tumours, including 369 concentrations from 92 patients with SCAC receiving 500 mg Q4W by IV infusion over 60 minutes. Nineteen percent (1441/7590) of scheduled PK concentrations were reported as missing. It is also noted that when analysed by the retifanlimab ECL assay, lipemic samples were not reported as valid due to failed validation of the selectivity parameter for lipemic samples. It is not clear whether or how lipemic samples were considered in the popPK dataset. The reasons for the relatively high number of missing records and the handling of lipemic samples in the popPK dataset should be explained, and impact on conclusions discussed (**OC**). A clarification regarding the number of lipemic samples in each study has also been requested (**OC**, bioanalysis).

The PK modeling methodology was not sufficiently described which reduces model credibility. Apparent deviations from the data analysis plan and lack of clarity and details leaves the assessor with several assumptions on what has been done. Several methodological issues have been identified related to the available PK data set, data cleaning (justification of data exclusion, missing information, BLQs) and the model building process (structural and statistical aspects of base model selection, covariate inclusion and final selection of covariates) (**OC**). These concerns are important as the popPK analysis is the main analysis used to support conclusions regarding the dosing rationale (fixed vs. weight-based) and to understand the PK in special populations. Depending on the adequacy of the applicant's response a new covariate modelling analysis may be necessary (**OC**).

There is presumably an error in the table presenting the final popPK model PK parameters (*i.e.* confidence interval for CL), and the applicant should clarify and provide updated table on model parameters to ensure correct results in the EPAR (**OC**). The final model was validated using visual predictive checks (VPCs) per dose regimen, however these graphs were difficult to interpret due to separation of the data into several dose sub-plots and due to some of the time axes spanning over 100 days. Updated and additional prediction-corrected VPCs (pcVPCs) overall and in subgroups of the data have been requested to allow full model assessment (**OC**).

Several covariates were identified to have a statistically significant impact on retifanlimab clearance and volume of distribution, but the effect on exposure was not sufficiently addressed. The applicant should provide updated plots showing the covariates impact on exposures based on the final model fixed effect parameters and discuss the clinical relevance of these covariates with respect to efficacy and safety (**OC**).

No dose adjustments in special populations has been proposed. Due to the current uncertainties with the popPK modelling methodology, conclusions regarding PK in special populations are considered preliminary only.

Target population/disease: SCAC was not identified as a predictor of retifanlimab PK in the popPK modelling analysis. Disease-related factors (type and state of the disease) are known drivers of variability in mAb clearance, and NSCLC, ECOG status and tumour burden were correlated with retifanlimab CL. The identified inverse correlation between albumin and retifanlimab CL is commonly observed for mAbs, and is generally attributed to albumin as an indicator of catabolic state in oncology indications. The rationale for why albumin should impact on Vc is not clear. It is currently not known whether time-varying changes in CL was observed in the target population (**OC**). The exposures observed in study **INCMGA 0012-202**, and model-predicted steady state exposures (Cmax, AUC) in SCAC patients and in the overall population should be summarised and reported (**OC**). The number of patients in each cancer group (18.2% SCAC, 11.7% NSCLC, 14.2% endometrial cancer, 7.9% MCC, 48.0% others [*e.g.* UC, RCC]) are too low to allow a reliable analysis on PK differences between cancer types, and the SmPC should be amended accordingly (**SmPC**).

Renal impairment: From current knowledge of mAbs, elimination is not expected to be affected by renal impairment. Based on popPK analysis retifanlimab CL is not affected by mild or moderate renal

impairment. The popPK dataset included four patients with severe renal impairment for which available PK data should be provided (**OC**). No dose adjustment is needed for mild hepatic impairment. Subjects with moderate and severe hepatic impairment have not been studied. In section 4.2 of the SmPC, the statement that there are insufficient data in patients with moderate or severe hepatic impairment should be changed into "Zynyz has not been studied in patients with moderate or severe hepatic impairment".

Since severe renal impairment and end-stage renal disease, as well as moderate and severe hepatic impairment were not investigated, a clear statement how to deal with such situations should be given in the SmPC (**OC**).

Body weight: Based on popPK analysis, the volume of distribution (Vc) was found to increase with increasing body weight. Body weight was not a significant predictor of clearance, but graphical presentation of body weight vs CL indicate that this potential relationship may not have been properly captured by the model. Clarifications on the covariate inclusion process in general, and with respect to body weight, have been requested (**OC**). Further, the predictive ability of the final popPK model in relation to body weight needs to be addressed before a final conclusion on the impact of this covariate on retifanlimab PK and hence appropriateness of the flat dose can be drawn (**OC**).

Pharmacodynamics

Retifanlimab is a humanised, hinge-stabilised, IgG4κ monoclonal antibody that recognises human PD-1. Retifanlimab is designed to target PD-1-expressing cells, including T cells, and restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its ligands, PD-L1 and PD-L2.

In study INCMGA 0012-101 full PD-1 receptor occupancy was observed on PD-1 expressing CD4+ and CD8+ cells with effects on circulating cytokines that are typical for a PD-1 inhibitor in all dose regimens studied. In addition, an array of serum proteins and metabolites, including cytokines, chemokines, and the tryptophan metabolite kynurenine, rapidly increased after retifanlimab treatment. The IFNγ-inducible chemokines CXCL9 and CXCL10 were among the highest upregulated serum proteins. Furthermore, a transient increase in the frequency of proliferating and activated T cells was observed and analysis of baseline tumour samples indicated that clinical response to retifanlimab was associated with T-cell infiltration and the presence of an inflamed signature in the tumour.

A concentration-QTc analysis showed that a large QT/QTc effect 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).

Regarding the exposure-efficacy relationship, a flat relationship was observed between AUC after the first dose and ORR and PFS. Also for the exposure-safety relationship, there seems to be no clinically relevant increase in safety events with increasing exposures to retifanlimab. As shrinkage in PK parameters was not calculated for study INCMGA 0012-202 separately, the reliability of the individual exposure metrics used in the analysis is not clear (**OC**).

3.3.4. Conclusions on clinical pharmacology

The pharmacokinetics of retifanlimab were in general studied adequately. There are however other concerns regarding the validation of the analytical methods, the population PK analysis, bioequivalence, immunogenicity and interactions.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

The single study considered to be key to the proposed indication is study INCMGA 0012-202 (referred to as PODIUM-202), an ongoing single arm phase 2, multicentre, open-label study (Table 2).

Table 2: Summary of clinical studies included in the clinical efficacy assessment

Study Identifier; Report Location; Study Status; Type of Report	Study Objectives	Study Design and Type of Control	Test Product(s) Dose Regimen(s) Route of Administration	Duration of Treatment	Diagnosis	Participants Enrolled/ Participants Planned	Efficacy Endpoints
INCMGA 0012-202; 5.3.5.2; Ongoing; Interim	Efficacy, safety, tolerability	Open-label, multicenter study	Retifanlimab 500 mg Q4W IV	Up to 2 years	SCAC	94/81	Primary: ORR (based on confirmed tumor response by ICR) Secondary: DOR, PFS, DCR, and OS

One phase 3 study in locally advanced or metastatic SCAC is ongoing, in an earlier line of treatment (INCMGA 0012-303; PODIUM-303). This randomised study compares retifanlimab added to first line chemotherapy with placebo added to chemotherapy. PODIUM-303 is proposed as specific obligation as the confirmatory study for the current CMA application.

Dose-response study

PODIUM-101: A Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics of INCMGA00012 (formerly MGA012) in Patients with Advanced Solid Tumors.

Table 3: Summary of dose escalation study PODIUM-101

Study ID	Population	Number of subjects in population PK analysis	Dosing regimen	PK sampling
INCMGA 0012-101	Patients with relapsed/ refractory, unresectable locally advanced or metastatic solid tumors	249	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 IV over 60 minutes	**Q2W body weight–based dose** Cycle 1 Day 1: predose, EOI, 6 h and Day 2, Day 4, Day 8 after infusion Cycle 1 Day 15: predose, EOI Cycle 2 and beyond: Day 1 predose, EOI and Day 15 predose, EOI EOTV **Q4W body weight–based dose** Cycle 1: predose, EOI, 6 h and Day 2, Day 4, Day 8, and Day 15 after infusion Cycle 2 and beyond: Day 1 predose, EOI and Day 15 any

				time EOTV **Q4W flat dose** Cycle 1: predose, EOI, 6 h and Day 2, Day 4, Day 8, and Day 15 after infusion Cycle 2 and beyond: Day 1 predose, EOI EOTV **Q3W flat dose** Cycle 1: Predose, EOI, 6 h and Day 2, Day 4, Day 8, and Day 15 after infusion Cycle 2: Day 1 predose, EOI and Day 8 and Day 15 after infusion Cycle 3 and beyond: Day 1 predose, EOI EOTV

Study design and methodology

PODIUM-101 is an ongoing open-label, dose escalation and cohort expansion study evaluating retifanlimab in participants with advanced solid tumours. As of the data cutoff date of 07 Apr 2020 (interim CSR), dose escalation is complete. Enrollment is also complete in the following expansion cohorts:

- Cohort A: biomarker-unselected endometrial cancer, retifanlimab 3 mg/kg every 2 weeks (Q2W)
- Cohort B: cervical cancer, retifanlimab 3 mg/kg Q2W
- Cohort C: soft tissue sarcoma, retifanlimab 3 mg/kg Q2W
- Cohort D: non–small-cell lung cancer (NSCLC), retifanlimab 3 mg/kg Q2W
- Cohort E: tumour-agnostic, flat-dose retifanlimab 500 mg every 4 weeks (Q4W)
- Cohort F: tumour-agnostic, flat-dose retifanlimab 750 mg Q4W
- Cohort G: tumour-agnostic, flat-dose retifanlimab 375 mg every 3 weeks (Q3W)

Enrollment in Cohort H (microsatellite instability-high/deficient mismatch repair [MSI-H/dMMR] endometrial cancer, retifanlimab 500 mg Q4W) is ongoing, and enrollment in China-specific Cohort I (MSI-H/dMMR endometrial cancer, retifanlimab 500 mg Q4W) has not yet started.

Dose escalation used a conventional 3 + 3 design to characterize the safety and tolerability of retifanlimab 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, and 10 mg/kg Q4W.

Cohort expansion aims to further characterize safety, PK, pharmacodynamics, and immunogenicity of weight-based (3 mg/kg Q2W) and flat-dose (500 mg Q4W, 750 mg Q4W, and 375 mg Q3W) retifanlimab regimens and to evaluate antitumour activity in participants with advanced biomarker-unselected endometrial cancer, cervical cancer, soft tissue sarcoma, NSCLC, and MSI-H/dMMR endometrial cancer that has progressed on or after prior therapy.

Treatment continues for up to 2 years as long as participants are clinically stable and have not met any criteria for treatment discontinuation or study withdrawal. Safety is assessed continuously based on the evaluation of AEs. Efficacy is assessed based on tumour assessments obtained at screening and every 8 weeks for the first 24 weeks for participants receiving Q2W or Q4W doses and every 9 weeks

for the first 27 weeks for participants receiving Q3W doses and every 12 weeks thereafter. Following the last dose of study drug, all participants are followed for 30 days for safety assessments, for 90 days for collection of AEs, and for up to 2 years for survival assessments.

Results

Retifanlimab was well tolerated over the entire dosing range, and an MTD was not reached. The proposed dosing regimen of 500 mg Q4W was based on results from a population PK analysis with 37 participants from dose escalation of Study INCMGA 0012-101. Simulations demonstrated that the median steady-state trough concentration of retifanlimab 500 mg Q4W was approximately 21.1 µg/mL, which is the median trough concentration for pembrolizumab 2 mg/kg Q3W. The 500 mg Q4W regimen resulted in similar steady-state exposure compared with the 3 mg/kg Q2W regimen (C_{trough}). The provided pharmacodynamic results from study INCMGA 0012-101 demonstrate full PD-1 receptor occupancy on PD-1 expressing CD4+ and CD8+ cells at different weight based and flat dosing of retifanlimab. An array of serum proteins and metabolites, including cytokines, chemokines, and the tryptophan metabolite kynurenine, rapidly increased after retifanlimab treatment. The IFNγ-inducible chemokines CXCL9 and CXCL10 were among the highest upregulated serum proteins. In addition, a transient increase in the frequency of proliferating and activated T cells was observed, with a peak 8 days following the first retifanlimab infusion. Moreover, analysis of baseline tumour samples indicated that clinical response to retifanlimab was associated with T-cell infiltration and the presence of an inflamed RNA signature in the tumour.

The 500 mg Q4W dose was selected for further development in SCAC based on the comparable benefit-risk profiles to weight-based dosing, similar PK exposures, longer dosing interval, and the practical advantages inherent to flat dosing regimens such as easier dose preparation, reduced drug wastage, and a reduced risk of dosing error.

Main study

PODIUM-202: A Phase 2 Study of INCMGA00012 in Participants With Squamous Carcinoma of the Anal Canal Who Have Progressed Following Platinum-Based Chemotherapy.

The main study is PODIUM-202, an ongoing, open-label, single-arm, multicentre phase II trial. PODIUM-202 was designed to investigate the safety and efficacy of retifanlimab monotherapy in patients with locally advanced or metastatic SCAC who progressed on or were intolerant to platinum-based chemotherapy. Briefly, after a screening period of up to 28 days, eligible patients were enrolled to be administered retifanlimab 500mg as a sterile intravenous (IV) infusion over 60 minutes, every 4 weeks. Patients were treated until progression of disease or intolerable toxicity, for a maximum of two years. The target enrolment was 81 patients, and the primary analysis of ORR was to be performed after all subjects had reached a minimum duration of follow-up of 6 months (DCO 8 Jun 2020). An updated analysis of DOR was to be performed after all responding patients had reached a minimum duration of follow-up of 6 months, from the first response (DCO update 01 Oct 2020). The study is closed for enrolment with 94 patients enrolled, but is ongoing for treatment (18/94 patients; 19%) and follow-up (54/94 patients; 57%).

Methods

Study Participants

PODIUM-202 enrolled participants with locally advanced or metastatic SCAC that have progressed on or after a standard-of-care platinum-based chemotherapy regimen or who are ineligible for or intolerant of platinum-based therapy. Participants who were ineligible for platinum-based

chemotherapy must have received at least 1 prior line of systemic therapy, and participants who had received platinum-based radiosensitizing chemotherapy were eligible if relapse occurred < 6 months from completion of treatment. No more than 2 prior lines of additional systemic therapy for metastatic disease were permitted. Participants must have had measurable disease according to RECIST v1.1 and an ECOG performance status of 0 or 1. Participants known to be HIV-positive were eligible if their CD4+ count was ≥ 300 cells/μL, viral load was undetectable, and antiretroviral therapy was being administered.

Participants were enrolled at 40 sites in France, the United Kingdom, Italy, Spain, Denmark, the United States, Norway, Belgium, and Germany.

Treatments

All participants received retifanlimab 500 mg on day 1 of every 28-day cycle by 60-minute infusion for up to 2 years in the absence of disease progression, intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation for any other reason.

Participants who had been treated for at least 6 months and achieved a confirmed CR could discontinue retifanlimab after 2 additional cycles.

Investigators were blinded to ICR assessment of response and permitted to manage participants according to either RECIST v1.1 or iRECIST, with the decision to treat beyond conventional RECIST progression after consultation with the medical monitor of the sponsor.

Subsequent treatment cycles were to be delayed for up to 12 weeks until the following criteria were met:

- Hemoglobin ≥ 8 gm/dL
- ANC ≥ 1.0 × 109/L
- Platelet count ≥ 75 × 109/L
- ALT/AST/bilirubin ≤ Grade 2
- Resolution of all immune-related toxicity to ≤ Grade 1 (with the exception of endocrinopathy that is controlled on hormonal replacement), other than unacceptable toxicity
- Resolution of all non–immune-related toxicity to Grade ≤ 1 or baseline (with the exception of alopecia or non–transfusion-dependent anaemia)
- Daily dose of corticosteroid ≤ 10 mg prednisone or equivalent

Participants unable to restart study drug treatment ≤ 12 weeks from the start of the treatment delay due to toxicity were permanently discontinued from study treatment. Treatment interruptions of > 12 weeks for reasons other than toxicity (eg, for targeted radiotherapy or surgical resection of oligometastatic disease) were to be considered on a case-by-case basis by the medical monitor.

Dose modifications for retifanlimab were not allowed.

Antiretroviral therapy (ART) was to be continued for participants known to be HIV-positive. Growth factors, bisphosphonates, anticoagulants, and transfusional support were also permitted.

Immunosuppression in excess of physiologic maintenance corticosteroid doses (> 10 mg of prednisone or equivalent) within 14 days of first dose and throughout the treatment period of the study (with the exception of acute treatment for an AE) were not allowed during the study.

Objectives

Primary objective was to assess efficacy of retifanlimab in terms of the ORR in participants with locally advanced or metastatic SCAC who have progressed after platinum-based chemotherapy. Secondary objectives were amongst others to evaluate other efficacy endpoints (DoR, PFS and OS) and to evaluate safety and PK.

No formal hypothesis testing was planned for this study, but based on sample size considerations the clinically relevant target ORR was set at 25%. With a sample size of 81 subjects, the study was powered to rule out a response rate of below 13%. While not directly stated, it is inferred that an ORR below 13% was not considered to be clinically relevant.

Outcomes/endpoints

The primary efficacy endpoint of the study is ORR, defined as the percentage of participants who achieved a confirmed CR or a confirmed PR at any postbaseline visit before the first PD or new anticancer therapy based on RECIST v1.1 criteria as determined by independent central review (ICR).

Secondary efficacy endpoints include

- DOR, defined as the time from the initial objective tumour response (CR or PR) to the earlier of PD based on RECIST v1.1 criteria or death.
- PFS, defined as the time from the first dose to PD based on RECIST v1.1 criteria or death.
- OS, defined as the time from the start of therapy until death due to any cause.
- DCR, defined as the proportion of participants with a best overall response of CR, PR, or SD based on RECIST v1.1.

Exploratory efficacy endpoints are

- Blood and/or tumour analytes, immune cell profile, viral profiles, and other relevant markers will be evaluated with respect to safety and efficacy outcome measures.
- Efficacy parameters as evaluated according to iRECIST as assessed by the investigator.
- PRO assessments scheduled to align with tumour response evaluations.

Safety endpoints are determined by the frequency, duration, and severity of AEs per CTCAE v5.0, monitoring of laboratory tests, vital signs and ECGs.

PK endpoints are described and discussed in the PK part of this AR.

Randomisation and blinding (masking)

PODIUM-202 was a single-arm trial, therefore randomisation was not performed and blinding was not possible.

Statistical methods

Sample size

Th target ORR was set at 25%. With a sample size of 81 subjects, the study was powered to rule out a response rate of below 13%. PODIUM-202 was over-enrolled, with 94 patients being enrolled in the study.

Analysis populations

Full Analysis Set (FAS): The FAS includes all participants enrolled in the study who received at least 1 dose of study drug. The FAS was used for the summary of demographics, baseline characteristics, and participant disposition as well as efficacy analysis.

Safety Evaluable Population: The safety evaluable population includes all enrolled participants who received at least 1 dose of study drug. All safety analyses will be conducted using the safety evaluable population.

Pharmacokinetic Evaluable Population: The PK evaluable population includes all participants who received at least 1 dose of study drug and have provided a baseline and at least 1 postdose serum sample (1 PK measurement). The study pharmacokineticist will review data listings of study drug administration and sample records to identify subjects to be excluded from analyses of PK data. The study research investigator will review data listings of pharmacodynamic data and sample records to identify subjects to be excluded from analyses of pharmacodynamic data.

Tumour measurements

Tumour measurements were performed by radiological imaging (preferably CT-scan) at screening and during the study every 8 weeks (± 7 days). A CR or PR was to be confirmed by repeat imaging at least 4 weeks after initial documentation.

Participants who discontinued study treatment without experiencing disease progression entered the follow-up period and continued to undergo tumour assessments according to the schedule of activities until they experience disease progression, the start of a new anticancer treatment, withdrawal of consent, lost to follow-up, the end of the study, or death.

Primary efficacy analyses

The primary endpoint of the study was ORR, defined as the percentage of participants with CR or PR at any postbaseline visit before the first PD or new anticancer therapy, according to RECIST v1.1 as determined by an ICR. The primary analysis of ORR was to be based on the FAS. Overall response rate and its exact 95% CI were to be presented. In addition, ORR by investigator assessment was to be provided as sensitivity analysis for the primary endpoint.

The study required measurable disease at baseline per RECIST v1.1 as part of the inclusion criteria. However, if a participant did not have measurable disease, this participant was to be considered non-responder. Participants with subsequent missing assessments that prevented the evaluation of the primary endpoint were considered non-responders. No data imputation was to be applied. A response assessment of CR or PR reported before any additional anticancer therapy was to be considered as a response in the calculation of ORR irrespective of the number of missed assessments before response.

The best overall response was the best response recorded from the start of the treatment until the first PD, in the order of CR, PR, SD, PD, and NE.

In the case of SD, measurements were required to meet the SD criteria at least after the date of first dose at a minimum of 7 weeks (49 days). Participants who failed to meet this criterion were to have a best overall response of PD if the next available assessment indicated PD or NE if there was no additional assessment available.

Secondary efficacy analyses

Secondary efficacy analyses included DoR, PFS and OS as expressed in the estimated median with 95% CIs, and expressed by the Kaplan-Meier estimate of the distribution function. Furthermore, DCR, and the best percent change in the sum of diameters of measurable tumours using the FAS were evaluated.

The following censoring rules were applied for DoR and PFS, see Table 4.

Table 4: Evaluation and censoring of DoR and PFS

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Day 1
No valid postbaseline response assessments in the absence of death prior to first scheduled tumor assessment	Censored	Day 1
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

For OS, participants who were lost to follow-up or still alive at the time of analysis were to be censored at the last known alive date.

The best percentage change from baseline, defined as the largest decrease in tumour size for each participant, was to be summarised descriptively. In addition, the best percentage change was to be presented by a waterfall plot. The analysis was to be performed in all participants in the FAS with baseline tumour size available.

Exploratory analyses

Exploratory analyses were to be performed for which the iRECIST criteria are applied to determine ORR and DoR.

Subgroup analyses of the primary endpoint (ORR) were to be performed on the FAS by presenting the point estimates in the subgroup with the exact 95% Cis, only if at least 5 participants were present in each subgroup.

Interim analysis

An interim analysis for futility was planned after approximately 25 participants were assessable for investigator-assessed response according to RECIST v1.1. The study was to be stopped for futility at the interim analysis if conditional power based on interim result was lower than 20%, which is equivalent to less than 2 participants responding. The interim analysis for futility was performed at a data cut-off of 07 Oct 2019, and the IDMC decided that the study should continue.

Results

Participant flow

An overview of participant flow, with respect to patients screened, treated and censored/analysed, was not provided.

Recruitment

The first patient received the first dose of study drug on 8 Oct 2018.

DCO for the primary analysis of ORR was set at 08 Jun 2020 (DCO), which was set to occur after approximately 6 months of follow-up from the date of the first dose of the last subject enrolled.

DCO for the updated analysis of DoR was set at 01 Oct 2020 (DCO update), which corresponds to a follow-up interval of at least 6 months from the time of the initial response for all responders.

Follow-up is ongoing, with the end of the study defined as the date of the last visit of the last participant in the study. Participants completing treatment or prematurely discontinuing the study drug will be followed for survival until all participants have completed at least 2 years of treatment with retifanlimab or discontinued.

Study disposition

At the time of the DCO (08 Jun 2020), 94 participants with locally advanced or metastatic SCAC were enrolled in PODIUM-202. At DCO, enrolment was complete, and the median duration of treatment was 85 days (range: 1 day to 19.4 months [592 days]). Study disposition is shown in Table 5.

As of DCO, 18 participants (19.1%) were continuing to receive retifanlimab, and 76 participants (80.9%) had discontinued treatment. The most common reason for retifanlimab discontinuation was PD (37 participants [39.4%] with clinical progression and 21 participants [22.3%] with confirmed radiographic progression). Fifty-four participants (57.4%) remained in the study, and 40 participants (42.6%) had withdrawn from the study. The most common reason for study withdrawal was death (37 participants [39.4%]). All participants had at least 6 months of follow-up from the time of enrolment or discontinued the study earlier.

Table 5: Summary of participant disposition in Study PODIUM-202 (Full Analysis Set, DCO)

Variable, n (%)	**Retifanlimab 500 mg Q4W (N = 94)**
Participants treated	94 (100.0)
Participants who completed treatment	0
Participants with ongoing treatment	18 (19.1)
Participants who discontinued treatment	76 (80.9)
Primary reason:	
PD – clinical progression	37 (39.4)
PD – confirmed radiographic progression	21 (22.3)
AE	6 (6.4)
Death	6 (6.4)
Lost to follow-up	1 (1.1)
Physician decision	2 (2.1)
Withdrawal by participant	1 (1.1)
Other	2 (2.1)

Variable, n (%)	Retifanlimab 500 mg Q4W (N = 94)
Participants ongoing in study	54 (57.4)
Participants who withdrew from study	40 (42.6)
Primary reason:	
Death	37 (39.4)
Lost to follow-up	3 (3.2)

Study conduct

The initial protocol (version 0) was dated 12 Jun 2018. There were 4 global amendments (and 1 country specific amendment) to the initial protocol, mainly related to clarification of the inclusion criteria such as the criterion on previous treatment with chemotherapy. One amendment included a change to the original statistical analysis plan, which was the removal of 'at least 6 months duration' of stable disease from the definition of disease control rate.

Most protocol deviations were minor. From the minor protocol deviations, 54.3% concerned out-of-window assessments. Five participants had important protocol deviations (5%).

Baseline data

Participant age ranged from 37 to 94 years, with a mean age of 62.1 years. Most participants were female (64.9%), white/Caucasian (76.6%). Demographic characteristics of study participants are summarised in Table 6.

Table 6: Demographic characteristics of participants in PODIUM-202 (Full Analysis Set)

Variable	Retifanlimab 500 mg Q4W (N = 94)
Age (years)	
Mean (standard deviation)	62.1 (11.44)
Median	64.0
Minimum, maximum	37, 94
Age group, n (%)	
< 65 years	48 (51.1)
≥ 65 years	46 (48.9)
< 75 years	84 (89.4)
≥ 75 years	10 (10.6)
Sex, n (%)	
Male	33 (35.1)
Female	61 (64.9)
Race, n (%)	
White/Caucasian	72 (76.6)
Black/African-American	1 (1.1)
Other[a]	15 (16.0)
Missing[b]	6 (6.4)

Variable	Retifanlimab 500 mg Q4W (N = 94)
Ethnicity, n (%)	
Hispanic or Latino	4 (4.3)
Not Hispanic or Latino	49 (52.1)
Not reported	33 (35.1)
Unknown	4 (4.3)
Missing	4 (4.3)

The most common sites of disease at baseline were the lymph nodes (64.9%) and liver (41.5%). Of participants with tumour tissue available for review, 2 of 69 had evidence for MMR deficiency, 44 of 67 had a PD-L1 status ≥ 1%, and 54 of 58 were positive for HPV (majority were HPV 16). Nine participants (9.6%) were known to be HIV-positive at baseline.

Approximately half of the participants had mild (33.0%) or moderate (22.3%) renal impairment, and 17.0% of participants had mild hepatic impairment. Eleven participants had baseline laboratory evidence for hypercalcemia. Cancer history and baseline disease characteristics are summarised in Table 7.

Table 7: Summary of cancer history and baseline disease characteristics (Full Analysis Set)

Variable, n (%)	Retifanlimab 500 mg Q4W (N = 94)
M staging at current diagnosis	
M0	18 (19.1)
M1	76 (80.9)
Current sites of disease	
Lymph nodes	61 (64.9)
Liver	39 (41.5)
Lung	31 (33.0)
Bone	14 (14.9)
Anus/anal canal	13 (13.8)
Rectum	10 (10.6)
Other	8 (8.5)
Pelvis	6 (6.4)
Omentum/peritoneum	5 (5.3)
Skin or subcutaneous tissue	3 (3.2)
Colon	2 (2.1)
Kidney	2 (2.1)
Soft tissue	2 (2.1)
Vagina	2 (2.1)
Central nervous system	1 (1.1)
Head and neck	1 (1.1)
Pleural effusion	1 (1.1)
Stomach	1 (1.1)
PD-L1 status at baseline[a]	
< 1%	23 (24.5)
≥ 1%	44 (46.8)
Unknown	27 (28.7)
MMR/MSI status at baseline[b]	
Proficient/negative	67 (71.3)
Deficient/positive	2 (2.1)
Unknown	25 (26.6)

2

Variable, n (%)	Retifanlimab 500 mg Q4W (N = 94)
HPV status at baseline	
Positive	54 (57.4)
Negative	4 (4.3)
Unknown	36 (38.3)
HIV infection at baseline	
Positive	9 (9.6)
Negative/unknown	85 (90.4)
ECOG performance status at baseline	
0	39 (41.5)
1	55 (58.5)
Creatinine clearance at baseline[c]	
≥ 90 mL/min (normal GFR)	42 (44.7)
≥ 60 to < 90 mL/min (mild decrease in GFR)	31 (33.0)
≥ 30 to < 60 mL/min (moderate decrease in GFR)	21 (22.3)
< 30 mL/min (severe decrease in GFR)	0
Hepatic impairment at baseline[d]	
Normal	77 (81.9)
Mild	16 (17.0)
Moderate	0
Severe	0
Missing	1 (1.1)
Hypercalcemia at baseline[e], n	11

[a] The PD-L1 score was based on central laboratory tumor cell staining, except for 1 participant without a central laboratory result. For that participant, the local PD-L1 score was used.
[b] Proficient/negative = proficient by MMR IHC or microsatellite stable (MSS) by PCR assay. Deficient/positive = deficient MMR (dMMR) by IHC or microsatellite instable (MSI-hi) by PCR assay. Central and local laboratory results were included.
[c] Creatinine clearance is calculated based on Cockcroft-Gault formula: ({140 − age [years]} × weight {kg} × {0.85 if female}) /(72 × serum creatinine {mg/dL}) and classified based on FDA Guidance (2020) and EMA Guidance (2015).
[d] 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.
[e] Hypercalcemia (Grades 1-4) based on CTC shift table of derived calcium corrected for albumin.

Prior cancer therapy

All participants received platinum-based therapy, except 3 participants who were not candidates for platinum-based therapy because of intolerance to chemotherapy, reduced hearing and myelodysplastic syndrome respectively. The majority of participants (87.2%) had also received prior radiotherapy, either as part of chemoradiotherapy (73.4%) or radiotherapy alone (17.0%). Forty-three participants (45.7%) had a prior surgery or procedure, which included an exenterative procedure in 21 participants (22.3%). Prior anticancer therapy is summarised in Table 8.

Table 8: Summary of prior cancer therapy

Variable	INCMGA00012 500mg Q4W (N=94)
Number of participants with Prior CRT - n(%)	69 (73.4)
FU-based CRT	55 (58.5)
Platinum-based CRT	17 (18.1)
Unknown CRT	1 (1.1)
Number (%) of participants with Prior RT (without chemo) - n(%)	16 (17.0)
Number of participants with Prior Systemic Therapy - n(%)	87 (92.6)
Platinum based	84 (89.4)
Not platinum based	6 (6.4)
Other (eg investigational)	2 (2.1)
Number of participants with prior platinum based therapy - n (%)	
Yes	91 (96.8)
No	3 (3.2)
Purpose of Most Recent Prior Systemic Therapy	
Adjuvant	4 (4.3)
Advanced/Metastatic	75 (79.8)
Neoadjuvant	5 (5.3)
Palliative	10 (10.6)

Exposure to study treatment

As of DCO, median duration of retifanlimab treatment was 85 days (range: 1 day to 19.4 months [592 days]. Forty-one participants (43.6%) were treated for >3 months, 23 participants (24.5%) were treated for > 6 months, 7 participants (7.4%) were treated for > 9 months, and 2 participants (2.1%) were treated for > 12 months. The median number of infusions administered was 4 (range: 1-18).

Concomitant medications

Overall, 91.5% of participants reported prior medications. The most common (> 10%) prior medications were paracetamol (39.4%), morphine sulfate (17.0%), and pregabalin (11.7%). Overall, all participants reported concomitant medications. The most common (> 10%) concomitant medications were paracetamol (71.3%) and morphine sulfate (24.5%).

Most participants (67 participants [71.3%]) did not receive any anticancer therapy following progression on retifanlimab. Of those who did receive poststudy treatment, no participant received an immune checkpoint inhibitor. No responses to poststudy therapy were reported.

Numbers analysed

The full analysis set (FAS) includes all participants enrolled in the study who received at least 1 dose of study drug, and is comprised of all 94 enrolled patients. The FAS was identical to the intention-to-treat population, and also to the safety evaluable population

Outcomes and estimation

Primary endpoint of ORR

The primary analysis of ORR was performed after all participants had been followed for a minimum of 6 months or discontinued the study earlier. The median duration of follow-up for all participants in the study was 7.1 months (range: 0.9-19.4 months) at the data cut-off of 8 Jun 2020.

ORR was 13.8% (95% CI: 7.6, 22.5) based on confirmed tumour responses by ICR according to RECIST v1.1. Best overall response was CR in 1 participant (1.1%) and PR in 12 participants (12.8%). Of the 13 confirmed responders, 1 participant (with complete response) discontinued treatment following a single infusion because of an intractable skin rash and 1 participant started a new

anticancer therapy while still responding to retifanlimab. The characteristics of the 13 responding patients are listed in Table 11.

An additional 33 participants (35.1%) had SD (1 with unconfirmed PR at the time of the data cut-off), see Table 9.

Table 9: Best overall response based on ICR according to RECIST v1.1 in Study PODIUM-202 (Full Analysis Set, DCO)

Variable	Retifanlimab 500 mg Q4W (N = 94)
Best overall response (%)[a], n (%)	
CR	1 (1.1)
PR	12 (12.8)
SD	33 (35.1)
PD	43 (45.7)
Missing	5 (5.3)
ORR (%)[b], n (%)	13 (13.8)
95% CI for ORR[c]	(7.6, 22.5)
DCR (%)[d], n (%)	46 (48.9)
95% CI for DCR[cc]	(38.5, 59.5)

[a] The best overall response was defined as the best confirmed response in the order of CR > PR > SD > PD > NE 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.
[cc] Confidence intervals were calculated based on the exact method for binomial distributions.
[d] Disease control rate was defined as the proportion of participants with a confirmed overall response of CR, PR, or SD at any postbaseline visit until the first PD or start of new anticancer therapy.

A sensitivity analysis of ORR based on investigator-assessed tumour response according to RECIST v1.1 showed an ORR of 14.9% (Table 10).

Table 10: Investigator-assessed best overall response according to RECIST v1.1 in Study PODIUM-202 (Full Analysis Set, DCO)

Variable	INCMGA00012 500mg Q4W (N=94)
Best Overall Response (%) [1]	
Complete Response	4 (4.3)
Partial Response	10 (10.6)
Stable Disease	30 (31.9)
Progressive Disease	43 (45.7)
Not Assessed	0 (0.0)
Not Evaluable	2 (2.1)
Missing	5 (5.3)
Objective Responders (%)[2]	14 (14.9)
95% CI for Objective Response Rate[3]	(8.4- 23.7)

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Abbreviations: CI = Confidence interval.
[1] The best overall response was defined as the best confirmed response in the order of CR > PR > SD > PD > NE recorded until the first PD or new anti-cancer therapy.
[2] A participant was considered as an objective responder if the participant has a confirmed overall response of CR or PR at any post-baseline visit until the first PD or new anti-cancer therapy.
[3] Confidence intervals were calculated based on the exact method for binomial distributions.

Table 11: Characteristics of confirmed responders by ICR according to RECIST v1.1, DCO

Participant No.	Age/ Sex	HIV Status	HPV Status (subtype)	Prior Treatment	Sites of Current Disease	PD-L1 Score[a]	MMR/ MSI Status	Best Overall Response	DOR[b] (months)	Number of Cycles	Treatment Status
002001	67/F	−	NR	CRTn, plat sys	Liver, LN	1% to < 50% (local)	NR	PR	14.8+	18	Ongoing
104004	73/F	−	+ (HPV 16)	CRTp, CRTn	Liver, lung, LN	80	Proficient	PR	5.6	10	Ongoing
107004	41/M	−	NR	CRTn, plat sys	LN	20	Proficient	PR	5.6	11	Ongoing
113001	65/F	−	NR	CRTn, plat sys	Bone, liver	NR	NR	PR	1.8+	3	Discontinued (PD)
302004	68/F	−	NR	CRTp, plat sys	LN	NR	NR	CR	1.6+	1	Discontinued (AE)
303001	77/F	−	+ (HPV 16)	CRTn, plat sys	Bone, liver, LN	80	Proficient	PR	9.5+	12	Ongoing
401002	39/M	+	NR	CRTn, plat sys	Rectum[c]	NR	NR	PR	5.4	8	Discontinued (PD)
401004	77/M	−	NR	RT, plat sys	LN	5	Proficient	PR	9.5	12	Ongoing
401009	58/F	+	+ (subtype unknown)	CRTn, plat sys	Anus/anal canal[c], lung, LN	NR	NR	PR	4.1+	6	Ongoing
404004	71/F	−	+ (HPV 16)	RT, plat sys	Anus/anal canal, bone, liver	60	Proficient	PR	4.0+	8	Ongoing
406003	55/F	−	+ (HPV 16)	CRTn, plat sys	Liver, LN	30	Proficient	PR	3.9	11	Ongoing
410002	59/F	−	+ (HPV 16)	CRTn, plat sys	LN	0	Proficient	PR	5.6+	8	Ongoing
902001	50/F	−	+ (HPV 16)	CRTp, plat sys × 2	LN	0	Proficient	PR	9.4+	14	Ongoing

CRTn = radiotherapy + fluoropyrimidine/mitomycin-C (Nigro et al 1983); CRTp = radiotherapy + fluoropyrimidine-platinum; F = female; LN = lymph nodes; M = male; MMR = mismatch repair; MSI = microsatellite instability; NR = not reported; plat sys = platinum-based chemotherapy (no RT); Pt = participant; RT = radiotherapy.
[a] The PD-L1 score is based on tumor cell staining from a central laboratory, except for 1 participant who has a local PD-L1 score reported.
[b] Duration of response is based on available scans read by ICR. Ongoing responses are denoted with a "+."
[c] With local extension.

Secondary endpoint of DoR

Duration of response was evaluated at the data cut-off of the primary analysis (08 Jun 2020) when all participants had at least 6 months of follow-up from the time of enrollment or discontinued the study

earlier. An additional DoR analysis was performed using the available tumour response data based on ICR as of 01 Oct 2020 (DCO update), which corresponds to a follow-up interval of at least 6 months from the time of the initial response for all responders (both analyses in Table 12).

Estimated median DoR among the 13 participants with confirmed tumour responses by ICR according to RECIST v1.1 was 9.5 months (95% CI: 4.4, NE), both at the primary and the updated analysis.

At the 8 Jun 2020 DCO, investigator-assessed median DoR according to RECIST v1.1 was 7.6 months (95% CI: 3.7, NE).

Table 12: Duration of response based on ICR according to RECIST v1.1 in Study INCMGA 0012-202 (Full Analysis Set)

Variable	DCO 8 Jun 2020 Retifanlimab 500 mg Q4W (N = 94)	DCO 1 Oct 2020 Retifanlimab 500 mg Q4W (N = 94)
Number (%) of participants who had response[a]	13 (13.8)	13 (13.8)
Number (%) of participants with events[b]	4 (30.8)	7 (53.8)
Disease progression	4 (30.8)	7 (53.8)
Death	0	0
DOR (months) (95% CI)[c]		
25th percentile	5.6 (3.9, NE)	5.6 (3.9, 9.5)
50th percentile (median)	9.5 (5.6, NE)	9.5 (4.4, NE)
75th percentile	NE (5.6, NE)	13.2 (7.8, NE)
Follow-up time (months)		
Median	5.6	7.4
Minimum, maximum	1.6, 14.8	3.6, 18.2
% Event-free probability estimates (95% CI)[d]		
Month 3	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
Month 6	64.9 (24.9, 87,4)	64.8 (31.0, 85.2)
Month 9	64.9 (24.9, 87,4)	54.0 (21.7, 78.0)
Month 12	43.3 (7.5, 76,3)	40.5 (11.3, 68.8)

Note: Months were calculated as the number of days divided by 30.4375.

[a] Participants who had confirmed CR or PR prior to PD according to RECIST v1.1 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.

Secondary endpoint of DCR

33 patients had stable disease as best overall response. Disease control rate was therefore 48.9% (46/94 patients).

Secondary endpoints of PFS and OS

Analysis of the time-to-event endpoints PFS and OS are presented for the FAS. For details on analysis of PFS and OS by response category – refer to the clinical AR.

Median PFS was 2.3 months (95% CI 1.9-3.6 months) in the full analysis set of 94 enrolled patients, see Table 13. A large proportion of subjects was censored (n=23/94; 24.5%).

Table 13: Progression-free survival based on ICR according to RECIST v1.1 in Study PODIUM-202 (Full Analysis Set)

Variable	Total (N = 94)
Participants with disease progression or death observed, n (%)	71 (75.5)
Disease progression	65 (69.1)
Death	6 (6.4)
Censored, n (%)	23 (24.5)
Median time to event (months) (95% CI)[e]	2.3 (1.9, 3.6)
Month 3 PFS rate (95% CI)	46.6 (36.2, 56.4)
Month 6 PFS rate (95% CI)	25.0 (16.1, 34.8)
Month 9 PFS rate (95% CI)	16.0 (8.1, 26.3)
Month 12 PFS rate (95% CI)	12.0 (4.5, 23.6)
Follow-up time (months)	
Median	2.1
Minimum, maximum	0.0, 16.8

Note: According to RECIST 1.1, 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. Months were calculated as the number of days divided by 30.4375.

Error! Reference source not found. Nonresponders includes participants with SD, PD, or missing response.

[e] 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.

Median OS was 10.1 months in the FAS, with a 95% CI lower limit of 7.9 months and a non-evaluable upper limit, see Table 14. Median follow-up time for OS was 7.1 months. At the time of the OS-analysis provided, 39.4% of patients had died. A large proportion of patients was censored (n=57/94; 60.6%).

Table 14: Overall survival in Study PODIUM-202 (Full Analysis Set)

Variable	Total (N = 94)
Number (%) of participants with:	
Death	37 (39.4)
Censoring	57 (60.6)
Median time to event (months) (95% CI)[f]	10.1 (7.9, NE)
Month 3 OS rate (95% CI)	88.1 (79.5, 93.2)
Month 6 OS rate (95% CI)	76.7 (66.5, 84.1)
Month 9 OS rate (95% CI)	58.9 (46.4, 69.4)
Month 12 OS rate (95% CI)	45.7 (31.6, 58.6)
Follow-up time (months)	
Median	7.1
Minimum, maximum	0.9, 19.4

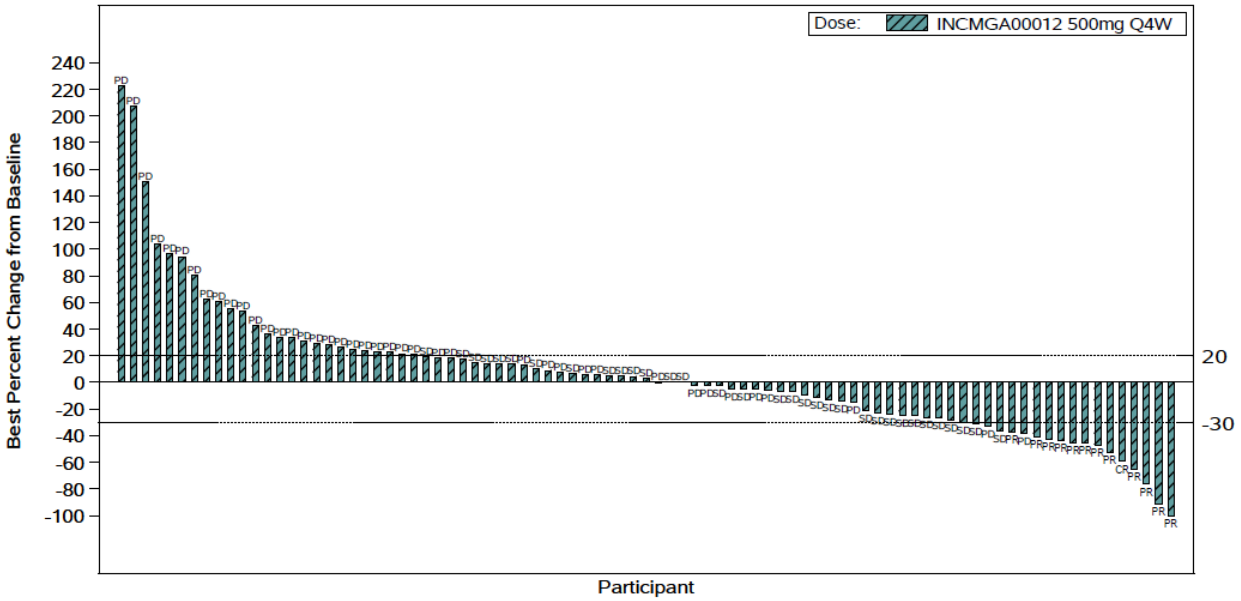
Note: Overall survival was defined as the time in months between the first dose date (Day 1) and the date of death due to any cause. Months were calculated as the number of days divided by 30.4375.

Error! Reference source not found. Nonresponders includes participants with SD, PD, or missing response.

[e] Median survival time was estimated using the Kaplan-Meier method. The CI for median survival time was calculated using the method of Brookmeyer and Crowley.

Best change from baseline sum of diameters of target lesions

Figure 1: Waterfall plot of best percentage change in sum of target lesion diameters from baseline based on ICR in Study INCMGA 0012-202 (Full Analysis Set)



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). Confirmed best overall response is listed for each participant in the figure. The best percentage change in sum of target lesions was prior to new anticancer therapy. Ninety-four participants enrolled in the study, but 7 participants had missing baseline or postbaseline target lesion assessments.

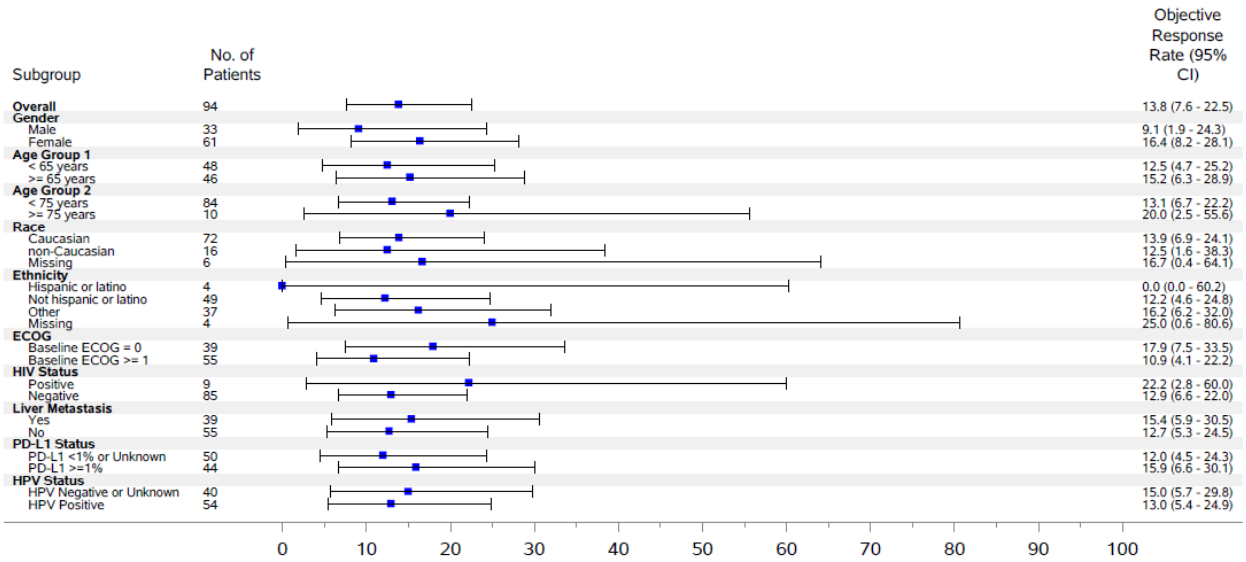
Ancillary analyses

Subgroup analyses

Exploratory subgroup analyses of ORR based on confirmed tumour responses by ICR were performed based on the following intrinsic and extrinsic factors: age group, sex, race, ethnicity, ECOG performance status, HIV status, liver metastases, PD-L1 status, and HPV status.

The confirmed ORRs based on ICR were generally consistent across participant groups within each subgroup. The 95% CIs of the ORRs for participant groups within each subgroup overlapped the 95% CI of the overall ORR (see Figure 2).

Figure 2: Objective response rates based on ICR according to RECIST v1.1 by subgroup in Study PODIUM-202 (Full Analysis Set)



Analysis by iRECIST criteria

The ORR according to iRECIST was 14.9% (95% CI: 8.4, 23.7; see Table 15). Best overall response was CR in 4 participants (4.3%) and PR in 10 participants (10.6%).

Estimated median DoR among the 14 participants with confirmed tumour responses according to iRECIST was 7.6 months (95% CI: 3.7, NE) based on Kaplan-Meier analysis. Estimated probabilities of confirmed responders surviving or not experiencing disease progression for at least 6 and 12 months were 66.7% (95% CI: 27.2, 88.1) and 44.4% (95% CI: 7.8, 77.3), respectively.

Table 15: Summary of best overall response according to iRECIST (FAS)

Type of Response	INCMGA00012 500mg Q4W (N=94)
Best Overall Response (%) [1]	
Complete Response-iCR	4 (4.3)
Partial Response-iPR	10 (10.6)
Stable Disease-iSD	31 (33.0)
Unconfirmed Progressive Disease-iUPD	18 (19.1)
Confirmed Progressive Disease-iCPD	23 (24.5)
Not Assessed	1 (1.1)
Not Evaluable	2 (2.1)
Missing	5 (5.3)
Objective Responders (%)[2]	14 (14.9)
95% CI for Objective Response Rate[3]	(8.4- 23.7)

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Biomarker analysis of PD-L1 expression

Of participants with tumour tissue available for review, 2 of 69 had evidence for MMR deficiency, and 44 of 67 had a PD-L1 status ≥ 1%. The two patients with MMR deficiency did not respond to retifanlimab treatment. Of the 13 responders, MMR status was available for 8/13 patients, all of which had an MMR proficient tumour. PD-L1 expression analysis was available for 9/13 patients, of which 2 did not have any PD-L1 expression and 7 had PD-L1 expression >1%. These numbers are too small to

draw any firm conclusions on the value of MMR-deficiency or PD-L1 expression as predictive biomarker for retifanlimab treatment efficacy in SCAC.

Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16: Summary of efficacy for trial PODIUM-202

Title: A Phase 2 Study of INCMGA00012 in Participants With Squamous Carcinoma of the Anal Canal Who Have Progressed Following Platinum-Based Chemotherapy (POD1UM-202)			
Study identifier	Protocol number INCMGA 0012-202 ; EudraCT 2018-002070-51; NCT03597295		
Design	Single-arm, phase II, open label, multi-centre study		
	Duration of treatment phase: Duration of Run-in phase: Duration of Extension phase:		Until progression or intolerable toxicity, with a maximum of two years not applicable not applicable
Hypothesis	Exploratory: no formal hypothesis was stated. Study was powered based on a target ORR of 25%, with an 80% power to exclude a lower 95% CI limit of 13%.		
Treatment groups	Patients treated (FAS)		Retifanlimab 500mg Q4W, n=94
Endpoints and definitions	Overall response rate Primary endpoint	ORR	percentage of participants with CR or PR at any postbaseline visit before the first PD or new anticancer therapy, according to RECIST v1.1 as determined by ICR
	Duration of response	DoR	time from initial objective tumor response (CR or PR) to the earlier of PD based on RECIST v1.1 criteria or death
	Progression free survival	PFS	time from first dose to PD based on RECIST v1.1 criteria or death
	Overall survival	OS	time from start of therapy until death due to any cause

	Disease control rate	DCR	percentage of participants with a best overall response of CR, PR, or SD based on RECIST v1.1
Database lock	DCO 8 Jun 2020; DCO update (DoR) 01 Oct 2020		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Full analysis set (FAS), includes all participants enrolled in the study who received at least 1 dose of study drug At data cut-off for the primary analysis (DCO 08 Jun 2020), all participants had at least 6 months of follow-up from the time of enrolment or discontinued the study earlier. The additional DoR analysis was performed using the available tumour response data based on ICR as of 01 Oct 2020 (DCO update), which corresponds to a follow-up interval of at least 6 months from the time of the initial response for all responders.	
Descriptive statistics and estimate variability	Treatment group	FAS
	Number of subjects	94
	ORR, % 95% CI	13.8 7.6-22.5
	DoR, median 95% CI	9.5 months 4.4-NE
	PFS, median 95% CI	2.3 months 1.9-3.6
	OS, median 95% CI	10.1 months 7.9-NE
	DCR, % 95% CI	48.9 38.5-59.5
Notes	Planned sample size was 81 patients, but 94 patients were enrolled and included in the primary analysis. As of DCO 8 Jun 2020, 18 participants (19.1%) were continuing to receive retifanlimab, and 76 participants (80.9%) had discontinued treatment. The most common reason for retifanlimab discontinuation was PD in 58 participants (61.7%). Fifty-four participants (57.4%) remained in the study, and 40 participants (42.6%) had withdrawn from the study, mostly because of death (37/94 participants; 39.4%).	

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

Not applicable

Clinical studies in special populations

Not applicable.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials			
Non Controlled trials			

Supportive study(ies)

Not applicable.

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The single pivotal study supporting this application for a CMA is PODIUM-202, an ongoing, open-label, single-arm, multicentre phase II trial in 94 patients with squamous carcinoma of the anal canal. A phase 3 RCT in the target disease but in an earlier line of treatment (first line) is ongoing.

The main deficiency in the study design is the lack of a comparator arm, hampering the understanding of the findings. There is no standard of care treatment for patients progressing after first-line systemic chemotherapy, but a comparative study with best supportive care as control would have been possible.

The flat dose regimen of 500mg Q4W used in PODIUM-202 is adequately justified based on the phase 1 dose-escalation study PODIUM-101 and the performed pop-PK modelling.

PODIUM-202 enrolled participants with locally advanced or metastatic SCAC that had progressed on or after a standard-of-care platinum-based chemotherapy regimen (n=91/94) or who were ineligible for or intolerant of platinum-based therapy (n=3/94). Participants who were ineligible for platinum-based chemotherapy had received at least 1 prior line of systemic therapy, but no more than 2. Participants who had received platinum-based radiosensitizing chemotherapy were eligible if relapse occurred <6 months from completion of treatment. The number of participants that fit this inclusion criterion should be provided (**OC**). Participants had measurable disease according to RECIST v1.1 and an ECOG performance status of 0 or 1. This is acceptable but needs to be reflected in section 5.1 of the SmPC to characterise the study population (**OC**). Participants known to be HIV-positive were eligible if their CD4+ count was ≥ 300 cells/μL, viral load was undetectable, and antiretroviral therapy was being administered.

The study population is considered highly selected, because patients were required to have received at least one prior line of systemic chemotherapy and have an ECOG-PS of 0 or 1 to be eligible to participate.

Eighty percent of patients had metastatic disease at baseline, which is not reflective of the general population as most SCAC patients with relapsed disease have a local recurrence only. In clinical practice, if patients were primarily treated with chemoradiotherapy, salvage surgery (exenterative procedure) is considered for some patients with curative intent – in PODIUM-202 22% of patients had undergone an exenterative procedure. Metastases were mainly to the lymph nodes (65%), liver (42%), and lung (33%). It is not clear how many patients had disease localised in the pelvic region only (e.g. sites previously treated with chemoradiotherapy), without distant visceral metastasis. The applicant is asked to provide the percentage of patients with and without distant visceral metastasis (**OC**).

From a clinical perspective, patients with localised recurrent disease only, could suffer from different symptoms (e.g. local pain) compared to patients with widespread metastatic disease. If pain is the most important symptom for a patient with locally recurrent disease, only a response to treatment (with shrinkage of the tumour) would be of clinical benefit, and DCR cannot be considered a clinically relevant endpoint for these patients.

Given the single arm design, response rate (ORR), based on confirmed CR + PR, and the durability of these confirmed responses (DoR) are interpretable for tumour efficacy and acceptable as primary and key secondary endpoint. However, when these data are used as pivotal evidence to apply for CMA, outstanding results are expected. As discussed during the Scientific Advice, the main issue is whether the results of ORR and DoR translate into a clinical benefit in terms of PFS and OS. This also relates to contextualisation of the results of these time-dependent endpoints in the absence of a comparator arm.

The applicant states that the study had no formal hypotheses, but based on sample size considerations the clinically relevant target ORR was set at 25%. With a sample size of 81 subjects, the study was powered to rule out a response rate of below 13%. While not directly stated by the applicant, it is inferred that an ORR below 13% was not considered to be clinically relevant. It is agreed with the applicant that an ORR of 13% cannot be considered a clinically relevant effect.

The primary analysis was performed after all patients had a follow-up of at least 6 months which suffices for ORR.

The targeted sample size was 81, but 94 patients were enrolled in study PODIUM-202. This difference needs to be explained by the applicant. Furthermore, it needs to be clarified if efficacy and safety results for the first 81 patients were assessed before the study was over-enrolled (**OC**).

An interim analysis for futility was planned after approximately 25 participants were assessable for investigator-assessed response according to RECIST v1.1. Details or results of this interim analysis are not described. The applicant is asked to provide the results of the interim analysis for futility and provide details on the advice given by the DMC (**OC**).

The study was conducted in accordance with the ICH for GCP and the Declaration of Helsinki, as stated by the applicant. There were 4 global amendments to the study protocol. For clarity, the applicant is asked to explain if protocol amendments 1 and 2 were implemented after the study started (**OC**). From the minor protocol deviations, 54.3% concerned out-of-window assessments. The applicant is asked to provide a summary of these assessments. Especially, it should be clarified if any of these assessments were radiological assessments of tumour response (**OC**). If this is the case, details on the participants concerned should be provided – including if these were assessments influencing the primary endpoint of ORR or the important secondary endpoint of DoR. If the tumour response assessments of responding patients were performed later than planned, this could influence the duration of response estimation (**OC**). No GCP inspections were performed. Information on audits and monitoring visits is lacking however and needs to be provided.(**OC**).

Efficacy data and additional analyses

As of the DCO of 08 Jun 2020 enrolment of the study was complete with 94 patients being enrolled. Al 94 patients received the study drug and were therefore included in the FAS. The number of patients that were screened for enrolment, and the reason for patients excluded for not meeting the inclusion criteria, patient refusal or other reasons are not provided. The applicant is asked to provide this information, which is essential to assess the selection of the study population and its representativeness for the general population (**OC**). At DCO, 19/94 patients were still receiving treatment and 54/94 patients remained in the study for follow-up. The applicant is asked for an update on the number of patients in the study and still receiving treatment (**OC**).

The primary endpoint of ORR based on ICR in the full analysis set was 13.8%, with a 95% CI of 7.6-22.5%. The ORR of 13.8% is calculated based on 12 partial responses and 1 complete response observed in the 94 enrolled and treated patients. 33 patients had stable disease as best overall response. Disease control rate was therefore 48.9% (46/94 patients). A sensitivity analysis of ORR based on investigator-assessed tumour response according to RECIST v1.1 showed a comparable ORR of 14.9%. Based on response analysis by iRECIST, there were 4 complete responders, compared to the 1 patient with CR based on response evaluation by conventional RECIST criteria. The applicant is asked to provide a detailed description of the three patients that experienced a CR by iRECIST but not by RECIST, with respect to the location of target and non-target lesions and their assessment over time (**OC**). The confirmed ORRs based on ICR were generally consistent across participant groups within prespecified subgroups based on age group, sex, race, ethnicity, ECOG performance status, HIV status, liver metastases, PD-L1 status, and HPV status. The numbers of patients with available information on PD-L1 expression or MMR-deficiency are too small to draw any firm conclusions on the value of MMR-deficiency or PD-L1 expression as predictive biomarker for retifanlimab treatment efficacy.

The median DoR was 9.5 months, estimated in the 13 responding patients after a median follow-up of 7.4 months. The 95% CI lower limit of the DoR was 4.4 months, with the upper limit not being evaluable. Given that only 13 patients responded, and regarding the fact that the lower limit of the 95% CI for DoR was lower at DCO update compared to DCO (4.4 months versus 5.6 months), the applicant is asked for an update of the DoR estimation by ICR (**OC**). The applicant is also requested to provide an updated summary of the responding patients with the DoR duration for the individual patients (**OC**). The reasons for censoring for the analyses of DoR are not provided. Several of these are potentially informative (study discontinuation for undocumented progression, study discontinuation for toxicity, new anticancer treatment started, death or documented progression immediately after missing 2 or more consecutive tumour assessments). Specific details on reasons for censoring in the DoR analyses should be provided, as well as additional sensitivity analyses for which these censoring times are considered events (**OC**).

Study PODIUM-202 was planned to have a sample size of 81 patients, but 94 patients were enrolled and included in the analysis of ORR and DoR. It cannot be assessed if the addition of 13 extra patients has influenced these efficacy results, and if the applicant was informed about the results for the first 81 patients at the time enrolment was decided to be continued beyond the planned sample size. The applicant should provide an analysis of ORR and DoR for the first 81 patients enrolled and treated in PODIUM-202 (**OC**).

The study had no formal hypotheses, but based on sample size considerations the clinically relevant target ORR was set at 25%. The lower limit of the 95% CI was chosen so that the study was powered to rule out a clinically non-relevant ORR of below 13%. The 95% CI of the observed ORR in study PODIUM-202 does not include the target ORR of 25%, and it does not exclude the as clinically non-relevant designated ORR target of 13%. Based on what the applicant has prespecified as a clinically

relevant effect, the clinical value of the observed ORR of 13.8% is already questionable. Indeed, it is agreed with the applicant that an ORR of 13% cannot be considered a compelling and clinically relevant effect by itself. Furthermore, the ORR does not seem better than reported for other investigated systemic therapies in this setting where there is no clear SOC. Response rates reported are 26.4% for 5-FU and mitomycin combination chemotherapy (ORR in 19 patients; Saint et al. 2019) and 11.6% for pembrolizumab (ORR in 112 patients; Marabelle et al. 2020).

The estimation of the median DoR of 9.5 months by ICR (and 7.6 months by investigator-assessment) is not considered stable given the limited duration of follow-up. Given that only 13 patients responded, and regarding the fact that the lower limit of the 95% CI for DoR was lower for at *DCO update* compared to *DCO* (4.4 months versus 5.6 months), the applicant is asked for an update of the DoR estimation by ICR (**OC**).The applicant has provided analysis of the time-to-event endpoints PFS and OS by response category, as well as Kaplan-Meier curves for these endpoints for responders versus non-responders. These analyses are considered not valid because of immortal time bias, which can falsely inflate the observed difference in survival between responders versus non-responders.

Median PFS was 2.3 months (95% CI 1.9-3.6 months) in the full analysis set of 94 enrolled patients. It is noted that a large proportion of subjects was censored (n=23/94; 24.5%). Median OS was 10.1 months in the FAS, with a 95% CI lower limit of 7.9 months and a non-evaluable upper limit. Median follow-up time for OS was 7.1 months. At the time of the OS-analysis provided, 39.4% of patients had died. A large proportion of patients was censored (n=57/94; 60.6%).The PFS and OS results are possibly biased by informative censoring, requiring a sensitivity analysis. However, because the PFS and OS results are not considered in the evaluation of benefit in the context of a single arm trial, this issue is not further pursued. Even so, the applicant is asked for an update of the OS-analysis with a more recent data cut-off (**OC**).

From a clinical perspective, patients without distant visceral metastasis, but with localised recurrent disease only, could suffer from different symptoms (e.g. local pain) compared to patients with widespread metastatic disease. Furthermore, patients with visceral metastases might have a different (shorter) prognosis compared to patients with localised disease only. One could therefore argue that these patients have a different clinical need. If pain is the most important symptom for a patient with locally recurrent disease, only a response to treatment (with shrinkage of the tumour) would be of clinical benefit, whereas for a patient with metastatic disease a disease stabilisation (SD as included in the DCR) could be of importance. However, any analysis of clinical benefit in subgroups of patients based on localisation of their disease (local recurrence versus distant visceral metastases) is hampered by the low number of responders. Results of the exploratory health-related PRO data (EORTC-QLQ-C30, EORTC-QLQ-ANL27, and EQ-5D-3L) are not presented as part of this application. The applicant is asked to clarify if these results are available, and if so, to provide these analyses (**OC**).

The secondary time-to-event endpoints of PFS and OS are difficult to interpret in the setting of a single-arm trial. Whether the observed effects in terms of ORR can be expected to translate into a clinically meaningful prolongation of survival is unclear (**part of the MO)**. The applicant has provided limited data from literature, in which PFS and OS are described in SCAC patients treated in second line with mitomycin/5-FU chemotherapy (Saint et al.) and immunotherapy with nivolumab (Morris et al.) or pembrolizumab (Marabelle et al.). The median PFS and OS as reported for PODIUM-202 (PFS 2.3 months and OS 10.1 months) fall within the ranges described in these studies: PFS 2-4 months and OS 7-12 months. OS-data from PODIUM-202 are considered immature and the applicant is asked for an updated OS-analysis.

Additional efficacy data needed in the context of a Conditional MA

The applicant proposes to provide additional efficacy data in the target population from study PODIUM-303. PODIUM-303 is a randomised double-blind study comparing first-line treatment with

chemotherapy+placebo to chemotherapy+retifanlimab. The clinical study report based on the primary endpoint of PFS is planned for December 2024. OS is a key secondary endpoint. Crossover to retifanlimab monotherapy for subjects treated in the control arm of the study is allowed in PODIUM-303. This will provide some additional information on the efficacy for retifanlimab (in terms of ORR and DoR) in the platinum-refractory setting. The study might also provide extra information on the efficacy of retifanlimab in locally advanced versus metastatic disease because this is a stratification factor for PODIUM-303. However, PODIUM-303 will not provide comparative data on time-to-event endpoints of PFS and OS for retifanlimab monotherapy for the target population currently applied for **(part of CMA MO)**.

3.3.7. Conclusions on clinical efficacy

In conclusion, the reported ORR results from study PODIUM-202 are considered insufficient to support a clinical benefit for retifanlimab in the intended population. Whether the observed effects in terms of ORR can be expected to translate into clinical meaningful benefit in terms of time-dependent endpoints, i.e. PFS and OS is not clear. The B/R is therefore considered negative. (**MO**). Disease control rate, which includes patients with stable disease on treatment, cannot be considered a valuable clinical endpoint, especially for patients with symptomatic locally advance diseased who can only expect to experience improvement of symptoms following shrinkage of the tumour. While the unmet need for the target population is acknowledged, currently the requirements for the conditional marketing authorisation have not been met (**MO**).

Finally, the proposed wording of the indication is not endorsed as it opens up for treatment with retifanlimab in treatment-naive patients intolerant to platinum-based chemotherapy. This prior untreated population was not studied in the pivotal trial as participants ineligible for platinum must have received at least one prior line of systemic therapy. The indication should be rephrased to clarify that retifanlimab is only indicated after prior systemic therapy, also in platinum intolerant patients. Further, the wording "progressed on" is considered imprecise as it gives associations to a platinum-refractory setting. As the study population also includes patients with progression/relapse after platinum-based therapy, the wording should be adjusted accordingly (**MO**).

3.3.8. Clinical safety

This marketing application includes integrated safety data from the clinical studies of retifanlimab as monotherapy described in Table 17. Safety data are reported for:

- The pooled All Cancer Population (N = 521), which includes all participants with solid tumours who received at least 1 dose of retifanlimab as monotherapy (ie, the safety evaluable population). The All Cancer Population is inclusive of the SCAC and Non-SCAC Populations.
  - SCAC Population (N = 94), which includes all participants with SCAC who received at least 1 dose of retifanlimab. All participants in the SCAC Population received retifanlimab 500 mg Q4W and were enrolled in Study INCMGA 0012-202.
  - Non-SCAC Population (N = 427), which includes all participants with solid tumours other than SCAC who received at least 1 dose of retifanlimab as monotherapy.

Baseline characteristics for the SCAC population are described in the efficacy part. For the All Cancer Population the most common types of cancer were SCAC (18.0%), endometrial cancer (15.9%), and NSCLC (11.5%). Less frequent tumour types were sarcoma (8.8%), Merkel cell carcinoma (4.7%), cervical cancer (7.3%), renal cell carcinoma (6.5%), melanoma (6.3%), and bladder cancer (6.0%). The remaining tumour types occurred in less than 4%. Ten participants (1.9%) were HIV-positive and 156 participants (29.9%) had liver metastases. The median age was 64 years (range: 18-94 years)

and the 58.9% was female. Most participants had an ECOG performance status of 0 (37.2%) or 1 (62.0%). Most participants in the All Cancer Population had normal renal function (37.6%) or mild renal impairment (36.9%) and normal hepatic function (88.1%). Regarding prior therapy, the majority of participants (76.8%) in the All Cancer Population had received prior systemic therapy, 281 participants (53.9%) received prior radiotherapy, and 19 participants (3.6%) received prior immunotherapy. Among the 427 participants in the Non-SCAC Population, in accordance with the protocols, the majorities of participants in studies INCMGA 0012-203 (85/121 [70.2%]) and INCMGA 0012-201 (35/40 [87.5%]) had not received prior systemic therapy.

Table 17: Summary of Integrated Clinical Studies Included in the Summary of Clinical Safety

Study Identifier (Type of Study); Location of Study Report or Safety Data	**Primary Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s), Dosage Regimen, and Route of Administration**	**Number of Participants Enrolled[a]**	**Diagnosis of Participants**	**Estimated Duration of Treatment**	**Study Status; Type of Report (Data Cutoff Date for Integrated Safety Data)**
SCAC study							
INCMGA 0012-202 (Efficacy, safety); 5.3.5.2	Efficacy (ORR)	Phase 2, open-label, single-arm, multicenter study	Retifanlimab 500 mg Q4W IV over 60 minutes	94	Locally advanced or metastatic SCAC	Up to 2 years	Ongoing, enrollment complete; Interim (08 JUN 2020)
Other pooled studies							
INCMGA 0012-101 (Safety, tolerability, PK); 5.3.3.2	Safety and tolerability	Phase 1, open-label, multicenter, dose escalation and cohort expansion study	Retifanlimab 1 mg/kg Q2W IV, 3 mg/kg Q2W IV, 3 mg/kg Q4W IV, 10 mg/kg Q2W IV, 10 mg/kg Q4W IV, 500 mg Q4W IV, 750 mg Q4W IV, 375 mg Q3W IV over 60 minutes	260	Advanced solid tumors	Up to 2 years	Ongoing; Interim (07 APR 2020)
INCMGA 0012-203 (Efficacy); 5.3.5.2	Efficacy (ORR)	Phase 2, open-label, multicenter study	Retifanlimab 500 mg Q4W IV over 30 minutes	121	Metastatic or locally advanced NSCLC, UC, melanoma, or RCC	Up to 2 years	Ongoing, enrollment complete; Interim (05 MAY 2020)
INCMGA 0012-104[b] (Safety, tolerability, PK); 5.3.3.2[c]	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, enrollment complete; Not applicable (21 APR 2020)

Study Identifier (Type of Study); Location of Study Report or Safety Data	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, and Route of Administration	Number of Participants Enrolled[a]	Diagnosis of Participants	Estimated Duration of Treatment	Study Status; Type of Report (Data Cutoff Date for Integrated Safety Data)
INCMGA 0012-201 (Efficacy); 5.3.5.2[c]	Efficacy (ORR)	Phase 2, open-label, multicenter study	Retifanlimab 500 mg Q4W IV over 60 minutes	40	Metastatic Merkel cell carcinoma	Up to 2 years	Ongoing; Not applicable (07 APR 2020)

As of the data cutoff date.
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 SAEs in participants who received retifanlimab in combination with INCB001158.
Location of Protocol, participant safety narratives, CRFs, and PK report (INCMGA 0012-104 only). Integrated safety data are included in Module 5.3.5.3. An interim CSR is not included in submission.

Source: INCMGA 0012-101 CSR, INCMGA 0012-202 CSR, and INCMGA 0012-203 CSR; INCMGA 0012-104 Protocol and INCMGA 0012-201 Protocol; and ISS Listing 2.1.1.

Patient exposure

Table 18 presents a summary of participants by dose regimen and study. Of the 521 participants in the All Cancer Population, 320 participants (61.4%) received the proposed dose regimen of 500 mg Q4W, including all 94 participants with SCAC in Study INCMGA 0012-202. All participants in the SCAC Population were enrolled in Study INCMGA 0012-202 and received 500 mg Q4W.

Table 18: Summary of the Number of Participants Who Received at Least 1 Dose of Retifanlimab as Monotherapy by Dose Regimen and Study

	Retifanlimab Dose Regimen								
Study INCMGA	**1 mg/kg Q2W**	**3 mg/kg Q2W**	**10 mg/kg Q2W**	**3 mg/kg Q4W**	**10 mg/kg Q4W**	**375 mg Q3W**	**750 mg Q4W**	**500 mg Q4W**	**Total**
0012-101	3	144	8	10	6	15	15	59	260
0012-104	0	0	0	0	0	0	0	6	6
0012-201	0	0	0	0	0	0	0	40	40
0012-202	0	0	0	0	0	0	0	94	94
0012-203[a]	0	0	0	0	0	0	0	121	121
Total	3	144	8	10	6	15	15	320	521

[a] Retifanlimab administered by 30-minute infusion; all other studies administered retifanlimab by 60-minute infusion.
Source: INCMGA 0012-101 CSR Tables 3.1.1.1 and 3.1.1.2, INCMGA 0012-202 CSR Table 3.1.1, INCMGA 0012-203 CSR Table 3.1.2, and ISS Table 1.2.2.

As of the data cutoff dates for each study, 162 of the 521 participants (31.1%) in the All Cancer Population, including 18 of the 94 participants (19.1%) in the SCAC Population, were continuing to receive retifanlimab. The most common reason for treatment discontinuation was progressive disease (radiographic and clinical progression in 35.5% and 17.5% of the All Cancer Population, 22.3% and 39.4% of the SCAC Population, respectively). The most common reason for study withdrawal was death (39.7% of the All Cancer Population, 39.4% of the SCAC Population). A summary of exposure is provided in Table 19.

Table 19: Summary of Retifanlimab Exposure

Variable	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing [a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Total number of infusions								
Mean (STD)	4.9 (3.41)	7.3 (9.66)	12.7 (14.39)	5.0 (6.14)	4.5 (3.20)	4.7 (5.61)	4.9 (4.08)	6.8 (8.91)
Median	4.0	4.0	7.0	3.0	4.0	3.0	3.0	4.0
Min, Max	1, 18	1, 52	1, 52	1, 24	1, 20	1, 24	2, 17	1, 52
Total dose administered (mg)								
Mean (STD)	2446.81 (1703.046)	2484.23 (2756.109)	2813.86 (3338.906)	2882.30 (5408.787)	2273.44 (1597.730)	3500.00 (4210.955)	1850.00 (1529.618)	2477.48 (2596.520)
Median	2000.00	1533.00	1562.80	1211.00	2000.00	2250.00	1125.00	1648.00
Min, Max	500.0, 9000.0	104.0, 26,400.0	129.0, 17,035.0	104.0, 26,400.0	500.0, 10,000.0	750.0, 18,000.0	750.0, 6375.0	104.0, 26,400.0
Average dose (mg)								
Mean (STD)	500.00 (0)	410.92 (169.671)	220.20 (53.669)	514.04 (327.547)	500.00 (0)	750.00 (0)	375.00 (0)	426.99 (157.352)
Median	500.00	500.00	205.50	500.00	500.00	750.00	375.00	500.00
Min, Max	500.0, 500.0	47.7, 1211.0	120.0, 404.5	47.7, 1211.0	500.0, 500.0	750.0, 750.0	375.0, 375.0	47.7, 1211.0
Duration of treatment (days)								
Mean (STD)	117.7 (103.31)	124.0 (153.54)	171.8 (209.98)	99.7 (180.13)	104.8 (94.71)	118.4 (177.58)	84.7 (85.17)	122.9 (145.70)
Median	85.0	73.0	97.5	31.0	85.0	57.0	43.0	85.0
Min, Max	1, 592	1, 757	1, 757	1, 696	1, 592	1, 723	22, 337	1, 757
Variable	**SCAC Population (N = 94)**	**Non-SCAC Population (N = 427)**	**All Cancer Population**					
			3 mg/kg Q2W (N = 144)	**Other W-B Dosing[a] (N = 27)**	**500 mg Q4W (N = 320)**	**750 mg Q4W (N = 15)**	**375 mg Q3W (N = 15)**	**Total (N = 521)**

Variable	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing [a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Dose intensity								
Mean (STD)	17.10 (1.628)	17.54 (5.960)	15.21 (3.688)	25.62 (19.162)	17.44 (1.188)	24.85 (2.571)	17.55 (0.815)	17.46 (5.440)
Median	17.86	17.86	14.46	17.86	17.86	26.79	17.86	17.86
Min, Max	8.2, 18.5	3.4, 58.0	8.6, 27.9	3.4, 58.0	8.2, 18.9	20.1, 26.8	15.3, 18.1	3.4, 58.0
Participants treated – n (%)								
< 1 month	20 (21.3)	125 (29.3)	34 (23.6)	13 (48.1)	90 (28.1)	4 (26.7)	4 (26.7)	145 (27.8)
1 to < 3 months	33 (35.1)	127 (29.7)	37 (25.7)	10 (37.0)	100 (31.3)	6 (40.0)	7 (46.7)	160 (30.7)
3 to < 6 months	18 (19.1)	92 (21.5)	33 (22.9)	1 (3.7)	71 (22.2)	2 (13.3)	3 (20.0)	110 (21.1)
6 to < 9 months	16 (17.0)	39 (9.1)	15 (10.4)	0	38 (11.9)	2 (13.3)	0	55 (10.6)
9 to < 12 months	5 (5.3)	15 (3.5)	3 (2.1)	0	16 (5.0)	0	1 (6.7)	20 (3.8)
12 to < 15 months	1 (1.1)	6 (1.4)	3 (2.1)	1 (3.7)	3 (0.9)	0	0	7 (1.3)
15 to < 18 months	0	3 (0.7)	3 (2.1)	0	0	0	0	3 (0.6)
18 to < 21 months	1 (1.1)	6 (1.4)	5 (3.5)	0	2 (0.6)	0	0	7 (1.3)
21 to < 24 months	0	10 (2.3)	7 (4.9)	2 (7.4)	0	1 (6.7)	0	10 (1.9)
≥ 24 months	0	4 (0.9)	4 (2.8)	0	0	0	0	4 (0.8)[b]

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).

[b] These 4 participants completed up to 26 cycles (52 infusions) of retifanlimab, which was the maximum permitted per the INCMGA 0012-101 Protocol.

Note: Months were calculated as the number of days divided by 30.4375.

Source: ISS Tables 3.1.1 and 3.1.2.9.

Adverse events

Overall summary of adverse events

Table 20: Overall Summary of Treatment-Emergent Adverse Events

Participants (n [%]) with:	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
TEAE	90 (95.7)	373 (87.4)	135 (93.8)	27 (100.0)	273 (85.3)	14 (93.3)	14 (93.3)	463 (88.9)
Treatment-related TEAE	55 (58.5)	231 (54.1)	85 (59.0)	17 (63.0)	168 (52.5)	7 (46.7)	9 (60.0)	286 (54.9)
Serious TEAE	51 (54.3)	107 (25.1)	45 (31.3)	10 (37.0)	93 (29.1)	4 (26.7)	6 (40.0)	158 (30.3)
Grade 3 or higher TEAE	55 (58.5)	165 (38.6)	71 (49.3)	19 (70.4)	116 (36.3)	7 (46.7)	7 (46.7)	220 (42.2)
Fatal TEAE	10 (10.6)	11 (2.6)	4 (2.8)	0	17 (5.3)	0	0	21 (4.0)
Serious treatment-related TEAE	6 (6.4)	19 (4.4)	10 (6.9)	0	13 (4.1)	2 (13.3)	0	25 (4.8)
Grade 3 or higher treatment-related TEAE	11 (11.7)	41 (9.6)	22 (15.3)	0	26 (8.1)	1 (6.7)	3 (20.0)	52 (10.0)
Infusion interruption due to TEAE	1 (1.1)	2 (0.5)	0	0	3 (0.9)	0	0	3 (0.6)
Dose delayed due to TEAE	25 (26.6)	84 (19.7)	35 (24.3)	6 (22.2)	63 (19.7)	4 (26.7)	1 (6.7)	109 (20.9)
Discontinued study drug due to TEAE	7 (7.4)	36 (8.4)	19 (13.2)	0	22 (6.9)	1 (6.7)	1 (6.7)	43 (8.3)

Note: TEAEs leading to "drug interruption" or "infusion interruption" are summarised with "next scheduled dose delay" for Study INCMGA 0012-101.

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).

Source: ISS Tables 3.2.1.1 and 3.2.1.10.

Common adverse events

In the SCAC Population, TEAEs were most frequently associated with the MedDRA system organ classes of gastrointestinal disorders (59.6%), general disorders and administration site conditions (51.1%), and infections and infestations (42.6%). In the All Cancer Population, TEAEs were most frequently associated with the MedDRA system organ classes of general disorders and administration site conditions (43.0%) and gastrointestinal disorders (41.7%). Gastrointestinal disorders was the only system organ class with a higher (> 20%) frequency of TEAEs in the SCAC Population compared with the Non-SCAC Population (59.6% vs 37.7%).

By MedDRA preferred term, the most frequent TEAEs in the SCAC Population were asthenia (22.3%), anaemia and diarrhoea (19.1% each), and fatigue (17.0%; see Table 21). The most frequent TEAEs in

the All Cancer Population were fatigue (15.7%), anaemia (13.8%), and diarrhoea (13.1%). Most of these frequent TEAEs were Grade 1 or 2 in severity. Treatment-emergent events that occurred at higher (> 5%) frequencies in the SCAC Population compared with the Non-SCAC Population were asthenia (22.3% vs 10.8%), anaemia (19.1% vs 12.6%), diarrhoea (19.1% vs 11.7%), and dyspnea (13.8% vs 6.8%).

Table 21: Summary of TEAEs Occurring in ≥ 5% of Participants by MedDRA Preferred Term in Decreasing Order of Frequency for the All Cancer Population Total

MedDRA Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Fatigue	16 (17.0)	66 (15.5)	27 (18.8)	12 (44.4)	38 (11.9)	3 (20.0)	2 (13.3)	82 (15.7)
Anaemia	18 (19.1)	54 (12.6)	18 (12.5)	5 (18.5)	41 (12.8)	6 (40.0)	2 (13.3)	72 (13.8)
Diarrhoea	18 (19.1)	50 (11.7)	22 (15.3)	2 (7.4)	42 (13.1)	1 (6.7)	1 (6.7)	68 (13.1)
Asthenia	21 (22.3)	46 (10.8)	11 (7.6)	2 (7.4)	54 (16.9)	0	0	67 (12.9)
Nausea	14 (14.9)	47 (11.0)	18 (12.5)	7 (25.9)	31 (9.7)	4 (26.7)	1 (6.7)	61 (11.7)
Pyrexia	12 (12.8)	42 (9.8)	15 (10.4)	5 (18.5)	33 (10.3)	1 (6.7)	0	54 (10.4)
Pruritus	11 (11.7)	42 (9.8)	11 (7.6)	2 (7.4)	36 (11.3)	2 (13.3)	2 (13.3)	53 (10.2)
Decreased appetite	13 (13.8)	39 (9.1)	10 (6.9)	6 (22.2)	35 (10.9)	0	1 (6.7)	52 (10.0)
Vomiting	13 (13.8)	34 (8.0)	17 (11.8)	3 (11.1)	23 (7.2)	4 (26.7)	0	47 (9.0)
Cough	11 (11.7)	35 (8.2)	13 (9.0)	3 (11.1)	25 (7.8)	3 (20.0)	2 (13.3)	46 (8.8)
Constipation	13 (13.8)	31 (7.3)	16 (11.1)	0	28 (8.8)	0	0	44 (8.4)
Dyspnoea	13 (13.8)	29 (6.8)	14 (9.7)	0	26 (8.1)	0	2 (13.3)	42 (8.1)
Hypo-thyroidism	8 (8.5)	33 (7.7)	16 (11.1)	1 (3.7)	21 (6.6)	3 (20.0)	0	41 (7.9)
Arthralgia	6 (6.4)	33 (7.7)	7 (4.9)	2 (7.4)	27 (8.4)	3 (20.0)	0	39 (7.5)
Abdominal pain	10 (10.6)	28 (6.6)	15 (10.4)	1 (3.7)	20 (6.3)	1 (6.7)	1 (6.7)	38 (7.3)
Rash	4 (4.3)	34 (8.0)	11 (7.6)	1 (3.7)	24 (7.5)	2 (13.3)	0	38 (7.3)
Urinary tract infection	9 (9.6)	28 (6.6)	12 (8.3)	3 (11.1)	21 (6.6)	0	1 (6.7)	37 (7.1)
Back pain	8 (8.5)	26 (6.1)	12 (8.3)	1 (3.7)	20 (6.3)	0	1 (6.7)	34 (6.5)
AST increased	7 (7.4)	22 (5.2)	8 (5.6)	2 (7.4)	14 (4.4)	2 (13.3)	3 (20.0)	29 (5.6)
Weight decreased	9 (9.6)	17 (4.0)	11 (7.6)	1 (3.7)	13 (4.1)	1 (6.7)	0	26 (5.0)

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).
Source: ISS Tables 3.2.3.1 and 3.2.3.3.

Treatment-related adverse events

In the SCAC Population, treatment-related TEAEs were most frequently associated with the MedDRA system organ classes of skin and subcutaneous tissue disorders (25.5%), gastrointestinal disorders (21.3%), and general disorders and administration site conditions (20.2%). In the All Cancer Population, treatment-related TEAEs were most frequently associated with the MedDRA system organ classes of general disorders and administration site conditions (20.2%), skin and subcutaneous tissue disorders (19.0%), and gastrointestinal disorders (15.5%). The most frequent treatment-related are shown in Table 22.

Table 22: Summary of Treatment-Related TEAEs Occurring in ≥ 2% of Participants by MedDRA Preferred Term in Decreasing Order of Frequency for the All Cancer Population Total

MedDRA Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Fatigue	9 (9.6)	41 (9.6)	14 (9.7)	8 (29.6)	25 (7.8)	1 (6.7)	2 (13.3)	50 (9.6)
Pruritus	11 (11.7)	29 (6.8)	6 (4.2)	2 (7.4)	30 (9.4)	1 (6.7)	1 (6.7)	40 (7.7)
Hypothyroidism	5 (5.3)	29 (6.8)	14 (9.7)	1 (3.7)	16 (5.0)	3 (20.0)	0	34 (6.5)
Asthenia	7 (7.4)	23 (5.4)	5 (3.5)	0	25 (7.8)	0	0	30 (5.8)
Diarrhoea	8 (8.5)	21 (4.9)	10 (6.9)	1 (3.7)	18 (5.6)	0	0	29 (5.6)
Rash	4 (4.3)	24 (5.6)	9 (6.3)	1 (3.7)	18 (5.6)	0	0	28 (5.4)
Nausea	6 (6.4)	20 (4.7)	8 (5.6)	4 (14.8)	12 (3.8)	2 (13.3)	0	26 (5.0)
Hyperthyroidism	4 (4.3)	15 (3.5)	8 (5.6)	2 (7.4)	7 (2.2)	2 (13.3)	0	19 (3.6)
Arthralgia	3 (3.2)	12 (2.8)	1 (0.7)	0	14 (4.4)	0	0	15 (2.9)
Decreased appetite	4 (4.3)	11 (2.6)	4 (2.8)	0	11 (3.4)	0	0	15 (2.9)
ALT increased	3 (3.2)	11 (2.6)	5 (3.5)	0	8 (2.5)	1 (6.7)	0	14 (2.7)
AST increased	5 (5.3)	8 (1.9)	3 (2.1)	0	8 (2.5)	1 (6.7)	1 (6.7)	13 (2.5)
Infusion related reaction	1 (1.1)	12 (2.8)	4 (2.8)	1 (3.7)	7 (2.2)	1 (6.7)	0	13 (2.5)
Anaemia	0	12 (2.8)	3 (2.1)	0	8 (2.5)	1 (6.7)	0	12 (2.3)
Lipase increased	1 (1.1)	10 (2.3)	5 (3.5)	0	5 (1.6)	0	1 (6.7)	11 (2.1)
Pyrexia	3 (3.2)	8 (1.9)	3 (2.1)	1 (3.7)	7 (2.2)	0	0	11 (2.1)

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).
Source: ISS Tables 3.2.11.1 and 3.2.11.2.

Adverse events of ≥Grade 3

In the SCAC Population, Grade 3 or higher TEAEs were most frequently associated with the system organ classes of gastrointestinal disorders (16.0%), infections and infestations (13.8%), and general disorders and administration site conditions (12.8%). In the All Cancer Population, Grade 3 or higher TEAEs were most frequently associated with the system organ classes of investigations (7.9%), metabolism and nutrition disorders (7.7%), and gastrointestinal disorders and infections and infestations (7.3% each). Similar to the frequent TEAEs of any grade, gastrointestinal disorders was the only system organ class with a higher frequency (>10%) of Grade 3 or higher TEAEs in the SCAC Population compared with the Non-SCAC Population (16.0% vs 5.4%). The most frequent Grade 3 or higher TEAE are reported in Table 23. Grade 3 or higher TEAEs that occurred at a higher (>3%)

frequency in the SCAC Population compared with the Non SCAC Population were dyspnea (4.3% vs 1.2%), abdominal pain (4.3% vs 0.7%), and general physical health deterioration (4.3% vs 0.5%).

Table 23: Summary of ≥ Grade 3 TEAEs Occurring in ≥ 1% of Participants by MedDRA Preferred Term in Decreasing Order of Frequency for the All Cancer Population Total

MedDRA Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Anaemia	6 (6.4)	23 (5.4)	4 (2.8)	5 (18.5)	16 (5.0)	3 (20.0)	1 (6.7)	29 (5.6)
Hyponatraemia	3 (3.2)	8 (1.9)	4 (2.8)	1 (3.7)	6 (1.9)	0	0	11 (2.1)
Blood alkaline phosphatase increased	0	10 (2.3)	2 (1.4)	2 (7.4)	5 (1.6)	0	1 (6.7)	10 (1.9)
Pneumonia	1 (1.1)	9 (2.1)	0	2 (7.4)	8 (2.5)	0	0	10 (1.9)
Pulmonary embolism	1 (1.1)	9 (2.1)	6 (4.2)	1 (3.7)	2 (0.6)	1 (6.7)	0	10 (1.9)
Dyspnoea	4 (4.3)	5 (1.2)	3 (2.1)	0	5 (1.6)	0	1 (6.7)	9 (1.7)
Asthenia	3 (3.2)	5 (1.2)	1 (0.7)	1 (3.7)	6 (1.9)	0	0	8 (1.5)
Lipase increased	0	8 (1.9)	6 (4.2)	0	1 (0.3)	1 (6.7)	0	8 (1.5)
Abdominal pain	4 (4.3)	3 (0.7)	1 (0.7)	0	5 (1.6)	0	1 (6.7)	7 (1.3)
Urinary tract infection	3 (3.2)	4 (0.9)	3 (2.1)	1 (3.7)	3 (0.9)	0	0	7 (1.3)
Amylase increased	0	6 (1.4)	3 (2.1)	0	1 (0.3)	0	2 (13.3)	6 (1.2)
AST increased	0	6 (1.4)	3 (2.1)	1 (3.7)	2 (0.6)	0	0	6 (1.2)
General physical health deterioration	4 (4.3)	2 (0.5)	2 (1.4)	0	4 (1.3)	0	0	6 (1.2)
Hypercalcaemia	2 (2.1)	4 (0.9)	1 (0.7)	0	5 (1.6)	0	0	6 (1.2)
Hypertension	0	6 (1.4)	1 (0.7)	2 (7.4)	3 (0.9)	0	0	6 (1.2)
Pleural effusion	2 (2.1)	4 (0.9)	0	1 (3.7)	5 (1.6)	0	0	6 (1.2)
ALT increased	0	5 (1.2)	1 (0.7)	0	4 (1.3)	0	0	5 (1.0)
Blood bilirubin increased	0	5 (1.2)	1 (0.7)	1 (3.7)	2 (0.6)	1 (6.7)	0	5 (1.0)
Hypokalaemia	0	5 (1.2)	3 (2.1)	0	2 (0.6)	0	0	5 (1.0)
Sepsis	2 (2.1)	3 (0.7)	0	0	5 (1.6)	0	0	5 (1.0)

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).
Source: ISS Tables 3.2.7.1 and 3.2.7.3.

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

Frequencies of irAEs are shown in Table 24. Most irAEs were Grade 1 or 2 in severity. Immune-related irAEs were Grade 3 in 19 participants (3.6%), Grade 4 in 2 participants (0.4%), and Grade 5 in 2 participants (0.4%). Serious irAEs occurred in 20 participants (3.8%), and 14 participants (2.7%) had irAEs leading to retifanlimab discontinuation. Fatal irAEs occurred in 2 participants (0.4%) and, by group term, included nephritis (preferred term: nephritis) and pneumonitis (preferred term: interstitial lung disease), neither of which were considered related to retifanlimab by the investigator. IrAEs by group term are presented in Table 25.

Table 24: Overall Summary of Immune-Related Adverse Events

Participants (n [%]) With:	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Any irAE	24 (25.5)	86 (20.1)	45 (31.3)	2 (7.4)	59 (18.4)	4 (26.7)	0	110 (21.1)[b]
Serious irAE	3 (3.2)	17 (4.0)	10 (6.9)	0	8 (2.5)	2 (13.3)	0	20 (3.8)
Grade 3 or higher irAE	6 (6.4)	17 (4.0)	11 (7.6)	0	11 (3.4)	1 (6.7)	0	23 (4.4)
Fatal irAE	1 (1.1)	1 (0.2)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)[c]
irAE leading to dose delay of the next scheduled dose	6 (6.4)	13 (3.0)	8 (5.6)	0	9 (2.8)	2 (13.3)	0	19 (3.6)
irAE leading to retifanlimab discontinuation	2 (2.1)	12 (2.8)	7 (4.9)	0	6 (1.9)	1 (6.7)	0	14 (2.7)

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).

[b] Does not include the sponsor-identified irAEs of immune-mediated enterocolitis and hepatitis; includes the events of nephritis in the 4 participants for which there is insufficient evidence to support a diagnosis of immune-related nephritis.

[c] Both fatal irAEs were considered not related to retifanlimab by the investigator (refer to ISS Listing 2.7.3).

Note: TEAEs leading to "drug interruption" or "infusion interruption" are summarised with "next scheduled dose delay" for Study INCMGA 0012-101.

Source: ISS Tables 3.2.1.4 and 3.2.1.13.

Table 25: Immune-Related Adverse Events by Group Term in the SCAC and All Cancer Populations

Group Term, n (%)	SCAC Population (N = 94)		All Cancer Population (N = 521)	
	All Grades	Grades ≥ 3	All Grades	Grades ≥ 3
Endocrine irAEs				
Hypothyroidism	8 (8.5)	0	41 (7.9)	1 (0.2)
Hyperthyroidism	4 (4.3)	0	23 (4.4)	0
Adrenal insufficiency	1 (1.1)	1 (1.1)	2 (0.4)	1 (0.2)
Thyroiditis	0	0	2 (0.4)	0
Type 1 diabetes	0	0	2 (0.4)	2 (0.4)
Non-endocrine irAEs				
Skin reactions[a]	8 (8.5)	2 (2.1)	26 (5.0)	4 (0.8)
Pneumonitis[b]	4 (4.3)	2 (2.1)	9 (1.7)	4 (0.8)
Colitis[c]	2 (2.1)	1 (1.1)	7 (1.3)	5 (1.0)
Nephritis[d]	1 (1.1)	1 (1.1)	5 (1.0)	5 (1.0)
Hepatitis[e]	1 (1.1)	1 (1.1)	3 (0.6)	1 (0.2)
Polyarthritis	0	0	3 (0.6)	0
Myositis	1 (1.1)	0	2 (0.4)	1 (0.2)
Uveitis[f]	0	0	1 (0.2)	0
Myocarditis	0	0	1 (0.2)	0
Radiculopathy	0	0	1 (0.2)	1 (0.2)

[a] Includes preferred terms of rash, pruritus, rash maculo-papular, rash erythematous, rash pruritic, toxic skin eruption, rash pustular, dermatitis, and palmar-plantar erythrodysaesthesia syndrome.
[b] Includes preferred terms of interstitial lung disease and pneumonitis.
[c] Includes preferred term of colitis and 1 participant who had a TEAE of immune-mediated enterocolitis (ileitis; refer to Module 2.7.4 Section 2.1.8.1.5).
[d] Includes preferred terms of acute kidney injury and nephritis. Excludes the events of nephritis in the 4 participants for which there is insufficient evidence to support a diagnosis of immune-related nephritis (refer to Module 2.7.4 Section 2.1.8.1.4).
[e] Includes preferred terms of autoimmune hepatitis and hepatitis, and 1 participant with concurrent Grade 3 elevations of AST and ALT (based on laboratory results) with investigator-suspected immune related hepatitis (refer to Module 2.7.4 Section 2.1.8.1.6).
[f] Includes preferred term of iritis.
Source: ISS Tables 3.2.2.7 and 3.2.6.7.

Immune-related endocrinopathies

Immune-related endocrine AEs reported were hypothyroidism (7.9% in the All Cancer Population), hyperthyroidism (4.4%), adrenal insufficiency (0.4%), thyroiditis (0.4%), and type I diabetes (0.4%). Most of the immune-related endocrine AEs were Grade 1 or 2, none were fatal, and 1 led to discontinuation (type I diabetes mellitus). Median time to onset ranged from 1-577 days. Median time of onset was 85.0 days for hypothyroidism, 55.0 days for hyperthyroidism, 219 days for adrenal insufficiency, 74.5 days for thyroiditis, and 156.5 days for type I diabetes. The majority of the patients were treated with endocrine therapy (30.4-100% depending on the type of AE) and none were treated with immunosuppression. All cases of type I diabetes were resolved, about half of the cases with hyperthyroidism, adrenal insufficiency, and thyroiditis; and 14.6% of the hypothyroidism cases resolved.

Table 26: Detailed Summary of Endocrine Immune-Related Adverse Events by Group Term and Preferred Term

Group Term *Preferred Term* Population, n (%)	**Any Grade**	**≥ Grade 3[a]**	**Serious**	**Treated With Endocrine Therapy[b]**	**Led to Discontinuation**	**Resolved[b]**	**Fatal**
Hypothyroidism	**41 (7.9)**	**1 (0.2)**	**1 (0.2)**	**34 (82.9)**	**0**	**6 (14.6)**	**0**
Hypothyroidism							
SCAC (n = 94)	8 (8.5)	0	0	–	0	–	0
Non-SCAC (n = 427)	33 (7.7)	1 (0.2)	1 (0.2)	–	0	–	0
All Cancer (n = 521)	41 (7.9)	1 (0.2)	1 (0.2)	–	0	–	0
Hyperthyroidism	**23 (4.4)**	**0**	**0**	**7 (30.4)**	**0**	**12 (52.2)**	**0**
Hyperthyroidism							
SCAC (n = 94)	4 (4.3)	0	0	–	0	–	0
Non-SCAC (n = 427)	19 (4.4)	0	0	–	0	–	0
All Cancer (n = 521)	23 (4.4)	0	0	–	0	–	0
Adrenal insufficiency	**2 (0.4)**	**1 (0.2)**	**1 (0.2)**	**1 (50.0)**	**0**	**1 (50.0)**	**0**
Adrenal insufficiency							
SCAC (n = 94)	1 (1.1)	1 (1.1)	1 (1.1)	–	0	–	0
Non-SCAC (n = 427)	1 (0.2)	0	0	–	0	–	0
All Cancer (n = 521)	2 (0.4)	1 (0.2)	1 (0.2)	–	0	–	0
Thyroiditis	**2 (0.4)**	**0**	**1 (0.2)**	**2 (100.0)**	**0**	**1 (50.0)**	**0**
Autoimmune thyroiditis							
SCAC (n = 94)	0	0	0	–	0	–	0
Non-SCAC (n=427)	1 (0.2)	0	0	–	0	–	0
All Cancer (n=521)	1 (0.2)	0	0	–	0	–	0
Thyroiditis							
SCAC (n=94)	0	0	0	–	0	–	0
Non-SCAC (n = 427)	1 (0.2)	0	1 (0.2)	–	0	–	0
All Cancer (n = 521)	1 (0.2)	0	1 (0.2)	–	0	–	0
Type 1 diabetes	**2 (0.4)**	**2 (0.4)**	**2 (0.4)**	**1 (50.0)**	**1 (0.2)**	**2 (100.0)**	**0**
Diabetic ketoacidosis							
SCAC (n = 94)	0	0	0	–	0	–	0
Non-SCAC (n = 427)	1 (0.2)	1 (0.2)	1 (0.2)	–	0	–	0
All Cancer (n = 521)	1 (0.2)	1 (0.2)	1 (0.2)	–	0	–	0
Type 1 diabetes mellitus							
SCAC (n = 94)	0	0	0	–	0	–	0
Non-SCAC (n = 427)	1 (0.2)	1 (0.2)	1 (0.2)	–	1 (0.2)	–	0
All Cancer (n = 521)	1 (0.2)	1 (0.2)	1 (0.2)	–	1 (0.2)	–	0

[a] Maximum severity.
[b] Number of participants with events is denominator.
Source: ISS Tables 3.2.2.7, 3.2.6.7, 3.2.8.7, 3.2.16.6, 3.2.20.8, 3.2.26.2, and 3.2.27.2.

Immune-related skin reactions

Immune-related skin AEs were reported in 5.0% of the All Cancer Population and in 8.5% of the SCAC Population. Skin reactions consisted of rash, pruritus, rash maculo-papular, rash erythematous, rash pruritic, toxic skin eruption, rash pustular, dermatitis, and palmo-plantar erythrodysaesthesia syndrome (PPES). In the All Cancer Population, skin reactions Grade 1 occurred in 0.2%, Grade 2 in 4.0%, and Grade 3 in 0.8%. Skin reactions led to discontinuation in 1 patient (0.2%), which was a case of PPES. The median onset time of observed skin reactions was 92.0 days (range: 1-628 days). Among the patients with skin reactions, 38.5% received systemic glucocorticoids, 26.9% received high dose systemic glucocorticoids, and none of the participants received other immunosuppressants. Skin reactions resolved in 15 participants (57.7%), with a median time to resolution of 40.0 days (range: 3-191 days). There were no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis.

Table 27: Detailed Summary of Skin Reactions

Group Term *Preferred Term* Population, n (%)	**Any Grade**	**≥ Grade 3[a]**	**Serious**	**Treatment Administered[b,c]**			**Led to Discontinuation**	**Resolved[b]**	**Fatal**
				Systemic Gluco-corticoids	**High Dose Gluco-corticoids**	**Other Immuno-suppressant**			
Skin reactions	**26 (5.0)**	**4 (0.8)**	**1 (0.2)**	**11 (42.3)[d]**	**7 (26.9)**	**0**	**1 (0.2)**	**15 (57.7)**	**0**
Rash									
SCAC (n = 94)	1 (1.1)	1 (1.1)	0	–	–	–	0	–	0
Non-SCAC (n = 427)	9 (2.1)	0	0	–	–	–	0	–	0
All Cancer (n = 521)	10 (1.9)	1 (0.2)	0	–	–	–	0	–	0
Pruritus									
SCAC (n = 94)	4 (4.3)	0	0	–	–	–	0	–	0
Non-SCAC (n = 427)	4 (0.9)	0	0	–	–	–	0	–	0
All Cancer (n = 521)	8 (1.5)	0	0	–	–	–	0	–	0
Rash maculo-papular									
SCAC (n = 94)	2 (2.1)	1 (1.1)	0	–	–	–	0	–	0
Non-SCAC (n = 427)	2 (0.5)	1 (0.2)	0	–	–	–	0	–	0
All Cancer (n = 521)	4 (0.8)	2 (0.4)	0	–	–	–	0	–	0
Rash erythematous									
SCAC (n = 94)	1 (1.1)	0	0	–	–	–	0	–	0
Non-SCAC (n = 427)	2 (0.5)	1 (0.2)	1 (0.2)	–	–	–	0	–	0
All Cancer (n = 521)	3 (0.6)	1 (0.2)	1 (0.2)	–	–	–	0	–	0
Rash pruritic									
SCAC (n = 94)	0	0	0	–	–	–	0	–	0
Non-SCAC (n = 427)	2 (0.5)	0	0	–	–	–	0	–	0
All Cancer (n = 521)	2 (0.4)	0	0	–	–	–	0	–	0
Toxic skin eruption									
SCAC (n = 94)	0	0	0	–	–	–	0	–	0
Non-SCAC (n = 427)	2 (0.5)	0	0	–	–	–	0	–	0
All Cancer (n = 521)	2 (0.4)	0	0	–	–	–	0	–	0
Rash pustular									
SCAC (n = 94)	0	0	0	–	–	–	0	–	0
Non-SCAC (n = 427)	1 (0.2)	0	0	–	–	–	0	–	0
All Cancer (n = 521)	1 (0.2)	0	0	–	–	–	0	–	0
Dermatitis									
SCAC (n = 94)	1 (1.1)	0	0	–	–	–	0	–	0
Non-SCAC (n = 427)	0	0	0	–	–	–	0	–	0

Group Term *Preferred Term* Population, n (%)	Any Grade	≥ Grade 3[a]	Serious	Treatment Administered[b,c]			Led to Discontinuation	Resolved[b]	Fatal
				Systemic Gluco-corticoids	High Dose Gluco-corticoids	Other Immuno-suppressant			
All Cancer (n = 521)	1 (0.2)	0	0	–	–	–	0	–	0
PPES									
SCAC (n = 94)	1 (1.1)	0	0	–	–	–	1 (1.1)	–	0
Non-SCAC (n = 427)	0	0	0	–	–	–	0	–	0
All Cancer (n = 521)	1 (0.2)	0	0	–	–	–	1 (0.2)	–	0

PPES = Palmar-plantar erythrodysaesthesia syndrome.

[a] Maximum severity.

[b] Number of participants with events is denominator.

[c] See Section **Error! Reference source not found.** for definitions of irAE treatments.

[d] One of 8 participants in the Non-SCAC Population reported as having received systemic glucocorticoids for skin reactions received betamethasone sodium phosphate administered cutaneously that was incorrectly coded to the Glucocorticoid drug class (refer to INCMGA 0012-203 errata). Excluding this participant, 7 participants (38.9%) in the Non-SCAC Population and 10 participants (38.5%) in the All Cancer Population received systemic glucocorticoids for skin reactions.

Source: ISS Tables 3.2.2.7, 3.2.6.7, 3.2.8.7, 3.2.16.6, 3.2.20.8, 3.2.26.2, and 3.2.27.2.

Immune-related pneumonitis

Overall, pneumonitis occurred in 1.7% in the All Cancer Population and in 4.3% of the SCAC Population. In the All Cancer Population Grade 2 pneumonitis was reported in 1.0%, Grade 3 in 0.6%, and Grade 5 in 0.2%. The fatal case of pneumonitis occurred in the SCAC population and was not considered to be related to retifanlimab by the investigator and sponsor and was assessed as a complication of progression of metastatic disease in the lung. The fatal case concerned participant 404001 with SCAC and metastases to lung and liver at baseline. The patient had received prior chemotherapy of cisplatin, fluorouracil, mitomycin and paclitaxel, and radiotherapy to the anal canal, mediastinum and chestm but had no prior surgery. The participant received the last dose of retifanlimab (500 mg Q4W) prior to the onset of the AEs on Day 85. On Day 111, the participant presented to the site for a follow-up visit with a performance status deterioration but with no respiratory symptoms. On the same day, a CT scan revealed a bilateral progressive interstitial pulmonary process. Work-up was negative for infectious causes, including viral causes and pneumocystis. On that same day, the participant's CRP was 52 (units and reference values not provided). The participant was diagnosed as having interstitial pneumonia (preferred term: interstitial lung disease). To treat the interstitial pneumonia, methylprednisolone 60 mg IV QD was initiated without performing fibroscopy with bronchoalveolar lavage given the poor performance status of the participant. From Day 118 to Day 146, the participant was treated with a tapering dose of prednisolone from 60 mg to 30 mg PO QD every 7 days, ending with an ongoing dose of 20 mg PO QD on Day 147. On Day 139, the participant experienced a fever (preferred term: pyrexia) of 39.1 degrees Celsius and cognitive disturbance (preferred term: cognitive disorder). On this same date, the participant was admitted to the hospital. CRP was at 110.6 mg/L (normal values: <5). On the same date, treatment with Perfalgan and ceftriaxone was initiated. On Day 140, a brain scan showed no abnormalities except for a diffuse atrophy. On Day 141, ceftriaxone treatment was stopped. On Day 142, CRP was 114.4 mg/L. On Day 142, Bactrim treatment was initiated, and on Day 143, piperacillin tazobactam was started. On Day 144, CRP was 280.8 mg/L. On Day 145, the participant received furosemide. No improvement in the participant's clinical condition was observed. The participant continued to experience fever, dyspnoea, and oxygen desaturation and his CRP was at 380 (unit and reference values not provided). A CT scan showed worsening in pulmonary infiltration despite the corticosteroid treatment. Bacteriological tests remained negative, including SARS COVID-19 and tuberculosis. Per the

investigator, a test for pneumocystosis was performed. On Day 147, CRP was 342.4 mg/L, cytomegalovirus test was 41.4 U/ml (normal values: <12), and cytomegalovirus IgG analysis was positive. The outcome of the event of interstitial pneumonia was reported as fatal. It was also reported that the most likely causes of death were pulmonary cancer progression or infection of an undetermined nature. No autopsy was performed. The investigator considered that there is not a reasonable possibility that retifanlimab caused the reported SAE of interstitial pneumonia. Alternative causality was provided as progression of study indication. Pneumonitis leading to discontinuation occurred in 0.4%. The median onset time of observed pneumonitis events was 89.0 days (range: 43-162 days). Among the 9 patients with pneumonitis, 8 (88.9%) received systemic glucocorticoids, 6 (66.7%) high dose systemic glucocorticoids, and 1 (11.1%) another immunosuppressant (infliximab). Pneumonitis resolved in 66.7%, with a median time to resolution of 40.5 days (range: 9-213 days).

Table 28: Detailed Summary of Pneumonitis

Group Term *Preferred Term* Population, n (%)	**Any Grade**	**≥ Grade 3[a]**	**Serious**	**Treatment Administered[b,c]**			**Led to Discontinuation**	**Resolved[b]**	**Fatal**
				Systemic Gluco-corticoids	**High Dose Gluco-corticoids**	**Other Immuno-suppressant**			
Pneumonitis	**9 (1.7)**	**4 (0.8)**	**4 (0.8)**	**8 (88.9)**	**6 (66.7)**	**1 (11.1)**	**2 (0.4)**	**6 (66.7)**	**1 (0.2)**
Interstitial lung disease									
SCAC (n = 94)	1 (1.1)	1 (1.1)	1 (1.1)	–	–	–	0	–	1 (1.1)
Non-SCAC (n = 427)	2 (0.5)	0	0	–	–	–	0	–	0
All Cancer (n = 521)	3 (0.6)	1 (0.2)	1 (0.2)	–	–	–	0	–	1 (0.2)
Pneumonitis									
SCAC (n = 94)	3 (3.2)	1 (1.1)	0	–	–	–	1 (1.1)	–	0
Non-SCAC (n = 427)	3 (0.7)	2 (0.5)	3 (0.7)	–	–	–	1 (0.2)	–	0
All Cancer (n = 521)	6 (1.2)	3 (0.6)	3 (0.6)	–	–	–	2 (0.4)	–	0

[a] Maximum severity.
[b] Number of participants with events is denominator.
[c] See Section **Error! Reference source not found.** for definitions of irAE treatments.
Source: ISS Tables 3.2.2.7, 3.2.6.7, 3.2.8.7, 3.2.16.6, 3.2.20.8, 3.2.26.2, and 3.2.27.2.

Immune-related nephritis

In the All Cancer Population, nephritis occurred in 1.7%. Nephritis Grade 1 was observed in 0.4%, Grade 2 in 0.4%, Grade 3 in 0.6%, Grade 4 in 0.2%, and Grade 5 0.2%. The Grade 4 event occurred in the SCAC Population in a patient that discontinued retifanlimab treatment due to radiographic progression. The patient developed acute kidney injury 85 days after the last dosing during hospitalisation because of anaemia. The patient was treated with IV fluid, but did not receive immunosuppressants. The event did not resolve before the patient died on Day 193 due to progression. The investigator and sponsor did not assess the event as related. The fatal event of nephritis in the Non-SCAC population was observed in a NSCLC patient with metastases to liver, lymph node, and pleural effusion at baseline and had received 2 prior lines of therapy, including cisplatin, vinorelbine, and docetaxel. The participant received 7 infusions of retifanlimab 3 mg/kg Q2W. Onset of nephritis was on Day 120, 8 days after the final retifanlimab infusion. On that day, laboratory results included high C-reactive protein, high leukocytes, and bacteria in urine, white blood cell count of 11,300/µL, absolute neutrophil count of 10,200/µL, low haemoglobin, high creatinine (CTCAE Grade 4), estimated glomerular filtration rate of 13 mL/min/1.73 m2, and bacteria in many of the fields

(CTCAE Grade 3). A chest x-ray revealed a small effusion in the left pleural cavity and left lung atelectasis. An abdominal ultrasound was performed with no significant findings and no metastases in the kidneys. On an unspecified date, the participant was treated with a red blood cell transfusion, metoprolol, pantoprazole, dexamethasone, levofloxacin, normal saline, potassium, oxygen, fluconazole, ceftriaxone, furosemide and torsemide (dosage and frequency were not provided). The clinical laboratory abnormalities continued until the participant died on Day 124. An autopsy was inconclusive, and the investigator reported the cause of death as unknown. The event was not considered to be related to retifanlimab by the investigator or the sponsor. The patient experienced a Grade 3 event of nephritis before that resolved with oral prednisolone. In 1 patient (0.2%), nephritis led to discontinuation of retifanlimab. The median onset time of observed nephritis events was 73 days (range: 15-170 days). Among the 9 patients with events of nephritis, 1 (11.1%) received systemic glucocorticoids, including high dose systemic glucocorticoids. Nephritis resolved in 7 patients (77.8%), with a median time to resolution of 11.0 days (range: 2-144 days).

Table 29: Detailed Summary of Nephritis

Group Term *Preferred Term* Population, n (%)	**Any Grade**	**≥ Grade 3**[a]	**Serious**	**Treatment Administered**[b,c]			**Led to Discontinuation**	**Resolved**[b]	**Fatal**
				Systemic Gluco-corticoids	**High Dose Gluco-corticoids**	**Other Immuno-suppressant**			
Nephritis	**9 (1.7)**[d]	**5 (1.0)**	**4 (0.8)**	**1 (11.1)**	**1 (11.1)**	**0**	**1 (0.2)**	**7 (77.8)**	**1 (0.2)**
Acute kidney injury									
SCAC (n = 94)	1 (1.1)	1 (1.1)	1 (1.1)	–	–	–	0	–	0
Non-SCAC (n = 427)	3 (0.7)	3 (0.7)	2 (0.5)	–	–	–	0	–	0
All Cancer (n = 521)	4 (0.8)	4 (0.8)	3 (0.6)	–	–	–	0	–	0
Nephritis									
SCAC (n = 94)	0	0	0	–	–	–	0	–	0
Non-SCAC (n = 427)	5 (1.2)	1 (0.2)	1 (0.2)	–	–	–	1 (0.2)	–	1 (0.2)
All Cancer (n = 521)	5 (1.0)	1 (0.2)	1 (0.2)	–	–	–	1 (0.2)	–	1 (0.2)

[a] Maximum severity.
[b] Number of participants with events is denominator.
[c] See Section **Error! Reference source not found.** for definitions of irAE treatments.
[d] Excluding the events of nephritis in the 4 participants listed below, the incidence of nephritis was 5/427 (1.2%) in the Non-SCAC Population and 5/521 (1.0%) in the All Cancer Population.
Source: ISS Tables 3.2.2.7, 3.2.6.7, 3.2.8.7, 3.2.16.6, 3.2.20.8, 3.2.26.2, and 3.2.27.2.

Immune-related colitis

In the All Cancer Population, colitis occurred in 7 patients (1.3%), including 2 patients in the SCAC population. In the All Cancer Population, colitis Grade 2 occurred in 2 patients (0.4%), Grade 3 in 3 (0.6%), and Grade 4 in 2 (0.4%). Colitis led to retifanlimab discontinuation in 5 patients (1.0%). Among the 7 patients with events of colitis, 6 (85.7%) received systemic glucocorticoids, 5 (71.4%) received high dose systemic glucocorticoids, and 1 (16.7%) received another immunosuppressant (infliximab). Colitis resolved in 4 of the 7 patients (57.1%).

Table 30: Detailed Summary of Colitis

Group Term *Preferred Term* Population, n (%)	Any Grade	≥ Grade 3[a]	Serious	Treatment Administered[b,c]			Led to Discontinuation	Resolved[b]	Fatal
				Systemic Gluco-corticoids	High Dose Gluco-corticoids	Other Immuno-suppressant			
Colitis	**6 (1.2)[d]**	**4 (0.8)**	**4 (0.8)**	**3 (50.0)[e]**	**3 (50.0)[e]**	**1 (16.7)**	**4 (0.8)**	**4 (66.7)**	**0**
Colitis									
SCAC (n = 94)	1 (1.1)	0	0	–	–	–	0	–	0
Non-SCAC (n = 427)	5 (1.2)	4 (0.9)	4 (0.9)	–	–	–	4 (0.9)	–	0
All Cancer (n = 521)	6 (1.2)	4 (0.8)	4 (0.8)	–	–	–	4 (0.8)	–	0

[a] Maximum severity.
[b] Number of participants with events is denominator.
[c] See Section **Error! Reference source not found.** for definitions of irAE treatments.
[d] One additional participant in the SCAC Population had a Grade 4, serious TEAE of immune-mediated enterocolitis (ileitis; refer to ISS Listing 2.7.1 and the narrative for Participant 401010 in INCMGA 0012-202 CSR). Including this participant, colitis occurred in 7 participants (1.3%) in the All Cancer Population.
[e] Three additional participants received systemic glucocorticoids (2 participants had prednisone incorrectly coded to the Corticosteroids acting locally drug class [refer to INCMGA 0012-101 CSR errata] and the 1 participant added above with ileitis received prednisone). Including these participants, 6 of 7 participants (85.7%) received systemic glucocorticoids and 5 of 7 participants (71.4%) received high dose systemic glucocorticoids.
Source: ISS Tables 3.2.2.7, 3.2.6.7, 3.2.8.7, 3.2.16.6, 3.2.20.8, 3.2.26.2, and 3.2.27.2.

Immune-related hepatitis

In the All Cancer Population, hepatitis occurred in 3 patients (0.6%), including 1 Grade 3 event in the SCAC Population. Hepatitis Grade 2 was reported in 2 patients (0.4%) and Grade 3 in 1 patient (0.2%). Hepatitis led to discontinuation of retifanlimab in 1 patient (0.2%). Among the 3 patients with hepatitis, 2 (66.7%) received high dose systemic glucocorticoids. Hepatitis resolved in 1 of 3 patients (33.3%, based on improvement of Grade 3 AST and ALT elevations to Grade 1).

Table 31: Detailed Summary of Hepatitis

Group Term *Preferred Term* Population, n (%)	Any Grade	≥ Grade 3[a]	Serious	Treatment Administered[b,c]			Led to Discontinuation	Resolved[b]	Fatal
				Systemic Gluco-corticoids	High Dose Gluco-corticoids	Other Immuno-suppressant			
Hepatitis	**2 (0.4)[d]**	**0**	**0**	**1 (50.0)**	**1 (50.0)**	**0**	**0**	**0**	**0**
Autoimmune hepatitis									
SCAC (n = 94)	0	0	0	–	–	–	0	–	0
Non-SCAC (n = 427)	1 (0.2)	0	0	–	–	–	0	–	0
All Cancer (n = 521)	1 (0.2)	0	0	–	–	–	0	–	0
Hepatitis									
SCAC (n = 94)	0	0	0	–	–	–	0	–	0
Non-SCAC (n = 427)	1 (0.2)	0	0	–	–	–	0	–	0
All Cancer (n = 521)	1 (0.2)	0	0	–	–	–	0	–	0

[a] Maximum severity.
[b] Number of participants with events is denominator.
[c] See Section **Error! Reference source not found.** for definitions of irAE treatments.
[d] One additional participant in the SCAC Population had concurrent Grade 3 elevations of AST and ALT (based on laboratory results) with immune-related hepatitis suspected by the investigator (refer to ISS Listing 2.7.1 and the narrative for Participant 302002 in INCMGA 0012-202 CSR). Including this participant, hepatitis occurred in 3 participants (0.6%) in the All Cancer Population.
Source: ISS Tables 3.2.2.7, 3.2.6.7, 3.2.8.7, 3.2.16.6, 3.2.20.8, 3.2.26.2, and 3.2.27.2.

Immune-related myositis

In the All Cancer Population, myositis occurred in 2 patients (0.4%), including 1 patient in the SCAC Population. Myositis Grade 1 to 2 was reported in 1 patient (0.2%) and Grade 3 also in 1 patient (0.2%). Myositis led to discontinuation of retifanlimab 1 patient (0.2%). The median onset time of observed myositis events was 112 days (range: 51-173 days). Both patients (100.0%) received systemic glucocorticoids, including high dose systemic glucocorticoids. Myositis resolved in 1 patient (50.0%) after 13.0 days.

Immune-related uveitis

One patient was reported to have uveitis in the All Cancer Population (0.2%). The event was Grade 2, started at Day 35 and was treated with local immunosuppression. At Day 71 the patient discontinued retifanlimab due to the uveitis event and the event was ongoing when the patient died due to an unrelated cause at Day 109.

Immune-related myocarditis

One patient was reported to have myocarditis in the All Cancer Population (0.2%). The event was Grade 2, started at Day 65 and was treated with high dose systemic glucocorticoids. The patient discontinued retifanlimab due to the myocarditis event and the event resolved after 67 days.

Other immune-related adverse events

Other irAEs reported were polyarthritis and radiculopathy. Polyarthritis occurred in 3 patients (0.6%) in the All Cancer Population, none were in the SCAC Population. Grade 1 polyarthritis was reported in 1 patient (0.2%) and Grade 2 in 2 patients (0.4%). In one case polyarthritis led to discontinuation of study treatment (0.2%). The onset time of polyarthritis ranged from 31 to 142 days. All 3 patients (100.0%) received systemic glucocorticoids, of whom 1 (33.3%) received high dose systemic glucocorticoids. Polyarthritis resolved in all patients (100%) with time to resolution ranging from 11 to 59 days. Radiculopathy occurred in 1 patient (0.2%) in the All Cancer Population, who was in the Non-SCAC Population. The event was Grade 3 and started on Day 20 of study treatment. The patient received a high dose systemic glucocorticoid and retifanlimab was discontinued due to the event. The event was ongoing at the time of the participant's death due to disease progression on Day 129.

Infusion-related reactions

Infusion-related reactions occurred in 37 participants (7.1%) in the All Cancer Population, including 4 participants (4.3%) in the SCAC Population and 33 participants (7.7%) in the Non-SCAC Population (see Table 32). Infusion-related reactions are presented by group term and preferred term in Table 33. All infusion-related reactions were Grade 1 or 2 in severity with the exception of the following 2 Grade 3 events in 2 participants (0.4%).

- Participant UA004-0003 in Study INCMGA 0012-101 received 6 infusions of retifanlimab 3 mg/kg Q2W and had a nonserious, Grade 3 IRR on the day of the fifth retifanlimab infusion (Day 72). Premedication prophylaxis was not reported. The IRR was treated with single doses of paracetamol 100 mL IV and methylprednisolone 125.0 mg IV and resolved the same day as onset. Retifanlimab administration continued unchanged. The participant had 1 additional retifanlimab infusion without recurrence of IRR before discontinuing study treatment due to radiographic disease progression on Day 100.
- Participant 202001 in Study INCMGA 0012-201 received 2 infusions of retifanlimab 500 mg Q4W and had 2 IRRs, both following the second (final) infusion, which was administered on Day 28. Premedication prophylaxis was not reported. The first IRR was Grade 1 in severity and occurred on

Day 36. The second IRR was Grade 3 in severity and occurred on Day 54 when the participant was hospitalised with swollen tongue, impaired breathing, and visual impairment. The event resolved the same day as onset. Treatment with corticoids (methylprednisolone, 32 mg TID PO) was reported on Day 56. Sponsor medical review of the Grade 3 IRR determined this event not to be a true IRR to retifanlimab based on the duration of the interval from the last retifanlimab infusion on Day 28 and the onset of the reported IRR on Day 54.

Two participants (0.4%) had serious IRRs that were considered related to retifanlimab: Participant 202001 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 with metastases to the lung at baseline and a medical history that included chronic cough, pneumonia, and vocal cord paralysis. The serious Grade 1 IRR 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 IRR 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 IRR before discontinuing study treatment on Day 118 due to radiographic disease progression.

Two additional participants had serious IRR that were unrelated to retifanlimab; 1 participant had a serious allergic reaction to infusion premedication (ranitidine), and 1 participant had a serious IRR to a pamifos infusion.

The incidences of IRRs in participants receiving retifanlimab in Study INCMGA 0012-203 (30-minute infusions) and Studies INCMGA 0012-101, INCMGA 0012-104, INCMGA 0012-201, and INCMGA 0012-202 (60-minute infusions) were 6.6% (8/121 participants) and 7.3% (29/400 participants), respectively.

Table 32: Overall Summary of Infusion-Related Reactions

Participants (n [%]) with:	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Infusion-related reaction	4 (4.3)	33 (7.7)	13 (9.0)	4 (14.8)	18 (5.6)	2 (13.3)	0	37 (7.1)
Treatment-related infusion-related reaction	3 (3.2)	24 (5.6)	9 (6.3)	2 (7.4)	15 (4.7)	1 (6.7)	0	27 (5.2)
Serious infusion-related reaction	0	4 (0.9)	2 (1.4)	0	2 (0.6)	0	0	4 (0.8)
Grade 3 infusion-related reaction	0	2 (0.5)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)[b]
Fatal infusion-related reaction	0	0	0	0	0	0	0	0
Serious treatment-related infusion-related reaction	0	2 (0.5)	0	0	2 (0.6)	0	0	2 (0.4)

Participants (n [%]) with:	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Grade 3 treatment-related infusion-related reaction	0	2 (0.5)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)[b]
Infusion interruption due to infusion-related reaction	1 (1.1)	2 (0.5)	0	0	3 (0.9)	0	0	3 (0.6)[c]
Discontinued study drug due to infusion-related reaction	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).
[b] One participant in Study INCMGA 0012-201 had a Grade 3 infusion-related reaction that was determined by clinical adjudication by the sponsor to be not related 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 (see Participant 202001 narrative).
[c] In Study INCMGA 0012-101, 1 participant had an infusion-related reaction that led to infusion interruption, which is captured as study drug interruption in the eCRF and referred to as "dose delay" in the CSR.
Note: TEAEs leading to "'drug interruption'" or "'infusion interruption'" are summarised with "'next scheduled dose delay'" for Study INCMGA 0012-101.
Source: ISS Tables 3.2.1.3 and 3.2.1.12.

Table 33: Summary of Infusion-Related Reactions by Group Term and Preferred Term

Group Term Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Infusion-related reaction	**1 (1.1)**	**15 (3.5)**	**6 (4.2)**	**1 (3.7)**	**8 (2.5)**	**1 (6.7)**	**0**	**16 (3.1)**
Drug hypersensitivity	0	2 (0.5)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Hypersensitivity	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Infusion related reaction	1 (1.1)	12 (2.8)	4 (2.8)	1 (3.7)	7 (2.2)	1 (6.7)	0	13 (2.5)
Symptom of potential infusion-related reaction	**3 (3.2)**	**22 (5.2)**	**9 (6.3)**	**3 (11.1)**	**11 (3.4)**	**2 (13.3)**	**0**	**25 (4.8)**
Chills	0	4 (0.9)	3 (2.1)	0	1 (0.3)	0	0	4 (0.8)
Dyspnoea	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Erythema	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Flushing	0	1 (0.2)	0	1 (3.7)	0	0	0	1 (0.2)
Hypotension	0	2 (0.5)	2 (1.4)	0	0	0	0	2 (0.4)
Pruritus	1 (1.1)	5 (1.2)	0	0	5 (1.6)	1 (6.7)	0	6 (1.2)
Pruritus generalised	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Pyrexia	1 (1.1)	9 (2.1)	5 (3.5)	1 (3.7)	3 (0.9)	1 (6.7)	0	10 (1.9)
Rash	0	1 (0.2)	0	0	0	1 (6.7)	0	1 (0.2)
Tachycardia	0	1 (0.2)	0	1 (3.7)	0	0	0	1 (0.2)

Note: Infusion-related reactions include AEs indicating diagnosis of infusion-related reaction that occurred during the treatment

period, as well as symptoms of infusion-related reaction that occurred within 1 day of infusion, and resolved within 2 days from AE onset.
Note: Participants were counted once under each group term and preferred term.
[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).
Source: ISS Tables 3.2.2.2 and 3.2.2.6.

Long-term adverse effects

At the time of the data cutoff dates for the individual studies, the median duration of safety follow-up in the All Cancer Population was 139.0 days (range: 1-830 days), 31 participants (6.0%) in the All Cancer Population had received retifanlimab for ≥ 12 months and 21 participants (4.0%) had received retifanlimab for ≥ 18 months. Time to first event onset was analyzed for irAEs based on observed events and shown in Table 34. Delayed onset of irAE (i.e., after 12 months of retifanlimab treatment) were reported in 3 participants. These irAEs were skin reactions (rash erythematous with onset on Day 487 and toxic skin eruption with onset on Day 628) and hypothyroidism (onset on Day 577).

Table 34: Summary of Estimated Time to First Onset of Observed Immune-Related Adverse Events

Variable		**All Cancer Population N = 521**
Median (min, max) duration of safety follow-up[a]		139.0 (1, 830) days
Number of participants treated for ≥ 12 months - n (%)		31 (5.95)
Number of participants treated for ≥ 18 months - n (%)		21 (4.0)
irAE	**Number of Events**	**Median (Min, Max) Time to First Onset[b] (Days)**
Endocrine irAEs		
Adrenal Insufficiency	2	219.0 (163, 275)
Hyperthyroidism	23	55.0 (8, 162)
Hypothyroidism	41	85.0 (1, 577)
Thyroiditis	2	74.5 (28, 121)
Type 1 diabetes	2	156.5 (29, 284)
Non-Endocrine irAEs		
Colitis	6	93.5 (37, 331)
Hepatitis	2	42.5 (15, 70)
Myocarditis	1	65.0
Myositis	2	112.0 (51, 173)
Nephritis	9	73.0 (15, 170)
Pneumonitis	9	89.0 (43, 162)
Skin reactions	26	92.0 (1, 628)
Uveitis	1	35.0
Other rare irAEs	4	45.5 (20, 142)

Error! Reference source not found. Median, minimum, and maximum safety follow-up is summarised from date of first dose of retifanlimab to earliest among date of last dose plus 90 days, data cutoff date, death date, or last contact date.
Error! Reference source not found. Median, minimum, and maximum are summarised from observed event data of time to first onset of AESI.

Serious adverse events and deaths

Serious adverse events

In the SCAC Population, serious TEAEs were most frequently associated with the system organ classes of gastrointestinal disorders and infections and infestations (16 participants [17.0%] each). In the All Cancer Population, serious TEAEs were most frequently associated with the system organ class of infections and infestations (42 participants [8.1%]) and gastrointestinal disorders (35 participants [6.7%]). By MedDRA preferred term, the most frequent serious TEAEs are reported in Table 35.

Serious TEAEs that were considered related to retifanlimab by the investigator in the SCAC Population were adrenal insufficiency, abdominal pain, immune-mediated enterocolitis, herpes zoster, lymphangiosis carcinomatosa, and hepatic coma (1 participant [1.1%] each). Serious TEAEs that were considered related to retifanlimab by the investigator occurring in more than 1 participant in the All Cancer Population were colitis (4 participants [0.8%]), pneumonitis (3 participants [0.6%]), and herpes zoster and infusion related reaction (2 participants [0.4%] each). The sponsor assessed that 1 case of herpes zoster was not related to retifanlimab due to the extended latency (193 days) from initial retifanlimab infusion to event onset and the participant's age (50 years) as a risk factor. The sponsor assessed that the other case of herpes zoster was related to retifanlimab despite several risk factors (i.e., age and underlying malignancy) due to the temporal association between initiation of retifanlimab and onset of symptoms (approximately 20 days) and because drug-related zoster has been observed following treatment with other therapies in the PD-(L)1 inhibitor class. The sponsor assessed that the serious, treatment-related TEAE of abdominal pain was not related to retifanlimab and that the participant's prior abdominal-peritoneal surgery complicated by eventration was an alternative explanation for the event.

Table 35: Summary of Serious TEAEs in > 1 Participant by MedDRA Preferred Term in Decreasing Order of Frequency for the All Cancer Population Total

Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Pneumonia	2 (2.1)	9 (2.1)	0	2 (7.4)	9 (2.8)	0	0	11 (2.1)
Abdominal pain	5 (5.3)	4 (0.9)	1 (0.7)	0	6 (1.9)	1 (6.7)	1 (6.7)	9 (1.7)
Urinary tract infection	4 (4.3)	4 (0.9)	3 (2.1)	0	5 (1.6)	0	0	8 (1.5)
Anaemia	4 (4.3)	3 (0.7)	1 (0.7)	1 (3.7)	5 (1.6)	0	0	7 (1.3)
Dyspnoea	3 (3.2)	4 (0.9)	2 (1.4)	0	4 (1.3)	0	1 (6.7)	7 (1.3)
Pleural effusion	2 (2.1)	5 (1.2)	2 (1.4)	1 (3.7)	3 (0.9)	0	1 (6.7)	7 (1.3)
Acute kidney injury	1 (1.1)	5 (1.2)	4 (2.8)	0	2 (0.6)	0	0	6 (1.2)
Pulmonary embolism	1 (1.1)	5 (1.2)	3 (2.1)	1 (3.7)	2 (0.6)	0	0	6 (1.2)
Asthenia	1 (1.1)	3 (0.7)	0	1 (3.7)	3 (0.9)	0	0	4 (0.8)
Colitis	0	4 (0.9)	4 (2.8)	0	0	0	0	4 (0.8)
General physical health deterioration	3 (3.2)	1 (0.2)	1 (0.7)	0	3 (0.9)	0	0	4 (0.8)
Hydronephrosis	1 (1.1)	3 (0.7)	1 (0.7)	1 (3.7)	2 (0.6)	0	0	4 (0.8)
Hypercalcaemia	2 (2.1)	2 (0.5)	0	0	4 (1.3)	0	0	4 (0.8)
Pelvic pain	3 (3.2)	1 (0.2)	1 (0.7)	0	3 (0.9)	0	0	4 (0.8)
Pyrexia	3 (3.2)	1 (0.2)	0	0	4 (1.3)	0	0	4 (0.8)

Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Sepsis	2 (2.1)	2 (0.5)	0	0	4 (1.3)	0	0	4 (0.8)
Back pain	1 (1.1)	2 (0.5)	0	0	3 (0.9)	0	0	3 (0.6)
Diarrhoea	1 (1.1)	2 (0.5)	2 (1.4)	0	1 (0.3)	0	0	3 (0.6)
Haematuria	2 (2.1)	1 (0.2)	1 (0.7)	0	2 (0.6)	0	0	3 (0.6)
Pneumonitis	0	3 (0.7)	1 (0.7)	0	1 (0.3)	1 (6.7)	0	3 (0.6)
Pyelonephritis	0	3 (0.7)	2 (1.4)	0	1 (0.3)	0	0	3 (0.6)
Acute respiratory failure	1 (1.1)	1 (0.2)	0	0	2 (0.6)	0	0	2 (0.4)
Atrial fibrillation	0	2 (0.5)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Bone pain	1 (1.1)	1 (0.2)	0	0	2 (0.6)	0	0	2 (0.4)
Cellulitis	1 (1.1)	1 (0.2)	0	0	2 (0.6)	0	0	2 (0.4)
Cholangitis	1 (1.1)	1 (0.2)	0	0	2 (0.6)	0	0	2 (0.4)
Chronic obstructive pulmonary disease	0	2 (0.5)	0	0	2 (0.6)	0	0	2 (0.4)
Dehydration	1 (1.1)	1 (0.2)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Gastric ulcer	1 (1.1)	1 (0.2)	0	0	2 (0.6)	0	0	2 (0.4)
Gastroenteritis	1 (1.1)	1 (0.2)	0	0	2 (0.6)	0	0	2 (0.4)
Herpes zoster	1 (1.1)	1 (0.2)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Ileus	1 (1.1)	1 (0.2)	0	0	2 (0.6)	0	0	2 (0.4)
Inadequate analgesia	2 (2.1)	0	0	0	2 (0.6)	0	0	2 (0.4)
Infusion related reaction	0	2 (0.5)	0	0	2 (0.6)	0	0	2 (0.4)
Intestinal obstruction	2 (2.1)	0	0	0	2 (0.6)	0	0	2 (0.4)
Nausea	2 (2.1)	0	0	0	2 (0.6)	0	0	2 (0.4)
Proctalgia	2 (2.1)	0	0	0	2 (0.6)	0	0	2 (0.4)
Rectal haemorrhage	1 (1.1)	1 (0.2)	0	0	2 (0.6)	0	0	2 (0.4)
Small intestinal obstruction	0	2 (0.5)	0	1 (3.7)	1 (0.3)	0	0	2 (0.4)
Tumour pain	0	2 (0.5)	0	0	0	0	2 (13.3)	2 (0.4)
Urinary retention	1 (1.1)	1 (0.2)	0	0	2 (0.6)	0	0	2 (0.4)
Vomiting	1 (1.1)	1 (0.2)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).
Source: ISS Tables 3.2.9.1 and 3.2.9.3.

Deaths

In the SCAC Population, fatal TEAEs were most frequently associated with the system organ classes of infections and infestations and respiratory, thoracic, and mediastinal disorders (3 participants [3.2%] each; see Table 36). Similarly, in the All Cancer Population, fatal TEAEs were most frequently associated with the system organ classes of respiratory, thoracic, and mediastinal disorders (5 participants [1.0%]) and infections and infestations (4 participants [0.8%]). By MedDRA preferred term, fatal TEAEs are reported in Table 36.

The only fatal TEAE considered related to retifanlimab by the investigator was lymphangiosis carcinomatosa, which was considered to be a possible manifestation of treatment-induced hyperprogression by the investigator. This concerned a 71-year-old woman with no relevant medical history, was diagnosed with SCAC approximately 1 year prior to study enrollment. Pulmonary metastases were present at baseline, and an unspecified pulmonary infection was diagnosed approximately 1 week before initiation of study treatment. On Day 1, the participant received retifanlimab 500 mg. On Day 10, she was hospitalised with dizziness, declining general condition, anorexia, and dyspnea. On Day 11, pulmonary infiltrates were noted on a CT scan, consistent with a lymphangitic tumour, and lymphangiosis carcinomatosa was diagnosed. The participant had no response to high-dose steroids but showed some improvement with antibiotics and supplemental oxygen. She refused further evaluation (including bronchoscopy) and was transferred to a hospice. On Day 38, the participant died (no autopsy performed). The sponsor assessed the event as not related to retifanlimab as there were many confounding factors including antecedent lung infection and minimal diagnostic work-up.

Table 36: Summary of TEAEs With a Fatal Outcome by MedDRA System Organ Class and Preferred Term

MedDRA System Organ Class Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Cardiac disorders	0	3 (0.7)	2 (1.4)	0	1 (0.3)	0	0	3 (0.6)
Cardiac failure	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Cardiovascular insufficiency	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Right ventricular failure	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
General disorders and administration site conditions	0	2 (0.5)	0	0	2 (0.6)	0	0	2 (0.4)
Asthenia	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Death	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Infections and infestations	3 (3.2)	1 (0.2)	0	0	4 (1.3)	0	0	4 (0.8)
Pelvic infection	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Peritonitis	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Pneumocystis jirovecii pneumonia	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Sepsis	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)

MedDRA System Organ Class Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Injury, poisoning and procedural complications	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Femur fracture	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Metabolism and nutrition disorders	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Hypercalcaemia	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.1)	0	0	0	2 (0.6)	0	0	2 (0.4)
Lymphangiosis carcinomatosa	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Pancreatic carcinoma	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Nervous system disorders	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Hemiparesis	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Renal and urinary disorders	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Nephritis	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	3 (3.2)	2 (0.5)	1 (0.7)	0	4 (1.3)	0	0	5 (1.0)
Acute respiratory failure	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Interstitial lung disease	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Pleural effusion	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Pulmonary embolism	1 (1.1)	1 (0.2)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Vascular disorders	0	2 (0.5)	0	0	2 (0.6)	0	0	2 (0.4)
Haemorrhage	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Hypotension	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).
Source: ISS Tables 3.2.16.1 and 3.2.16.4.

Laboratory findings

Laboratory testing

Haematology- A part of the patients in the All Cancer Population entered study treatment with abnormal haematology parameters at baseline with for example low haemoglobin in 57.2%, low

lymphocyte counts in 42.6%, and low leukocyte counts in 8.1%. Treatment-emergent worsening of haematology parameters was observed most frequently for haemoglobin decreased (37.2%) and lymphocytes decreased (33.6%). The majority of abnormalities were Grade 1 or 2. Worsening to ≥Grade 3 worst postbaseline values was observed most frequently for lymphocytes decreased (9.2%) and haemoglobin decreased (4.8%). Shifts to Grade 4 occurred for lymphocytes decreased 1.2%, leukocytes decreased in 0.6%, neutrophils decreased in 0.4%, and platelets decreased in 0.4%.

Chemistry- In the All Cancer Population, treatment-emergent worsening of chemistry parameters was observed most frequently for albumin decreased (30.9%), AST increased (26.1%), and alkaline phosphatase increased (25.1%). The majority of abnormalities were Grade 1 or 2 in severity. Worsening to ≥Grade 3 worst postbaseline values was observed most frequently for lipase increased (3.5%), alkaline phosphatase increased (2.9%), magnesium increased (2.9%), and sodium decreased (2.7%). Shifts to Grade 4 occurred for urate increased in 2.3%, lipase increased in 1.2%, calcium increased in 1.0%, calcium decreased in 0.8%, and glucose decreased, magnesium increased, and sodium increased in 0.4% each. Shifts to Grade 4 occurred in 1 patient (0.2%) each for ALT increased, AST increased, bilirubin increased, creatinine increased, GGT increased, magnesium decreased, potassium increased, potassium decreased, sodium decreased, and triglycerides increased. Increases in amylase and lipase (including worsening to ≥Grade 3) were frequently observed. No patient in the All Cancer Populations met the criteria for Hy's Law. Twelve patients (2.3%) had concurrent ALT or AST elevations (3×ULN) and bilirubin elevations (>1×ULN). Eight of the 12 patients with concurrent elevations had liver metastases at baseline. Liver function test abnormalities in the 4 other patients could be explained by unsuspected pancreatic cancer with widespread carcinomatosis and portal vein thrombosis; clavulanic acid-associated drug-induced liver injury; history of hepatitis A infection and use of ketorolac tromethamine (which lists elevated liver enzymes as an adverse reaction); and contributing factors of multiple prior and concomitant medications (atorvastatin, eplerenone, enoxaparin sodium, amiodarone) that list transaminases increased and/or liver function test abnormalities as adverse reactions.

Other laboratory results- Regarding TSH values, around 20% of the patients had an abnormal value at baseline (17.1% in the All Cancer Population and 17.1% in the SCAC Population). On-treatment TSH values >ULN were observed in 27.4% of the All Cancer Population and in 32.8% of the SCAC Population. For TSH values <LLN these numbers were 21.4% and 8.2%, respectively. According to the applicant this difference reflects the more frequent endocrine testing schedule used for most of the studies in Non-SCAC patients studies (every cycle) compared with the every third cycle testing in the SCAC Population. TSH values alone are however not meaningful without the knowledge of thyroid hormones and clinically it is therefore more valuable to look into the incidences of endocrine irAEs as reported above.

For coagulation parameters, worsening to ≥Grade 3 worst postbaseline values was observed for 1 patient (1.1%) each for increased activated partial thromboplastin time and prothrombin international normalised ratio. No shifts to Grade 4 occurred.

For the results of urinalysis the applicant refers to the respective CSRs of the individual studies.

Vital signs

According to the applicant, no meaningful effects of retifanlimab on vital parameters (systolic blood pressure, diastolic blood pressure, pulse, respiration rate, body temperature) were observed. This is based on individual CSRs of the included studies in the All Cancer Population.

Electocardiograms

ECG findings in studies INCMGA 0012-101, INCMGA 0012-202, and INCMGA 0012-203 showed low number of patients with QTcF >480 and ≤500 ms (1.6% in study INCMGA 0012-101 and none in the

other studies) or with QTcF >500 ms (0.8% in study INCMGA 0012-101 and none in the other studies). Only 1 patient in study INCMGA 0012-101 had a change of >60 ms compared to baseline.

In the All Cancer Population 2 patients were reported with an AE due to ECG abnormalities. One patient had a nonserious, Grade 1 TEAE of ECG QT prolonged who had received doxorubicin (which includes a warning for cardiomyopathy) and pazopanib (which includes a warning for prolonged QT intervals) prior to study entry. The other patient had a Grade 1 TEAE of ECG T wave inversion that was an isolated finding of no clinical significance that occurred concurrently with hypothyroidism.

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 also expected that monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not deemed necessary (see also ICH E14 Q&A (R3)).

Safety in special populations

Age- The All Cancer Population was composed of 269 participants (51.6%) who were <65 years of age and 252 participants (48.4%) who were ≥65 years of age; 440 participants (84.5%) were <75 years of age and 81 participants (15.5%) were ≥75 years of age. Frequencies of (severe) AEs or irAEs were comparable between the subgroups younger or older than 65 years and younger or older than 75 years.

Gender- The All Cancer Population was composed of 214 men (41.1%) and 307 women (58.9%). Median durations of retifanlimab treatment were similar for male and female participants. Female participants had a higher frequency of irAEs (25.4%) than male participants (15.0%). The frequency of serious and Grade 3 or higher irAEs was similar between males and females. In the SCAC Population, male participants had a higher frequency of fatal TEAEs (5 participants [15.2%]) as compared with female participants (5 participants [8.2%]). A similar trend is observed in the All Cancer Population, but with lower frequencies (5.6% vs 2.9%).

Race- The All Cancer Population was composed of 430 Caucasian participants (82.5%), 81 Non-Caucasian participants, and 10 participants with no race reported. The median duration of retifanlimab treatment was longer for Caucasian participants (85 days) than Non-Caucasian participants (57 days). Of note, the frequencies of serious (37.0% vs 28.6%) and Grade 3 or higher (50.6% vs 40.2%) TEAEs were higher for Non-Caucasian participants than Caucasian participants. The frequency of irAEs was higher for Caucasian participants (23.0%) than Non-Caucasian participants (12.3%). Of note, non-Caucasian includes races reported as "other," which includes non-Caucasian participants and participants with no race reported.

ECOG-status- The All Cancer Population was composed of 194 participants (37.2%) with a baseline ECOG performance status of 0 and 327 participants with a baseline ECOG performance status of ≥ 1. The median duration of retifanlimab treatment was longer for participants with an ECOG performance status of 0 (90 days) than participants with an ECOG performance status ≥ 1 (58 days). Participants with an ECOG performance status ≥ 1 had higher frequencies of serious, Grade 3 or higher, and fatal TEAEs than participants with an ECOG performance status of 0. Participants with an ECOG performance status of 0 had a higher frequency of irAEs (26.8%) than participants with an ECOG performance status ≥ 1 (17.7%).

HIV status- The All Cancer Population was composed of 10 participants (1.9%) who were HIV-positive. The median duration of retifanlimab treatment was longer for the HIV-positive population (113 days) than the non-HIV population (85 days). No HIV-positive participant had a fatal TEAE, a TEAE leading to infusion interruption or delay, or an irAE. None of the participants who were known to

be HIV-positive had an infusion-related reaction. Results were similar in the SCAC Population since it is largely overlapping with 9 HIV-positive participants.

For the 10 participants (1.9%) who were known to be HIV-positive at baseline in the All Cancer 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. No opportunistic infections were reported. Participants were permitted to continue their antiretroviral therapy per the study protocols.

Renal impairment- The All Cancer Population was composed of 196 participants (37.6%) with normal renal function, 192 participants (36.9%) with mild renal impairment, 129 participants (24.8%) with moderate renal impairment, and 4 participants (0.8%) with a severe renal impairment. No participant had end stage renal disease (ie, < 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.

Hepatic impairment- The All Cancer Population was composed of 459 participants (88.1%) with normal hepatic function, 57 participants (10.9%) with mild hepatic impairment, and 1 participant (0.2%) with moderate hepatic impairment at baseline. None of the participants had severe hepatic impairment, and 4 participants (0.8%) had a missing hepatic impairment status at baseline. The median duration of retifanlimab treatment was longer for participants with normal hepatic function (85 days) than participants with mild hepatic impairment (29 days). When comparing the patients with normal and mild hepatic impairment, more serious AEs, ≥Grade 3 AEs, and AEs leading to discontinuations were reported in the patients with mild hepatic impairment. irAEs were less often observed in patients with mild hepatic impairment.

Immunological events

As of the data cutoff date of each study, 2860 human serum samples from 510 evaluable participants were analyzed for anti-retifanlimab antibodies. At the participant level, an assessable participant was defined as a participant treated with retifanlimab and with at least 1 postdose sample with a reportable ADA result. Immunogenicity of retifanlimab was assessable in 467 participants in the All Cancer Population, including 84 participants in the SCAC population. Excluding the inconclusive participants based on drug tolerance level (DTL), the total number of negative and positive participants was 395, including 9 ADA-positive participants (see Table 37). Five of these 9 participants had nontreatment-emergent ADA with only baseline positive ADAs, and 4 of them had treatment-emergent ADA. Out of these 4 treatment-emergent positive participants, no persistent positive ADA were observed. Among the 4 treatment-emergent positive participants, 2 participants were from Study INCMGA 0012-101, 1 participant was from Study INCMGA 0012-201, and 1 participant was from Study INCMGA 0012-203. None of the treatment-emergent positive participants were from Study INCMGA 0012-202.

Table 37: 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

ADA Status	All Dose Regimens	Retifanlimab Dose Regimen							
		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	510	3	144	10	8	6	15	309	15
Assessable participants	467	3	137	9	8	6	15	274	15
Inconclusive participants	72	0	5	0	0	0	0	67	0
Negative participants	386	3	129	8	8	6	15	202	15
Positive participants	9	0	3	1	0	0	0	5	0
Nontreatment emergent positive participants	5	0	2	0	0	0	0	3	0
Treatment-emergent positive participants	4	0	1	1	0	0	0	2	0
Persistent treatment-emergent positive participants	0	0	0	0	0	0	0	0	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 status to efficacy

No participant in Study INCMGA 0012-202 was treatment-emergent ADA positive, so the relationship of ADA status to efficacy could not be assessed.

Relationship of ADA status to safety

Treatment-emergent ADA were observed in 4 of 467 ADA assessable participants in the All Cancer Population. All 4 participants who had treatment-emergent ADA were positive at a single timepoint. Three of the participants had transient treatment-emergent ADA (negative ADA testing at ≥ 1 subsequent timepoint), and 1 participant did not have a subsequent ADA analysis. No participant in the SCAC Population had treatment-emergent ADA. There was no apparent clinically meaningful impact of ADA on the incidence of infusion-related reactions or on the overall safety profile (see Table 38).

Table 38: Participants with Treatment-Emergent ADA

Study/ Participant	Retifanlimab Dose/ Number of Infusions	ADA Results	TEAEs (Grade)	Infusion-Related Reactions	irAEs
INCMGA 0012-101/ US002-0006	3 mg/kg Q4W/ 2	Positive: EOT Negative: C1D1, C2D1	Anaemia (3), fatigue (1), abdominal pain (2), infusion related reaction (2)	Grade 2; second infusion	None
INCMGA 0012-101/ UA005-0006	3 mg/kg Q2W/ 50 (ongoing treatment as of DCO)	Positive: C21D1 Negative: C1D1-C20D1, C22D1, C23D1, C25D1	None	None	None

Study/ Participant	Retifanlimab Dose/ Number of Infusions	ADA Results	TEAEs (Grade)	Infusion-Related Reactions	irAEs
INCMGA 0012-203/ 301-002	500 mg Q4W/ 9 (ongoing treatment as of DCO)	Positive: C4D1 Negative: C1D1,C2D1, C6D1	Anaemia (1/2)	None	None
INCMGA 0012-201/ 501-001	500 mg Q4W/ 10 (ongoing treatment as of DCO)	Positive: C4D1 Negative: C1D1, C2D1, C6D1-C10D1	Pyrexia (1), arthralgia (1), oropharyngeal pain (1), cough (1), muskuloskeletal pain (1), erythema (1), pruritus (1), ALT increased (1), AST increased (1), ALP increased (1), GGT increased (1)	None	None

CxDx = Cycle x Day x; DCO = data cutoff.
Source: ISS Listings 2.1.1, 2.5, 2.7.1, 2.7.6, 2.7.7, and 2.8.5; INCMGA 0012-101 CSR Listing 2.5.1.

Safety related to drug-drug interactions and other interactions

No dedicated drug-drug interactions studies have been performed. Please refer to the pharmacokinetics section.

Discontinuation due to AES

The study protocols include guidelines on retifanlimab dose modifications for the management of irAEs and infusion-related reactions. Permitted dose modifications include delay of the next scheduled dose, infusion interruptions, and retifanlimab discontinuation. Across all studies, all TEAEs leading to infusion interruption were infusion-related reactions and are discussed in the section AEs of special interest.

Adverse events leading to dose delay

Table 39: Summary of TEAEs Leading to Next Scheduled Dose Delay in > 1 Participant by MedDRA Preferred Term in Decreasing Order of Frequency for the All Cancer Population Total

Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Pyrexia	2 (2.1)	6 (1.4)	1 (0.7)	0	7 (2.2)	0	0	8 (1.5)
Blood creatinine increased	0	6 (1.4)	3 (2.1)	1 (3.7)	2 (0.6)	0	0	6 (1.2)
Diarrhoea	2 (2.1)	4 (0.9)	2 (1.4)	0	4 (1.3)	0	0	6 (1.2)
Abdominal pain	2 (2.1)	3 (0.7)	1 (0.7)	0	3 (0.9)	0	1 (6.7)	5 (1.0)
AST increased	1 (1.1)	3 (0.7)	2 (1.4)	0	2 (0.6)	0	0	4 (0.8)
Dyspnoea	1 (1.1)	3 (0.7)	3 (2.1)	0	1 (0.3)	0	0	4 (0.8)
Pneumonia	1 (1.1)	3 (0.7)	0	1 (3.7)	3 (0.9)	0	0	4 (0.8)
ALT increased	0	3 (0.7)	1 (0.7)	0	2 (0.6)	0	0	3 (0.6)
Anaemia	0	3 (0.7)	1 (0.7)	1 (3.7)	1 (0.3)	0	0	3 (0.6)
Blood alkaline phosphatase increased	0	3 (0.7)	1 (0.7)	0	2 (0.6)	0	0	3 (0.6)
Cough	1 (1.1)	2 (0.5)	0	0	3 (0.9)	0	0	3 (0.6)

Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Fatigue	0	3 (0.7)	1 (0.7)	2 (7.4)	0	0	0	3 (0.6)
Lipase increased	0	3 (0.7)	1 (0.7)	0	2 (0.6)	0	0	3 (0.6)
Rash	0	3 (0.7)	1 (0.7)	0	2 (0.6)	0	0	3 (0.6)
Urinary tract infection	2 (2.1)	1 (0.2)	1 (0.7)	0	2 (0.6)	0	0	3 (0.6)
Acute kidney injury	0	2 (0.5)	2 (1.4)	0	0	0	0	2 (0.4)
Amylase increased	0	2 (0.5)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Asthenia	0	2 (0.5)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Blood bilirubin increased	0	2 (0.5)	1 (0.7)	0	0	1 (6.7)	0	2 (0.4)
Colitis	1 (1.1)	1 (0.2)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
GGT increased	0	2 (0.5)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Hepatocellular injury	0	2 (0.5)	0	0	2 (0.6)	0	0	2 (0.4)
Herpes zoster	1 (1.1)	1 (0.2)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Hydronephrosis	1 (1.1)	1 (0.2)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Hyperbilirubinaemia	0	2 (0.5)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Hypothyroidism	1 (1.1)	1 (0.2)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Muscular weakness	0	2 (0.5)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Pneumonitis	1 (1.1)	1 (0.2)	0	0	1 (0.3)	1 (6.7)	0	2 (0.4)
Pulmonary embolism	0	2 (0.5)	2 (1.4)	0	0	0	0	2 (0.4)
Rash maculo-papular	1 (1.1)	1 (0.2)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Respiratory tract infection	0	2 (0.5)	1 (0.7)	0	1 (0.3)	0	0	2 (0.4)
Sepsis	1 (1.1)	1 (0.2)	0	0	2 (0.6)	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 summarised as "dose delay."

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).

Source: ISS Tables 3.2.19.8 and 3.2.19.16.

Adverse events leading to study drug discontinuation

In the SCAC Populations, TEAEs leading to study drug discontinuation were most frequently associated with the system organ class of respiratory, thoracic, and mediastinal disorders (2 participants [2.1%]). In the All Cancer Population, TEAEs leading to study drug discontinuation were most frequently associated with the system organ class of gastrointestinal disorders (7 participants [1.3%]). By MedDRA preferred term, TEAEs leading to retifanlimab discontinuation that occurred in more than 1 participant were colitis (4 participants [0.8%]) and pneumonitis (2 participants [0.4%]) in the All Cancer Population. No TEAE leading to discontinuation occurred in more than 1 participant in the SCAC Population (see Table 40).

Table 40: Summary of TEAEs Leading to Discontinuation by MedDRA Preferred Term in Decreasing Order of Frequency for the All Cancer Population Total

MedDRA Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Colitis	0	4 (0.9)	4 (2.8)	0	0	0	0	4 (0.8)
Pneumonitis	1 (1.1)	1 (0.2)	0	0	1 (0.3)	1 (6.7)	0	2 (0.4)
ALT increased	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Arrhythmia	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Asthenia	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Brain oedema	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Cardiac failure	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Cardiovascular insufficiency	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Chronic obstructive pulmonary disease	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Coma hepatic	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Diarrhoea	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Diffuse large B-cell lymphoma	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Dry mouth	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Failure to thrive	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Female genital tract fistula	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
General physical health deterioration	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Haemorrhage	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Hepatic failure	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Immune-mediated enterocolitis	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Infusion related reaction	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Iritis	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Myocardial infarction	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Myocarditis	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Myositis	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Nephritis	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Oedema peripheral	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Palmar-plantar erythrodysaesthesia syndrome	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Pleural effusion	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Pneumothorax	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Polyarthritis	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)

MedDRA Preferred Term, n (%)	SCAC Population (N = 94)	Non-SCAC Population (N = 427)	All Cancer Population					
			3 mg/kg Q2W (N = 144)	Other W-B Dosing[a] (N = 27)	500 mg Q4W (N = 320)	750 mg Q4W (N = 15)	375 mg Q3W (N = 15)	Total (N = 521)
Polymyalgia rheumatic	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Pseudomonas infection	1 (1.1)	0	0	0	1 (0.3)	0	0	1 (0.2)
Pulmonary embolism	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Radiculopathy	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Right ventricular failure	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Sepsis	0	1 (0.2)	0	0	1 (0.3)	0	0	1 (0.2)
Transaminases increased	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)
Tumour pain	0	1 (0.2)	0	0	0	0	1 (6.7)	1 (0.2)
Type 1 diabetes mellitus	0	1 (0.2)	1 (0.7)	0	0	0	0	1 (0.2)

[a] Other weight-based doses include 1 mg/kg Q2W (n = 3), 10 mg/kg Q2W (n = 8), 3 mg/kg Q4W (n = 10), and 10 mg/kg Q4W (n = 6; refer to INCMGA 0012-101 CSR for details).
Source: ISS Tables 3.2.20.4 and 3.2.20.9.

Post marketing experience

Retifanlimab is an investigational drug and is not approved or marketed in any country. Therefore, no post-marketing data are available.

3.3.9. Discussion on clinical safety

The provided safety data for treatment with retifanlimab is based on the pivotal INCMGA 0012-202 study in patients with SCAC (data cut-off 08 Jun 2020) and on pooled data including patients with advanced solid tumours (INCMGA 0012-101, 0012-104, 0012-201, and 0012-203 with data cut-offs April-May 2020). Patients who received at least 1 dose of retifanlimab monotherapy were included in the safety evaluable population. In total 521 patients were included in the safety evaluable population, which is called the All Cancer Population. The All Cancer Population consists of the SCAC population (n=94, all patients that were enrolled in study 0012-202 and received retifanlimab 500 mg Q4W) and the Non-SCAC population (n=427). In the Non-SCAC population, patients received weight-based (1 mg/kg Q2W, 3 mg kg Q2W or Q4W, 10 mg/kg Q2W or Q4W) of fixed dosing of retifanlimab (500 mg Q4W, 750 mg Q4W, 375 mg Q3W). The safety data set for the SCAC population is limited in number and pooling data from retifanlimab monotherapy in solid cancer patients allows for a more comprehensive evaluation of the safety profile. Patients were included in the safety analyses regardless of retifanlimab dose since, according to the applicant, the safety profile was consistent across multiple dose regimens in study INCMGA 0012-101 and the PK of 3 mg/kg Q2W and 500 mg Q4W, the two doses most frequently administered in clinical studies, are comparable. The applicant's rationale to evaluate the safety data in the All Cancer Population to increase the likelihood of identifying less common, potentially important events, is acknowledged. The pooling regardless of retifanlimab dose is however questioned, given that there appear to be substantial differences for C_{max} and AUC between 3 mg/kg Q2W and 500 mg Q4W (please refer to PK assessment). It is therefore considered that the pooled safety analysis for the patients treated with the proposed posology (i.e. 500 mg Q4W; n=320)

is more appropriate to compare with the SCAC Population. For part of the safety profile, data for the All Cancer Population treated with 500 mg Q4W was already provided and will be discussed in the assessment. For the missing information, the applicant is requested to provide the data for the All Cancer Population treated with 500 mg Q4W (**OC**). Based on the above, the applicant should make a proposal which data should be the basis for the information described in section 4.8 of the SmPC (**OC**).

Baseline characteristics for the SCAC population are discussed in the efficacy part, where it is noted that all patients had an ECOG-PS of 0 or 1 per inclusion criteria, which is considered a selection of fit patients compared to the general SCAC population. The requirement of previous chemotherapy adds to this selection bias, as patients with a contra-indication for chemotherapy (comorbidities) or refusing chemotherapy were not enrolled. This is important to consider in light of contextualisation of the safety results in clinical practice. For the All Cancer Population the most common types of cancer were SCAC (18.0%), endometrial cancer (15.9%), and NSCLC (11.5%). Less frequent tumour types were sarcoma (8.8%), Merkel cell carcinoma (4.7%), cervical cancer (7.3%), renal cell carcinoma (6.5%), melanoma (6.3%), and bladder cancer (6.0%). Regarding prior therapy, the majority of patients (76.8%) in the All Cancer Population had received prior systemic therapy, 53.9% received prior radiotherapy, and 3.6% received prior immunotherapy. Baseline characteristics for the All Cancer Population treated with 500 mg Q4W are requested (**OC**). In addition, the number of included patients >85 years should be clarified (**OC**).

Exposure- As of the data cut-off dates for each study, 162 of the 521 patients (31.1%) in the All Cancer Population, including 18 of the 94 patients (19.1%) in the SCAC Population, were continuing to receive retifanlimab. The most common reason for treatment discontinuation was progressive disease (radiographic and clinical progression in 35.5% and 17.5% All Cancer Population, 22.3% and 39.4% SCAC Population, respectively). The most common reason for study withdrawal was death (39.7% All Cancer Population, 39.4% SCAC Population). Median duration of safety follow-up in the All Cancer Population was 139.0 days (range: 1-830 days) and not reported for the SCAC and All Cancer Population treated with 500 mg Q4W Population (**OC**).

Median duration of retifanlimab treatment was 85 days (range: 1 day-757 days) in the All Cancer Population, 85 days (range: 1-592 days) in the All Cancer Population treated with 500 mg Q4W, and 85 days (range: 1 day-592 days) in the SCAC Population. In the All Cancer Population, 106/521 patients (20.3%) had received retifanlimab for ≥6 months, 31/521 (6.0%) ≥12 months, and 21/521 (4.0%) ≥18 months. For the All Cancer Population treated with 500 mg Q4W these numbers were 59/320 (18.4%) for ≥6 months and 5/320 (1.6%) for ≥12 months. In the SCAC Population, 23/94 (24.5%) had received retifanlimab for ≥6 months and 2/94 (2.1%) ≥12 months. The mean average dose in the All Cancer Population was 426.99 mg and at median 500 mg. This is close to the proposed posology of 500 mg.

The limited exposure to retifanlimab and duration of safety follow-up lead to an uncertainty of establishing the longer term safety profile. It is known for PD-(L)1 inhibitors that immune-related toxicities can develop along the period in which patients are treated. It is acknowledged that the median exposure of 85 days and median follow-up of 139 days should be valued against the median PFS in the SCAC population of 2.3 months (95% CI 1.9-3.6 months). However, since 20-30% of the patients received retifanlimab at data cut-offs in April-June 2020, the limited number of patients receiving retinfalimab for more than 12 months and retifanlimab steady state being achieved after approximately 336 days, a safety update is requested including the numbers of patients that still receive treatment and patients still have ongoing follow-up in the individual studies (**OC**).

Adverse events- Almost all patients treated with retifanlimab monotherapy experienced an AE (95.7% SCAC Population, 88.9% All Cancer Population, 85.3% All Cancer Population treated with 500 mg Q4W). Treatment-related AEs were reported in 58.5% in the SCAC, 54.9% in the All Cancer

Population, and 52.5% in the All Cancer Population treated with 500 mg Q4W. In general, more severe AEs were reported in the SCAC Population compared to the All Cancer Population and the All Cancer Population treated with 500 mg Q4W. In the SCAC population 54.3% experienced a serious AE, 58.5% ≥Grade 3 AE, 11.7% treatment-related ≥Grade 3 AE, and 10.6% fatal AE. In the All Cancer Population corresponding frequencies were 30.3% for serious AEs, 42.2% for ≥Grade 3 AEs, 10.0% for treatment-related ≥Grade 3 AEs, and 4.0% for fatal AEs. For the All Cancer Population treated with 500 mg Q4W serious AEs occurred in 29.1%, ≥Grade 3 AEs in 36.3%, treatment-related ≥Grade 3 AEs in 8.1%, and fatal AEs in 5.3%. The number of discontinuations of the study drugs due to an AE were similar: 7.4% in the SCAC, 8.3% in the All Cancer Population, and 6.9% in the All Cancer Population treated with 500 mg Q4W.

By MedDRA preferred term, the most frequent AEs in the SCAC Population were asthenia (22.3%), anaemia (19.1%), diarrhoea (19.1%), and fatigue (17.0%). These were also most commonly reported in the All Cancer Population and All Cancer Population treated with 500 mg Q4W, although in lower frequencies. Most AEs were Grade 1 or 2. AEs that occurred at higher (>5%) frequencies in the SCAC Population compared with the Non-SCAC Population were asthenia (22.3% vs 10.8%), anaemia (19.1% vs 12.6%), diarrhoea (19.1% vs 11.7%), and dyspnoea (13.8% vs 6.8%). The most frequent treatment-related AEs in the SCAC Population were pruritus, fatigue, and diarrhoea. In the All Cancer Population these were fatigue, pruritus, and hypothyroidism.

Anaemia was the most often reported Grade ≥3 AE in both SCAC and All Cancer Populations. Other Grade ≥3 AEs most frequently occurring in the SCAC Population (>2%) were dyspnoea, abdominal pain, general physical health deterioration, hyponatraemia, asthenia, urinary tract infection, hypercalcaemia, pleural effusion, and sepsis. The only other Grade ≥3 AE reported in >2% of the All Cancer Population besides anaemia was hyponatraemia and pneumonia in the All Cancer Population treated with 500 mg Q4W. When comparing the SCAC to the Non-SCAC Population, more often Grade ≥3 AEs of dyspnoea, abdominal pain, and general physical health deterioration were observed in the SCAC Population.

The interpretation of the safety profile is hampered by the lack of a randomised control arm. Overall, the type and frequency of the most common AEs seem to correspond to the PD-1 immune checkpoint inhibitor class of drugs. The tolerability of retifanlimab seems to be worse with higher frequency of serious AEs, ≥Grade 3 AEs, and fatal AEs in SCAC patients compared to patients with other solid tumours. This can be explained by the tumour type and prior therapies specific to SCAC. Furthermore, the data of SCAC vs Non-SCAC patients already suggest that the frailty of patients with SCAC patients leads to a more severe safety profile of retifanlimab. As the SCAC study population consisted of selected, fit patients, there is a concern that the safety profile might be even more severe in clinical practice.

The applicant's evaluation of which AEs to include as ADRs for retifanlimab in the SmPC appears to be insufficient. A more thorough assessment should be undertaken, which takes into consideration all available evidence (**OC**).

Serious adverse events- SAEs were reported in 30.3% of the All Cancer Population, 29.1% in the All Cancer Population treated with 500 mg Q4W, and in 54.3% of the SCAC Population. Most frequently reported SAEs were abdominal pain, anaemia, urinary tract infection, dyspnoea, general physical health deterioration, pelvic pain, and pyrexia in the SCAC Population. In the All Cancer Population, including those patients treated with 500 mg Q4W, these were pneumonia, abdominal pain, and urinary tract infection. Most frequently observed SAEs that were assessed as related to the study treatment by the investigator were adrenal insufficiency, abdominal pain, immune-mediated enterocolitis, herpes zoster, lymphangiosis carcinomatosa, and hepatic coma in the SCAC Population. Colitis, pneumonitis, herpes zoster and infusion related reaction were the most common treatment-

related SAEs in the All Cancer Population per investigator assessment and not reported for the All Cancer Population treated with 500 mg Q4W (**OC**).

Deaths- In the All Cancer Population 21 patients had a fatal AE (4.0%), in the All Cancer Population treated with 500 mg Q4W 17 cases of fatal AEs occurred (5.3%), and in the SCAC Population this number was 10 (10.6%). Fatal AEs in the SCAC Population were caused by pelvic infection, peritonitis, *Pneumocystis jirovecii* pneumonia, femur fracture, hypercalcaemia, lymphangiosis carcinomatosa, pancreatic carcinoma, interstitial lung disease, pleural effusion, and pulmonary embolism. AEs with a fatal outcome in the Non-SCAC Population were cardiac failure, cardiovascular insufficiency, right ventricular failure, asthenia, death, sepsis, hemiparesis, nephritis, acute respiratory failure, pulmonary embolism, haemorrhage, and hypotension. The applicant's explanation that the higher incidence of fatal TEAEs in the SCAC Population reflects the more advanced stage of disease in the SCAC Population compared with patients included in the Non-SCAC Population, where the majority had not received prior therapy, is acknowledged.

One fatal AE was assessed by the investigator to be related to retifanlimab. This concerned a patient in the SCAC population with lymphangiosis carcinomatosa, which the investigator considered to be a possible manifestation of treatment-induced hyperprogression. At baseline the patient had pulmonary metastases and 1 week before study treatment she was diagnosed with a pulmonary infection. A CT scan at Day 11 showed lymphangiosis carcinomatosa. The patient refused further evaluation and died on Day 38. According to the applicant, the event was not related to retifanlimab as there were confounding factors such as the 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 retifanlimab was not (partly) causative and the fatal AE could be related to retifanlimab.

In addition, fatal AEs that could be part of irAEs were reported such as interstitial lung disease, nephritis, and acute respiratory failure. The applicant is requested to discuss why a possible relation to retifanlimab was excluded (**OC**).

Adverse events of special interest- Immune-related adverse events (irAEs) and infusion-related reactions (IRRs) were defined as AEs of special interest (AESI).

IrAEs occurred in 21.1% in the All Cancer Population, 18.4% in the All Cancer Population treated with 500 mg Q4W, and in 25.5% in the SCAC Population. Most irAEs were Grade 1 or 2 in severity. IrAEs Grade 3 occurred in 3.6%, Grade 4 in 0.4%, and Grade 5 in 0.4% in the All Cancer Population. Specific grades were not described for the All Cancer Population treated with 500 mg Q4W, but irAEs were ≥Grade 3 in 3.4% and there was one (0.3%) fatal case. IrAEs leading to retifanlimab discontinuation were observed in 2.7% in the All Cancer Population and in 1.9% of the All Cancer Population treated with 500 mg Q4W. The two fatal immune-related AEs, nephritis and pneumonitis, were not considered to be related to retifanlimab by the investigator. The applicant is requested to elaborate why the fatal cases of nephritis and pneumonitis were not considered to be related, including the previous event of nephritis in the patient with nephritis (**OC**). In the All Cancer Population, the most frequent irAE was hypothyroidism (7.9%) and the most frequent non-endocrine irAE was "skin reactions" (5.0% in the All Cancer Population), which are known to be the more frequent irAEs with PD-1 inhibitory treatment. Other reported endocrine irAEs were hyperthyroidism (4.4%), adrenal insufficiency (0.4%), thyroiditis (0.4%), and type I diabetes (0.4% All Cancer Population). In the category non-endocrine irAEs also pneumonitis (1.7%), colitis (1.3%), nephritis (1.0%), hepatitis (0.6%), polyarthritis (0.6%), myositis (0.4%), uveitis (0.2%), myocarditis (0.2%), and radiculopathy (0.2% All Cancer Population) were observed. Median time of onset varied largely from Day 1 to Day 628. Endocrine irAEs were not treated with systemic immunosuppressants, but the majority did receive endocrine therapy. Except for uveitis the majority of patients received systemic glucocorticoids. Other immunosuppressants such as infliximab were given to a patient with pneumonitis and one with colitis. Most, but not all irAEs

resolved at the time of data cut-off. IrAEs that led to discontinuation of study treatment were type I diabetes mellitus, palmo-plantar erythrodysaethesia ("skin reactions"), pneumonitis, nephritis, colitis, hepatitis, myositis, uveitis, myocarditis, polyarthritis, and radiculopathy. Although no unexpected signals were observed for irAEs, clarifying questions are asked regarding calculating frequencies of colitis and hepatitis (**OCs**). Furthermore, for the All Cancer Population treated with 500 mg Q4W and the applicant no information was provided regarding the occurrence of irAEs by group term and detailed information about the specific irAEs (**OC**). The proposed SmPC for retifanlimab includes a warning/precautionary statement for immune-related reactions, including immune-related endocrinopathies, immune-related pneumonitis, immune-related hepatitis, immune-related colitis and immune-related nephritis, in addition to a warning statement for other immune-related adverse reactions including polyarthritis, iritis, radiculopathy, myositis, myocarditis, based on reports from the All Cancer Population. Similar statements are included for the other products in the pharmacological class.

It was, however, noted that the overall frequency of reported irAEs in the All Cancer population appears to be quite low (21.1%), which may be in part due to the short treatment durations and immaturity of data, since the treatment period in the SCAC population was relatively short (median 85 days), and all studies are currently ongoing. From pharmacological class effects, it is well known that irAEs may have delayed onset, and may also occur long after discontinuation of treatment (Haanen et al 2017). However, it is also noticed that the list of predefined terms used to identify events of irAEs appears to be quite limited compared to immune-mediated adverse events definition used for other PD-1 inhibitors (nivolumab). Also impacting the reported frequencies of irAEs for retifnalimab was the exclusion by the sponsor of four reported events of nephritis because the sponsor assessed that there was insufficient evidence for a diagnosis of immune-related nephritis. The applicant is requested to perform a more thorough analysis of immune-related adverse events, taking into account the above. Analysis of TEAEs for which treatment with immunosuppressive drugs (e.g. systemic corticosteroids) was initiated, should be included in the analysis of potential irAEs (**OC**).IRRs occurred frequently and were reported in 7.1% in the All Cancer Population and 5.6% in the All Cancer Population treated with 500 mg Q4W. In the SCAC Population IRRs occurred in 4.3%. Grade 3 IRRs were observed in 2 patients (0.4%) in the All Cancer Population, in 1 patients (0.3%) of the All Cancer Population 500 mg Q4W, and in none of the SCAC Population. One of the Grade 3 cases, which occurred in the All Cancer Population treated with 500 mg Q4W, was not considered to be related to retifanlimab based on the duration of the interval from the last retifanlimab infusion on Day 28 and the onset of the reported IRR on Day 54, which can be supported. In one patient in the All Cancer Population study treatment was discontinued due to an IRR and none of the cases were fatal. Data on time to onset and time to resolution of IRRs are requested (**OC**).

Discontinuations- AEs leading to retifanlimab discontinuation were observed in 8.3% of the All Cancer Population, 6.9% of the All Cancer Population treated with 500 mg Q4W, and in 7.4% of the SCAC Population. Discontinuations were most frequently reported due to colitis and pneumonitis, but it is unknown how often AEs leading to discontinuations were assessed as related to retifanlimab (**OC**). Dose delays due to an AE occurred in similar frequencies in the All Cancer Population (20.9%), All Cancer Population treated with 500 mg Q4W (19.7%), and the SCAC Population (19.7%).

Laboratory findings- Laboratory values for haematology, chemistry, TSH, and coagulation parameters did not show unexpected clinically meaningful changes, but increases in amylase and lipase (including worsening to ≥Grade 3) were frequently observed and the applicant is requested whether there were signals of pancreatitis in these patients (**OC**). Data for the All Cancer Population treated with 500 mg Q4W for completeness of the EPAR are requested (**OC**). The only laboratory abnormalities included as ADRs for retifanlimab in the SmPC are grade 3 or 4 worsening of AST increased, lipase increased and ALT increased. A more thorough analysis of possible relatedness to

treatment should be undertaken for observed laboratory abnormalities, also considering listed laboratory abnormalities for other drugs of the pharmacological class (**OC**). In addition, summarising overviews for urinalysis and vital signs are requested (**OCs**).

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, which is as expected for monoclonal antibodies having a low likelihood of direct ion channel interactions.

Safety in special populations- In the All Cancer Population, 252 patients were 65 years or older (48.4%) and 81 (15.5%) were 75 years or older. Frequencies of (severe) AEs or irAEs were comparable between the subgroups younger or older than 65 years and younger or older than 75 years. The applicant is requested to provide the table of different age subgroup as shown in the LoQ (**OC**). Female patients had a ~8% 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 Population. According to the applicant, the gender difference in irAEs may be attributable to the higher frequency of thyroid-related endocrine irAEs in female patients, but those numbers were not provided (**OC**). Fatal AEs occurred more often in males in both the SCAC and All Cancer Population and the applicant is also asked to elaborate on this finding (**OC**). As expected, the number of serious and ≥Grade 3 AEs were higher in patients with ECOG ≥1 vs ECOG 0 and median treatment duration was shorter in patients with worse performance status. Patients with ECOG of 2 or higher were not included, but it might be expected that tolerability will be worse in that subgroup. In section 5.1 of the SmPC it is described that patients with ECOG performance score (PS) ≥2 were excluded. Pending on the response to the MO on the results, it should be considered to include this exclusion criterium as a warning in section 4.4 of the SmPC (see SmPC assessment). In the All Cancer 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 according to the applicant. Additional discussion on a patient with declining CD4+ counts and an update of the CD4+ counts of ongoing patients are requested (**OC**). Interpretation of the HIV-positive subgroup is hampered by the small sample size, but no safety signals occurred regarding the frequencies of (ir)AEs. A more robust characterisation of safety and viral load control in HIV-positive subjects is expected to be forthcoming with the confirmatory study (conducted in an earlier stage of SCAC) which is expected to enrol HIV-positive subjects. The number of patients with renal or hepatic impairment are also small and therefore subgroup analyses are difficult to interpret and information is provided in section 4.2 of the SmPC. The subpopulation of non-Caucasian race includes also patients with no race reported and the results should therefore be interpreted with caution. 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 SCAC 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 will not be requested. The applicant performed the subgroup analysis on the pooled All Cancer Population regardless of posology. The applicant is also requested to perform the subgroup analyses on patients in the All Cancer Population treated with 500 mg Q4W and discuss whether these data influence the conclusions based on the data in the All Cancer Population regardless of posology (**OC**).

Immunogenicity- In the All Cancer Population 467 patients were assessable for immunogenicity of whom 72 had inconclusive results (see pharmacokinetics assessment). Of the remaining 395 patients, 9 were ADA positive during the study. Five of 9 ADA-positive patients had nontreatment-emergent ADAs with only baseline positive ADAs, and 4 of them had treatment-emergent ADAs. Out of these 4 treatment-emergent positive patients, no persistent positive ADAs were observed. One of the treatment-emergent positive patients had a positive sample at EOT after 2 infusions. The other treatment-emergent positive patients had a positive sample during treatment and tested negative thereafter. None of the treatment-emergent positive patients were from study INCMGA 0012-202,

therefore no relationship of ADA status to efficacy could be assessed for the SCAC Population. Regarding safety, there were no safety concerns in the patients that were treatment-emergent ADA positive. No results were reported on neutralizing antibodies (see pharmacokinetics assessment).

Infusion time- The applicant uses the occurrence of IRRs as support for the infusion time. Based on PK assessments, simulated Cmax after the first dose and at steady state showed no relevant difference after an infusion (please refer to PK assessment). However, a shorter infusion time leads to a higher infusion rate, which may potentially affect tolerability. Currently, the applicant compares all patients treated with -minutes infusion (all received 500 mg Q4W) with all patients treated with -minutes infusion (different posologies). IRRs occurred in 6.6% (8/121) in patients that were treated with -minute infusions (study INCMGA 0012-203) and 7.3% (29/400) in patients receiving -minute infusions (studies INCMGA 0012-101, 0012-104, 0012-201, and 0012-202). Based on the previous discussion that the All Cancer Population treated with 500 mg Q4W might be a better comparison than the All Cancer Population treated with different posologies, the applicant should provide the frequencies of IRRs in the patients treated with -minutes infusion with a posology of 500 mg Q4W, overall and during/after the first infusion and first three infusions (**OC**). In addition, comparisons should be extended to more safety parameters, such as hypersensitivity, anaphylactic reactions, irAEs (including ≥Grade 3) and overall AEs (including ≥Grade 3 and discontinuations (**OC**). Although the updated analyses will be more appropriate, a comparison between the two infusion times is limited because of the lack of randomisation and differences between study populations. The applicant is therefore also requested to discuss how the provided data can be used to support a -min infusion in the applied for indication (**OC**).

3.3.10. Conclusions on clinical safety

Although the type of AEs are reflective of the known safety profile of PD-(L)1 inhibitory treatment and no new safety issues were identified, the toxicity in the SCAC Population is more severe compared to other oncology populations treated with retifanlimab monotherapy and should be valued against the observed benefit. There is a higher frequency of serious AEs, ≥Grade 3 AEs, and fatal AEs in SCAC patients compared to patients with other solid tumours treated with the same posology. Toxicity in clinical practice might even be higher given that the studied SCAC Population was a selected fit population. Furthermore, the safety data comes from open-label, uncontrolled studies hampering the interpretation of the data. In addition, (duration of) exposure is limited and an update of the safety database is requested including pooled analysis of patients with solid tumours treated with retifanlimab monotherapy 500 mg Q4W and a more thorough analysis of immune-related adverse events.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None

Summary of safety concerns	
Missing information	Uncontrolled HIV

3.4.2. Discussion on safety specification

The applicant proposes to include "Uncontrolled HIV" as missing information. The interest in a patient population with uncontrolled HIV in the context of SCAC is acknowledged and these patients were excluded from the clinical trials, but not contraindicated in the SmPC. There is insufficient exposure in patients with uncontrolled HIV to determine whether the safety profile differs from the toxicity characterised so far and this might affect the B/R in this subpopulation. However, the applicant does not propose further additional pharmacovigilance activity or risk minimisation measures, nor specific information in the SmPC. This is not acceptable and the applicant is requested how additional information in patients with uncontrolled HIV will be collected, for example during PSURs and with ongoing and future clinical studies, and how the lack of information in this subgroup should be reflected in the SmPC, i.e. whether a warning is needed (**OC**).

It is considered that irAEs and IRRs are important identified risks based on clinical observations and class effects. In addition, irAEs and IRRs are important risks in the EU-RMP for all drugs in the PD-(L)1 class. To be in line with other PD-(L)1 inhibitors and in order to harmonise educational material, the applicant should include irAEs and IRRs in the list of safety specifications (**OC**).

Furthermore, long-term exposure and long-term follow-up is limited and should also be included in the list of safety specifications, which is also in line with the recently approved PD-1 inhibitors cemiplimab and dostarlimab (**OC**).

In addition, it is noted that immunogenicity or lack of efficacy due to ADAs is not listed as important potential risk, which is the case for some of the other PD-(L)1 inhibitors. The applicant should discuss and include in the RMP the reason why this is not listed as a safety specification for retifanlimab, taking into account the response to the pharmacokinetics OCs regarding ADAs (**OC**).

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification the Rapporteur considers that the following issues should be addressed:

The Rapporteur considers that immune-related adverse reactions, infusion-related reactions, and long-term safety should also be safety concerns. In addition, further discussion is needed about lack of efficacy due to anti-drug antibodies and uncontrolled HIV (**OCs**).

3.4.4. Pharmacovigilance plan

Routine Pharmacovigilance activities are proposed to further collect data and evaluate missing information – Uncontrolled HIV.

No additional pharmacovigilance activities have been proposed by the applicant.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, and the comments and recommendations of the CHMP Rapporteur is of the opinion that the applicant should further discuss how information on safety in patients with uncontrolled HIV will be collected and whether routine pharmacovigilance is appropriate for that. **(OC)**

The applicant should also propose appropriate pharmacovigilance plan for additional safety concerns recommended by the CHMP Rapporteur to be add on. **(OC)**

3.4.5. Risk minimisation measures

Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Uncontrolled HIV	Routine risk communication: SmPC Section 4.2, 4.5, 4.8, 5.1, 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: recommendation for retifanlimab use in HIV-positive patients are included in SmPC sections 4.2

It has been recommended to add additional safety concerns to the RMP. The risk minimisation measures should be proposed for these additional safety concerns. **(OC)**

Additional risk minimisation measures

No additional risk minimisation measures were proposed.

The additional important identified risks, such as immune related adverse events and infusion related reactions, are requested to be included to the RMP by the CHMP Rapporteur. Having considered that additional risk minimisation measures to minimise the risk of IrAEs are implemented for other products of the class - dostarlimab indicated for endometrial cancer and cemiplimab indicated for cutaneous squamous cell carcinoma, the applicant is encouraged to implement additional risk minimisation measures, e.g. educational material, in order to mitigate the risk. (**OC**)

Having considered the data submitted it is concluded that the proposed risk minimisation measures are not sufficient to minimise the risks of the product in the proposed indication(s).

3.4.1. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 1.0 is not acceptable. Details are provided in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

3.5. Pharmacovigilance system

<It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.>

<Having considered the data submitted in the application, it is not appropriate to conclude on pharmacovigilance system at this time.><See list of questions>.

<Having considered the data submitted in the application, a pre-authorisation pharmacovigilance inspection is required>.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points.> 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 <not> request an alignment of the PSUR cycle with the international birth date (IBD)>. <The IBD is {DD.MM.YYYY.}>.

<The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD)>.

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

The indication claimed for retifanlimab is as follows:

Retifanlimab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic squamous carcinoma of the anal canal (SCAC) who have progressed on or who are intolerant of platinum based chemotherapy.

Retifanlimab is a monoclonal antibody that recognises human PD-1, designed to target PD-1-expressing cells, including T cells, and restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

The recommended dose is 500 mg retifanlimab every 4 weeks (Q4W) administered as an intravenous infusion over 30 minutes.

Locally advanced or metastatic SCAC is an incurable disease with a poor prognosis. There are no registered treatment options beyond first line. The two main goals of therapy in this setting are 1) to prolong survival and 2) to induce tumour shrinkage in patients with locally recurrent disease in order to relieve pain and morbidity.

4.1.2. Available therapies and unmet medical need

There is no standard of care treatment beyond first line in patients with locally advanced or metastatic SCAC. There are few reports in literature in which relatively short PFS and OS are described in SCAC patients treated in second line with mitomycin/5-FU chemotherapy (Saint et al.; n=19; ORR 26%, PFS 3 months and OS 7 months), immunotherapy with nivolumab (Morris et al.; n=37; ORR 24%, PFS 4 months and OS 11.5 months) or pembrolizumab (Marabelle et al. (abstract); n=112; ORR 11%, PFS 2 months and OS 12 months).

Therefore, there remains a significant unmet medical need for locally advanced or metastatic SCAC patients who have progressed despite receiving platinum-based chemotherapy.

4.1.3. Main clinical studies

The main study is PODIUM-202, an ongoing, open-label, single-arm, multicentre phase II trial. PODIUM-202 was designed to investigate the safety and efficacy of retifanlimab monotherapy in patients with locally advanced or metastatic SCAC who progressed on or were intolerant to platinum-based chemotherapy. Only patients with measurable disease were included as per inclusion criterion and these were treated with retifanlimab 500mg as an intravenous (IV) infusion over 60 minutes every

4 weeks, until progression of disease or intolerable toxicity, for a maximum of two years. The target enrolment was 81 patients, and the primary analysis of ORR was to be performed after all subjects had reached a minimum duration of follow-up of 6 months (DCO 8 Jun 2020). An updated analysis of DOR was to be performed after all responding patients had reached a minimum duration of follow-up of 6 months, from the first response (DCO update 01 Oct 2020). The study had no formal hypotheses, but based on sample size considerations the clinically relevant target ORR was set at 25%. The lower limit of the 95% CI was chosen so that the study was powered to rule out a clinically non-relevant ORR of below 13%. The study is closed for enrolment with 94 patients enrolled, but is ongoing for treatment (18/94 patients at DCO; 19%) and follow-up (54/94 patients at DCO; 57%).

4.2. Favourable effects

The flat dose regimen of 500mg Q4W used in PODIUM-202 is acceptable based on the phase 1 dose-escalation study PODIUM-101 and the performed pop-PK modelling.

The primary endpoint of ORR based on independent central review (ICR) in the full analysis set was 13.8%, with a 95% CI of 7.6-22.5%. The ORR of 13.8% is calculated based on 12 partial responses and 1 complete response observed in the 94 enrolled and treated patients.

A sensitivity analysis of ORR based on investigator-assessed tumour response according to RECIST v1.1 showed a comparable ORR of 14.9%.

The confirmed ORRs based on ICR were generally consistent across participant groups within prespecified subgroups based on age group, sex, race, ethnicity, ECOG performance status, HIV status, liver metastases, PD-L1 status, and HPV status.

The median DoR was 9.5 months, estimated in the 13 responding patients after a median follow-up of 7.4 months. The 95% CI lower limit of the DoR was 4.4 months, with the upper limit not being evaluable.

Median PFS was 2.3 months (95% CI 1.9-3.6 months), and median OS was 10.1 months (95% CI 7.9 months – NE).

4.3. Uncertainties and limitations about favourable effects

The main deficiency in the study design is the lack of a comparator arm, hampering the contextualisation of the findings. It is uncertain whether the mariginal ORR and DoR results represent clinical benefit.

The study population is considered highly selected, because patients were required to have received at least one prior line of systemic chemotherapy and have an ECOG-PS of 0 or 1 to be eligible to participate.

The targeted sample size was 81, but 94 patients were enrolled in study PODIUM-202. This difference is unexplained and it needs to be clarified if efficacy and safety results for the first 81 patients were assessed before the study was over-enrolled.

A large proportion of patients was censored for DoR (n=6/13; 46%), PFS (n=23/94; 24.5%) and OS (n=57/94; 60.6%), with some reasons for censoring potentially being informative.

4.4. Unfavourable effects

The database used for the safety profile of retifanlimab consists of 94 patients with SCAC (treated with 500 mg Q4W) and 512 pooled advanced solid tumours patients treated with retifanlimab monotherapy

at different posologies with data cut-offs from April-June 2020. As there appear to be substantial differences for C_{max} and AUC between 3 mg/kg Q2W and 500 mg Q4W, it seems most appropriate to use the pool of the All Cancer Population treated with 500 mg Q4W. In total 320 patients received retifanlimab 500 mg Q4W in the All Cancer Population (All Cancer Population treated with 500 mg Q4W). Median duration of retifanlimab treatment was 85 days in all three populations with a median duration of safety follow-up of 139 days in the All Cancer Population. Next, the SCAC Population will be compared to the All Cancer Population treated with 500 mg Q4W unless the data for this pooled population were not provided. In that case, the data for the All Cancer Population are reported.

Almost all patients experienced an AE (>85%) and treatment-related AEs were reported in >52%. In general, more severe AEs were reported in the SCAC Population compared to the All Cancer Population treated with 500 mg Q4W, including more frequent observations of serious AEs, ≥Grade 3 AEs, and fatal AEs in the SCAC Population (see Effects Table). The number of discontinuations of the study drug due to an AE was similar in all populations.

Most frequent AEs in the SCAC Population were asthenia, anaemia, diarrhoea, and fatigue. These were also most commonly reported in the All Cancer Population treated with 500 mg Q4W, although in lower frequencies. Most AEs were Grade 1 or 2. AEs that occurred at higher (>5%) frequencies in the SCAC Population compared with the Non-SCAC Population were asthenia, anaemia, diarrhoea, and dyspnoea. The most frequent treatment-related AEs in the SCAC Population were pruritus, fatigue, and diarrhoea. Anaemia was the most often reported Grade ≥3 AE in all populations.

In the All Cancer Population treated with 500 mg Q4W 5.3% had a fatal AE, and in the SCAC Population this number was 10.6%. One fatal AE was assessed by the investigator to be related to retifanlimab, which concerned a patient in the SCAC population with lymphangiosis carcinomatosa being a possible manifestation of treatment-induced hyperprogression.

IrAEs occurred in 18.4% in the All Cancer Population treated with 500 mg Q4W and in 25.5% in the SCAC Population. Most irAEs were Grade 1 or 2 in severity. Detailed data on irAEs were provided for the All Cancer Population, but not for the All Cancer Population treated with 500 mg Q4W. IrAEs Grade 3 occurred in 3.6%, Grade 4 in 0.4%, and Grade 5 in 0.4% in the All Cancer Population. IrAEs leading to retifanlimab discontinuation were observed in 2.7%. The two fatal immune-related AEs, nephritis and pneumonitis, were not considered to be related to retifanlimab by the investigator. In the All Cancer Population, the most frequent irAE was hypothyroidism (7.9%) and the most frequent non-endocrine irAE was "skin reactions" (5.0% in the All Cancer Population). IRRs were reported in 5.6% in the All Cancer Population treated with 500 mg Q4W and in 4.3% of the SCAC Population; Grade 3 IRRs were observed in 0.4% of the All Cancer Population.

In the All Cancer Population, 4 patients had treatment-emergent ADAs with no persistent positive ADAs. None of the treatment-emergent positive patients were from study INCMGA 0012-202, therefore no relationship of ADA status to efficacy could be assessed for the SCAC Population. There were no safety concerns in the patients that were treatment-emergent ADA positive.

4.5. Uncertainties and limitations about unfavourable effects

Part of the safety data is missing for the All Cancer 500 mg Q4W pooled population and requested, such as detailed information on irAEs.

One of the main uncertainties is that the source for the safety database is from ongoing, open label, uncontrolled studies, hampering the interpretation of the safety profile. Adding to the difficulty interpreting the safety data for clinical practice is that all patients had an ECOG-PS of 0 or 1 per inclusion criteria and the requirement of previous chemotherapy. This is considered a selection of fit

patients compared to the general SCAC population and is expected to have a relevant adverse effect on the safety profile. Characterisation of safety in elderly patients >85 years of age is lacking.

Next, the median exposure and follow-up for safety are limited. At the data cut-offs 20-30% of the patients were still receiving retifanlimab and a limited number of patients received retinfalimab for more than 12 months while retifanlimab steady state is achieved after approximately 336 days. This is of concern because it is known for PD-(L)1 inhibitors that immune-related toxicities can develop over the full period in which patients are treated. The data analyses provided for immune-related adverse events are often not sufficiently thorough to ensure that important safety aspects have been captured.

Moreover, the support for a 30-minute infusion is considered to be too limited and additional clarifying questions are proposed regarding frequencies of (fatal) irAEs, timing of IRRs, discontinuations due to AEs related to retifanlimab, subgroup analyses including HIV-positive patients, and laboratory findings.

4.6. Effects Table

Table 41: Effects Table for retifanlimab in locally advanced or metastatic SCAC

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	Percentage of participants with CR or PR at any postbaseline visit before first PD or new anticancer therapy, according to RECIST v1.1 as determined by ICR	%	13.8% (7.6-22.5)	NA	Single-arm trial	CSR
DoR	Time from initial objective tumour response (CR or PR) to earlier of PD based on RECIST v1.1 criteria or death	Months	9.5 months (4.4-NE)	NA	Single-arm trial, limited follow-up	CSR
Unfavourable Effects						

			SCAC Population	**All Cancer Population**	**All Cancer Population 500 mg Q4W**		
			(n=94)	**(n=521)**	**(n=320)**		

Effect	Short Description	Unit	Treatment	Control		Uncertainties/ Strength of evidence	References
Grade ≥3 AEs	All causality (drug-related)	%	58.5 (11.7)	42.2 (10.0)	36.3 (8.1)	Open label studies, lack of control arm, limited duration of treatment and follow-up	CSR, summary clinical safety
SAEs	All causality (drug-related)	%	54.3 (6.4)	30.3 (4.8)	29.1 (4.1)		
AEs leading to DC	All causality (drug-related)	%	7.4 (NR)	8.3 (NR)	6.9 (NR)		
Deaths	Due to AE (drug-related)	%	10.6 (1.1)	4.0 (0.2)	5.3 (0.3)		
AESI	All causality	%					
	Endocrine		13.9	13.5	NR		
	Skin reactions		8.5	5.0	NR		
	Pneumonitis		4.3	1.7	NR		
	Colitis		2.1	1.3	NR		
	Nephritis		1.1	1.0	NR		
	Hepatitis		1.1	0.6	NR		
	Polyarthritis		0	0.6	NR		
	Myositis		1.1	0.4	NR		
	Uveitis		0	0.2	NR		
	Myocarditis		0	0.2	NR		
	Radiculopathy		0	0.2	NR		
	IRR		4.3	7.1	5.6		

Abbreviations: AE= adverse event, AESI= AE of special interest, CSR= clinical study report, DC= discontinuation, DoR= duration of response, IRR= infusion reaction, NR= not reported, ORR= overall response rate, SAE= serious adverse event

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Retifanlimab monotherapy was studied in a small, single-arm trial of 94 patients with locally advanced or metastatic SCAC, with most patients (91/94) progressing after platinum-based chemotherapy. The study population is considered highly selected in light of the target population, because all included patients had to be eligible for first line chemotherapy and had an ECOG-PS of 0 or 1. The selection of fit patients already living long enough to participate in PODIUM-202 is important to consider for contextualisation of the results of this single-arm trial.

There is no standard of care treatment beyond first line in patients with locally advanced or metastatic SCAC. There are few reports in literature in which relatively short PFS and OS are described. Therefore, there remains a significant unmet medical need in the targeted population.

As the basis for this application is a single pivotal, uncontrolled trial, several aspects need explicit consideration.

The results showed marginal anti-tumour activity (ORR 13.6%) that does not seem better than reported for other investigated systemic therapies in this setting with no clear SOC. The observed ORR of 13.8% did not meet the target ORR that was used to power the pivotal study (i.e. 25%), which also does not fall within the observed 95% CI of ORR (7.6-22.5%). Furthermore, the 95% CI for the ORR does not even exclude the as clinically non-relevant designated ORR target of 13%. The estimation of median duration of response of 9.5 months by ICR (and 7.6 months by investigator-assessment) is not

considered stable given the limited duration of follow-up. PFS and OS results are difficult to interpret due to the study design. Additional information regarding the high number of patients censored for the efficacy analysis and potentially informative censoring is warranted. It is uncertain whether the ORR and DoR results represent clinically relevant benefit for the target population. The phase 3 trial in first line treatment will provide some additional information on the B/R for retifanlimab in the platinum-refractory setting because participants experiencing confirmed progression on the placebo control arm will be allowed to cross over to retifanlimab monotherapy. However, this study will not provide comparative data on PFS and OS for retifanlimab monotherapy and can therefore not resolve the identified uncertainties in relation to efficacy.

The clinical relevance of the efficacy results is even more questionable taking into account that patients with a local recurrence of disease can experience severe pain as the most important symptom and are expected to mainly benefit from significant tumour shrinkage. Any analysis of clinical benefit in subgroups of patients based on localisation of their disease (local recurrence versus distant visceral metastases) is hampered by the low number of responders.

From a safety point of view, the safety data comes from open-label, uncontrolled studies hampering the interpretation of the data and (duration of) exposure is limited. Notable is that the toxicity in the SCAC Population is more severe compared to other oncology populations with higher frequencies of serious AEs, ≥Grade 3 AEs, and fatal AEs in SCAC patients compared to patients with other solid tumours treated with the same retifanlimab posology. Toxicity in clinical practice might even be more severe given that the studied SCAC Population was a selected fit population. This should all be valued against the limited observed benefit. It is acknowledged that the type of AEs observed with the treatment of retifanlimab monotherapy are reflective of the known safety profile of PD-(L)1 inhibitory treatment and no new safety issues were identified, but updated safety data and additional analyses for immune-related adverse events are requested.

4.7.2. Balance of benefits and risks

The reported ORR are of questionable clinical relevance considering the target population, as it is uncertain if these effects translate into a clinical benefit in terms of PFS or OS. The toxicity profile is as expected for an anti-PD1 antibody, however, toxicity appears more severe in SCAC patients compared to other tumour types. Toxicity in clinical practice might even be higher given that the studied SCAC population was a selected fit population. Considering that efficacy is not established while unfavourable effects are notable, the benefit-risk balance is considered negative.

4.7.3. Additional considerations on the benefit-risk balance

Therapeutic indication

The proposed wording of the indication is not endorsed as it opens up for treatment with retifanlimab in treatment-naive patients intolerant to platinum-based chemotherapy. This prior untreated population was not studied in the pivotal trial as participants ineligible for platinum must have received at least one prior line of systemic therapy. The indication should be rephrased to clarify that retifanlimab is only indicated after prior systemic therapy, also in platinum intolerant patients. Further, the wording "progressed on" is considered imprecise as it gives associations to a platinum-refractory setting. As the study population also includes patients with progression/relapse after platinum-based therapy, the wording should be adjusted accordingly.

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease, and is designated as an orphan medicinal product.

In terms of the requirements for a conditional marketing authorisation:

- The benefit-risk balance is currently considered negative, as discussed.
- It is uncertain whether the applicant will be able to provide comprehensive data.

  The applicant plans to confirm the B/R of retifanlimab in previously treated SCAC as observed in Study INCMGA 0012-202 with the confirmatory Study INCMGA 0012-303, which is currently ongoing. This PODIUM-303 study is a randomised double-blind study comparing first-line treatment with chemotherapy+placebo to chemotherapy+retifanlimab. The clinical study report based on the primary endpoint of PFS is planned for December 2024. OS is a key secondary endpoint. Crossover to retifanlimab monotherapy for subjects treated in the control arm of the study is allowed in PODIUM-303. This study will provide some additional information on the B/R for retifanlimab in the platinum-refractory setting. The confirmatory study design will also provide extra data on the relative efficacy of retifanlimab in locally advanced versus metastatic disease because this is a stratification factor for PODIUM-303. The phase 3 trial in first line treatment will not provide comparative data on PFS and OS for retifanlimab monotherapy. The applicant is requested how the PODIUM-303 study can be used to gain more safety information about patients with uncontrolled HIV, irAEs, IRRs, and long-term data (please refer to the assessment of the safety specifications).
- It is agreed that there exists an unmet medical need for patients with locally advanced or metastatic SCAC, as prognosis is poor and there is no SOC treatment. However, the reported ORR and DoR show marginal anti disease activity and the clinical relevance thereof is questionable. Therefore, it is not certain that retifanlimab will address the unmet medical need in the target population.
- The benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required. Further data are needed before a final conclusion can be drawn.

The product is not recommended for a conditional marketing authorisation as, the benefit-risk balance is negative (as discussed) and it has not been demonstrated that the product can be expected to address the unmet medical need **(MO)**.

4.8. Conclusions

The overall B/R of retifanlimab is negative due to outstanding major objections on the NAS, clinical efficacy, CMA and the therapeutic indication.