29 January 2026
EMADOC-1700519818-2817991
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ZYNYZ

International non-proprietary name: retifanlimab

Procedure No. EMA/VR/0000247788

Note

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

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List of abbreviations

5-FU	5-fluorouracil
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUS	Australia
BICR	blinded independent central radiographic review
CD4	cluster of differentiation 4
CI	confidence interval
Cmin1	first dose minimum observed serum concentration
COVID-19	coronavirus disease 2019
CR	complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCR	disease control rate
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECIS	European Cancer Information System
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMA	European Medicines Agency
E-R	exposure-response
EU	European Union
FAS	full analysis set
Fc	fragment crystallizable
FDA	Food and Drug Administration

HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG4	immunoglobulin G4
IPCW	Inverse probability of censoring weighting
irAE	immune-related adverse event
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
ISI	Integrated Summary of Immunogenicity
IV	intravenous(ly)
LDH	lactate dehydrogenase
LLN	lower limit of normal
MCC	Merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MMR	mismatch repair
NA	not available
NAb	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NE	not evaluable
NOR	Norway
NR	not reached
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1/2	programmed death receptor-ligand 1/2
PFS	progression-free survival
PK	pharmacokinetic(s)
popPK	population pharmacokinetics

PR	partial response
PRO	patient-reported outcomes
PT	preferred term
QOL	quality of life
QTc	corrected QT interval
QxW	every x weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
ROW	rest of the world
RPSFT	rank-preserving structural failure time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCAC	squamous cell carcinoma of the anal canal
SOC	system organ class
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
UK	United Kingdom
ULN	Upper limit of normal.
US	United States
Vss	volume of distribution at steady-state
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Incyte Biosciences Distribution B.V. submitted to the European Medicines Agency on 29 January 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include in combination with carboplatin and paclitaxel treatment of adult patients with metastatic or with inoperable locally recurrent squamous cell carcinoma of the anal canal (SCAC) for ZYNYZ, based on interim results from study INCMGA 0012-303 (POD1UM-303/InterAACT-2); this is a phase 3 global, multicenter, double-blind randomized study of carboplatin-paclitaxel with retifanlimab or placebo in participants with inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal not previously treated with systemic chemotherapy; As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce editorial changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

ZYNYZ, was designated as an orphan medicinal product EU/3/22/2743 on 13 Jan 2023. ZYNYZ was designated as an orphan medicinal product in the following indication:

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

ZYNYZ, was designated as an orphan medicinal product EU/3/20/2343 on 19 October 2020 for the indication treatment of anal cancer.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision EMEA-002798-PIP01-20 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Peter Mol Co-Rapporteur: Selma Arapovic Dzakula

Timetable	Actual dates
Submission date	5 February 2025
Start of procedure:	20 February 2025
CHMP Rapporteur's preliminary assessment report circulated on:	16 April 2025
PRAC Rapporteur's preliminary assessment report circulated on:	24 April 2025
Joint Rapporteur's updated assessment report circulated on:	15 May 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	22 May 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	19 August 2025
PRAC RMP advice and assessment overview adopted by PRAC	4 September 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	11 September 2025
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	18 September 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	5 January 2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	22 January 2026
CHMP Opinion	29 January 2026
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Zynyz in comparison with existing therapies (Appendix)	29 January 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

The proposed indication for retifanlimab is in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with metastatic or with inoperable locally recurrent squamous cell carcinoma of the anal canal (SCAC).

Epidemiology and risk factors

Anal cancer is a rare, life-threatening disease involving the anus, anal canal, or anorectum. Almost all primary cancers of the anal canal (85%) are of squamous cell histology, or SCAC. It is estimated that about 10,198 new cases of anal cancer were diagnosed in the EU-27 in 2022. This corresponds to a crude incidence rate of 2.2 per 100,000 in the EU-27 (ECIS 2022). In European countries, the incidence rate varies from 1 per 100,000 men and women in the UK to 3 per 100,000 in Switzerland (Pessia et al 2020). Although SCAC is rare, the incidence is increasing due to sexual transmission of oncogenic strains of HPV (Ghosn et al 2015, Nelson et al 2013, Symer and Yeo 2018). In Europe, there has been an increase of SCAC from 0.595/100,000 per year from 1999 to 2002 to 0.728/100,000 per year from 2003 to 2007 (RARECARENet 2020). This trend is also noted particularly in developed countries: the incidence of SCAC more than doubled between 1988 to 1992 and 2008 to 2012, in men and women, when data were pooled from 7 high income countries in North America, Europe, and Oceania (Kang et al 2018). The increasing incidence of anal carcinoma is particularly evident in HIV positive patients (Abramowitz et al 2009, Moureau-Zabotto et al 2017, Piketty et al 2012). The risk of being diagnosed with anal cancer is 25 to 35 fold higher in individuals who are HIV-positive than in individuals who are HIV-negative (NCCN 2024).

Biologic features

Persistent infection with high-risk oncogenic forms of HPV (e.g., HPV 16, HPV-18) is the underlying cause of approximately 85% to 95% of cases of SCAC. Similarly, HPV infection causes almost all cervical and genital cancers, a vast majority of oropharyngeal head and neck squamous cell carcinoma (HNSCC), as well as other cancers. Additional risk factors for SCAC include a history of high number of lifetime sexual partners, unsafe sexual practices, gynaecologic cancers, immunosuppressive conditions, hematologic malignancies, HIV, and smoking.

Clinical presentation, diagnosis and prognosis

Most patients with SCAC present with localized disease, with the most frequent presenting symptoms being rectal bleeding, anal pain and sensation of a rectal mass. Patients with locally recurrent disease can also experience pain, incontinence, impaired sexual function, and diarrhoea, which lead to a reduced quality of life and are related not just to the disease but also to complications of treatment.

While most patients with SCAC have localized disease at the time of initial diagnosis, systemic metastases will develop in up to 25% of patients. In addition, relapse after primary treatment occurs in up to 40% of patients within 5 years. The prognosis for patients who experience relapse or who present with de novo metastatic disease is poor, with a 5-year OS rate of only 15% to 20%.

Management

The current standard of care treatment for localized disease is fluoropyrimidine-based chemotherapy in combination with radiotherapy, with a 5-year disease-free survival rate of approximately 60%. Surgery as primary treatment has generally been abandoned because comparable survival without the need for permanent colostomy can be achieved with these regimens.

The current first-line standard of care for metastatic SCAC is platinum-based chemotherapy (NCCN 2023, ESMO 2021). The randomized Phase 2 InterAACT study established carboplatin in combination with weekly paclitaxel as the preferred first-line treatment based on better tolerability of this regimen compared with cisplatin plus 5-FU. Nevertheless, clinical outcomes remain limited with this regime, with a median PFS of 8.1 months and median OS of 20 months. There is no established systemic therapy for patients with SCAC whose disease has progressed following initial first-line treatment.

2.1.2. About the product

Retifanlimab (INCMGA00012; MGA012) is a humanized, hinge-stabilized, IgG4κ monoclonal antibody that recognizes 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 2 ligands, PD-L1 and PD L2.

Retifanlimab 500 mg Q4W IV is approved in the US and EU for the first-line treatment of adults with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation therapy.

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

On 19 October 2020, orphan designation EU/3/20/2343 was granted for retifanlimab for the treatment of anal cancer.

The applicant received CHMP Scientific Advice for the development of retifanlimab in SCAC (EMEA/H/SA/4152/3/2019/II). Advice was given on the development of the phase 2 study INCMGA00012 to support an application for conditional marketing authorization as second line treatment and on Study INCMGA 0012-303, at that time proposed as a confirmatory study from the CHMP on 30 January 2020. The Scientific Advice pertained to the following clinical aspects:

The CHMP agreed on design aspects of the randomized double-blind phase III INCMGA0012-303 study, such as the patient population and eligibility criteria, the choice of carboplatin and weekly paclitaxel as comparators, the assumptions supporting the sample size calculation and the statistical methods.

The CHMP considered overall survival to be the most appropriate primary endpoint in patients with advanced malignancy and limited treatment options and dismal prognosis. However, the acceptability of PFS to support approval would depend on the actual magnitude of PFS benefit and the observed toxicity of the combination treatment. Supportive mature OS data would be expected for the demonstration of the clinical benefit at the time of MAA.

The CHMP considered that whether data would suffice for a B/R assessment in the subgroup of HIV positive patients, would depend on the number of patients recruited, any indication of heterogeneity of response, and whether the applicant can make a scientific argument that overall results are relevant to this subgroup.

A pre-submission meeting for the current procedure was held on 23 September 2024. The most important requests from the Rapporteurs to the applicant were to provide final OS data within the dossier, and to perform granular analyses of the predictive value of PD-L1 expression for retifanlimab efficacy, i.e. provide post-hoc subgroup analyses based on extra PD-L1 expression cut-offs, e.g., 5%, 10%, 20% and/or 50% in the dossier.

2.1.4. General comments on compliance with GLP, GCP

The CSR for study PODIUM-303 states that this study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Guidelines.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Retifanlimab (INCMGA00012) is a humanized, hinge-stabilized, IgG4κ monoclonal antibody, and, in accordance with the EMA ERA Guideline EMEA/CHMP/SWP/4447/00 Rev. 1-Corr.*; 22 Aug 2024), is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

To support this procedure, the MAH submitted five clinical trials (**INCMGA 0012-202**, **INCMGA 0012-101**, **INCMGA 0012-104**, **INCMGA 0012-201**, **INCMGA 0012-203**), in which retifanlimab was administered as monotherapy (previously assessed during initial marketing authorisation application, procedure: EMEA/H/C/006194/0000). Furthermore, one clinical trial (**INCMGA-0012-303**, **PODIUM 303/INTERAACT2**) was submitted, in which retifanlimab was administered in combination with chemotherapy (carboplatin and paclitaxel). The results of these trials were analysed with population pharmacokinetic and exposure-response analyses. No new *in vitro* or *in vivo* clinical pharmacology trials were submitted

GCP

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

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

- Tabular overview of clinical studies

Table 1: Overview of clinical trials submitted in this procedure.

Study	Study Design	Population	N	Study Treatment(s), Regimen, Route of Administration	PK Sampling Timepoints	ADA Sampling Timepoints
INCMGA 0012-303 (POD1UM 303/ INTERAACT 2)	Phase 3, double-blinded	Inoperable, locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy	308	Retifanlimab 500 mg Q4W IV or placebo Q4W IV plus chemotherapy	Retifanlimab in combination with chemotherapy during randomized period Cycle 1 Day 1: preinfusion (within 2 h), within 10 min postinfusion (before dose/IV of other agent[s]) Cycle 2 Day 1: preinfusion (within 24 h)	Retifanlimab in combination with chemotherapy during randomized period Cycle 1 Day 1: preinfusion (within 2 h) Cycles 2, 4, 6, 8, 12 Day 1: preinfusion

Study	Study Design	Population	N	Study Treatment(s), Regimen, Route of Administration	PK Sampling Timepoints	ADA Sampling Timepoints
					Cycle 4 Day 1: preinfusion (within 24 h), within 10 min postinfusion (before dose of other agent[s]) Cycles 6, 8, 12 Day 1: preinfusion (within 24 h)	(within 24 h)
INCMGA 0012-202	Phase 2, open label, single-arm	Advanced or metastatic SCAC	94	Retifanlimab 500 mg Q4W IV	Cycles 1, 6 Day 1: predose, 10 min and 4 h postinfusion Cycles 2, 4, 7 Day 1: predose	Cycle 1, 2, 4, 6 (and every 2 cycles thereafter) Day 1: predose EOTV
INCMGA 0012-101	Phase 1, open label, dose escalation, cohort expansion	Relapsed/ refractory, unresectable locally advanced or metastatic solid tumors	315	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	**Q2W body weight–based dose** Cycle 1 Day 1: predose, EOI, 6 h postinfusion; Days 2, 4, 8: postinfusion Cycle 1 Day 15: predose, EOI Cycle 2 and beyond Day 1: predose, EOI; Day 15: predose, EOI EOTV **Q4W body weight–based dose** Cycle 1 Day 1: predose, EOI, 6 h postinfusion; Days 2, 4, 8, 15: postinfusion Cycle 2 and beyond Day 1: predose, EOI; Day 15: any time EOTV **Q4W flat dose** Cycle 1 Day 1: predose, EOI, 6 h postinfusion; Days 2, 4, 8, 15: postinfusion Cycle 2 and beyond Day 1: predose and EOI EOTV **Q3W flat dose** Cycle 1 Day 1: predose, EOI, 6 h postinfusion; Days 2, 4, 8, 15 postinfusion Cycle 2 Day 1: predose, EOI; Days 8, 15: postinfusion Cycle 3 and beyond Day 1: predose, EOI EOTV	**Q2W body weight–based dose** Cycle 1 Days 1, 15: predose Cycle 2 and beyond Days 1, 15: predose EOTV **Q4W body weight–based dose** Cycle 1 Day 1: predose Cycle 2 and beyond Day 1: predose EOTV **Q4W and Q3W flat doses** Cycle 1 Days 1, 15: predose Cycle 2 and beyond Day 1: predose EOTV
INCMGA 0012104	Phase 1b, openlabel,	Advanced or	6	Retifanlimab 500 mg Q4W	Monotherapy Cycle 1 Day 1: predose,	Monotherapy Cycle 1 Day: 1

Study	Study Design	Population	N	Study Treatment(s), Regimen, Route of Administration	PK Sampling Timepoints	ADA Sampling Timepoints
(retifanlimab monotherapy only)	nonrandomized dose escalation	metastatic solid tumors; Japanese participants		IV	EOI, 6 h postinfusion; Days 2, 8, 15: postinfusion Cycle 2 and beyond Day 1: predose (every cycle until Cycle 8, then every 4 cycles after Cycle 8); EOI (only Cycles 2, 6)	predose Cycle 2 and beyond Day 1: predose (every cycle until Cycle 8 and every 4 cycles after Cycle 8) EOTV
INCMGA 0012-201	Phase 2, openlabel, single-arm	Recurrent locally advanced or metastatic MCC	107	Retifanlimab 500 mg Q4W IV	Cycles 1, 6 Day 1: predose, 10 min and 4 h postinfusion Cycles 2, 4, 7 Day 1: predose	Cycle 1, 2, 4, 6 (and every 2 cycles thereafter) Day 1: predose EOTV
INCMGA 0012-203	Phase 2, openlabel	Advanced or metastatic NSCLC, urothelial carcinoma, renal cell carcinoma, and melanoma	121	Retifanlimab 500 mg Q4W IV	Cycle 1 Day 1: predose, 10 min, 4 h postinfusion Cycles 2, 4*, 6 Day 1: predose and 10 min postinfusion EOTV or 28-day safety follow-up visit *Cycle 4 Day 1: postinfusion (added in Protocol Amendment 2)	Cycles 1, 2, 4, 6 (and every 2 cycles thereafter) Day 1: predose EOTV or 28-day safety followup visit

2.3.2. Pharmacokinetics

Methods

Bioanalytical method – retifanlimab concentration

The bioanalytical methods, validated for determination of retifanlimab concentrations in human serum, used the ELISA and MSD-ECL assay platforms that were described in the assessment reports of the initial marketing authorisation application (DMB-19.155, Syneos – MSD-ECL).

The bioanalytical report for study **INCMGA 0012-303** (DMB-24.122, Syneos) was provided. The longest interval from individual sample draw date to last analysis data was 1127 days. Long-term stability experiments are ongoing (current longest period: 664 days). All samples (n = 1804) were received in acceptable condition and samples were stored at -80 °C, but three samples were removed as these did not reconcile with internal data management. Additionally, one duplicate sample was removed, which translated in 1800 samples included in the bioanalyses. A total of 883 out of these1800 samples concerned placebo samples, which were not to be analysed (although 143 were analysed). A total of 37.9% of samples were reassayed, primarily due to QCs not meeting the acceptance criteria (n = 147), value above the (revised) upper limit of quantification (n = 147), value below the (revised) lower limit of quantification (n = 108).

A total of 75.9% of the samples in the incurred sample reproducibility (ISR) met the acceptance criteria (±30.0% assay variability).

Bioanalytical method - immunogenicity

The immunogenicity screening, neutralising antibody assays and confirmatory assays for the detection and confirmation of (neutralising) antibodies to retifanlimab in human serum were described in the assessment reports of the initial marketing authorisation application (DMB-19.156, Syneos Health).

The immunogenicity report for study **INCMGA 0012-303** (DMB-24.123, Syneos Health / DMB-24.126) were also provided. Limited immunogenicity and no neutralising antibodies were observed. Samples for assessing ADAs were collected from each participant at baseline, as well as at multiple visits prior to retifanlimab infusions for all six clinical studies (See pharmacokinetics in target population section).

Population pharmacokinetic analyses

Aims

The population pharmacokinetic analysis aimed to:

- Update the existing population pharmacokinetic model of retifanlimab with data of the combination therapy with chemotherapy
- Identify predictors of drug exposure and identify subpopulations with altered pharmacokinetic behaviour
- Estimate interindividual variability of retifanlimab pharmacokinetics

Data

Data from six clinical studies (Table 1) were used in this population pharmacokinetic analysis. A total of 949 participants were enrolled and received at least 1 dose of retifanlimab/placebo as of the respective data cutoff dates. The analysis population was defined as all participants who received at least 1 dose of retifanlimab and provided at least 1 evaluable postdose sample for serum PK analysis. A total of 788 participants with 8540 serum retifanlimab concentration records were included in the popPK analysis of retifanlimab. Study **INCMGA 0012-303** was the only study included where retifanlimab was administered in combination with chemotherapy.

Study **INCMGA 0012-303** is a Phase 3 multiregional, multicenter, double-blind randomised study of carboplatin-paclitaxel with retifanlimab or placebo in participants with inoperable locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy. Participants received up to 6 induction cycles (24 weeks) of carboplatin and paclitaxel (80 mg/m^2 on Days 1, 8, and 15) concurrently with retifanlimab 500 mg IV Q4W or placebo IV Q4W. Treatment continued for up to 13 cycles (1 year) in the absence of disease progression, intolerable toxicity, death, withdrawal of consent, lost to follow-up, premature discontinuation of all assigned study drug administration, or for any other reason. Participants assigned to placebo + chemotherapy had the option of receiving open-label retifanlimab monotherapy in a crossover period following blinded ICR documentation of progressive disease.

The pooled population was 61.2% female, had a median age of 64 years (range: 18-94 years), and was primarily White/Caucasian (81.2%). The median body weight and body mass index were 70.1 kg (range: 33.0-133 kg) and 25.6 kg/m^2 (range: 13.5-48.7 kg/m^2), respectively. Serum albumin (median = 40.0 g/L), bilirubin (median = 7.20 µM), and aspartate aminotransferase (median = 21.0 U/L) levels were generally within the normal range. The median value of alkaline phosphatase in Study **INCMGA 0012-104** (248 U/L) was modestly higher than the median for all studies (89.0 U/L). The majority of the 788 participants (87.8%) had normal hepatic function; 93 participants (11.8%) had mild hepatic impairment, 1 participant (0.1%) had moderate hepatic function, and 2 participants (0.3%) had unknown hepatic function. The median value of the estimated glomerular filtration rate (MDRD

equation) was 80.0 mL/min/1.73 m^2, consistent with advanced age and underlying advanced cancers in this population. The majority of the 788 participants had normal renal function (n = 264, 33.4%) or mild renal impairment (n = 354, 44.9%), 151 participants (19.2%) had moderate renal impairment, 4 participants (0.5%) had severe renal impairment, and 16 participants (2.0%) had unknown renal impairment.

Method

The analyses were performed using NONMEM (v7.5; Icon Development Solutions, Ellicott City, Maryland), and the GFortran Compiler v11.0 or later. The first-order estimation and/or first-order conditional estimation method with interaction was used in the model development process. NONMEM runs were executed using PDx Pop® for NONMEM (v5.2.2; Icon Development Solutions). Diagnostic graphs and GAM analysis were performed using Xpose v4.7.1 in R v4.0.3. Visual predictive check and bootstrap were performed with pSN (Uppsala, Sweden).

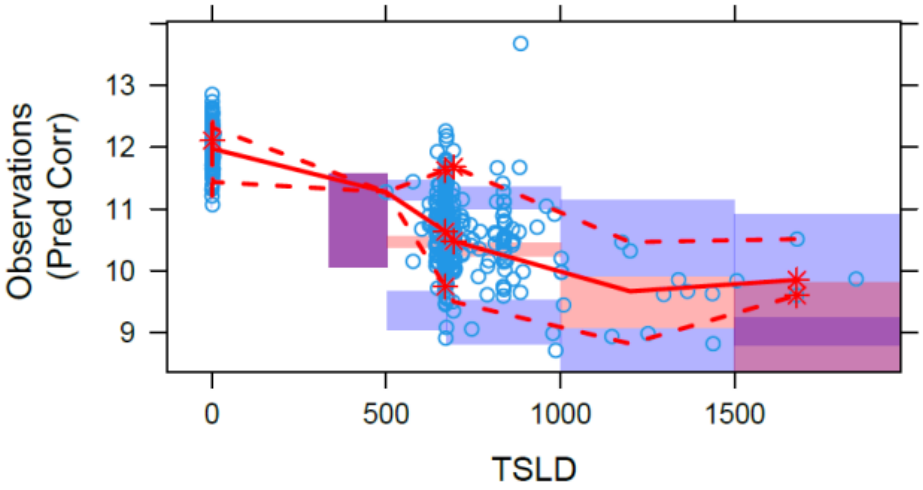
A change in the objective function value of at least 3.84 points (α = 0.05, 1 df) was used to define statistical significance for the addition of a single parameter. Standard goodness-of-fit criteria were used in the analysis.

Previously, a 2-compartment model with first-order and time-varying clearance disposition was developed. Interindividual variability was included on the shared central and peripheral Vc/Vp and CL. The residual error model was mixed additive and proportional on a logarithmic scale. This previous population pharmacokinetic model was validated using prediction-corrected visual predictive checks.

External validation

The performance of the previously developed population pharmacokinetic model for the study **INCMGA 0012-303** is graphically displayed in Figure PK1.

Figure 1: PK1. Prediction-Corrected Visual Predictive Check for the Population Pharmacokinetic Model on the Logarithm Scale – Newly Added Data



Furthermore, model parameters were re-estimated based on the full dataset and the difference in parameter estimates was evaluated (Table 2).

Table 2: Comparison of model parameters between the previously developed "final" model and the re-estimation of this model using the updated population pharmacokinetic dataset.

Parameter	Typical value		Relative Change
	Final Model	New model	
CL (L/h)	0.0122	0.0118	−3.28%
V_c (L)	3.76	3.73	−0.80%
Q (L/h)	0.0285	0.0276	−3.16%
V_p (L)	2.64	2.76	4.55%
I_{max}	−0.232	−0.24	3.45%
T_{50} (day)	86.2	88.2	2.32%
Hill coefficient	2.61	2.59	−0.77%
Body weight (median = 72 kg) on V_c	0.401	0.423	5.49%
Body weight (median = 72 kg) on CL	0.553	0.629	13.7%
Albumin (median = 40 g/L) on CL	−0.854	−0.777	−9.02%
Sex (female) on V_c	−0.153	−0.147	−3.92%
Albumin (median = 40 g/L) on V_c	−0.390	−0.38	−2.56%
Tumor burden (median tumor diameter = 60 mm) on CL	0.0416	0.0351	−15.6%
ECOG (> 0 vs = 0) on CL	0.0534	0.0636	19.1%
Body weight (median = 72 kg) on V_p	0.470	0.366	−22.1%
EC vs other on I_{max}	0.664	0.534	−19.6%
NSCLC on CL	0.165	0.194	17.6%
STD (I_{max})	0.106	0.106	0.00%
Correlated (I_{max}, CL)	−0.0511	−0.0499	−2.35%
IIV (CL)	0.0984	0.103	4.67%
Correlated (CL, V_c)	0.0192	0.0197	2.60%
IIV (V_c)	0.0319	0.0313	−1.88%
Correlated (I_{max}, V_p)	0	0	—
Correlated (CL, V_p)	0	0	—
Correlated (V_c, V_p)	0.0178	0.0182	2.25%
IIV (V_p)	0.126	0.119	−5.56%
Residual error	0.153	0.159	3.92%
Additive residual (ng/mL)	1760	1820	3.41%

Pharmacokinetics in target populations

As the previous pharmacokinetic model was considered validated with the updated dataset, empirical Bayesian estimates of the PK parameters and PK metrics were generated for each individual participant from all studies included in the analysis (Table 3).

Table 3: Summary statistics of steady-state retifanlimab empirical Bayesian pharmacokinetic parameters for exposure-response analysis

Study Parameter	Statistic	1 mg/kg Q2W	3 mg/kg Q2W	3 mg/kg Q4W	10 mg/kg Q2W	10 mg/kg Q4W	375 mg Q3W	500 mg Q4W	750 mg Q4W
AUC_{ss} (day*mg/L)	n	3	144	10	8	6	15	587	15
	Mean (STD)	196 (50.4)	857 (312)	903 (215)	2680 (595)	3340 (472)	1480 (495)	2410 (935)	2970 (889)
	Median	206	800	949	2670	3370	1330	2280	2660
	Min, max	142, 241	182, 2010	597, 1130	1890, 3500	2750, 3990	780, 2570	788, 10300	1660, 4380
	Q1, Q3	142, 241	654, 1010	668, 1110	2190, 3160	2880, 3690	1100, 1770	1810, 2770	2340, 3840
	Geometric mean (CV)	192 (27.8)	803 (38.1)	877 (26.1)	2620 (23.3)	3310 (14.4)	1410 (33.0)	2270 (35.1)	2840 (31.5)
$C_{max,ss}$ (mg/L)	n	3	144	10	8	6	15	587	15
	Mean (STD)	25.2 (6.38)	103 (30.1)	84.0 (12.5)	329 (74.0)	298 (49.2)	154 (41.5)	203 (51.8)	258 (61.4)
	Median	27.4	97.2	82.2	312	272	149	197	251
	Min, max	18.0, 30.2	42.4, 205	67.8, 102	229, 443	260, 384	86.2, 230	89.7, 525	164, 376
	Q1, Q3	18.0, 30.2	80.6, 123	72.6, 96.6	276, 392	270, 332	129, 189	166, 235	201, 300
	Geometric mean (CV)	24.6 (28.0)	98.7 (29.7)	83.1 (14.8)	322 (22.8)	295 (15.6)	148 (28.1)	197 (25.4)	252 (24.2)
$C_{min,ss}$ (mg/L)	n	3	144	10	8	6	15	587	15
	Mean (STD)	9.22 (2.46)	43.1 (19.2)	16.2 (6.72)	133 (35.8)	61.6 (13.8)	41.9 (18.4)	49.0 (28.8)	58.1 (25.3)
	Median	9.70	40.1	17.7	136	67.5	37.4	43.5	56.3
	Min, max	6.55, 11.4	3.41, 118	5.85, 24.8	75.7, 187	38.7, 76.4	19.1, 87.6	4.97, 315	24.7, 101
	Q1, Q3	6.55, 11.4	30.8, 52.9	9.47, 21.8	108, 155	51.4, 67.9	27.2, 51.5	31.1, 59.0	30.6, 86.6
	Geometric mean (CV)	8.98 (29.1)	39.0 (50.5)	14.6 (55.7)	128 (29.7)	60.1 (25.6)	38.6 (43.0)	43.1 (54.0)	52.8 (49.4)

Retifanlimab belongs to the class of IgG antibodies that are administered parenterally and cleared by protein catabolism; thus, extrinsic factors, such as food and drug-drug interactions, are not anticipated to affect the exposure of retifanlimab. Carboplatin and paclitaxel were used in Study INCMGA 0012-303 as background therapy. The coadministration of carboplatin and paclitaxel was explored as a time-dependent predictor for PK variability in the population pharmacokinetic model. Carboplatin and paclitaxel coadministrations were not identified as a significant predictor for PK parameter variabilities; as a result, no dose modifications were recommended. Furthermore, Japanese versus non-Japanese and absence/presence of HIV was not estimated to affect the pharmacokinetics.

Immunogenicity

As of the data cutoff date for **Study INCMGA 0012-303**, 1269 human serum samples from 305 evaluable participants (152 from placebo + chemotherapy and 153 from retifanlimab + chemotherapy) were analysed for anti-retifanlimab antibodies. At the sample level, 24 (1.9%) positive ADA samples were detected. Seven (7) (0.6%) were baseline positive and 17 (1.3%) were post-baseline positive (Table 4). The majority were from the placebo group. No post-baseline positive samples were observed in the retifanlimab + chemotherapy treatment group.

At the participant level, excluding the inconclusive participants based on drug tolerance level (DTL), the total number of negative and positive participants was 291 (95.4%), including 8 ADA-positive participants. Three (1.0%) of the 8 ADA-positive participants had nontreatment emergent ADAs with only baseline positive ADAs. Five (1.6%) of the 8 participants had treatment emergent positive ADAs, which were persistently positive.

As of the data cutoff date for Study **INCMGA 0012-303**, 24 human serum samples from 8 participants were ADA positive and were analysed for NAb anti-retifanlimab antibodies. None of the participants were positive for NAb. Due to the lack of ADA-positive and NAb-positive participants from Study **INCMGA 0012 303**, the assessment of the ADA/NAb status on clinical efficacy was not performed.

Table 4: Summary of Sample Immunogenicity Results for INCMGA 0012-303

ADA Status	All Treatment	Study INCMGA 0012-303	
		Placebo + Chemotherapy	Retifanlimab + Chemotherapy
Total number of samples	1269	620	649
Negative	1245 (98.1%)	597 (96.3%)	648 (99.8%)
Positive	24 (1.9%)	23 (3.7%)	1 (0.2%)
Baseline positive	7 (0.6%)	6 (1.0%)	1 (0.2%)
Postbaseline positive	17 (1.3%)	17 (2.7%)	0
Neutralizing ADA positive	0	0	0

2.3.3. PK/PD modelling

Exposure-response analyses

Aims

The exposure-response analysis aimed at characterising the relationship between retifanlimab exposure (C_{max}, C_{min}, AUC) and response in participants with SCAC that received chemotherapy:

- Efficacy: Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), duration of response (DOR), and disease control rate (DCR)
- Safety: adverse events of special interest (AESIs) and possibly frequently occurring treatment-emergent adverse event (TEAEs), Grade ≥ 3 adverse events (AEs), and laboratory abnormalities.

Data

The data of **INCMGA 0012-303** were used for the exposure-response analysis. Exposure metrics were derived based on the empirical bayes estimates. A total of 302 participants (including 150 participants in the retifanlimab + chemotherapy group and 152 participants in the placebo + chemotherapy group) were included in the E-R efficacy dataset for ORR, DCR, DOR and PFS. A total of 302 participants with SCAC (including 150 in the retifanlimab + chemotherapy group and 152 in the placebo + chemotherapy group) were included in the E-R safety analysis dataset.

Method

Logistic regression or time-to-event type models were used to evaluate the relationship between exposure metrics and outcomes of interest. PROC PHREG (SAS v9.4) was used for Cox proportional hazards regression. The PROC LIFETEST (SAS v9.4) was used for log-rank tests.

Results - efficacy

The $C_{min,ss}$ showed a positive correlation with ORR; however, it was not a significant predictor of ORR after covariate evaluation. The disease status (locally recurrent vs metastatic), ECOG score (0 vs > 0), duration of chemotherapy, and duration of retifanlimab treatment were identified as predictors for ORR.

The C_{min1} was identified as the predictor for DCR in the final model. The effect of C_{min1} was driven by lower DCR rate in first quartile and > 90% response rate in the last 3 quartiles. The lower DCR rate in the first quartile in the treatment group may have been due to a short duration of chemotherapy treatment and a limited number of participants. Disease severity (ECOG score) and duration of

chemotherapy treatment impacted DCR (i.e., a longer DCR was associated with less severe disease and longer duration of chemotherapy).

The C_{max1} was identified as the predictor for DOR. The impact of C_{max1} was no longer significant after the inclusion of other covariates. The treatment, ECOG score, race, and sum of tumour diameter were selected as the predictors for the hazard ratio by the Cox proportional hazards model.

The C_{min1} was a predictor for PFS; the longer PFS, the higher the C_{min1}. The similarity between participants in the first quartile and the placebo + chemotherapy treatment group may be due to the limited number of participants. Disease severity (e.g., ECOG score and sum of tumour diameter) and duration of chemotherapy treatment impacted PFS (i.e., longer PFS was associated with less severe disease and longer duration of chemotherapy).

Overall survival was only evaluated in the retifanlimab + chemotherapy treatment group. The C_{min1} effected the OS; the higher C_{min1} results, the longer the OS. Disease severity (e.g., ECOG score and sum of tumour diameter) and duration of chemotherapy treatment impacted OS (i.e., longer OS was associated with less severe disease and longer duration of chemotherapy).

Results – safety

For the 34 TEAEs with a frequency > 10%, there was no statistically significant correlation identified for retifanlimab exposures. The only TEAE evaluated as a statistically significant correlation was between retifanlimab AUC_1 and paraesthesia. The C_{min1} and C_{max1} were identified to have a significantly positive association with AESIs and irAEs, respectively, by univariate logistic regression analysis. However, these events were no longer statistically significant after the inclusion of treatment and duration of chemotherapy, which were the cause of higher AESI/irAE incidents.

Flat E-R curves were observed for ≥ Grade 3 treatment-related TEAEs and ≥ Grade 3 TEAEs.

The C_{min1} was identified to have a significantly positive association with any ADR and Group ADR-neutropenia. The AUC_1 was identified to have a significantly positive association with Group ADR-rash. Group ADR-rash incidents were similar among the 4 quartiles. The final model included treatment and baseline haemoglobin. No statistical relationship existed between Group ADR-lymphopenia and retifanlimab exposure.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical method: The bioanalytical method validation was previously assessed in the context of the initial MAA (EMEA/H/C/006194/0000). The bioanalytical report of the newly submitted clinical trial (INCMGA 0012-303) indicated that this method may be suboptimal as many repeat analyses were required for samples above/below the upper/lower limit of quantification, failure of QC samples, samples analysed outside the long-term stability period and failure of the incurred sample reanalysis. Thirty-seven (37) samples (3.8%) were measured outside the demonstrated long-term stability. As stability testing is still ongoing, it remains uncertain whether the clinical samples exceeding the established storage stability can be considered unstable or not. However, this is not expected to have a relevant impact on the outcome of the PK analysis.

An additional assay validation study (TRS-24.21.) was performed for analysis of PD-L1 expression in SCAC tumour samples from Study INCMGA 0012-303. Based on the validation results the assay can be regarded as adequate for the analysis of PD-L1 expression in SCAC tumour samples and therefore it was used for participant stratification.

Immunogenicity: The observed immunogenicity results do not indicate an altered immunogenicity during concomitant administration of carboplatin/paclitaxel in the SCAC population compared to the monotherapy MCC population. Overall, the immunogenicity potential is low.

Pharmacokinetics in the target population: The population pharmacokinetic analysis was mainly limited to an external validation of a previously developed population pharmacokinetic model on the new dataset. Although the binning of the prediction-corrected visual predictive check is mainly focussed on the later (less relevant time points), no strong deviations from the median and variability can be observed. This observation is strengthened by the re-estimation of the model parameters that did not show strong deviations from the previously estimated pharmacokinetic parameters (although it has not been mentioned by the MAH whether the data would be informative enough to quantify strong deviations in pharmacokinetic parameters). These should be considered limitations of the current approach. Nonetheless, it can be concluded that there is no indication of a different pharmacokinetic behaviour in patients with SCAC using chemotherapy versus patients with MCC. The proposed update of section 5.2 of the SmPC based on these new results is considered acceptable.

Exposure-response analysis: The exposure-response analyses should be interpreted with caution as only one dose level was evaluated in the pivotal phase 3 trial. Furthermore, the pharmacokinetics display a time-dependent change in clearance that is presumably caused by target-mediated drug disposition. Any findings of correlations between pharmacokinetic parameters after first dose ("1") could indicate differences in the amount of target available at baseline and thus indirectly be a measure of disease state. The data provided by the model does not influence the proposed indication or posology.

2.3.5. Conclusions on clinical pharmacology

There is no indication of a different pharmacokinetic behaviour of retifanlimab in patients with SCAC using the combination of retifanlimab + chemotherapy versus patients with MCC.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study for the combination of retifanlimab plus chemotherapy as first line treatment in SCAC was performed. The proposed retifanlimab dose of 500mg Q4w is the same as the posology for the authorized MCC indication.

2.4.2. Main study

INCMGA 0012-303 (PODIUM-303/InterAACT 2) is an ongoing, phase 3, double-blind study comparing retifanlimab in combination with carboplatin and paclitaxel to placebo plus chemotherapy in adult patients with inoperable locally recurrent or metastatic SCAC.

Methods

Study participants

Inclusion criteria:

- Are 18 years of age or older (or as applicable per local country requirements).
- Histologically or cytologically verified, inoperable locally recurrent or metastatic SCAC.
- No prior systemic therapy other than the following:

  a. Chemotherapy administered concomitantly with radiotherapy as a radiosensitizing agent is permitted.

  b. Prior neoadjuvant or adjuvant therapy if completed ≥ 6 months before study entry.
- Has measurable disease per RECIST v1.1 as determined by local site investigator/radiology assessment. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- Able and willing to provide adequate tissue sample and whole blood sample with central testing result prior to randomization. Biopsy for archival samples should have occurred within 9 months prior to randomization.
- ECOG performance status 0 to 1.
- If HIV-positive, then must be stable as defined by: a. CD4+ count ≥ 200/μL, b. Undetectable viral load per standard of care assay, c. Receiving antiretroviral therapy (ART/HAART) for at least 4 weeks prior to study enrollment, and have not experienced any HIV-related opportunistic infection for at least 4 weeks prior to study enrollment.
- Willingness to avoid pregnancy or fathering children.

Exclusion criteria:

- Has received prior PD-(L)1 directed therapy
- Has received prior radiotherapy with or without radiosensitizing chemotherapy within 28 days of Cycle 1 Day 1 except for palliative radiation (30 Gy or less) which is restricted for 14 days of Cycle 1 Day 1 (note: all toxicities associated should have resolved to Grade ≤ 1).
- Participants with laboratory outside of the protocol defined ranges.
- History of second malignancy within 3 years (with exceptions).
- Clinically significant pulmonary, cardiac, gastrointestinal or autoimmune disorders.
- Active bacterial, fungal, or viral infections, including hepatitis A, B, and C and IV antibiotic use within 7 days of Cycle 1 Day 1.
- Receipt of a live vaccine within 28 days of planned start of study therapy.
- History of organ transplant, including allogeneic stem cell transplantation.
- Known active CNS metastases and/or carcinomatous meningitis.
- Known hypersensitivity to platinum, paclitaxel, another monoclonal antibody, or any of the excipients that cannot be controlled with standard measures (eg, antihistamines, corticosteroids).
- Participant is pregnant or breastfeeding.
- Current use of protocol defined prohibited medication.
- Has pre-existing peripheral neuropathy that is ≥ Grade 2 by CTCAE v5.

- Inability or unlikely, in the opinion of the investigator, to comply with the Protocol requirements

Treatments

Participants were randomized to retifanlimab 500 mg IV Q4W + chemotherapy or placebo Q4W + chemotherapy.

Participants received up to 6 induction cycles (24 weeks) of carboplatin (AUC5 on Day 1) and paclitaxel (80 mg/m2 on Days 1, 8, and 15) concurrently with retifanlimab or placebo. Retifanlimab or placebo was administered for up to 13 cycles (1 year) in the absence of disease progression or intolerable toxicity. Retifanlimab or placebo was administered by IV infusion 30 minutes prior to the scheduled chemotherapy on Day 1 of each 28-day cycle.

Pre-infusion prophylaxis for retifanlimab was recommended only for participants who had previous systemic reactions to protein product infusions or when recommended by institutional policy. Pre-medications prior to administration of chemotherapy agents were allowed in accordance with prescribing information and standard practice. Highly active ART was to be continued for participants who were known to be HIV positive.

The study consists of 4 periods: screening, randomized study drug treatment, optional crossover treatment, and follow-up (safety, disease status, and survival).

During randomized study drug treatment, participant management followed either RECIST v1.1 or iRECIST, with the decision to treat beyond conventional RECIST progression documented in the study file.

Participants who received placebo in combination with chemotherapy who had documented disease progression by RECIST v1.1 verified by BICR could receive open-label retifanlimab monotherapy for up to one year (13 cycles) in the optional crossover period.

The safety follow-up period began once a participant discontinued all assigned study drugs. Participants were followed for AEs until at least 28 days after the last dose of study drug regardless of whether a new anticancer therapy was initiated. Immune related AEs were collected for 90 days after the last dose of retifanlimab or placebo, regardless of continuation of chemotherapy during induction cycles or start of a new anticancer therapy.

The disease status follow-up period began once a participant discontinued study treatment for a reason other than PD. Participants were followed for disease status until the start of new anticancer therapy, second PD (verified by BICR), death, the end of the study, or lost to follow up.

The survival follow-up period began once a participant received the last dose of study drug/treatment, had confirmed disease progression, or started a new anticancer therapy. Survival follow-up was to continue until death, withdrawal of consent, or study completion.

Objectives

The primary objective was to compare the efficacy of carboplatin-paclitaxel with retifanlimab versus carboplatin-paclitaxel with placebo in participants with inoperable locally advanced or metastatic SCAC not previously treated with systemic chemotherapy.

Secondary objectives were to evaluate safety and PK of the combination of carboplatin-paclitaxel with retifanlimab and to compare PFS2 of carboplatin-paclitaxel with retifanlimab or placebo.

Exploratory objectives were to evaluate efficacy of crossover retifanlimab monotherapy, to assess biomarkers predictive of response to retifanlimab, to assess immunogenicity, to evaluate changes in HRQoL from baseline and to assess impact of retifanlimab on HIV control.

Outcomes/endpoints

The primary endpoint is PFS, defined as the time from the date of randomization until disease progression according to RECIST v1.1 as assessed by BICR or death from any cause.

A formal estimand for the primary endpoint was not prespecified. Censoring rules were provided and are described in the statistical methods section. Based on these censoring rules, the estimand corresponding to the primary objective can be inferred as follows:

In adults with inoperable locally advanced or metastatic SCAC not previously treated with systemic chemotherapy, what is the difference between carboplatin-paclitaxel in combination with retifanlimab versus carboplatin-paclitaxel alone in time to disease progression or death, irrespective of treatment discontinuation and assuming a hypothetical scenario where alternative anti-cancer therapies are not available?

Key secondary endpoint is OS, defined as the time from the date of randomisation to the date of death from any cause. For the primary OS analysis, deaths were considered regardless of the receipt of any new anticancer therapy, including following crossover from placebo to retifanlimab.

Additional secondary efficacy endpoints include comparison of ORR, DOR, and DCR according to RECIST v1.1 by BICR.

- Objective response rate is defined as the percentage of participants with CR or PR at any postbaseline visit before the first PD or new anticancer therapy.
- Duration of response is defined as the time from first-documented response (CR or PR) that is subsequently confirmed to the time of first-documented PD or death from any cause.
- Disease control rate is defined as the proportion of participants with an objective response (CR or PR) or SD.

Safety endpoints included the number of participants experiencing AEs (graded per CTCAE v5.0) and number of participants discontinuing study drug due to AEs.

Population PK parameters included Cmax, Tmax, Cmin, and AUC0-t.

PFS2 was defined as the time from randomization to subsequent disease progression after initiation of new anticancer therapy (second disease progression), or death from any cause, whichever occurs first, as assessed by investigator review using RECIST v1.1.

Objective response rate – crossover (ORR-CO) was defined as the percentage of participants in crossover treatment having a CR or PR, according to RECIST v1.1 as assessed by investigator.

Biomarker endpoints included blood and/or tumor analytes, immune cell profile and viral profiles.

HRQoL was evaluated using the EORTC QLQ-C30, the EuroQoL-5D and the Quality of Life Questionnaire for Anal Cancer, with assessments scheduled to align with tumor response evaluation.

HIV viral load and CD4+ counts were monitored in participants who were known to be HIV positive.

Sample size

It was assumed that the median PFS would be 8 months with the carboplatin-paclitaxel arm (Rao et al 2018). It was expected that treatment with retifanlimab would result in a 33% reduction in hazard rate (corresponding to an increase in median PFS from 8 months to 12 months under exponential model assumption).

If the true HR is 0.67 (under alternative hypothesis), a total of 207 PFS events would be required to have 83% power at a 1-sided overall 2.5% level of significance to reject the null hypothesis (HR = 1) using a log-rank test. Considering a recruitment period of 32 months at a uniform rate of 10 participants/month with a 6-month ramp up period, approximately 300 participants were to be randomized to the 2 treatment arms in a 1:1 ratio, assuming monthly dropout rate of 2% from exponential distribution for PFS.

It was assumed that the median OS would be 20 months with the chemotherapy arm (Rao et al 2018). It was expected that treatment with retifanlimab would result in a 33% reduction in hazard rate (corresponding to an increase in median OS from 20 months to 30 months under exponential model assumption).

If the true HR is 0.67 (under alternative hypothesis), a total of approximately 300 participants (around 165 OS events) would provide around 73% power at a 1-sided overall 2.5% level of significance to reject the null hypothesis (HR = 1) using a log-rank test. The power estimation assumes 1% dropout from exponential distribution for OS.

Randomisation

Randomisation to retifanlimab 500 mg IV Q4W + chemotherapy or placebo Q4W + chemotherapy was 1:1. Randomisation was stratified by PD-L1 expression (< 1% vs ≥ 1%), region (AUS/EU/NA/UK vs ROW), and extent of disease (locally recurrent vs metastatic).

A central laboratory was used for confirmation of PD-L1 status and stratification using the SP263 PD-L1 (Ventana) assay. PD-L1 expression was evaluated using a modified SP263 scoring algorithm that independently assesses PD-L1 expression in tumour cells (TC%) and immune cells (IC%) and is validated for SCAC. Participants with PD-L1–negative or non-evaluable tumours were grouped into the PD-L1 <1% stratum. The modified SP263 algorithm used in the PODIUM-303 study provides a close approximation to the proprietary CPS-based categorization.

Blinding (masking)

The study was double-blinded. Blinding of investigators and study personnel was continued following the primary analysis of PFS, until the final analysis of OS.

Statistical methods

Analysis sets

The analysis sets are provided in Table 5.

Table 5: Analysis populations PODIUM-303

Population	Description
FAS	The FAS includes all randomized participants. According to the intent-to-treat principle, participants were analyzed according to the treatment and strata they were assigned during randomization. The FAS was the primary population for all efficacy analyses and was used for the summary of demographics, baseline characteristics, and participant disposition.
Safety	The safety population includes all randomized participants who received at least 1 dose of study treatment. Treatment groups for this population were determined according to the actual treatment the participant received regardless of assigned study treatment. All safety analyses were conducted using the safety population.
CAS	The CAS includes all participants randomized to Group A, who received at least 1 dose of placebo and then crossed over and received at least 1 dose of retifanlimab. The CAS was used for all analyses during the crossover treatment period.

Analysis methods

Progression-free survival: The stratified log-rank test was used to compare PFS between treatment groups in the FAS at a 1-sided 2.5% level of significance, stratified for region, PD-L1 expression, and extent of disease. The strata identified in the randomization process were to be used for the analysis. Progression-free survival will be analysed using a stratified log-rank test at an overall 1-sided 2.5% level of significance in the FAS population; this will be done according to how the treatment group participants were randomized and the strata they were assigned during randomization. The HR and its 95% CI will be estimated based on the stratified Cox regression model using the same stratification factors as for the log-rank test with Efron's method (1977) accounting for ties in event times.

The censoring rules applied for the primary PFS analysis are provided in Table 6.

Table 6: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Day 1 (date of randomization)
No valid postbaseline response assessments in the absence of death prior to first scheduled tumor assessment	Censored	Day 1 (date of randomization)
Progression documented between scheduled response assessments	Progressed	Date of first objective response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE or missing)
Study withdrawal for undocumented progression	Censored	Date of last valid radiologic assessment (not NE or missing)
Study withdrawal for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not 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 after missing 2 or more consecutive scheduled tumor assessments	Censored	Date of last valid radiologic assessment (not NE or missing) prior to missed assessments

Two sensitivity analyses were planned: The unstratified log-rank test for PFS and an alternative definition of an event for which study withdrawal due to clinical progression and death or documented progression by BICR after more than 1 missed scheduled tumour assessment were to be considered events for PFS.

Overall survival: The efficacy analysis of OS comparing the 2 treatment groups in the FAS was evaluated by a stratified log-rank test at an overall 1-sided 2.5% level of significance stratified in the same manner as PFS. Kaplan-Meier curves, medians, and 95% CIs of the median OS were to be presented for each treatment group. The HR for OS was to be calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as the log-rank test (ie, with Efron's likelihood approximation to account for ties in event times).

Other secondary endpoints: The ORR and its exact 95% CI for each treatment group was to be presented. Overall response rate was compared between treatment arms using the stratified CMH test. The 95% CI for odds ratio between the 2 randomized treatment groups was to be computed using the normal approximation to the binomial distribution.

Analysis of DOR was to be based on the FAS and only be summarized for participants who responded to the treatment. If a participant did not have an event, DOR was censored at the date of the last adequate tumour assessment before data cutoff or new anticancer therapy, following the same algorithm as censoring of PFS. The Kaplan-Meier estimate of the distribution function will be constructed for DOR. The estimated median, along with 95% CIs, will be reported.

Exploratory endpoints: Health-related quality of life will be assessed using standard instruments (EORTC QLQ-C30, QLQ-ANL27 and EQ-5D-5L) and summarised according to treatment group. The number of participants completing each questionnaire and the number of missing or incomplete assessments were to be summarized by each treatment group for each scheduled assessment timepoint for the questionnaires (ie, compliance rate). No formal statistical tests will be performed on

PRO data, and hence no multiplicity adjustment was applied. Descriptive statistics were to be used to summarise the scored scales at each scheduled assessment timepoint.

Error probabilities, adjustment for multiplicity and interim analyses

The level of significance for the primary and key secondary endpoints of PFS and OS, respectively, were controlled at 1-sided 2.5%. A 1-sided 2.5% level of significance was to be initially assigned to the PFS endpoint. If the hypothesis testing of the PFS endpoint was rejected, the alpha was to be allocated to test the OS endpoint. Within the OS endpoints, the Type I error was to be controlled by a group sequential design with Lan-DeMets (O'Brien and Fleming 1979) alpha spending function. If both the PFS and OS tests indicate statistical significance, ORR, according to RECIST v1.1 by BICR, will be tested in an alpha-controlled manner.

For overall survival, the interim analysis was to be performed at the time of the PFS analysis (estimated number of events 132) and the final OS analysis planned at 165 events.

Results

The data cutoff date for the primary efficacy analysis of the primary endpoint of PFS based on BICR was 15 April 2024. An interim analysis of OS at this DCO is also provided.

Participant flow

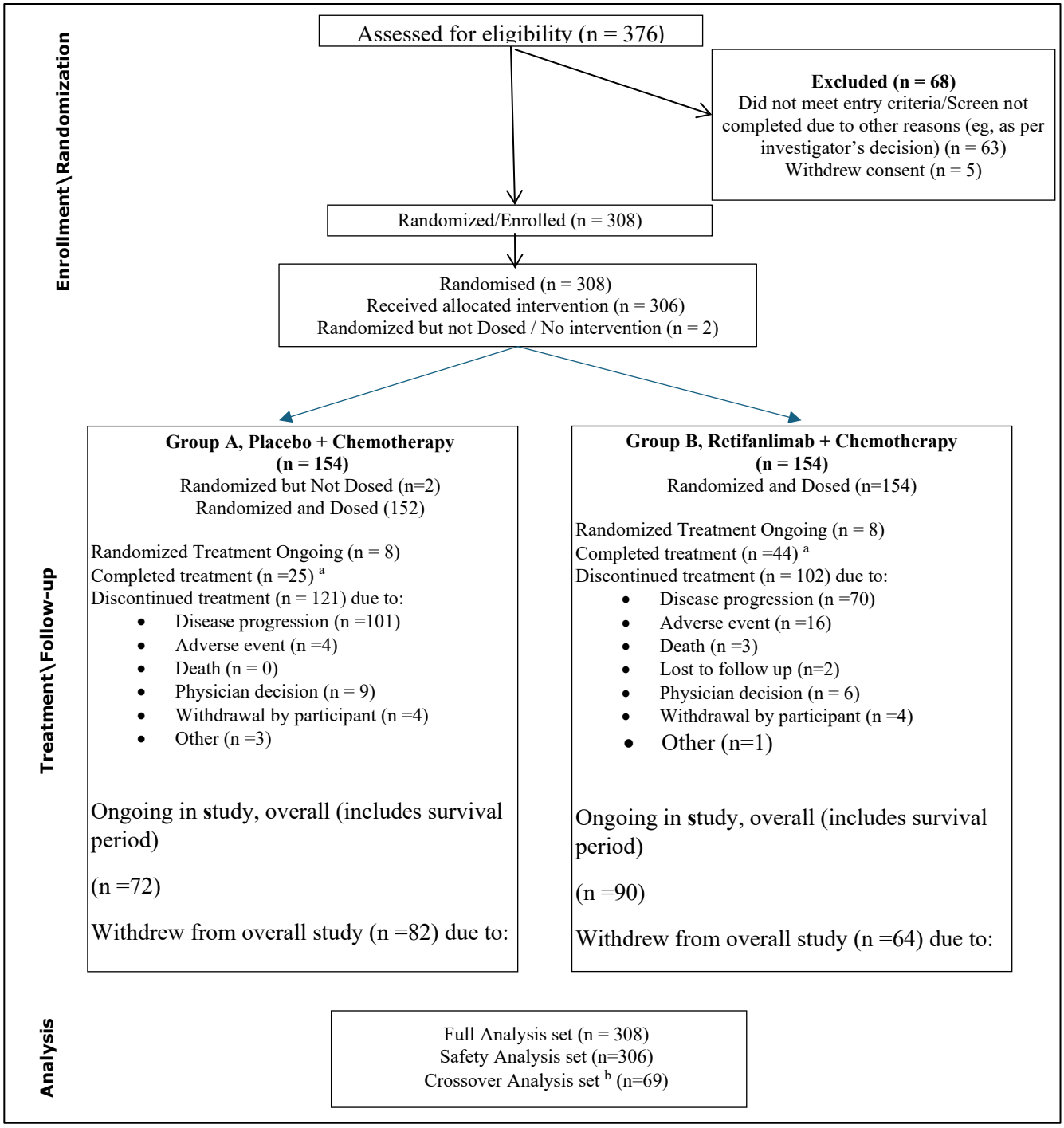
A total of 376 patients were screened for the study, of which 60 (16%) were not randomized due to screen failure (Table 7). The most frequent reason for screen failure was lack of a biopsy sample to centrally confirm PD-L1 status prior to randomization.

Table 7: Reasons for screen failure

Inclusion Criterion	Description	Number of Failures
1	Able to comprehend and willing to sign a written ICF for the study	3
3	Histologically or cytologically verified, inoperable locally recurrent or metastatic SCAC	4
5	Has measurable disease per RECIST v1.1 as determined by local site investigator/radiology assessment	4
6	Able and willing to provide adequate tissue sample and whole blood sample with central testing result prior to randomization. Biopsy for archival samples should have occurred within 9 months prior to randomization	13
7	ECOG performance status 0 to 1	7
8a	If HIV-positive, then must be stable as defined by: CD4+ count ≥ 200/μL	6
	All Inclusion Criteria	37
Exclusion Criterion	**Description**	**Number of Failures**
2	Has received prior radiotherapy with or without radiosensitizing chemotherapy within 28 days of Cycle 1 Day 1; or 14 days for palliative radiotherapy (30 Gy or less) that is not directed to the pelvic region.	1

3e	AST > 2.5 × ULN or > 5 × ULN for participants with liver metastases	1
3f	Bilirubin ≥ 1.5 × ULN unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin.	1
3g	CrCl < 50 mL/min calculated by Cockcroft-Gault equation (glomerular filtration rate can also be used in place of CrCl)	3
4	Known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 3 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy or cancers from which the participant has been disease-free for > 1 year, after treatment with curative intent	2
6	Evidence of interstitial lung disease or active noninfectious pneumonitis	1
8	Known active CNS metastases and/or carcinomatous meningitis	2
9	Known active HAV, HBV, or HCV infection, as defined by elevated transaminases with the following serology: positivity for HAV IgM antibody, anti–HCV, anti–HBc IgG or IgM, or HBsAg (in the absence of prior immunization)	1
10	Active infections requiring systemic therapy, or IV antibiotic use up to 7 days before Cycle 1 Day 1. Note: If required by country or local regulations to be tested for COVID-19 during screening, a participant should be excluded if they have a positive test result for SARS CoV-2 infection until both the retest result is negative and clinical recovery is obtained	6
17	Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data	8
	All Exclusion Criteria	26

Figure 2: PODIUM-303 participant flow



[a] Completed Protocol-specified treatment period of 1 year (13 cycles)
[b] Crossover Analysis Set: all eligible participants who were randomized to placebo + chemotherapy (Group A) and received at least 1 dose of placebo and who then crossed over and received at least 1 dose of retifanlimab.

As of the data cutoff date, 16 participants (5.2%) continued to receive randomized study treatment. 72.4% had discontinued study treatment, including 102 participants (66.2%) in the retifanlimab + chemotherapy group and 121 participants (78.6%) in the placebo + chemotherapy group, the most common reason for treatment discontinuation was disease progression (Table 8).

Table 8: Participant disposition (Full Analysis Set)

Variable, n (%)	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)	Total (N = 308)
Participants treated	152 (98.7)	154 (100.0)	306 (99.4)
Participants who completed randomized treatment	25 (16.2)	44 (28.6)	69 (22.4)
Participants with ongoing randomized treatment	8 (5.2)	8 (5.2)	16 (5.2)
Participants who discontinued randomized treatment	121 (78.6)	102 (66.2)	223 (72.4)
Primary reason			
Disease progression	101 (65.6)	70 (45.5)	171 (55.5)
AE	4 (2.6)	16 (10.4)	20 (6.5)
Death	0 (0.0)	3 (1.9)	3 (1.0)
Lost to follow-up	0 (0.0)	2 (1.3)	2 (0.6)
Physician decision	9 (5.8)	6 (3.9)	15 (4.9)
Withdrawal by participant	4 (2.6)	4 (2.6)	8 (2.6)
Other	3 (1.9)	1 (0.6)	4 (1.3)
Participants who received crossover treatment	69 (44.8)	0 (0.0)	69 (22.4)
Participants ongoing in overall study	72 (46.8)	90 (58.4)	162 (52.6)
Participants who withdrew from overall study	82 (53.2)	64 (41.6)	146 (47.4)
Primary reason			
Death	72 (46.8)	52 (33.8)	124 (40.3)
Lost to follow-up	2 (1.3)	4 (2.6)	6 (1.9)
Physician decision	2 (1.3)	1 (0.6)	3 (1.0)
Withdrawal by participant	5 (3.2)	6 (3.9)	11 (3.6)
Other	1 (0.6)	1 (0.6)	2 (0.6)
Participants ongoing in study (randomized period)	40 (26.0)	90 (58.4)	130 (42.2)
Participants who withdrew from study (randomized period)	45 (29.2)	64 (41.6)	109 (35.4)
Primary reason			
Death	37 (24.0)	52 (33.8)	89 (28.9)
Lost to follow-up	0 (0.0)	4 (2.6)	4 (1.3)
Physician decision	2 (1.3)	1 (0.6)	3 (1.0)
Withdrawal by participant	5 (3.2)	6 (3.9)	11 (3.6)
Other	1 (0.6)	1 (0.6)	2 (0.6)

In total, 69 participants (44.8%) in the placebo + chemotherapy group had crossed over into the optional crossover treatment period following BICR-confirmed disease progression (Table 8).

Table 9: Summary of participant disposition during the crossover treatment period (Crossover Analysis Set)

Variable, n (%)	Retifanlimab Monotherapy (N = 69)
Participants who received crossover treatment	69 (100.0)
Participants who completed crossover treatment	2 (2.9)
Participants with ongoing crossover treatment	9 (13.0)
Participants who discontinued crossover treatment	58 (84.1)
Primary reason	
Disease progression	55 (79.7)
AE	1 (1.4)
Death	1 (1.4)
Physician decision	1 (1.4)
Participants ongoing in study	32 (46.4)
Participants who withdrew from study (crossover period)	37 (53.6)
Primary reason	
Death	35 (50.7)
Lost to follow-up	2 (2.9)

Recruitment

A total of 308 participants at 70 study centers were randomized in the study. The highest enrolling countries (each enrolling >30 participants (10%)) were France, UK, Italy and Spain.

The first participant received study treatment on 12 Nov 2020.

Conduct of the study

During the study, there were two protocol amendments.

Protocol Amendment 1 (21 Dec 2021) removed a planned interim analysis for efficacy to address FDA concerns that an interim analysis of PFS may not provide an accurate or reproducible estimate of treatment effect. Furthermore, the frequency of tumour imaging was updated from Q12W to Q8W, to allow for of analysis of PFS2 and ORR-CO.

Protocol Amendment 2 (25 May 2022) included the updated use of iRECIST for participant management to be applied during both blinded and crossover phases of the study.

Among the 308 participants randomized, 8 participants randomized to placebo + chemotherapy and 4 participants randomized to retifanlimab + chemotherapy had protocol deviations that were potentially of clinical importance.

In the retifanlimab + chemotherapy group:

- Two participants had deviations related to study treatment administration (both related to chemotherapy).
- One participant had a deviation related to missed laboratory assessments.
- One participant had a deviation related to inclusion criterion 4b (neoadjuvant therapy within 6 months of study).

In the placebo + chemotherapy group:

- Three participants had deviations related to unblinding after investigator-assessed disease progression.
- Two participants had deviations related to entry criteria (1 participant was HIV-positive but not taking ART and 1 participant's haemoglobin value was low).
- Two participants had deviations related to safety (baseline endocrinology panel missed and delay in SAE reporting to the pharmacovigilance database).
- One participant had a deviation related to randomization (incorrectly stratified as metastatic versus locally recurrent).

No participant's data were excluded from analyses due to important protocol deviations.

Baseline data

Table 10: Demographic characteristics (Full Analysis Set)

Variable	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)	Total (N = 308)
Age (years)			
Mean	61.1	61.6	61.3
STD	10.51	9.81	10.15
Median	61.0	62.0	62.0
Minimum, maximum	35, 84	29, 86	29, 86
Age group, n (%)			
< 65 years	100 (64.9)	96 (62.3)	196 (63.6)
≥ 65 years	54 (35.1)	58 (37.7)	112 (36.4)
65-74 years	37 (24.0)	44 (28.6)	81 (26.3)
< 75 years	137 (89.0)	140 (90.9)	277 (89.9)
≥ 75 years	17 (11.0)	14 (9.1)	31 (10.1)
75-84 years	17 (11.0)	13 (8.4)	30 (9.7)
≥ 85 years	0 (0.0)	1 (0.6)	1 (0.3)
Sex, n (%)			
Male	36 (23.4)	50 (32.5)	86 (27.9)
Female	118 (76.6)	104 (67.5)	222 (72.1)
Race, n (%)			
White/Caucasian	137 (89.0)	132 (85.7)	269 (87.3)
Black/African American	2 (1.3)	3 (1.9)	5 (1.6)
Asian	8 (5.2)	10 (6.5)	18 (5.8)
Multiple	0 (0.0)	1 (0.6)	1 (0.3)
Other	2 (1.3)	3 (1.9)	5 (1.6)
Not reported	3 (1.9)	5 (3.2)	8 (2.6)
Missing	2 (1.3)	0 (0.0)	2 (0.6)
Ethnicity, n (%)			

Variable	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)	Total (N = 308)
Hispanic or Latino	8 (5.2)	13 (8.4)	21 (6.8)
Not Hispanic or Latino	132 (85.7)	129 (83.8)	261 (84.7)
Not reported	1 (0.6)	1 (0.6)	2 (0.6)
Unknown	11 (7.1)	10 (6.5)	21 (6.8)
Missing	2 (1.3)	1 (0.6)	3 (1.0)
Geographic region, n (%)			
Australia/EU/North America/UK	146 (94.8)	146 (94.8)	292 (94.8)
ROW[a]	8 (5.2)	8 (5.2)	16 (5.2)

a. All participants included in ROW were enrolled in Japan.

Evidence for HPV infection was detected in the vast majority (>90%) of tumour biopsies for which this information was available.

Table 11: Cancer history and baseline disease characteristics (Full Analysis Set)

Variable, n (%)	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Current M stage		
M0	27 (17.5)	26 (16.9)
M1	127 (82.5)	127 (82.5)
Missing	0 (0.0)	1 (0.6)
HPV status (local)		
Positive	28 (18.2)	29 (18.8)
Negative	4 (2.6)	3 (1.9)
Unknown	2 (1.3)	0 (0.0)
Missing	120 (77.9)	122 (79.2)
P16/INK4A status (local)		
Positive	56 (36.4)	61 (39.6)
Negative	3 (1.9)	5 (3.2)
Unknown	1 (0.6)	2 (1.3)
Missing	94 (61.0)	86 (55.8)
P16 status (central)		
Positive	74 (48.1)	76 (49.4)
Negative	15 (9.7)	16 (10.4)
Indeterminate	8 (5.2)	10 (6.5)
Missing	57 (37.0)	52 (33.8)
Microsatellite instability status (local)		
Positive	1 (0.6)	2 (1.3)
Negative (microsatellite stable)	3 (1.9)	4 (2.6)

Variable, n (%)	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Missing	150 (97.4)	148 (96.1)
ECOG evaluation results at baseline		
0	86 (55.8)	82 (53.2)
1	68 (44.2)	71 (46.1)
Missing	0 (0.0)	1 (0.6)
HIV status		
Positive	5 (3.2)	6 (3.9)
Negative or unknown[a]	149 (96.8)	148 (96.1)
Extent disease group (EDC)[b]		
Locally recurrent	24 (15.6)	23 (14.9)
Metastatic	125 (81.2)	129 (83.8)
Missing	5 (3.2)	2 (1.3)
Liver metastases		
Yes	56 (36.4)	55 (35.7)
No	98 (63.6)	99 (64.3)
PD-L1 expression group (IRT)[c]		
< 1%	14 (9.1)	15 (9.7)
≥ 1%	140 (90.9)	139 (90.3)

[a] HIV testing was only required for participants known to be HIV-positive.
[b]Derived based on current overall stage from EDC.
[c]PD-L1 detection for stratification was performed centrally using the VENTANA PD-L1 (SP263) assay. One participant with PD-L1 ≥ 1% was stratified into the < 1% group at randomization.

Table 12: Summary of prior therapies (Full Analysis Set)

Variable, n (%)	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Prior therapy[a]		
Yes	99 (64.3)	95 (61.7)
No	55 (35.7)	58 (37.7)
Missing	0 (0.0)	1 (0.6)
Prior radiation therapy		
Yes	113 (73.4)	104 (67.5)
No	41 (26.6)	49 (31.8)
Missing	0 (0.0)	1 (0.6)
Prior surgery		
Yes	51 (33.1)	56 (36.4)
No	103 (66.9)	97 (63.0)
Missing	0 (0.0)	1 (0.6)

[a] Prior therapy is chemoradiotherapy.

Subsequent Anticancer Therapies

During the observation period up to the data cutoff, 83 participants (53.9%) in the retifanlimab + chemotherapy group and 66 participants (42.9%) in the placebo + chemotherapy group received anticancer therapy subsequent to discontinuation of study treatment. The most common (> 10% of participants in the retifanlimab + chemotherapy group) earliest post-treatment anticancer therapies administered were post-treatment radiation (18.2% and 9.1% in the retifanlimab + chemotherapy group and in the placebo + chemotherapy group, respectively), chemotherapy with fluorouracil (16.2% and 14.9%, respectively), and with paclitaxel (10.4% and 8.4%, respectively). In general, complete or partial responses to earliest post treatment anticancer therapy were uncommon, with a CR observed in 5 participants randomized to retifanlimab + chemotherapy and 3 participants randomized to placebo + chemotherapy. Of the 154 participants originally randomized to placebo + chemotherapy, 6 participants (4.0%) received a PD-L1 inhibitor as post-study treatment (pembrolizumab [3 participants], avelumab [2 participants], and nivolumab [1 participant]). No documented responses to any of these immunotherapies were observed. Similarly, no documented poststudy responses to another PD-(L)1 inhibitor were observed in any of the participants randomized to retifanlimab + chemotherapy (5 participants).

Numbers analysed

A total of 308 participants were randomized 1:1 in the study to retifanlimab + chemotherapy (Group B) or placebo + chemotherapy (Group A) and included in the FAS.

In total, 306 participants received at least 1 dose of study treatment and were included in the safety population, of which 154 patients in the retifanlimab + chemotherapy group.

Sixty-nine participants originally randomized to the placebo + chemotherapy group who crossed over at disease progression received at least 1 dose of retifanlimab monotherapy and were included in the CAS.

Outcomes and estimation

As of the DCO of 15 April 2024, the median duration of retifanlimab/placebo treatment for participants was 7.4 months in the retifanlimab + chemotherapy group and 6.8 months in the placebo + chemotherapy group.

Median follow-up time for the PFS-analysis in the retifanlimab + chemotherapy group was 7.57 months (range: 0.0-33.9 months), and 7.13 months (range: 0.0-27.4 months) in the placebo + chemotherapy group.

Median follow-up time for overall survival at the DCO was 14.8 months (range: 0.6 - 38.3 months) and 12.9 months (range: 0.0 - 40.4 months) in both treatment groups, respectively.

Primary endpoint: progression free survival

A statistically significant longer median PFS was observed in the retifanlimab + chemotherapy group compared to the placebo + chemotherapy group (HR: 0.63 [95% CI: 0.47, 0.84]; p = 0.0006), with an absolute difference in median PFS of 1.9 months.

The Kaplan-Meier estimate of median PFS in the retifanlimab + chemotherapy group was 9.3 months (95% CI: 7.5, 11.3), compared to 7.4 months (95% CI: 7.1, 7.7), in the placebo + chemotherapy group. Reasons for censoring are provided in Table 14.

Table 13: Summary of Progression-Free Survival by BICR according to RECIST v1.1 (Full Analysis Set)

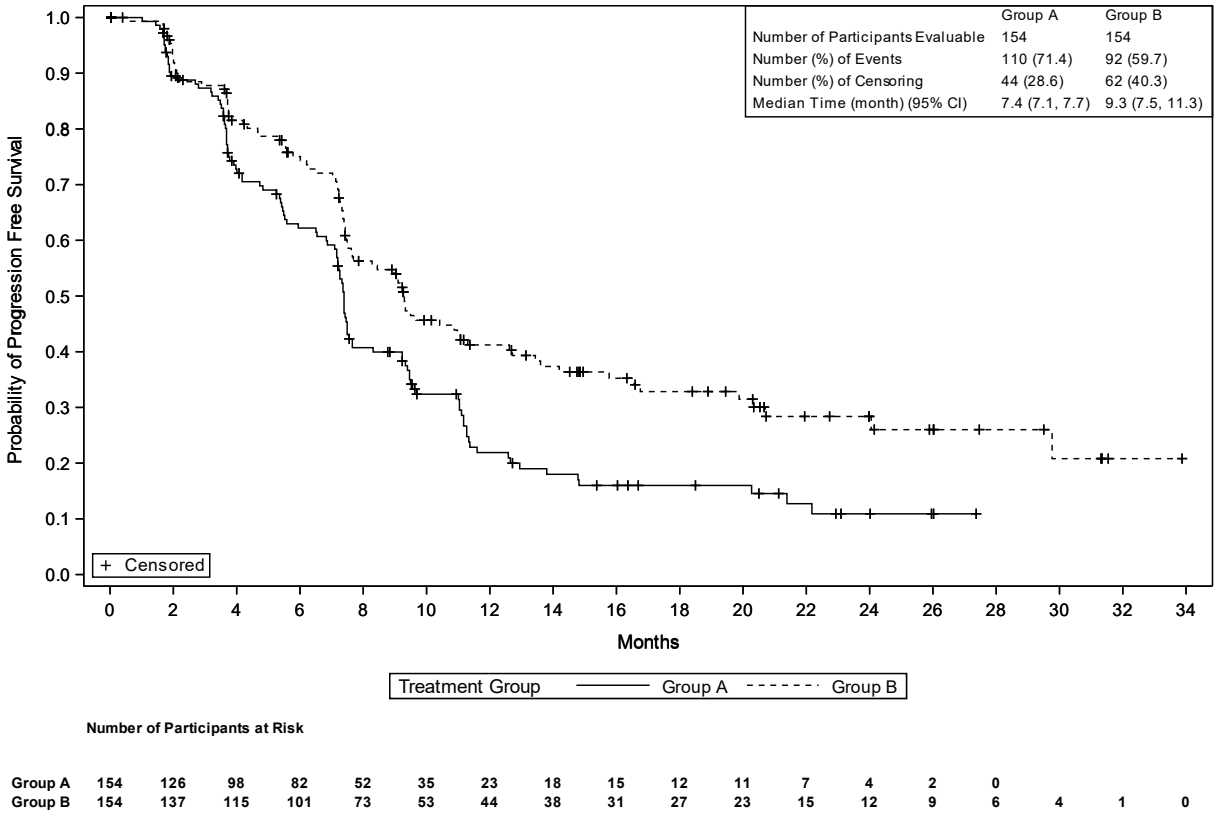
Variable	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants with events, n (%)	110 (71.4)	92 (59.7)
Death	4 (3.6)	6 (6.5)
Disease progression	106 (96.4)	86 (93.5)
Number (%) of participants censored	44 (28.6)	62 (40.3)
Median PFS (months) (95% CI)[a]	7.4 (7.1, 7.7)	9.3 (7.5, 11.3)
Month 3 PFS rate (95% CI)	87.3 (80.7, 91.8)	87.8 (81.3, 92.1)
Month 6 PFS rate (95% CI)	62.2 (53.5, 69.7)	75.0 (67.1, 81.3)
Month 9 PFS rate (95% CI)	40.0 (31.6, 48.2)	54.0 (45.2, 61.9)
Month 12 PFS rate (95% CI)	21.9 (14.9, 29.7)	41.2 (32.7, 49.6)
P-value for stratified logrank test[b]	—	0.0006
HR from stratified Cox model (95% CI)[c]	—	0.63 (0.47, 0.84)
Follow-up time (months)		
Median	7.13	7.57
Minimum, maximum	0.0, 27.4	0.0, 33.9

Note 1: According to RECIST v1.1, PFS was defined as the length of time from date of randomization until the earliest date of disease progression, determined by BICR, or death due to any cause, if occurring sooner than progression.
Note 2: The number of months was calculated as the number of day(s) divided by 30.4375.
Note 3: Stratification factors were based on information from the IRT.
[a] Median PFS time was estimated using the Kaplan-Meier method. The CI for median PFS time was calculated using the method of Brookmeyer and Crowley.
[b] PFS was tested at the 1-sided 2.5% level.
[c] A stratified Cox regression with Efron's method for tie handling was used to estimate the HR.

Table 14: Reasons for censoring, Progression-Free Survival by BICR according to RECIST v1.1 (Full Analysis Set)

Censoring Reason	Group A Placebo + Chemotherapy (N=154) Frequency (%)	Group B Retifanlimab + Chemotherapy (N=154) Frequency (%)
Total number of participants censored (%)	44 (28.6)	62 (40.3)
Death/progression after 2 or more missed assessments	1 (0.6)	1 (0.6)
New anticancer treatment started	14 (9.1)	20 (13.0)
Study completed	6 (3.9)	10 (6.5)
Ongoing at cut off	19 (12.3)	29 (18.8)
No valid post-baseline response assessments	4 (2.6)	2 (1.3)

Figure 3: Kaplan-Meier estimates of Progression-Free Survival by BICR according to RECIST v1.1 (Full Analysis Set)



Two sensitivity analyses were pre-planned, one based on BICR by unstratified log-rank test (HR: 0.63 [95% CI: 0.48, 0.83]; nominal p = 0.0005) and one by modified censoring rules (HR: 0.62 [95% CI: 0.47, 0.82]; nominal p = 0.0003).

Table 15: Progression-Free Survival Sensitivity Analyses (Full Analysis Set)

Variable	Unstratified Analysis[a]		Different Censoring Rules[b]	
	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants with events, n (%)	110 (71.4)	92 (59.7)	117 (76.0)	96 (62.3)
Death	4 (3.6)	6 (6.5)	5 (4.3)	7 (7.3)
Disease progression	106 (96.4)	86 (93.5)	106 (90.6)	86 (89.6)
Clinical progression	—	—	6 (5.1)	3 (3.1)
Number (%) of participants censored	44 (28.6)	62 (40.3)	37 (24.0)	58 (37.7)
Median PFS (months) (95% CI)[c]	7.4 (7.1, 7.7)	9.3 (7.5, 11.3)	7.4 (6.8, 7.6)	9.3 (7.5, 11.1)
Month 3 PFS rate (95% CI)	87.3 (80.7, 91.8)	87.8 (81.3, 92.1)	86.9 (80.2, 91.4)	87.9 (81.5, 92.2)
Month 6 PFS rate (95% CI)	62.2 (53.5, 69.7)	75.0 (67.1, 81.3)	60.4 (51.9, 68.0)	74.0 (66.0, 80.3)
Month 9 PFS rate (95% CI)	40.0 (31.6, 48.2)	54.0 (45.2, 61.9)	38.3 (30.2, 46.4)	53.4 (44.8, 61.3)
Month 12 PFS rate (95% CI)	21.9 (14.9, 29.7)	41.2 (32.7, 49.6)	20.0 (13.6, 27.4)	39.3 (31.0, 47.6)
P-value[d]	—	0.0005	—	0.0003
HR (95% CI)[e]	—	0.63 (0.48, 0.83)	—	0.62 (0.47, 0.82)
Follow-up time (months)				
Median	7.13	7.57	7.16	7.64
Minimum, maximum	0.0, 27.4	0.0, 33.9	0.0, 27.4	0.0, 33.9

Note 1: The number of months was calculated as the number of day(s) divided by 30.4375.
Note 2: Stratification factors were based on information from the IRT.

[a] According to RECIST v1.1, PFS was defined as the length of time from date of randomization until the earliest date of disease progression, determined by BICR, or death due to any cause, if occurring sooner than progression.

[b] PFS was defined as the length of time from date of randomization until the earliest date of disease progression determined by BICR or death due to any cause, if occurring sooner than progression, regardless of missing tumor assessments. Treatment discontinuation due to clinical progression was also considered as event.

[c] 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.

[d] Nominal p-values are provided as summary statistics.

[e] For the unstratified analysis, an unstratified Cox regression with Efron's method for tie handling was used to estimate the HR. For the analysis with different censoring rules, a stratified Cox regression with Efron's method for tie handling was used to estimate the HR.

Following a request during the assessment, an additional analysis of PFS by BICR was performed. For this analysis, patients continued to be followed up regardless of start of new anti-cancer treatment or any missed visits. The results demonstrated a median PFS time of 9.3 months (95% CI: 7.7 to 11.0 months) for the retifanlimab + chemotherapy group and 7.4 months (95% CI: 7.2 to 7.8 months) for the placebo + chemotherapy group; the HR is 0.67, with a 95% CI of 0.51 to 0.87.

PFS by investigator assessment was evaluated as a secondary endpoint. A longer median PFS was observed in the retifanlimab + chemotherapy group compared to the placebo + chemotherapy group

(HR: 0.72 [95% CI: 0.55, 0.95]; p = 0.0099). The Kaplan-Meier estimate of median PFS by investigator assessment in the retifanlimab + chemotherapy group was 9.2 months (95% CI: 7.7, 10.9), compared to 7.4 months (95% CI: 7.2, 9.1), in the placebo + chemotherapy group.

Key secondary endpoint: overall survival

The Kaplan-Meier estimate of median OS in the retifanlimab + chemotherapy group was 29.2 months (95% CI: 24.2, NE), compared to 23.0 months (95% CI: 15.1, 27.9) in the placebo + chemotherapy group. These estimates did not reach the prespecified threshold for a statistically significant difference: HR: 0.70 [95% CI: 0.49, 1.01]; p = 0.0273.

At the timing of this interim analysis for OS, 34.4% of participants in the retifanlimab + chemotherapy group and 47.4% in the placebo + chemotherapy group had died, respectively.

Figure 4: Kaplan-Meier estimates of Overall Survival (Full Analysis Set) – interim analysis

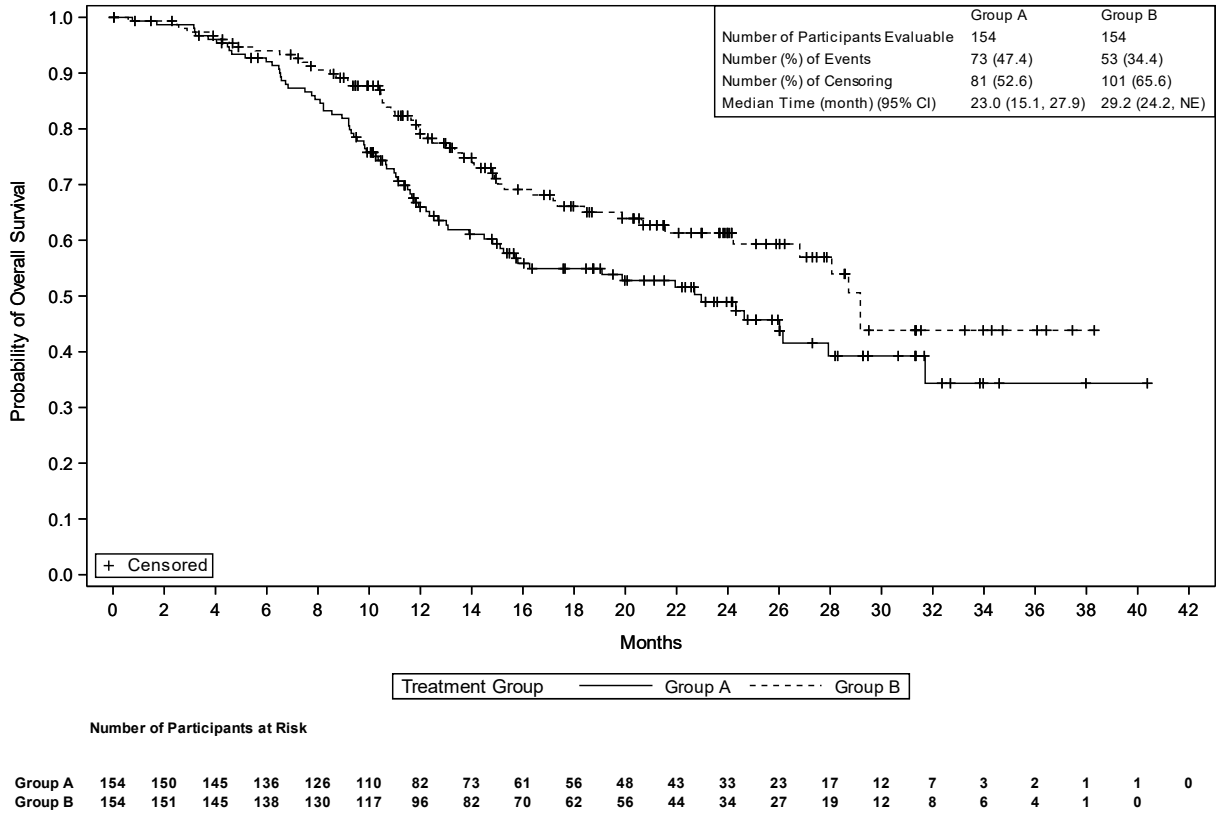


Table 16: Summary of Overall Survival (Full Analysis Set) – interim analysis

Variable	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants with events, n (%)		
Death	73 (47.4)	53 (34.4)
Censoring	81 (52.6)	101 (65.6)
Median OS (months) (95% CI)[a]	23.0 (15.1, 27.9)	29.2 (24.2, NE)
Month 12 OS rate (95% CI)	66.0 (57.5, 73.1)	79.1 (71.3, 85.0)
Month 15 OS rate (95% CI)	59.4 (50.6, 67.1)	71.1 (62.3, 78.1)

Variable	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Month 18 OS rate (95% CI)	54.9 (46.0, 63.0)	66.1 (56.9, 73.8)
Month 24 OS rate (95% CI)	48.9 (39.6, 57.6)	61.3 (51.6, 69.7)
P-value for stratified log-rank test[b]	—	0.0273
HR from stratified Cox model (95% CI)[c]	—	0.70 (0.49, 1.01)
Follow-up time (months)		
Median	12.86	14.77
Minimum, maximum	0.0, 40.4	0.6, 38.3

Note 1: OS was defined as the time in days between date of randomization and the date of death due to any cause.
Note 2: The number of months was calculated as the number of day(s) divided by 30.4375.
Note 3: Stratification factors were based on information from the IRT.
[a] Median survival time in months was estimated using Kaplan-Meier method. The CI for median survival time was calculated using the method of Brookmeyer and Crowley.
[b] OS was tested if PFS was statistically significant at the 1-sided 2.5% level. P-value under Group B was based on stratified log rank test at an overall 1-sided 2.5% level of significance, using O'Brien and Fleming boundary to adjust for alpha spending at interim analysis.
[c] A stratified Cox regression with Efron's method for tie handling was used to estimate the HR.

Sensitivity analyses for OS were performed, aiming to adjust for crossover of participants in the placebo + chemotherapy group using two different methods (Table 17): an RPSFT model (rank-preserving structural failure time) and IPCW model (inverse probability of censoring weighting).

Table 17: Summary of Crossover-Adjusted Overall Survival (Full Analysis Set) – Interim Analysis

Variable	Group A Placebo + Chemotherapy RPSFT Method[a] (N = 154)	Group A Placebo + Chemotherapy IPCW Method[b] (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants with events, n (%)			
Death	73 (47.4)	38 (24.7)	53 (34.4)
Censoring	81 (52.6)	116 (75.3)	101 (65.6)
Median OS (months) (95% CI)[c]	19.1 (13.4, 27.9)	23.0 (11.5, 27.9)	29.2 (24.2, NE)
Month 12 OS rate (95% CI)	61.7 (53.2, 69.2)	61.2 (44.9, 74.0)	79.1 (71.3, 85.0)
Month 15 OS rate (95% CI)	56.6 (47.8, 64.4)	59.7 (43.7, 72.6)	71.1 (62.3, 78.1)
Month 18 OS rate (95% CI)	52.5 (43.6, 60.7)	56.3 (40.4, 69.5)	66.1 (56.9, 73.8)
Month 24 OS rate (95% CI)	43.6 (33.7, 53.0)	47.5 (28.7, 64.1)	61.3 (51.6, 69.7)
P-value for stratified log-rank test[d]	—	—	RPSFT: 0.0055
	—	—	IPCW: 0.0063
HR from stratified Cox model (95% CI)[e]	—	—	RPSFT: 0.63 (0.44, 0.90)
	—	—	IPCW: 0.61 (0.40, 0.95)
Follow-up time (months)			
Median	11.96	NC	14.77
Minimum, maximum	0.0, 40.4	NC	0.6, 38.3

NC = not calculated.

Note 1: OS was defined as the time in days between date of randomization and the date of death due to any cause.
Note 2: The number of months was calculated as the number of day(s) divided by 30.4375.
Note 3: Stratification factors were based on information from the IRT.

[a] The crossover-adjusted analysis using the RPSFT model followed a naïve multistep approach and did not account for the part of the variation in the counterfactual survival time that arose from the variation in the acceleration factor for participants who crossed over from the placebo group to the treatment group.

[b] The crossover-adjusted analysis employed the IPCW method. Within the probability of censoring (crossover) models, stratification factors, along with age, sex, baseline ECOG status, and baseline sum of diameters from independent assessor were incorporated as baseline covariates. Time-varying covariates included ECOG status, percentage change in the sum of diameters from independent assessors, indicators for disease progression, indicators for the occurrence of new lesions, and indicators for SAEs. Stabilized weights were derived from the probability of censoring models, trimmed at value 10, and incorporated into the weighted stratified log-rank test and the weighted stratified Cox proportional hazards model. Number of deaths considered death in participants who did not cross over, while participants who crossed over were all censored at the time of crossover in this analysis; thus, follow-up time was not calculated.

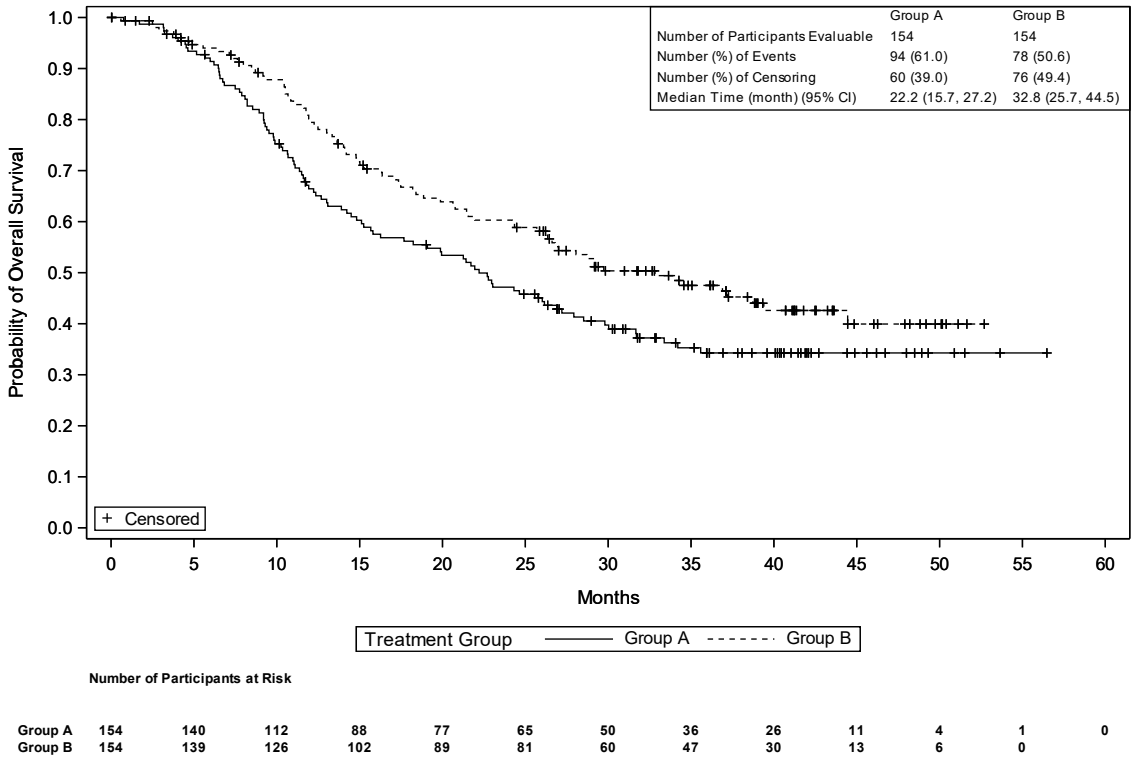
[c] Median survival time in months was estimated using Kaplan-Meier method. The CI for median survival time was calculated using the method of Brookmeyer and Crowley.

[d] Nominal p-values are provided as summary statistics.

[e] A stratified Cox regression with Efron's method for tie handling was used to estimate the HR.

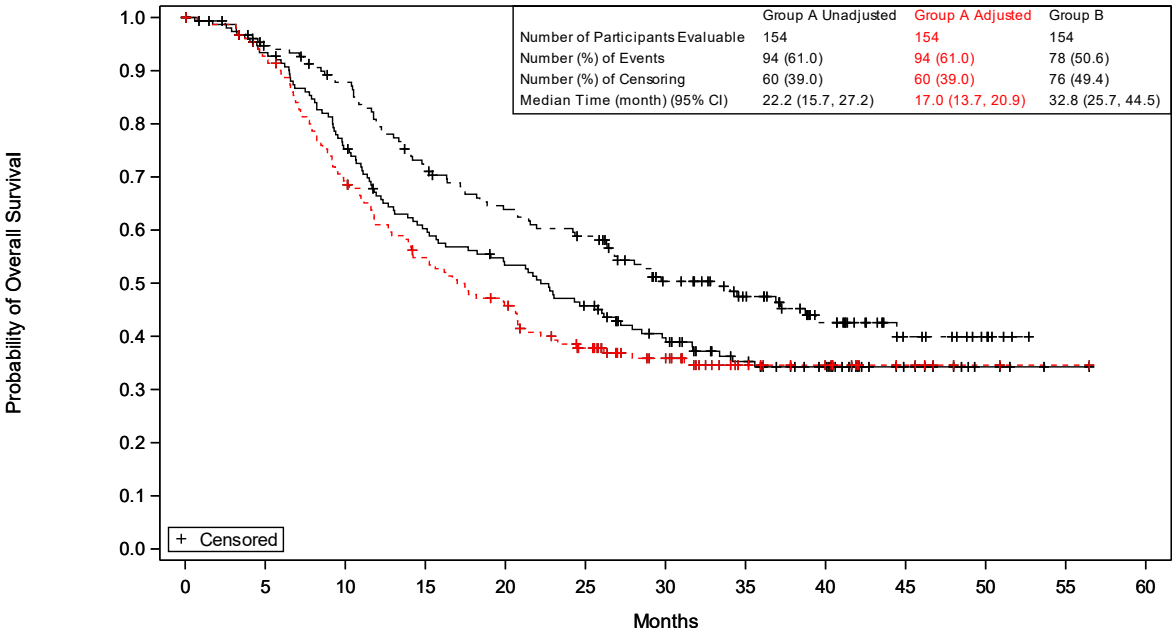
At a data cutoff of 01 Aug 2025, the protocol-specified final analysis of OS was performed, at which time 172 deaths had been recorded. Median survival in the retifanlimab + chemotherapy treatment group was 32.8 months (95% CI: 25.7, 44.5) compared to 22.2 months (95% CI: 15.7, 27.2) for the placebo + chemotherapy treatment group. These estimates did not reach the prespecified threshold for a statistically significant difference: HR: 0.75 [95% CI: 0.55, 1.01]; p = 0.0305 (Figure 4).

Figure 5: Kaplan-Meier Estimates of Overall Survival (Full Analysis Set), Final analysis with DCO 01 Aug 2025



When corrected for crossover to retifanlimab using either of two established methods, the hazard ratio was lower (RPSFT model HR: 0.63 [95% CI: 0.47, 0.86] and IPCW method HR: 0.53 [95% CI: 0.36, 0.79]; respectively), with 95% CIs excluding 1.

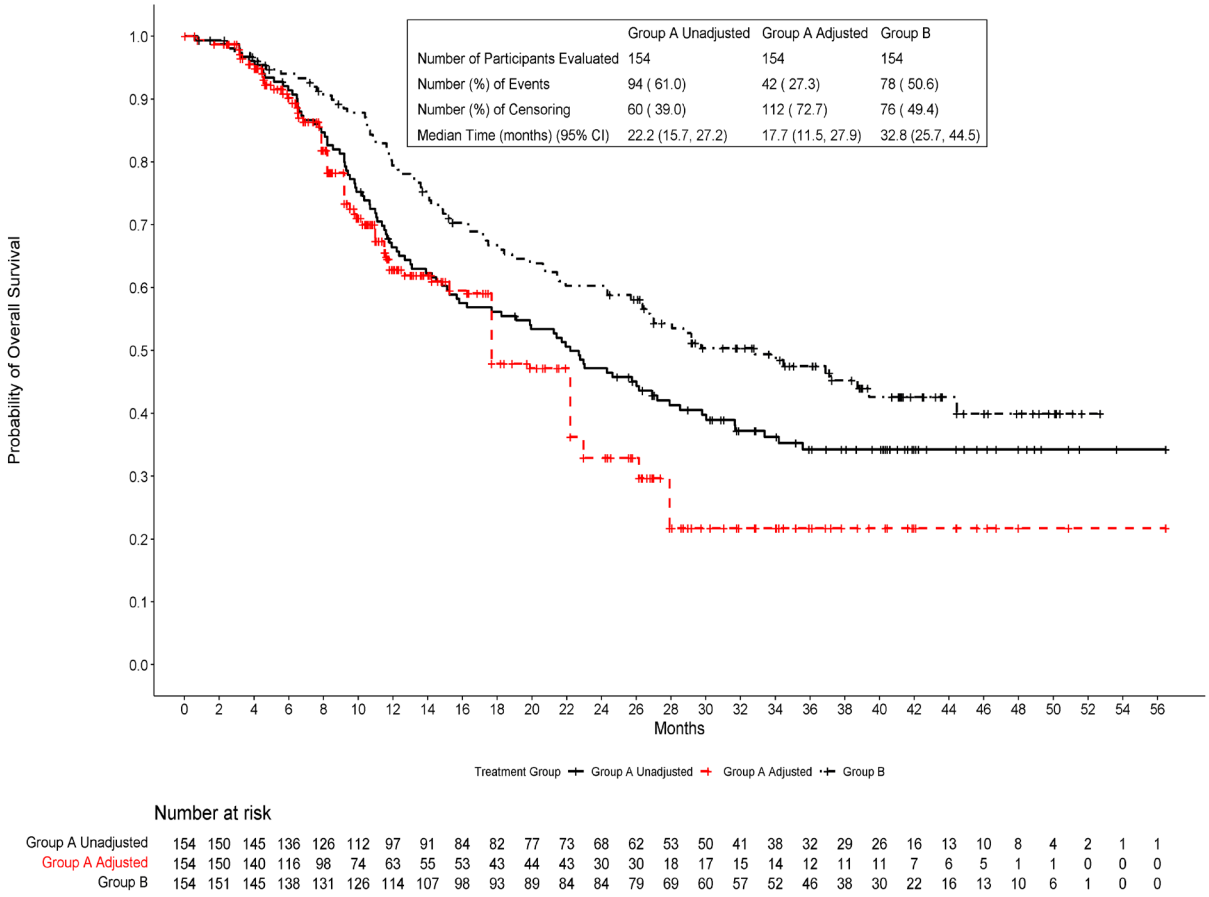
Figure 6: Kaplan-Meier Estimates of Overall Survival Including RPSFT Method (Full Analysis Set), Final analysis with DCO 01 Aug 2025



Number of Participants at Risk

Group A Unadjusted	154	140	112	88	77	65	50	36	26	11	4	1	0
Group A Adjusted	154	139	102	79	65	48	33	18	13	6	2	1	0
Group B	154	139	126	102	89	81	60	47	30	13	6	0	

Figure 7: Kaplan-Meier Estimates of Overall Survival Including IPCW Method (Full Analysis Set), Final analysis with DCO 01 Aug 2025



Secondary endpoint: objective response rate

ORR in the retifanlimab + chemotherapy group was 55.8% (95% CI: 47.6, 63.8), and ORR in the placebo + chemotherapy group was 44.2% (95% CI: 36.2, 52.4).

In the retifanlimab + chemotherapy group, the best overall confirmed response of CR was reported in 34 participants (22.1%) and PR in 52 participants (33.8%).

In the placebo + chemotherapy group, the best overall confirmed response of CR was reported in 21 participants (13.6%) and PR in 47 participants (30.5%).

Table 18: Summary of Best Overall Response by BICR according to RECIST v1.1 (Full Analysis Set)

Variable	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
BOR[a], n (%)		
CR	21 (13.6)	34 (22.1)
PR	47 (30.5)	52 (33.8)
SD	52 (33.8)	45 (29.2)
Non-CR/Non-PD	3 (1.9)	3 (1.9)

Variable	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
PD	19 (12.3)	15 (9.7)
NE	5 (3.2)	1 (0.6)
Missing	7 (4.5)	4 (2.6)
Objective responders[b], n (%)	68 (44.2)	86 (55.8)
95% CI for ORR[c]	(36.2, 52.4)	(47.6, 63.8)
P-value[d]	—	0.0129
DCR[e], n (%)	123 (79.9)	134 (87.0)
95% CI for DCR[c]	(72.7, 85.9)	(80.7, 91.9)

Note 1: Stratification factors were based on information from the IRT.

[a] The BOR was defined as the best confirmed response in the order of CR > PR > SD (non-CR/non-PD) > PD > NE recorded until the first PD or new anticancer therapy.

[b] A participant was considered as objective responder if the participant had a confirmed overall response of CR or PR at any postbaseline visit until the first PD or new anticancer therapy.

[c] CIs were calculated based on the exact method for binomial distributions.

[d] The p-value was calculated from stratified Cochran-Mantel-Haenszel test.

[e] A participant was considered as disease control if the participant had a confirmed overall response of CR, PR, SD, or nonCR/non-PD at any postbaseline visit until the first PD or new anticancer therapy.

Per investigator assessment, ORR in the retifanlimab + chemotherapy group was 61.7% (95% CI: 53.5, 69.4) compared with 53.2% (95% CI: 45.0, 61.3) in the placebo + chemotherapy group.

Secondary endpoint: Duration of response

Median DOR based on Kaplan-Meier analysis was 14.0 months for the retifanlimab + chemotherapy group (95% CI: 8.6, 22.2; median follow-up time of 7.70 months), and 7.2 months in the placebo + chemotherapy group (95% CI: 5.6, 9.3; median follow-up time of 5.75 months).

Table 19: Summary of Duration of Confirmed Response by BICR according to RECIST v1.1 (Full Analysis Set)

Variable	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants who had response[a], n (%)	68 (44.2)	86 (55.8)
Participants with events[b]	47 (69.1)	42 (48.8)
Death	1 (1.5)	1 (1.2)
Disease progression	46 (67.6)	41 (47.7)
Participants censored[b], n (%)	21 (30.9)	44 (51.2)
Duration of confirmed response (months)[c], 95% CI		
25th	5.5 (4.4, 5.6)	6.1 (5.5, 7.5)
50th	7.2 (5.6, 9.3)	14.0 (8.6, 22.2)
75th	18.4 (9.3, NE)	NE (22.2, NE)
Event-free probability estimates[d], 95% CI		
Month 3	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)

Variable	Group A Placebo + Chemotherapy (N = 154)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Month 6	50.6 (37.9, 62.0)	75.6 (64.4, 83.7)
Month 9	40.2 (28.0, 52.1)	61.2 (49.1, 71.3)
Month 12	30.5 (19.3, 42.5)	55.0 (42.7, 65.7)
Follow-up time (months)		
Median	5.75	7.70
Minimum, maximum	2.0, 25.7	1.8, 32.1

Note 1: The number of month(s) was calculated as the number of days divided b 30.4375.

[a] Participants who had confirmed CR or PR prior to PD or until start of new anticancer therapy.

[b] Denominator is total number of responders.

[c] The 95% CI was calculated using the Brookmeyer and Crowley method and the Klein and Moeschberger method with log-log transformation.

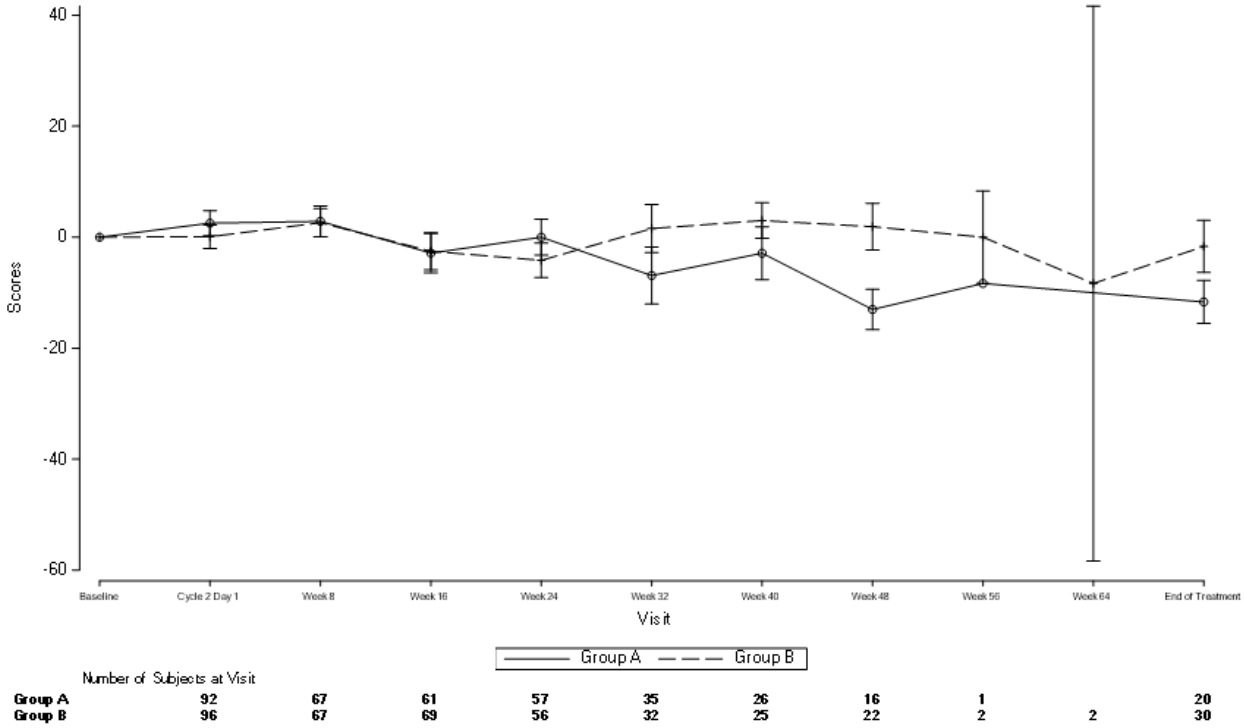
[d] The 95% CI was calculated using Greenwood's formula to estimate the standard error.

The estimated median DOR based on investigator assessment in the retifanlimab + chemotherapy group was 10.9 months (95% CI: 9.2, 14.7; median follow-up time of 9.23 months) compared to 9.1 months (95% CI: 7.2, 9.5; median follow-up time of 7.39 months) in the placebo + chemotherapy group.

Exploratory endpoint: Patient-reported outcomes

Mean change from baseline in EORTC-QLQ-C30 scores over time are presented in Figure 8. From baseline to Week 24, no consistent trends or differences between the 2 groups in global health status were observed. At Week 24, participants in the retifanlimab + chemotherapy group had worse score and score change from baseline for dyspnoea symptoms compared to the placebo + chemotherapy group (mean: 28.99 vs 18.23; 14.75 vs 5.26). Score changes from baseline for the rest of the functioning domains (physical, role, emotional, cognitive, and social) and symptom domains (fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) were not obviously different between the 2 treatment groups.

Figure 8: Mean (± Standard Error) Change from Baseline of EORTC-QLQ-C30 Score (Full Analysis Set)

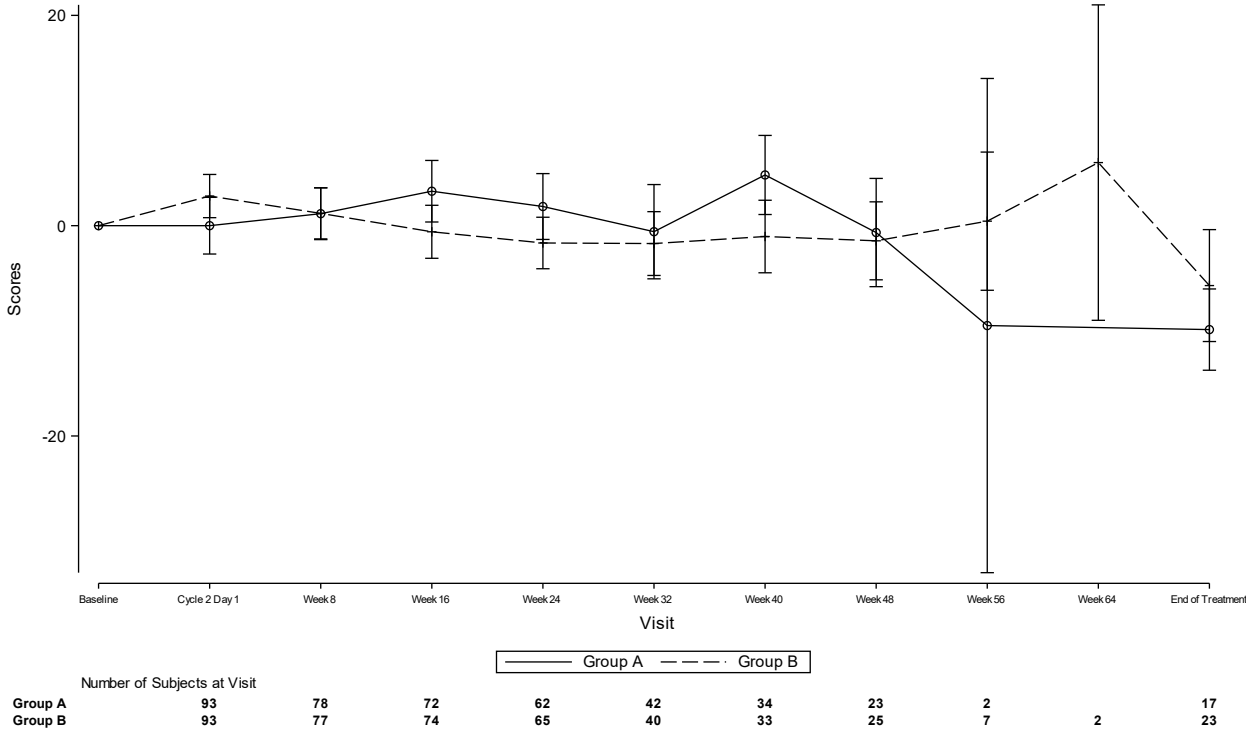


Number of Subjects at Visit										
Group A	**92**	**67**	**61**	**57**	**35**	**26**	**16**	**1**		**20**
Group B	**96**	**67**	**69**	**56**	**32**	**25**	**22**	**2**	**2**	**30**

No differences in mean EQ-5D VAS score and mean score change from baseline were observed for the retifanlimab + chemotherapy group compared to the placebo + chemotherapy group (see Figure 9).

At Week 24, fewer participants had no pain or discomfort (27.1% vs 42.0%), and fewer participants were not anxious or depressed (41.4% vs 53.6%) in the retifanlimab + chemotherapy group.

Figure 9: Mean (± Standard Error) Change from Baseline of EQ-5D VAS (Full Analysis Set)



Number of Subjects at Visit										
Group A	**93**	**78**	**72**	**62**	**42**	**34**	**23**	**2**		**17**
Group B	**93**	**77**	**74**	**65**	**40**	**33**	**25**	**7**	**2**	**23**

Score changes from baseline for QLQ-ANL27 questionnaire were not different between the 2 treatment groups, but data was only available for 78 participants in total.

Ancillary analyses

Subgroup analyses were performed for PFS and OS by stratification factors and other baseline patient and disease characteristics (see Figure 10 and Figure 11). These subgroup analyses are considered exploratory.

Figure 10: Forest plot of Progression-Free Survival and 95% CIs by BICR (Full Analysis Set)

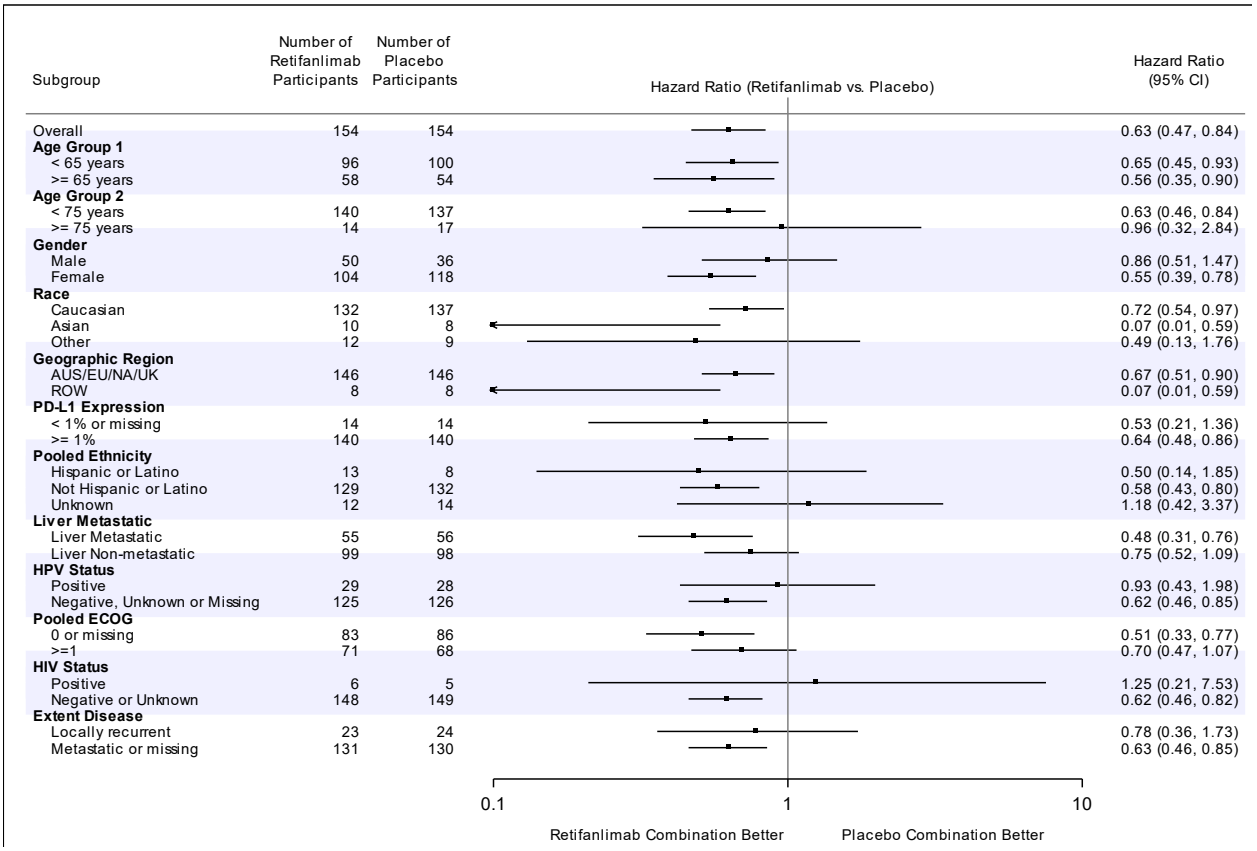
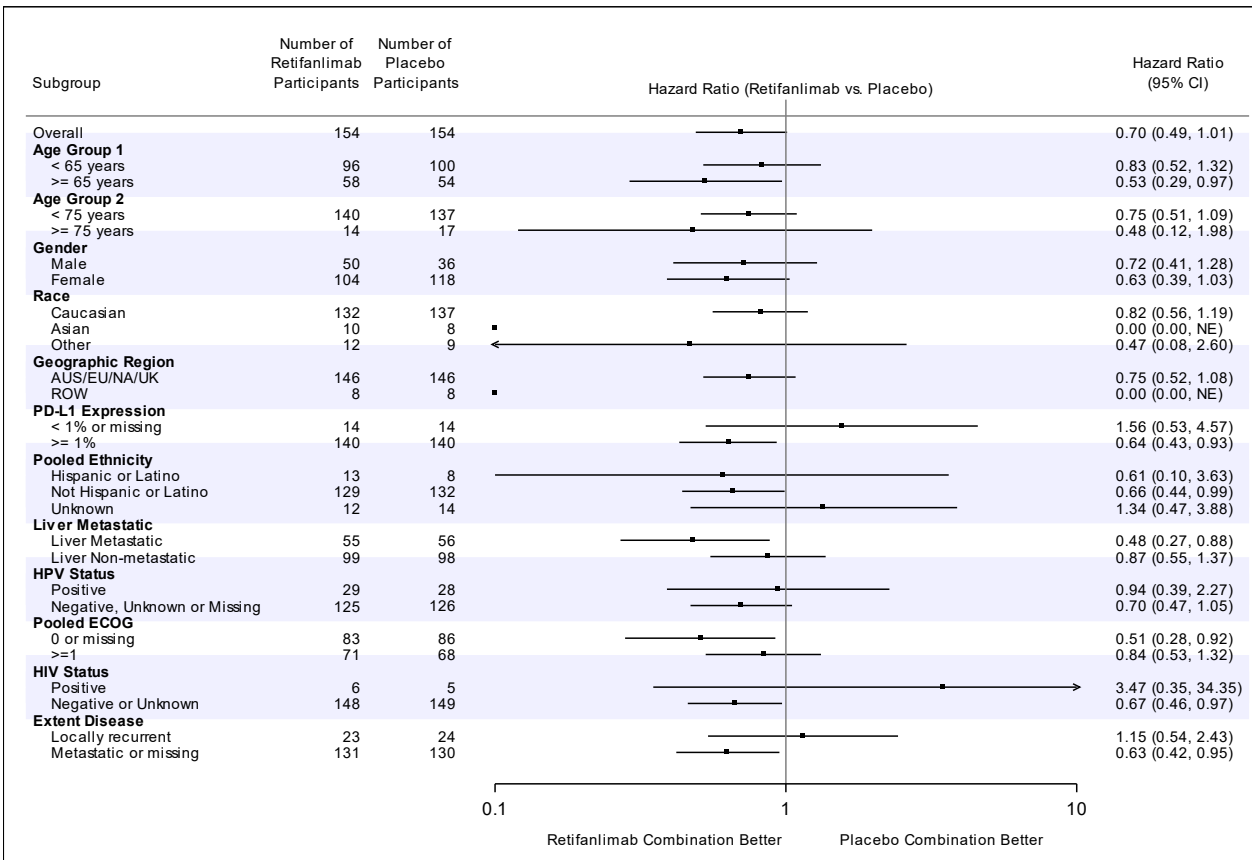


Figure 11: Forest plot of Overall Survival and 95% CIs (Full Analysis Set) – Interim Analysis



Of note, pre-specified subgroup analyses based on PD-L1 status were performed using a cut-off of <1%. In both treatment groups, only 14 participants were included from this subgroup.

In the subgroup of participants with a tumour with low PD-L1 expression (<1% or missing), the HR for PFS was 0.53 (95% CI 0.21-1.36) and the HR for OS was 1.56 (0.53-4.57).

In the subgroup of participants with a tumour with a PD-L1 expression ≥1% (n=280, 91% of the FAS), the HR for PFS was 0.64 (95% CI 0.48-0.86) and the HR for OS was 0.64 (95% CI 0.43-0.93).

Additional ad hoc analyses with different cut-off points were performed on the primary PFS results and final OS data as shown in Table 20.

Table 20: Planned and Ad Hoc Analyses of Efficacy Based on Different Cut Points for PD-L1 Expression

Subset	Overall population	≥1% (stratified analysis)	>5%	>10%	>20%
N	308	280	214	169	114
HR PFS (95% CI)	0.63 (0.47,0.84)	0.64 (0.48,0.86)	0.56 (0.40,0.79)	0.64 (0.44,0.95)	0.75 (0.46,1.22)
HR OS (95% CI)	0.75 (0.55,1.01)	0.69 (0.50,0.95)	0.60 (0.42,0.86)	0.65 (0.44,0.97)	0.64 (0.39,1.07)

A subgroup analysis was performed for HIV+ patients, of which only 11 participants were included in the study. In the subgroup of HIV+ patients, the HR for PFS was 1.25 (95% CI 0.21-7.53) and the HR for OS was 3.47 (0.35-34.35).

Summary of main study

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

Table 21: Summary of Efficacy for trial PODIUM-303

A phase 3 global, multicenter, double-blind randomized study of carboplatin-paclitaxel with INCMGA00012 or placebo in participants with inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal not previously treated with systemic chemotherapy		
Study identifier	INCMGA 0012-303; NCT04472429; EudraCT 2020‑000826‑24; EU CT 2024-512331-72-00; jRCT2031200380	
Design	Double-blind randomized phase 3 study, add-on experimental treatment with active comparator and placebo-control	
	Duration of main phase:	12 Nov 2020 – 15 Apr 2024 (DCO)
	Duration of Run-in phase:	not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Group A: placebo + chemotherapy		placebo Q4W + chemotherapy (6 cycles of carboplatin AUC5 on Day 1 and paclitaxel 80 mg/m2 on Days 1, 8, and 15) followed by placebo IV Q4W for up to 13 cycles (1 year) in the absence of disease progression or intolerable toxicity n=154
	Group B: retifanlimab + chemotherapy		retifanlimab 500 mg IV Q4W + chemotherapy (6 cycles of carboplatin AUC5 on Day 1 and paclitaxel 80 mg/m2 on Days 1, 8, and 15) followed by retifanlimab 500mg IV Q4W for up to 13 cycles (1 year) in the absence of disease progression or intolerable toxicity n=154
Endpoints and definitions	Primary endpoint Progression free survival	PFS	time from the date of randomization to the date of the first documented progression or death due to any cause according to RECIST v1.1 by BICR
	Key secondary endpoint Overall survival	OS	time from the date of randomization to the date of death due to any cause

	Secondary endpoint Objective response rate	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 by BICR
	Secondary endpoint Duration of response	DOR	time from first-documented confirmed response (CR or PR) to the time of first-documented disease progression per RECIST v1.1 or death due to any cause
Database lock	15 APR 2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat PFS analysis was to be performed when around 207 PFS events were reached, at which point the study was unblinded.		

Descriptive statistics and estimate variability	Treatment group	A: placebo + chemotherapy	B: retifanlimab + chemotherapy
	Number of subject	n=154	N=154
	PFS (median, months)	7.4	9.3
	95% CI	7.1-7.7	7.5-11.3
	OS (median, months)	23	29.2
	95% CI	15.1-27.9	24.2-NE

	OS (median, months) Final analysis at updated DCO	32.8	22.2
	95%CI	25.7-44.5	15.7-27.2
	ORR (%)	44.2	55.8
	95% CI	36.2-52.4	47.6-63.8
	DOR (median, months)	7.2	14
	95% CI	5.6-9.3	8.6-22.2
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	A: placebo + chemotherapy B: retifanlimab + chemotherapy
		Hazard ratio	0.63
		95% CI	0.47-0.84
		P-value	0.0006
	Secondary Endpoint OS Final analysis at updated DCO of 01 August 2025	Comparison groups	A: placebo + chemotherapy B: retifanlimab + chemotherapy
		Hazard ratio	0.75
		95% CI	0.55-1.01
		P-value	0.0305

Notes	At the DCO for the final PFS analysis, an interim-analysis for OS was performed. At this IA, there were 126 death events (41% of FAS). The final analysis for OS was performed with a DCO of 01-AUG-2025, with a median follow-up of 26.3 months in the retifanlimab + chemotherapy group and 172 death events in the FAS (56%). At DCO, median follow-up times for PFS were 7.1 months and 7.6 months in group A and B, respectively. Median follow-up times for OS were 12.9 months and 14.8 months in group A and B.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy data are derived from a single pivotal study, PODIUM-303 which is an ongoing, phase 3, double blind study comparing retifanlimab in combination with chemotherapy to placebo plus chemotherapy as first line treatment in adult patients with inoperable locally recurrent or metastatic SCAC. Enrolment is complete with 308 patients. The data cutoff date for the primary efficacy analysis of the primary endpoint of PFS based on BICR was 15 April 2024. The final OS analysis with DCO 1 August 2025 has also been provided.

The study population consists of participants with inoperable locally recurrent or metastatic SCAC, and no prior systemic therapy other than chemotherapy administered with curative intent, i.e. as a radiosensitizing agent or as neoadjuvant or adjuvant therapy before or after surgery if completed ≥ 6 months before study entry. Participants had measurable disease per RECIST v1.1 and were fit, with an ECOG performance status of 0 or 1 and adequate organ function. Participants known to be HIV-positive were eligible if their disease was well controlled with undetectable viral load. The proposed indication adequately reflects the studied population, and the most important inclusion and exclusion criteria for the pivotal study are described in section 5.1 of the SmPC.

A total of 376 patients were screened for the study, of which 60 (16%) were not randomized due to screen failure. The most frequent reason for screen failure was lack of a biopsy sample to centrally confirm PD-L1 status prior to randomization. Other frequent reasons for screen failure were an ECOG-PS higher than 1, inadequately controlled HIV-infection or any condition interfering with the ability to participate in a clinical trial. These three criteria contributed to the selection of relatively fit participants for the study, which is adequately included in the description of the study population in section 5.1 of the SmPC. A participant who failed screening could repeat the screening process as specified in the protocol.

Participants were randomized 1:1 to receive the current standard first-line chemotherapy treatment with carboplatin and paclitaxel combined with either retifanlimab 500mg Q4W or placebo. Chemotherapy was administered for a maximum of 6 cycles, which is considered adequate, while treatment with retifanlimab or placebo was continued for a maximum total duration of one year. While there is no data to support the optimal duration of treatment with PD-1 inhibitors in patients with SCAC, a total treatment duration of one year is applied in several other indications in which immunotherapy is administered in combination with chemotherapy. Participants randomised to the placebo group could cross-over to treatment with retifanlimab after confirmed disease progression.

The primary objective of PODIUM-303 was to compare the efficacy of retifanlimab in combination with carboplatin-paclitaxel versus carboplatin paclitaxel with placebo, as evaluated by the primary endpoint of PFS assessed by BICR per RECIST v1.1 criteria. A formal estimand for the primary endpoint was not prespecified. Based on the censoring rules, the primary estimand considered the situation where alternative anti-cancer therapies are not available and irrespective of treatment discontinuation (i.e. use of new anticancer therapy was censored at the time of the last available assessment or randomisation). This approach is not fully aligned with the preferred estimand strategies outlined in the current EMA guideline on the clinical evaluation of anticancer medicinal products. Therefore, supplementary analyses were requested, and the results were consistent with the primary analysis.

Considering the poor prognosis of patients with advanced SCAC, and the lack of an effective second line treatment, overall survival is considered the most suitable endpoint in this setting. OS was analysed as a key secondary endpoint, included in the prespecified hierarchical testing strategy and only to be formally tested after the PFS analysis showed a statistically significant result. This strategy is acceptable.

The applicant confirmed that blinding of investigators and study personnel was continued following the primary analysis of PFS, in order to maintain the integrity of the OS secondary endpoint. The original study protocol (Version 1, 17 MAR 2020) was not initially submitted and was provided by the MAH upon request. With protocol Amendment 1 (21 Dec 2021), the frequency of tumour imaging was updated from Q12W to Q8W, to allow for analysis of PFS2 and ORR-CO (cross-over) as secondary endpoints. As the assessment frequency was modified only for the post-treatment period, it did not impact the assessment of the primary PFS endpoint or any of the secondary efficacy measures.

A summary of important protocol deviations for the full analysis set (FAS) was presented. Clinically significant protocol deviations occurred in 8 participants in the placebo plus chemotherapy group and 4 in the retifanlimab in combination with chemotherapy group, with no exclusions from analysis due to these deviations. The deviations were mostly isolated incidents with no evidence of systemic issues or consistent patterns. Regarding unblinding, 3 of 5 events deemed clinically important occurred without confirmation of radiographic progression by BICR before unblinding. PFS was censored at the last pre-unblinding assessment in these cases, minimizing impact on PFS validity and integrity. The other 2 unblinding events were considered acceptable as BICR confirmed progression per protocol timing.

During the randomized study drug treatment, efficacy evaluations were conducted exclusively by BICR following RECIST version 1.1 criteria. Clinical management, however followed either RECIST v1.1 or iRECIST, with a possibility to treat beyond conventional RECIST progression. iRECIST response assessment was performed for only 3 participants, and the impact on the interpretability of the study results is probably negligible.

Although no detailed information regarding the participants treated beyond disease progression was provided, the MAH specified that this concerns a small number of patients and a short duration of time. In section 5.1 of the SmPC it is stated that treatment with retifanlimab should continue until disease progression (i.e. not beyond disease progression), which is agreed.

The stratification factors for randomization of region and extent of disease are considered important. Participant randomization was also stratified by PD-L1 expression. Tumor PD-L1 expression was determined centrally prior to randomization using the Ventana SP263 antibody. PD-L1 status was determined based on a modified algorithm for the Ventana PD-L1 (SP263) commercial assay, that is validated for SCAC and similar to the concept of combined-positive score (CPS).

Efficacy data and additional analyses

As of the DCO of 15 April 2024, after a median follow-up time for PFS of about 7.5 months, a statistically significant longer median PFS was observed in the retifanlimab + chemotherapy group compared to the placebo + chemotherapy group with an absolute difference in median PFS of 1.9 months (HR: 0.63 [95% CI: 0.47, 0.84]; one-sided p = 0.0006). Median PFS was 7.4 months for placebo + chemotherapy and 9.3 months for retifanlimab + chemotherapy.

The reported median PFS in the chemotherapy + placebo arm is consistent with the most important previous study establishing carboplatin + paclitaxel chemotherapy as the current standard of care (InterAACT study).

Two additional analyses for the primary endpoint were performed, one sensitivity analysis based on BICR by unstratified log-rank test (HR: 0.63, 95% CI: 0.48, 0.83]) and one supplemental analysis by modified censoring rules (HR: 0.62, 95% CI: 0.47, 0.82]), with results generally consistent with the primary analysis. In the latter patients are followed up for a PFS event regardless of use of new anticancer therapy, the results of which were consistent with the primary analysis.

At DCO 15 April 2024, a prespecified interim analysis for OS was performed, at which time 34.4% of participants in the retifanlimab + chemotherapy group and 47.4% in the placebo + chemotherapy group had died, respectively. Median follow-up time for overall survival in the retifanlimab + chemotherapy group was 14.8 months at DCO.

Median OS in the retifanlimab + chemotherapy group was 29.2 months compared to 23.0 months in the placebo + chemotherapy group. These estimates did not reach the prespecified threshold for a statistically significant difference: HR: 0.70 [95% CI: 0.49, 1.01]; p = 0.0273. Of note, 69 participants from the placebo group crossed over to retifanlimab treatment (44.8%).

The secondary endpoints of ORR and DOR are supportive of the primary endpoint, with a higher response rate in the retifanlimab + chemotherapy group (55.8% versus 44.2%) and a longer median duration of response (14.0 versus 7.2 months).

Given the poor prognosis of patients with SCAC, the most important and relevant endpoints are OS or QoL. The reported median PFS-gain of 1.9 month required supportive OS or quality of life data.

The MAH provided the final OS analysis, at which DCO (1 August 2025), median follow-up was 26.3 months in the retifanlimab + chemotherapy group and 172 death events had taken place in the FAS (56%). Median OS was 32.8 months for retifanlimab + chemotherapy, compared to 22.2 months for placebo + chemotherapy; with a HR of 0.75 (0.55-1.01) and a p-value of 0.0305 not reaching the prespecified criterion for statistical significance. At the updated DCO (1 August 2025), an extra 8 participants from the placebo-group had crossed over to receive retifanlimab monotherapy after confirmed disease progression, resulting in a 50% cross-over rate. The additional analyses aiming to adjust for cross-over using the RPSFT and IPCW methods, resulted in lower hazard ratios with 95% CIs excluding 1 (RPSFT model HR: 0.63 [95% CI: 0.47, 0.86] and IPCW method HR: 0.53 [95% CI: 0.36, 0.79]; respectively).

The OS-curves show an early separation at approximately 6 months, which is maintained over time until, taking into account the decreasing number of patients at risk, a plateau of both curves from around 40-45 months. It is agreed with the MAH that the high percentage of cross-over influences the OS comparison. The estimated absolute difference in median OS between the two treatment groups can be considered large in the context of the poor prognosis of the target population. In addition, the additional analyses aiming to adjust for the crossover effect provide supportive and reassuring results.

It is, therefore, considered reasonable to conclude that the addition of retifanlimab to first-line chemotherapy in patients with inoperable or metastatic SCAC leads to a clinically relevant improvement in overall survival. Subgroup analyses according to PD-L1 status were performed using a cut-off of <1%. In both treatment groups, most participants had a 'PD-L1 positive' tumour by the ≥1% definition, and only 14 participants were included in each group with a tumour with PD-L1 <1%. This limits the interpretability of the prespecified PD-L1 subgroup analysis.

Post-hoc subgroup analysis of efficacy outcomes (PFS and updated OS) across additional PD-L1 expression cutoffs (<1%, <5%, <10% and <20%) were provided. Across these subgroups, HR estimates for both PFS and OS were consistently below 1 in favour of retifanlimab; however, for the subgroups with lower PD-L1 expression (<1%, <5%, <10%), the corresponding 95% CI were wide and included 1, reflecting the limited number of patients in these subgroups. No clear trend for a larger benefit with increasing PD-L1 expression was observed.

Overall, while the available subgroup analyses are exploratory and limited by small numbers of patients, they do not suggest a differential treatment effect according to PD-L1 expression. Most SCAC tumors express PD-L1, and a lack of benefit of retifanlimab treatment cannot be concluded in patients with low or negative tumor PD-L1 expression. Therefore, restriction of the indication according to PD-L1 status is not considered warranted.

Only few HIV+ participants were included in the study (n=11), however, there are no signs of a lack of efficacy or a more severe safety profile in these patients.

Analyses of the PRO data were descriptive in nature and were based on observed data only at each visit. As a result, the PRO results are considered exploratory, and no firm conclusions can be drawn based on these results.

2.4.4. Conclusions on the clinical efficacy

The addition of retifanlimab to carboplatin and paclitaxel resulted in a statistically significant improvement in PFS, with a median PFS gain of 1.9 months, which is considered of limited clinical relevance per se.

However, the estimated absolute difference in median OS between the two treatment groups is notable in the context of the poor prognosis of the target population, although the estimated HR was not statistically significant. The additional analyses adjusting for the high rate of treatment crossover provide supporting and reassuring context.

Based on the PFS gain combined with supportive OS data, a beneficial effect can be concluded with the addition of retifanlimab to first-line chemotherapy in patients with inoperable or metastatic SCAC regardless of PD-L1 expression, although uncertainty remains regarding the magnitude of the OS benefit.

2.5. Clinical safety

Introduction

The safety of retifanlimab as monotherapy has been evaluated in 452 patients with advanced solid malignancies who received the recommended 500 mg every 4 weeks dose, including 107 patients with metastatic or recurrent locally advanced MCC. Median duration of treatment was 5.4 months (range, 1 day – 27 months). The most common adverse reactions were fatigue (35.4%), rash (18.8%), diarrhoea (18.6%), anaemia (16.2%), pruritus (15.9%), arthralgia (13.3%), constipation (13.3%), nausea (13.3%), pyrexia (13.1%) and decreased appetite (12.6%). Adverse reactions were serious in

11.7% of patients. Retifanlimab was permanently discontinued due to adverse reactions in 8% of patients. Immune-related AEs (irAEs) and infusion-related reactions (IRR) were considered adverse events of special interest for retifanlimab, and long-term safety is considered to be missing information on the RMP.

Retifanlimab is to be given in combination with carboplatin and paclitaxel, which are well known chemotherapy agents. Notable adverse events to paclitaxel include hypersensitivity reactions, peripheral neuropathy, bone marrow suppression (mostly neutropenia), arthralgia, myalgias, mucositis and alopecia. For carboplatin these include myelosuppression (leukopenia, neutropenia and thrombocytopenia) and associated infections, nausea and vomiting, gastro-intestinal effects, sensory neuropathy, ototoxicity, asthenia and alopecia.

Patient exposure

Safety data from two studies of retifanlimab in adult patients with locally advanced or metastatic SCAC have been provided:

- INCMGA 0012-303 (POD1UM-303/InterAACT-2), an ongoing, Phase 3, double blind, randomized, multiregional study of retifanlimab in combination with carboplatin and paclitaxel in adult patients with inoperable, locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy (N=306). Safety analyses are presented as of the data cutoff date of 15 APR 2024.
- INCMGA 0012-202, a completed, Phase 2, open-label, multiregional study of retifanlimab monotherapy in adult patients with locally advanced or metastatic SCAC who have progressed on or are intolerant of platinum-based chemotherapy. Safety analyses are presented as of the LPLV date of 10 NOV 2021 (N=94). In this study Retifanlimab 500 mg was given IV over 60 minutes, versus 30 minutes in the INCMGA 0012-303 study/approved posology.

The safety population included all randomized participants from the INCMGA 0012-303 study who received at least 1 dose of study treatment.

Exposure

In Study INCMGA 0012-303 N=154 patients received retifanlimab + chemotherapy and N=152 patients received chemotherapy. The patient disposition is reported in Table 8.

As of the data cutoff date, the median duration of blinded study treatment in the safety population was 225.5 days (range: 1-445 days) in the retifanlimab + chemotherapy group and 207.0 days (range: 1-416 days) in the placebo + chemotherapy group. Refer to Table 22 for more details on patient exposure to Placebo or Retifanlimab and refer to Table 23 for more details on patient exposure to chemotherapy.

Table 22: Summary of Exposure to Placebo or Retifanlimab During the Randomized Treatment Period in Study INCMGA 0012-303 (Safety Population)

Variable	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Total number of infusions[a]		
Mean (STD)	7.8 (3.86)	8.5 (3.90)

Variable	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Median	8.0	9.0
Minimum, maximum	1, 13	1, 13
Total dose administered (mg)[b]		
Mean (STD)	0.0 (0.00)	4262.75 (1948.472)
Median	0.0	4500.00
Minimum, maximum	0, 0	464.0, 6500.0
Average dose (mg)[c]		
Mean (STD)	0.0 (0.00)	499.77 (2.901)
Median	0.0	500.00
Minimum, maximum	0, 0	464.0, 500.0
Duration of treatment (months)[d]		
Mean (STD)	6.763 (3.7510)	7.476 (3.8090)
Median	6.801	7.409
Minimum, maximum	0.03, 13.67	0.03, 14.62
Duration of treatment, n (%)		
≤ 3 months	39 (25.7)	25 (16.2)
> 3 months	113 (74.3)	129 (83.8)
> 6 months	88 (57.9)	98 (63.6)
> 9 months	53 (34.9)	67 (43.5)
> 12 months [e]	6 (3.9)	10 (6.5)

[a] Total number of infusions per participant who received at least 1 dose of placebo or retifanlimab.

[b] Sum of the cumulative dose that has been administered.

[c] Total dose administered (mg)/total number of infusions.

[d] The number of months is calculated as the number of days divided by 30.4375.

[e] Per the Protocol, maximum duration of treatment with retifanlimab or placebo was 1 year. However, the actual duration of treatment may have been slightly longer due to delays from AEs, planned surgical procedures, and other clinical decisions.

Table 23: Summary of Exposure to Chemotherapy During the Randomized Treatment Period in Study INCMGA 0012-303 (Safety Population)

Variable	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Carboplatin[a]		

Variable	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Total number of infusions[b]		
Mean (STD)	5.0 (1.47)	5.2 (1.41)
Median	6.0	6.0
Minimum, maximum	1, 6	1, 6
Total dose administered (mg)[c]		
Mean (STD)	2568.77 (940.036)	2598.69 (874.894)
Median	2700.00	2610.00
Minimum, maximum	430.0, 4500.0	264.0, 4500.0
Average dose (mg)[d]		
Mean (STD)	515.89 (110.383)	507.97 (114.023)
Median	500.00	493.00
Minimum, maximum	266.7, 750.0	261.7, 750.0
Duration of treatment (days)[e]		
Mean (STD)	121.7 (44.66)	127.4 (43.35)
Median	141.0	141.0
Minimum, maximum	1, 184	1, 225
Duration of treatment (months)[f]		
Mean (STD)	3.997 (1.4674)	4.186 (1.4242)
Median	4.632	4.632
Minimum, maximum	0.03, 6.05	0.03, 7.39
Duration of treatment, n (%)		
≤ 2 months	23 (15.1)	21 (13.7)
> 2 months	129 (84.9)	132 (86.3)
> 4 months	100 (65.8)	108 (70.6)
> 6 months[g]	2 (1.3)	4 (2.6)
Paclitaxel		
Total number of infusions[b]		
Mean (STD)	13.4 (4.52)	13.4 (4.57)
Median	15.0	15.0
Minimum, maximum	1, 18	1, 18
Total dose administered (mg)[c]		
Mean (STD)	1775.83 (671.998)	1777.75 (655.165)
Median	1895.00	1869.50
Minimum, maximum	2.1, 2916.0	35.8, 3028.0
Average dose (mg)[d]		
Mean (STD)	131.50 (21.657)	132.62 (21.428)
Median	130.25	132.00

Variable	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Minimum, maximum	2.1, 198.0	35.8, 190.0
Duration of treatment (months)[f]		
Mean (STD)	4.380 (1.5144)	4.481 (1.5502)
Median	5.092	5.092
Minimum, maximum	0.03, 6.70	0.03, 8.08
Duration of treatment, n (%)		
≤ 2 months	18 (11.8)	18 (11.7)
> 2 months	134 (88.2)	136 (88.3)
> 4 months	105 (69.1)	116 (75.3)
> 6 months[g]	8 (5.3)	9 (5.8)

[a] One participant in the retifanlimab + chemotherapy group did not receive carboplatin.

[b] Total number of infusions for participants who received at least 1 dose of chemotherapy.

[c] Sum of the cumulative dose that has been administered.

[d] Total dose administered (mg)/total number of infusions.

[e] Date of last dose of the drug – date of first dose of the drug + 1.

[f] The number of months is calculated as the number of days divided by 30.4375.

[g] Maximum duration of treatment with chemotherapy was 6 months. However, the actual duration of treatment may have been slightly longer due to delays from AEs, planned surgical procedures, and other clinical decisions.

Any dose delay of retifanlimab or placebo was observed in 61.0% of the participants in the retifanlimab + chemotherapy group and 61.8% of the participants in the placebo + chemotherapy group. The most frequent reason for dose delay of retifanlimab or placebo was adverse event in 39.6% versus 41.4% of the participants, respectively. There were no infusion/dose interruptions of retifanlimab or placebo observed in either arm.

Any dose delay of any chemotherapy was observed in 51.9% of the participants in the retifanlimab + chemotherapy group and in 50.7% of the participants in the placebo + chemotherapy group. The most frequent reason for dose delay of any chemotherapy was adverse event in 39.0% and 42.1%, respectively. Infusion interruption of any chemotherapy was reported in 10.4% and in 8.6% of the participants respectively and adverse event was the most frequent reason for any chemotherapy infusion interruption in 7.1% and 6.6% of the participants, respectively.

Study INCMGA 0012-303: Retifanlimab Monotherapy - Crossover Period

As of the data cutoff date (15 April 2024), 69 participants (44.8%) in the placebo + chemotherapy group were treated in the crossover period; 58 of these (84.1%) discontinued retifanlimab. The most common reason for retifanlimab discontinuation was disease progression (55 participants [79.7%]). Thirty-two participants (46.4%) in the crossover period remained in follow-up on the study. The most common reason for study withdrawal was death (35 participants [50.7%]). Exposure to retifanlimab during the crossover period is summarized in Table 24.

Table 24: Summary of Exposure to Retifanlimab During the Crossover Period in Study INCMGA 0012-303 (Crossover Analysis Set)

Variable	Retifanlimab Monotherapy (N = 69)
Total number of infusions[a]	
Mean (STD)	4.1 (3.17)
Median	3.0
Minimum, maximum	1, 13
Total dose administered (mg)[b]	
Mean (STD)	2057.97 (1587.025)
Median	1500.00
Minimum, maximum	500.0, 6500.0
Average dose (mg)[c]	
Mean (STD)	500.00 (0.000)
Median	500.00
Minimum, maximum	500.0, 500.0
Duration of treatment (days)[d]	
Mean (STD)	92.1 (92.19)
Median	57.0
Minimum, maximum	1, 367
Duration of treatment (months)[e]	
Mean (STD)	3.025 (3.0288)
Median	1.873
Minimum, maximum	0.03, 12.06
Duration of treatment, n (%)	
≤ 3 months	48 (69.6)
> 3 months	21 (30.4)
> 6 months	9 (13.0)
> 9 months	5 (7.2)
> 12 months[f]	1 (1.4)

[a] Total number of infusions for participants who received at least 1 dose of retifanlimab.

[b] Sum of the cumulative dose that has been administered.

[c] Total dose administered (mg)/total number of infusions.

[d] Date of last dose of the drug – date of first dose of the drug + 1.

[e] The number of months is calculated as the number of days divided by 30.4375.

[f] Per the Protocol, the maximum duration of treatment with retifanlimab was 1 year. However, the actual duration of treatment may have been slightly longer due to delays from AEs, planned surgical procedures, and other clinical decisions.

Study INCMGA 0012-202: retifanlimab monotherapy

In Study INCMGA 0012-202, 94 participants were enrolled and treated with retifanlimab monotherapy. The most common reason for treatment discontinuation was progressive disease. The most common reason for study withdrawal was death (70 participants [74.5%]). The median duration of retifanlimab treatment was 85.0 days (range: 1-823 days), with 41 participants (43.6%) treated for > 3 months, 24 participants (25.5%) treated for > 6 months, 15 participants (16.0%) treated for > 9 months, and 9 participants (9.6%) treated for > 12 months. The median number of infusions administered was 4 (range: 1-26 infusions). The median total dose administered was 2000.00 mg.

Adverse events

An overall summary of TEAEs based on the safety population is presented in Table 25.

Table 25: Overall Summary of TEAEs During the Randomized Treatment Period in Study INCMGA 0012-303 (Safety Population)

Participants (n [%]) with:	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
TEAE	152 (100.0)	154 (100.0)
Retifanlimab/placebo-related TEAE	118 (77.6)	138 (89.6)
Serious TEAE	59 (38.8)	73 (47.4)
Grade 3 or higher TEAE	114 (75.0)	128 (83.1)
Fatal TEAE	1 (0.7)	4 (2.6)
Serious retifanlimab/placebo-related TEAE	10 (6.6)	25 (16.2)
Grade 3 or higher retifanlimab/placebo-related TEAE	39 (25.7)	53 (34.4)
Retifanlimab/placebo infusion interruption due to TEAE[a]	2 (1.3)	6 (3.9)
Retifanlimab/placebo dose delayed due to TEAE	75 (49.3)	81 (52.6)
Retifanlimab/placebo discontinued due to TEAE	4 (2.6)	17 (11.0)
Chemotherapy-related TEAE	148 (97.4)	152 (98.7)
Chemotherapy discontinued due to TEAE	8 (5.3)	16 (10.4)
Chemotherapy infusion interruption due to TEAE	18 (11.8)	18 (11.7)
Chemotherapy dose delayed due to TEAE	108 (71.1)	107 (69.5)

[a] These events may have been incorrectly categorized as infusion interruptions; based on exposure data, these are more likely to have been cycle delays as permitted in the Protocol.

TEAEs

All participants in the retifanlimab + chemotherapy group and the placebo + chemotherapy group had at least 1 TEAE. In the retifanlimab + chemotherapy group, the most frequently reported (> 50%)

MedDRA SOCs were gastrointestinal disorders (87.7% vs 87.5% in the placebo +chemotherapy arm), general disorders and administration site conditions (83.8% vs 84.2%), blood and lymphatic system disorders (80.5% vs 81.6%), skin and subcutaneous tissue disorders (72.1% vs 63.8%), nervous system disorders (68.2% vs 72.4%), investigations (54.5% vs 49.3%), and infections and infestations (51.9% vs 54.6%). There was a higher incidence of the following SOCs in participants in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group: skin and subcutaneous tissue disorders (72.1% vs 63.8%), investigations (54.5% vs 49.3%), respiratory, thoracic and mediastinal disorders (42.2% vs 28.3%) and cardiac disorders (11.0% vs 5.3%).

By PT, the most frequently reported (> 15%) TEAEs in the retifanlimab + chemotherapy group are shown in 18. Of the frequently reported TEAEs, there was a higher incidence of the following TEAEs in participants in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group: diarrhoea (48.7% vs 40.1%), asthenia (47.4% vs 39.5%), pruritus (24.0% vs 6.6%), headache (16.2% vs 11.2%), rash (15.6% vs 7.9%), hypothyroidism (14.3% vs 3.3%), lymphopenia (11.0% vs 5.9%), mucosal inflammation (11.0% vs 5.9%), alanine aminotransferase increased (10.4% vs 4.6%), hyperthyroidism (8.4% vs 0.7%) and adrenal insufficiency(5.2% vs 0.0%).

Table 26: Summary of TEAEs Occurring in > 10% of Participants in the Retifanlimab + Chemotherapy Group During the Randomized Treatment Period by MedDRA Preferred Term in Decreasing Order of Frequency in Study INCMGA 0012-303 (Safety Population)

MedDRA PT, n (%)	**Group A** **Placebo + Chemotherapy** **(N = 152)**	**Group B** **Retifanlimab 500 mg Q4W + Chemotherapy** **(N = 154)**
Participants with a TEAE	152 (100.0)	154 (100.0)
Anaemia	106 (69.7)	102 (66.2)
Nausea	87 (57.2)	87 (56.5)
Alopecia	75 (49.3)	79 (51.3)
Diarrhoea	61 (40.1)	75 (48.7)
Neutropenia	67 (44.1)	73 (47.4)
Asthenia	60 (39.5)	73 (47.4)
Constipation	61 (40.1)	55 (35.7)
Neuropathy peripheral	46 (30.3)	46 (29.9)
Fatigue	50 (32.9)	45 (29.2)
Neutrophil count decreased	34 (22.4)	42 (27.3)
Vomiting	31 (20.4)	38 (24.7)
Decreased appetite	39 (25.7)	37 (24.0)
Pruritus	10 (6.6)	37 (24.0)
Arthralgia	21 (13.8)	25 (16.2)
Paraesthesia	18 (11.8)	25 (16.2)

MedDRA PT, n (%)	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Headache	17 (11.2)	25 (16.2)
White blood cell count decreased	20 (13.2)	24 (15.6)
Rash	12 (7.9)	24 (15.6)
Pyrexia	20 (13.2)	23 (14.9)
Dyspnoea	19 (12.5)	23 (14.9)
Thrombocytopenia	31 (20.4)	22 (14.3)
COVID-19	19 (12.5)	22 (14.3)
Hypothyroidism	5 (3.3)	22 (14.3)
Oedema peripheral	28 (18.4)	21 (13.6)
Leukopenia	17 (11.2)	20 (13.0)
Platelet count decreased	15 (9.9)	20 (13.0)
Dysgeusia	13 (8.6)	20 (13.0)
Hypokalaemia	12 (7.9)	19 (12.3)
Rectal haemorrhage	11 (7.2)	19 (12.3)
Abdominal pain	19 (12.5)	18 (11.7)
Back pain	20 (13.2)	17 (11.0)
Urinary tract infection	20 (13.2)	17 (11.0)
Cough	16 (10.5)	17 (11.0)
Peripheral sensory neuropathy	15 (9.9)	17 (11.0)
Lymphopenia	9 (5.9)	17 (11.0)
Mucosal inflammation	9 (5.9)	17 (11.0)
Alanine aminotransferase increased	7 (4.6)	16 (10.4)

TEAEs of Grade 3 or Higher

The retifanlimab + chemotherapy group had a higher proportion of participants who had at least 1 Grade 3 or higher TEAE (128 participants [83.1%]) than the placebo + chemotherapy group (114 participants [75.0%]). Of the most frequently reported SOCs, there was a higher incidence of Grade 3 or higher TEAEs in the SOCs of blood and lymphatic system disorders (51.9% vs 44.7%) and investigations (28.6% vs 16.4%) in participants in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group.

By PT, the most frequently reported (> 5%) Grade 3 or higher TEAEs in the retifanlimab + chemotherapy group are reported in Table 27. There was a higher incidence of the Grade 3 or higher TEAEs of neutropenia (35.1% vs 29.6%) and neutrophil count decreased (16.9% vs 8.6%) in participants in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group.

Table 27: Summary of Grade 3 or Higher TEAEs Occurring in > 3% of Participants in the Retifanlimab + Chemotherapy Group During the Randomized Treatment Period by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Population)

MedDRA PT, n (%)	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants with a Grade 3 or higher TEAE	114 (75.0)	128 (83.1)
Neutropenia	45 (29.6)	54 (35.1)
Anaemia	31 (20.4)	30 (19.5)
Neutrophil count decreased	13 (8.6)	26 (16.9)
White blood cell count decreased	13 (8.6)	14 (9.1)
Diarrhoea	9 (5.9)	8 (5.2)
Asthenia	5 (3.3)	6 (3.9)
Leukopenia	6 (3.9)	6 (3.9)
Lymphopenia	3 (2.0)	6 (3.9)
Lipase increased	0 (0.0)	5 (3.2)
Neuropathy peripheral	2 (1.3)	5 (3.2)
Pulmonary embolism	5 (3.3)	5 (3.2)
Sepsis	6 (3.9)	5 (3.2)

Treatment-Related TEAEs

Overall, 138 participants (89.6%) in the retifanlimab + chemotherapy group and 118 participants (77.6%) in the placebo + chemotherapy group had at least 1 TEAE considered by the investigator to be related to blinded study drug (Table 28). There was a higher incidence of TEAEs considered by the investigator to be related to blinded study drug in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group in the SOCs of general disorders and administration site conditions (54.5% vs 43.4%), skin and subcutaneous tissue disorders (40.9% vs 19.7%), investigations (27.3% vs 17.8%), endocrine disorders (21.4% vs 3.3%), and musculoskeletal and connective tissue disorders (14.9% vs 9.9%).

By PT, of the frequently reported TEAEs in the retifanlimab + chemotherapy group that were considered related to blinded study drug by the investigator, there was a higher incidence of the following TEAEs in participants in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group: asthenia (33.1% vs 24.3%), diarrhea (25.3% vs 12.5%), pruritus (15.6% vs

3.3%), rash 8 (11.0% vs 5.3%), hypothyroidism (13.0% vs 2.6%), lymphopenia (7.8% vs 2.0%) and hyperthyroidism (7.8% vs 0.7%); there was also a lower incidence of nausea (16.9% vs 25.0%).

Table 28: Summary of Retifanlimab/Placebo-Related TEAEs Occurring in > 5% of Participants in the Retifanlimab + Chemotherapy Group During the Randomized Treatment Period by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Population)

MedDRA PT, n (%)	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants with a retifanlimab/placebo-related TEAE	118 (77.6)	138 (89.6)
Asthenia	37 (24.3)	51 (33.1)
Diarrhoea	19 (12.5)	39 (25.3)
Anaemia	34 (22.4)	28 (18.2)
Fatigue	25 (16.4)	27 (17.5)
Nausea	38 (25.0)	26 (16.9)
Pruritus	5 (3.3)	24 (15.6)
Hypothyroidism	4 (2.6)	20 (13.0)
Rash	8 (5.3)	17 (11.0)
Neutropenia	26 (17.1)	15 (9.7)
Arthralgia	10 (6.6)	12 (7.8)
Constipation	14 (9.2)	12 (7.8)
Hyperthyroidism	1 (0.7)	12 (7.8)
Lymphopenia	3 (2.0)	12 (7.8)
Neutrophil count decreased	12 (7.9)	12 (7.8)
Alopecia	14 (9.2)	11 (7.1)
Decreased appetite	13 (8.6)	11 (7.1)
Aspartate aminotransferase increased	5 (3.3)	10 (6.5)
Vomiting	15 (9.9)	10 (6.5)
Platelet count decreased	5 (3.3)	9 (5.8)
Alanine aminotransferase increased	5 (3.3)	8 (5.2)

Of the most frequently reported TEAEs that were considered by the investigator to be related to chemotherapy in the retifanlimab + chemotherapy group, there was a higher incidence of the following TEAEs in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group: asthenia (41.6% vs 31.6%), diarrhea (37.0% vs 24.3%), paresthesia (14.9% vs 9.9%), mucosal inflammation

(9.7% vs 3.9%), lymphopenia (7.8% vs 2.0%) and pruritus (7.1% vs 1.3%); and there was a lower incidence of anemia (57.8% vs 63.2%) and fatigue (22.7% vs 29.6%).

Table 29: Summary of Chemotherapy-Related TEAEs Occurring in > 10% of Participants in the Retifanlimab + Chemotherapy Group During the Randomized Treatment Period by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Population)

MedDRA PT, n (%)	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants with a chemotherapy-related TEAE	148 (97.4)	152 (98.7)
Anaemia	96 (63.2)	89 (57.8)
Nausea	80 (52.6)	79 (51.3)
Alopecia	74 (48.7)	77 (50.0)
Neutropenia	66 (43.4)	72 (46.8)
Asthenia	48 (31.6)	64 (41.6)
Diarrhoea	37 (24.3)	57 (37.0)
Neuropathy peripheral	43 (28.3)	44 (28.6)
Neutrophil count decreased	34 (22.4)	41 (26.6)
Fatigue	45 (29.6)	35 (22.7)
Vomiting	27 (17.8)	31 (20.1)
Decreased appetite	27 (17.8)	26 (16.9)
Paraesthesia	15 (9.9)	23 (14.9)
White blood cell count decreased	20 (13.2)	23 (14.9)
Thrombocytopenia	29 (19.1)	22 (14.3)
Platelet count decreased	15 (9.9)	20 (13.0)
Constipation	26 (17.1)	19 (12.3)
Dysgeusia	13 (8.6)	19 (12.3)
Leukopenia	17 (11.2)	19 (12.3)
Peripheral sensory neuropathy	15 (9.9)	16 (10.4)

Retifanlimab monotherapy

Study INCMGA 0012-303: Retifanlimab Monotherapy - Crossover Period

During the crossover period, 58 of the 69 participants (84.1%) had at least 1 TEAE. Retifanlimab-related TEAE were observed in 37.7%, serious TEAE in 23.2% and Grade 3 or higher TEAE in 33.3% of the participants. No participants had fatal TEAE, serious retifanlimab-related TEAE, or TEAE leading to

retifanlimab infusion interruption. The retifanlimab dose was delayed due to a TEAE in 20.3% of the participants and retifanlimab was discontinued due to a TEAE in 1.4% of the patients.

The most frequently reported (> 5%) TEAEs by PT were constipation (15.9%); asthenia (13.0%); anemia, diarrhea, and hypothyroidism (11.6% each); decreased appetite and pyrexia (10.1% each); abdominal pain and fatigue (8.7% each), aspartate aminotransferase increased and vomiting (7.2% each); and arthralgia, dysuria, gastrooesophageal reflux disease, hypokalaemia, nausea, pain and pruritus (5.8% each).

During the crossover period, 14 participants (20.3%) had at least 1 irAE. One participant (1.4%) had a serious irAE (acute kidney injury), and 2 participants (2.9%) had a Grade 3 irAE (acute kidney injury and hyperthyroidism). IRRs occurred infrequently (2 participants [2.9%]), and all were Grades 1 or 2.

Study INCMGA 0012-202: Retifanlimab Monotherapy

Treatment-emergent AEs occurred in 90 of the 94 participants (95.7%). Treatment-emergent AEs considered related to retifanlimab by the investigator occurred in 55 participants (58.5%). Fifty participants (53.2%) had at least 1 serious TEAE, 54 participants (57.4%) had a at least 1 Grade 3 or higher TEAE, 10 participants (10.6%) had a fatal TEAE (Table 34) and 9 participants (9.6%) had a TEAE leading to retifanlimab discontinuation. Infusion interruption due to TEAE was observed in 1 participant (1.1%), retifanlimab dose was delayed due to a TEAE in 34.0% and retifanlimab was discontinued due to a TEAE in 9.6% of the participants.

The most frequent TEAEs were asthenia (24.5%); diarrhea (22.3%); anemia (20.2%); fatigue (19.1%); nausea (16.0%); constipation (14.9%); decreased appetite, dyspnoea, pyrexia and vomiting (each 13.8%); cough, pruritus, abdominal pain, arthralgia and urinary tract infection (each 10.6%); back pain, headache, hypothyroidism, proctalgia, rectal haemorrhage and weight decreased (each 9.6%); aspartate aminotransferase increased and pelvic pain (each 7.4%); hypercalcaemia and insomnia (each 6.4%); and cystitis and hypokalaemia (5.3% each).

The most frequent (> 5%) Grade 3 or higher TEAE was anemia (6.4%). Other Grade 3 or higher TEAEs occurring in > 2% of the participants were fatigue and pelvic pain (4.3% each); abdominal pain, asthenia, dyspnea, general physical health deterioration, hyponatremia, intestinal obstruction, and proctalgia (3.2% each); and decreased appetite, hematuria, hypercalcemia, hypertriglyceridemia, inadequate analgesia, pain, pleural effusion, pyrexia, sepsis, and urinary tract infection (2.1% each).

Safety in the combination therapy phase vs the monotherapy phase

Table 30 Summary of treatment-emergent adverse events during the randomized combination therapy period (population:safety population)

Variable	Group A (N=152)	Group B (N=154)	Total (N=306)
Participants who had a TEAE	152(100.0)	154(100.0)	306(100.0)
Participants who had a Retifanlimab/Placebo related TEAE	112(73.7)	130(84.4)	242(79.1)
Participants who had a serious TEAE	48(31.6)	58(37.7)	106(34.6)
Participants who had a Grade 3 or higher TEAE	111(73.0)	124(80.5)	235(76.8)
Participants who had a fatal TEAE	0(0.0)	4(2.6)	4(1.3)
Participants who had a serious Retifanlimab/Placebo related TEAE	7(4.6)	17(11.0)	24(7.8)
Participants who had a Grade 3 or higher Retifanlimab/Placebo related TEAE	37(24.3)	47(30.5)	84(27.5)
Participants who had Retifanlimab/Placebo dose interrupted because of TEAE	70(46.1)	76(49.4)	146(47.7)
Participants who had Retifanlimab/Placebo infusion interrupted because of TEAE	2(1.3)	5(3.2)	7(2.3)
Participants who had Retifanlimab/Placebo dose delayed at next schedule because of TEAE	70(46.1)	74(48.1)	144(47.1)
Participants who permanently discontinued Retifanlimab/Placebo because of TEAE	3(2.0)	10(6.5)	13(4.2)
Participants who had a Chemo related TEAE	148(97.4)	152(98.7)	300(98.0)
Participants who had a Paclitaxel related TEAE	147(96.7)	151(98.1)	298(97.4)
Participants who had a Carboplatin related TEAE	148(97.4)	149(96.8)	297(97.1)
Participants who permanently discontinued Chemo because of TEAE	7(4.6)	16(10.4)	23(7.5)
Participants who had Chemo dose interrupted because of TEAE	111(73.0)	112(72.7)	223(72.9)
Participants who had Chemo infusion interrupted because of TEAE	18(11.8)	18(11.7)	36(11.8)
Participants who had Chemo dose delayed at next schedule because of TEAE	108(71.1)	107(69.5)	215(70.3)

Footnotes

TEAE: any AE either reported starting on or after 31 days of the last Chemotherapy and within one year of the first administration of study treatment, or within 90 days of the last administration of Retifanlimab/Placebo, whichever occurred earlier. AEs that occurred after new anticancer therapy (including crossover treatment) would be excluded.
Retifanlimab/Placebo Related TEAEs: treatment-emergent adverse events judged as related to Retifanlimab/Placebo by the investigator or with a missing causality.
Chemo Related TEAEs: treatment-emergent adverse events judged as related to Chemotherapy by the investigator.
MedDRA Version: 26.1.
Reference: Listing 2.7.1.

Table 31 Summary of treatment-emergent adverse events during the randomized mono therapy period (population: safety population)

Variable	Group A (N=152)	Group B (N=154)	Total (N=306)
Participants who had a TEAE	87(57.2)	96(62.3)	183(59.8)
Participants who had a Retifanlimab/Placebo related TEAE	27(17.8)	53(34.4)	80(26.1)
Participants who had a serious TEAE	17(11.2)	19(12.3)	36(11.8)
Participants who had a Grade 3 or higher TEAE	21(13.8)	26(16.9)	47(15.4)
Participants who had a fatal TEAE	1(0.7)	0(0.0)	1(0.3)
Participants who had a serious Retifanlimab/Placebo related TEAE	2(1.3)	9(5.8)	11(3.6)
Participants who had a Grade 3 or higher Retifanlimab/Placebo related TEAE	1(0.7)	13(8.4)	14(4.6)
Participants who had Retifanlimab/Placebo dose interrupted because of TEAE	10(6.6)	20(13.0)	30(9.8)
Participants who had Retifanlimab/Placebo infusion interrupted because of TEAE	0(0.0)	1(0.6)	1(0.3)
Participants who had Retifanlimab/Placebo dose delayed at next schedule because of TEAE	10(6.6)	19(12.3)	29(9.5)
Participants who permanently discontinued Retifanlimab/Placebo because of TEAE	1(0.7)	7(4.5)	8(2.6)
Participants who had a Chemo related TEAE	34(22.4)	36(23.4)	70(22.9)
Participants who had a Paclitaxel related TEAE	34(22.4)	36(23.4)	70(22.9)
Participants who had a Carboplatin related TEAE	22(14.5)	28(18.2)	50(16.3)
Participants who permanently discontinued Chemo because of TEAE	2(1.3)	1(0.6)	3(1.0)
Participants who had Chemo dose interrupted because of TEAE	2(1.3)	2(1.3)	4(1.3)
Participants who had Chemo infusion interrupted because of TEAE	0(0.0)	0(0.0)	0(0.0)
Participants who had Chemo dose delayed at next schedule because of TEAE	2(1.3)	2(1.3)	4(1.3)

TEAE: any AE either reported for the first time or worsening of a pre-existing event after first dose of study treatment and within 90 days of the last administration of Retifanlimab/Placebo, or within 30 days of the last Chemotherapy. AEs that occurred after new anticancer therapy (including crossover treatment) would be excluded.
Note 1: Participants are counted once under the highest grade; TEAEs with missing severity are included under 'Any Grade' only.
Note 2: Adverse drug reactions are identified using pre-defined preferred terms.
Severity vs CTCAE Grade: Mild = Grade 1, Moderate = Grade 2, Severe = Grade 3, Life-Threatening = Grade 4, Fatal = Grade 5.
Reference: Listing 99.2.7.9.

Serious adverse event/deaths/other significant events

Serious TEAEs

The retifanlimab + chemotherapy group had a higher proportion of participants who had at least 1 serious TEAE (73 participants [47.4%]) than the placebo + chemotherapy group (59 participants [38.8%]). By PT, the most frequently reported (> 3%) serious TEAEs in the retifanlimab + chemotherapy group were sepsis and pulmonary embolism (5 participants [3.2%] each vs respectively, 4 participants [2.6%] and 1 participant 0.7% in the chemotherapy arm).

Table 32: Summary of Serious TEAEs Occurring in > 1% of Participants in the Retifanlimab + Chemotherapy Group During the Randomized Treatment Period by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Population)

MedDRA PT, n (%)	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants with a serious TEAE	59 (38.8)	73 (47.4)
Pulmonary embolism	1 (0.7)	5 (3.2)
Sepsis	4 (2.6)	5 (3.2)
Diarrhoea	4 (2.6)	4 (2.6)
Vomiting	3 (2.0)	4 (2.6)
Urinary tract infection	5 (3.3)	2 (1.3)
Pyrexia	3 (2.0)	3 (1.9)
Anaemia	2 (1.3)	3 (1.9)
Nausea	0 (0.0)	3 (1.9)
Acute kidney injury	2 (1.3)	2 (1.3)
Febrile neutropenia	2 (1.3)	2 (1.3)
Neutropenic sepsis	2 (1.3)	2 (1.3)
Adrenal insufficiency	0 (0.0)	2 (1.3)
COVID-19	0 (0.0)	2 (1.3)
Lipase increased	0 (0.0)	2 (1.3)
Rash maculo-papular	0 (0.0)	2 (1.3)
Rectal haemorrhage	0 (0.0)	2 (1.3)

Participants that had at least 1 serious TEAE considered by the investigator to be related to retifanlimab/placebo were more frequent in the retifanlimab + chemotherapy group (25 participants [16.2%]) than the placebo + chemotherapy group (10 participants [6.6%]).

By PT, the most frequently reported (> 1%) serious TEAEs that were considered by the investigator to be related to retifanlimab in the retifanlimab + chemotherapy group were anemia, adrenal insufficiency, lipase increased, and rash maculo-papular (2 participants [1.3%] each vs 0% each). In

the placebo + chemotherapy group diarrhoea (0.6% vs. 2.0%) and pyrexia (0.0% vs 1.3%) were also observed.

Study INCMGA 0012-202: Retifanlimab Monotherapy

Serious TEAEs occurred in 50 participants (53.2%). The most frequent serious TEAEs were abdominal pain, anemia, and pelvic pain (4 participants [4.3%] each); pyrexia and urinary tract infection (3 participants [3.2%] each); and dyspnea, general physical health deterioration, hematuria, hypercalcemia, inadequate analgesia, intestinal obstruction, pleural effusion, pneumonia, proctalgia, and sepsis (2 participants [2.1%] each). Six participants (6.4%) had serious TEAEs that were considered related to retifanlimab by the investigator and included adrenal insufficiency, abdominal pain (not considered related by the sponsor), immune-mediated enterocolitis, hepatitis, herpes zoster, and lymphangiosis carcinomatosa (1 participant [1.1%] each).

Deaths

Four participants (2.6%) in the retifanlimab + chemotherapy group and 1 participant (0.7%) in the placebo + chemotherapy group had a fatal TEAE (Table 33). The fatal TEAE of pancytopenia was considered by the investigator to be related to retifanlimab.

This participant had a medical history of tobacco use, decompensated enolic cirrhosis (Child-Pugh A-5), Model for End-Stage Liver Disease score 7, sensory polyneuropathy, asthenia, and abdominal pain. On Day 14, the participant developed pancytopenia without evidence of infection or bleeding and was admitted to the hospital. Laboratory evidence for decompensated liver failure was also apparent. Transfusions were administered and supportive management with antibiotics, filgrastim, morphine, dexamethasone, enoxaparin, and antiemetics were instituted. Despite these measures, the participant deteriorated rapidly and died on Day 18. No autopsy was performed. The sponsor assesses the pancytopenia as not related to retifanlimab and confounded by the participant's underlying malignancy and advanced liver disease, along with concurrent administration of cytotoxic chemotherapy.

Table 33: Summary of Fatal TEAEs During the Randomized Treatment Period by MedDRA System Organ Class and Preferred Term (Safety Population)

MedDRA SOC, n (%) **PT, n (%)**	**Group A** **Placebo + Chemotherapy** **(N = 152)**	**Group B** **Retifanlimab 500 mg** **Q4W + Chemotherapy** **(N = 154)**
Participants with a fatal TEAE	1 (0.7)	4 (2.6)
Blood and lymphatic system disorders	0 (0.0)	1 (0.6)
Pancytopenia	0 (0.0)	1 (0.6)
Infections and infestations	1 (0.7)	2 (1.3)
Pneumonia	1 (0.7)	1 (0.6)
Sepsis	0 (0.0)	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (0.6)
Metastases to peritoneum	0 (0.0)	1 (0.6)

Study INCMGA 0012-202: Retifanlimab Monotherapy

Fatal TEAEs occurred in 10 participants (10.6%) in Study INCMGA 0012-202 (see Table 34). Fatal TEAEs were most frequently associated with the SOCs of infections and infestations and neoplasms benign, malignant and unspecified (3 participants [3.2%] each), and respiratory, thoracic, and mediastinal disorders (2 participants [2.1%] each).

By MedDRA PT, fatal TEAEs included pelvic infection, peritonitis, *Pneumocystis jirovecii* pneumonia, femur fracture, hypercalcemia, lymphangiosis carcinomatosa, pancreatic carcinoma, tumor embolism, interstitial lung disease, and pleural effusion (1 participant [1.1%] each).

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. 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. An autopsy was not performed.

Table 34: Summary of TEAEs With a Fatal Outcome by MedDRA System Organ Class and Preferred Term in Study INCMGA 0012 202 (Safety Evaluable Population)

MedDRA SOC **PT, n (%)**	**Retifanlimab 500 mg Q4W** **(N = 94)**
Participants with a fatal TEAE	10 (10.6)
Infections and infestations	3 (3.2)
Pelvic infection	1 (1.1)
Peritonitis	1 (1.1)
Pneumocystis jirovecii pneumonia	1 (1.1)
Injury, poisoning and procedural complications	1 (1.1)
Femur fracture	1 (1.1)
Metabolism and nutrition disorders	1 (1.1)
Hypercalcaemia	1 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (3.2)
Lymphangiosis carcinomatosa	1 (1.1)
Pancreatic carcinoma	1 (1.1)
Tumor embolism	1 (1.1)
Respiratory, thoracic and mediastinal disorders	2 (2.1)
Interstitial lung disease	1 (1.1)
Pleural effusion	1 (1.1)

TEAEs Leading to (Dose/)Infusion Interruption

In total, 3.9% of the participants in the retifanlimab + chemotherapy group and 1.3% of the participants in the placebo + chemotherapy group had at least 1 TEAE leading to infusion interruption of retifanlimab/placebo.

In the retifanlimab + chemotherapy group, all TEAEs leading to infusion interruption of retifanlimab were reported in 1 participant (0.6% vs 0.0% in the placebo + chemotherapy arm) each: anemia, atrial fibrillation, extravasation, toxicity to various agents, increased blood ALP, and dry skin. TEAEs leading to infusion interruption of placebo in the placebo + chemotherapy group included anal abscess, lower respiratory tract infection, and lung abscess (these events were not observed in the retifanlimab + chemotherapy arm). Of note, according to the MAH, these events may have been incorrectly categorized as infusion interruptions and these are more likely to have been cycle delays as permitted in the Protocol.

In total, 11.7% of the participants in the retifanlimab + chemotherapy group and 11.8% of the participants in the placebo + chemotherapy group had at least 1 TEAE leading to infusion interruption of chemotherapy. The most frequently reported (> 1 participant) TEAEs leading to infusion interruption of chemotherapy for participants in the retifanlimab + chemotherapy group were infusion related reaction and neutrophil count decreased (4 participants [2.6%] each vs respectively 3.3% and 0.7% in the placebo+chemotherapy arm) and neutropenia (2 participants [1.3] vs 1 participant [0.7] in the placebo+ chemotherapy arm); all other TEAEs leading to infusion interruption of chemotherapy were reported in 1 participant (0.6%) each.

TEAEs Leading to Dose Delay

Similar proportions of participants in the retifanlimab + chemotherapy group (52.6%) and the placebo + chemotherapy group (49.3%) had at least 1 TEAE leading to dose delay of retifanlimab/placebo.

The most frequently reported (> 2%) TEAE leading to dose delay of retifanlimab for participants in the retifanlimab + chemotherapy group were neutropenia (23 participants [14.9%] vs 21 [13.8] in the placebo + chemotherapy group), anaemia (7.1% vs 3.3%), thrombocytopenia 7 (3.2% vs 4.6%), COVID-19 (5.2% vs 5.3%), urinary tract infection (2.6% vs 4.6%), neutrophil count decreased (5.2% vs 4.6%), platelet count decreased (2.6% vs 0.7%) and white blood cell count decreased (2.6% vs 0.7%). In addition, the most frequently reported (> 2%) TEAE leading to dose delay of placebo for participants in the placebo + chemotherapy group also included asthenia (1.9% vs 3.3 %) and fatigue (0.6% vs 2.0%).

Similar proportions of participants in the retifanlimab + chemotherapy group (69.5%) and the placebo + chemotherapy group (71.1%) had at least 1 TEAE leading to dose delay of chemotherapy. The most frequently reported (> 5%) TEAEs leading to dose delay of chemotherapy for participants in the retifanlimab + chemotherapy group were neutropenia (27.3% vs 30.3% in the placebo + chemotherapy group), neutrophil count decreased (17.5% vs 10.5%), anemia (14.3% vs 11.2%), white blood cell count decreased (7.8% vs 4.6%), asthenia (5.8% vs 4.6%). In addition, the most frequently reported (> 5%) TEAE leading to dose delay of chemotherapy for participants in the placebo + chemotherapy group also included thrombocytopenia (4.5% vs 7.9%) and COVID-19 (4.5% vs 7.9%).

TEAEs of special interest

Immune-Related Adverse Events

Immune-related AEs included predefined PTs that were grouped into irAE categories by the sponsor and used to identify irAEs independent of investigator assessment of causality.

The retifanlimab + chemotherapy group had a higher proportion of participants that had at least 1 irAE (48.7% vs 26.3%) than the placebo + chemotherapy group (Table 35).

Table 35: Overall Summary of Sponsor-Assessed Immune-Related TEAEs During the Randomized Treatment Period (Safety Population)

Participants (n [%]) with:	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
irAE	40 (26.3)	75 (48.7)
Retifanlimab/placebo-related irAE	23 (15.1)	54 (35.1)
Serious irAE	7 (4.6)	18 (11.7)
Grade 3 or higher irAE	9 (5.9)	21 (13.6)
Fatal irAE	0 (0.0)	0 (0.0)
Serious retifanlimab/placebo-related irAE	4 (2.6)	15 (9.7)
Grade 3 or higher retifanlimab/placebo-related irAE	6 (3.9)	17 (11.0)
Retifanlimab/placebo infusion interruption due to irAE	0 (0.0)	0 (0.0)
Retifanlimab/placebo dose delayed due to irAE	2 (1.3)	9 (5.8)
irAE leading to discontinuation of retifanlimab/placebo	0 (0.0)	10 (6.5)
Chemotherapy-related irAE	25 (16.4)	30 (19.5)
irAE leading to discontinuation of chemotherapy	1 (0.7)	5 (3.2)

In the retifanlimab + chemotherapy group, the most frequent (> 10%) sponsor-assessed irAEs by group term were hypothyroidism (22 participants [14.3%]); other, nervous system (19 participants [12.3%]), skin reactions (18 participants [11.7%]), and colitis (16 participants [10.4%]; see Table 36).

There was a higher incidence (> 5% difference) for the following irAEs group terms in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group: hypothyroidism (14.3% vs 3.3%), colitis (10.4% vs 3.9%), hyperthyroidism (8.4% vs 0.7%), and adrenal insufficiency (5.8% vs 0.0%).

By PT, in the retifanlimab + chemotherapy group, the most frequent (> 5%) sponsor-assessed irAEs were peripheral sensory neuropathy (11.0% vs 9.9% in the placebo + chemotherapy group), hypothyroidism (14.3% vs 3.3%), diarrhoea (9.7% vs 3.3%), hyperthyroidism (8.4% vs 0.7%), pruritus (7.1% vs 2.0%) and adrenal insufficiency (5.2% vs 0.0%).

Table 36: Summary of Sponsor-Assessed Immune-Related TEAEs During the Randomized Treatment Period by Group Term and Preferred Term in Decreasing Order of Frequency in the Retifanlimab + Chemotherapy Group Total (Safety Population)

Group Term, n (%)	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants with an irAE	40 (26.3)	75 (48.7)
Hypothyroidism	5 (3.3)	22 (14.3)
Other, Nervous System[a]	16 (10.5)	19 (12.3)
Skin Reactions[b]	14 (9.2)	18 (11.7)
Colitis[c]	6 (3.9)	16 (10.4)
Hyperthyroidism	1 (0.7)	13 (8.4)
Adrenal Insufficiency[d]	0 (0.0)	9 (5.8)
Hepatitis[e]	1 (0.7)	2 (1.3)
Hypophysitis	0 (0.0)	2 (1.3)
Nephritis[f]	2 (1.3)	2 (1.3)
Myasthenic Syndrome	0 (0.0)	1 (0.6)
Other, rare - Hematologic[g]	0 (0.0)	1 (0.6)
Other, rare - Hepatobiliary[h]	0 (0.0)	1 (0.6)
Pneumonitis	3 (2.0)	1 (0.6)
Thyroiditis[i]	0 (0.0)	1 (0.6)
Other, rare - Musculoskeletal and connective tissue[j]	1 (0.7)	0 (0.0)
Pancreatitis[k]	1 (0.7)	0 (0.0)

[a] Group term includes the PTs of peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and vocal cord paralysis.

[b] Group term includes the PTs of pruritus, rash maculo-papular, rash, dermatitis, rash pruritic, dermatitis acneiform, palmar-plantar erythrodysaesthesia syndrome, rash erythematous, and rash pustular.

[c] Group term includes the PTs of diarrhoea, colitis, and immune-mediated enterocolitis.

[d] Group term includes the PTs of adrenal insufficiency and secondary adrenocortical insufficiency.

[e] Group term includes the PTs of immune-mediated hepatitis and hepatitis.

[f] Group term includes the PT of acute kidney injury.

[g] Group term includes the PT of warm autoimmune haemolytic anaemia.

[h] Group term includes the PT of immune-mediated cholangitis.

[i] Group term includes the PT of autoimmune thyroiditis.

[j] Group term includes the PTs of Raynaud's phenomenon and rheumatoid arthritis.

[k] Group term includes the PT of pancreatitis acute.

The most frequent (> 1.5%) Grade 3 or higher irAEs by group term in the retifanlimab + chemotherapy group were colitis (3.2% vs 2.0% in the placebo + chemotherapy group), adrenal insufficiency (1.9% vs 0.0%) and skin reactions (1.9% vs 0.7%).

The most frequent irAEs (>1%) leading to dose delay of retifanlimab/placebo by group term in the retifanlimab + chemotherapy group were adrenal insufficiency (1.9% vs 0.0% in the placebo + chemotherapy group), colitis (1.3% vs 0.7%), hypophysitis (1.3% vs 0.0%) and skin reactions (1.3% vs 0.0%).

IrAEs leading to retifanlimab/placebo drug discontinuation by group term in more than one participant in the retifanlimab + chemotherapy group were colitis and skin reactions (2 participants [1.3%] versus 0.0% placebo + chemotherapy group each).

The number of participants with irAEs occurring (first onset) after 6 months of initiation of retifanlimab/placebo was 22 (14.3%) in the retifanlimab + chemotherapy group versus 10 (6.6%) in the in the placebo + chemotherapy group. Of these irAEs the most frequent (>1.5%) in the retifanlimab + chemotherapy group by group term were: hypothyroidism (4.5% vs 2.0% in the placebo + chemotherapy group), adrenal insufficiency (3.9% vs 0.0%) and colitis (1.9% vs 0.7%). The number of participants with IrAEs occurring (first onset) after 12 months of initiation of retifanlimab/placebo was 2 (1.3%) in the retifanlimab + chemotherapy group versus 1 (0.7%) in the placebo + chemotherapy group. In the retifanlimab + chemotherapy group these were by group term: hypothyroidism (0.6% vs 0.0% in the placebo + chemotherapy group) and skin reactions (0.6% vs 0.0%).

Resolving of irAEs is summarized in Table 37. for the most frequent irAEs (>5%) in the retifanlimab + chemotherapy group.

Table 37: Summary of Resolution of Treatment-Emergent Adverse Events of Special Interest During Randomized Period (Population: Safety Population)

Group Term, n (%)	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Hypothyroidism		
Resolved	2 (40.0)	6 (27.3)
Ongoing	3 (60.0)	16 (72.7)
Other, Nervous System		
Resolved	2 (12.5)	5 (26.3)
Ongoing	14 (87.5)	14 (73.7)
Skin Reactions		
Resolved	13 (92.9)	13 (72.2)
Ongoing	1 (7.1)	5 (27.8)
Colitis		
Resolved	6 (100.0)	15 (93.8)
Ongoing	0 (0.0)	1 (6.3)
Hyperthyroidism		
Resolved	0 (0.0)	10 76.9)
Ongoing	1 (100.0)	3 (23.1)
Adrenal Insufficiency		
Resolved	0 (0.0)	4 (44.4)
Ongoing	0 (0.0)	5 (55.6)

TEAE: any AE either reported for the first time or worsening of a pre-existing event after first dose of study treatment and within 90 days of the last administration of Retifanlimab/Placebo, or within 30 days of the last Chemotherapy. AEs that occurred after new anticancer therapy (including crossover treatment) would be excluded.

Note 1: Immune-related AEs are identified using pre-defined preferred terms regardless of investigator's assessment of causality. Note 2: Infusion reactions include AEs indicating diagnosis of infusion reaction occurred during the entire treatment period, as well as symptoms of infusion reaction occurred within 1 day of infusion and resolved within 2 days from AE onset. Note 3: For a particular group term, time to onset of AESI is defined as the time between the start date of the study treatment and the start date of the earliest AESI in days.

MedDRA Version: 26.1.

Detailed summaries for these group terms are provided below:

Hypothyroidism was maximum severity Grade 1 (4.5% vs 2.0%), Grade 2 (9.1% vs 1.3%), or Grade 4 (0.6% vs 0%) for the retifanlimab + chemotherapy and placebo + chemotherapy groups, respectively. One participant (0.6%) in the retifanlimab + chemotherapy group and no participants in the placebo + chemotherapy group had serious hypothyroidism and hypothyroidism leading to retifanlimab discontinuation. No participants had hypothyroidism leading to dose delay. Median time to onset of hypothyroidism was 138.5 days (range: 55-390 days) in the retifanlimab + chemotherapy group. Among the 22 participants with hypothyroidism in the retifanlimab + chemotherapy group, 10 participants (45.5.%) received systemic steroid therapy, including 3 participants (13.6%) who received high dose systemic steroid therapy; 17 participants (77.3%) received thyroid endocrine therapy and 1 participant (4.5%) received other irAE treatment. Hypothyroidism resolved in 6 of 22 participants (27.3%) who received retifanlimab + chemotherapy and 2 of 5 participants (40%) who received placebo + chemotherapy. The median time to resolution in the retifanlimab arm was 114 days (range, 57 – 212 days).

Colitis was maximum severity Grade 1 (3.9% vs 1.3%), Grade 2 (3.2% vs 0.7%), Grade 3 (2.6% vs 2.0%), or Grade 4 (0.6% vs 0%) for the retifanlimab + chemotherapy and placebo + chemotherapy groups, respectively. Three participants (1.9%) in the retifanlimab + chemotherapy group and 3 participants (2.0%) in the placebo + chemotherapy group had serious colitis. Two participants (1.3%) in the retifanlimab + chemotherapy group and 1 participant (0.7%) in the placebo + chemotherapy group had colitis leading to dose delay. Two participants (1.3%) in the retifanlimab + chemotherapy group and no participants in the placebo + chemotherapy group had colitis leading to retifanlimab discontinuation. Median time to onset of colitis was 83.5 days (range: 3 - 271 days) in the retifanlimab + chemotherapy group. Among the 16 participants with colitis in the retifanlimab + chemotherapy group, 15 participants (93.8%) received systemic steroid therapy, including 12 participants (75%) who received high dose systemic steroid therapy; 1 participant (6.3%) received systemic immunosuppressants. Colitis resolved in 15 of 16 participants (93.8%) who received retifanlimab + chemotherapy and all 6 participants (100%) who received placebo + chemotherapy.

Hyperthyroidism was maximum severity Grade 1 (4.5% vs 0%), Grade 2 (3.2% vs 0.7%), or Grade 3 (0.6% vs 0%) for the retifanlimab + chemotherapy and placebo + chemotherapy groups, respectively. One participant (0.6%) in the retifanlimab + chemotherapy group and no participants in the placebo + chemotherapy group had serious hyperthyroidism. No participants had hyperthyroidism leading to dose delay or discontinuation). Median time to onset for hyperthyroidism was 82.0 days (range: 8 - 278 days) in the retifanlimab + chemotherapy group. Among the 13 participants with hyperthyroidism in the retifanlimab + chemotherapy group, 3 participants (23.1%) received systemic steroid therapy, including 1 participant (7.7%) who received high dose systemic steroid therapy; 4 participants (30.8%) received thyroid endocrine therapy. Hyperthyroidism resolved in 10 of 13 participants (76.9%) who received retifanlimab + chemotherapy and 0 of 1 participant (0%) who received placebo + chemotherapy. The median time to resolution in the retifanlimab arms was 29 days (range, 8 – 130 days).

Adrenal insufficiency was maximum severity Grade 1, Grade 2, or Grade 3 (1.9% each) for the retifanlimab + chemotherapy group; no participants in the placebo + chemotherapy group had adrenal insufficiency. In the retifanlimab + chemotherapy group, 3 participants (1.9%) had serious adrenal insufficiency or adrenal insufficiency leading to dose delay, and 1 participant (0.6%) had adrenal insufficiency leading to retifanlimab discontinuation. Median time to onset of adrenal insufficiency was 197.0 days (range: 63 - 302 days) in the retifanlimab + chemotherapy group. Among the 9 participants with adrenal insufficiency in the retifanlimab + chemotherapy group, 9 participants (100%) received systemic steroid therapy, including 1 participant (11.1%) who received high dose

systemic steroid therapy; no participants received endocrine therapy, immunosuppressants, or other irAE treatment. All patients were considered to have secondary adrenal insufficiency by the MAH. Adrenal insufficiency resolved in 4 of 9 participants (44.4%) who received retifanlimab + chemotherapy with a time to resolution of 13.5 days.

Other nervous system disorder (group term includes the PTs of peripheral sensory neuropathy (11.0% vs 9.9%), peripheral motor neuropathy (0.6% vs 0), peripheral sensorimotor neuropathy (0.6% vs 0%, and vocal cord paralysis (0.6% vs 0%) was maximum severity Grade 1 in (7.8% vs 5.9%), Grade 2 in (3.9% vs 3.9%), or Grade 3 in (0.6% vs 0.7%) for the retifanlimab + chemotherapy group and placebo + chemotherapy groups, respectively. In the retifanlimab + chemotherapy group, no participants had serious other nervous system disorders, or other nervous system disorders leading to dose delay, and 1 participant (0.6 %) had other nervous system disorders leading to retifanlimab discontinuation. Median time to onset of other nervous system disorders was 56.0 days (range 1-225 days) in the retifanlimab + chemotherapy group. Among the 19 participants with other nervous system disorders in the retifanlimab + chemotherapy group, no participants received systemic steroid therapy; 4 (21.1%) participants received endocrine therapy, no participants received immunosuppressants, and 1 (5.3%) received other irAE treatment. Other nervous system disorders resolved in 5 out of 19 participants (26.3%.) who received retifanlimab + chemotherapy.

Skin reaction was maximum severity Grade 1 in (0.0% vs 0.0%), Grade 2 in (9.7% vs 8.6%), or Grade 3 in (1.9% vs 0.7%) for the retifanlimab + chemotherapy group and placebo + chemotherapy groups, respectively. In the retifanlimab + chemotherapy group, 2 participants (1.3%) had serious, or skin reactions leading to dose delay, and 2 participants (1.3%) had skin reactions leading to retifanlimab discontinuation. Median time to onset of skin reactions was 46.5 days (range: 2-443 days) in the retifanlimab + chemotherapy group. Among the 18 participants with skin reactions in the retifanlimab + chemotherapy group, 6 participants (33.3%) received systemic steroid therapy, including 4 participants (22.2.%) who received high dose systemic steroid therapy. No participants received immunosuppressants, or other irAE treatment. Skin reactions resolved in 13 of 18 participants (72.2%) who received retifanlimab + chemotherapy with a median time to resolution of 22 days (range, 5 – 385 days).

Hypophysitis was reported in 2 patients (1.3%, both Grade 2, vs. 0%). The median time to onset of hypophysitis was 192 days (range, 90 – 294 days). Neither of the events led to discontinuation of retifanlimab. Hypophysitis resolved in 1 of the 2 patients, with a time to resolution of 8 days.

Hepatitis occurred in 2 patients (1.3%, both Grade 3 vs 0.7%). The median time to onset of hepatitis was 195.5 days (range, 140 – 251 days). Hepatitis led to discontinuation of retifanlimab in 1 patient. Both patients with hepatitis received systemic corticosteroids and another immunosuppressant (mycophenolate mofetil). Hepatitis resolved in both patients, with a median time to resolution of 58.5 days (range, 57 – 60 days).

Study INCMGA 0012-202: Retifanlimab Monotherapy

In Study INCMGA 0012-202, irAEs occurred in 25 participants (26.6%). Immune related AEs were Grade 3 in 4 participants (4.3%), Grade 4 in 3 participants (3.2%), and Grade 5 in 1 participant (1.1%). Serious irAEs and irAEs leading to retifanlimab discontinuation occurred in 5 participants (5.3%) and 4 participants (4.3%), respectively. One participant (1.1%) had a fatal irAE, pneumonitis (PT: interstitial lung disease), which was considered related to retifanlimab. See Table 38.

Table 38: Summary of Treatment-Emergent Immune-Related Adverse Events by Group Term in Study INCMGA 0012 202 (Safety Evaluable Population)

irAE, n (%)	Retifanlimab 500 mg Q4W (N = 94)	
	All Grades	Grades ≥ 3
Endocrine irAEs		
Hypothyroidism	9 (9.6)	0 (0.0)
Hyperthyroidism	4 (4.3)	0 (0.0)
Adrenal insufficiency	1 (1.1)	1 (1.1)
Nonendocrine irAEs		
Skin reactions[a]	8 (8.5)	2 (2.1)
Pneumonitis[b]	4 (4.3)	2 (2.1)
Colitis[c]	1 (1.1)	1 (1.1)
Hepatitis	1 (1.1)	1 (1.1)
Myositis	1 (1.1)	0 (0.0)
Nephritis[d]	1 (1.1)	1 (1.1)
Other rare irAEs		
Pericarditis	1 (1.1)	0 (0.0)

[a] Skin reactions includes the PTs of dermatitis, palmar-plantar erythrodysaesthesia syndrome, pruritus, psoriasis, rash, rash erythematous, and rash maculo-papular.

[b] Pneumonitis includes the PTs of interstitial lung disease and pneumonitis.

[c] Colitis includes the PT of immune-mediated enterocolitis.

[d] Nephritis includes the PT of acute kidney injury.

Study INCMGA 0012-303: Retifanlimab Monotherapy - Crossover Period

During the crossover period, 14 participants (20.3%) had at least 1 irAE. One participant (1.4%) had a serious irAE (acute kidney injury), and 2 participants (2.9%) had a Grade 3 irAE (acute kidney injury and hyperthyroidism).

IRRs

Infusion-related reactions included diagnosis of infusion reactions that occurred anytime during the treatment period and symptoms of potential infusion reactions that occurred within 1 day of infusion and resolved within 2 days of AE onset.

In the retifanlimab + chemotherapy group and the placebo + chemotherapy group participants had at least 1 IRR in 9.7% vs 7.9% and at least 1 IRR considered by the investigator to be related to chemotherapy in 8.4% vs 6.6% (see Table 39).

Table 39: Overall Summary of Sponsor-Assessed Infusion-Related Reactions During the Randomized Treatment Period (Safety Population)

Participants (n [%]) with:	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
IRR	12 (7.9)	15 (9.7)
Retifanlimab/placebo-related IRR	2 (1.3)	4 (2.6)
Serious IRR	1 (0.7)	0 (0.0)
Grade 3 or higher IRR	2 (1.3)	3 (1.9)
Fatal IRR	0 (0.0)	0 (0.0)
Serious retifanlimab/placebo-related IRR	0 (0.0)	0 (0.0)
Grade 3 or higher retifanlimab/placebo-related IRR	0 (0.0)	1 (0.6)
Retifanlimab/placebo infusion interruption due to IRR	0 (0.0)	0 (0.0)
Retifanlimab/placebo dose delayed due to IRR	1 (0.7)	0 (0.0)
IRR leading to discontinuation of retifanlimab/placebo	1 (0.7)	0 (0.0)
Chemotherapy-related IRR	10 (6.6)	13 (8.4)
IRR leading to discontinuation of chemotherapy	1 (0.7)	2 (1.3)

Potential symptoms for IRRs are shown in Table 40.

Three participants (1.9%) in the retifanlimab + chemotherapy group had at least 1 Grade 3 or higher IRR, which were dyspnea and hyperhidrosis (2 participants [1.3%] each) and infusion related reaction, hypersensitivity, and tachypnea (1 participant [0.6%] each).

Table 40: Summary of Sponsor-Assessed Infusion-Related Reaction During the Randomized Treatment Period by Group Term and Preferred Term in Decreasing Order of Frequency (Safety Population)

MedDRA Group Term, n (%) MedDRA PT, n (%)	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Participants with an IRR	12 (7.9)	15 (9.7)
Diagnosis of Infusion Reaction	10 (6.6)	10 (6.5)
Infusion related reaction	8 (5.3)	5 (3.2)

MedDRA Group Term, n (%) MedDRA PT, n (%)	Group A Placebo + Chemotherapy (N = 152)	Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)
Drug hypersensitivity	1 (0.7)	3 (1.9)
Hypersensitivity	0 (0.0)	2 (1.3)
Anaphylactic shock	1 (0.7)	0 (0.0)
Symptom of Potential Infusion Reaction	4 (2.6)	7 (4.5)
Erythema	1 (0.7)	2 (1.3)
Dyspnoea	0 (0.0)	2 (1.3)
Hyperhidrosis	0 (0.0)	2 (1.3)
Pyrexia	1 (0.7)	2 (1.3)
Tachycardia	0 (0.0)	1 (0.6)
Tachypnoea	0 (0.0)	1 (0.6)
Hypotension	2 (1.3)	0 (0.0)
Rash	1 (0.7)	0 (0.0)

Study INCMGA 0012-202: Retifanlimab Monotherapy

Infusion-related reactions occurred in 5 participants (5.3%) in Study INCMGA 0012-202. All IRRs were Grade 1 or 2 in severity and nonserious. Infusion related reactions led to retifanlimab infusion interruptions infrequently (1 participant [1.1%]).

Study INCMGA 0012-303: Retifanlimab Monotherapy - Crossover Period

During the crossover period, IRRs occurred infrequently (2 participants [2.9%]), and all were Grades 1 or 2.

Laboratory findings

Clinical Haematology

At baseline in the retifanlimab + chemotherapy group, 67 participants (43.5%) had low lymphocytes, 65 participants (42.2%) had low haemoglobin, 47 participants (41.6%) had high neutrophils/leukocytes, 58 participants (37.9%) had low haematocrit, 57 participants (37.3%) had low erythrocytes, 42 participants (37.2%) had low lymphocytes/leukocytes, and 31 participants (20.1%) had high neutrophils. A summary of treatment-emergent worsening of haematology parameters in the retifanlimab + chemotherapy group is shown in Table 41.

Table 41: Treatment-Emergent Worsening of CTCAE-Graded Haematology Laboratory Parameters During the Randomized Treatment Period in Decreasing Order of Frequency in the Retifanlimab + Chemotherapy Group in Study INCMGA 0012-303 (Any Grade, Safety Population)

Laboratory Parameter, n/n (%)	Group A Placebo + Chemotherapy (N = 152)					Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)				
	n	Any Grade	Grade 3	Grade 4	Grades 3-4	n	Any Grade	Grade 3	Grade 4	Grades 3-4
Hemoglobin (decreased)	152	140 (92.1)	36 (23.7)	NA	36 (23.7)	154	140 (90.9)	30 (19.5)	NA	30 (19.5)
Leukocytes (decreased)	152	136 (89.5)	51 (33.6)	10 (6.6)	61 (40.1)	154	135 (87.7)	58 (37.7)	9 (5.8)	67 (43.5)
Neutrophils (decreased)	152	118 (77.6)	43 (28.3)	16 (10.5)	59 (38.8)	154	122 (79.2)	62 (40.3)	18 (11.7)	80 (51.9)
Lymphocytes (decreased)	152	105 (69.1)	48 (31.6)	9 (5.9)	57 (37.5)	154	118 (76.6)	49 (31.8)	13 (8.4)	62 (40.3)
Platelets (decreased)	151	79 (52.3)	6 (4.0)	0 (0.0)	6 (4.0)	154	85 (55.2)	6 (4.0)	3 (1.9)	9 (5.8)
Hemoglobin (increased)	152	2 (1.3)	0 (0.0)	NA	0 (0.0)	154	4 (2.6)	1 (0.6)	NA	1 (0.6)
Lymphocytes (increased)	152	2 (1.3)	1 (0.7)	NA	1 (0.7)	154	2 (1.3)	0 (0.0)	NA	0 (0.0)
Leukocytes (increased)	152	0 (0.0)	0 (0.0)	NA	0 (0.0)	154	1 (0.6)	1 (0.6)	NA	1 (0.6)

Note: Worst CTCAE grade postbaseline. If baseline grade was missing, any postbaseline abnormality (Grade 1-4) was considered worsening from baseline. Denominator is total number of participants with both baseline and postbaseline assessments within each parameter. NA indicates Grade 3 or 4 CTCAE grade is not applicable to the parameter.

In the CSR a summary of hematology laboratory values in CTCAE Grade to the worst abnormal value during the randomized period (Population: Safety Population) has been provided. A shift from baseline to a Grade 3 or 4 laboratory abnormality occurring in > 3% of patients was observed for the following ADRs in the retifanlimab + chemotherapy group vs the placebo + chemotherapy group:

- Decreased lymphocytes: 42.8% vs 38.1%
- Decreased neutrophils: 52.0% vs 38.8%

Clinical Chemistry

Treatment-emergent worsening of chemistry parameters in the retifanlimab + chemotherapy group is summarized in Table 42.

Table 42: Treatment-Emergent Worsening of CTCAE-Graded Chemistry Laboratory Parameters During the Randomized Treatment Period in Decreasing Order of Frequency in the Retifanlimab + Chemotherapy Group in Study INCMGA 0012 303 (Any Grade; Safety Population)

Laboratory Parameter, n/n (%)	Group A Placebo + Chemotherapy (N = 152)					Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)				
	n	Any Grade	Grade 3	Grade 4	Grades 3-4	n	Any Grade	Grade 3	Grade 4	Grades 3-4
Albumin (decreased)	149	43 (28.9)	2 (1.3)	NA	2 (1.3)	152	56 (36.8)	3 (2.0)	NA	3 (2.0)
ALT (increased)	152	35 (23.0)	1 (0.7)	0 (0.0)	1 (0.7)	153	53 (34.6)	6 (3.9)	0 (0.0)	6 (3.9)
LDH (increased)	151	40 (26.5)	NA	NA	NA	151	45 (29.8)	NA	NA	NA
Sodium (decreased)	152	34 (22.4)	2 (1.3)	0 (0.0)	2 (1.3)	153	44 (28.8)	0 (0.0)	0 (0.0)	0 (0.0)
ALP (increased)	150	38 (25.3)	0 (0.0)	0 (0.0)	0 (0.0)	153	40 (26.1)	3 (2.0)	0 (0.0)	3 (2.0)
AST (increased)	152	25 (16.4)	0 (0.0)	0 (0.0)	0 (0.0)	153	39 (25.5)	6 (3.9)	0 (0.0)	6 (3.9)
Potassium (decreased)	152	24 (15.8)	4 (2.6)	0 (0.0)	4 (2.6)	153	36 (23.5)	8 (5.2)	0 (0.0)	8 (5.2)
Derived calcium corrected for albumin (increased)	149	29 (19.5)	1 (0.7)	1 (0.7)	2 (1.3)	151	34 (22.5)	3 (2.0)	0 (0.0)	3 (2.0)
Creatinine (increased)	152	17 (11.2)	1 (0.7)	1 (0.7)	2 (1.3)	153	34 (22.2)	1 (0.7)	0 (0.0)	1 (0.7)
Amylase (increased)	137	13 (9.5)	0 (0.0)	NA	0 (0.0)	133	27 (20.3)	1 (0.8)	NA	1 (0.8)
Lipase (increased)	142	21 (14.8)	1 (0.7)	NA	1 (0.7)	143	26 (18.2)	7 (4.9)	NA	7 (4.9)
Potassium (increased)	152	21 (13.8)	0 (0.0)	0 (0.0)	0 (0.0)	153	27 (17.6)	1 (0.7)	0 (0.0)	1 (0.7)
Glucose (decreased)	150	13 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)	151	20 (13.2)	0 (0.0)	0 (0.0)	0 (0.0)

Laboratory Parameter, n/n (%)	Group A Placebo + Chemotherapy (N = 152)					Group B Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)				
	n	Any Grade	Grade 3	Grade 4	Grades 3-4	n	Any Grade	Grade 3	Grade 4	Grades 3-4
Bilirubin (increased)	152	7 (4.6)	2 (1.3)	0 (0.0)	2 (1.3)	151	15 (9.9)	2 (1.3)	0 (0.0)	2 (1.3)
Derived calcium corrected for albumin (decreased)	149	12 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)	151	11 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)
Sodium (increased)	152	3 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	153	4 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Worst CTCAE grade postbaseline. If baseline grade was missing, any postbaseline abnormality (Grade 1-4) was considered worsening from baseline. NA indicates Grade 3 or 4 CTCAE grade is not applicable to the parameter. Denominator is total number of participants with both baseline and postbaseline assessments within each parameter.

No participant in either treatment group met the laboratory criteria for potential Hy's law, defined as ALT or AST >= 3xULN, BILI >= 2xULN, and ALP < 2xULN.

In the CSR a summary of chemistry laboratory values in CTCAE Grade to the worst abnormal value during the randomized period (Population: Safety Population) has been provided. A shift from baseline to a Grade 3 or 4 laboratory abnormality occurring in > 3% of patients was observed for the following ADRs in the retifanlimab + chemotherapy group vs the placebo + chemotherapy group:

- Lipase: 4.5% vs. 0.7%
- alanine aminotransferase: 3.9% vs 0.7%
- aspartate aminotransferase: 3.9% vs. 0%

ECGs

At any time on study, clinically significant ECG abnormalities occurred infrequently, with similar proportions of participants in the retifanlimab + chemotherapy group (1.9%) and the placebo + chemotherapy group (1.3%) having at least 1 clinically significant ECG abnormality.

In the retifanlimab + chemotherapy group, at any time on study, of the 133 participants with QTc values during the study, 3 participants (2.3% vs 2.3% in the placebo + chemotherapy group) had measured QTc values ≥ 480 ms, 1 participant (0.8% vs 0.0%) had a measured QTc value ≥ 500 ms, 22 participants (16.5% vs 16.5%) had QTc changes from baseline of ≥ 30 ms, and 2 participants (1.5% vs 0.0%) had QTc changes from baseline of ≥ 60 ms.

Immunogenicity

ADA status at baseline and during the study is shown in Table 43.

Table 43: Summary of Anti-drug Antibody Status during Randomized Period

Parameter: ADA Analysis Result

Treatment Group: Carboplatin+Paclitaxel+Retifanlimab

		Baseline			
Visit	Result	Positive	Negative	Missing	Total
Any time during study	Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Negative	0 (0.0)	149 (96.8)	1 (0.6)	150 (97.4)
	Missing	1 (0.6)	2 (1.3)	1 (0.6)	4 (2.6)
	Total	1 (0.6)	151 (98.1)	2 (1.3)	154 (100.0)

Treatment Group: Carboplatin+Paclitaxel+Placebo

		Baseline			
Visit	Result	Positive	Negative	Missing	Total
Any time during study	Positive	6 (3.9)	2 (1.3)	0 (0.0)	8 (5.3)
	Negative	0 (0.0)	134 (88.2)	2 (1.3)	136 (89.5)
	Missing	0 (0.0)	8 (5.3)	0 (0.0)	8 (5.3)
	Total	6 (3.9)	144 (94.7)	2 (1.3)	152 (100.0)

None of the participants were positive for NAb.

Safety in special populations

Safety subgroup analyses for age are shown in Table 44 and Table 45. Subgroup analyses for sex and ECOG performance status do not show a consistently worse safety profile of retifanlimab in either subgroup. In addition, safety data for the subgroup with HIV positive status (N=6 vs 5 patients) has been provided in the CSR, however are not shown due to the small sample size. Subgroup analyses based on hepatic and renal function at baseline do not indicate differences in safety in the retifanlimab + chemotherapy group (data not shown).

Table 44: Overall Summary of Treatment-Emergent Adverse Events by Age Subgroup in Study INCMGA 0012 303 (Safety Population)

			Treatment-Emergent Adverse Events, n (%)							
Age Subgroup	Treatment Group	N	All	Retifanlimab/ Placebo-Related	≥ Grade 3	Serious	With Fatal Outcome	Leading to Retifanlimab/ Placebo Infusion Interruption	Leading to Retifanlimab/ Placebo Dose Delay	Leading to Retifanlimab/ Placebo Discontinuation
< 65 years	Group A Placebo + Chemotherapy	99	99 (100.0)	75 (75.8)	75 (75.8)	35 (35.4)	0 (0.0)	1 (1.0)	49 (49.5)	2 (2.0)
	Group B Retifanlimab 500 mg Q4W + Chemotherapy	96	96 (100.0)	83 (86.5)	79 (82.3)	42 (43.8)	2 (2.1)	2 (2.1)	42 (43.8)	12 (12.5)
≥ 65 years	Group A Placebo + Chemotherapy	53	53 (100.0)	43 (81.1)	39 (73.6)	24 (45.3)	1 (1.9)	1 (1.9)	26 (49.1)	2 (3.8)
	Group B Retifanlimab 500 mg Q4W + Chemotherapy	58	58 (100.0)	55 (94.8)	49 (84.5)	31 (53.4)	2 (3.4)	4 (6.9)	39 (67.2)	5 (8.6)
< 75 years	Group A Placebo + Chemotherapy	135	135 (100.0)	105 (77.8)	101 (74.8)	52 (38.5)	1 (0.7)	2 (1.5)	67 (49.6)	4 (3.0)
	Group B Retifanlimab 500 mg Q4W + Chemotherapy	140	140 (100.0)	125 (89.3)	118 (84.3)	69 (49.3)	3 (2.1)	5 (3.6)	73 (52.1)	15 (10.7)
≥ 75 years	Group A Placebo + Chemotherapy	17	17 (100.0)	13 (76.5)	13 (76.5)	7 (41.2)	0 (0.0)	0 (0.0)	8 (47.1)	0 (0.0)
	Group B Retifanlimab 500 mg Q4W + Chemotherapy	14	14 (100.0)	13 (92.9)	10 (71.4)	4 (28.6)	1 (7.1)	1 (7.1)	8 (57.1)	2 (14.3)

Table 45: Study INCMGA 0012-303 TEAEs by Treatment Group and Age Group during the Randomized Period (Safety Population)

	Group A **Placebo + Chemotherapy**				**Group B** **Retifanlimab + Chemotherapy**			
MedDRA[a] Terms **Age**	**Age** **< 65** **N = 99**	**Age** **65-74** **N = 36**	**Age** **75-84** **N = 17**	**Age** **85+** **N = 0**	**Age** **< 65** **N = 96**	**Age** **65-74** **N = 44**	**Age** **75-84** **N = 13**	**Age** **85+** **N = 1**
Total AEs	99 (100.0)	36 (100.0)	17 (100.0)	0 (0.0)	96 (100.0)	44 (100.0)	13 (100.0)	1 (100.0)
Serious AEs – Total	35 (35.4)	17 (47.2)	7 (41.2)	0 (0.0)	42 (43.8)	27 (61.4)	4 (30.8)	0 (0.0)
- Fatal	0 (0.0)	1(2.8)	0 (0.0)	0 (0.0)	2 (2.1)	1 (2.3)	1 (7.7)	0 (0.0)
-Hospitalization /prolong existing hospitalization	34 (34.3)	15 (41.7)	7 (41.2)	0 (0.0)	41 (42.7)	26 (59.1)	4 (30.8)	0 (0.0)
- Life-threatening	1 (1.0)	2 (5.6)	1 (5.9)	0 (0.0)	4 (4.2)	2 (4.5)	0 (0.0)	0 (0.0)
-Disability/ incapacity	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
- Other (medically significant)	5 (5.1)	4 (11.1)	2 (11.8)	0 (0.0)	12 (12.5)	5 (11.4)	1 (7.7)	0 (0.0)
AE leading to drop-out	2 (2.0)	2 (5.6)	0 (0.0)	0 (0.0)	12 (12.5)	3 (6.8)	1 (7.7)	1 (100.0)
Psychiatric disorders (SOC)	15 (15.2)	7 (19.4)	0 (0.0)	0 (0.0)	18 (18.8)	7 (15.9)	1 (7.7)	0 (0.0)
Nervous system disorders (SOC)	72 (72.7)	26 (72.2)	12 (70.6)	0 (0.0)	65 (67.7)	32 (72.7)	8 (61.5)	0 (0.0)
Accidents and injuries (SMQ)	5 (5.1)	6 (16.7)	3 (17.6)	0 (0.0)	11 (11.5)	6 (13.6)	1 (7.7)	0 (0.0)
Cardiac disorders (SOC)	4 (4.0)	4 (11.1)	0 (0.0)	0 (0.0)	12 (12.5)	4 (9.1)	1 (7.7)	0 (0.0)
Vascular disorders (SOC)	25 (25.3)	8 (22.2)	1 (5.9)	0 (0.0)	17 (17.7)	7 (15.9)	4 (30.8)	0 (0.0)
Cerebrovascular disorders (PT)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations (SOC)	55 (55.6)	21 (58.3)	7 (41.2)	0 (0.0)	54 (56.3)	20 (45.5)	6 (46.2)	0 (0.0)
Anticholinergic syndrome (PT)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Group A Placebo + Chemotherapy				Group B Retifanlimab + Chemotherapy			
MedDRA[a] Terms **Age**	**Age < 65** **N = 99**	**Age 65-74** **N = 36**	**Age 75-84** **N = 17**	**Age 85+** **N = 0**	**Age < 65** **N = 96**	**Age 65-74** **N = 44**	**Age 75-84** **N = 13**	**Age 85+** **N = 1**
Quality of life decreased (PT)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[b]	8 (8.1)	7 (19.4)	3 (17.6)	0 (0.0)	13 (13.5)	5 (11.4)	0 (0.0)	0 (0.0)

TEAE: any AE either reported for the first time or worsening of a pre-existing event after first dose of study treatment and within 90 days of the last administration of retifanlimab/placebo, or within 30 days of the last chemotherapy AEs that occurred after new anticancer therapy (including crossover treatment) would be excluded.

Note: Participants are counted only once under each variable

a MedDRA Version 26.1

b Includes the following PTs: ankle fracture, ataxia, dizziness, dizziness postural, fall, femoral neck fracture, femur fracture, hand fracture, humerus fracture, loss of consciousness, lumbar vertebral fracture, orthostatic hypotension, radius fracture, spinal compression fracture, spinal fracture, syncope, traumatic fracture, upper limb fracture, vertigo positional, wrist fracture.

Safety related to drug-drug interactions and other interactions

NA.

Discontinuation due to adverse events

A higher proportion of participants in the retifanlimab + chemotherapy group (17 participants [11.0%]) than the placebo + chemotherapy group (4 participants [2.6%]) had at least 1 TEAE leading to discontinuation of retifanlimab and placebo.

In the retifanlimab + chemotherapy group, the only reported TEAE leading to discontinuation of retifanlimab in more than 1 participant was immune-mediated enterocolitis (2 participants [1.3%]). All other TEAEs leading to discontinuation of retifanlimab were reported in 1 participant (0.6%) each. In total, irAEs leading to discontinuation of retifanlimab were reported in 10 (6.5%) participants (adrenal insufficiency, hypothyroidism, immune-mediated enterocolitis, hepatitis, immune-mediated cholangitis, warm autoimmune haemolytic anaemia, peripheral sensorimotor neuropathy, pruritus and rash). In the placebo + chemotherapy group, all TEAEs leading to discontinuation of placebo occurred in 1 participant (0.7%) each, none of which were immune-mediated. Infusion reactions led to discontinuation of retifanlimab or placebo in 1 participant in the placebo + chemotherapy group.

A higher proportion of participants in the retifanlimab + chemotherapy group (16 participants [10.4%]) than the placebo + chemotherapy group (8 participants [5.3%]) had at least 1 TEAE leading to discontinuation of chemotherapy.

In the retifanlimab + chemotherapy group, the most frequently reported (> 1 participant) TEAEs leading to discontinuation of chemotherapy was peripheral neuropathy (3 participants [1.9%]). All other TEAEs leading to discontinuation of chemotherapy were reported in 1 participant (0.6%) each in

the retifanlimab + chemotherapy group. Peripheral neuropathy leading to discontinuation of chemotherapy was not observed in the placebo + chemotherapy group.

There were 6 TEAEs leading to discontinuation of all study therapy in the retifanlimab +chemotherapy group versus 1 in the placebo +chemotherapy group. The event of immune-mediated enterocolitis was considered related to retifanlimab, in addition the event of adrenal insufficiency could be related to retifanlimab, but no imaging was performed to confirm the diagnosis.

Study INCMGA 0012-202: Retifanlimab Monotherapy

Treatment-emergent AEs leading to retifanlimab discontinuation occurred in 9 participants (9.6%) in Study INCMGA 0012-202: blood bilirubin increased, diffuse large B-cell lymphoma, hepatitis, immune mediated enterocolitis, palmar-plantar erythrodysesthesia syndrome, pelvic pain, pleural effusion, pneumonitis, and pseudomonas infection (1 participant [1.1%] each).

ADR selection

The adverse reactions identified for retifanlimab in combination with chemotherapy in participants with SCAC are based on the sponsor's medical assessment of each individual TEAE where a causal relationship with the treatment is considered a reasonable possibility. The review consisted of all TEAEs, independent of the causality assessment by the investigator, including irAEs, IRRs, ≥ Grade 3 TEAEs, serious TEAE, fatal TEAEs, TEAEs leading to discontinuation or dose interruption (e.g., dose delay), and laboratory abnormalities regardless of incidence. The following factors (EMA 2024, Kommu et al 2024, Norén and Edwards 2009) were considered when making decisions on whether a causal relationship to retifanlimab when given in combination with chemotherapy in SCAC is plausible:

- Frequency of reporting
- TEAE rates seen with retifanlimab + chemotherapy versus placebo + chemotherapy
- Biological plausibility based on the mechanism of action of retifanlimab and known effects of PD-(L)1 class
- Temporal relationship to retifanlimab exposure (e.g., timing of an event relative to the time of retifanlimab exposure)
- Evaluation of the clinical course, including medical interventions (e.g., corticosteroids)
- Population under study (including comorbidities, prior/concomitant therapy, and prior medical history)

These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing incidence.

Table 46 Adverse Reactions in Participants Receiving Retifanlimab + Chemotherapy in Study INCMGA 0012-303 (Safety Population). Updated Dec 22 2025.

	Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)		**Placebo + Chemotherapy (N = 152)**	
System Organ Class	**Frequency of All Grades (%)**	**Frequency of Grades 3-4 (%)**	**Frequency of All Grades (%)**	**Frequency of Grades 3-4 (%)**
Blood and lymphatic system disorders	**Very common** Neutropenia[a] (70.1) Lymphopenia[b] (14.3)	**Very common** Neutropenia[a] (50.0) **Common** Lymphopenia[b] (5.8)	**Very common** Neutropenia[a] (66.4) **Common** Lymphopenia[b] (9.2)	**Very common** Neutropenia[a] (38.1) **Common** Lymphopenia[b] (3.9)
Endocrine disorders	**Very common** Hypothyroidism (14.3) **Common** Hyperthyroidism (8.4) Adrenal insufficiency (5.2) Hyperglycaemia (3.9) Hypophysitis (1.3) **Uncommon** Autoimmune thyroiditis (0.6) Secondary adrenocortical insufficiency (0.6)	**Common** Adrenal insufficiency (1.3) **Uncommon** Hypothyroidism (0.6) Hyperthyroidism (0.6) Secondary adrenocortical insufficiency (0.6)	**Common** Hypothyroidism (3.3) **Uncommon** Hyperthyroidism (0.7) **Uncommon** Hyperglycaemia (0.7)	
Metabolism and nutrition disorders	**Common** Hyponatraemia (3.9)	**Common** Hyponatraemia (1.3)	**Common** Hyponatraemia (1.3)	**Uncommon** Hyponatraemia (0.7)
Nervous system disorders[c]	**Very Common** Peripheral sensory neuropathy (11) **Uncommon** Peripheral motor neuropathy (0.6) Peripheral sensorimotor neuropathy (0.6)	**Uncommon** Peripheral sensorimotor neuropathy (0.6)	**Common** Peripheral sensory neuropathy (9.9) **Uncommon** Vocal cord paralysis[c] (0.7)	**Uncommon** Peripheral sensory neuropathy (0.7)
Gastrointestinal disorders	**Very common** Colitis[d] (10.4) **Common** Stomatitis (4.5)	**Common** Colitis[d] (3.2)	**Common** Colitis (3.9) Stomatitis (2.0)	**Common** Colitis (2.0)
Hepatobiliary disorders	**Common** Hepatitis[e] (1.3) **Uncommon** Immune-mediated cholangitis (0.6)	**Common** Hepatitis[e] (1.3) **Uncommon** Immune-mediated cholangitis (0.6)	**Uncommon** Hepatitis[f] (0.7)	**Uncommon** Hepatitis[f] (0.7)

System Organ Class	Retifanlimab 500 mg Q4W + Chemotherapy (N = 154)		Placebo + Chemotherapy (N = 152)	
	Frequency of All Grades (%)	**Frequency of Grades 3-4 (%)**	**Frequency of All Grades (%)**	**Frequency of Grades 3-4 (%)**
Skin and subcutaneous tissue disorders	**Very common** Pruritus (24.0) Rash[g] (23.4)	**Common** Rash[g] (1.3) **Uncommon** Pruritus (0.6)	**Very common** Rash[h] (12.5) **Common** Pruritus (6.6)	**Uncommon** Rash[h] (0.7)
Musculoskeletal and connective tissue disorders	**Common** Arthritis (2.6)		**Uncommon** Arthritis (0.7)	
General disorders administration site conditions	**Very common** Asthenia (47.4)	**Common** Asthenia (3.9)	**Very Common** Asthenia (39.5)	**Common** Asthenia (3.3)
Investigations	**Very common** Alanine aminotransferase increased (10.4) **Common** Aspartate aminotransferase increased (8.4) Lipase increased (5.2) Blood creatinine increased (5.2) Amylase increased (2.6)	**Common** Lipase increased (3.2) Alanine aminotransferase increased (2.6) Aspartate aminotransferase increased (2.6) **Uncommon** Blood creatinine increased (0.6) Amylase increased (0.6)	**Common** Aspartate aminotransferase increased (6.6) Alanine aminotransferase increased (4.6) Lipase increased (2.0) Amylase increased (1.3) Blood creatinine increased (1.3)	**Uncommon** Blood creatinine increased (0.7)
Injury, poisoning and procedural complications	**Common** Infusion-related reaction (3.2)	**Uncommon** Infusion-related reaction (0.6)	**Common** Infusion-related reaction (5.3)	**Uncommon** Infusion-related reaction (0.7)

Note: Graded according to NCI CTCAE v5.0.
a Includes neutropenia and neutrophil count decreased.
b Includes lymphocyte count decreased and lymphopenia.
c Group term includes the PTs of peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and vocal cord paralysis. NOTE: vocal cord paralysis only occurred in placebo plus chemotherapy study treatment arm.
d Includes colitis, immune-mediated enterocolitis, and immune mediated diarrhoea.
e Includes hepatitis and immune-mediated hepatitis.
f Includes immune-mediated hepatitis only.
g Includes rash, rash erythematous, rash maculo-papular, and rash pruritic.
h Includes rash, rash maculo-papular, and rash pruritic.

Post marketing experience

A periodic safety update report (PSUR) has been submitted to the EMA covering the period of 21/03/2024 to 21/09/2024. The evaluation procedure started on 12 December 2024. Based on the PRAC review of data on safety and efficacy, the PRAC considered that the risk-benefit balance of medicinal products containing retifanlimab remained unchanged and therefore recommended the maintenance of the marketing authorisation.

2.5.1. Discussion on clinical safety

The safety profile of retifanlimab in combination with carboplatin and paclitaxel has not been previously described and is based on the safety data from pivotal randomized Study INCMGA 0012-303. The safety population includes all randomized participants who received at least 1 dose of study treatment.

Exposure

As of the data cutoff date of 15 April 2024, a total of 154 patients were treated in the retifanlimab + chemotherapy group with a median treatment duration of 7.4 months, compared with 6.8 months in the placebo + chemotherapy group. In relation to the proposed target population, the extent of exposure is considered acceptable for assessment of the benefit-risk balance.

Long-term safety data of retifanlimab monotherapy remain limited, as only a small proportion of patients received treatment beyond 12 months (8.4% at updated DCO of 01 August 2025). Considering the poor prognosis of SCAC patients, this limitation is considered acceptable, although it contributes to residual uncertainty regarding long-term safety. Long-term safety is reflected as missing information in the RMP and addressed through routine pharmacovigilance activities.

Exposure to chemotherapy was similar between the two study arms and therefore differences in chemotherapy exposure are not expected to be of large influence on the observed AEs. It should also be noted that participants enrolled in SCAC studies were relatively fitter than the broader population, and thus more toxicity could be expected in clinical practice.

Supportive study data of retifanlimab monotherapy in patients with locally advanced or metastatic SCAC who have progressed on or are intolerant to platinum-based chemotherapy from study INCMGA 0012-202 has also been provided. This data has been assessed during the initial marketing authorisation (EMEA/H/C/006194/0000) and are only briefly discussed here.

Adverse events

Overall, the addition of retifanlimab to chemotherapy led to more serious TEAEs (47.4% vs 38.8%), Grade 3 or higher TEAEs (83.1% vs 75.0%) and more discontinuations due to TEAEs of retifanlimab/placebo (11.0% vs 2.6%) as well of chemotherapy (10.4% vs 5.3%) in the retifanlimab + chemotherapy group compared with the placebo + chemotherapy group. In addition, there were more treatment-related serious and Grade 3 or higher TEAEs in the retifanlimab + chemotherapy group.

Based on a comprehensive review of all reported TEAEs and subsequent discussion of several events identified as potential ADRs, no new or major safety concerns were identified. The overall safety profile is in line with other PD-L1 inhibitors. The ADRs have been adequately reflected in section 4.8 of the SmPC.

TEAEs more frequently observed in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group were associated with the mechanism of action of immunotherapy and are known ADRs for retifanlimab monotherapy (pruritus [24.0% vs 6.6%], rash [15.6% vs 7.9%], hypothyroidism [14.3% vs 3.3%], hyperthyroidism [8.4% vs 0.7%], adrenal insufficiency [5.2% vs 0.0%] and alanine aminotransferase increased [10.4% vs 4.6%]). Other AEs more frequently observed in the retifanlimab + chemotherapy group (headache [16.2% vs 11.2%] and mucosal inflammation [11.0% vs 5.9%]) are known ADRs for paclitaxel/carboplatin and therefore agreed not to consider these ADRs for retifanlimab + chemotherapy. Asthenia, initially not identified as an ADR by the MAH, occurs more frequently in the retifanlimab + chemotherapy group compared to placebo+ chemotherapy (47.4% vs 39.5%) and may be a risk for chemotherapy, however asthenia is often considered to be related to retifanlimab/placebo by the investigator and therefore considered to be an ADR. Arthritis, initially not identified as an ADR by the MAH, had a numerically higher incidence in the retifanlimab +

chemotherapy group than in the placebo + chemotherapy group and is considered to be an ADR for retifanlimab + chemotherapy.

Treatment-related TEAEs with a higher incidence in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group were asthenia, diarrhea, pruritus, rash, hypothyroidism, lymphopenia and hyperthyroidism. There were several chemotherapy-related TEAEs with a higher incidence in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group (asthenia, diarrhea, paresthesia, mucosal inflammation and pruritus). Paresthesia and mucosal inflammation are typically associated with chemotherapy.

The higher frequency of Grade 3 or higher TEAEs in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group was mostly due to higher frequencies of neutropenia (35.1% vs 29.6%) and neutrophil count decreased (16.9% vs 8.6%). Neutropenia, although typically related to chemotherapy, has been identified by the MAH as an ADR for retifanlimab + carboplatin and paclitaxel, which is supported as this ADR is also reported for other PD-1/PD-L1 targeted therapies. A warning has been added in section 4.4 of the SmPC stating that the concomitant administration of retifanlimab with carboplatin and paclitaxel increased the risk and severity of neutropenia and that frequent haematological monitoring is recommended and treatment guidelines for neutropenia should be followed.

The TEAEs observed for retifanlimab monotherapy in the crossover period and in Study 0012-202 are in line with the known safety profile. The overview of safety per combination therapy phase and monotherapy phase in the randomized period indicates that much higher frequencies of all categories of AEs are observed in the combination therapy phase compared to the monotherapy phase. Still tolerability issues leading to discontinuation may arise in the retifanlimab monotherapy phase (discontinuations of retifanlimab/placebo due to AEs is 4.5% vs 0.7% in the placebo arm).

SAEs and deaths

SAEs were more frequent in the retifanlimab + chemotherapy group compared to the placebo + chemotherapy group (47.4% vs 38.8%). Sepsis (3.2% vs 2.6%) and pulmonary embolism (PE) (3.2 vs 0.7%) were the most frequently reported serious TEAEs in the retifanlimab + chemotherapy group. SAEs appear mostly related to chemotherapy or to the underlying disease, though some serious TEAEs were related to immune therapy (diarrhoea [2.6% vs 2.6%], adrenal insufficiency, lipase increased and rash maculo-papular [each 1.3% vs 0%]). There is a numerical difference in the number of fatal TEAEs not favouring the retifanlimab + chemotherapy group versus the placebo + chemotherapy group (4 [2.6%] vs 1 [0.7%]). The fatal TEAEs in the retifanlimab + chemotherapy group were pancytopenia, pneumonia, sepsis and metastases to peritoneum and pneumonia in the placebo + chemotherapy group. Fatal events reported as TEAEs are considered disease or chemotherapy related. Narratives for fatal cases do not indicate a relationship with retifanlimab treatment. In supportive study 202 there was a relatively high number of fatal TEAEs, in 10 participants (10.6%). This study was part of the initial marketing authorisation (EMEA/H/C/006194/0000) and has been previously assessed.

TEAEs of special interest: irAEs and IRRs

As expected more patients in the retifanlimab + chemotherapy group had at least 1 irAE (48.7% vs 26.3%) than the placebo + chemotherapy group. Serious irAEs were observed in 11.7% vs 4.6% of the patients, Grade 3 or higher irAEs in 13.6% vs 5.9% and irAE leading to discontinuation of retifanlimab/placebo 6.5 vs 0%.

By group term the most frequent irAEs in the retifanlimab + chemotherapy group were hypothyroidism (14.3%); nervous system disorders (12.3%), skin reactions (11.7%), and colitis (10.4%). The most

frequent Grade 3 or higher irAEs by group terms were colitis (3.2% vs 2.0%), adrenal insufficiency (1.9% vs 0%) and skin reactions (1.9% vs 0.7%). In the ADR table the frequency of colitis was corrected to "very common" (10.4%), and Grade 3-4 colitis "common". Immune-mediated diarrhoea is included under the term "colitis". "Not immune mediated diarrhoea" was reported for 60 participants (39%) in retifanlimab group and 56 participants in placebo group (37%) and therefore "diarrhoea" was not included as an ADR.

The reported irAEs are generally in line with the known safety profile of retifanlimab and PD-L1 inhibitors. However, the frequency of irAEs and irAEs by SOC was higher in patients with SCAC than in patients with MCC. This is perhaps due to the longer exposure in patients with SCAC compared with patients with MCC (median treatment duration of 7.4 vs 5.4 months, respectively).

Several uncommon or rare irAEs were observed in SCAC patients, including immune-mediated cholangitis, autoimmune thyroiditis and stomatitis, which have been added in the ADR table in section 4.8 of the SmPC. In addition, section 4.4 is updated to include further information on these rare irAEs. IrAEs are extensively described in sections 4.2, 4.4 and 4.8 of the SmPC.

With respect to adrenal insufficiency, which is usually associated with the life-long need for hormone substitution therapy, a proportion of patients were reported as resolved. However, it remains unclear if patients were considered recovered while they were on successful replacement therapy, and this contributes to uncertainty regarding the reversibility of this event.

The review of reported PTs in the SOC Skin and subcutaneous tissue disorders did not identify additional events of suspected irAEs, except one event of skin hypopigmentation, which was not considered sufficient to be classified as an ADR. Events of peripheral motor neuropathy and peripheral sensorimotor neuropathy reported only in retifanlimab + chemotherapy group were considered ADRs and were added to the ADR table.

IRRs occurred slightly more frequently in the retifanlimab + chemotherapy group compared with the placebo + chemotherapy group (9.7% vs 7.9%). Grade 3 or higher IRRs were rare (1.9% vs 1.3%) and occurred at comparable rates in the two study arms. No dose modifications or discontinuations due to IRRs were observed in the retifanlimab + chemotherapy group.

Dose modifications and discontinuations due to AEs

The frequency of dose modifications was comparable between the study arms, the most frequent reason for dose modifications were AEs. The MAH has reported that there were no dose/infusion interruptions of retifanlimab/placebo, however infusion interruptions of retifanlimab/placebo due to TEAEs were reported in both study arms (3.9% vs 1.3%). It is considered unlikely that the reported TEAEs (e.g. laboratory abnormalities, abscesses) manifested during infusion and therefore it is agreed with the MAH that these are likely events leading to dose delay that have been incorrectly categorized as infusion interruptions.

Rates of TEAEs leading to dose delays were comparable in both study arms and are mostly AEs associated with chemotherapy (haematological toxicity and infections). Rates of dose modifications of chemotherapy were comparable in the two study arms. Discontinuation of retifanlimab and placebo due to TEAEs was more frequent in the retifanlimab + chemotherapy group than in the placebo + chemotherapy group (11.0% vs 2.6%). TEAEs leading to discontinuation of retifanlimab were mostly immune-related (6.5% vs 0%). Discontinuation of chemotherapy due to TEAEs were also more frequent in the retifanlimab + chemotherapy group (than the placebo + chemotherapy group (10.4% vs 5.3%). TEAEs leading to discontinuation of all study therapy were observed in 6 patients in the retifanlimab +chemotherapy group versus 1 in the placebo +chemotherapy group. One of these events

(immune-mediated enterocolitis) was considered related to retifanlimab, and the event of adrenal insufficiency could be related to retifanlimab.

Laboratory abnormalities

Frequencies of worsening of haematology laboratory parameters were generally comparable between the two treatment arms except for Grade 3-4 neutrophils decreased (51.9% vs 38.8%) and lymphocytes decreased 76.6% vs 69.1%). Both have been added as ADRs, which is supported.

For several parameters, the frequency of worsening of chemistry laboratory parameters is higher in the retifanlimab + chemotherapy group compared with the placebo + chemotherapy group. Most of these parameters are reported as ADRs, including ALT increased, AST increased, lipase increased and sodium decreased, which is supported.

The following parameters are known ADRs for retifanlimab monotherapy but were initially not identified as ADRs for retifanlimab + carboplatin and paclitaxel; creatinine increased (22.2% vs 11.2%) and amylase increased (20.3% vs 9.5%). Based on the observed imbalance, these events are considered ADRs in the combination setting. In addition, hyperglycaemia (4.0% vs 0.7%) is considered an ADR.

Gamma glutamyl transferase increase was initially identified as an ADR by the MAH, however, due to lack mechanistic evidence linking PD-L1 inhibition or retifanlimab exposure to isolated GGT elevations, this was not considered an ADR.

No patient in either treatment group met the laboratory criteria for potential Hy's law. ECG abnormalities are comparable between the two study arms.

There were no ADA positive patients in the retifanlimab + chemotherapy group during the study.
A paragraph on laboratory abnormalities has been added to section 4.8 of the SmPC.

Safety in special populations

In the retifanlimab + chemotherapy group, patients ≥ 65 years of age had a higher frequency of related TEAEs, serious TEAEs, TEAEs leading to dose delay of retifanlimab or placebo and dose delays and dose interruptions for chemotherapy compared to patients >65 years of age. However, in the placebo + chemotherapy group this could also be observed, except for TEAEs leading to dose delay of retifanlimab or placebo. As this only considers one type of event, it is not needed to report in the SmPC that elderly patients may have different safety compared to younger patients. There were few patients included of 75 years and older (14 vs 17 patients) and thus the results of the subgroup analyses in these patients are not considered reliable.

Subgroup analyses for sex and ECOG performance status do not show a consistently worse safety profile of retifanlimab in either subgroup. The subgroup with HIV positive status (N=6 vs 5 patients) was too small for reliable interpretation of the data.

It should also be noted that participants enrolled in SCAC studies were generally fitter than the broader population, and thus tolerability of retifanlimab in combination with chemotherapy should be interpreted with caution when extrapolating to clinical practice, since more toxicity could be expected.

Hepatic/renal impairment

The SmPC states that no dose adjustment is needed for patients with mild or moderate renal impairment and for patients with mild hepatic impairment. There are no or insufficient data in patients with severe renal impairment and with end stage renal disease and in patients with severe hepatic impairment. In this procedure, subgroup analyses based on hepatic and renal function at baseline do not indicate differences in safety in the retifanlimab + chemotherapy group.

2.5.2. Conclusions on clinical safety

The frequencies and types of AEs observed are consistent with the known safety profile of PD-(L)1 inhibitors and no new safety issues were identified. The safety profile of retifanlimab in combination with carboplatin and paclitaxel in patients with SCAC is considered acceptable and manageable in the context of the disease.

Overall, the addition of retifanlimab to chemotherapy was associated with a higher frequency of treatment discontinuations and a moderate increase in serious and severe AEs, mainly driven by immune related adverse reactions. As duration of exposure remains limited, uncertainty regarding long-term safety remains and is included in the RMP as missing information, to be addressed through routine pharmacovigilance activities.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 1.1 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.1 with the following content:

Safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-Mediated Adverse Reactions Infusion-Related Reactions
Important potential risks	None
Missing information	Long-term safety

Pharmacovigilance plan

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. No additional pharmacovigilance activities are ongoing or planned.

Risk minimisation measures

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

Safety concern	**Routine risk minimisation activities**
Immune-mediated adverse reactions	Routine risk communication: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4

	Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for dose modifications for immune-mediated adverse reactions are included in SmPC sections 4.2 and 4.4 Signs and symptoms of immune-mediated adverse reactions and potential dose modifications are included in PL sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription
Infusion-related reactions	Routine risk communication: SmPC sections 4.2, 4.4, 4.8 PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for prophylaxis and dose modifications for infusion-related reactions are included in SmPC sections 4.2 and 4.4 Signs and symptoms of infusion-related reactions and potential dose modifications are included in PL sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription
Long term safety data	Routine risk communication: N/A Routine risk minimisation activities recommending specific clinical measures to address the risk: N/A Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are being updated to reflect the addition of the new indication. The Package Leaflet (PL) is updated accordingly. In addition, editorial changes are also made to the PI.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes introduced by this variation do not substantially impact the readability of the package leaflet, no user consultation with target patient groups on the PL is deemed necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication is:

Zynyz is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with metastatic or with inoperable locally recurrent squamous cell carcinoma of the anal canal (SCAC).

3.1.2. Available therapies and unmet medical need

The current standard of care treatment for localized disease is fluoropyrimidine-based chemotherapy in combination with radiotherapy, with a 5-year disease-free survival rate of approximately 60% (Ajani et al 2008, Bartelink et al 1997, Flam et al 1996, Nigro et al 1974). Relapse after primary treatment occurs in up to 40% of patients within 5 years, and the prognosis for those who experience relapse or who present with de novo metastatic disease is poor. The 5-year OS rate for these patients is only 15% to 20% (Gunderson et al 2012).

The current first-line standard of care for metastatic SCAC is platinum-based chemotherapy. The randomized Phase 2 InterAACT study established carboplatin in combination with weekly paclitaxel as the preferred first-line treatment. Nevertheless, clinical outcomes remain limited with this regime, with a median PFS of 8.1 months and a median OS of 20 months (NCCN 2023, Rao et al 2020, Rao et al 2021). There is no established systemic therapy for patients with SCAC whose disease has progressed following initial first-line treatment.

Considering the poor prognosis and limited treatment options there is a high unmet medical need for patients with inoperable or metastatic SCAC

3.1.3. Main clinical studies

The efficacy data in support of this application comes from a single pivotal study. INCMGA 0012-303 (PODIUM-303/InterAACT 2) is an ongoing, Phase 3, double-blind study comparing retifanlimab in combination with carboplatin + paclitaxel chemotherapy compared with placebo plus chemotherapy in adult patients with inoperable locally recurrent or metastatic SCAC. Enrolment is complete with 308 patients. The data cutoff date was 15 April 2024 for the primary efficacy analysis of the primary endpoint of PFS based on BICR and for the safety analysis. An interim analysis of OS at this DCO is also provided.

The final OS analysis was performed at the updated DCO of 01 August 2025. at which time the median follow-up in the retifanlimab + chemotherapy group was 26.3 months, with 172 death events observed in the FAS (56%).

The primary safety population comprised 154 patients in the retifanlimab + chemotherapy group. As of the DCO, the median treatment duration with retifanlimab was 7.4 months.

3.2. Favourable effects

As of the DCO of 15 April 2024, after a median PFS follow-up of approximately 7.5 months, a statistically significant improvement in median PFS was observed in the retifanlimab + chemotherapy

group compared with the placebo + chemotherapy group, with an absolute difference in median PFS of 1.9 months (HR: 0.63 [95% CI: 0.47, 0.84]; p = 0.0006). Median PFS was 7.4 months for placebo + chemotherapy and 9.3 months for retifanlimab + chemotherapy.

At the primary DCO of 15 April 2025, a prespecified interim-analysis showed a median OS of 28.2 months in the retifanlimab + chemotherapy group compared with 23.0 months in the placebo + chemotherapy group. These estimates did not reach the prespecified threshold for a statistically significant difference: HR: 0.70 [95% CI: 0.49, 1.01]; p = 0.0273.

At the final OS analysis, the median OS was 32.8 months for retifanlimab + chemotherapy, compared with 22.2 months for placebo + chemotherapy (HR: 0.75 [95% CI: 0.55, 1.01]; p = 0.0305). The secondary endpoints of ORR and DOR are supportive of the primary endpoint, with a higher response rate in the retifanlimab + chemotherapy group (55.8% versus 44.2%) and a longer median duration of response (14.0 versus 7.2 months).

3.3. Uncertainties and limitations about favourable effects

- Both interim and final OS results did not meet the prespecified threshold for statistical significance, resulting in uncertainty regarding the magnitude of the overall survival benefit associated with retifanlimab in combination with chemotherapy. Exploratory analyses adjusting for the high rate of treatment crossover (approximately 50%), using the RPSFT and IPCW methods, resulted in lower HR estimates with 95% CIs excluding 1. However, these analyses are subject to methodological assumptions and are considered supportive only. As a consequence, uncertainty remains with regards to the extent of the OS benefit.
- Due to the limited number of patients with low or negative tumour PD-L1 expression, uncertainty remains regarding the magnitude of benefit in this subgroup; however, this does not support a restriction of the indication based on PD-L1 status.

3.4. Unfavourable effects

The addition of retifanlimab to chemotherapy led to more serious TEAEs (47.4% vs 38.8%), Grade 3 or higher TEAEs (83.1% vs 75.0%) and more discontinuations due to TEAEs of retifanlimab/placebo (11.0% vs 2.6%) and chemotherapy (10.4% vs 5.3%) in the retifanlimab + chemotherapy group compared with the placebo + chemotherapy group. These differences were mostly due to irAEs.

irAEs (48.7% vs 26.3%) were more frequent in the retifanlimab + chemotherapy group compared with the placebo + chemotherapy group. The most frequent irAEs in the retifanlimab + chemotherapy group were hypothyroidism (14.3% vs 3.3%); nervous system disorders (12.3% vs 10.5%), skin reactions (11.7% vs 9.2%), colitis (10.4% vs 3.9%), hyperthyroidism (8.4% vs 0.7%), and adrenal insufficiency (5.8% vs 0.0%). Grade 3 or higher irAEs were observed in 13.6% vs 5.9% of the patients, the most frequent were colitis (3.2% vs 2.0%), adrenal insufficiency (1.9% vs 0%) and skin reactions (1.9% vs 0.7%). Grade 3 or higher IRRs were rare (1.9% vs 1.3%) in both study arms.

Four fatal TEAEs were observed in the retifanlimab + chemotherapy group (2.6%) versus one in the placebo + chemotherapy group (0.7%).

Discontinuations of retifanlimab/placebo due to TEAEs (11.0% vs 2.6%) were mostly immune-related (6.5% vs 0%) in the retifanlimab + chemotherapy group. TEAEs leading to discontinuation of all study therapy were observed in 6 patients in the retifanlimab +chemotherapy group versus 1 in the placebo +chemotherapy group.

3.5. Uncertainties and limitations about unfavourable effects

- Due to the limited duration of safety follow-up, long-term safety of retifanlimab is missing. Long-term safety is reflected as missing information in the RMP and will be monitored through routine pharmacovigilance activities.
- There were few patients included of 75 years and older (9.1% of patients). While no overall age-specific differences in efficacy or safety were identified, this limits the available evidence in this subgroup.

3.6. Effects Table

Table 47: Effects Table for retifanlimab in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with metastatic or with inoperable locally recurrent squamous cell carcinoma of the anal canal (data cut-off: 15 April 2024)

Effect	Short description	Unit	Treatment Retifanlimab +chemo (N=154)	Control Placebo +chemo (N=154)	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint **PFS**	Progression-free survival by BICR per RECIST v1.1	Median (95% CI) in months	9.3 (7.5-11.3)	7.4 (7.1-7.7)	<u>Strengths:</u> - Derived from randomized, double blind Phase 3 study <u>Uncertainties:</u> - Absolute PFS-gain is limited - OS results did not meet prespecified statistical significance criteria; cross-over of 50%	Table 13
		Hazard Ratio (HR) (95% CI)	0.63 (0.47-0.84) p-value 0.0006			
Key secondary endpoint **OS**	Overall survival	Median (95% CI) in months	32.8 (25.7, 44.5)	22.2 (15.7, 27.2		Figure 4
		Hazard Ratio (HR) (95% CI)	0.75 (0.55-1.01) p-value 0.0273			
Unfavourable Effects						
Gr3 TEAE	Grade 3 or higher TEAE	%	83.1%	75.0%	<u>Strengths:</u> Safety data derived from placebo-controlled RCT <u>Uncertainties:</u> Long term safety is missing	Section 11.
SAEs	Serious TEAEs	%	47.4%	38.8%		
TEAE leading to discont.	Discontinuations due to TEAEs -retifanlimab -chemo - all study therapy	%	 11.0% 10.4% 3.9%	 2.6% 5.3% 0.7%		

Effect	Short description	Unit	Treatment Retifanlimab +chemo (N=154)	Control Placebo +chemo (N=154)	Uncertainties / Strength of evidence	References
irAE	Immune related AEs	%	48.7%	26.3%		

Abbreviations: AE - adverse event; discont – discontinuation; irAE- immune-related AE; NE – not estimable; SAE - serious TEAE; TEAE- treatment-emergent adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The addition of retifanlimab to carboplatin and paclitaxel resulted in a statistically significant improvement in PFS, with a median increase of 1.9 months (HR: 0.63; 95% CI: 0.47, 0.84), which is of limited clinical relevance by itself in the context of the poor prognosis of patients with inoperable or metastatic SCAC.

The final OS analysis showed an absolute difference in median OS of 10.6 months, with a HR of 0.75 (95% CI: 0.55-1.01), which did not meet the prespecified criterion for statistical significance. The OS curves show an early separation at approximately 6 months, which is maintained over time until, considering the decreasing number of patients at risk, a plateau of both curves from around 40-45 months. The estimated absolute difference in median OS between the two treatment groups is notable in the context of the poor prognosis of the target population. In addition, the sensitivity analyses adjusting for the high rate of treatment crossover provide supporting and reassuring context. Overall, these findings, suggest a meaningful beneficial effect on OS with the addition of retifanlimab to first-line chemotherapy in patients with inoperable or metastatic SCAC, although uncertainty remains regarding the magnitude of the OS benefit.

Because most participants had a PD-L1-positive tumour using a cut-off of 1%, the interpretation of the prespecified PD-L1 subgroup analyses is limited. Post-hoc subgroup analyses of efficacy outcomes (PFS and updated OS) across additional PD-L1 expression cut-offs were exploratory and based on a small number of patients but did not suggest a clear differential treatment effect according to PD-L1 expression with retifanlimab treatment. Therefore, restriction of the indication based on PD-L1 expression is not justified, and an all-comer population can be supported.

The frequencies and types of AEs are consistent with the known safety profile of PD-(L)1 inhibitors, and no new safety signals were identified. The safety profile of retifanlimab in combination with carboplatin and paclitaxel in SCAC patients is considered acceptable and manageable. Enrolled participants were relatively fit, and more toxicity could be expected in clinical practice, though this uncertainty is in line with other regulatory decisions and therefore acceptable. Overall, the addition of retifanlimab to chemotherapy was associated with a higher frequency of treatment discontinuations and a moderate increase in serious and severe AEs, mainly driven by immune-related adverse reactions. As the duration of exposure remains limited, uncertainty regarding long-term safety remains and is reflected as missing information in the RMP and addressed through routine pharmacovigilance activities.

3.7.2. Balance of benefits and risks

The addition of retifanlimab to carboplatin and paclitaxel resulted in an increase in median PFS of 1.9 months, which was statistically significant although of modest clinical relevance.

In the final OS analysis, an absolute difference in median OS of 10.6 months was observed, with a HR of 0.75 (95% CI: 0.55-1.01); however, the prespecified criterion for statistical significance was not met. Exploratory analyses adjusting for the high rate of treatment crossover (approximately 50%) resulted in lower HR estimates with 95% CIs excluding 1, but these results are considered supportive only and subject to methodological limitations. Although uncertainty remains with regards to the magnitude of any OS benefit, it is considered reasonable to conclude that the addition of retifanlimab to first-line chemotherapy in patients with inoperable or metastatic SCAC leads to an improvement in overall survival which is of clinical relevance in the context of inoperable or metastatic SCAC.

The addition of retifanlimab to chemotherapy was associated with a moderate increase in treatment-related toxicity. No new safety signals were identified and the safety profile of retifanlimab in combination with chemotherapy is considered acceptable and manageable in the context of SCAC.

Taking into account the PFS benefit shown with supportive OS findings and the manageable safety profile, the overall benefit-risk balance of retifanlimab in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with metastatic or with inoperable locally recurrent SCAC is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

No applicable.

3.8. Conclusions

The overall benefit-risk of retifanlimab in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with metastatic or with inoperable locally recurrent SCAC is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	II	I, IIIB

Extension of indication to include in combination with carboplatin and paclitaxel treatment of adult patients with metastatic or with inoperable locally recurrent squamous cell carcinoma of the anal canal (SCAC) for ZYNYZ, based on interim results from study INCMGA 0012-303 (POD1UM-303/InterAACT-2); this is a phase 3 global, multicenter, double-blind randomized study of carboplatin-paclitaxel with retifanlimab or placebo in participants with inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal not previously treated with systemic chemotherapy; As a consequence,

sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce editorial changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.