Official Title: A Randomized, Double-Blind, Multicenter, Phase 2 Study of Retifanlimab in Combination With INCAGN02385 (Anti‑LAG-3) and INCAGN02390 (Anti‑TIM-3) as First-Line Treatment in Participants With PD-L1‑Positive (CPS ≥ 1) Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck

NCT Number: NCT05287113

Document Date: Protocol INCAGN 2385-203 Am 2 Version 3 19 DEC 2023

Clinical Study Protocol

INCAGN 2385-203

A Randomized, Double-Blind, Multicenter, Phase 2 Study of Retifanlimab in Combination With INCAGN02385 (Anti–LAG-3) and INCAGN02390 (Anti–TIM-3) as First-Line Treatment in Participants With PD-L1–Positive (CPS ≥ 1) Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck

Product:	**INCAGN02385; INCAGN02390; retifanlimab (INCMGA00012)**
IND Number:	[redacted]
EudraCT Number:	**2021-005775-39**
EU CT Number:	**2023-504270-38-00**
Phase of Study:	**2**
Sponsor:	**Incyte Biosciences International Sàrl** **Rue Docteur-Yersin 12** **1110 Morges, Switzerland**
Original Protocol:	**15 NOV 2021**
Version 1-BE:	**06 JUL 2022**
Version 1-FR:	**11 JUL 2022**
Version 1-KR:	**11 JUL 2022**
Version 1-TW:	**01 AUG 2022**
Version 1-DE:	**30 AUG 2022**
Amendment 1:	**04 NOV 2022**
Amendment 2:	**19 DEC 2023**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Brazil 2013) and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations, including WMO (Medical Research Involving Human Participants Act) and Clinical Trials Regulation (EU) No. 536/2014, in which the study is being conducted.

INVESTIGATOR'S AGREEMENT

I have read the INCAGN 2385-203 Protocol Amendment 2 (dated 19 DEC 2023) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	antihepatitis B core
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BNP	B-type natriuretic peptide
cfDNA	circulating free deoxyribonucleic acid
CFR	Code of Federal Regulations
CI	confidence interval
CL	total systemic clearance
CMH	Cochran-Mantel-Haenszel test
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Regulation
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECD	extracellular domain
ECOG	Eastern Cooperative Oncology Group

Abbreviations and Special Terms	Definition
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ESMO	European Society for Medical Oncology
Fc	fragment crystallizable
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLOBOCAN	Global Cancer Incidence, Mortality, and Prevalence
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HPV	human papilloma virus
HR	hazard ratio
HRT	hormone-replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICI	immune-checkpoint inhibitor
IEC	independent ethics committee
IFN-γ	interferon gamma
IgG	immunoglobulin G
IgG_1	immunoglobulin gamma 1
IgSF	immunoglobulin superfamily
IHC	immunohistochemistry
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent-to-treat

Abbreviations and Special Terms	Definition
K_D	equilibrium dissociation constant between the antibody and its antigen
LAG-3	lymphocyte-activation gene 3
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	not applicable
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	once every 2 weeks
Q4W	once every 4 weeks
Q8W	once every 8 weeks
Q12W	once every 12 weeks
R/M	recurrent/metastatic
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2

Abbreviations and Special Terms	Definition
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SITC	Society for Immunotherapy of Cancer
SoA	schedule of activities
SoC	standard of care
SOP	Standard Operating Procedure
TCGA	The Cancer Genome Atlas
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TG	treatment group
TIL	tumor-infiltrating lymphocyte
TIM-3	T-cell immunoglobulin and mucin domain-containing protein 3
TnI	troponin I
TnT	troponin T
TPS	tumor proportion score
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title:

A Randomized, Double-Blind, Multicenter, Phase 2 Study of Retifanlimab in Combination With INCAGN02385 (Anti–LAG-3) and INCAGN02390 (Anti–TIM-3) as First-Line Treatment in Participants With PD-L1–Positive (CPS ≥ 1) Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck.

Protocol Number: INCAGN 2385-203

Objectives and Endpoints:

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of the combinations of retifanlimab + INCAGN02385 (TG2) and retifanlimab + INCAGN02385 + INCAGN02390 (TG3) compared with retifanlimab alone (TG1) in the overall study population.	PFS, defined as the interval between the date of randomization and the earliest date of disease progression, based on investigator assessment per RECIST v1.1, or death due to any cause.
Secondary	
To assess disease response per RECIST v1.1 in TG2 and TG3 compared with TG1.	• Objective response, defined as having a CR or PR, determined based on investigator assessment per RECIST v1.1. • DOR, defined as the time from earliest date of disease response (CR or PR) until earliest date of disease progression, based on investigator assessment per RECIST v1.1, or death from any cause if occurring sooner than progression. • Disease control, defined as having CR, PR, or SD (≥ 6 months) as best response, based on investigator assessment per RECIST v1.1.
To determine the OS of TG2 and TG3 compared with TG1.	OS, defined as the interval between the date of randomization until death due to any cause.
To determine the safety of TG2 and TG3 compared with TG1.	• AEs, assessed in body systems with symptoms, through physical examinations, changes in vital signs and ECGs, and through clinical laboratory blood sample evaluations. • Impact on-study treatment, assessed by treatment interruptions, dose delays, and withdrawal of study treatment due to AEs.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Recurrent or metastatic SCCHN that is PD-L1–positive (CPS ≥ 1)
Population	Male and female participants at least 18 years of age who have R/M SCCHN that is PD-L1–positive and systemic therapy–naive in the advanced disease setting
Number of Participants	Approximately 162 total participants will be enrolled and randomized to 3 treatment groups (approximately 54 participants per group)
Study Design	Randomized, double-blind, multicenter study evaluating the efficacy and safety of TG2 (retifanlimab + INCAGN02385) and TG3 (retifanlimab + INCAGN02385 + INCAGN02390) compared with TG1 (retifanlimab alone)
Estimated Duration of Study Participation	Up to 28 days for screening, continuous treatment in consecutive 4-week cycles as long as participants have not met any criteria for discontinuation, and 90 days for safety follow-up. Participants will be allowed to receive study treatment for a maximum of 2 years. It is estimated that an individual will participate for approximately 1 year.
DSMB	Yes (external)
Coordinating Principal Investigator	Robert Haddad, MD

Treatment Groups and Duration:

This is a randomized, double-blind, Phase 2 study to evaluate the efficacy and safety of the combination of retifanlimab plus INCAGN02385(TG2) and retifanlimab plus INCAGN02385 and INCAGN02390 (TG3) compared with retifanlimab alone as first-line treatment in participants with PD-L1–positive and systemic therapy–naive R/M SCCHN.

Approximately 162 participants will be randomized in a 1:1:1 ratio to 1 of the above treatment groups. At randomization, participants will be stratified based on the following factors:

- LAG-3 expression status (determined centrally): positive (≥ 5%) versus negative (< 5%)
- PD-L1 CPS (determined centrally): 1-19 versus ≥ 20
- HPV p16 status (oropharyngeal only): p16-positive versus p16-negative; HPV p16 status for participants without oropharynx cancer (eg, cancers of the oral cavity, hypopharynx, larynx) are considered HPV p16 negative.

Study treatment will begin on Day 1. Randomized participants will continue study treatment in 4-week cycles for up to 2 years or until discontinuation criteria are met. The duration for enrollment is expected to be approximately 12 months.

After 30 participants have been randomized and have received treatment for at least 4 weeks (at least 2 doses), an interim analysis of safety will be performed by an independent external DSMB.

The study design schema is presented in Figure 1. The schedules of activities, laboratory assessments, and PK and PD assessments are presented in Table 3, Table 4, and Table 5, respectively.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema

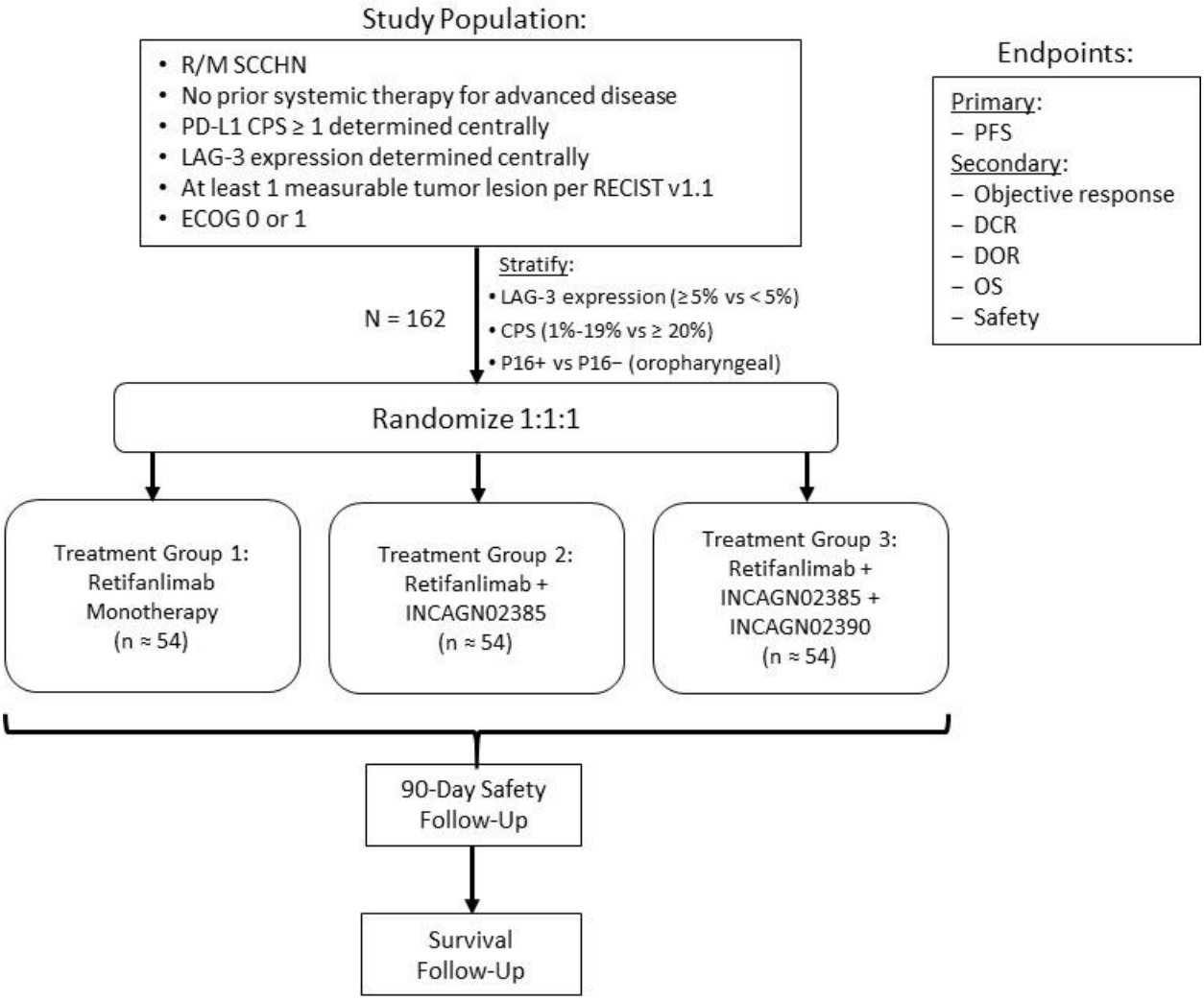


Table 3: Schedule of Activities

Visit Day (Range)	Screening	Treatment						EOT	Safety Follow-Up	Survival Follow-Up	Notes
		Cycle 1			Cycle 2+						
	Days –28 to –1	Day 1	Day 8 (± 2 d)	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Q8W (± 7 d)		EOT + 30 and 90 days (± 7 d)	Q12W (± 14 d)	
Administrative procedures											
Informed consent	X										See Section 8.1.1 for details.
Contact IRT	X	X		X	X	X		X	X		See Section 8.1.3 for details.
Inclusion/exclusion criteria	X	X									See Section 5 for details.
Demographics and general and disease medical history	X										See Section 8.1.5 for details.
HPV p16 testing	X										Participants with primary oropharyngeal tumors must have known HPV status (determined locally; otherwise, request central testing per sponsor) prior to randomization. See Section 5.1 for details.
Prior/concomitant medications	X	X	X	X	X	X		X	X		Section 8.1.6 for details.
Administer retifanlimab		X			X						Retifanlimab administered on Day 1 of each cycle (Q4W). See Section 6.1 for details.
Administer INCAGN02385/placebo		X		X	X	X					Administered Q2W of each cycle. See Section 6.1 for details.
Administer INCAGN02390/placebo		X*		X	X	X					*Following completion of the Cycle 1 Day 1 INCAGN02390/placebo infusion, participants will be observed at the study site for 4 hours per Section 6.5.2.
Distribute reminder card		X	X	X	X	X		X	X		See Section 8.1.4 for details.
Safety assessments											
AE assessments	X	X	X	X	X	X		X	X		See Section 8.3.1 for details.
Physical examination/body weight/height	X	X	X	X	X	X		X	X		Complete physical exam at screening; targeted physical thereafter. Height at screening only. Body weight at screening and Day 1 of each cycle. See Section 8.3.2 for details.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening Days –28 to –1	Treatment Cycle 1 Day 1	Cycle 1 Day 8 (± 2 d)	Cycle 1 Day 15 (± 2 d)	Cycle 2+ Day 1 (± 3 d)	Cycle 2+ Day 15 (± 2 d)	Treatment Q8W (± 7 d)	EOT	Safety Follow-Up EOT + 30 and 90 days (± 7 d)	Survival Follow-Up Q12W (± 14 d)	Notes
Safety assessments (continued)											
Vital signs	X	X*		X*	X*	X†		X	X		See Section 8.3.3 for details. *On Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 2 Day 1, vital signs will be monitored prior to each study drug infusion (−10 minutes) and 30 and 60 minutes (± 10 minutes) following completion of the INCAGN02390/placebo infusion, and additionally as clinically indicated. †On Cycle 2 Day 15 and all subsequent study drug infusions, vital signs will be monitored prior to each study drug infusion (−10 minutes) and additionally as clinically indicated.
12-lead ECG	X	X*			X†			X			*Not required if screening assessment performed within 7 days of Cycle 1 Day 1, unless clinical signs or symptoms are present. †Performed on Day 1 of Cycles 2 through 5, and then on Day 1 of every fourth cycle (ie, Cycles 9, 13, etc.) thereafter. Additional ECGs during treatment should be performed if clinically indicated. All ECGs will be performed in triplicate. All ECGs should be checked and interpreted prior to dose administration. See Section 8.3.4 for details.
ECOG status	X	X			X			X			See Section 8.3.5 for details.
Survival status										X*	*After documented disease progression, or the start of new anticancer therapy; contacts are approximately Q12W. See Section 8.8.3 for details.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment						EOT	Safety Follow-Up	Survival Follow-Up	Notes
		Cycle 1			Cycle 2+						
	Days –28 to –1	Day 1	Day 8 (± 2 d)	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Q8W (± 7 d)		EOT + 30 and 90 days (± 7 d)	Q12W (± 14 d)	
Efficacy assessments											
Radiologic tumor assessments (CT and/or MRI of neck, CT of chest and CT or MRI of abdomen). Imaging of the pelvis is optional. Imaging is required with contrast unless contraindicated.	X						X*	X	X†		*Imaging will be performed Q8W (± 7 days) for the first 12 months, then Q12W (± 7 days) thereafter. †Participants who discontinue for reasons other than radiographic PD should be assessed according to the imaging schedule (ie, Q8W for the first 12 months, then Q12W thereafter) until radiographic PD or the start of new anticancer therapy. See Section 8.2 for details.
Brain MRI or CT	X*						X†	X†	X†		*Screening brain imaging should be performed on all participants who have previous history of CNS metastasis or as clinically indicated (eg, based on clinical symptoms). On-study brain imaging will be performed only if the screening brain imaging was positive or as clinically indicated. †If indicated, brain imaging should occur at same time as disease assessment scans. Whenever feasible, contrast-enhanced brain MRI is preferred to CT. See Section 8.2 for details.

Table 4: Schedule of Laboratory Assessments

Procedure	Screening	Treatment				EOT	Safety Follow-Up	Notes
		Cycle 1		Cycle 2+				
	Days –28 to -1	Day 1	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 15 (± 3 d)		EOT + 30 and 90 days (± 7 d)	
Local laboratory assessments								
Blood chemistries	X	X*	X	X		X	X†	*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. † 30-day visit only.
Hematology with differential	X	X*	X	X		X	X†	
Fasting lipid panel	X			X		X		Performed at screening, Cycle 2 Day 1, Day 1 of every third cycle thereafter (ie, Cycles 5, 8, etc), and EOT.
Coagulation panel	X			X		X		
Urinalysis	X			X		X		
Thyroid function panel	X			X		X		Performed at screening, Day 1 of every even cycle (ie, Cycles 2, 4, etc), and EOT. Note: Participants may be administered study treatment in subsequent cycles after Cycle 1 Day 1 while thyroid test results are pending.
Hepatitis screening	X							Results obtained within the last 3 months before Cycle 1 Day 1 are acceptable.
TnI or TnT monitoring	X	X*	X	X†	X‡	X		*Only required at Cycle 1 Day 1 if screening assessment was not performed within 3 days. †Cycles 2, 3, and 4 only. ‡Cycles 2 and 3 only. Note: To be performed within 3 calendar days prior to dose administration and all labs should be checked prior to dose administration. Note: Day 15 labs should be checked as soon as possible. In case of high troponin, perform cardiac imaging via echocardiography with/without cardiac MRI.

Table 4: Schedule of Laboratory Assessments (Continued)

Procedure	Screening	Treatment				EOT	Safety Follow-Up	Notes
		Cycle 1		Cycle 2+				
	Days –28 to -1	Day 1	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 15 (± 3 d)		EOT + 30 and 90 days (± 7 d)	
Local laboratory assessments (continued)								
HIV diagnostic testing HIV management testing (only applicable for participants known to be HIV-positive: HIV viral load, CD4+ cell count)	X*			X†		X‡	X‡	*HIV antibodies diagnostic testing is required only if mandated by local health authorities or regulations. If a participant is known to be HIV-positive, HIV management testing (HIV viral load CD4+ cell count) is required at screening. †For participants with positive HIV only: within 7 days of Cycle 3 Day 1 and every odd numbered cycle (ie, C5, C7, etc) for the first year. Frequency may be reduced to every 3 months during the second year of treatment and during the follow-up period. ‡For participants with positive HIV only: Final sample at the EOT visit or 30-day follow-up visit if no separate EOT visit is performed.
Pregnancy testing (WOCBP only)	X*	X†		X†		X*	X‡	*Serum pregnancy test; must be within 72 hours before the first dose of study treatment and at EOT (optional if participant is going to hospice). †Serum or urine pregnancy test before first dose and on Day 1 of each cycle. ‡Serum or urine pregnancy test will be performed monthly for 6 months after the last dose of study treatment. See Appendix A for definition of WOCBP.

Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments

Procedure	Screening	Treatment						Safety Follow-Up	Notes
		Cycle 1			Cycles 2 and 3	Cycle 4	Cycle 6		
	Days –28 to –1	Day 1	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 1 (± 1 d)	Day 1 (± 1 d)	Day 1 (± 1 d)	EOT + 30 and 90 days (± 7 d)	
Serum sample for PK		X	X	X	X*	X	X†	X‡	*Cycle 2 Day 1 only †Samples for PK and ADA will continue to be collected on Day 1 of all even-numbered cycles (ie, Cycles 8, 10, etc). ‡Samples for PK and ADA will be collected at EOT, 30-day, and 90-day follow-up visits. See Section 8.4 for details and Table 15 for timing.
Serum sample for ADA		X		X	X*	X	X†	X‡	
Plasma biomarker		X	X	X	X	X			See Table 16 for timing.
Plasma cfDNA		X			X*				See Table 16 for timing. *Collected at Cycle 3 Day 1 only.
Whole blood for flow cytometry		X	X	X	X	X			See Table 16 for timing. Only to be collected for the first 75 participants randomized.
Whole blood for PBMC		X	X	X	X	X			See Table 16 for timing.
Tumor biopsy	X*							X†	*Mandatory pretreatment tumor tissue collection (archival or fresh). LAG-3 and PD-L1 (CPS) expression status must be determined per central laboratory testing before randomization. †Optional fresh tumor biopsy at EOT for disease progression only. See Section 8.5.1 for details.

2. INTRODUCTION

2.1. Background

While antibodies directed toward the PD-(L)1 axis have revolutionized the treatment of cancer, the majority of patients either do not respond or lose response to these drugs. The mechanisms for failure of anti–PD-1 therapy are poorly understood, but in some cases are likely due to existence of additional checkpoint pathways that either abrogate a response when present or cause loss of response when induced. This study aims to evaluate the clinical and biological effects of blocking additional key checkpoint pathways, LAG-3 and TIM-3, which have been implicated in the lack of/loss of response to PD-1 inhibitors.

This is a randomized, Phase 2 study to evaluate the efficacy and safety of the combination of retifanlimab and INCAGN02385 and the triplet combination of retifanlimab, INCAGN02385, and INCAGN02390 compared with retifanlimab alone in participants with systemic therapy–naive, metastatic or with unresectable, recurrent SCCHN whose tumors express PD-L1.

Retifanlimab is a humanized, hinge-stabilized, IgG4κ monoclonal antibody that recognizes human PD-1. Retifanlimab contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1–expressing cells, including T cells, and sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2. Additional information regarding preclinical and in vitro experience with retifanlimab can be found in the retifanlimab IB.

INCAGN02385 is an Fc-modified $IgG_1κ$ monoclonal antibody that binds to human LAG-3 with an estimated affinity (K_D) of 1.7 nM and was chosen for clinical development based on its selectivity for human LAG-3 with no cross-reactivity to related IgSF proteins. INCAGN02385 functions as a potent LAG-3 antagonist antibody via its ability to inhibit LAG-3 binding to MHC class II, leading to enhanced TCR signaling. Additional information regarding preclinical and in vitro experience with INCAGN02385 can be found in the INCAGN02385 IB.

INCAGN02390 is a recombinant, aglycosylated fully human $IgG_1κ$ monoclonal antibody that binds to the ECD of the TIM-3 receptor. Antagonist TIM-3 antibodies have demonstrated enhanced antitumor activity in several mouse tumor models when combined with blockade of the PD-(L)1 pathway (Ngiow et al 2011, Sakuishi et al 2010). Additional information regarding preclinical and in vitro experience with INCAGN02390 can be found in the INCAGN02390 IB.

2.1.1. Scientific Rationale for Inhibition of PD-(L)1, LAG-3, and TIM-3 in Human Cancer

Significant focus has been placed on understanding the activity of the immune system within the tumor microenvironment and identification of mechanisms of tumor resistance to immune surveillance. Loss of CD8+ T-cell effector function has been one such proposed mechanism. This loss of function, or T-cell exhaustion, has been described to be due in part to the accumulation and increased diversity of inhibitory receptors, or checkpoints, on the cell surface of CD8+ T cells (Wherry 2011).

Recovery of function has been accomplished in an in vivo viral model of T-cell exhaustion by simultaneous blockade of PD-1 and LAG-3 (Blackburn et al 2009). Further, in murine models, it has been demonstrated that PD-1 and LAG-3 act synergistically to promote tumor immune escape, and simultaneous blockade of LAG-3 and PD-1 results in synergistic inhibition of tumor growth (Woo et al 2012). Evidence for synergy of anti–PD-1 and anti–TIM-3 was shown in an in vivo murine model of chronic infection resulting in T-cell exhaustion characterized by coexpression of TIM-3 and PD-1. Combined blockade of these 2 inhibitory receptors markedly improved CD8+ T-cell responses (Jin et al 2010, INCAGN02385 IB, INCAGN02390 IB).

Early clinical evidence of the efficacy of these combinations in patients who have progressed on anti–PD-(L)1 therapy have been evolving. Blockade of the PD-(L)1 axis in combination with blockade of either LAG-3 or TIM-3 has resulted in only modest responses in patients who have progressed on anti–PD-1 therapy alone (Ascierto et al 2017, Davar et al 2018). Potentially, multiple checkpoint inhibitors are potentially required in order to restore antitumor T-cell effector function in situ. Evidence for this approach was presented by Kauffman and colleagues at SITC 2018 (Kaufmann et al 2018). In this study, the triple combination of antibodies directed against PD-1, TIM-3, and LAG-3 demonstrated enhanced tumor growth inhibition relative to inhibition of either PD-1 and LAG-3 or PD-1 and TIM-3 in a murine model. In addition, the combination of all 3 antibodies resulted in greater restoration of function to TILs isolated from patients with ovarian cancer. This suggests a requirement for inhibition of all 3 checkpoints in concert is more relevant for returning immune function and tumor growth inhibition. It could also be that the population of patients that have prior exposure to checkpoint inhibitors represent a very difficult-to-treat population.

While no clinical data exist for combination blockade of PD-1, LAG-3, and TIM-3 in patients with SCCHN, recent clinical data have emerged that suggests promising efficacy and safety of the combination of PD-1– and LAG-3–directed agents in checkpoint inhibitor–naive solid tumor populations. The RELATIVITY-047 study, which was a Phase 3 trial evaluating the anti–LAG-3 antibody relatlimab plus nivolumab versus nivolumab alone in previously untreated melanoma, demonstrated significantly longer PFS in the combination group (10.1 months [95% CI: 6.4, 15.7] vs 4.6 months [95% CI: 3.4, 5.6]), with a manageable safety profile and without unexpected safety signals (Lipson et al 2021). Additionally, the anti–LAG-3 antibody fianlimab, when added to the anti–PD-1 antibody cemiplimab, resulted in an ORR of 63.6% in 33 treatment-naive patients with advanced/metastatic melanoma (Hamid et al 2021), which is above the historical ORR of PD-1 monotherapy (Robert et al 2019). Lastly, the anti–LAG-3 fusion protein etilagimod alpha in combination with pembrolizumab demonstrated an encouraging response rate of 45.8% in patients with PD-L1–positive (CPS ≥ 1) SCCHN who had previously received 1 line of platinum-based chemotherapy and were naive to PD(L)-1 treatment (Brana et al 2021). Taken together, these recently reported data provide experimental support for the combination of anti–PD-1 therapy with LAG-3 blocking agents in a checkpoint inhibitor–naive population.

2.1.2. Treatment of Patients With Recurrent/Metastatic SCCHN

According to GLOBOCAN epidemiological estimates of incidence and mortality of cancer worldwide, in 2018, there were approximately 835,000 new cases of cancer arising from the lips, oral cavity, oropharynx, hypopharynx, and larynx, the primary tumor sites that generally

comprise SCCHN, with the number of deaths in the same year being approximately 431,000 (Bray et al 2018).

A large percentage of patients with SCCHN primarily present with locally advanced, stage III/IV disease that is initially treated with multimodal therapy including systemic treatment, radiation, and/or surgery. Patients who progress after initial definitive therapy require subsequent treatment for R/M disease; patients who initially present with metastatic disease generally receive the same therapy as those with recurrent disease after definitive treatment.

For patients with recurrent unresectable or metastatic SCCHN, platinum-based chemotherapy (the EXTREME regimen) has been the standard first-line treatment for the last decade, conferring a median OS of around 10 months. In 2016, the PD-1 inhibitors nivolumab and pembrolizumab were approved by the FDA as second-line treatment for patients who had progressed after platinum-based therapy following positive data demonstrating improved OS of nivolumab/pembrolizumab over investigator's choice systemic therapy in this population. In 2019, based on the results of the KEYNOTE-048 study, the approval of pembrolizumab as first-line therapy has changed the treatment paradigm for patients with R/M SCCHN (Burtness et al 2019, NCCN 2020). Pembrolizumab as monotherapy in patients with PD-L1–positive (CPS ≥ 1) tumors, or in combination with chemotherapy irrespective of PD-L1 status, demonstrated superior OS over the EXTREME regimen.

The KEYNOTE-048 study included participants in the first-line setting of R/M SCCHN, 85% had PD-L1 CPS ≥ 1 and 21% had HPV p16-positive status. The response rate was 19% in participants with PD-L1 CPS ≥ 1 tumors (16.9% in all participants) for pembrolizumab monotherapy, and 36% when combined with platinum-based chemotherapy (Rischin et al 2019). An estimated 85% to 95% of patients with R/M SCCHN have no response to these treatments, or have a response that is followed by disease progression (Chow 2020), highlighting the need for alternative treatment strategies and for biomarkers predictive of response.

Mechanisms of immune evasion in SCCHN and other cancer types include tumor cell adaptation, direct T-cell suppression via inhibitory cell surface receptors or soluble factors, decreased immune stimulation, and the recruitment of immuno-suppressive cell populations (Horton et al 2019, Kok 2020).

For patients with R/M SCCHN who have progressed on anti–PD-1 therapy, there are limited therapeutic options. Those who progressed on or after PD-1 plus chemotherapy may be treated with single-agent chemotherapy, cetixumab, or other experimental therapies. Those whose disease progresses on PD-1 monotherapy may be eligible for treatment with platinum-based chemotherapy regimens or single-agent platinum chemotherapy, other single-agent chemotherapies, cetuximab, or other experimental treatments (NCCN 2020).

2.1.3. Anti–PD-1 Plus Anti–LAG-3 With or Without Anti–TIM-3 in SCCHN

While the role of LAG-3 in SCCHN is not fully characterized, there is a growing body of evidence that suggests that LAG-3 expression may play an important role in resistance to immune surveillance and potentially to PD-1 blockade. Analysis of LAG-3 expression in a TCGA dataset showed that among multiple solid tumors, SCCHN had considerably high expression of LAG-3 (Panda et al 2020). Further, an internal survey using a commercially available SCCHN cohort found that approximately 58% of patients have tumors that express

≥ 5% LAG-3 (data on file). LAG-3 expression is mainly restricted to T cells; in SCCHN, LAG-3 has been shown to be expressed on tumor-infiltrating Tregs (Jie et al 2013), suggesting that that is may contribute to immunosuppression in the tumor microenvironment. LAG-3 expression may be expected to correlate with PD-L1 expression in SCCHN (Mishra et al 2016) and has been independently associated with poor prognosis (Deng et al 2016). LAG-3 expression has also been found to be enriched in HPV-positive SCCHN and other virally mediated tumors, suggesting that such a "T-cell–inflamed" phenotype may benefit from combined PD-1 and LAG-3 expression (Gameiro et al 2018). Given these findings, it is reasonable to hypothesize that dual blockade of both PD-1 and LAG-3 will result in improved clinical response relative to PD-1 inhibition alone in patients with SCCHN.

Similar to LAG-3, the role of TIM-3 in SCCHN has not been fully elucidated, although there is accumulating evidence that it may contribute to immune suppression in the tumor microenvironment in this tumor histology. TIM-3 expression on tumor-infiltrating lymphocytes has been shown to be upregulated in response to PD-1 blockade on both murine and human T cells in freshly excised SCCHN tumors, suggesting that compensatory upregulation of TIM-3 may represent a specific adaptive response that functions to sustain the exhaustion status of TIL in response to PD-1 blockade (Shayan et al 2016). TIM-3+ TILs also correlate with poorer OS and may be considered an independent prognostic factor of poor disease outcome (Yang et al 2021). Oweida et al (2018) demonstrated that TIM-3 is upregulated on CD8 T cells and Tregs in SCCHN tumors treated with radiotherapy and PD-L1 blockade and that treatment with an anti–TIM-3 antibody concurrently with anti–PD-L1 and radiotherapy led to significant tumor growth delay, enhanced T-cell cytotoxicity, decreased Tregs, and improved survival. Further, Galectin-9 expression by CD4+ T cells has been shown to be increased in patients with HPV-positive oral SCCHN, which in turn leads to expansion of TIM-3+ monocytes, further suppressing IFN-γ production from activated CD8+ T cells (Dong et al 2017).

2.1.4. Justification for Dose of INCAGN02385 and INCAGN02390

Doses for INCAGN02385 and INCAGN02390 were chosen based on safety, receptor occupancy, and pharmacodynamic data obtained from study results from INCAGN 2385-101 and INCAGN 2390-101, respectively (INCAGN02385 IB, INCAGN02390 IB). In both cases, doses chosen were below the highest dose tested.

2.1.4.1. INCAGN02385 Dose

As of 21 MAR 2022, a total of 22 unique participants were enrolled and received at least 1 dose of INCAGN02385 IV at doses of 25, 75, 250, 350, and 750 mg Q2W in an open-label, nonrandomized, dose-escalation, and cohort-expansion study, INCAGN2385-101. All doses were well tolerated with no DLTs observed, and there were no treatment-related deaths. INCAGN02385 PK was independent of dose after the first dose and showed moderate to high interindividual variability (see Figure 2). At a dose of 350 mg Q2W (N = 2), the steady-state AUC was 29,500 µg/mL·h. The dose of 350 mg Q2W was chosen for INCAGN02385 based on the results that the receptor on the surface of the cells was fully occupied at trough concentration (see Figure 3) and that pharmacodynamic markers supported this dose to be pharmacologically active as measured by an increase in peripheral T-cell activation observed in doses greater than 250 mg.

Figure 2: INCAGN02385 Concentrations Over Time (Mean ± SE) After the First Dose and at Steady-State at Various Dose Levels

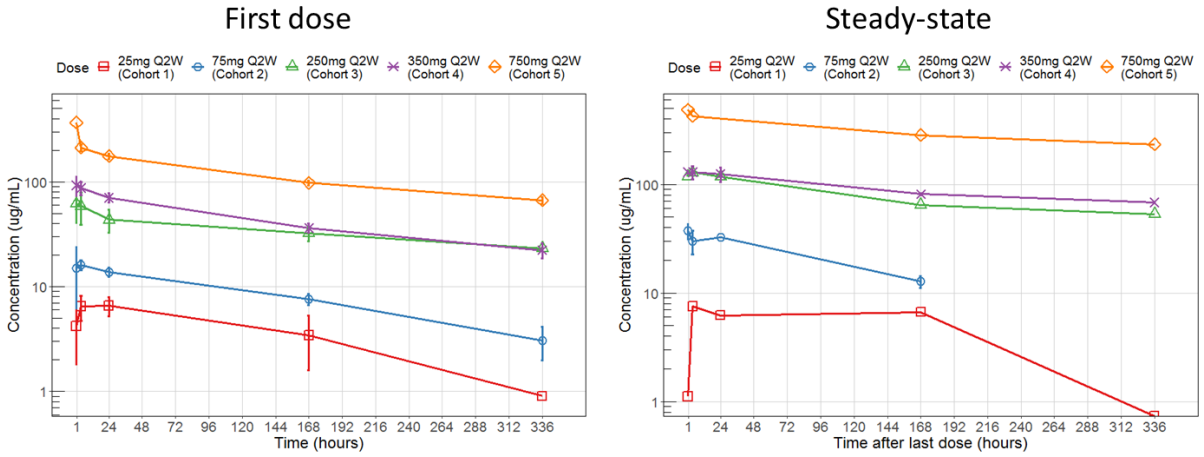


Figure 3: Average Receptor Occupancy in Participants Infused With Various Doses of INCAGN02385

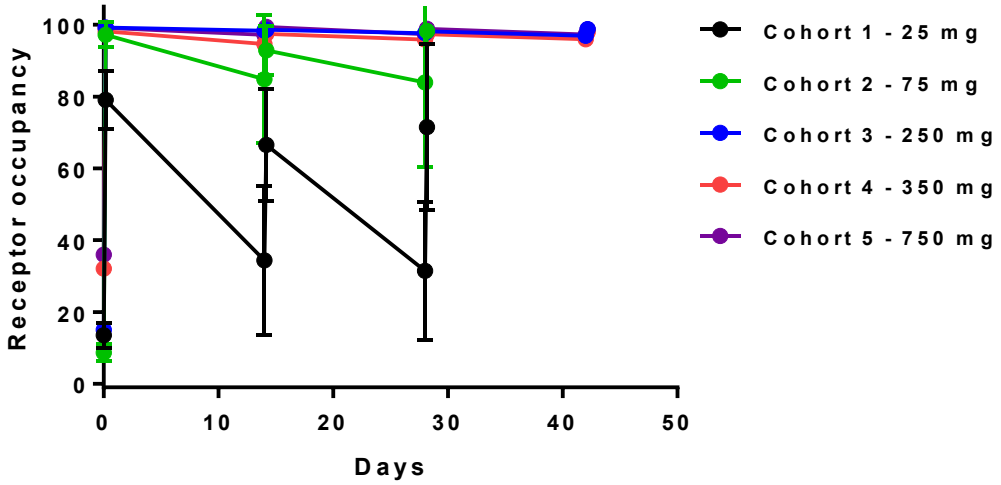
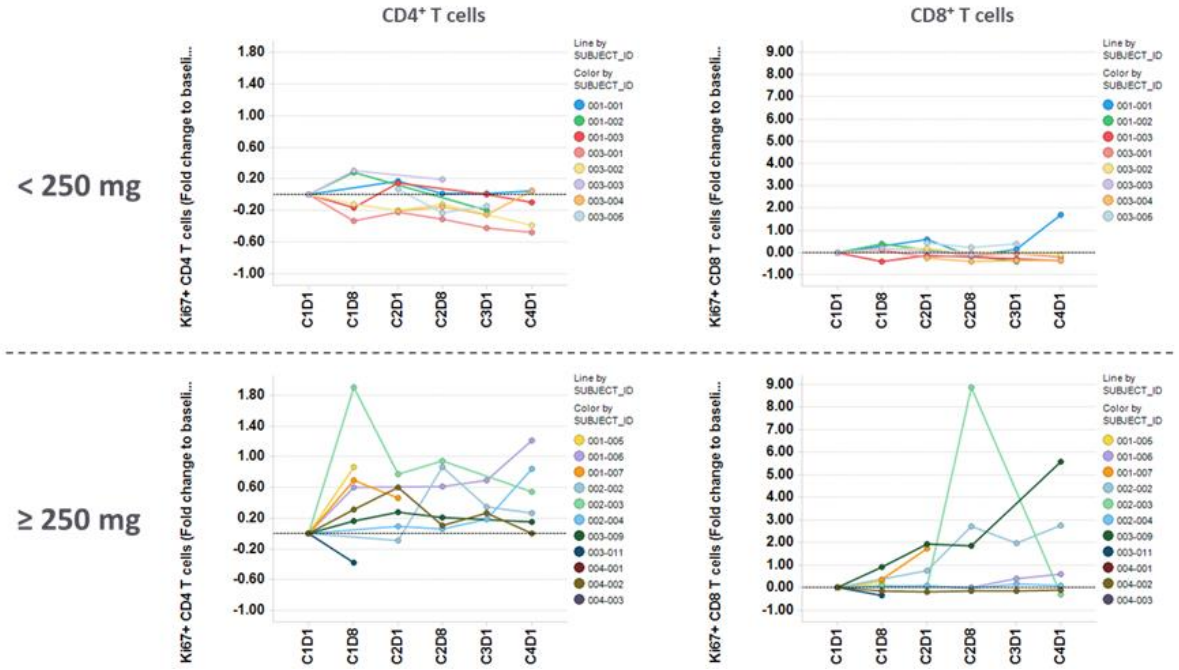


Figure 4: Frequency of Proliferating T Cells in the Blood of Participants Receiving Various Doses of INCAGN02385



2.1.4.2. INCAGN02390 Dose

As of 28 JUN 2022, a total of 40 unique participants were enrolled and received at least 1 dose of INCAGN02390 at doses of 10, 30, 100, 200, 400, 800, and 1600 mg Q2W in the open-label, nonrandomized, dose-escalation, and cohort-expansion study INCAGN 2390-101, evaluating monotherapy INCAGN02390. All doses were well-tolerated, no DLTs were observed, and there were no treatment-related deaths. INCAGN02390 showed supraproportional PK after the first dose from 30 mg to 800 mg Q2W and low interindividual variability on PK exposures (see Figure 5). At a dose of 400 mg Q2W, the mean steady-state AUC determined in 4 participants was 43,400 µg/mL·h. The dose of 400 mg was chosen for INCAGN02390 based on the results that the TIM-3 receptor was fully occupied on the surface of circulating monocytes (see Figure 6).

Figure 5: INCAGN02390 Concentrations Over Time (Mean ± SE) After the First Dose and at Steady-State at Various Dose Levels

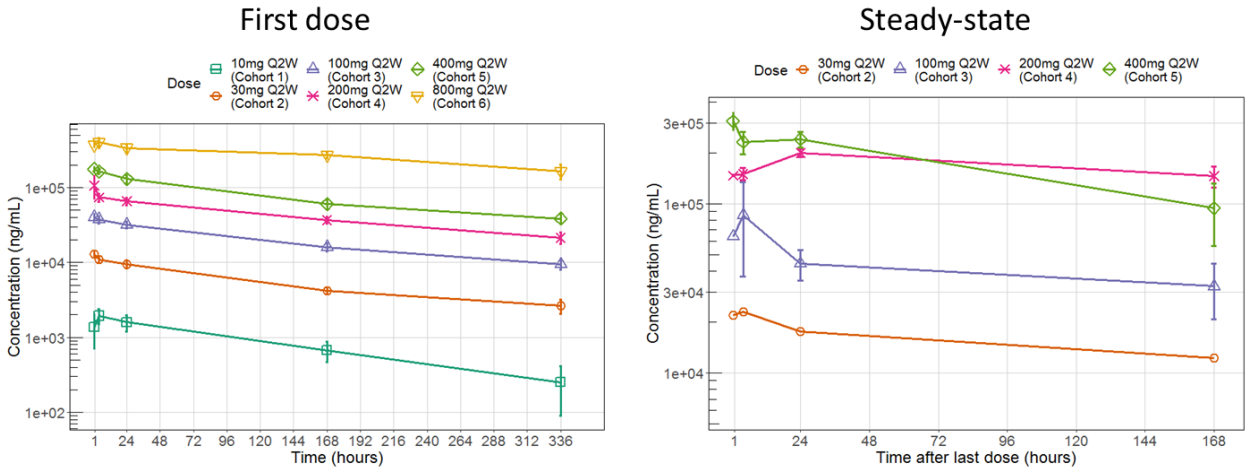
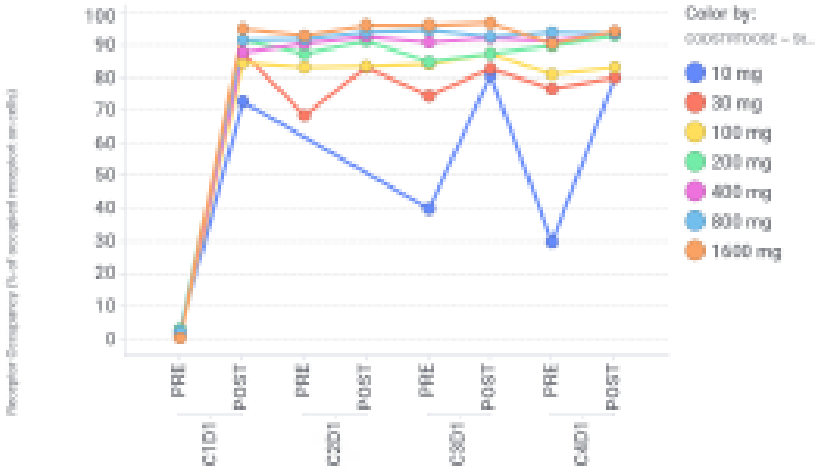


Figure 6: Average Receptor Occupancy in Participants Infused With Various Doses of INCAGN02390



2.1.5. Justification for Retifanlimab Dose

Retifanlimab will be administered at 500 mg Q4W. The selection of this dose was based on modeling of clinical PK data from the first-in-human monotherapy study, INCMGA 0012-101, in which 219 participants were treated with both body weight-based doses and flat doses of 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, and 750 mg Q4W (retifanlimab IB).

Pharmacokinetic data from Study INCMGA 0012-101 suggested that retifanlimab exposure increased in a dose-dependent manner with doses ranging from 1 mg/kg to 10 mg/kg (including flat doses of 375 mg to 750 mg). Full and sustained PD-1 receptor occupancy was observed with all doses studied on both PD-1 expressing CD4+ and CD8+ cells. The PK of retifanlimab following IV administration was well-characterized by a 2-compartment linear disposition model with time-dependent elimination. A population PK model estimated typical retifanlimab CL

as 0.0127 L/h with a steady-state $t_{½}$ of 18.4 days. Similar PK profiles were observed for the 3 mg/kg Q2W and 500 mg Q4W doses.

A simulation was conducted to investigate the use of weight-based and fixed doses for retifanlimab with the aim of targeting a steady-state trough concentration of approximately 21 µg/mL, which is the median trough concentration for pembrolizumab 2 mg/kg Q3W (Freshwater et al 2017). The 500 mg Q4W regimen resulted in steady-state exposure that was similar to the 3 mg/kg Q2W regimen (C_{trough}). In addition, full PD-1 receptor occupancy was observed on PD-1 expressing CD4+ and CD8+ cells with effects on circulating cytokines that are typical for a PD-1 inhibitor in all dose regimens of Study INCMGA 0012-101. Therefore, the 500 mg Q4W dose was selected as a dose for further development in monotherapy treatments and combination treatment. For more information, refer to the retifanlimab IB.

2.2. Benefit/Risk Assessment

2.2.1. Retifanlimab Monotherapy

Treatment directed at the PD-(L)1 axis is a promising approach to the diseases under study. Monoclonal antibodies against PD-1 have shown benefit for these and other indications, and safety of these agents has been well-characterized.

Antibodies targeting the PD-1 pathway have demonstrated activity in a wide variety of cancer types (Sun et al 2020), and the available preclinical and clinical data from study participants suggest that the pharmacologic and clinical profile of retifanlimab should be consistent with experience with other drugs in this class (Chen et al 2019, Condamine et al 2019, Lakhani et al 2017, Maio et al 2021, Mehnert et al 2018, Mehnert et al 2019). Based on these observations, the benefit/risk for retifanlimab should also be favorable, provided efficacy objectives in the proposed study are met, since the intended populations have a very limited prognosis with available therapy.

As of 23 SEP 2021, 660 participants have been treated with retifanlimab monotherapy across 6 clinical studies, and the overall safety profile is consistent with those observed with other anti–PD-1 antibodies (retifanlimab IB). Preliminary efficacy was been demonstrated in multiple tumor types with durable RECIST v1.1 responses observed in NSCLC (Mehnert et al 2019), cervical cancer (Mehnert et al 2018), biomarker-unselected endometrial cancer (Mehnert et al 2018), sarcoma (Mehnert et al 2018), Merkel cell carcinoma (Grignani et al 2020), and microsatellite instability-high or deficient mismatch repair endometrial cancer (Berton-Rigaud et al 2020). Retifanlimab has also demonstrated a clinical profile consistent with the PD(L)-1 class and across multiple solid tumor types that are known to be sensitive to PD-1 blockade (Maio et al 2021) with ORRs consistent with historical controls (melanoma ORR: 40.0%; TPS ≥ 50% NSCLC ORR: 34.8%; CPS ≥ 10 urothelial cancer ORR: 37.9%; renal cell carcinoma ORR: 23.5%). Given this, consistent clinical activity can be anticipated in patients with PD-L1–positive SCCHN.

Combination of PD-1 inhibitors with inhibitors of other checkpoints is supported by substantial preclinical and clinical data. Also, dose-ranging for all individual components in the combination regimen under study has been completed as well as combination treatment with the selected doses; thus, the selected dose levels are not anticipated to produce unexpected or unmanageable toxicity. Based on results from studies combining PD-1 inhibitors with antibodies directed at

either LAG-3 (Ascierto et al 2017, Lipson et al 2021) or TIM-3 (Davar et al 2018), toxicity of these combinations is expected to be similar to single-agent PD-1. Additionally, based on available preclinical and clinical data, combination of PD-1 inhibitors with other immune-checkpoint inhibitors may potentially provide responses in populations either unresponsive or who have lost response to PD-1 inhibitors.

2.2.2. INCAGN02385 Monotherapy

As of 21 MAR 2022, 22 participants with advanced malignancies have received INCAGN02385 Q2W at doses of 25 mg (n = 4), 75 mg (n = 4), 250 mg (n = 4), 350 mg (n = 3), and 750 mg (n = 7) in Part 1 (dose-escalation) of Study INCAGN 2385-101 (INCAGN02385 IB). All participants had at least 1 TEAE. Treatment-emergent AEs related to INCAGN02385 occurring in more than 1 participant were fatigue (n = 7) and creatinine increase, lymphopenia, myalgia, pruritus, and tumor pain (n = 2 each).

Eight participants had serious TEAEs; none of the serious TEAEs were considered by the investigator to be related to INCAGN02385. One participant (350 mg Q2W) had a TEAE leading to discontinuation of study drug (transient ischemic attack; not related to INCAGN02385). One participant (250 mg Q2W) had a fatal TEAE (failure to thrive), which was considered not related to INCAGN02385 by the investigator.

An MTD was not reached for INCAGN02385, and there have been no DLTs. Enrollment in Part 1 of Study INCAGN 2385-101 is complete.

2.2.3. INCAGN02390 Monotherapy

As of 28 JUN 2022, 40 participants have been exposed to monotherapy INCAGN02390 in Study INCAGN 2390-101 at doses of 10, 30, 100, 200, 400, 800, and 1600 mg Q2W (INCAGN02390 IB). All participants had at least 1 TEAE. The most frequently reported TEAEs (≥ 15%) for INCAGN02390 monotherapy in participants with advanced or metastatic immunogenic solid tumors were anemia (35.0%); back pain (30.0%), fatigue (27.5%); decreased appetite, nausea, and pruritus (17.5% each); and abdominal pain, diarrhea, and hyponatremia (15.0% each).

Eighteen participants (45.0%) had at least 1 serious TEAE, including pleural effusion (4 participants; 10.0%), acute respiratory failure (3 participants; 7.5%), and sepsis (2 participants; 5.0%). All other serious TEAEs were reported in 1 participant (2.5%) each.

One participant (2.5%) had 1 fatal TEAE, multiple organ dysfunction syndrome due to disease progression, which was considered not related to study treatment.

Six participants (15.0%) had at least 1 TEAE leading to discontinuation of study drug, including sepsis (2 participants [5.0%]) and acute respiratory failure, female genital tract fistula, impaired healing, pleural effusion, and supraventricular tachycardia (1 participant each; 2.5%).

Infusion-related reactions included sponsor-predefined preferred terms indicating a diagnosis of IRRs or symptoms potentially associated with IRRs. One participant (2.5%) had an infusion-related TEAE, which was Grade 1 pyrexia. Immune-related AEs were identified using sponsor-predefined preferred terms based on the ICI class regardless of investigator's assessment of causality. Four participants (10.0%) had at least 1 immune-related TEAE, including adrenal

insufficiency, hypothyroidism, acute kidney injury, dermatitis, and pruritus in 1 participant (2.5%) each.

The MTD of INCAGN02390 was not identified, and there were no DLTs. The RP2D of INCAGN02390 has been identified as 400 mg Q2W. There were no safety concerns identified with INCAGN02390 monotherapy.

2.2.4. Combinations of Retifanlimab, INCAGN02385, and INCAGN02390

INCAGN 2385-201 in an ongoing Phase 1/2 study evaluating the safety and preliminary efficacy of combinations of the Phase 1 doses of INCAGN02385 and INCAGN02390 described above together, as well as in combination with retifanlimab 500 mg Q4W. As of 28 JUN 2022, a total of 27 unique participants were enrolled and received at least 1 dose of INCAGN02385 IV at doses of 350 mg Q2W in combination with INCAGN02390 400 mg Q2W (N = 10) or INCAGN02390 400 mg Q2W + retifanlimab 500 mg Q4W (N = 17) in this open-label, nonrandomized, safety evaluation, and cohort-expansion study. During Phase 1 of INCAGN 2385-201, no DLTs were observed; 25 participants had at least 1 TEAE (9 participants who received the doublet and 16 participants who received the triple combination).

For the doublet combination of INCAGN02385 and INCAGN02390, 9 participants (90.0%) had at least 1 TEAE. Five participants (50.0%) had serious TEAEs, which included asthenia, pancreatitis, dyspnea, hypoxia, rectal hemorrhage, vulval hemorrhage, vasculitis, COVID-19, sepsis, and pyrexia; only 1 of which (vasculitis) was considered related to both study agents by the investigator. One participant had a fatal TEAE of sepsis. Sepsis was related to the COVID-19 infection and considered to not be related to study treatment.

Infusion-related reactions included sponsor-predefined preferred terms indicating a diagnosis of IRRs or symptoms potentially associated with IRRs. One participant (10.0%) had an infusion-related TEAE, which was Grade 1 chills and was considered related to study treatment by the investigator.

Immune-related AEs were identified using sponsor-predefined preferred terms based on the ICI class regardless of investigator's assessment of causality. Two participants (20.0%) had an immune-related TEAE, which were pancreatitis and vasculitis in 1 participant (10.0%) each. Pancreatitis was considered not related to study treatment, and vasculitis was considered related to study treatment by the investigator.

There were no DLTs in Study INCAGN 2385-201. Enrollment in Phase 1, Part 1 of Study INCAGN 2385-201 has been completed.

For the triplet combination of retifanlimab, INCAGN02385, and INCAGN02390, 16 participants (94.1%) had at least 1 TEAE. Three participants (17.6%) had serious TEAEs, which included pericardial effusion, myocarditis, acute respiratory failure, and pyrexia in 1 participant (5.9%) each.

Two participants (11.8%) had TEAEs leading to discontinuation of study drug, which included pericardial effusion, myocarditis, and pneumonitis.

No fatal TEAEs were reported after administration of INCAGN02385 in combination with INCAGN02390 and retifanlimab.

Immune-related AEs were identified using sponsor-predefined preferred terms based on the ICI class regardless of investigator's assessment of causality. Two participants (11.8%) had at least 1 immune-related TEAE, which included myocarditis, pruritus, and pneumonitis in 1 participant (5.9%) each. All immune-related reactions were assessed as related to study treatment.

Infusion-related reactions included sponsor-predefined preferred terms indicating a diagnosis of IRRs or symptoms potentially associated with IRRs. Four participants (23.5%) had at least 1 infusion-related TEAE, which included pyrexia and IRR in 2 participants (11.8%) each and chills in 1 participant (5.9%). Two of these participants had infusion-related TEAEs considered related to study treatment, which was pyrexia in both participants. Chills was considered to not be related to study treatment by the investigator, and both events of IRR were considered related only to INCAGN02385. All infusion-related TEAEs were nonserious and Grades 1 or 2 in severity.

There were no DLTs in Study INCAGN 2385-201. Enrollment in Phase 1, Part 2 of Study INCAGN 2385-201 has been completed.

Overall, the preliminary toxicity profiles of the combination regimens, including the triplet combination of INCAGN02385, INCAGN02390, and retifanlimab, were consistent with those anticipated with checkpoints blockade with no safety signals based on those preliminary data.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of the study drugs retifanlimab, INCAGN02385, and INCAGN02390 may be found in the respective IBs (retifanlimab IB, INCAGN02385 IB, INCAGN02390 IB).

2.2.5. Benefit/Risk Assessment During the COVID-19 Pandemic

Participants to be enrolled into this study have recurrent or metastatic SCCHN and may be at higher risk for complications if they contract COVID-19. An ESMO multidisciplinary panel highlighted the importance of clinical cancer research to find better therapeutic options for participants even during the pandemic, including potential investigational therapies similar to immunotherapy with a known survival benefit (Curigliano et al 2020). Preliminary data released based on real-world data indicate that the use of immunotherapy either alone or in combination with chemotherapy does not appear to increase the risk of hospitalization upon COVID-19 infection (Horn et al 2020) or cause an increased risk of mortality (Lee et al 2020). Effects of immune-checkpoint inhibitors on SARS-CoV2 infection is yet unknown. However, it has been reported that at early stages of SARS-CoV2 infection, CD8+ T-cell exhaustion and PD-1 upregulation have been observed in patients (Riva et al 2020, Zheng et al 2020). Those findings may suggest the hypothesis that immune-checkpoint inhibitors may ameliorate the early phase of COVID-19 disease through the reactivation of T cells expressing PD-1 (Maio et al 2020). Conversely, potential risks of cytokine release syndrome, pneumonitis, or myocarditis related to immune-checkpoint inhibitors therapy, may represent a clinical issue and impact a course of COVID-19 disease (Maio et al 2020, Sullivan et al 2020). Considering the critical medical need for therapies in the setting of R/M SCCHN and the importance of continuing clinical cancer research even during the pandemic, and taking into account the lack of conclusive clinical data on the impact of immune-checkpoint inhibitors therapy on COVID disease course, the sponsor will implement additional guidance in this clinical study for participation in the study in the context of the COVID-19 pandemic and study treatment management in the event of SARS-CoV2 infection (see Appendix C).

During the COVID-19 pandemic, additional risks to participants exist either related to going to a healthcare facility or as a result of study-related activities. The investigators will need to carefully assess both the benefit/risk and participant's available medical data (eg, performance status, past medical history, comorbidities) at screening in order to determine whether it is in the best interests of the potential participant to enroll and participate in the study. In addition, country-specific requirements will be followed with regard to COVID-19 testing as specified in Appendix C.

Investigators will be warranted to follow-up with repeated tests during the study as per medical judgment and/or local practices, for enrolled participants who may be newly suspected of being exposed to or have symptoms of SARS-CoV2, or to demonstrate recovery.

Participants will be monitored with safety procedures as described and with additional safety assessments as per SoC. Additional information regarding the flexibility of assessments/visits scheduling, where possible and warranted, and strategy for participant management during the dynamic pandemic as applicable are described in Appendix C.

3. OBJECTIVES AND ENDPOINTS

Table 6 presents the objectives and endpoints.

Table 6: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of the combinations of retifanlimab + INCAGN02385 (TG2) and retifanlimab + INCAGN02385 + INCAGN02390 (TG3) compared with retifanlimab alone (TG1) in the overall study population.	PFS, defined as the interval between the date of randomization and the earliest date of disease progression, based on investigator assessment per RECIST v1.1, or death due to any cause.
Secondary	
To assess disease response using RECIST v1.1 in TG2 and TG3 compared with TG1.	• Objective response, defined as having a CR or PR, determined based on investigator assessment per RECIST v1.1. • DOR, defined as the time from earliest date of disease response (CR or PR) until earliest date of disease progression, based on investigator assessment per RECIST v1.1, or death from any cause if occurring sooner than progression. • Disease control, defined as having CR, PR, or SD (≥ 6 months) as best response, based on investigator assessment per RECIST v1.1.
To determine the OS of TG2 and TG3 compared with TG1.	OS, defined as the interval between the date of randomization until death due to any cause.
To determine the safety of TG2 and TG3 compared with TG1.	• AEs, assessed in body systems with symptoms, through physical examinations, changes in vital signs and ECGs, and through clinical laboratory blood sample evaluations. • Impact on-study treatment, assessed by treatment interruptions, dose delays, and withdrawal of study treatment due to AEs.

Table 6: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, Phase 2 study to evaluate the efficacy and safety of the combination of retifanlimab plus INCAGN02385, and retifanlimab plus INCAGN02385 and INCAGN02390, compared with retifanlimab alone as first-line treatment in participants with PD-L1–positive, systemic therapy–naive, R/M SCCHN.

Approximately 162 participants will be randomized in a 1:1:1 ratio (approximately 54 participants per group) to 1 of the following treatment groups:

- TG1: retifanlimab plus placebo (INCAGN02385) and placebo (INCAGN02390)
- TG2: retifanlimab plus INCAGN02385 and placebo (INCAGN02390)
- TG3: retifanlimab plus INCAGN02385 and INCAGN02390

At randomization, participants will be stratified based on the following factors:

- LAG-3 expression status (determined centrally): positive (≥ 5%) versus negative (< 5%)
- PD-L1 CPS (determined centrally): 1-19 versus ≥ 20
- HPV p16 status (oropharyngeal only): p16-positive versus p16-negative; HPV p16 status for participants without oropharynx cancer (eg, cancers of the oral cavity, hypopharynx, larynx) is considered HPV p16 negative.

The study design schema is shown in Figure 1.

The study will include a 28-day screening period to determine eligibility, a treatment period in 4-week cycles for up to 2 years or until discontinuation criteria are met, an EOT visit, and 30-day and 90-day safety follow-up visits. Tumor assessments will be performed at baseline and subsequently Q8W for the first year of treatment and Q12W thereafter by site investigator review according to RECIST v1.1. Safety will be evaluated from the time the participant signs the ICF until the 90-day safety follow-up regardless of the start of a new anticancer therapy. Study treatment will begin on Day 1.

After 30 participants have been randomized and have received treatment for at least 4 weeks (at least 2 doses), an interim analysis of safety will be performed by an independent, external DSMB. Additional DSMB review of unblinded safety data will occur per the DSMB Charter.

4.2. Number of Participants

Approximately 162 participants will be randomized into the study (approximately 54 participants per group). Enrollment of participants whose tumors have low LAG-3 expression (ie, < 5%) will be capped at approximately 40% of the total.

4.3. Overall Study Duration

The duration for enrollment is expected to be approximately 12 months. The study begins when the first participant signs the ICF. The end of the study is defined as the date of the last visit (last scheduled procedure shown in the SoA) of the last participant in the study (ie, globally).

In the EU/EEA, the results of the study will be posted when the study is globally complete; this will ensure the data are robust, meaningful, and representative of all regions. Additionally, with the follow-up data complete, relevant statistical hypotheses can then be accurately and thoroughly evaluated.

For this study, a participant is considered to have completed the study if they have finished both the treatment and survival follow-up periods. Study treatment will be provided for a maximum of 2 years.

Additional follow-up for OS may be conducted up to approximately 2 years after the randomization of the last participant or, if earlier, at the time which the Sponsor terminates the study.

4.4. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/EC in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, if required by regulatory decision, or upon advice of the DSMB. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study. Reduced data collection activities and procedures as per SoC for remaining participants on-study treatment may be performed for participants who wish to remain on study if they derive clinical benefit as per investigator. The DSMB will recommend termination of the study if warranted, as described in Section 5.6.

In addition, further recruitment in the study or at a particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements; procedure-related problems; or the number of discontinuations for administrative reasons is too high.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Age 18 years or older (or as applicable per local country requirements), inclusive at the time of signing the ICF.
3. Histologically or cytologically confirmed R/M SCCHN that is not amenable to therapy with curative intent (surgery and/or radiation therapy with or without chemotherapy). Participants who refuse potentially curative salvage surgery for recurrent disease are ineligible.
   a. Eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.
   b. Participants with primary tumors of the nasopharynx, sinonasal cavity, or salivary gland are excluded.
   c. Participants must not have received prior systemic therapy for R/M SCCHN.

   Note: Participants may have received prior adjuvant or neoadjuvant chemotherapy or chemotherapy as part of multimodal treatment for locally advanced disease. Systemic therapy given in the neoadjuvant/adjuvant setting must have been completed at least 6 months prior to enrollment, with no evidence of disease progression within 6 months of completion of systemic treatment.

   Note: Participants enrolled will be eligible for first-line treatment with anti–PD-1 monotherapy for R/M SCCHN (and would not require combination therapy with chemotherapy) at the discretion of the investigator.
4. PD-L1 positive tumor status defined by CPS ≥ 1 per central laboratory determination.
5. For participants with primary oropharyngeal tumors, documentation of HPV p16 status (positive or negative) based on local institutional standard is required. HPV p16 status is not required for other eligible SCCHN primary tumor sites.

   Note: If local p16 testing results are not available or cannot be assessed by the institution, a tumor tissue sample may be submitted for p16 testing at the designated central laboratory. The result must be available prior to randomization. Tissue requirements are detailed in the Laboratory Manual.

6. Participant must have at least 1 measurable tumor lesion per RECIST v1.1.

   Note: For the purpose of response assessment, a biopsied lesion may only be selected as a target lesion if postbiopsy imaging confirms that it still qualifies as a RECIST-defined measurable lesion, unless there are other lesions that qualify the participant for RECIST assessment. Further, lesions used for the purpose of response assessment must either a) not reside in a field that has been subjected to prior radiotherapy or b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment.

7. Availability of archival tissue for biomarker analysis from a core or excisional biopsy or willingness to undergo a fresh biopsy.

   Note: Biopsy should be from a tumor site that has not been irradiated following occurrence or recurrence of the lesion. Formalin-fixed archival specimens after the participant has been diagnosed with recurrent or metastatic disease, or a fresh biopsy sample, are required for central determination of LAG-3 and PD-L1 CPS status prior to randomization.

8. ECOG performance status of 0 or 1.

9. Willingness to avoid pregnancy or fathering children based on the criteria below:

   a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 180 days after the last dose of study treatment and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative serum or urine pregnancy test before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 180 days after the last dose of study treatment and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   c. Female participants not considered to be of childbearing potential as defined in Appendix A are eligible.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Progressive or recurrent disease within 6 months of the last dose of systemic treatment for locally advanced SCCHN.
2. Prior PD-(L)1, LAG-3, or TIM-3 directed therapy, or any other checkpoint inhibitor therapy, for SCCHN (in any disease setting) or any other malignancy.
3. Treatment with anticancer therapies or participation in another interventional clinical study within 21 days before the first administration of study treatment (this includes curative radiation to the thorax or systemic anticancer therapies).

4. Presence of tumors that invade major blood vessels, as shown unequivocally by imaging, and with active bleeding.
5. Less than 3-month life expectancy (based on investigator judgment).
6. Participant has not recovered to ≤ Grade 1 or baseline from residual toxicities of prior therapy (with exceptions for anemia not requiring transfusion support, fatigue, or any grade of alopecia).
7. Participant has not recovered adequately from toxicities and/or complications from surgical intervention before starting study treatment.
8. Palliative radiation therapy administered within 1 week before the first dose of study treatment or radiation therapy in the thoracic region that is > 30 Gy within 6 months before the first dose of study treatment.

   Note: Participants must have recovered from all radiation-related toxicities, not require corticosteroids for this purpose, and not have had radiation pneumonitis.
9. Known active CNS metastases and/or carcinomatous meningitis. Participants will be excluded if it has been < 4 weeks since radiation therapy was delivered to the CNS.

   Note: Participants with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS edema, and have not required steroids for this purpose for at least 7 days before the first dose of study treatment.
10. Participants with laboratory values at screening defined in Table 7.

Table 7: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a.	Platelets	≤ 100×10^9/L
b.	Hemoglobin	≤ 9 g/dL
c.	ANC	≤ 1.5×10^9/L
Hepatic		
d.	ALT	≥ 1.5 × ULN or ≥ 2.5 × ULN for participants with liver metastases
e.	AST	≥ 1.5 × ULN or ≥ 2.5 × ULN for participants with liver metastases
f.	Total bilirubin	≥ 1.5 × ULN or ≥ 2.5 × ULN if Gilbert's syndrome or liver metastasis
Renal		
g.	Calculated CrCl	< 30 mL/min (calculated by Cockcroft-Gault equation)
Coagulation		
h.	INR or PT	> 1.5 × ULN unless on therapeutic anticoagulants

Laboratory Parameter		Exclusion Criterion
i.	aPTT	> 1.5 × ULN unless on therapeutic anticoagulants
Cardiac		
j.	TnT or TnI	> 2 × Institutional ULN. Participants with TnT or TnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤ 1 × ULN.[a]

Note: If the screening chemistry and hematology tests were conducted > 7 days before treatment initiation, they will need to be repeated on Day 1 before initiation of treatment to reconfirm eligibility.

[a] If TnT or TnI levels are > 1 to 2 × ULN within 24 hours, the participant may undergo a cardiac evaluation and be considered for treatment following a discussion with the sponsor's medical monitor or designee. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If TnT or TnI repeat levels beyond 24 hours are < 2 × ULN, the participant may undergo a cardiac evaluation and be considered for treatment following a discussion with the sponsor's medical monitor or designee.

11. Has known active HBV or HCV infection, or risk of reactivation of HBV or HCV, defined as follows (testing must be performed to determine eligibility):
    a. Active HBV infection is defined by positive HBsAg and positive total anti-HBc results.
       Note: If HBsAg is negative AND HBcAb and/or HBsAb is positive, HBV-DNA will be evaluated; when HBV-DNA is negative, the participant can then be enrolled with close monitoring of HBV activities.
    b. Active HCV is defined as a positive HCV antibody result and quantitative HCV-RNA results greater than the lower limits of detection of the assay.
       Note: Participants positive for HCV antibody will be eligible if they are negative for HCV-RNA. Participants who have had definitive treatment for HCV are permitted if HCV-RNA is undetectable.

    Note: HBV-DNA and the following hepatitis B serology must be conducted prior to randomization: HbsAg, total anti-HBc, and anti-HBs.
12. Participants who are known to be HIV-positive, unless all of the following criteria are met:
    a. CD4+ count ≥ 300/μL.
    b. Undetectable viral load.
    c. Receiving antiretroviral therapy that is not a potential risk for a drug-drug interaction with the assigned study drug.

    Note: Screening HIV antibody testing is required only if mandated by local health authorities or local regulations.
13. Any known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 3 years of the first dose of study treatment 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 completed treatment > 2 years before randomization in this study and has been disease-free since completion of treatment with curative intent.

14. Has active autoimmune disease requiring systemic immunosuppression with corticosteroids (> 10 mg/day of prednisone or equivalent) or immunosuppressive drugs within 2 years before the first dose of study treatment.
15. Is on chronic systemic steroids (> 10 mg/day of prednisone or equivalent).

    Notes:

    a. Physiologic corticosteroid replacement therapy at doses > 10 mg/day of prednisone or equivalent for adrenal or pituitary insufficiency and in the absence of active autoimmune disease is permitted.
    b. Participants with a condition (eg, asthma or COPD) that requires intermittent use of bronchodilators, inhaled steroids, or local steroid injections may participate.
    c. Participants using topical, ocular, intra-articular, or intranasal steroids (with minimal systemic absorption) may participate.
    d. Brief courses of corticosteroids for prophylaxis (eg, contrast dye allergy) or study treatment-related standard premedication are permitted.
16. Active infections (besides those described in Exclusion Criteria 11 and 12) requiring systemic antibiotics or antifungal or antiviral treatment (within 14 days before first dose of study treatment).

    Note: A participant with a positive test result for SARS-CoV2 infection at any time during screening should not be randomized until a negative antigen test is confirmed and any clinical symptoms (as applicable) have resolved.
17. Evidence of interstitial lung disease or history of interstitial lung disease, or active, noninfectious pneumonitis.
18. History of organ transplant, including allogeneic stem cell transplantation.
19. Receiving probiotics as of the first dose of study treatment.
20. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 460 milliseconds is excluded (corrected by Fridericia or Bazett formula). In the event that a single QTc is > 460 milliseconds, the participant may enroll if the average QTc for the 3 ECGs is ≤ 460 milliseconds.
21. Has had a significant cardiac event within 6 months before the first dose of study treatment, including New York Heart Association Class III/IV, acute myocardial infarction (including severe/unstable angina), cardiomyopathy, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, critical conduction delay, cerebrovascular accident or transient ischemic attack, or pulmonary embolism.

    Note: Medically-controlled arrhythmia is permitted.

    Note: Recovery from uncontrolled or Grade ≥ 3 hypertension to ≤ Grade 1 is required.
22. Has received a live vaccine within 30 days of planned start of study treatment.

    Note: Examples of live vaccines include but are not limited to the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus

vaccines and are allowed; however, intranasal influenza vaccines are live-attenuated vaccines and are not allowed.

23. Known hypersensitivity to another monoclonal antibody that cannot be controlled with standard measures (eg, antihistamines and corticosteroids).
24. Known allergy or hypersensitivity to any component of either retifanlimab, INCAGN02385, or INCAGN02390 study drug formulation (including excipients and additives).
25. Women who are pregnant or breastfeeding.
26. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
27. The following participants are excluded in France: vulnerable populations according to article L.1121-6 of the French Public Health Code and adults under legal protection, or who are unable to express their consent per article L.1121-8 of the French Public Health Code.

5.3. Lifestyle Considerations

No restrictions are required. Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after consultation with the sponsor and will receive a new participant number. Participants who rescreen must reconsent if more than 28 days have elapsed from the original consent date.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. For screening visit procedures, see Section 8.1.2.

5.5. Replacement of Participants

No participants will be replaced at any time during this study.

5.6. Data Safety Monitoring Board

After 30 participants have been randomized and have received treatment for at least 4 weeks (at least 2 doses), an interim analysis of safety will be performed by an independent, external DSMB. Enrollment will not be held during the safety interim analysis.

The external DSMB will consist of qualified individuals who are not involved with the conduct of the study. Additionally, the DSMB will review safety data of the ongoing study at regular intervals as specified in the DSMB Charter. Such safety data will be summarized by treatment

group. The process by which the DSMB will make recommendations and decisions will be documented in the DSMB Charter.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Table 8 presents the study treatment information.

Table 8: Study Treatment Information

	Study Treatment 1	Study Treatment 2	Study Treatment 3
Study treatment name:	Retifanlimab (INCMGA00012)	INCAGN02385/placebo	INCAGN02390/placebo
Dose formulation:	Solution for infusion	Solution for infusion	Solution for infusion
Unit dose strength(s)/ dose level(s):	25 mg/mL in a glass vial for single use Dose level: 500 mg Q4W	50 mg/mL Dose level: 350 mg Q2W	50 mg/mL Dose level: 400 mg Q2W
Route of administration	IV (30-minute infusion with filter followed by 10-minute flush)	IV (30-minute infusion with filter followed by 10-minute flush)	IV (30-minute infusion with filter followed by 10-minute flush)
Packaging and labeling	Study drug will be provided in a vial. Each vial will be labeled as required per country requirement.	Study drug will be provided in a vial. Each vial will be labeled as required per country requirement.	Study drug will be provided in a vial. Each vial will be labeled as required per country requirement.
Status of treatment in participating countries:	Investigational	Investigational	Investigational

The order of administration of study drugs on Day 1 of each cycle should be retifanlimab, followed by INCAGN02385/placebo, followed by INCAGN02390/placebo.

The order of administration of study drugs on Day 15 of each cycle should be INCAGN02385/placebo followed by INCAGN02390/placebo; retifanlimab is <u>not</u> administered on Day 15.

As outlined in Table 8, infusions are 30 minutes each with a 10-minute flush followed by the next infusion. For additional details regarding infusion of study drugs, refer to the Pharmacy Manual.

Study treatment will be administered for up to 2 years, or until discontinuation criteria are met (see Section 7.1.1). Study treatment may be administered ± 3 days of the scheduled Day 1 for each cycle (except for Cycle 1 Day 1, on which the study treatment will be administered specifically on Day 1) and ± 2 days of the scheduled Day 15 for each cycle. INCAGN02385/placebo and INCAGN02390/placebo doses should not be administered < 12 days apart.

Before administration of study treatment, premedication with an antipyretic agent (eg, acetaminophen/paracetamol or ibuprofen) and a histamine blocker (eg, diphenhydramine) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended according to institutional policy. On Cycle 1 Day 1, Cycle 1

Day 15, and Cycle 2 Day 1, vital signs will be monitored prior to each study drug infusion (−10 minutes), as well as 30 and 60 minutes (± 10 minutes) following completion of the INCAGN02390/placebo infusion and additionally as clinically indicated. For subsequent study drug infusions (Cycle 2 Day 15 and beyond), vital signs will be monitored prior to each study drug infusion (−10 minutes) and additionally as clinically indicated. If the participant experiences an IRR, vital sign monitoring should continue at the specified timepoints for subsequent study drug infusions until no suspected IRR is observed.

6.2. Preparation, Handling, and Accountability

For detailed information concerning the reconstitution, preparation, and infusion of the study drugs, refer to the Pharmacy Manual.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drugs to the study site.
- Inventory of study drugs at the site.
- Participant use of the study drugs including vial counts from each supply dispensed.
- Lot numbers and/or vial numbers (as applicable) of study drugs used to prepare the infusion solution.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of the study drugs until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drugs back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the

investigative site. At sites where the study drugs are destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT. Full details will be provided in the IRT Manual.

Study treatment will be dispensed at the study visits summarized in the SoA (see Table 3).

Centralized randomization numbers within each stratum will be created for treatment assignment. Participants will be assigned to study treatment in accordance with the randomization schedule. Participants, investigators, the sponsor, and the study team will be blinded to treatment assignment. See emergency unblinding procedures in Section 9.6.

A sponsor statistician who is not part of the study team will be unblinded and may provide summary aggregated data by treatment group to the DSMB, but individual participant data will remain blinded.

6.4. Study Treatment Compliance

Compliance with study treatment administration will be calculated by the sponsor based on study drug accountability and infusion records documented by the site staff and monitored by the sponsor/designee.

6.5. Dose Modifications

6.5.1. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drugs

Individual decisions regarding dose modifications of study treatment should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition. Adverse events that have a clear alternative explanation, or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms, may be exempt from dose-interruption rules.

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Dose modification of study drugs (INCAGN02385, INCAGN02390, and retifanlimab) is not permitted. If a dose-interruption is necessary for management of treatment-related TEAEs, study drugs will be reinitiated at the starting dose.

Treatment with study drugs may be interrupted up to 4 weeks (28 days) to allow for resolution of toxicity, unless a longer interruption is approved by the sponsor. All study drugs should be interrupted at the same time for the same duration. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. The treating investigator

should contact the sponsor to discuss the case of any participant whose treatment has been delayed for more than 28 days before restarting the study treatment.

Given the Q2W infusion schedule for INCAGN02385/placebo and INCAGN02390/placebo, if Day 15 infusions had to be delayed because of toxicity, the next dose of INCAGN02385/placebo and INCAGN02390/placebo can be resumed once the toxicity resolves as per protocol guidance:

- If treatment is restarted < 2 weeks from the last treatment visit, resume INCAGN02385/placebo plus INCAGN02390/placebo only (that would be considered Day 15), then the subsequent treatment visit should occur 2 weeks later with the triplet (including retifanlimab) and continue per protocol schedule.
- If treatment is restarted ≥ 2 weeks from last treatment visit, proceed with the triplet combination (ie, omit the Day 15 dose of the doublet INCAGN02385/placebo plus INCAGN02390/placebo) and continue per study schedule.

Decisions regarding these dose interruptions and restart of study drugs will be made according to Section 6.5.1.1 for non-irAEs, Section 6.5.2 for suspected infusion reactions and Section 6.5.3 for irAEs and, when needed, jointly by the investigator and medical monitor on a case-by-case basis.

Dose interruptions are permitted in the case of medical or surgical events (eg, elective surgery, unrelated medical events). In such a case, study treatment should resume within 4 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. Delayed study treatment administration in the case of logistical reasons not related to study therapy (eg, participant vacation, holidays) is permitted. In such a case, study treatment should resume within 3 to a maximum of 7 days of the scheduled interruption, unless otherwise discussed with the sponsor.

For participants who have active, confirmed (positive results from an approved COVID-19 test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection, guidelines in Appendix C should be followed.

If treatment is permanently discontinued for toxicity, all 3 study drugs must be discontinued and the EOT visit should be conducted.

6.5.1.1. Procedures for Participants Exhibiting Drug-Related, Non–Immune-Related Adverse Events

The guidance presented in Table 9 should be followed as best practice for decisions regarding management of non-irAEs.

Table 9: Management Guidelines for Drug-Related, Non–Immune-Related Adverse Events

CTCAE Grade	Suggested Modification for INCAGN02385, INCAGN02390, and Retifanlimab
Grade 1 or Grade 2	Continue treatment at the discretion of the investigator.
Grade 3	• Withhold treatment until resolution to ≤ Grade 1. • Permanently discontinue study treatment after third occurrence of toxicity, unless approved by the medical monitor to continue.
Grade 4	Permanently discontinue study treatment or discuss with medical monitor if treatment algorithm for CTCAE Grade 3 events (above) is appropriate.

6.5.2. Management of Suspected Infusion Reactions

Immunotherapies have been associated with the occurrence of infusion reactions. Infusion or hypersensitivity reactions may be observed with administration of any foreign protein. Premedication with an antipyretic (eg, acetaminophen/paracetamol or ibuprofen) and a histamine blocker (eg, diphenhydramine) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy. Routine prophylaxis is not required.

Participants should be monitored closely during the study drug infusion period and are required to remain at the study site on Cycle 1 Day 1 for safety observation for potential IRRs for at least 4 hours after completion of the final infusion (INCAGN02390/placebo). From Cycle 2 onwards, participants may be required to stay at the investigator's discretion.

Guidelines for management of suspected infusion reactions are provided in Table 10.

Table 10: Guidelines for Management of Suspected Infusion Reactions

Grade	Description	Treatment	Subsequent Infusions
1	Mild reaction; infusion interruption not indicated; intervention not indicated.	Monitor vital signs closely until medically stable.	Premedication with an antipyretic (eg, acetaminophen/paracetamol) and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
2	Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate medical measures (eg, IV fluids, antihistamines, NSAIDs, antipyretics, narcotics) per institutional preferences. Monitor vital signs until medically stable. If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. **Subsequent occurrences (after recommended prophylaxis):** Permanently discontinue study treatment.	Premedicate at least 30 minutes before infusion with antihistamines (eg, diphenhydramine 50 mg PO) and an antipyretic (eg, acetaminophen/paracetamol 500-1000 mg PO). Additional supportive measures may be acceptable (per institutional preference) but should be discussed with medical monitor. Next infusion should start at 50% of the original infusion rate. If no reaction, rate of infusion can be increase by 25% every 15 minutes until a rate of 100% has been reached. Subsequent infusions can begin at 100%.
3 or 4	**Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). **Grade 4:** Life-threatening; pressor or ventilatory support indicated.	Stop infusion and initiate appropriate medical therapy (eg, IV fluids, antihistamines NSAIDs, antipyretics, narcotics, oxygen, pressors, epinephrine, corticosteroids) per institutional preferences. Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	Permanently discontinue study treatment.

Note: Per NCI CTCAE v5.0, appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of study treatment administration (NCI 2017).

6.5.3. Procedures for Participants Exhibiting Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or irAEs, may be defined as AEs of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxic, or other etiologic causes before labeling an AE as an irAE.

General recommendations for the management of specific irAEs known to be associated with other PD-1 inhibitors (eg, pembrolizumab, nivolumab) are detailed in Table 11. Algorithms for evaluation of selected immune toxicities that have previously been attributed to PD-1 inhibitors and management guidelines for irAEs not detailed elsewhere in the protocol should follow the ASCO or ESMO Clinical Practice Guidelines (Haanen et al 2017, Schneider et al 2021).

Continuous evaluation of toxicity events will be performed throughout the study to assess for any late-onset immune-related toxicities that occur up to a minimum of 90 days after the last dose of study drug. If warranted, enrollment of participants may be suspended until the sponsor, investigators, and DSMB have determined the appropriate course of action.

Table 11: Guidelines for Management of Immune-Related Adverse Events

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Study Treatment	Adverse Event Management With Corticosteroid and/or Other Supportive Care Therapies
Pneumonitis	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	• Administer systemic corticosteroids per local practice followed by taper. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue.	
Diarrhea/colitis	Grade 1	No action.	None.
	Grades 2 or 3	Withhold until ≤ Grade 1.	• Consider prompt initiation of standard antidiarrheal agents and other necessary supportive care as needed (eg, oral and/or IV fluids). • Administer systemic corticosteroids per local practice followed by taper. • Consider prophylactic antibiotics per local practice. • Consider gastrointestinal consultation and performing endoscopy to rule out colitis.
	Grade 4 or recurrent Grade 3	Permanently discontinue.	
AST/ALT elevation and/or increased total bilirubin/hepatitis	Grade 1	No action.	• Administer systemic corticosteroids per local practice followed by taper. • Consider monitoring liver enzymes weekly (or more frequently) until liver enzyme value returns to baseline or is stable. • Consider monitoring total bilirubin, direct bilirubin, and alkaline phosphatase weekly (or more frequently) if needed.
	Grade 2 ALT or AST increase or Total bilirubin increases to > 1.5 × and up to 3 × ULN	Withhold.	
	Grades 3 or 4 ALT or AST increase or In participants with liver metastases with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week or Total bilirubin increases to > 3 × ULN	Permanently discontinue.	

Table 11: Guidelines for Management of Immune-Related Adverse Events (Continued)

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Study Treatment	Adverse Event Management With Corticosteroid and/or Other Supportive Care Therapies
Endocrinopathies • Type 1 diabetes mellitus • Hyperglycemia • Hyperthyroidism • Hypothyroidism • Adrenal insufficiency	Grades 1 and 2	No action if clinically appropriate.	None.
	Grade 2 adrenal insufficiency	Withhold until ≤ Grade 1 or otherwise clinically stable	Initiate treatment with HRT as clinically indicated.
	Grades 3 and 4 adrenal insufficiency	Withhold until ≤ Grade 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or is otherwise clinically stable.	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and HRT as clinically indicated.
	Grades 3 and 4 hypothyroidism	Withhold until ≤ Grade 2 or is otherwise clinically stable.	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per SoC.
	Grades 3 and 4 hyperthyroidism	Withhold until ≤ Grade 2 or is otherwise clinically stable.	Initiate symptomatic management.
	Grades 3 or 4 type 1 diabetes mellitus (or hyperglycemia)	Withhold until ≤ Grade 1 or is otherwise clinically stable.	Initiate treatment with antihyperglycemics as clinically indicated.
Endocrinopathies • Hypophysitis	Grade 1	No action.	None.
	Grade 2 (asymptomatic)	Withhold until ≤ Grade 1. May restart study treatment after controlled by HRT.	Administer hormonal replacement.
	Grade 2 (symptomatic; eg, headaches, visual disturbances)	Withhold until ≤ Grade 1. May restart study treatment after controlled with HRT, if indicated, and steroid taper is complete.	• Administer corticosteroids at initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper, and initiate other HRTs as clinically indicated. • Consult with endocrinologist as needed.
	Grade 3 or 4 (symptomatic)	• Permanent discontinuation should occur if after withholding study treatment, the toxicity does not resolve to ≤ Grade 1 within 12 weeks after last dose of study treatment, or if corticosteroid dose cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. • Permanent discontinuation should take place earlier at the investigator's discretion if corticosteroids and/or HRT cannot balance the participant's pituitary function.	• Administer corticosteroids at initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and initiate other HRTs as clinically indicated. • Consult with endocrinologist as needed.

Table 11: Guidelines for Management of Immune-Related Adverse Events (Continued)

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Study Treatment	Adverse Event Management With Corticosteroid and/or Other Supportive Care Therapies
Nephritis with renal dysfunction	Grade 1	No action.	None.
	Grade 2 increased blood creatinine	Withhold until ≤ Grade 1.	Administer corticosteroids per local practice followed by taper.
	Grade 3 or 4 increased blood creatinine	Permanently discontinue.[a]	
Skin (eg, Stevens-Johnson syndrome, or toxic epidermal necrolysis)	Grade 1	No action.	None.
	Grade 2	No action.	Manage with topical steroids with or without drug interruption.
	Grade 3[b] or persistent Grade 2 (≥ 2 weeks) or suspected Stevens-Johnson syndrome[c]	Withhold until ≤ Grade 1. Study treatment can be resumed at same dose.	• Administer corticosteroids per local practice followed by taper. • Additionally, oral antihistamines such as diphenhydramine or famotidine (per institutional preference) may be utilized as needed. • Should refer to dermatology if no resolution with these measures.
	Recurrent Grade 3[d] after resuming study treatment or Grade 4 rash or confirmed Grade 4 Stevens-Johnson syndrome[c] or toxic epidermal necrolysis[e]	Permanently discontinue.	• Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. • Refer to dermatology consult.
Myocarditis	Grade 2	• Depending on severity of symptoms withhold until symptoms fully resolve and management with corticosteroids is complete. • Permanent discontinuation may take place earlier at the investigator's discretion.	• Treatment with systemic corticosteroids should be initiated (initial dose of 1 to 2 mg/kg/day of prednisone or equivalent). Taper as appropriate. • Manage cardiac symptoms according to SoC and with guidance from cardiology. Consider cardiac MRI and myocardial biopsy for diagnosis.
	Grades 3 or 4	Permanently discontinue.	
TnI or TnT increase	All grades (including asymptomatic cases)	Withhold until cardiac evaluation is completed, myocarditis is ruled out, and a cardiologist recommends that treatment may proceed.	• Refer to cardiology consult and initiate diagnostic workup including ECG, echocardiogram (plus cardiac MRI as needed for diagnostic confirmation), and further relevant biological markers (eg, BNP, CPK) as per the cardiologist recommendation. • Confirmatory tests should be repeated within 24 hours – If troponin elevation is not confirmed within 24 hours in an asymptomatic participant, the dose delay may not be needed provided that the cardiac evaluation is completed and a cardiologist-recommended treatment may proceed. • If troponin elevation is confirmed, continue serial monitoring and consider initiating corticosteroids per cardiologist recommendation. Study treatment may resume when the cardiac evaluation is complete, myocarditis is ruled out, and a cardiologist recommends that treatment may proceed.

Table 11: Guidelines for Management of Immune-Related Adverse Events (Continued)

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Study Treatment	Adverse Event Management With Corticosteroid and/or Other Supportive Care Therapies
Important nervous system events (eg, Guillain-Barre syndrome, autoimmune encephalitis, myasthenia gravis, autonomic neuropathy, or transverse myelitis)	Grade 2	Withhold until ≤ Grade 1.	• Neurology consultation is recommended for all neurologic irAEs ≥ Grade 2. • Treatment with systemic corticosteroids should be initiated (initial dose of 1 to 2 mg/kg/day of prednisone or equivalent). Taper as appropriate. • For Grade 2 transverse myelitis, consider permanent discontinuation. • Manage symptoms according to SoC and with guidance from neurology.
	Grades 3 or 4	Permanently discontinue.	
All other irAEs	Grade 2 or Grade 3 based on severity and type of reaction	Withhold until ≤ Grade 1.	Based on severity of AE, administer corticosteroids.
	Recurrent Grade 3 or persistent Grade 2 and Grade 3	Permanently discontinue.	
	Grade 4	Permanently discontinue.	

[a] If study drug(s) are implicated in the renal toxicity.
[b] Participants with first onset of Grade 3 rash with desquamation, and/or mucosal involvement, requiring systemic steroids and not resolving or improving to ≤ Grade 1 within 14 days must permanently discontinue study treatment.
[c] Grade 3 Stevens-Johnson syndrome is defined as skin sloughing covering < 10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment). Grade 4 Stevens-Johnson syndrome is defined as skin sloughing covering 10% to 30% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment).
[d] Refers to single recurrence after first onset of Grade 3 that did not require systemic steroids and participant recovered and resumed study treatment. Investigators are required to define the medical term or type of "rash" as best as possible and not to enter in eCRFs the term generically as rash only. Severe skin rashes per CTCAE criteria are generally a rash that covers > 30% BSA and can be in the form of macules/papules or pustules; limiting self-care activities of daily living.
[e] Toxic epidermal necrolysis is Grade 4 by definition and is defined as skin sloughing covering ≥ 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment).

6.5.4. Criteria for Permanent Discontinuation of Study Treatment

The occurrence of unacceptable toxicity not caused by the underlying disease will require that the study treatment be permanently discontinued. Unacceptable toxicity is defined as follows:

- The occurrence of an AE that is related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- A persistent AE requiring a delay of therapy for more than 4 weeks (28 days) unless a greater delay has been approved by the sponsor. See exception for irAEs related to study treatment below.
- An irAE that does not resolve within 12 weeks of the last dose of study treatment, or corticosteroids cannot be reduced to ≤ 10 mg/day prednisone or equivalent within 12 weeks.

See Section 7 for discontinuation procedures.

6.5.5. Treatment After Initial Evidence of Radiologic Disease Progression

Combinations of immunotherapeutic agents such as the combination of retifanlimab, INCAGN02385, and INCAGN02390 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such as approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows PD, tumor assessment should be repeated ≥ 4 weeks later to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared with the initial scan demonstrating PD, treatment may be continued as per the treatment calendar. If repeat imaging confirms PD, participants will be discontinued from study therapy. In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions.

When feasible, participants should not be discontinued until PD is confirmed; however, the decision to continue study treatment after the first evidence of PD is at the investigator's discretion based on the clinical status of the participant as described in Table 12. Treatment should not continue beyond 2 years.

Participants may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating PD
- No decline in ECOG performance status
- Absence of rapid PD
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

Participants who are eligible to continue treatment past progression should be reconsented prior to continuation of therapy.

Table 12: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	NA
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments Q8W for the first year and Q12W thereafter	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments Q8W for the first year and Q12W thereafter	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any medication received up to 28 days before the first dose of study treatment and up to 30 days after the last dose of study treatment, regardless of the start of a new anticancer therapy, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered more than 30 days after the last dose of study treatment should be recorded for SAEs as defined in Section 9.3. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care, except those specifically defined as prohibited (see Section 6.6.3).

Recommended supportive measures for specific toxicities are described in Section 6.5.1. Permitted medications and procedures include the following:

- The use of growth factors on a nonroutine basis (and following ASCO guidelines for cerebrospinal fluid use), anticoagulants, and transfusional support will be permitted.
- Prior to administration of study treatment, premedication with an antipyretic (eg, acetaminophen/paracetamol or ibuprofen) and a histamine blocker should be considered for participants who have had previous systemic reactions to protein-product infusions or when recommended by institutional policy as described in Section 6.5.2.
- The use of corticosteroids is permitted in the following situations:
  - Acute treatment for an AE.
  - Physiologic corticosteroid replacement therapy at doses < 10 mg daily of prednisone or equivalent for adrenal or pituitary insufficiency and in the absence of active autoimmune disease.
  - Participants with asthma who require intermittent use of bronchodilators, inhaled corticosteroids, or local corticosteroid injections.
  - Topical, ocular, intra-articular, or intranasal corticosteroids (with minimal systemic absorption).
  - Brief course of corticosteroids for prophylaxis (eg, < 3 weeks for contrast dye allergy), for study treatment-related premedication as per SoC, for chronic obstructive pulmonary disease exacerbation, or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen).

6.6.2. Restricted Medications and Procedures

Use of systemic glucocorticoids is restricted to prophylaxis for contrast allergies for radiographic procedures or to modulate symptoms or treat an AE of suspected immunologic etiology as per Section 6.6.1.

6.6.2.1. Palliative Surgery and Radiation Therapy While on Study Treatment

Guidance regarding palliative surgery and radiation therapy while on study treatment is as follows:

- Palliative radiation: any use of palliative radiation should not involve target lesions and should be discussed and agreed upon with the study medical monitor. Study treatment should be withheld for at least 1 week before, during, and 1 week after radiation. Participants should be closely monitored for any potential acute toxicity during and after receiving radiotherapy, and AEs should resolve to ≤ Grade 1 prior to resuming immunotherapy agents.

- Palliative surgical procedures: permitted for the underlying medical condition and management of symptoms but should not involve target lesions. Study treatment adjustments and safety washout periods should be discussed and agreed upon with the study medical monitor based on the extent and nature of surgery.

Other restrictions and precautions include the following:

- Study-related MRIs of the brain, if required, will be performed per the frequency specified in SoA (see Table 3). Investigators may obtain additional follow-up MRI scans as medically indicated. For other locally performed imaging, it is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated GFR < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants with surgically implanted devices (eg, pacemaker, deep brain stimulator, metallic implants) incompatible with MRI should not undergo such imaging techniques. The local imaging facility and investigator should determine the appropriate precautions or guidelines that should be instituted for participants with tattoos, body piercings, or other body art. The ultimate decision to perform an MRI in an individual participant in this study rests with the site radiologist, the investigator, and the standards set by the local ethics committee.

6.6.3. Prohibited Medications and Procedures

Medications or vaccinations specifically prohibited in the exclusion criteria (see Section 5.2) are not allowed during study treatment. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study treatment may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the medical monitor, and the participant.

Participants are prohibited from receiving the following therapies during the screening, and study treatment of this trial:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this Protocol.
- Immunotherapy not specified in this Protocol.
- Investigational agents other than retifanlimab, INCAGN02385, and INCAGN02390.
- Curative radiation therapy or surgery.
  - Surgery or radiotherapy for tumor control is <u>not</u> permitted during the study

- Systemic immunosuppression for active autoimmune disease using immunosuppressive drugs or corticosteroids (> 10 mg daily of prednisone or equivalent), within 2 years before Day 1 of study treatment and throughout the study treatment period (with the exception of acute treatment for an AE; see Section 6.6.1).
- Chronic use of systemic corticosteroids (> 10 mg daily of prednisone or equivalent). Exceptions for corticosteroid use are outlined in Section 6.6.1.
- Live vaccines within 30 days before the first dose of study treatment, while participating in the study, and until 90 days after last dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live-attenuated vaccines and are not allowed.
- The use of probiotic dietary supplements.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Participants may receive other medications that the investigator deems to be medically necessary.

6.7. Treatment After the End of the Study

Once a participant has discontinued study treatment, no further treatment will be provided in this study. Participants who discontinue study treatment will enter the follow-up period to be evaluated for safety and survival. Any participants entering the follow-up period for any reason other than PD will continue to be evaluated for disease status according to the scheduled assessments found in Table 3.

In the event of early termination of the study, participants ongoing on-study treatment who are deriving clinical benefit (ie, do not have progressive disease) will be supplied with study drug through the 2-year treatment duration, until disease progression, or if any other treatment discontinuation criteria are met (eg, unacceptable toxicity, participant decision, physician decision), whichever occurs first.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons:

- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.

- Confirmed or unequivocal PD per RECIST v1.1 as assessed by the investigator.

  Note: Guidance for treatment with immunotherapy beyond initial objective disease progression is provided in Section 6.5.5.

- The participant is lost to follow-up as described in Section 7.3.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.5.
- The participant has received the maximum duration of 2 years of study treatment.
- The investigator decides to discontinue the participant from study treatment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A participant **may** be discontinued from study treatment as follows:

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- If a participant is noncompliant with study procedures or study drug/treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for the required follow-up visits. These visits are described in Table 3, Table 4, and Table 5. Each participant will be followed for 90 days for AE monitoring following cessation of study treatment. The last date of the last dose of study treatment and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The EOT visit should be performed and date recorded.
- The status of the participant should be updated to EOT in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study treatment-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data, then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See Table 3, Table 4, and Table 5 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF if more than 28 days have elapsed from the original consent date.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is randomized in the study (Cycle 1 Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 28 days of Cycle 1 Day 1). If chemistry and hematology laboratory assessments were performed more than 7 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1. For participants who are randomized in the study, information associated with eligibility requirements must be entered into the appropriate eCRFs.

Results from the screening visit evaluations will be reviewed to confirm eligibility before randomization or the administration of study treatment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before randomization will be used to determine eligibility. Treatment should start as soon as possible but no later than 3 days after the date of randomization.

See Sections 5.4 and 5.5 for information regarding screen failures and replacement of participants, respectively.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of a country's abbreviation, the site ID, and the participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for randomization, the IRT will be contacted to obtain the blinded treatment assignment. Additionally, the IRT will be contacted at each study visit specified in Table 3. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards

Participants will be provided with a reminder card at each visit. The reminder card will indicate the date/time of the next visit and will also provide any specific instructions, as applicable.

8.1.5. Demographics and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, medical and surgical history, and current illnesses. The participant's history of tobacco and alcohol consumption use will also be collected. Medical history will include relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's SCCHN history, including date of diagnosis, initial and current cancer stage, tumor histology, relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded. At screening, PD-L1 expression (CPS) and HPV status (for oropharyngeal primary tumors) must be determined and documented. The combined positive score will be determined centrally for all participants prior to randomization; prior local CPS results may also be collected in the Case Report Form. HPV p16 status is only required for participants with primary oropharyngeal tumors and may be determined locally (per the requirements in Section 5.1) or centrally if local testing is not feasible.

8.1.6. Prior/Concomitant Medications Review

The investigator or qualified designee will record medication, if any, taken within 28 days before the first dose of study treatment through the 30-days after the last dose of study treatment. Antibiotic use up to 2 months prior to the start of treatment will be collected.

8.2. Efficacy Assessments

Objective assessment of disease status is required using the evaluations per RECIST v1.1 (Eisenhauer et al 2009). The investigator's assessment will be used to determine responses and will be recorded in the eCRF.

Efficacy baseline assessments will be performed at screening, and further efficacy assessments will be performed throughout the study at the intervals defined in the SoA (see Table 3). Cycle delays should not interrupt the specified scan interval (see Section 8.2.1.2); thus tumor assessments and cycles may become out of sync.

8.2.1. Tumor Imaging per RECIST v1.1

The same imaging technique should be used for a participant throughout the study. All scans must be a contrast-enhanced CT or MRI, except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a positron emission tomography/CT scan uses higher energy and thinner slices (ie, of diagnostic quality), it may be acceptable with medical monitor approval. Images of the neck, chest, and abdomen are required for all participants. Additional imaging of other anatomical sites (eg, pelvis, brain), should be performed as applicable.

8.2.1.1. Tumor Imaging During Screening

Initial tumor imaging should be performed within 28 days before the first dose of study treatment. The site study team must review prestudy images to confirm that the participant has measurable disease per RECIST v1.1. For the purpose of response assessment, a biopsied lesion may only be selected as a target lesion if postbiopsy imaging confirms that it still qualifies as a RECIST defined measurable lesion, unless there are other lesions that qualify the participant for RECIST assessment. Further, lesions used for the purpose of response assessment must either a) not reside in a field that has been subjected to prior radiotherapy or b) have demonstrated clear

evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment..

An MRI scan or CT of the brain will be performed at screening if there is a previous history of CNS metastasis or there are signs or symptoms suggesting that the participant has disease involvement in the CNS.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study treatment.

8.2.1.2. Tumor Imaging During the Study

The first imaging assessment should be performed 8 weeks (± 7 days) after the first dose of study treatment and then Q8W (± 7 days) for 12 months and then Q12W (± 7 days) thereafter until PD is determined. Imaging assessments may be done more frequently if clinically indicated. Imaging should not be delayed for delays in cycle starts.

Repeated brain imaging during the treatment phase will be performed only if the screening brain imaging was positive or as clinically indicated. If indicated, brain imaging should occur at same time (± 2 weeks) as disease assessment scans. Whenever feasible, contrast-enhanced brain MRI is preferred to CT.

Per RECIST v1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date that the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response or at the next scheduled scan, whichever is clinically indicated.

Imaging should continue to be performed until documented PD, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. A central imaging vendor will not be used in this study.

8.2.2. Health Economics

Not applicable; health economics parameters are not evaluated in this study.

8.3. Safety Assessments

See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 90 days after the last dose of study treatment regardless of the start of a new anticancer therapy. Adverse events for randomized participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study treatment. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious, considered related to the study treatment/procedures, or that caused the participant to discontinue the study treatment. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height and body weight, and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen; extremities; and lymph nodes; as well as a brief neurological examination.

During the study, participants will be assessed by the investigator or medically qualified designee per institutional SoC. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the AE eCRF. Body weight will also be assessed on Day 1 of each cycle.

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, and body temperature at each required assessment timepoint. Vital signs will be monitored before and/or after study drug infusions as per Table 3 and Section 6.1. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment.

8.3.4. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in Table 3 at screening, Day 1 of Cycles 1 through 5, on Day 1 of every fourth cycle beginning at Cycle 9, at EOT, and as clinically indicated. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

All 12-lead ECGs will be performed using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Triplicate ECGs require 3 individual ECG tracings obtained as closely as possible in succession and up to approximately 2 minutes apart. The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or discontinue a participant from the study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. In the event that a single QTc is > 460 milliseconds at screening, the participant may enroll if the average QTc for the 3 ECGs is ≤ 460 milliseconds or with approval from the medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. In addition, the JTc interval should be used for all subsequent assessments.

8.3.5. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be assessed at the timepoints indicated in Table 3 according to the criteria in Table 13.

Table 13: Eastern Cooperative Oncology Group Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al 1982.

8.3.6. Laboratory Assessments

See Table 14 for the list of clinical laboratory tests to be performed and Table 4 for the timing and frequency. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, lipid panel, thyroid function, serology, pregnancy testing, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional

testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 28 days before Cycle 1 Day 1. If screening chemistry and hematology analyses are performed within 7 days before initial administration of study treatment, they do not need to be repeated on Cycle 1 Day 1.

Laboratory sample collection on Cycle 1 Day 1 must be performed before study treatment administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration (within the 3-day study window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

Table 14: Required Laboratory Analytes

<table>
<tr><th>Blood Chemistries</th><th>Hematology</th><th>Urinalysis</th><th>Serology</th></tr>
<tr><td rowspan="3">Albumin
Alkaline phosphatase
ALT
AST
Amylase
Bicarbonate, CO_2 or HCO_3 (if clinically indicated)
Blood urea nitrogen or urea
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Lipase
Phosphate
Potassium
Sodium
Total bilirubin (also direct bilirubin, if total bilirubin is elevated above ULN)
Total protein
Troponin (TnT or TnI) level (per local standard)
Uric acid</td><td>Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• WBC count

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils

Absolute values must be provided for:
• WBC differential laboratory results</td><td>pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein
Urobilinogen
Microscopic examination (if blood or protein is abnormal)</td><td>HBV screening and management (required):
• HbsAg
• Total anti-HBc
• Anti-HBs
• HBV-DNA

When applicable per investigator discretion:
• IgM anti-HBc

HCV screening:
• HCV antibody
• HCV-RNA quantitative

HIV antibodies <u>only</u> if mandated by local health authorities or local regulations.

HIV management (if HIV-positive):
• HIV viral load
• CD4+ cell count</td></tr>
<tr><th>Lipids</th><th>Coagulation</th><th>Pregnancy Testing</th></tr>
<tr><td rowspan="2">Total cholesterol
Triglycerides
LDL
HDL</td><td>PT
PTT or aPTT
INR</td><td rowspan="2">Human chorionic gonadotropin (serum or urine)</td></tr>
<tr><td>Thyroid Function

TSH
T4
fT4
FT3/T3 as clinically indicated</td></tr>
</table>

Note: Additional laboratory analytes used for management of AEs/SAEs, ruling out a diagnosis, or participant management are permissible during the study.
Note: Alternative tests to the above may be conducted instead or in addition if they are the SoC in a particular region.
Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data, or based on regional geographical differences, or depending on the extent of COVID-19 pandemic. Relevant test results will be documented in eCRFs.

8.3.6.1. Urine Sample Collection

Urine will be collected as a predose sample at screening, Cycle 2 Day 1, every 3 cycles thereafter, and at EOT (see Table 4). A urine dipstick analysis will be performed. If clinically significant abnormalities are observed, further analysis, including microscopic analysis, should be performed as clinically indicated. The Laboratory Manual should be consulted for more complete instructions.

8.3.6.2. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening and at the EOT visit. The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study treatment; the test performed at EOT is optional if the participant is going to hospice. Serum or urine pregnancy tests will be performed locally as outlined in Table 4, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirements (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study treatment and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7 for reporting requirements.

8.3.6.3. Serology

Hepatitis and HIV (if applicable) screening assessments will be performed at the screening visit (see Table 4) to rule out hepatitis and HIV infection (see Section 5.2); required analytes are shown in Table 14. Generally, hepatitis and HIV tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

Note: HIV testing is not required unless mandated by the local health authority.

8.4. Pharmacokinetic and Immunogenicity Assessments

8.4.1. Blood Sample Collection

Pharmacokinetic and ADA samples will be obtained at the visits indicated in Table 5. Timing of blood samples for the measurement of serum concentrations and ADAs of retifanlimab, INCAGN02385, and INCAGN02390 is specified in Table 15. Predose is defined as within 24 hours before administration of study treatment. For predose PK draws, contents of prior meals may be recorded. Adjustments to the timing of blood sampling may be made based on emerging PK data. The exact date and time of each PK blood draw will be recorded in the eCRF. Instructions for sample preparation and shipping will be provided in the Laboratory Manual.

Table 15: Pharmacokinetic and Antidrug Antibody Sample Blood Sample Timing

Study Visit	Assessment	Timing of Sample
Cycle 1 Day 1	PK and ADA	• Preinfusion samples for all 3 agents prior to retifanlimab infusion
	PK	• Immediately after retifanlimab infusion (≤ 10 min) • Immediately after INCAGN02385 infusion (≤ 10 min) • Immediately after INCAGN02390 infusion (≤ 10 min)
Cycle 1 Day 8	PK	Untimed PK sample
Cycle 1 Day 15	PK and ADA	Preinfusion of INCAGN02385/placebo andINCAGN02390/placebo
	PK	Untimed PK sample of retifanlimab
Cycle 2 Day 1	PK and ADA	Preinfusion samples for all 3 agents prior to retifanlimab infusion
Cycle 4 Day 1	PK and ADA	Preinfusion samples for all 3 agents prior to retifanlimab infusion
Cycle 6 Day 1[a]	PK and ADA	Preinfusion samples for all 3 agents prior to retifanlimab infusion
EOT, 30-day, and 90-day safety follow-up	PK and ADA	Untimed sample

[a] PK and ADA measurements will continue on Day 1 of all even-number cycles, for example, Cycle 8 Day 1, Cycle 10 Day 1, etc.

8.4.2. Immunogenicity (Antidrug Antibody) Assessments

Blood samples will be assessed for antibodies binding to retifanlimab, INCAGN02385, and INCAGN02390, and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to retifanlimab, INCAGN02385, and INCAGN02390 and/or further characterize the immunogenicity of study drug.

The detection and characterization of antibodies to retifanlimab, INCAGN02385, and INCAGN02390 will be performed using a validated assay method by or under the supervision of the sponsor or designee. All samples collected for detection of antibodies to study drugs will also be evaluated for concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug.

8.5. Pharmacodynamic and Translational Assessments

Whole blood, plasma, and tumor tissue will be collected for assessments as outlined in Table 4 and Table 16 to investigate biomarkers relevant for participant stratification, as well as changes in the peripheral blood of participants given INCAGN02385 with or without INCAGN02390 in combination with retifanlimab. Biomarker assessments beyond those listed may be evaluated at the discretion of the sponsor using excess biomarker or PK samples. Analyses will be conducted by the sponsor or its designee.

For information regarding handling/shipping of specimens, refer to the Laboratory Manual.

Table 16: Biomarker/Translational Sample Timing

Biomarker Assessment	Study Visit	Timing of Sample	
		Anytime	Preinfusion
Fresh tumor biopsy/archival tissue	Screening	X	
	EOT[a]	X	
• Whole blood for flow cytometry[b] • Whole blood for PBMC • Plasma biomarker	Cycle 1 Day 1		X
	Cycle 1 Day 8	X	
	Cycle 1 Day 15		X
	Cycle 2, Cycle 3, and Cycle 4 Day 1		X
Plasma cfDNA	Cycle 1 Day 1	X	
	Cycle 3 Day 1	X	

[a] If discontinuing treatment for PD (optional).
[b] First 75 participants only.

8.5.1. Tumor Tissue Collection

A baseline tumor tissue sample, either fresh or archival, is **required** for all participants at screening for central determination of LAG-3 and PD-L1 (CPS) expression status, and HPV p16 status (as applicable) if not determined locally. Archived tissue is acceptable if there is adequate sample available (preferably at least 1 tissue block or 30 slides; see Laboratory Manual for specifics) and the sample was collected after the completion of the most recent systemic therapy, after the participant has been diagnosed with recurrent or metastatic disease, and less than 12 months prior to the date of screening. Fine needle aspirates are not acceptable. LAG-3 expression will be assessed by IHC using an investigative test at a central laboratory. The tumor sample will be assessed for PD-L1 expression at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA) and may be used for assessment of the tumor microenvironment by IHC or RNA analysis.

Tissue biopsy samples will also be used to investigate molecular signatures associated with response or resistance to treatment with the study drug. DNA and/or RNA may be extracted from these samples to perform somatic mutation analysis, epigenetic analysis, and gene expression analysis. Tissue may also be examined by histology and IHC or by exploratory methods to evaluate markers of immune cell populations, growth, signaling, apoptosis, etc. that may be associated with safety, response, or resistance to treatment with the study drug.

8.5.2. Whole Blood Correlative Flow Cytometry Assessments

Whole blood correlative samples will be analyzed by flow cytometry to identify relevant changes in cell populations or in various markers expression by cell populations with treatment. Receptor occupancy for LAG-3, TIM-3, and PD-1 may be assessed by flow cytometry in a retrospective manner, following completion of the final study analysis. Other assays relevant to the objectives of the study may be performed based upon emerging data.

8.5.3. Whole Blood for PBMC Assessments

Whole blood PBMC samples will be analyzed by DNA and/or RNA profiling or similar methods to identify cell populations and changes in cell populations or expression by cell populations

with treatment. RNA analysis may include expression analysis by RNASeq or RNAscope analysis for specific gene expression. Immune cell subsets function may also be assessed using ex vivo restimulation assays. Other assays relevant to the objectives of the study may be performed based upon emerging data.

8.5.4. Plasma Correlative Assessments

A number of tumor and immune response–derived proteins can be shed from tumors or activated normal cells and released into the blood. Correlation of presence and abundance of certain proteins with clinical response may identify new approaches for predictive biomarkers in blood. Plasma analytes may include cytokines and other markers of inflammation and immune status, tumor markers, and markers of metabolism and nutritional status. Other assays relevant to the objectives of the study may be performed based on emerging data.

8.5.5. Plasma cfDNA Assessments

A sample of plasma will be collected for possible analysis of mutations identified in tumor biopsies using tumor circulating DNA.

8.6. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted, including scheduled cycle visits in which a study treatment hold is indicated for toxicity purposes. Any assessments performed at those visits should be recorded in the eCRF.

8.7. End of Treatment and/or Early Termination

Once a participant permanently discontinues all study treatment (whether the participant is withdrawing from the study early or the participant has completed the study treatment period), the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. All EOT assessments should be completed within 3 days of the decision to discontinue study treatment. Should EOT visit occur ≤ 21 days after the final dose of study treatment, a separate 30-day safety follow-up visit is required and should be conducted according to Table 3, Table 4, and Table 5. The participant should be encouraged to return for the safety follow-up visits. If the EOT visit occurs > 21 days after the last dose of study treatment, only a single EOT/30-day safety follow-up visit is required, and all unique assessments for the EOT and 30-day follow-up visit will be performed once.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period starts once the participant discontinues study treatment. Approximately 30 days (± 7 days) and 90 days (± 7 days) after the EOT, participants are to attend a clinic visit for safety evaluation. Adverse events and SAEs must be reported up until 1) at least 90 days after the last dose of study treatment regardless of the start of a new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

Reasonable efforts should be made to have the participant return for the follow-up visits and report any AEs that may occur during this period. If the participant cannot return to the site for the safety follow-up visit, the participant should be contacted by telephone or other methods of communication for assessment of any AEs; this contact should be documented in the source.

If a participant is scheduled to begin a new anticancer therapy before the planned 30-day safety follow-up visit, the safety follow-up visit should be performed before a new anticancer therapy is started. Once a new anticancer therapy has been initiated, the participant will move into the survival follow-up period.

8.8.2. Post-Treatment Disease Follow-Up

Participants who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed by radiologic imaging to monitor disease status Q8W (± 7 days) from the first 12 months following the start of study treatment, and then Q12W (± 7 days) thereafter. Every effort should be made to collect information regarding disease status until:

- The start of new anticancer therapy
- Disease progression
- Death
- The end of the study

8.8.3. Survival Follow-Up

Once a participant has received the last dose of study treatment, has confirmed disease progression, or starts a new anticancer therapy, the participant moves into the survival follow-up period. The participant should be contacted by telephone, email, or visit at least Q12W (± 14 days) to assess for survival status until death, withdrawal of consent, the end of the study, or the participant is lost to follow-up, whichever occurs first.

For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, participant records, and public records/databases at intervals of no longer than 12 weeks (± 14 days). Participants may be contacted for survival status at any time during the course of the study to support planned survival analyses.

Participants may withdraw their consent at any time from any or all portions or periods of the study. Participants who withdraw consent for treatment and/or imaging are encouraged to remain on the noninvasive survival follow-up portion of the study. The procedures associated with this phase may be only telephone contacts to assess survival status and the current state of the participant's SCCHN. The noninvasive nature and societal benefit of survival follow-up should be explained to the participant by the site staff, particularly when discontinuing treatment and imaging.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study treatment administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dose administration errors of a study treatment (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE.

Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) are not considered SAEs.

d. Results in persistent or significant disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers (excluding the disease[s] under study), intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. Secondary malignancies should always be considered SAEs.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. AEs/SAEs should be reported for randomized participants, but only SAEs need to be reported for screen failure participants. For randomized participants, conditions that were present at the time informed consent was given should be recorded on the Medical History eCRF. For detailed information refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Event Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Reference Manual.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine the following:

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study treatment as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form, and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive treatment indicated; limiting age-appropriate activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent treatment indicated.
- Grade 5: Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. If appropriate, the relationship to each study drug must be assessed, and the relationship to the combination may be assessed as well.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IBs in making his/her assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • Once an AE is detected, it should be followed in the AE eCRFs until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study treatment or study procedures), all SAEs occurring after the participant has signed the ICF through at least 90 days after the last dose of study treatment, regardless of the start of a new anticancer therapy, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or 90 days after the last dose of study treatment. If the investigator learns of any SAE, including a death, at any time during the disease status follow-up or survival status follow-up period, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and irAEs (as defined in Section 6.5.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor regarding an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the RSI of the IB for any of the study drugs (new occurrence; refer to retifanlimab IB, INCAGN02385 IB, and INCAGN02390 IB) and is thought to be related to the study treatment, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with

the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, EU CTR No. 536/2014, and FDA 21 CFR Part 312 or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

Serious Adverse Event Reporting
• Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF. • The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available. The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual or as per the Incyte Reference Guide for Completing the Serious Adverse Event Report Form). • In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form or Study Reference Manual for details and for the email address or fax number). • Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study treatment because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Events of Clinical Interest

No specific AEs are expected to be sent to the sponsor within an expedited manner aside from the AEs that meet the seriousness category as described in Section 9.4.

Immune-related AEs will be identified by investigator assessment as well as using sponsor-predefined preferred terms based on the ICI class regardless of investigator's assessment of causality. Both investigator assessed and sponsor-assessed irAEs will be summarized.

9.6. Emergency Unblinding of Treatment Assignment

In a medical emergency, if knowledge of the treatment assignment is necessary to determine optimal medical management of the participant, the procedure for emergency unblinding is provided in the IRT Manual. This option may be used *only* if the participant's well-being requires the investigator to be aware of the participant's treatment assignment. If a participant's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone.

If an investigator, the site personnel performing assessments, or a participant is unblinded, then the participant must discontinue study treatment unless there are ethical reasons to have the participant remain on the study treatment. In these cases, the investigator must obtain specific approval from the sponsor's (or its designee's) medical monitor for the participant to continue in the study.

9.7. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant during maternal or paternal exposure to study treatment, the following procedures should be followed in order to ensure safety:

- The study treatment must be interrupted immediately (female participants only).
- If the female participant is no longer pregnant and meets the treatment continuation criteria within 28 days of the scheduled start of a cycle, study treatment may be resumed after approval has been received from the sponsor's medical monitor.
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or its designee.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.8. Warnings and Precautions

Special warnings or precautions for the study treatment, derived from safety information collected by the sponsor or its designee, are presented in the IBs. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study as necessary. If new significant risks are identified, they will be added to the ICF.

9.9. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9.10. Treatment of Overdose

For retifanlimab, a dose > 1500 mg within a 24-hour time period will be considered an overdose. In the event of an overdose of retifanlimab, the following should occur:

- Appropriate supportive treatment should be provided if clinically indicated.
- The investigator should contact the medical monitor immediately and closely monitor the participant for any AEs/SAEs and laboratory abnormalities per Section 9.3.
- The quantity of the excess dose as well as the duration of the overdose should be documented in the eCRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

There has been no clinical experience with overdose of INCAGN02385 or INCAGN02390. Treatment of overdose should consist of general supportive measures.

10. STATISTICS

This section outlines the statistical analysis strategy and procedures for this study. If changes are made to primary efficacy and safety and/or secondary efficacy hypotheses or the statistical methods related to those hypotheses after the study has begun, but before the final database lock, the Protocol will be amended, consistent with ICH E9 (1998) and ICH E9 (R1; 2021). The detailed statistical analyses will be documented in the Statistical Analysis Plan.

10.1. Sample Size Determination

The sample size calculation is based on the primary endpoint of PFS. Approximately 162 participants will be randomized in a 1:1:1 ratio into TG1:TG2:TG3. The study is event-driven and will be complete after approximately 94 PFS events have been observed between TG1 and TG2 or between TG1 and TG3 (approximately 140 PFS events across the 3 treatment groups). Based on a target of 94 PFS events for all participants at the final analysis between TG1 and TG2 or between TG1 and TG3 (approximately 140 PFS events across the 3 treatment groups), which is expected to occur about 20 months from the start of enrollment, the study has approximately 80% power to detect an HR of 0.6 at an overall alpha level of 5% (1-sided) favoring one of the combination therapies with the assumption of study parameters as specified in Table 17 for PFS.

The sample size and power calculations were performed in R package "gsDesign."

Table 17: Sample Size Assumptions for Progression-Free Survival

Variable	Assumptions
Median PFS in TG1 (All participants)	3 months[a]
Randomization ratio	1:1:1
Assumed HR (All participants)	0.6
Enrollment duration	12 months
Follow-up for PFS	8 months
Assumed annual dropout rate	1%

[a] Burtness et al 2019.

10.2. Populations for Analyses

Table 18 presents the populations for analysis.

Table 18: Populations for Analyses

Population	Description
ITT	All randomized participants. Treatment groups for this population are determined according to the treatment they have been assigned at the time of randomization. The ITT population will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data.
Safety	The safety population includes all randomized participants who receive at least 1 dose of study treatment. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned treatment at the time of randomization. All safety analyses will be conducted using the safety population.
PK/pharmacodynamic evaluable	The PK evaluable population will include all participants who received at least 1 dose of study treatment and provided at least 1 postdose serum sample (1 PK measurement). The pharmacodynamic evaluable population will include all participants who received at least 1 dose of study treatment and provided at least 1 postdose plasma sample (1 pharmacodynamic measurement).
ADA	The ADA-evaluable population comprises all participants who received at least 1 dose of study treatment and provided at least 1 ADA postdose sample.

Table 19 shows how the analysis population is associated with the endpoints.

Table 19: Endpoints and Analysis Populations

Primary/Secondary Endpoint	Population	Hypothesis	Population-Level Summary Metric
PFS	ITT	Hypothesis 1: TG3 is superior to TG1 with respect to PFS in all participants Hypothesis 2: TG2 is superior to TG1 with respect to PFS in all participants	HR
OS	ITT	NA	HR
Objective response	ITT	NA	ORR difference
Disease control	ITT	NA	DCR difference
DOR	ITT[a]	NA	Median DOR
AEs Impact on study treatment	Safety	NA	Rate

[a] Responder subpopulation.

10.3. Level of Significance

For the primary endpoint, the overall 1-sided alpha level will be strongly controlled 10%, with an initial 1-sided alpha allocation for each hypothesis at 5% (refer to SAP). The detailed multiplicity control will be specified in the Protocol Section 10.6. Unless otherwise stated, all CIs provided will be reported at a 95% confidence level.

10.4. Statistical Analyses

10.4.1. Primary Analysis

Progression-free survival, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause, whichever occurs first. Progression-free survival will be based on investigator assessment per RECIST v1.1. Survival data will be analyzed by the Kaplan-Meier method, treating participants with no observed death or disease progression as censored. Censoring for PFS will follow the primary analysis algorithm outlined in Table 20, which is based on regulatory guidelines (FDA 2015).

Table 20: Evaluation and Censoring of Progression-Free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No valid postbaseline response assessments in the absence of death prior to first scheduled tumor assessment	Censored at date of randomization	Censored at date of randomization	Censored at date of randomization
Progression documented between scheduled visits	Progressed at date of first overall response of PD	Progressed at date of first overall response of PD	Progressed at date of first overall response of PD
Death before first PD assessment	Progressed at date of death	Progressed at date of death	Progressed at date of death
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
No PD and no death; after ≥ 2 missed disease assessments	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Censored at last disease assessment	Censored at last disease assessment

Table 20: Evaluation and Censoring of Progression-Free Survival (Continued)

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death

The stratified log-rank test will be used to compare PFS between treatment groups in the ITT at a 1-sided 5% significance level, stratified for LAG-3 expression status (≥ 5% vs < 5%), PD-L1 CPS (1%-19% vs ≥ 20%), and HPV p16 status (p16-positive vs p16-negative, oropharyngeal only). The strata identified in the randomization process will be used for the analysis.

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 accounting for ties in event times (1977).

Kaplan-Meier curves for PFS will be presented by treatment groups. The Kaplan-Meier estimate of median PFS will be presented with its 95% CI. The 95% CI will be calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment at which PD was not documented and the assessment when PD is documented. In order to evaluate the robustness of the PFS endpoint per RECIST v1.1 based on investigator review, 2 sensitivity analyses with a different set of censoring rules will be performed. For the first sensitivity analysis, participants who miss more than 1 disease assessment are not handled differently from participants who miss 0 or 1 disease assessment (ie, the status depends on if there is PD or death).

The second sensitivity analysis handles participants who discontinue treatment or initiate an anticancer treatment subsequent to discontinuation of study-specified treatments differently from the primary analysis. The censoring rules for these 2 sensitivity analyses are also summarized in Table 20. Within each analysis, if a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

10.4.2. Secondary Analysis

10.4.2.1. Objective Response Rate

Objective response is a key secondary objective and will be determined by investigator assessment per RECIST v1.1. Objective response rate is defined as the proportion of participants with a CR or PR as best objective response.

The stratified CMH test will be used for comparison of ORR between treatment groups in the ITT population. The strata identified in the randomization process will be used for the analysis.

Estimates of ORR along with its exact 95% CIs using the Clopper-Pearson method will be computed for each treatment group. The odds ratio and its 95% CIs calculated from the stratified CMH test will also be presented.

10.4.2.2. Disease Control Rate

Disease control rate is defined as the proportion of participants with a CR, PR, or SD (≥ 6 months) as the best objective response based on investigator assessment per RECIST v1.1.

The stratified CMH test will be used for comparison of DCR between treatment groups in the ITT population. The strata identified in the randomization process will be used for the analysis. Estimates of DCR along with its exact 95% CIs using the Clopper-Pearson method will be computed for each treatment group. The odds ratio and its 95% CIs calculated from the stratified CMH test will also be presented.

10.4.2.3. Duration of Response

Duration of response is a key secondary objective defined as the time from earliest date of disease response (CR or PR) until earliest date of disease progression as determined by investigator assessment per RECIST v1.1, or death from any cause, if occurring sooner than progression. Participants with no observed death or disease progression will be censored. Censoring for DOR will follow the algorithm outlined in Table 20. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Kaplan-Meier estimation of median DOR and its 95% CIs will be presented by treatment group for participants who achieve an objective response.

10.4.2.4. Overall Survival

Overall survival is defined as the time from the date of randomization to the date of death due to any cause. The primary efficacy analysis comparing the 2 treatment groups will be a stratified log-rank test at an allocated overall 1-sided level of significance. The stratification will be based on the randomization stratification factors listed in Section 4.1 and based on the ITT population according to the randomized treatment group and strata assigned at randomization. Kaplan-Meier curves, medians, and 95% CIs of the medians will be presented for each treatment group. The HR for OS will be calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test with Efron's likelihood approximation to account for ties in event times. Participants without documented death at the time of analysis will be censored at the date of last known contact. Analysis using the restricted mean survival time method may be conducted for OS to account for the possible nonproportional hazards effect.

10.4.3. Overall Efficacy Conclusions

The overall efficacy conclusions from the study will be based on the totality of the efficacy endpoint analysis.

10.4.4. Safety Analyses

Safety analyses will be conducted for the safety population.

All TEAEs, clinical laboratory measurements, vital sign measurements, and ECG values will be summarized by treatment group. Quantitative safety variables and their changes from baseline (laboratory, vital signs, and ECG values) will be summarized with descriptive statistics. Abnormal values outside of established ranges will be flagged and tabulated based on predefined criteria.

Measures of exposure (eg, days of exposure, dose modification, dose intensity) of study drug will be summarized descriptively.

Adverse events will be coded by the MedDRA dictionary and severity of AEs will be based on the NCI CTCAE v5.0 using Grades 1 through 5. A TEAE is defined as an AE either reported for the first time or worsening of a pre-existing event after first dose of study drug and within 90 days of the last dose. The number and percentage (%) of participants reporting any TEAEs, any serious TEAEs, any Grade 3 or higher TEAEs, any treatment-related TEAEs, any treatment-related serious TEAEs, any treatment-related Grade 3 or higher TEAEs, any fatal TEAEs, and any TEAEs leading to treatment interruption/discontinuation will be tabulated by MedDRA system organ class and preferred term. Data listings will include all AEs regardless of their timing to study drug administration. Adverse events of clinical interest will be summarized as detailed in the SAP.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades when applicable and tabulated.

Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. The abnormal values for participants exhibiting vital sign abnormalities will be listed.

The abnormal values for participants exhibiting ECG abnormalities will be listed.

10.4.5. Pharmacokinetic Analysis

[redacted]

10.4.6. Exploratory Analysis

[redacted]

[redacted]

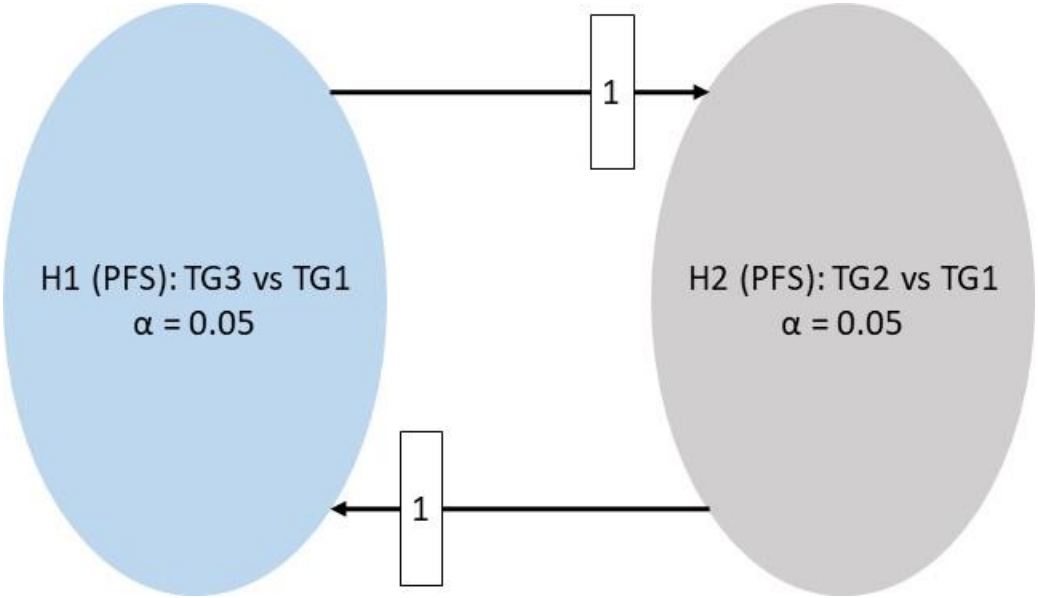
10.5. Interim Analysis

No formal efficacy interim analysis is planned for this study. However, DSMB-related activities are routinely conducted. One interim analysis to review safety will occur as outlined in Section 5.6.

10.6. Multiplicity Control

The study uses the graphical method of Maurer and Bretz (Maurer and Bretz 2013) to strongly control type I error for multiple hypotheses. A graphical display of the plans for reallocation of alpha is displayed in Figure 7 using the initial 1-sided alpha allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting the hypothesis. The detailed information for each hypothesis about the bounds and boundary properties for the final analysis for different alpha level due to the alpha reallocation will be tabulated in SAP.

Figure 7: Multiplicity Graph for 1-Sided Alpha Reallocation Strategy



10.7. Subgroup Analyses

[redacted]

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and health authorities before the study is initiated. In accordance with EU CTR No. 536/2014, the sponsor will be responsible for submitting all documents in participating countries.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
  - Ensuring study-site compliance with the requirements of EU CTR No. 536/2014.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

- All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of his or her responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and, as designated by the sponsor, will have their own data flow management plans, study charters, or biomarker plans, as applicable.

The sponsor (or designee) will be responsible for:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated, and/or collected including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, biomarker data, photographs, diary data), or as otherwise specified in the Protocol.

- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are in general all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.

- Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
- Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the monitoring plan.

Quality tolerance limits will be predefined in the operational manual or equivalent to identify systematic issues that can impact participants' safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

11.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice consent (as may be required by each applicable jurisdiction), for collection, use, disclosure, and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study

findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

11.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research participants, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.6. Publication Policy

By signing the study Protocol, the investigator and his/her institution agree that the results of the study may be used by the sponsor, Incyte Biosciences International Sàrl (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.7. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

12. REFERENCES

Ascierto PA, Bono P, Bhatia S, et al. Efficacy of BMS-986016, a monoclonal antibody that targets lymphocyte activation gene-3 (LAG-3), in combination with nivolumab in pts with melanoma who progressed during prior anti-PD-1/PD-L1 therapy in all-comer and biomarker-enriched populations. Ann Oncol 2017;28:v605-v649.

Berton-Rigaud D, Vergote I, Pautier P, et al. A phase 1 study of retifanlimab (INCMGA00012), a PD-1 inhibitor, in patients with advanced solid tumors: preliminary results in recurrent MSI-high or dMMR endometrial cancer (POD1UM-101). J Immunother Cancer 2020;8(suppl 3):A16-A165 [abstr 268].

Blackburn SD, Shin H, Haining WN, et al. Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection. Nat Immunol 2009;10:29-37.

Brana I, Forster M, Lopez-Pousa A, et al. Results from a phase II study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients with PD-L1 unselected metastatic second-line squamous head and neck carcinoma. J Clin Oncol 2021;39(suppl):Abstract 6028.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 2019;394:1915-1928.

Chen X, Wang P, Kaul S, Sumrow B, Yeleswaram S. Assessment of flat dosing strategy for INCMGA00012 in patients with advanced tumors. Cancer Res 2019;79(suppl):Abstract LB268.

Chow LQM. Head and neck cancer. N Engl J Med 2020;382:60-72.

Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. 2020.

Condamine T, Owens S, Feldman P, et al. Pharmacodynamic correlates in a Phase I study of INCMGA00012, a PD-1 antagonistic monoclonal antibody. Cancer Res 2019;79(suppl):Abstract CT085.

Curigliano G, Banerjee S, Cervantes A, et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31:1320-1335.

Davar D, Boasberg P, Eroglu Z, et al. A Phase 1 study of TSR-022, an anti-TIM-3 monoclonal antibody, in combination with TSR-042 (anti–PD-1) in patients with colorectal cancer and post PD-1 NSCLC and melanoma. Presented at: 33rd Annual Meeting of the Society for Immunotherapy of Cancer; November 7-11, 2018; Washington, DC. Abstract O21.

Deng WW, Mao L, Yu GT, et al. LAG-3 confers poor prognosis and its blockade reshapes antitumor response in head and neck squamous cell carcinoma. Oncoimmunology 2016;5:e1239005.

Dong J, Cheng L, Zhao M, Pan X, Feng Z, Wang D. Tim-3-expressing macrophages are functionally suppressed and expanded in oral squamous cell carcinoma due to virus-induced Gal-9 expression. Tumour Biol 2017;39:1-9.

Efron B. The efficiency of Cox's likelihood function for censored data. J Am Stat Assoc 1977;72:557-565.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics. 2015.

Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. J Immunother Cancer 2017;5:43.

Gameiro SF, Ghasemi F, Barrett JW, et al. Treatment-naive HPV+ head and neck cancers display a T-cell-inflamed phenotype distinct from their HPV- counterparts that has implications for immunotherapy. Oncoimmunology 2018;7:e1498439.

Grignani G, Burgess M, Depenni R. POD1UM-201: A Phase 2 study of retifanlimab (INCMGA00012) in locally advanced or metastatic merkel cell carcinoma. Presented at ESMO Virtual Congress 2020.

Haanen JBAG, Carbonnel F, Roberts C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol 2017;28:iv119-iv142.

Hamid O, Wang D, Kim TM, et al. Clinical activity of fianlimab (REGN3767), a human anti-LAG-3 monoclonal antibody, combined with cemiplimab (anti-PD-1) in patients (pts) with advanced melanoma. J Clin Oncol 2021;39(suppl):Abstract 9515.

Horn L, Whisenant J, Torri V, et al. Thoracic Cancers International COVID-19 Collaboration (TERAVOLT): impact of type of cancer therapy and COVID therapy on survival. J Clin Oncol 2020;39(suppl 18):Abstract LBA111.

Horton JD, Knochelmann HM, Day TA, Paulos CM, Neskey DM. Immune evasion by head and neck cancer: foundations for combination therapy. Trends Cancer 2019;5:208-232.

INCAGN02385 Investigator's Brochure. Wilmington, DE: Incyte Corporation.

INCAGN02390 Investigator's Brochure. Wilmington, DE: Incyte Corporation.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. E9: Statistical Principles for Clinical Trials. 1998.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. E9 (R1): Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. 2021.

Jie HB, Gildener-Leapman N, Li J, et al. Intratumoral regulatory T cells upregulate immunosuppressive molecules in head and neck cancer patients. Br J Cancer 2013;109:2629-2635.

Jin HT, Anderson A, Tan WG, et al. Cooperation of TIM-3 and PD-1 in CD8 T-cell exhaustion during chronic viral infection. Proc Natl Acad Sci U S A 2010;107:14733-14738.

Kaufmann JK, Sharma G, Ghosh S, et al. Triple checkpoint blockade targeting PD-1, TIM-3, and LAG-3 improves T cell reinvigoration and antitumor efficacy over single and double combinations. Presented at: 33rd Annual Meeting of the Society for Immunotherapy of Cancer; November 7-11, 2018; Washington, DC. Abstract P365.

Klein JP, Moeschberger ML. Survival Analysis: Techniques for Censored and Truncated Data. Springer-Verlag; 1997.

Kok VC. Current understanding of the mechanisms underlying immune evasion from PD-1/PD-L1 immune checkpoint blockade in head and neck cancer. Front Oncol 2020;10:268.

Lakhani N, Mehnert JM, Rasco D, et al. A Phase 1 study of the safety, tolerability, and pharmacokinetics (PK) of MGA012 (anti-PD-1 antibody) in patients with advanced solid tumors. Poster presented at: 32nd Congress of the Society for Immunotherapy of Cancer; November 8-12, 2017; National Harbor, MD. Abstract P249.

Lee LYW, Cazier JB, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020;395:1919-1926.

Lipson EJ, Tawbi HA, Schadendorf D, et al. Relatlimab (RELA) plus nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase III results from RELATIVITY-047 (CA224-047). J Clin Oncol 2021;39(suppl):Abstract 9503.

Maio M, Hamid O, Larkin J, et al. Immune checkpoint inhibitors for cancer therapy in the COVID-19 era. Clin Cancer Res 2020;26:4201-4205.

Maio M, Schenker M, Medioni J, et al. Phase 2 study of retifanlimab (INCMGA00012) in patients (pts) with selected solid tumors (POD1UM-203). J Clin Oncol 2021;39(suppl):Abstract 2571.

Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5:311-320.

Mehnert J, Joshua A, Lakhani N, et al. First-in-human phase 1 study of INCMGA00012 in patients with advanced solid tumors: interim results of the cohort expansion phase. J Immunother Cancer 2018;6(suppl 1):357 [abstr P669].

Mehnert J, Paz-Ares L, Pikiel J, et al. A phase 1 study of INCMGA00012, a PD-1 inhibitor, in patients with advanced solid tumors: preliminary results for patients with advanced cervical cancer (POD1UM-101). J Immunother Cancer 2019;7(suppl 1):215 [abstr P394].

Mishra AK, Kadoishi T, Wang X, et al. Squamous cell carcinomas escape immune surveillance via inducing chronic activation and exhaustion of CD8+ T Cells co-expressing PD-1 and LAG-3 inhibitory receptors. Oncotarget 2016;7:81341-81356.

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017.

National Comprehensive Cancer Network. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Head and Neck Cancers Version 2.2020. 2020.

Ngiow SF, von Scheidt B, Akiba H, Yagita H, Teng MW, Smyth MJ. Anti-TIM3 antibody promotes T cell IFN-γ-mediated antitumor immunity and suppresses established tumors. Cancer Res 2011;71:3540-3551.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Oweida A, Hararah MK, Phan A, et al. Resistance to radiotherapy and PD-L1 blockade is mediated by TIM-3 upregulation and regulatory T-cell infiltration. Clin Cancer Res 2018;24:5368-5380.

Panda A, Rosenfeld JA, Singer EA, Bhanot G, Ganesan S. Genomic and immunologic correlates of LAG-3 expression in cancer. Oncoimmunology 2020;9:e1756116.

Retifanlimab Investigator's Brochure. Wilmington, DE: Incyte Corporation.

Rischin D, Harrington KJ, Greil R et al. Protocol-specified final analysis of the phase 3 KEYNOTE-048 trial of pembrolizumab (pembro) as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). J Clin Oncol 2019;37(suppl):Abstract 6000.

Riva G, Nasillo V, Tagliafico E, Trenti T, Luppi M. COVID-19: room for treating T cell exhaustion? Crit Care 2020;24:229.

Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 2019;20:1239-1251.

Sakuishi K, Apetoh L, Sullivan JM, Blazar BR, Kuchroo VK, Anderson AC. Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. J Exp Med 2010;207:2187-2194.

Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update [erratum in J Clin Oncol 2022;40:315]. J Clin Oncol 2021;39:4073-4126.

Shayan G, Srivastava R, Li J, Schmitt N, Kane LP, Ferris RL. Adaptive resistance to anti-PD1 therapy by Tim-3 upregulation is mediated by the PI3K-Akt pathway in head and neck cancer. Oncoimmunology 2016;6:e1261779.

Sullivan RJ, Johnson DB, Rini BI, et al. COVID-19 and immune checkpoint inhibitors: initial considerations. J Immunother Cancer 2020;8:e000933.

Sun L, Zhang L, Yu J, et al. Clinical efficacy and safety of anti-PD-1/PD-L1 inhibitors for the treatment of advanced or metastatic cancer: a systematic review and meta-analysis. Sci Rep 2020;10:2083.

Wherry EJ. T cell exhaustion. Nat Immunol 2011;12:492-499.

Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res 2012; 72:917-927.

Yang F, Zeng Z, Li J, Ren X, Wei F. TIM-3 and CEACAM1 are prognostic factors in head and neck squamous cell carcinoma. Front Mol Biosci 2021;8:619765.

Zheng M, Gao Y, Wang G, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol 2020;17:533-535.

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

WOCBP: A woman who is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)
- Sexual abstinence[c]
  - Abstinence from penile-vaginal intercourse

The following are **not** acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method.
- Male condom with cap, diaphragm, or sponge with spermicide.
- Male and female condom used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

For female participants who are WOCBP
The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.[d] – oral – intravaginal – transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation[d] – oral – injectable – implantable[e] • Intrauterine device[e] • Intrauterine hormone-releasing system[e] • Bilateral tubal occlusion[e] • Vasectomized partner[e,f] • Sexual abstinence[c]

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner with childbearing potential, the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
Source: Clinical Trials Facilitation and Coordination Group (2020).

APPENDIX B. TEST FOR LAG-3 EXPRESSION

The IHC assay for LAG-3 expression was developed and validated at Neogenomics laboratories.

Summary of LAG-3 Assay

Assay category	Lab developed test
Reagent category	Research use only
Assay type	Semiquantitative IHC
Analyte name	Anti–LAG-3 antibody
Analyte clone	L4-PL33
Analyte manufacturer	Enzo Life Sciences
Intend use of the assay	Determine LAG-3 status in FFPE tumor samples of human SCCHN
Assay intended to be used on specimen type	FFPE tissue
Assay cut-off	≥ 5%
Assay accuracy at cut-off	97.2%
Prevalence of positivity in SCCHN (5% cut-off)	58%

APPENDIX C. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic presents challenges to the ongoing conduct of clinical studies. In line with regulatory guidance regarding clinical study execution during the pandemic, the sponsor has issued the following Protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain.

Recognizing the dynamic nature and flexibility required to manage the impact of the pandemic on this clinical study, additional details will be incorporated into respective study manuals and site-specific monitoring plans as applicable, with institutional requirements as warranted, and communicated to the investigative sites as needed. Relevant test results will be documented in the eCRF, and applicable changes to the ICF will be made and monitored.

Given the critical medical need for alternative treatments for patients in the setting of recurrent/metastatic cancer and the importance of continuing cancer research, a positive COVID-19 screening test should not result in definitive exclusion. Participants with a positive COVID-19 test during screening may be reassessed for eligibility in the study only after normalization of their COVID-19 screening test and clinical recovery as per the investigator's evaluation.

SARS-CoV2 Infection and Participation in the Study

Benefit/risk assessment in the context of the COVID-19 pandemic is provided in Section 2.2.5. During the COVID-19 pandemic, additional risks to participants exist either related to going to a healthcare facility or as a result of study-related activities. It is at the investigator's discretion to balance the risk/benefit while considering the participant's safety, existing comorbidities, and current malignancy. In addition, country-specific requirements are to be followed with regard to COVID-19 testing.

A participant who fails screening due to COVID-19 infection may repeat the screening process upon recovery and COVID test normalization.

Study Site Visits

If local travel restrictions, isolation requirements, or the investigator's benefit/risk assessment determines it to be unsafe for participants to attend study visits at the investigational site, the site staff may elect to pursue the following:

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (phone or video) or as per site institutional guidelines. At a minimum, a review of AEs and concomitant medications must be completed. On-site visits should be conducted whenever feasible and are required for administration of study treatment. The participant may also be asked to undergo additional safety laboratory assessments.

- In order to support investigator oversight of participant safety and disease management, the participant may be asked to undergo some laboratory tests or study procedures at a local laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed in certified laboratories.
- Some tests, such as ECG or CT scan assessments, may require longer windows of time to perform due to the COVID-19 pandemic and may be performed outside the regularly scheduled visit window or may be conducted at the next scheduled visit. It is the investigator's responsibility to check with the facility (if performed at a different facility) that the data will be obtained and available for evaluation. General procedures performed outside of protocol parameters will be captured as protocol deviations due to COVID-19.

Study Treatment Management in the Event of SARS-CoV2 Infection

If a participant develops a SARS-CoV2 infection, the event should be reported as SAE (if it meets the SAE definition requirements) and appropriate medical intervention provided.

Postbaseline COVID-19 testing should follow country-specific requirements depending on the extent of COVID19-pandemic, local institutional guidance, or investigator's clinical judgment.

For participants who are diagnosed with COVID-19 during the study (positive COVID-19 test) or presumed affected by SARS-CoV2 infection (test pending/clinical suspicion), study treatment should be delayed until COVID-19 test normalization and clinical recovery. Before restarting treatment, the study medical monitor should be notified with the participant's condition, that is, the participant should be afebrile for 72 hours and SARS-CoV2–related symptoms (if any) should have recovered for a minimum of 72 hours.

Safety monitoring following COVID-19 infection should be implemented as per institutional guidance or clinical judgment (eg, coagulation factors). Concomitant medication administered for treatment of SARS-CoV2 infection should be carefully considered for potential drug-drug interactions and recorded in the EDC.

COVID-19 Vaccination

Participants may receive a COVID-19 vaccine. COVID-19 vaccination will be captured in the eCRF as a concomitant medication. Vaccination on the day of study treatment administration is not recommended. Administration of study treatment may be delayed to ensure vaccination is completed.

Clinical Study Monitoring

Study monitoring visits could be postponed; however, the site monitor and sponsor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits) with the sites to get information on trial progress, participant status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness if allowed by the national regulatory body, investigational site, and/or in compliance with local authorities.

Reimbursement of Additional Expenses

The sponsor will reimburse for any extraordinary expenses, keeping appropriate documentation as evidence (eg, travel expenses for local laboratory visits, cost of local laboratory tests).

APPENDIX D. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Version 1-BE	06 JUL 2022
Version 1-FR	11 JUL 2022
Version 1-KR	11 JUL 2022
Version 1-TW	01 AUG 2022
Version 1-DE	30 AUG 2022
Amendment 1	04 NOV 2022
Amendment 2	19 DEC 2023

Amendment 2 (19 DEC 2023)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to update the statistical section, to clarify select eligibility criteria, to update select management guidelines for immune-related adverse events, to revise the guidance for resumption of treatment after a Day 15 dose delay, and to include the requirements set forth in the new Regulation EU No 536/2014 of the European Parliament and of the Council, as well as to harmonize the Protocol prior to transition to CTR. Additional changes are summarized below.

1. **Title Page**

   Description of change: Removed EudraCT Number; added EU CT Number.

   Rationale of change: Update was initiated by Protocol template and regulations.

2. Section 1, Protocol Summary (Table 2: Key Study Design Elements)

   Description of change: Updated Coordinating PI.

   Rationale for change: Current Coordinating PI elected to disaffiliate from study.

3. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints)**

   Description of change: Revised secondary endpoint from "dose reductions" to "dose delays."

   Rationale for change: To update endpoint description as dose reductions are not applicable to the study.

4. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 4.2, Number of Participants**

   Description of change: Removed acronym "TPS" from references to LAG-3 expression.

   Rationale for change: LAG-3 expression is being evaluated on immune cells in the tumor microenvironment and not on tumor cells.

5. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Added an "X" to Cycle 1 Day 15 and Cycle 2+ Day 15 columns for "Contact IRT" activity.

   Rationale for change: To correct prior omission on the Schedule of Activities, as the IRT will dispense the study drug at these visits.

6. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 5.1, Inclusion Criteria (Criterion #9b); Section 8.3.6, Laboratory Assessments (Table 14: Required Laboratory Analytes); Section 8.3.6.2, Pregnancy Testing**

   Description of change: Added text to include "serum or" where only urine pregnancy testing is specified.

   Rationale for change: Serum testing is more accurate than urine testing for detecting threshold levels of human chorionic gonadotropin.

7. **Section 4.3, Overall Study Duration**

   Description of change: Updated the definition of "end of the study" with regard to primary endpoint and overall study completion. Added text to clarify when results will post, as well as when follow-up for OS could occur.

   Rationale for change: Clarification of key study milestones for data collection and public disclosure.

8. **Section 5.1, Inclusion Criteria (Criterion #6); Section 8, Tumor Imaging During Screening; Section 8.2.1.1, Tumor Imaging During Screening**

   Description of change: Updated language to clarify criteria for assessing a previously biopsied lesion as a target lesion prior to randomization.

   Rationale for change: To provide specifications to ensure that postbiopsied imaging is done, and the tumor remains qualified per RECIST.

9. **Section 5.2, Exclusion Criteria (Criterion #11); Section 8.3.6, Laboratory Assessments (Table 14: Required Laboratory Analytes)**

   Description of change: Added a note, as well as specific tests, to clarify that HBV testing will be required at the screening visit (prior to randomization).

   Rationale for change: Clarification of HBV testing.

10. **Section 5.2, Exclusion Criteria (Criterion #16)**

    Description of change: Updated SARS-CoV2 test from PCR to antigen testing.

    Rationale for change: Research shows that antigen testing for SARS-CoV2 is more accurate when determining results.

11. **Section 6.1, Study Treatment Administered**

    Description of change: Updated minimum interval for INCAGN02385/placebo and INCAGN02390/placebo doses from 14 days to 12 days.

    Rationale for change: To align with Day 15 visit window of ± 2 days.

12. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drugs**

    Description of change: Revised the maximum duration for a Day 15 treatment delay from 4 weeks to 2 weeks, which would be before the visit must be skipped, and Day 1 of the subsequent treatment cycle should be conducted.

    Rationale for change: To allow a maximum delay of 2 weeks before dose administration with the anti–PD-1 antibody; this will enable the required dose intensity with a class of agent with established clinical activity in participants with R/M SCCHN.

13. **Section 6.5.2, Management of Suspected Infusion Reactions (Table 10: Guidelines for Management of Suspected Infusion Reactions)**

    Description of change: Updated guidelines to permanently discontinue study treatment in a participant with a Grade 3 or 4 infusion reaction.

    Rationale for change: To ensure that treatment is not resumed in participants who had a Grade ≥3 IRR.

14. **Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 11: Guidelines for Management of Immune-Related Adverse Events)**

    Description of change: Updated guidelines to allow participants to resume study treatment following improvement of Grade 3 and Grade 4 hyper- and hypothyroidism events.

    Rationale for change: To be consistent with clinical practice guidelines, participants will resume study treatment when adequate symptom control and/or thyroid hormone-replacement is achieved (ie, Grade 2 or better).

15. **Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 11: Guidelines for Management of Immune-Related Adverse Events)**

    Description of change: Updated guidelines to allow participants with an increase in serum troponin (ie, TnT or TnI) to resume study treatment following cardiologist evaluation.

    Rationale for change: To allow for a cardiology recommendation to determine whether it is appropriate to resume treatment after relevant evaluations for potential myocarditis are performed.

16. **Section 8.1.1, Informed Consent Process; Section 8.3.1, Adverse Events**

    Description of change: References to "legally authorized representative" were deleted.

    Rationale for change: EU CTR No. 536/2014 defines "legally authorized representative" in the context of incapacitated persons and minors; these participants are not eligible for this study.

17. **Section 8.3.6, Laboratory Assessments (Table 14: Required Laboratory Analytes)**

    Description of change: Added thyroid function tests.

    Rationale of change: Precision and details for assessments.

18. **Section 9.4, Reporting of Serious Adverse Events; Section 11.1, Investigator Responsibilities**

    Description of change: Added EU CTR No. 536/2014 and FDA 21 CFR Part 312 to list of applicable requirements for SAE reporting.

    Rationale for change: To include the current EU and US regulation requirements.

19. **Section 10, Statistics**

    Description of change: Added statement to outline the statistical analysis strategies and procedures with regard to future Protocol amendments.

    Rationale for change: To confirm the Protocol will be consistent with key statistical parameters (ie, primary and/or secondary efficacy and safety hypotheses and statistical methods related to hypotheses).

20. **Section 10.1, Sample Size Determination**

    Description of change: Updated the number of PFS events required for the final analysis to align with the Statistical Analysis Plan.

    Rationale for change: To harmonize the study Protocol and the Statistical Analysis Plan.

21. **Section 10.2, Populations for Analysis (Table 18: Populations for Analyses)**

    Description of change: Added an ADA-evaluable population.

    Rationale for change: To define a population of study participants that are evaluable for ADA analysis.

22. **Section 10.3, Level of Significance**

    Description of change: Added details for the level of significance.

    Rationale of change: Clarification.

23. **Section 10.4.1, Primary Analysis (Table 20: Evaluation and Censoring of Progression-Free Survival)**

    Description of change: Updated scenarios. Removed scenario, "No baseline tumor assessments"; added scenario, "No valid postbaseline response assessments in the absence of death prior to the first scheduled tumor assessment."

    Rationale for change: To clarify censoring methodology.

24. **Section 10.7, Subgroup Analysis**

    Description of change: Added an additional subgroup analysis by region (North America, EU, or Asia).

    Rationale for change: Added subgroup by region to the analysis.

25. **Incorporation of administrative changes.** Other regulatory guidance and administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1 (04 NOV 2022)

Overall Rationale for the Amendment:

The primary purpose for this amendment is to add eligibility criteria for serum troponin as well as monitoring and management guidelines for troponin elevations; to update the management of suspected irAEs; to clarify certain study assessments; and to incorporate changes requested by regulatory authorities; to incorporate country-specific amendments. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements)**

   Description of change: Added coordinating principal investigator.

   Rationale for change: To update the coordinating principal investigator field in the table.

2. **Section 1, Protocol Summary; Section 2.1.2, Treatment of Patients With Recurrent/Metastatic SCCHN; Section 2.2.1, Retifanlimab Monotherapy; Section 3, Objectives and Endpoints (Table 6: Objective and Endpoints); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Inclusion Criterion 4); Section 10.4.6, Exploratory Analysis; Section 10.7, Subgroup Analysis**

   Description of change: Deleted the "%" after CPS.

   Rationale for change: To conform to the accepted method for referencing CPS.

3. **Section 1, Protocol Summary; Section 4.1, Overall Design**

   Description of change: Updated HPV p16 stratification factor description to clarify that participants without oropharynx cancer are considered HPV p16 negative.

   Rationale for change: To add clarity to stratification factor.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 6.1, Study Treatments Administered; Section 6.5.2, Management of Suspected Infusion Reactions; Section 8.3.3, Vital Signs**

   Description of change: Added safety observation period following Cycle 1 Day 1 infusion and pre- and postinfusion vital sign monitoring for potential IRRs.

   Rationale for change: To increase participant monitoring for potential IRRs during and after administration of study drugs.

5. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.2.1, Tumor Imaging per RECIST v1.1**

   Description of change: Clarified imaging modality requirements; added additional text to SoA to indicate that contrast-enhanced images are required unless contraindicated.

   Rationale for change: To specify the study imaging requirements.

6. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.4, Electrocardiograms**

   Description of change: Added additional serial ECGs to include Day 1 of each cycle through Cycle 5.

   Rationale for change: Additional cardiac safety monitoring added based on data from other LAG-3 targeting agents.

7. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 5.2, Exclusion Criteria (Table 7: Exclusion Laboratory Values); Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 11: Guidelines for Management of Immune-Related Adverse Events); Section 8.3.6, Laboratory Assessments (Table 14: Required Laboratory Analytes)**

   Description of change: Added troponin monitoring through Cycle 4, or longer as needed, as well as management guidelines for elevated troponin. An exclusion of participants with high troponin levels at baseline was also added.

   Rationale for change: Additional cardiac safety monitoring added based on data from other LAG-3 targeting agents.

8. **Section 1, Protocol Summary (Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments); Section 8.4 (Table 15: Pharmacokinetic and Antidrug Antibody Sample Blood Sample Timing)**

   Description of change: Added additional PK and ADA timepoint at 90-day safety follow-up visit.

   Rationale for change: To further characterize the long-term study drug exposure and potential immunogenicity.

9. **Section 2.2.1, Retifanlimab Monotherapy; Section 2.2.2, INCAGN02385 Monotherapy; Section 2.2.3, INCAGN02390 Monotherapy; Section 2.2.4, Combinations of Retifanlimab, INCAGN02385, and INCAGN02390**

   Description of change: Updated clinical data summaries for retifanlimab monotherapy, INCAGN02385 monotherapy, INCAGN02390 monotherapy, and combinations of retifanlimab, INCAGN02385 and INCAGN02390.

   Rationale for change: To align the clinical data summaries with the current version(s) of the IB(s).

10. **Section 5.1, Inclusion Criteria (Inclusion Criterion 3)**

    Description of change: Added a note to indicate that participants enrolled will be eligible for first-line treatment with anti–PD-1 monotherapy for R/M SCCHN (and would not require combination therapy with chemotherapy) at the discretion of the investigator.

    Rationale for change: To ensure that potential participants who require chemotherapy, per investigator judgment, are not enrolled.

11. **Section 5.1, Inclusion Criteria (Inclusion Criterion 6)**

    Description of change: Updated to specify the conditions under which lesions used for response assessment can be used for biopsy.

Rationale for change: To clarify the criteria for using a potential target lesion for the study-required tissue biopsy.

12. **Section 5.1, Inclusion Criteria (Inclusion Criterion 7)**

    Description of change: Updated to specify the conditions under which lesions, which have been previously irradiated, can be used for biopsy.

    Rationale for change: To clarify the criteria for obtaining the study-required biopsy from a lesion which has previous been treated with radiation.

13. **Section 5.2, Exclusion Criteria (Exclusion Criterion 11)**

    Description of change: Exclusion criterion was updated to refine and clarify the definition of HBV infection.

    Rationale for change: To clarify the exclusion criterion for HBV infection.

14. **Section 5.2, Exclusion Criteria (Exclusion Criterion 13)**

    Description of change: Updated the exception for participants with a history of other malignancy within 3 years of first dose of study treatment to include cancers from which the participant has completed treatment > 2 years before randomization in this study and has been disease-free since completion of treatment with curative intent.

    Rationale for change: Clarification of exclusion criterion 13.

15. **Section 5.2, Exclusion Criteria (Exclusion Criterion 27)**

    Description of change: Exclusion criterion 27 has been added for vulnerable populations and adults under legal protection.

    Rationale for change: To address a regulatory requirement in France.

16. **Section 6.1, Study Treatment Administered**

    Description of change: Added text regarding dose administration window for Day 15 and minimum interval between INCAGN02385/placebo and INCAGN02390/placebo doses.

    Rationale for change: To clarify the Day 15 dose administration window and minimum dose administration interval.

17. **Section 6.1, Study Treatment Administered**

    Description of change: Premedication guidance for IRR prophylaxis was updated to reflect the allowance for any antipyretic and any histamine blocker discussed in Section 6.5.2.

    Rationale for change: To allow for investigator discretion when administering preinfusion IRR prophylaxis.

18. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drugs**

    Description of change: Updated to allow for longer interruption of treatment to allow for resolution of toxicity when approved by sponsor.

    Rationale for change: To provide additional flexibility regarding the duration of treatment interruptions.

19. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drugs**

    Description of change: Added guidance for whether to resume or skip a Day 15 visit in the event that the dose has been held for toxicity.

    Rationale for change: To provide specific parameters regarding whether to resume or skip the Day 15 visit if the dose has been held for toxicity, depending on the duration of the hold.

20. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drugs**

    Description of change: Updated to require discontinuation of all 3 study drugs in the event that treatment is terminated due to toxicity.

    Rationale for change: To ensure that the 3 treatment groups are evaluated using only the assigned combination of study drugs, so as to not confound the endpoint comparing the treatment arms versus the retifanlimab control.

21. **Section 6.5.1.1, Procedures for Participants Exhibiting Drug-Related, Non–Immune-Related Adverse Events (Table 9: Management Guidelines for Drug-Related, Non-Immune Related Adverse Events)**

    Description of change: Updated to correct the study drug names.

    Rationale for change: Correction of an administrative/editorial error in the table.

22. **Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 11: Guidelines for Management of Immune-Related Adverse Events)**

    Description of change: Revised the guidelines for ALT/AST and nephritis events.

    Rationale for change: To apply permanent treatment discontinuation criteria to Grade 3 events.

23. **Section 6.6.1, Permitted Medications and Procedures; Section 6.6.2, Restricted Medication and Procedures; Section 6.6.3, Prohibited Medications and Procedures**

    Description of change: Included additional guidance and requirements regarding permitted, restricted, and prohibited medications and procedures.

    Rationale for change: To provide additional specific details regarding medications and procedures which are permitted, restricted, and prohibited during study participation.

24. **Section 6.7, Treatment After the End of the Study**

    Description of change: Added a statement to clarify that participants will be supplied with study medication for up to 2 years total if the study is terminated early.

    Rationale for change: To clarify the availability of study medication to participants if the study is terminated early.

25. **Section 8.1.5.2, Disease Characteristics and Treatment History**

    Description of change: Corrected statement regarding local determination of CPS.

    Rationale for change: To update the statement to be consistent with the protocol requirements for central determination of tumor CPS status.

26. **Section 8.5.1, Tumor Tissue Collection**

Description of change: Included additional criteria regarding submission of archival tissue for baseline tumor tissue requirement.

Rationale for change: To further specify the requirements for archival tumor tissue.

27. **Section 8.5.2, Whole Blood Correlative Flow Cytometry Assessments**

    Description of change: Clarified the timing of receptor occupancy analysis.

    Rationale for change: To specify that an analysis of receptor occupancy, if performed, will occur following completion of the final study analysis.

28. **Section 8.8.2, Post-Treatment Disease Follow-Up**

    Description of change: Clarified the timing of post-treatment imaging for participants that have been discontinued from study treatment for reasons other than disease progression.

    Rationale for change: To further clarify the timing requirements for post-treatment imaging.

29. **Section 9.5, Events of Clinical Interest**

    Description of change: Added methods for identification and analysis of irAEs.

    Rationale for change: To clarify how irAEs will be summarized and reported for the study.

30. **Section 10.4.5, Pharmacokinetic Analysis**

    Description of change: Added section regarding PK analysis.

    Rationale for change: To clarify how PK will be analyzed for the study.

31. **Incorporation of administrative changes.** Other regulatory guidance and administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Version 1-DE (30 AUG 2022)

Overall Rationale for the Amendment:

The primary purpose for this amendment is to address health authority comments.

1. **Section 5.1, Inclusion Criteria**

   Description of change: Added a note to indicate that participants enrolled will be eligible for first-line treatment with anti–PD-1 monotherapy for R/M SCCHN (and would not require combination therapy with chemotherapy) at the discretion of the investigator.

   Rationale for change: To ensure that potential participants who require chemotherapy, per investigator judgment, are not enrolled.

2. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Version 1-TW (01 AUG 2022)

Overall Rationale for the Amendment:

The primary purpose for this amendment is to address health authority comments.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 6.1, Study Treatments Administered; Section 6.5.2, Management of Suspected Infusion Reactions; Section 8.3.3, Vital Signs**

   Description of change: Added safety observation period following Cycle 1 Day 1 infusion and pre- and postinfusion vital sign monitoring for potential IRRs.

   Rationale for change: To ensure that study participants are properly monitored for potential IRRs during and after administration of study drugs.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.4, Electrocardiograms**

   Description of change: Added additional serial ECGs to include Day 1 of each cycle through Cycle 5.

   Rationale for change: Additional cardiac safety monitoring is justified based on emerging data from other LAG-3 targeting agents.

3. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 5.2, Exclusion Criteria (Table 7: Exclusion Laboratory Values); Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 11: Guidelines for Management of Immune-Related Adverse Events); Section 8.3.6, Laboratory Assessments (Table 14: Required Laboratory Analytes)**

   Description of change: Added troponin monitoring through Cycle 4, or longer as needed. An exclusion of participants with high troponin levels at baseline was also added.

   Rationale for change: Additional cardiac safety monitoring is justified based on emerging data from other LAG-3 targeting agents.

4. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Version 1-KR (11 JUL 2022)

Overall Rationale for the Amendment:

The primary purpose for this amendment is to address health authority comments.

1. **Section 5.2, Exclusion Criteria (Criterion #13)**

   Description of change: Updated the exception for participants with a history of other malignancy within 3 years of first dose of study treatment to include cancers from which the participant has completed treatment > 2 years before randomization in this study and has been disease-free since completion of treatment with curative intent.

   Rationale for change: Clarification of exclusion criterion #13.

2. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Version 1-FR (11 JUL 2022)

Overall Rationale for the Amendment:

The primary purpose for this amendment is to address health authority comments.

1. **Section 6.5.1.1, Procedures for Participants Exhibiting Drug-Related, Non–Immune-Related Adverse Events (Table 9: Management Guidelines for Drug-Related, Non-Immune Related Adverse Events)**

   Description of change: Updated to correct the study drug names.

   Rationale for change: Correction of an administrative/editorial error in the table.

2. **Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 11: Guidelines for Management of Immune-Related Adverse Events)**

   Description of change: Revised the guidelines for ALT/AST and nephritis events.

   Rationale for change: To apply permanent treatment discontinuation criteria to Grade 3 events.

3. **Section 6.7, Treatment After the End of the Study**

   Description of change: Added a statement to clarify that participants will be supplied with study medication for up to 2 years if the study is terminated early.

   Rationale for change: To clarify the availability of study medication to participants if the study is terminated early.

4. **Section 8.5.2, Whole Blood Correlative Flow Cytometry Assessments**

   Description of change: Updated to clarify the timing of receptor occupancy analysis.

   Rationale for change: To specify that an analysis of receptor occupancy, if performed, will occur following completion of the final study analysis.

5. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Version 1-BE (06 JUL 2022)

Overall Rationale for the Amendment:

The primary purpose for this amendment is to address comments from the Belgium Health Authority.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 6.1, Study Treatments Administered; Section 8.3.3, Vital Signs**

   Description of change: Added pre- and post-infusion vital sign monitoring for potential IRRs.

   Rationale for change: To ensure that study participants are properly monitored for potential IRRs during and after administration of study drugs.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.4, Electrocardiograms**

   Description of change: Added additional serial electrocardiograms to include Day 1 of each cycle through Cycle 5.

   Rationale for change: Additional cardiac safety monitoring is justified based on emerging data from other LAG-3 targeting agents.

3. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 5.2, Exclusion Criteria (Table 7: Exclusion Laboratory Values); Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 11: Guidelines for Management of Immune-Related Adverse Events); Section 8.3.6, Laboratory Assessments (Table 14: Required Laboratory Analytes)**

   Description of change: Added troponin monitoring through Cycle 4, or longer as needed. An exclusion of participants with high troponin levels at baseline was also added.

   Rationale for change: Additional cardiac safety monitoring is justified based on emerging data from other LAG-3 targeting agents.

4. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Signature Page for VV-CLIN-018190 v5.0

Approval Task	[redacted] r [redacted] Clinical Operations 20-Dec-2023 08:28:35 GMT+0000
Approval Task	[redacted] [redacted] Hematology Oncology Clinical Development 20-Dec-2023 13:47:17 GMT+0000
Approval Task	[redacted] Approver [redacted] Clinical Research Scientist 20-Dec-2023 13:53:26 GMT+0000
Approval Task	[redacted] [redacted] Hematology/Oncology Clinical Development 20-Dec-2023 13:57:19 GMT+0000
Approval Task	[redacted] Approver [redacted] Biostatistics 20-Dec-2023 15:36:48 GMT+0000

Signature Page for VV-CLIN-018190 v5.0