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

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Statistical Analysis Plan

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

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SAP Author:	[redacted] Biostatistics
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This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
AUC	area under the curve
BMI	body mass index
BOR	best overall response
bpm	beats per minute
CI	confidence interval
C_{max}	maximum observed plasma or serum concentration over the dose interval
C_{min}	minimum observed plasma or serum concentration over the dose interval
CPS	combined positive score
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
H1	hypothesis 1
H2	hypothesis 2
HPV	human papillomavirus
HR	hazard ration
irAE	immune-related adverse event
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent-to-treat
LAG-3	lymphocyte activation gene-3
MedDRA	Medical Dictionary for Regulatory Activities
NA	not assessed
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate

Abbreviation	Definition
OS	overall survival
PD	progressive disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
Q2W	once every 2 weeks
Q4W	once every 4 weeks
Q8W	once every 8 weeks
Q12W	once every 12 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
R/M SCCHN	recurrent/metastatic squamous cell carcinoma of the head and neck
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
T3	triiodothyronine
TEAE	treatment-emergent adverse event
TG	Treatment Group
TIM-3	t cell immunoglobulin and mucin domain 3
t_{max}	time to maximum concentration
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This is a randomized, double-blind, controlled 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 (TG1) as first-line treatment in participants with PD-L1–positive and systemic therapy–naive R/M SCCHN.

Section 2 of the Protocol provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with INCAGN02385, INCAGN02390, and retifanlimab.

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.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCAGN 2385-203 Protocol.

Population PK results will be provided by the Incyte pharmacokineticist and will appear in a separate report.

The analysis of biomarkers and pharmacodynamics will be conducted by the Incyte translational scientist, and the details of the analysis methodology and results will appear in a separate report.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCAGN 2385-203 Protocol Amendment 2 dated 19 DEC 2023 and CRF approved 05 SEP 2024. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: 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.	Progression-free survival, 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.	Overall survival, 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.
Exploratory	
[redacted]	

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory (continued)	
[redacted]	

3. STUDY DESIGN

This is a randomized, double-blind, controlled 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:

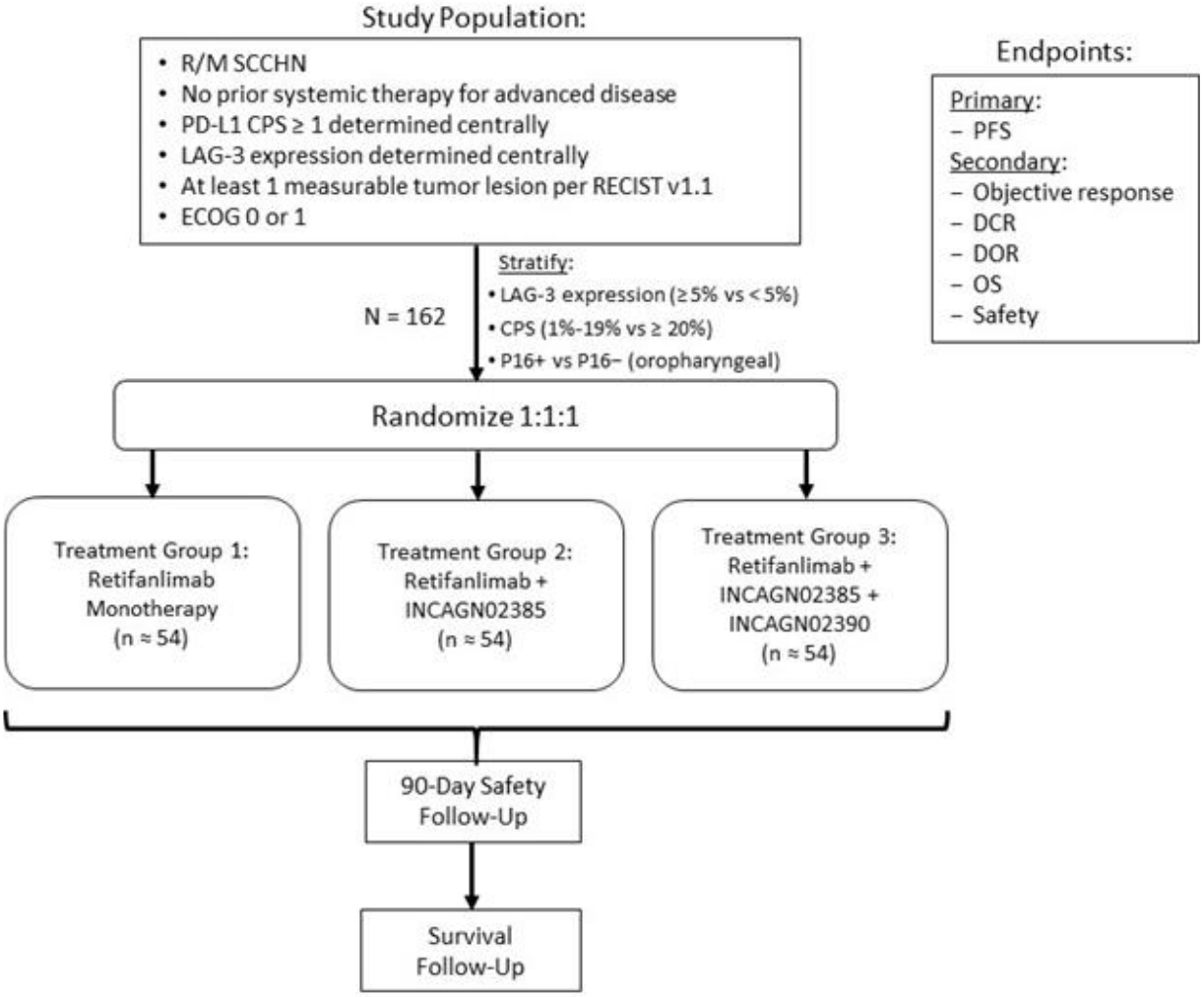
- TG1: retifanlimab plus placebo (INCAGN02385) and placebo (INCAGN02390)
- TG2: retifanlimab plus INCAGN02385 and placebo (INCAGN02390)
- TG3: retifanlimab plus INCAGN02385 and INCAGN02390

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.

Figure 1: Study Design Schema



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 end-of-treatment 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 informed consent form 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.

Details of the study design are in Section 4 of the Protocol.

3.1. Randomization

Approximately 162 participants will be randomized in a 1:1:1 ratio into 1 of 3 study treatment groups (ie, TG1, TG2, and TG3 with 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.

3.2. Sample Size Considerations and Timing of Final Analysis

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 final analysis will be performed 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) or the last participant has been followed up for at least 8 months after randomization, whichever is earlier.

The sample size and power calculations were performed in R package "gsDesign" and as tabulated in Table 2.

Table 2: Boundary Properties for Final Analysis of Progression-Free Survival Based on Potential Alpha Levels

Analysis	Value	α = 0.05 (1-Sided)	α = 0.10 (1-Sided)
Final	Z	1.645	1.2816
N: 108	p (1-sided)	0.0500	0.1000
Events: 94 (approximately 140 events across 3 treatment groups)	~HR at bound	0.7120	0.7670
Month: 20	P (Cross) if HR = 1	0.0500	0.1000
	P (Cross) if HR = 0.6	0.8000	0.8840

Based on a target of 94 PFS events for all participants at the final analysis between TG1 and TG2, which is expected to occur about 20 months from the start of enrollment if 108 participants are enrolled within 12 months, the study has approximately 80% power to detect an HR of 0.6 at an alpha level of 5% (1-sided), favoring a combination therapy versus TG1 with the assumption of study parameters as specified in Table 17 of the Protocol. When the 1-sided alpha level is 10%, the statistical power is 88.4%. The same assumption and sample size calculation approach is followed for TG3 and TG1.

The total sample size across the 3 treatment groups is calculated using 1.5 times the sample size from 2 treatment groups.

In case of delay in achieving the targeted number of PFS events, the primary analysis may be conducted when the last participant has been followed up for at least 8 months after randomization, even if the targeted number of events is not reached. In this case, the median PFS follow-up time across the blinded treatment groups will be quantified using the reverse Kaplan-Meier method and monitored by the study team. The study team will evaluate if the lower limit of the 95% CI for the median PFS follow-up time is achieved after 8 months. Table 3 shows the boundary properties for scenarios when the number of PFS events is approximately 108, 123, and 130 across the 3 treatment groups.

Table 3: Boundary Properties for Final Analysis of Progression-Free Survival Based on Different Number of PFS Events Across 2 Treatment Groups

Analysis	**Value**	**α = 0.05 (1-sided)**	**α = 0.10 (1-sided)**
Final	Z	1.6449	1.2816
N: 82	p (1-sided)	0.0500	0.1000
Events: 72 (approximately 108 events across 3 treatment groups)	~HR at bound	0.6786	0.7393
Month: 20.4	P (Cross) if HR = 1	0.0500	0.1000
	P (Cross) if HR = 0.6	0.7041	0.8147
Analysis	**Value**	**α = 0.05 (1-sided)**	**α = 0.10 (1-sided)**
Final	Z	1.6449	1.2816
N: 94	p (1-sided)	0.0500	0.1000
Events: 82 (approximately 123 events across 3 treatment groups)	~HR at bound	0.6954	0.7535
Month: 20.0	P (Cross) if HR = 1	0.0500	0.1000
	P (Cross) if HR = 0.6	0.7522	0.8509
Analysis	**Value**	**α = 0.05 (1-sided)**	**α = 0.10 (1-sided)**
Final	Z	1.6449	1.2816
N: 100	p (1-sided)	0.0500	0.1000
Events: 87 (approximately 130 events across 3 treatment groups)	~HR at bound	0.7028	0.7597
Month: 19.9	P (Cross) if HR = 1	0.0500	0.1000
	P (Cross) if HR = 0.6	0.7736	0.8665

3.3. Schedule of Assessments

Refer to Protocol Amendment 2 dated 19 DEC 2023 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the participant is randomized.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of INCAGN02385, INCAGN02390, or retifanlimab, unless otherwise defined.

When scheduled assessments and unscheduled assessments occur on the same day, and the time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled assessment are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified in this section or relevant sections. The original reported dates collected on the eCRF should be used in all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

When calculating time since diagnosis of cancer, partial cancer diagnosis date will be handled as follows:

- If only the day is missing, then the first day of the month will be used.
- If both the month and day are missing, then 01 JAN of the year will be used.
- If the diagnosis date is completely missing, then the time since diagnosis will not be calculated.

When the date of the last dose is used in deriving variables, such as duration of treatment or TEAE flag, a missing or partial date of the last dose will be handled as follows:

- If only the day is missing, then the earlier date of the last day of the month or the date that the participant discontinued treatment will be used.
- If both the month and day are missing, then the earlier date of 31 DEC of the year or the date that the participant discontinued treatment will be used.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, partial date of death will be handled as follows in the calculation:

- If mmyyyy for the last known alive date = mmyyyy for the death date, then the death date will be set to the day after the last known alive date.
- If mmyyyy for the last known alive date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

4.1.5. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of INCAGN02385, INCAGN02390, or retifanlimab is administered. The scheduled cycle length is 4 weeks. The actual Day 1 of subsequent cycles will correspond with the first day of administration of retifanlimab in that cycle.

4.2. Variable Definitions

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.2. Creatinine Clearance

Creatinine clearance by Cockcroft-Gault (1976) is estimated from serum creatinine (mg/dL) determination by using the following formula:

Creatinine clearance (mL/min) = [140 − age (years)] × weight (kg) × {0.85* for female participants} / [72 × serum creatinine (mg/dL)].

*Note: For male participants use 1.0.

4.2.3. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the randomization date.

Concomitant medication is defined as any nonstudy medication that is started:

- Before the randomization date and is ongoing throughout the study or ends on/after the date of first study medication administration, or
- On/after the randomization date and is ongoing or ends during the course of the study.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after the randomization date. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant; that is, if the start date and end date are missing, then the medication is considered as concomitant medication.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9.4 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

No formal interim analyses for efficacy are planned for this study as noted in Section 9 of the Protocol; however, DSMB-related activities will be routinely conducted regarding the safety data.

5.2. Treatment Groups

This is a Phase 2, randomized, double-blind, controlled, parallel treatment group design study. Data will be summarized by treatment groups.

5.3. Analysis Populations

Table 4 presents the populations for analysis.

Table 4: Populations for Analysis

Population	Description
ITT	All participants who are randomized will constitute the ITT population. Treatment groups for this population will be defined according to the treatment assignment at the time of randomization regardless of the actual study drug the participant might take during their participation in the study. 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 will include all 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. The actual treatment received corresponds to: The randomized treatment if the participant took at least 1 dose of that treatment. The first treatment received if the randomized treatment was never received. 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 study pharmacokineticist will review data listings of study drug administration and sample records to identify participants to be excluded from any analyses of PK data that may be performed. 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). The study research investigator will review data listings of pharmacodynamic data and sample records to identify participants to be excluded from analyses of pharmacodynamic data.
ADA evaluable	The ADA evaluable population will include all participants who received at least 1 dose of study treatment and provided at least 1 ADA postdose sample. The ADA-related analysis may be conducted by the PK group.

Table 5 shows how the analysis populations are associated with the primary and secondary endpoints.

Table 5: Endpoints and Analysis Populations

Primary/Secondary Endpoint	Population	Hypothesis	Population-Level Summary Metric
PFS	ITT	H1: TG3 is superior to TG1 with respect to PFS in all participants H2: TG2 is superior to TG1 with respect to PFS in all participants	Median PFS, HR
OS	ITT	NA	Median OS, HR
Objective response	ITT	NA	ORR difference
Disease control	ITT	NA	DCR difference
DOR	ITT[a]	NA	Median DOR
AEs	Safety	NA	Rate

Table 5: Endpoints and Analysis Populations (Continued)

Primary/Secondary Endpoint	Population	Hypothesis	Population-Level Summary Metric
AE impact on study treatment (treatment interruptions, dose reductions, and withdrawal of study treatment due to AEs)	Safety	NA	Rate

[a] Responder subpopulation.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

6.1. Demographics, Baseline Characteristics, and Disease History

The ITT will be used for all baseline disease characteristics and demographic summaries and data listings. All variables will be summarized by treatment group with groups presented separately.

6.1.1. Demographics

The following demographics and baseline characteristics will be summarized by treatment group and listed for participants in the ITT population: age, sex, race, ethnicity, height, body weight, and BMI; creatinine clearance; and region of enrollment. Qualitative data will be summarized by contingency tables and quantitative data will be summarized by descriptive summary statistics.

6.1.2. Baseline Disease Characteristics and Disease History

Baseline disease characteristics and disease history will be summarized by treatment group and listed for participants in the ITT population including time since initial diagnosis, time since diagnosis of recurrent metastatic disease, smoking status (current or former, never), disease status (locally recurrent and metastatic, locally recurrent, or metastatic recurrence), site of primary tumor (hypopharynx, larynx, oral cavity or oropharynx), baseline ECOG performance status, and relevant biomarkers per the central laboratory analysis (eg, LAG-3 expression, PD-L1 expression, HPV p16 status). Other information collected in the eCRF may be listed in detail.

Time since diagnosis will be calculated as follows:

Time since diagnosis (years) = (date of randomization – date of diagnosis + 1) / 365.25.

6.1.3. Prior Therapy

The number of prior systemic cancer therapy regimens will be summarized by treatment group for all participants in the ITT population. The component drugs of prior systemic therapy regimens will be coded using the WHO Drug Dictionary. The number and percentage of participants who received each drug will be summarized by WHO drug class and WHO drug

preferred term. The regimen name, component drugs, start and stop dates, purpose of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed.

The number of participants who received prior radiation will be summarized for the ITT population. The prior radiotherapy body site, start and stop dates will be listed.

The number of participants who had prior surgery or surgical procedure for the malignancies under study will be summarized for the ITT population. The prior surgery date and description of the surgery/procedure will be listed.

6.1.4. Medical History

For participants in the ITT population, medical history will be summarized by assigned treatment group. This summation will include the number and percentage of participants with medical history for each body system/organ class as documented on the eCRF.

6.2. Disposition of Participants

The number and percentage of participants who were randomized, who were treated, who were ongoing with study treatment, who completed study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in the study, who completed the study, and who withdrew from the study with a primary reason for withdrawal will be summarized for the ITT population. The number of participants randomized by country and/or site will also be provided by treatment group. A death listing with date of death and cause of death will be provided.

6.3. Protocol Deviations

Important Protocol deviations will be summarized by category and listed.

6.4. Exposure

For participants in the safety population, a summary of exposure to each study drug (ie, INCAGN02385, INCAGN02390, and/or retifanlimab) or the treatment group will be summarized descriptively, if feasible, as the following:

- Total number of cycles of INCAGN02385, INCAGN02390, and retifanlimab
- Total number of infusions of INCAGN02385, INCAGN02390, and retifanlimab
- Total dose administered (mg): sum of the cumulative dose administered to each participant
  - If partial infusion is administered for a visit (ie, "No" was selected for the question "Was entire infusion administered?" in the Dosing eCRF), the actual dose administered at this visit will be calculated as (Estimated Volume Delivered [mL] / Prepared Volume [mL] × Dose Level of the Study Drug [mg])
- Average dose per infusion (mg): total dose administered (mg) / total number of infusions

- Duration of treatment with study drug (days): date of last dose of study drug − date of first dose of study drug + 1
- Dose intensity (mg/day): total dose administered (mg) / (duration of treatment + cycle length – 1)
- Relative dose intensity: actual dose intensity (mg/day) / planned dose intensity (mg/day)

Duration of exposure in months will be calculated based on the assumption that each month has 30.4375 days. The number and percentage of participants in each duration category (ie, 0 to 3 months, ≥ 3 months, ≥ 6 months, ≥ 9 months, ≥ 12 months, ≥ 18 months, ≥ 24 months, and other timepoints as applicable) will be summarized.

6.5. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of participants in the ITT population for each prior and concomitant mediation will be summarized by WHO drug class and term. For the summary of concomitant medication, the medications will be included only if starting on or after the first dose of study treatment and no later than the last administration of retifanlimab, INCAGN02385, or INCAGN02390, whichever is later. Medications with missing start/end dates will be considered as concomitant medication in the summary. Post-treatment anticancer therapy will be summarized. Other medications will be provided in the listing. Drugs intended to manage irAEs, as well as prophylaxis/premedication used to prevent infusion reactions, may be summarized separately. Procedures and nondrug therapies will also be summarized/listed per eCRF.

7. EFFICACY

Appendix A provides a list of planned data displays. Sample data displays are included in a separate document.

7.1. General Considerations

All efficacy analyses will be performed using the ITT population. Efficacy endpoints of this study include PFS, objective response, DOR, disease control, based on RECIST v1.1, and OS. Response assessments, as determined by investigator, will be used for the efficacy analysis. Listings of response assessment at each visit will be provided. Unless otherwise stated, the strata identified in the randomization process will be used in all efficacy analyses.

7.2. Efficacy Hypotheses

Progression-Free Survival (Primary Endpoint):

- 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

7.3. Analysis of the Primary Efficacy Parameter

7.3.1. Response Assessment by RECIST

Overall disease status will be categorized using RECIST v1.1 (Eisenhauer et al 2009). Participants will have their overall response evaluated as CR, PR, SD, PD, or NE at each postbaseline radiologic assessment, which will be based on changes in target lesions, nontarget lesions, and appearance of new lesions.

7.3.2. Primary Efficacy Analysis

Progression-free survival is 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 as censored if there is no observed death or radiologic disease progression before the cutoff date or the date that a new anticancer therapy is started. Censoring for PFS will follow the primary analysis algorithm outlined in Table 6, which is based on regulatory guidelines (FDA 2015).

Table 6: Evaluation and Censoring of Progression-Free Survival

Situation	Primary Analysis	Sensitivity Analysis
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
Progression documented between scheduled visits	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
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD prior to the new anticancer treatment which is initiated	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
No PD and no death after ≥ 2 missed consecutive disease assessments	Censored at last disease assessment prior to the ≥ 2 missed disease assessments	Censored at last disease assessment
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
PD or death documented after ≥ 2 missed consecutive disease assessments	Censored at last disease assessment prior to the ≥ 2 missed disease assessments	Progressed at date of documented PD or death

Note 1: Those participants who discontinued from the study or started a new anticancer treatment in the absence of documented progression will be considered as dropouts at the time of final analysis.

Note 2: The date on which any participant received high-dose palliative radiotherapy to sites of known disease that have been selected as target or nontarget lesions will be censored for PFS on the day the first fraction was delivered. Participants who receive a single fraction of radiotherapy to a single site of known bone metastasis will not be censored for PFS.

The nominal 1-sided p-value from the stratified log-rank test will be reported, 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). 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).

To evaluate the robustness of the PFS endpoint per RECIST v1.1 based on investigator review, a sensitivity analysis will handle participants who miss more than 1 disease assessment indifferently from participants who miss 0 or 1 disease assessment (ie, the status depends on if there is PD or death) and will handle participants who discontinue treatment or initiate an anticancer treatment after discontinuation of study treatment differently from the primary analysis. The censoring rules for the sensitivity analyses are also summarized in Table 6. Within each analysis, if a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

The reverse Kaplan-Meier method will be used to estimate the median PFS follow-up time, 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).

7.3.3. Subgroup Analyses

Subgroups will be formed in the ITT population based on the following prognostic factors, participant characteristics, and baseline variables:

- Age: < 65 years, ≥ 65 years
- Sex: male, female
- Race: White, others
- Region: North America, EU, or Asia
- PD-L1: CPS 1% to 19% or ≥ 20%
- HPV p16 status (oropharyngeal only): p16-positive versus p16-negative
- LAG-3 expression status: positive (≥ 5%) or negative (< 5%)
- Number of target lesions (for PFS subgroup analysis only): 1, 2, or 3+

Subgroups may be further divided or combined based on emerging data. If the subgroup size is fewer than 5, then the analysis may not be conducted in this particular subgroup. To determine whether the treatment effect for the primary endpoint of PFS is consistent across various subgroups, the estimated HR and its 95% CIs will be provided within each category of subgroup

using the unstratified Cox regression model. A forest plot will be produced; this will provide the estimated point estimates and 95% CIs of the HR for PFS across subgroups.

Estimates of ORR and DCR, along with its exact 95% CIs using the Clopper-Pearson method, will be computed for subgroup analyses.

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

7.3.4. Sensitivity Analyses

An additional sensitivity analysis of PFS will be done to assess the effect of errors in the stratification factors on the primary analysis. This sensitivity analysis will use the correct or actual values of the stratification factors in the analysis rather than using the stratification factors assigned at randomization. The sensitivity analysis will be done if more than 5% of participants have at least 1 error identified in the stratification factors assigned at randomization. The HR and 95% CI will be estimated based on the stratified Cox regression model using the actual values of the stratification factors for the log-rank test. Additionally, the HR and its 95% CI will be estimated based on the unstratified Cox regression model.

7.4. Analysis of the Secondary Efficacy Parameters

7.4.1. Best Overall Response and Objective Response Rate by RECIST

Best overall response for participants is the best response recorded postbaseline prior to and including the first PD, in the order of CR, PR, SD, PD, and NE determined by investigator assessment per RECIST v1.1.

The BOR will be determined from response assessments prior to or on the same day as new anticancer therapy. If any alternative cancer therapy is taken while on-study, then any subsequent assessments will be excluded from the BOR determination.

Best overall response for each participant is determined from the sequence of overall responses according to the following rules:

- CR = at least 2 consecutive determinations of CR at least 4 weeks apart before progression
- PR = at least 2 consecutive determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR)
- SD = at least 1 SD assessment (or better) ≥ 6 months after start of treatment (and not qualifying for CR or PR)
- PD = meet progression criteria comparing with nadir (and not qualifying for CR, PR, or SD)
- NE = all other cases (ie, not qualifying for confirmed CR or PR and without SD after more than 7 weeks or PD)

In the case of SD, measurements must meet the SD criteria at least once after the date of first dose at a minimum interval of 6 months. Participants who fail to meet this criterion will have a

BOR of PD if the next available assessment after the initial assessment indicates PD, or a BOR of NE if there are no additional assessments available.

The largest percentage reduction in sum of diameters of target lesions will be listed. Spider plots (ie, percent change from baseline in sum of target lesions), waterfall plots (ie, best percentage change in sum of target lesions), and swimmer plots (ie, the overall response and duration of treatment) may be provided.

Objective response rate is defined as the proportion of participants with a CR or PR as BOR.

Estimates of ORR along with the exact 95% CIs using the Clopper-Pearson method will be computed for each treatment group.

Additionally, the difference of ORR between TG2 and TG1, between TG3 and TG1, and the corresponding 95% CIs for the difference using the Agresti-Caffo methods will be reported. This can be done using the SAS procedure PROC FREQ using the RISKDIFF option and selecting the Agresti-Caffo method for CIs. The common risk difference with the corresponding 95% CIs using the Newcombe method will be reported. This can be done using the SAS procedure PROC FREQ, adding IRT stratification factors in the analysis, using the COMMONRISKDIFF option and selecting the NEWCOMBE method for CIs.

Subgroup analyses for ORR will be performed as described in Section 7.3.3.

7.4.2. 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.

Estimates of DCR along with the exact 95% CIs using the Clopper-Pearson method will be computed for each treatment group.

Additionally, the difference of DCR between TG2 and TG1, between TG3 and TG1, and the corresponding CIs for the difference using the Agresti-Caffo methods will be reported. This can be done using the SAS procedure PROC FREQ using the RISKDIFF option and selecting the Agresti-Caffo method for CIs. The common risk difference with the corresponding 95% CIs using the Newcombe method will be reported. This can be done using the SAS procedure PROC FREQ adding IRT stratification factors in the analysis, using the COMMONRISKDIFF option and selecting the NEWCOMBE method for CIs.

Subgroup analyses will also be performed for DCR as described in Section 7.3.3.

7.4.3. 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, should the latter occur sooner than progression. Participants with no observed death or disease progression will be censored. Censoring for DOR will follow the same algorithm as censoring of PFS outlined in Section 7.3.2. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

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

Subgroup analyses will also be done for DOR as described in Section 7.3.3.

7.4.4. Overall Survival

Overall survival is defined as the time from the date of randomization to the date of death due to any cause. Participants without documented death at the time of analysis will be censored at the date of last known contact.

- Kaplan-Meier curves, medians, and 95% CIs of the medians will be presented for each treatment group. The median follow-up time for OS will be calculated using reverse Kaplan-Meier methodology.

The HR for OS will be calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as the log-rank test, using Efron's likelihood approximation to account for ties in event times.

7.5. Analysis of Exploratory Efficacy Variables

8. SAFETY AND TOLERABILITY

Appendix A provides a list of planned data displays. Sample data displays are included in a separate document.

8.1. General Considerations

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

All safety analyses will be conducted using the safety population.

A TEAE is any AE either reported for the first time, or worsening of a pre-existing event, after first dose of study drug until 90 days after the last dose of study drug. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration, flagging those that are not TEAE. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Adverse events will be tabulated by MedDRA SOC and PT. Severity of AEs will be graded using the NCI CTCAE v5.0 using Grades 1 through 5. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing or partial dates will be handled using the rules described in Section 4.1.4. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

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 SOC and PT. Data listings will include all AEs regardless of their timing to study drug administration.

Infusion-related reactions, as well as irAEs, may be summarized separately.

8.2.2. Adverse Events of Special Interest

Adverse events of special interest will include irAEs and IRRs; these events will be coded according to MedDRA along with all other AEs.

Immune-related AEs will be using the sponsor-predefined PTs based on the immune checkpoint inhibitor class regardless of the investigator's assessment of causality. The sponsor-assessed irAEs will be summarized by grouped term, PT, and severity grade (ie, CTCAE Grades 1, 2, 3, 4, 5).

Infusion-related reactions will be identified using sponsor-predefined PTs indicating a diagnosis of IRRs or symptoms potentially associated with IRRs. Diagnosis of infusion reaction occurring anytime of the treatment period, or symptom of infusion reaction that occurred within 1 day of infusion, and resolved within 2 days from AE onset, are captured as infusion reactions. The sponsor-assessed IRRs will be summarized by grouped term, PT, and severity grade (ie, CTCAE Grades 1, 2, 3, 4, 5).

8.2.3. Adverse Event Summaries

An overall summary of AEs by treatment group will include the following:

- Number (%) of participants reporting any TEAEs
- Number (%) of participants reporting any serious TEAEs
- Number (%) of participants reporting any Grade 3 or higher TEAEs
- Number (%) of participants who had any treatment related TEAEs
  - Number (%) of participants who had any TEAEs related to retifanlimab
  - Number (%) of participants who had any TEAEs related to INCAGN02385/placebo for INCAGN02385
  - Number (%) of participants who had any TEAEs related to INCAGN02390/placebo for INCAGN02390
- Number (%) of participants who had any treatment-related serious TEAEs
- Number (%) of participants who had any treatment-related Grade 3 or higher TEAEs
- Number (%) of participants who had a TEAE leading to study drug infusion interruption, next scheduled dose delay, or discontinuation
  - Number (%) of participants who had a TEAE leading to study drug infusion interruption
  - Number (%) of participants who had a TEAE leading to next scheduled dose delay of study drug
  - Number (%) of participants who had a TEAE leading to permanently discontinued study drug
- Number (%) of participants who had any immune-related TEAEs – sponsor-assessed
- Number (%) of participants who had any infusion-related TEAEs – sponsor-assessed
- Number (%) of participants who had a fatal TEAE

The following summaries will be produced by MedDRA term (if 10 or fewer participants appear in a table, a listing may be appropriate):

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of Grade 3 or higher TEAEs by SOC and PT
- Summary of Grade 3 or higher TEAEs by PT in decreasing order of frequency
- Summary of serious TEAEs by SOC and PT
- Summary of serious TEAEs by PT in descending order of frequency
- Summary of treatment-related TEAEs by SOC and PT
- Summary of treatment-related TEAEs by PT in decreasing order of frequency
- Summary of Grade 3 or higher treatment-related TEAEs by SOC and PT
- Summary of treatment-related serious TEAEs by SOC and PT
- Summary of TEAEs with a fatal outcome by SOC and PT
- Summary of TEAEs leading to study drug infusion interruption by SOC and PT
- Summary of TEAEs leading to next scheduled dose delay of the study drug by SOC and PT
- Summary of TEAEs leading to discontinuation of study drug by SOC and PT
- Summary of immune-related TEAEs by grouped term and PT (sponsor-assessed)
- Summary of immune-related TEAEs by PT in descending order of frequency (sponsor-assessed)
- Summary of immune-related TEAEs by grouped term, PT, and maximum severity (sponsor-assessed)
- Summary of infusion-related TEAEs by grouped term and PT (sponsor-assessed)
- Summary of infusion-related TEAEs by PT in descending order of frequency (sponsor-assessed)
- Summary of infusion-related TEAEs by grouped term, PT, and maximum severity (sponsor-assessed)

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. The baseline value will be determined using the last nonmissing value collected before the first dose using the priority defined in Table 7. The last record before administration in the highest

priority will be considered the baseline record. For baseline laboratory candidates with the same date and time in the same priority category, the in-window value will be used as the baseline.

Table 7: Baseline Laboratory Identification

Priority	Laboratory Visit	Proximity to Visit Window	Tiebreaker
1	Scheduled	In-window	Use smallest laboratory sequence number
2	Unscheduled	In-window	
3	Scheduled	Out-of-window	

Laboratory test values outside the normal range will be assessed for severity based on CTCAE grade or similar criteria where clinical intervention is required for CTCAE grading. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

8.3.2. Laboratory Value Summaries

Local laboratories will be used for this study. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units. If a tie still exists, the laboratory value with the smallest laboratory sequence number will be used in by-visit summaries. Table 8 will be used to determine the record used for by-visit tabulations and summaries.

Table 8: Identification of Records for Postbaseline By-Visit Summaries

Priority	Laboratory Visit	Proximity to Visit Window	Tiebreaker
1	Scheduled	In-window	Use smallest laboratory sequence number
2	Unscheduled	In-window	
3	Scheduled	Out-of-window	

Numeric laboratory values will be summarized descriptively in SI units; non-numeric test values will be tabulated when necessary. In addition, line graphs may be provided for alanine aminotransferase, alkaline phosphatase, total bilirubin, alkaline phosphatase, amylase, lipase, creatinine, blood urea nitrogen, hematocrit, hemoglobin, absolute neutrophil count, platelets, T3, Free T3, thyroxine, thyroid stimulating hormone, absolute lymphocyte count, white blood cell counts (leukocytes), troponin I, and troponin T.

Severity grades will be assigned to laboratory test values based on the numerical component of CTCAE v5.0. Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category. The number of participants who experienced worsening of laboratory abnormalities will be summarized by maximum severity.

8.3.3. Potential Hy's Law Events

Participants with elevated alanine aminotransferase or aspartate aminotransferase (ie, $\geq 3 \times$ ULN range and alkaline phosphatase $< 2 \times$ ULN range), accompanied by total bilirubin $\geq 2 \times$ ULN range at the same visit, will be listed by treatment group.

8.4. Vital Signs

Values at each scheduled timepoint, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, body temperature, and body weight will be summarized descriptively.

Normal ranges for vital sign values are defined in Table 9. For participants exhibiting vital sign abnormalities, the abnormal values will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined normal range and percentage change greater than 25%. Note that the definition of alert vital signs does not apply for body temperature and weight. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 9: Normal Ranges for Vital Sign Values

Parameter	High Threshold	Low Threshold
Systolic blood pressure	≤ 155 mmHg	≥ 85 mmHg
Diastolic blood pressure	≤ 100 mmHg	≥ 40 mmHg
Pulse	≤ 100 bpm	≥ 45 bpm
Temperature	≤ 38°C	≥ 35.5°C
Respiratory rate	≤ 24 breaths/min	≥ 8 breaths/min

8.5. Electrocardiograms

Twelve-lead ECGs including heart rate, PR, QRS, QT, QTcF, and QTcB intervals will be obtained for each participant during the study. Values at each scheduled timepoint, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of study drug.

Normal ranges for ECG values are defined in Table 10. Electrocardiogram values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Participants exhibiting ECG abnormalities will be listed with study visit and assigned treatment group. Abnormal values for participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed. Outliers of QT, QTcB, and QTcF values, defined as absolute values > 500 milliseconds, > 460 milliseconds, or change from baseline > 30 milliseconds, will be summarized.

Table 10: Normal Ranges for Electrocardiogram Intervals

Parameter	High Threshold	Low Threshold
PR	≤ 220 ms	≥ 75 ms
QRS	≤ 120 ms	≥ 50 ms
QT	≤ 500 ms	≥ 300 ms
QTcF, QTcB	≤ 460 ms	≥ 295 ms
Heart rate	> 100 bpm	< 50 bpm

QTcB = Bazett's correction; QTcF = Fridericia's correction.

9. INTERIM ANALYSES

No formal efficacy interim analysis is planned for this study; however, DSMB-related activities are routinely conducted. An interim analysis to review safety data will occur as outlined in the Protocol and DSMB charter.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All previous versions of the SAP are listed in Table 11.

Table 11: Statistical Analysis Plan Versions

SAP Version	Date
Original	17 MAR 2023
Amendment 1	12 DEC 2024
Amendment 2	04 MAR 2025

10.1. Changes to Protocol-Defined Analyses

The following changes were made in the original SAP:

- Clarification was provided to depict that the overall alpha level is strongly controlled at 10% (1 sided). Furthermore, it was clarified that the alpha level of 5% is used when comparing one combination therapy versus TG1.
- The number of PFS events was updated to 94 (see Table 2) and the approximate number of PFS events (140) across 3 treatment groups was added.
- The ADA evaluable population was added.
- The censoring rule for PFS was updated to align the situations with the primary analysis algorithm-based on FDA guidelines. A sensitivity analysis, which applied alternative censoring rules for PFS, is no longer needed.
- The classification variable, "Region (North America, EU, or Asia)," was added for subgroup analysis.

The following updates were made for SAP Amendment 1:

- Added boundary properties for scenarios when the number of PFS events is approximately 108, 123, and 130 across the 3 treatment groups if the primary analysis is conducted after the last participant has been followed up for at least 8 months after randomization.
- Added analysis of the difference in ORR and DCR between TG2 and TG1 and between TG3 and TG1.
- Updated the OS analysis to only provide estimates of median OS, its 95% CI, median follow-up time for OS, and HR. The number of OS events at the final analysis does not support a valid comparison between treatment groups, and the study is not powered for OS comparison. No formal statistical testing will be conducted.

The following updates were made for SAP Amendment 2:

- Updated ORR and DCR analysis to show only the differences in ORR or DCR between treatment groups and the corresponding 95% CIs. Odds ratio and 95% CI will not be provided, as the difference is more easily interpretable.

10.2. Changes to the Statistical Analysis Plan

The following updates were made for SAP Amendment 1:

- Removed Type I error control. This is not a registrational study and the Type I error was used only for the purpose of sample size calculation, not for any decision making.
- Updated the timing of final analysis, which is to occur when either the required number of PFS events has been observed or the last participant had been followed for a minimum of 8 months after randomization, whichever is earlier.
- Updated Table 6 to align with the Protocol. One sensitivity analysis was kept for the interests of the study.
- Added analysis for median PFS follow-up time.
- Added the number of target lesions for subgroup analysis.
- Updated the OS analysis to only provide estimates of median OS and landmark estimates, its 95% CI, median follow-up time for OS, and HR. The number of OS events at the final analysis does not support a valid comparison between treatment groups, and the study is not powered for OS comparison. No formal statistical testing will be conducted.
- Revised the planned tables.

The following updates were made for SAP Amendment 2:

- Removed summary of prior radiotherapy and surgery, as listings are adequate for reporting.
- Updated efficacy hypothesis description to align with the Protocol.
- Updated ORR and DCR analysis to show only the differences in ORR or DCR between treatment groups and the corresponding 95% CI. Common risk difference and the corresponding 95% CI was added to consider weighted average of differences according to the strata. Odds ratio and 95% CI will not be provided, as the differences are more easily interpretable.
- HPV p16 status for participants without oropharyngeal cancer in the primary PFS analysis will be considered HPV p16-negative, aligning with the strata used for randomization. However, in the sensitivity analysis with actual stratification factors and subgroup analysis, HPV p16 status for participants without oropharyngeal cancer will be marked as not applicable in the subgroup analysis.
- Clarified the subgroup analysis based on number of target lesions will be applicable for PFS analysis only.

- Removed the investigator-assessed irAE summary, as the sponsor-assessed irAE data will suffice for safety evaluation.
- Revised the overall summary of AEs to align with the required analysis.
- Revised the planned tables.

11. REFERENCES

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APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the Clinical Study Report. The DSMB column indicates if the table will also be included in the DSMB package. Shells are provided in a separate document for tables that are not in the Standard Safety Tables v1.13.

The lists of tables, figures, and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population	Standard	DSMB
Baseline and Demographic Characteristics				
1.1	Summary of Screening Disposition Status	All screened participants		X
1.1.1	Analysis Populations	ITT	X	
1.1.2	Summary of Participant Disposition	ITT	X	X
1.1.3	Summary of Number of Participants Enrolled by Country and Site	ITT	X	X
1.1.4	Summary of Protocol Deviations	ITT	X	
1.2.1	Summary of Demographics and Baseline Characteristics	ITT	X	X
1.3.1.	Summary of Baseline Disease Characteristics and Disease History	ITT	X	X
1.4.1	Summary of Prior Medications	ITT	X	
1.4.2	Summary of Concomitant Medications	ITT	X	
1.4.3	Summary of Prior Systemic Cancer Therapy	ITT		
1.4.4	Summary of Prior Systemic Cancer Medication by Drug Class and Preferred Term	ITT		
1.4.7	Summary of Post Anticancer Therapy	ITT		
1.5.1	Summary of General Medical History	ITT	X	
Efficacy				
2.1.1	Summary of Progression-Free Survival by RECIST	ITT		
2.1.1.1.1	Summary of Progression-Free Survival by RECIST - Sensitivity Analyses With Actual Stratification Factors	ITT		
2.1.1.1.2	Summary of Progression-Free Survival by RECIST - Sensitivity Analyses With Different Censoring Rules	ITT		
2.1.1.2	Summary of Progression-Free Survival by RECIST – Age < 65 years	ITT		
2.1.1.3	Summary of Progression-Free Survival by RECIST – Age ≥ 65 years	ITT		
2.1.1.4	Summary of Progression-Free Survival by RECIST - Male	ITT		
2.1.1.5	Summary of Progression-Free Survival by RECIST - Female	ITT		
2.1.1.6	Summary of Progression-Free Survival by RECIST - Race: White	ITT		
2.1.1.7	Summary of Progression-Free Survival by RECIST - Race: Others	ITT		

Table No.	Title	Population	Standard	DSMB
2.1.1.8	Summary of Progression-Free Survival by RECIST - Region: North America	ITT		
2.1.1.9	Summary of Progression-Free Survival by RECIST - Region: EU	ITT		
2.1.1.10	Summary of Progression-Free Survival by RECIST - Region: Asia	ITT		
2.1.1.11	Summary of Progression-Free Survival by RECIST - PD-L1: CPS 1%-19%	ITT		
2.1.1.12	Summary of Progression-Free Survival by RECIST - PD-L1: CPS ≥ 20%	ITT		
2.1.1.13	Summary of Progression-Free Survival by RECIST - HPV p16-Positive Oropharyngeal Cancer Participants	ITT		
2.1.1.14	Summary of Progression-Free Survival by RECIST - HPV p16-Negative Oropharyngeal Cancer Participants	ITT		
2.1.1.15	Summary of Progression-Free Survival by RECIST - LAG-3 Expression ≥ 5%	ITT		
2.1.1.16	Summary of Progression-Free Survival by RECIST - LAG-3 Expression < 5%	ITT		
2.1.1.17	Summary of Progression-Free Survival by RECIST - Exploratory Analysis	ITT		
2.1.1.18	Summary of Progression-Free Survival by RECIST - One Target Lesion	ITT		
2.1.1.19	Summary of Progression-Free Survival by RECIST - Two Target Lesions	ITT		
2.1.1.20	Summary of Progression-Free Survival by RECIST - Three or More Target Lesions	ITT		
2.2.1	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST	ITT		
2.2.1.1	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - Age < 65 years	ITT		
2.2.1.2	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - Age ≥ 65 years	ITT		
2.2.1.3	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - Male	ITT		
2.2.1.4	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - Female	ITT		
2.2.1.5	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - Race: White	ITT		
2.2.1.6	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - Race: Others	ITT		
2.2.1.7	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - Region: North America	ITT		
2.2.1.8	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - Region: EU	ITT		
2.2.1.9	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - Region: Asia	ITT		

Table No.	Title	Population	Standard	DSMB
2.2.1.10	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - PD-L1: CPS 1%-19%	ITT		
2.2.1.11	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - PD-L1: CPS ≥ 20%	ITT		
2.2.1.12	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - HPV p16-Positive Oropharyngeal Cancer Participants	ITT		
2.2.1.13	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - HPV p16-Negative Oropharyngeal Cancer Participants	ITT		
2.2.1.14	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - LAG-3 Expression ≥ 5%	ITT		
2.2.1.15	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST - LAG-3 Expression < 5%	ITT		
2.2.1.16	Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate by RECIST- Exploratory Analysis	ITT		
2.2.4	Summary of Duration of Response by RECIST	ITT		
2.2.4.1	Summary of Duration of Response by RECIST - Age < 65 years	ITT		
2.2.4.2	Summary of Duration of Response by RECIST - Age ≥ 65 years	ITT		
2.2.4.3	Summary of Duration of Response Rate by RECIST - Male	ITT		
2.2.4.4	Summary of Duration of Response by RECIST - Female	ITT		
2.2.4.5	Summary of Duration of Response by RECIST - Race: White	ITT		
2.2.4.6	Summary of Duration of Response by RECIST - Race: Others	ITT		
2.2.4.7	Summary of Duration of Response by RECIST - Region: North America	ITT		
2.2.4.8	Summary of Duration of Response by RECIST - Region: EU	ITT		
2.2.4.9	Summary of Duration of Response by RECIST - Region: Asia	ITT		
2.2.4.10	Summary of Duration of Response by RECIST - PD-L1: CPS 1%-19%	ITT		
2.2.4.11	Summary of Duration of Response by RECIST - PD-L1: CPS ≥ 20%	ITT		
2.2.4.12	Summary of Duration of Response by RECIST - HPV p16-Positive Oropharyngeal Cancer Participants	ITT		
2.2.4.13	Summary of Duration of Response by RECIST - HPV p16-Negative Oropharyngeal Cancer Participants	ITT		
2.2.4.14	Summary of Duration of Response by RECIST - LAG-3 Expression ≥ 5%	ITT		

Table No.	Title	Population	Standard	DSMB
2.2.4.15	Summary of Duration of Response by RECIST - LAG-3 Expression < 5%	ITT		
2.2.5	Summary of Overall Survival	ITT		
2.2.5.1	Summary of Overall Survival by RECIST - PD-L1: CPS 1%-19%	ITT		
2.2.5.2	Summary of Overall Survival by RECIST - PD-L1: CPS ≥ 20%	ITT		
2.2.5.3	Summary of Overall Survival by RECIST - HPV p16-Positive Oropharyngeal Cancer Participants	ITT		
2.2.5.4	Summary of Overall Survival by RECIST - HPV p16-Negative Oropharyngeal Cancer Participants	ITT		
2.2.5.5	Summary of Overall Survival by RECIST - LAG-3 Expression ≥ 5%	ITT		
2.2.5.6	Summary of Overall Survival by RECIST - LAG-3 Expression < 5%	ITT		
Safety				
3.1.1.1	Summary of Exposure - INCAGN02385	Safety	X	X
3.1.1.2	Summary of Exposure - INCAGN02390	Safety	X	X
3.1.1.3	Summary of Exposure - Retifanlimab	Safety	X	X
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety	X	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X	X
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	X	
3.2.5	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.6	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X	X
3.2.7	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.8	Summary of Serious Treatment-Emergent Adverse Events by Preferred Term in Decreasing Order of Frequency	Safety	X	X
3.2.9	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.10	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X	X
3.2.11	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X

Table No.	Title	Population	Standard	DSMB
3.2.12	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.13	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.14	Summary of Treatment-Emergent Adverse Events Leading to Study Drug Infusion Interruption by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.15	Summary of Treatment-Emergent Adverse Events Leading to Next Scheduled Dose Delayed by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.16	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.17.1	Summary of Immune-Related Treatment-Emergent Adverse Events by Grouped Term and Preferred Term (Sponsor-Assessed)	Safety		X
3.2.17.2	Summary of Immune-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency (Sponsor-Assessed)	Safety		X
3.2.17.3	Summary of Immune-Related Treatment-Emergent Adverse Events by Grouped Term, Preferred Term, and Maximum Severity Grade (Sponsor-Assessed)	Safety		X
3.2.18.1	Summary of Infusion-Related Treatment-Emergent Adverse Events by Grouped Term and Preferred Term (Sponsor-Assessed)	Safety		X
3.2.18.2	Summary of Infusion-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency (Sponsor-Assessed)	Safety		X
3.2.18.3	Summary of Infusion-Related Treatment-Emergent Adverse Events by Grouped Term, Preferred Term, and Maximum Severity Grade (Sponsor-Assessed)	Safety		X
3.2.24	Summary of death	ITT		X
3.3.1.1	Summary of Laboratory Values - Hematology	Safety	X	
3.3.1.2	Summary of Laboratory Values - Chemistry	Safety	X	
3.3.1.3	Summary of Laboratory Values - Coagulation	Safety	X	
3.3.1.4	Summary of Laboratory Values - Urinalysis	Safety	X	
3.3.1.5	Summary of Laboratory Values - Endocrine	Safety	X	
3.3.1.6	Summary of Laboratory Values - Troponin	Safety	X	X
3.3.2.1	Shift Summary of Hematology Laboratory Values in CTCAE Grade - To the Worst Abnormal Value	Safety	X	
3.3.2.2	Shift Summary of Chemistry Laboratory Values in CTCAE Grade - To the Worst Abnormal Value	Safety	X	
3.3.2.3	Shift Summary of Coagulation Laboratory Values in CTCAE Grade - To the Worst Abnormal Value	Safety	X	
3.3.2.4	Shift Summary of Urinalysis Laboratory Values in CTCAE Grade - To the Worst Abnormal Value	Safety	X	

Table No.	Title	Population	Standard	DSMB
3.3.2.5	Shift Summary of Endocrine Laboratory Values in CTCAE Grade - To the Worst Abnormal Value	Safety	X	
3.3.3.1	Treatment-Emergent Worsening of Laboratory Abnormalities - Hematology	Safety	X	
3.3.3.2	Treatment-Emergent Worsening of Laboratory Abnormalities - Chemistry	Safety	X	
3.3.3.3	Treatment-Emergent Worsening of Laboratory Abnormalities - Endocrine	Safety	X	
3.4.1	Summary of Systolic Blood Pressure	Safety	X	
3.4.2	Summary of Diastolic Blood Pressure	Safety	X	
3.4.3	Summary of Pulse	Safety	X	
3.4.4	Summary of Respiratory Rate	Safety	X	
3.4.5	Summary of Body Temperature	Safety	X	
3.4.6	Summary of Body Weight	Safety	X	
3.5.1	Summary of PR Interval (ms) From 12-Lead ECG	Safety	X	
3.5.2	Summary of QRS Interval (ms) From 12-Lead ECG	Safety	X	
3.5.3	Summary of QT Interval (ms) From 12-Lead ECG	Safety	X	
3.5.4	Summary of QTcB Interval (ms) From 12-Lead ECG	Safety	X	
3.5.5	Summary of QTcF Interval (ms) From 12-Lead ECG	Safety	X	
3.5.7	Summary of Heart Rate (bpm) From 12-Lead ECG	Safety	X	
3.5.8	Summary of Outliers of QT and QTcB and QTcF Interval Values From 12-Lead ECG	Safety	X	
3.5.9	Summary of Clinically Significant ECG Abnormality	Safety	X	

Figures

Figure No.	Title	DSMB
1.1	Kaplan-Meier Estimates of Progression-Free Survival by RECIST	
1.2	Forest Plot of Progression-Free Survival-TG2 vs TG1 by Subgroup	
1.3	Forest Plot of Progression-Free Survival-TG3 vs TG1 by Subgroup	
2.1	Kaplan-Meier Estimates of Duration of Response by RECIST	
2.2	Kaplan-Meier Estimates of Overall Survival	
3.1	Spider Plot of Percent Change from Baseline in Sum of Target Lesions	
3.2	Waterfall Plot of Best Percentage Change in Sum of Target Lesions	
3.3	Swimmer Plot of Overall Response and Duration of Treatment	
4.1	Line Graph of Selected Laboratory Values by Study Visit	X

Listings

Listing No.	Title	DSMB
2.1.1	Participant Enrollment and Disposition Status	X
2.2.1	Protocol Deviations	
2.2.2	Participant Inclusion and Exclusion Criteria Violations	
2.3.1	Analysis Populations	X
2.4.1	Demographic and Baseline Characteristics	X
2.4.2	Baseline Disease Characteristics and Disease History	X

Listing No.	Title	DSMB
2.4.3	Prior Radiation Treatment	
2.4.4	Prior Systemic Therapy	
2.4.5	Prior Surgery or Surgical Procedure	
2.4.7	Medical History	
2.4.8	Prior and Concomitant Medication	
2.5.1	Procedures and Nondrug Therapy	
2.5.2	Study Drug Administration	X
2.6.1	Deaths	
2.6.2	Best Overall Response, Duration of Response, and Progression-Free Survival	
2.6.3	Largest Percentage Reduction in Sum of Diameters of Target Lesions	
2.6.4	Overall Response Assessment by Visit	
2.6.5	Response Assessment: Target Lesions	
2.6.6	Response Assessment: Nontarget Lesions	
2.6.7	Response Assessment: New Lesions	
2.6.8	ECOG Status	
2.7.2	Adverse Events	X
2.7.3	Adverse Events Grade ≥ 3	X
2.7.4	Serious Adverse Events	X
2.7.5	Fatal Adverse Events	X
2.7.7.1	Adverse Events Leading to Interruption or Discontinuation of Study Drug	X
2.7.8.1	Immune-Related Adverse Events (Investigator-Assessed)	
2.7.8.2	Immune-Related Adverse Events (Sponsor-Assessed)	X
2.7.9.1	Infusion-Related Adverse Events (Sponsor-Assessed)	X
2.8.1	Clinical Laboratory Values - Hematology	X
2.8.2	Clinical Laboratory Values - Chemistry	X
2.8.3	Clinical Laboratory Values - Coagulation	
2.8.4	Clinical Laboratory Values - Urinalysis	
2.8.5	Clinical Laboratory Values – Endocrine	X
2.8.6	Clinical Laboratory Values - Troponin	X
2.8.7	Abnormal Clinical Laboratory Values - Hematology	X
2.8.8	Abnormal Clinical Laboratory Values - Chemistry	X
2.8.9	Abnormal Clinical Laboratory Values - Coagulation	
2.8.10	Abnormal Clinical Laboratory Values - Urinalysis	
2.8.11	Abnormal Clinical Laboratory Values - Endocrine	X
2.8.12	Abnormal Clinical Laboratory Values - Troponin	X
2.8.13	Potential Drug-Induced Liver Injuries	
2.9.1	Vital Signs	
2.9.2	Abnormal Vital Sign Values	
2.9.3	Alert Vital Sign Values	
2.10.1	12-Lead ECG Values	
2.10.2	Abnormal 12-Lead ECG Values	
2.10.3	Alert 12-Lead ECG Values	
2.11.1	Body Weight	