Official Title: A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies

NCT Number: NCT03126110

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Clinical Study Protocol

INCAGN 1876-201

A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies

Product:	**INCAGN01876**
IND Number:	[redacted]
EudraCT Number:	**2016-004989-25**
Phase of Study:	**1/2**
Sponsor:	**Incyte Biosciences International Sàrl** **Route de la Corniche 1** **1066 Epalinges, Switzerland**
Original Protocol (Version 0):	**20 DEC 2016**
Amendment (Version) 1:	**12 JUN 2017**
Amendment (Version) 2:	**22 AUG 2017**
Amendment (Version) 3:	**18 DEC 2017**
Amendment (Version) 4:	**24 OCT 2018**
Amendment (Version) 5:	**22 JAN 2021**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 11, 50, 54, 56, and 312, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have read the INCAGN 1876-201 Protocol Amendment 5 (Version 5 dated 22 JAN 2021) 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)

SYNOPSIS

Name of Investigational Product: INCAGN01876, nivolumab, ipilimumab	
Title of Study: A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies	
Protocol Number: INCAGN 1876-201	**Study Phase:** 1/2

Indication:

Phase 1: advanced or metastatic cervical cancer, endometrial cancer, gastric cancer [including stomach, esophageal, and gastroesophageal junction (GEJ) cancer], hepatocellular carcinoma (HCC), melanoma, Merkel cell carcinoma, mesothelioma, microsatellite instability-high (MSI-H) colorectal cancer (CRC), non–small cell lung cancer (NSCLC), ovarian cancer, squamous cell carcinoma of the head and neck (SCCHN), small cell lung cancer (SCLC), renal cell carcinoma (RCC), triple-negative breast cancer (TNBC), and urothelial carcinoma (or alternative tumor types with medical monitor approval)

Phase 2: advanced or metastatic cervical cancer, gastric cancer (including stomach, esophageal, and GEJ), SCCHN, PD-1 refractory SCCHN, and PD-1 or PD-L1 relapsed melanoma

Primary Objectives:

Phase 1

- To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of INCAGN01876 in combination with immune therapies and to define the recommended Phase 2 dose(s) of INCAGN01876 when given in combination with immune therapies.

Phase 2

- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies by assessing objective response rate (ORR) per RECIST v1.1.

Secondary Objectives:

Phase 1 and Phase 2

- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies by assessing ORR, duration of response (DOR), disease control rate (DCR), duration of disease control, and progression-free survival (PFS), per RECIST v1.1 and modified RECIST v 1.1 (mRECIST).
- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies with respect to 1-year and 2-year overall survival (OS).
- To evaluate the safety and tolerability of INCAGN01876 when given in combination with immune therapies.

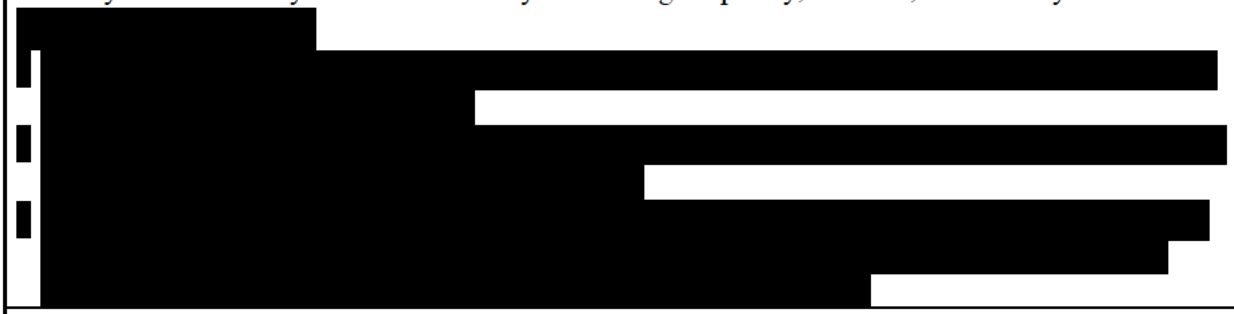
[redacted]

Primary Endpoints:

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs).
- ORR, defined as the percentage of subjects having complete response (CR) or partial response (PR), will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1.

Secondary Endpoints:

- ORR, defined as the percentage of subjects having CR or PR, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1 and mRECIST v1.1.
- Duration of response, defined as the time from the earliest date of disease response (CR or PR) until earliest date of disease progression or death due to any cause, if occurring sooner than progression, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1 and mRECIST v1.1.
- DCR, defined as the percentage of subjects having CR, PR, or stable disease (SD), will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1 and mRECIST v1.1.
- Duration of disease control (CR, PR, and SD) as measured from first report of SD or better until disease progression, will be determined by investigator assessment of radiographic disease per RECIST v1.1 and mRECIST v1.1, or death from any cause, if occurring sooner than progression.
- PFS, defined as the time from the start of combination therapy until the earliest date of disease progression or death due to any cause, if occurring sooner than progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1 and mRECIST v1.1.
- OS determined from the start of combination therapy until death due to any cause. Survival analyses will occur at 1-year, 2-years, and at the end of the study.
- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs.



Overall Study Design:

This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of INCAGN01876 when given in combination with immune therapies. Phase 1 will consist of a 3 + 3 + 3 dose escalation to determine the maximum tolerated dose (MTD), or pharmacologically active dose (PAD), defined as a dose that provides a maximal biochemical effect, or an increase in biomarkers of immune activity of INCAGN01876 when given in combination with immune therapies. Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach, esophageal, and GEJ), HCC, melanoma, Merkel cell carcinoma, mesothelioma, MSI-H CRC, NSCLC, ovarian cancer, SCCHN, SCLC, RCC, TNBC, and urothelial carcinoma who have progressed after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or who refuse standard of care will be enrolled in Phase 1. The Phase 2 expansion will further evaluate the safety, tolerability, and efficacy of the recommended dose(s) of INCAGN01876 selected in Phase 1 when given in combination with immune therapies. Subjects with advanced or metastatic cervical cancer, gastric cancer (including stomach, esophageal, and GEJ), SCCHN, PD-1 refractory SCCHN, and PD-1 or PD-L1 relapsed melanoma will be enrolled in Phase 2.

The sponsor may elect to prioritize (or deprioritize) enrollment to specific treatment groups or cohorts based on emerging safety or efficacy data in collaboration with investigational sites. Additionally, alternate dose administration schedules and/or fixed doses of INCAGN01876 (comparable to or less than the highest dose levels determined to be safe or pharmacologically active) may also be explored depending on [redacted] safety results.

Phase 1 – Dose Escalation

A minimum of 3 evaluable subjects will be enrolled in each treatment group beginning with INCAGN01876 Dose Cohort 1 (0.1 mg/kg; starting dose). A higher starting dose of INCAGN01876 may be used if safety data are available from the monotherapy study (INCAGN 1876-101) but will not exceed 1 dose level below the highest tolerated dose of INCAGN01876 monotherapy. If a higher starting dose is used, the dose will be communicated to investigational sites with an administrative letter.

The first 3 evaluable subjects enrolled within an INCAGN01876 dose cohort will be observed for the specified DLT observation period before the next dose cohort begins enrollment. If 0 DLTs occur in a cohort of 3 evaluable subjects, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 1 of 3 evaluable subjects experience a DLT, that cohort will be expanded to 6 evaluable subjects. If 1 of 6 evaluable subjects experiences a DLT, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 2 of 6 evaluable subjects experience a DLT, that cohort will be expanded to 9 evaluable subjects. If ≥ 2 of 3, 3 of 6, or 3 of 9 evaluable subjects experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD, and the previous dose level will be considered the MTD. If only 3 evaluable subjects were treated at the MTD or PAD, then a minimum of 3 additional evaluable subjects will be enrolled before this dose is administered in Phase 2 of the study.

Additional subjects will be enrolled in a dose cohort to achieve the minimum of 3 evaluable subjects. Depending on treatment group, a subject must receive at least 2 doses of the cohort-specified dose of INCAGN01876, 2 doses of nivolumab, and 1 dose of ipilimumab, or must have had a DLT during the DLT observation period, to be considered evaluable. Subjects who dropout for reasons other than a DLT (eg, events clearly associated with the underlying disease, disease progression, concomitant medication, or comorbidity), during the DLT observation period will result in the subject being nonevaluable and the subject being replaced. The doses of INCAGN01876 to be evaluated in each treatment group are summarized in Table S1.

Table S1: INCAGN01876 Dose Cohorts

Dose Cohort	Dose of INCAGN01876
-1	0.03 mg/kg
1 (Starting Dose)	**0.1 mg/kg[a]**
2	0.3 mg/kg
3	1.0 mg/kg
4	3.0 mg/kg
5	5.0 mg/kg
6	10.0 mg/kg

[a] A higher starting dose of INCAGN01876 may be used if safety data is available from the monotherapy study (INCAGN 1876-101), but will not exceed 1 dose level below the highest tolerated dose of INCAGN01876 monotherapy. If a higher starting dose is used, the dose will be communicated to investigational sites with an administrative letter.

Doublet Immune Therapy Combinations

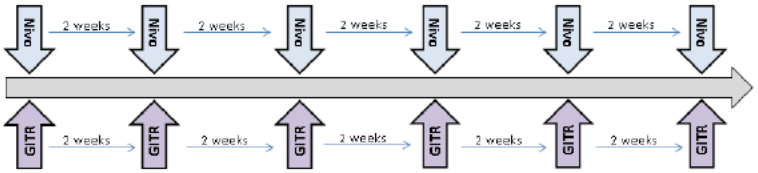
Phase 1 will begin with 3 doublet treatment groups, as outlined in Table S2, which will be explored in parallel.

Table S2: Doublet Immune Therapy Treatment Groups

Treatment Group A	**INCAGN01876 Concurrent Dosing**	**Nivolumab**	**DLT Observation Period**
	See INCAGN01876 dose cohorts (Table S1) Q2W	240 mg Q2W	28 days
Treatment Group B	**INCAGN01876 Sequenced Dosing**	**Nivolumab**	**DLT Observation Period**
	See INCAGN01876 dose cohorts (Table S1) Run-in with INCAGN01876 Q2W for 2 doses	240 mg Q2W starting at Cycle 3	28 days from the first nivolumab dose administered at Cycle 3
Treatment Group C	**INCAGN01876 Concurrent Dosing**	**Ipilimumab**	**DLT Observation Period**
	See INCAGN01876 dose cohorts (Table S1) Q2W	1 mg/kg Q6W	28 days

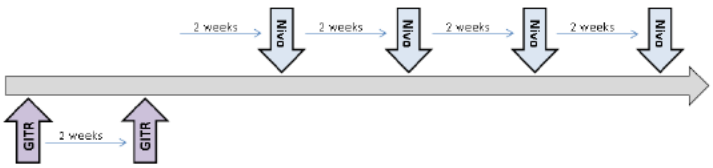
Treatment Group A (INCAGN01876 + Nivolumab)

Treatment Group A will treat subjects with INCAGN01876 at the assigned dose level administered intravenously (IV) every 2 weeks (Q2W) in combination with 240 mg of nivolumab administered IV Q2W (see figure below). **There will be a waiting period of 48 hours between dose administration of the first subject and second subject of each dosing cohort.** The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table S1 until the MTD or PAD of INCAGN01876 in combination with nivolumab is determined.



Treatment Group B (INCAGN01876 Sequenced Dosing + Nivolumab)

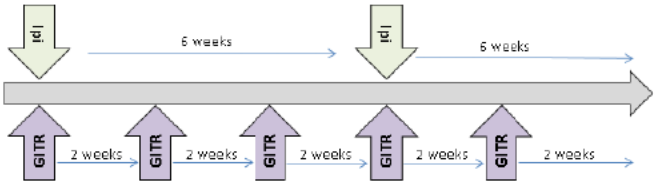
Treatment Group B will treat subjects with INCAGN01876 at the assigned dose level administered IV Q2W for a total of 2 doses followed by 240 mg of nivolumab administered IV Q2W starting at Cycle 3 (see figure below). Alternate dose administration schedules may also be explored depending on [redacted] safety results. The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days starting after the first dose of nivolumab has been administered before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table S1 until the MTD or PAD of INCAGN01876 in combination with nivolumab sequenced dosing is determined.



Treatment Group C (INCAGN01876 + Ipilimumab)

Treatment Group C will treat subjects with INCAGN01876 at the assigned dose level administered IV Q2W in combination with 1 mg/kg of ipilimumab administered IV every 6 weeks (Q6W; see figure below). **There will be a waiting period of 48 hours between dose administration of the first subject and second subject of each dosing cohort.** The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table S1 until the MTD or PAD of INCAGN01876 in combination with ipilimumab is determined.

At the sponsor's discretion, once the MTD or PAD of INCAGN01876 has been established with ipilimumab at 1 mg/kg Q6W, a higher dose of ipilimumab at 3 mg/kg Q6W and/or 3 mg/kg Q3W for 4 doses may be tested. If the MTD or PAD of INCAGN01876 in combination with higher doses of ipilimumab is not tolerated, dose de-escalation of INCAGN01876 will proceed as outlined in Table S1 until the MTD or PAD of INCAGN01876 is determined.



Triplet Immune Therapy Combinations

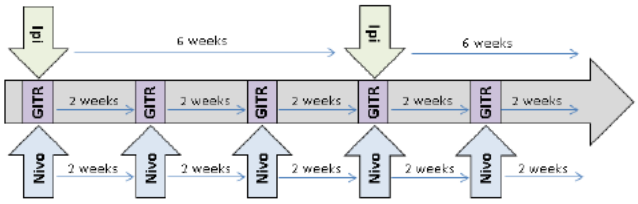
Dose escalation of the triplet immune therapy combinations will begin enrolling once all of the applicable doublet combinations have cleared 3 INCAGN01876 dose levels (see Table S1), or the MTD or PAD of INCAGN01876 has been determined (whichever occurs first). The starting dose of INCAGN01876 will be 2 dose levels below the last dose cohort deemed safe in the doublet combination. For example, if 3 mg/kg of INCAGN01876 is safe in the doublet combinations with both nivolumab and ipilimumab, then the starting dose in the triplet will be 0.3 mg/kg. If the MTD of INCAGN01876 is 1 mg/kg in the doublet combinations, then the starting dose of INCAGN01876 for the triplet immune therapy combination will be 0.1 mg/kg. If there are different MTDs of INCAGN01876 with nivolumab and ipilimumab, then the starting dose of the triplet will be 2 dose levels below the lowest MTD in the doublet. The triplet immune therapy combinations will be explored in parallel as outlined in Table S3.

Table S3: Triplet Immune Therapy Treatment Groups

Treatment Group D	**INCAGN01876 Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**DLT Observation Period**
	See INCAGN01876 dose cohorts (Table S1) Q2W	3 mg/kg Q2W	1 mg/kg Q6W	28 days
Treatment Group E	**INCAGN01876 Sequenced Followed by Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**DLT Observation Period**
	See INCAGN01876 dose cohorts (Table S1) Q2W Run-in with INCAGN01876 Q2W for 2 doses followed by INCAGN01876 Q2W	3 mg/kg Q2W starting at Cycle 3	1 mg/kg Q6W starting at Cycle 3	28 days from the first nivolumab/ipilimumab dose at Cycle 3

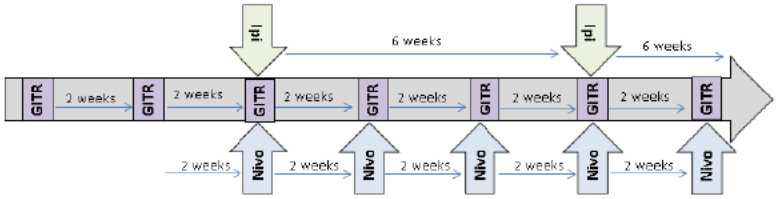
Treatment Group D (INCAGN01876 + Nivolumab + Ipilimumab)

Treatment Group D will treat subjects with INCAGN01876 at the assigned dose level administered IV Q2W in combination with 3 mg/kg of nivolumab administered IV Q2W and 1 mg/kg of ipilimumab administered IV Q6W (see figure below). **There will be a waiting period of 48 hours between dose administration of the first subject and second subject of each dosing cohort.** The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table S1 until the MTD or PAD of INCAGN01876 in combination with nivolumab and ipilimumab is determined; however, the dose of INCAGN01876 in the triplet combination will not exceed the lowest MTD of INCAGN01876 established in the applicable doublet combinations. For example, if the MTD of INCAGN01876 in combination with nivolumab is 5 mg/kg and the MTD of INCAGN01876 in combination with ipilimumab is 3 mg/kg, then the dose of INCAGN01876 would not exceed 3 mg/kg.



Treatment Group E (INCAGN01876 Sequenced Followed by Concurrent Dosing + Nivolumab + Ipilimumab)

Treatment Group E will treat subjects with a run-in of INCAGN01876 at the assigned dose level administered IV Q2W for 2 doses followed by INCAGN01876 at the assigned dose level Q2W in combination with 3 mg/kg of nivolumab administered IV Q2W, and 1 mg/kg of ipilimumab administered IV Q6W (see figure below). Alternate dose administration schedules may also be explored depending on [redacted] safety results. The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days starting after the first dose of nivolumab and ipilimumab has been administered before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table S1 until the MTD or PAD of INCAGN01876 in combination with nivolumab and ipilimumab is determined; however, the dose of INCAGN01876 in the triplet combination will not exceed the lowest MTD of INCAGN01876 established in the applicable doublet combinations. For example, if the MTD of INCAGN01876 in combination with nivolumab is 5 mg/kg and the MTD of INCAGN01876 in combination with ipilimumab is 3 mg/kg, then the dose of INCAGN01876 would not exceed 3 mg/kg.



Phase 2 – Dose Expansion

Phase 2 of the study will further evaluate the safety, tolerability, efficacy, [redacted] of the immune therapy combinations in subjects with advanced or metastatic cervical cancer, gastric cancer (including stomach, esophageal, and GEJ), SCCHN, and PD-1 or PD-L1 relapsed melanoma. Additional tumor-specific cohorts may be added, by protocol amendment, based on emerging data. Alternate dose administration schedules and/or fixed doses of INCAGN01876 (comparable to or less than the highest dose levels determined to be safe or pharmacologically active), may also be explored depending on [redacted] safety results.

[redacted]

The Phase 2 expansion treatment groups and tumor-specific cohorts for each treatment group are outlined in Table S4. A Simon 2-stage design will be used for the cervical cancer, gastric cancer, SCCHN and PD-1/PD-L1 relapsed melanoma cohorts in each treatment group with a stopping rule to

allow for early termination of a particular cohort at the end of Stage 1 if there are insufficient responses observed. The approximate number of subjects for Stage 1 and Stage 2 for the cervical cancer, gastric cancer, SCCHN, and PD-1/PD-L1 relapsed melanoma cohorts in each treatment group is described in Table S5. For the PD-1 refractory SCCHN cohort, a Simon 2-stage design with an expansion stage will be used with stopping rules to allow for early termination if there is an insufficient number of responses observed at the end of Stage 1 or Stage 2. The approximate number of subjects for Stage 1, Stage 2, and the Expansion Stage for the PD-1 refractory SCCHN cohort in Treatment Group F is described in Table S6. Enrollment in Phase 2 will begin when the MTD or PAD of INCAGN01876 for a given treatment group in Phase 1 has been determined.

Table S4: Phase 2 Expansion Treatment Groups

Doublet Expansion Treatment Groups				
Treatment Group C2	**INCAGN01876 Concurrent Dosing**	**Ipilimumab**		**Tumor Cohorts**
	RP2D of INCAGN01876 Q2W	1 mg/kg Q6W		Cohort 1 – PD-1/PD-L1 relapsed melanoma [redacted]
Treatment Group F	**INCAGN01876 Concurrent Dosing**	**Nivolumab**		**Tumor Cohorts**
	RP2D of INCAGN01876 Q2W	240 mg Q2W		Cohort 1 – Cervical Cohort 2 – Gastric Cohort 3 – SCCHN Cohort 4- PD-1/PDL-1 relapsed melanoma [redacted] Cohort 6 – PD-1 refractory SCCHN
Treatment Group H	**INCAGN01876 Sequenced Followed by Concurrent Dosing**	**Nivolumab**		**Tumor Cohorts**
	RP2D of INCAGN01876 run-in Q2W for 2 doses followed by INCAGN01876 Q2W	240 mg Q2W starting at Cycle 3 in combination with INCAGN01876 Q2W		Cohort 1 – Cervical Cohort 2 – Gastric Cohort 3 – SCCHN [redacted]
Triplet Expansion Treatment Groups				
Treatment Group J	**INCAGN01876 Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**Tumor Cohorts**
	RP2D of INCAGN01876 Q2W	3 mg/kg Q2W	1 mg/kg Q6W	Cohort 1 – Cervical Cohort 2 – Gastric Cohort 3 – SCCHN [redacted]
Treatment Group L	**INCAGN01876 Sequenced Followed by Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**Tumor Cohorts**
	RP2D of INCAGN01876 run-in Q2W for 2 doses followed by INCAGN01876 Q2W	3 mg/kg Q2W starting at Cycle 3	1 mg/kg Q6W starting at Cycle 3	Cohort 1 – Cervical Cohort 2 – Gastric Cohort 3 – SCCHN [redacted]

In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of Grade 3 or higher INCAGN01876-related AEs occurs in > 40% of subjects in a particular treatment group after 6 subjects have been enrolled, then further enrollment in that treatment group will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action (eg, lower the dose of INCAGN01876, change dose frequency, etc). If a treatment group is discontinued due to toxicity, it may be re-initiated at a previously tested lower dose level and/or alternate dosing schedule. All AEs, regardless of the time of occurrence on study, may be considered for DLT determination purposes.

Study Population: Key inclusion and exclusion criteria are noted below. Full subject eligibility criteria are located in the body of the Protocol.

Key Inclusion Criteria:

- Locally advanced or metastatic disease; locally advanced disease must not be amenable to resection with curative intent.
- Phase 1: Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach, esophageal, and GEJ), HCC, melanoma (excluding uveal melanoma), Merkel cell carcinoma, mesothelioma, MSI-H CRC, NSCLC, ovarian cancer, SCCHN, SCLC, RCC, TNBC, and urothelial carcinoma (or alternative tumor types with medical monitor approval).
- Phase 1: Subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or who refuse standard treatment. There is no limit to the number of prior treatment regimens.
- Phase 2: Subjects with advanced or metastatic cervical cancer, gastric cancer (including stomach, esophageal, and GEJ), SCCHN, PD-1 refractory SCCHN, or PD-1 or PD-L1 relapsed melanoma.
  - **For subjects with cervical cancer:** should have histologically confirmed squamous cell carcinoma of the cervix.
    Note: Should have received up to 2 prior therapy regimens for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy). Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.
    Note: Prior therapy should **not** have included an immune therapy (eg, anti–cytotoxic T-lymphocyte–associated protein 4 [CTLA-4], anti–programmed cell death protein 1 (PD-1), anti-programmed cell death protein ligand 1 (PD-L1), indoleamine 2,3-dioxygenase [IDO] inhibitors, tumor necrosis factor super family (TNFSF) agonists, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
  - **For subjects with gastric cancer:** adenocarcinoma of the stomach, esophagus, or GEJ.
    Note: Should have received only 1 prior chemotherapy regimen for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy). Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.
    Note: Prior therapy should **not** have included an immune therapy (eg, anti–CTLA-4, anti–PD-1, anti–PD-L1, IDO inhibitors, TNFSF agonists, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
    Note: HER-2/*neu* status known and subjects with HER2/*neu* positive tumors should have documented disease progression on or after treatment containing trastuzumab or other HER2/*neu*-targeted therapy.
  - **For subjects with SCCHN:** histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.
    Note: Subjects with tumors that are adjacent to or invade major blood vessels, as shown unequivocally by imaging studies are **not** eligible for participation.
    Note: Should consent to have tumor evaluated for HPV and Epstein-Barr virus (EBV) status of the tumor (per local institutional testing), or have documentation of HPV and EBV tumor status.
    Note: Should have received only 1 prior chemotherapy regimen for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy). Adjuvant regimens given within 6 months of screening would be counted as first-line therapy. Prior chemotherapy regimen should have been a platinum-containing regimen.
    Note (Stage 2 only): Should have progressive disease per RECIST v1.1 during or within 6 months after treatment with a platinum-containing regimen. The platinum-based therapy must be the **last** therapy the subject received before enrollment.
    Note: Prior therapy should **not** have included an immune therapy (eg, anti–CTLA-4, anti–PD-1, anti–PD-L1, IDO inhibitors, TNFSF agonists, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).

- **For subjects with PD-1 refractory SCCHN:** histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.
  Note: Should consent to have tumor evaluated for HPV and Epstein-Barr virus (EBV) status of the tumor (per local institutional testing), or have documentation of HPV and EBV tumor status.
  Note: PD-1 refractory SCCHN is defined as meeting all of the following criteria:
  a. Progressive disease per RECIST v1.1 as best overall response to treatment with an anti–PD-1 containing regimen that is confirmed at least 4 weeks (no less than 28 days) later.
  b. Progressive disease should be at least 12 weeks from first dose of anti–PD-1 therapy and confirmed 4 weeks (no less than 28 days) later.
  c. Should have received prior treatment with anti-PD-1 therapy for advanced or metastatic disease.
  d. Should have received at least 2 doses of a prior anti–PD-1 containing regimen.
  e. The PD-1 therapy must be the **last** therapy the subject received before enrollment.
- **For subjects with PD-1 or PD-L1 relapsed melanoma:** mucosal or cutaneous melanoma is acceptable; however, subjects with uveal melanoma are excluded. Subjects should have documented BRAF mutation status or consent to BRAF mutation testing during the screening period. BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criterion for BRAF mutation testing.
  Note: PD-1 or PD-L1 relapsed melanoma is defined as progressive disease per RECIST v1.1 after an objective response (PR or CR), or SD for at least 6 months while on treatment with an anti–PD-1 or anti–PD-L1 containing regimen (administered alone or in combination). The PD-1 or PD-L1 therapy must be the **last** therapy the subject received before enrollment.
- [redacted]

- Presence of measureable disease based on RECIST v1.1.
- ECOG performance status 0 to 1.

Key Exclusion Criteria:

- Laboratory and medical history parameters not within the Protocol-defined range.
  - Absolute neutrophil count < 1.0×10^9/L.
  - Platelets < 75×10^9/L.
  - Hemoglobin < 9 g/dL or < 5.6 mmol/L.

- Serum creatinine > 1.5 × institutional upper limit of normal (ULN), OR measured or calculated creatinine clearance < 50 mL/min for subjects with creatinine levels > 1.5 × ULN.
- Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≥ 2.5 × ULN.
- Total bilirubin ≥ 1.2 × ULN unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin.
- International normalized ratio, prothrombin time, or activated partial thromboplastin time > 1.5 × ULN.

- Prior treatment with any TNFSF agonist (eg, glucocorticoid-induced tumor necrosis factor receptor [GITR], OX40, 4-1BB/CD137, CD27, etc), for any indication.
- Transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors within 14 days before study Day 1.
- Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study drug:
  - ≤ 14 days for chemotherapy, targeted small molecule therapy, or radiation therapy.
    Note: Subjects must not have had radiation pneumonitis as a result of treatment. A 1-week washout is permitted for palliative radiation to non–central nervous system (CNS) disease with medical monitor approval.
    Note: Bisphosphonates and denosumab are permitted concomitant medications.
  - ≤ 28 days for prior immune therapy or persistence of active cellular therapy (ie, chimeric antigen receptor T-cell therapy; other cellular therapies must be discussed with medical monitor to determine eligibility).
  - ≤ 28 days for a prior monoclonal antibody used for anticancer therapy with the exception of denosumab.
  - ≤ 7 days for immune-suppressive–based treatment for any reason.
    Note: Use of inhaled or topical steroids or corticosteroid use for radiographic procedures is permitted.
    Note: Must not require chronic use of corticosteroids. The use of physiologic corticosteroid replacement therapy may be approved after consultation with the medical monitor.
  - ≤ 28 days or 5 half-lives (whichever is longer) before the first dose for all other investigational agents or devices. For investigational agents with long half-lives (eg, > 5 days), enrollment before the fifth half-life requires medical monitor approval.
- Has not recovered to ≤ Grade 1 from toxic effects of prior therapy (including prior immune therapy) and/or complications from prior surgical intervention before starting therapy.
  Note: Subjects with stable chronic conditions (≤ Grade 2) not expected to resolve (such as neuropathy and alopecia) are exceptions and may enroll.
  Note: Subjects with a history of any grade immune-related ocular AE (eg, episcleritis, scleritis, uveitis) will be excluded.
  Note: Subjects with a history of a Grade 3 or higher immune-related AE from prior immunotherapies are excluded from the dose escalation portion of the study.
- Active autoimmune disease that required systemic treatment in the past (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
  Note: Subjects who have not required systemic treatment in the past 2 years should discuss their case with medical monitor to determine eligibility.
  Note: Subjects with hyper/hypothyroidism, vitiligo, controlled asthma, Type I diabetes, Graves' disease, or Hashimoto's disease are eligible to participate.
  Note: Replacement and symptomatic therapies (eg, levothyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) are not considered a form of systemic treatment and are allowed.

- Known active CNS metastases and/or carcinomatous meningitis.
  Note: Subjects with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS edema, and have not required steroids for at least 7 days before the first dose of study drug.
- Evidence of active, noninfectious pneumonitis or history of interstitial lung disease.
- History or presence of an abnormal electrocardiogram that, in the investigator's opinion, is clinically meaningful.
- Evidence of hepatitis B virus or hepatitis C virus infection or risk of reactivation.
- Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies).

INCAGN01876, Dosage, and Mode of Administration:

Phase 1 and Phase 2: INCAGN01876 will be administered IV over a 30-minute period on Day 1 of each Q2W (ie, 14 days) cycle. During Phase 2, fixed doses of INCAGN01876 (comparable to or less than the MTD/PAD determined during dose escalation), may also be explored. INCAGN01876 will be the first drug administered, followed by a 30-minute wait before starting infusion with the next agent. Subjects will continue to receive INCAGN01876 as long as they are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal, or for up to 24 months from the first dose of study treatment, whichever occurs first.

Reference Therapies, Dosage, and Mode of Administration:

Dosage and Mode of Administration for Nivolumab:

In the doublet Treatment Groups A, B, F, and H, nivolumab will be administered IV per the package insert or institutional guidelines at a dose of 240 mg Q2W (eg, 14 days).

In the triplet Treatment Groups D, E, J, and L, nivolumab will be administered IV per the package insert or institutional guidelines at a dose of 3 mg/kg Q2W (eg, 14 days).

In the concurrent dosing Treatment Groups A, D, F, and J, nivolumab dosing will begin on Cycle 1 Day 1.

In the sequenced dosing Treatment Groups B, E, H, and L, nivolumab dosing will begin on Cycle 3 Day 1.

Nivolumab will be administered at least 30 minutes after the infusion of INCAGN01876 (when applicable). Subjects will continue to receive nivolumab as long as they are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal, or for up to 24 months from the first dose of study treatment, whichever occurs first.

Dosage and Mode of Administration for Ipilimumab:

Ipilimumab will be administered IV per the package insert or institutional guidelines to subjects in Treatment Groups C, C2 (Phase 2 expansion), D, E, J, and L, at a dose of 1 mg/kg Q6W (eg, 42 days). In the concurrent dosing Treatment Groups C, C2, D, and J, ipilimumab dosing will begin on Cycle 1 Day 1. In the sequenced dosing Treatment Groups E and L, ipilimumab dosing will begin on Cycle 3 Day 1.

Ipilimumab will be administered at least 30 minutes after the infusion of INCAGN01876 (when administered on the same day). Ipilimumab will always be administered after INCAGN01876 and nivolumab. Subjects will continue to receive ipilimumab as long as they are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal, or for up to 24 months from the first dose of study treatment, whichever occurs first.

At the sponsor's discretion, once the MTD or PAD of INCAGN01876 has been established with ipilimumab at 1 mg/kg Q6W (eg, 42 days), a higher dose of ipilimumab at 3 mg/kg Q6W (eg, 42 days) and/or 3 mg/kg Q3W (eg, 21 days) for 4 doses may be tested.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinical site on Day 1 of each cycle. Additional study visits may be required during some cycles to monitor for safety, efficacy [redacted]. Study visits are as follows:

Screening: Up to 28 days before enrollment. Screening will begin at the time that the subject signs the informed consent and will continue until the date that the subject is enrolled in the study (Cycle 1 Day 1).

Cycle 1 and Cycle 6: Day 1 and Day 8 (± 1 day).

All other treatment cycles: Day 1 (± 3 days).

Efficacy assessments: Every 8 weeks (± 7 days). After 12 months, efficacy assessments will occur every 12 weeks (± 7 days) until disease progression is determined.

End of treatment: ± 3 days of withdrawal from study.

Safety follow-up: 30 days (+ 7 days) and 60 days (+ 7 days) after the last dose of study treatment.

Note: As of Protocol Amendment 5, these safety follow-up visits will include AE and concomitant medication assessment only and may be completed remotely (such as by televisit).

Disease follow-up: Subjects who discontinue treatment for reasons other than disease progression will continue to be assessed every 8 weeks (± 7 days) for their disease status during the follow-up period and should continue to have tumor assessments until a new cancer therapy is started, disease progression, death, the end of the study, or the subject withdraws consent.

Note: As of Protocol Amendment 5, no further disease follow-up assessments will be required beyond the last safety follow-up visit.

Survival follow-up: Once a subject has confirmed disease progression or starts a new anticancer therapy, the subject moves into the survival follow-up period and should be contacted every 12 weeks from the last dose of treatment for survival follow-up. This follow-up may occur through a phone call, email, or visit by the subject or the subject's caregiver.

Note: As of Protocol Amendment 5, no further survival follow-up assessments will be required beyond the last safety follow-up visit.

Estimated Duration of Participation: Subjects may continue on treatment as long as they are receiving benefit and do not meet withdrawal criteria, or for up to 24 months from the first dose of treatment, whichever occurs first. All subjects will be followed for survival. Study participation, including post-treatment follow-up is expected to average approximately 12 to 18 months per individual subject.

Estimated Number of Subjects:

- Phase 1 Dose Escalation – Approximately 90 to 270 evaluable subjects.
  Note: The minimum number of subjects assumes that the starting dose is 0.1 mg/kg; however, fewer subjects would be enrolled if a higher starting dose is used based on available safety data from the monotherapy study INCAGN 1876-101.
  Note: The maximum number of subjects assumes that DLTs are observed in all dose cohorts to a maximum of 9 subjects per cohort across all treatment groups.
- Phase 2 Stage 1 – Approximately 264 evaluable subjects.
- [redacted]
- Phase 2 Stage 2 – Approximately 455 evaluable subjects.
- Phase 2 Expansion Stage (PD-1 refractory SCCHN cohort only) – Approximately 20 evaluable subjects
  Note: Assumes that all treatment groups and all tumor types proceed to Stage 2 and expansion stage (for PD-1 refractory SCCHN cohort only).

Coordinating Principal Investigator: [redacted]

Statistical Methods:

In Phase 2, a Simon 2-stage design will be run for the cervical cancer, gastric cancer, SCCHN and PD-1/PD-L1 relapsed melanoma cohorts within a given doublet or triplet treatment group. The planned Simon 2-stage designs are summarized in Table S5, assuming a 1-sided Type I error of 0.05 and power of 85%. Each Simon 2-stage design will have a stopping rule to allow early termination of a particular tumor type within the given drug combination at the end of Stage 1 if there is insufficient response observed (calculated response rate < p_0), while enrolling enough subjects to predict possible target responses ($\geq p_1$) worthy of cohort expansion and potentially further evaluation in future studies.

Table S5: Planned Simon 2-Stage Designs for Phase 2

Indication	Combination	r_1	n_1	r	n_2	n	p_0	p_1
SCCHN	GITR + Nivo	3	16	10	30	46	15%	35%
Gastric	GITR + Nivo	3	16	10	30	46	15%	35%
Cervical	GITR + Nivo	4	17	14	34	51	20%	40%
Relapsed melanoma	GITR + Nivo	2	20	8	30	50	10%	25%
Relapsed melanoma	GITR + Ipi	2	20	8	30	50	10%	25%
SCCHN	GITR + Nivo + Ipi	5	18	17	32	50	25%	45%
Gastric	GITR + Nivo + Ipi	5	18	17	32	50	25%	45%
Cervical	GITR + Nivo + Ipi	7	21	19	27	48	30%	50%

r_1: If r_1 or fewer responses are observed during Stage 1, the study cohort is stopped early for futility.

n_1: Number of subjects initially enrolled in the Stage 1.

n_2: Number of subjects enrolled in the Stage 2.

r: If r or fewer responses are observed by the end of Stage 2, then no further investigation of the drug combination is warranted in the selected tumor type.

n: Total number of subjects.

p_0: Insufficient response rate.

p_1: Target response rate.

For the PD-1 refractory SCCHN cohort in doublet Treatment Group F, a Simon 2-stage design with an expansion stage, summarized in Table S6, will be used. With this 3-stage design, the 1-sided Type I error is 0.0231, and the power is approximately 88%. The PD-1 refractory SCCHN cohort will be terminated early for futility at the end of Stage 1 or Stage 2 if there is insufficient response observed. At the end of the expansion stage, if there is sufficient response observed, the doublet schedule for the PD-1 refractory SCCHN cohort will be declared promising for further investigation; otherwise it is considered nonpromising.

Table S6: Planned Simon 2-Stage Design With Expansion Stage for PD-1 refractory SCCHN Cohort in Phase 2

Indication	Combination	r_1	n_1	r_2	n_2	r	n_3	n	p_0	p_1
PD-1 refractory SCCHN	GITR + Nivo	0	12	3	25	6	20	57	5%	20%

Note: The definitions of p_0, p_1, r_1, n, n_1, and n_2 are the same as those in Table S5.

r_2: If r_2 or fewer responses are observed by the end of Stage 2, the study cohort is stopped early for futility.

r: If r or fewer responses are observed by the end of expansion stage, then no further investigation of the drug combination is warranted in the study cohort.

n_3: Number of subjects enrolled in the expansion stage.

Integrated Futility Analysis:

For the cervical cancer, gastric cancer and SCCHN cohorts, when each subject enrolls in Phase 2, an integrated analysis of tumor and dosing strategies (including concurrent dosing and INCAGN01876 run-in Q2W for 2 doses followed by INCAGN01876 Q2W in combination with the combining drug[s]) will be conducted based on Simon et al (2016). Tumor types within a dosing strategy will jointly be analyzed using a Bayesian model before allowing sharing of information across tumor types. Similar sharing will be applied separately for dosing strategies across tumor types. The purpose of the integrated Bayesian analysis is to determine if INCAGN01876 is active within any of the given dosing strategies, given tumor types, or given dosing strategy-tumor type combinations. Enrollment in a dosing strategy-tumor type combination will be terminated if the probability of success is not above 20% for both analysis approaches. Collection of response data will be based on investigator assessments entered into an interactive response technology system and analyzed separately from the clinical database. Additional information regarding the futility analysis is detailed in the full Protocol.

The proposed designs for each tumor type and treatment combination will be used for any planned Simon 2-stage design in the treatment combination (including concurrent and sequential dosing). Each Simon 2-stage design is set up to have a 1-sided Type I error of 0.05 and power of 85%. The response rates for each tumor type within a drug combination will be estimated with 95% confidence intervals. Formal safety reviews, to be held at least every 6 months, will be conducted to review efficacy and safety data.

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The following abbreviations and special terms are used in this clinical study Protocol.

Abbreviation	Definition
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
AGM	African green monkey
anti-HBc	anti-hepatitis B core
aPTT	activated partial thromboplastin time
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte–associated protein 4
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
Fc	fragment, crystallizable
FcγR	Fc-gamma receptor
FDA	Food and Drug Administration
Foxp3	forkhead box P3
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GI	gastrointestinal
GITR	glucocorticoid-induced tumor necrosis factor receptor

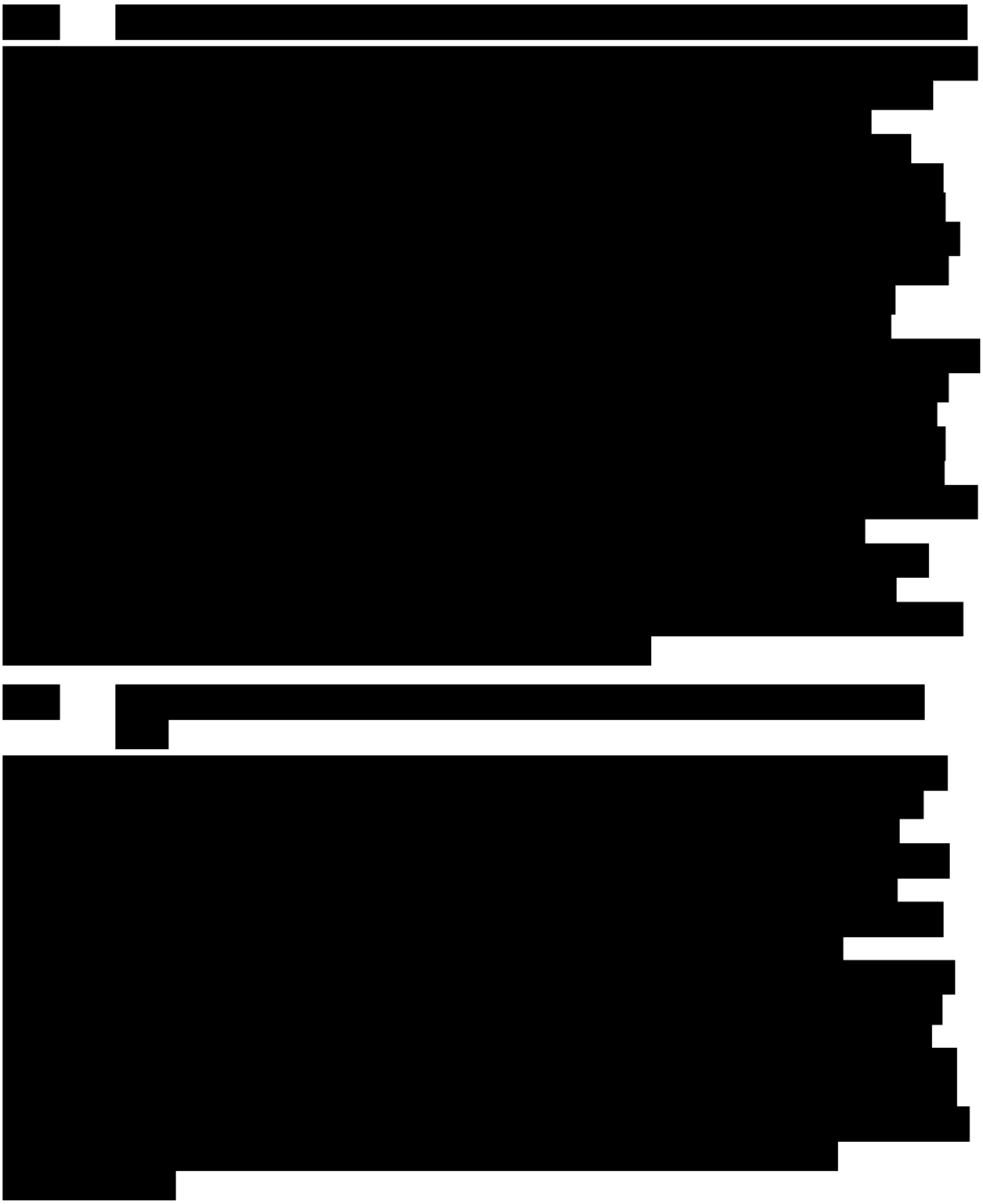
Abbreviation	Definition
GITRL	glucocorticoid-induced tumor necrosis factor receptor ligand
HCC	hepatocellular carcinoma
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HPV	human papillomavirus
ICF	informed consent form
ICH	International Conference on Harmonization
IDO	indoleamine 2,3-dioxygenase
IEC	independent ethics committee
IL	interleukin
INR	international normalized ratio
Ipi	ipilimumab
irAE	immune-related adverse event
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMR	mismatch repair
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
Nivo	nivolumab
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
ORR	objective response rate

Abbreviation	Definition
OS	overall survival
PAD	pharmacologically active dose
[redacted]	[redacted]
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
PFS	progression-free survival
[redacted]	[redacted]
PoS	probability of success
PR	partial response
PT	prothrombin time
Q2W	every 2 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	stable disease
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
TNBC	triple-negative breast cancer
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
TNFRSF	tumor necrosis factor receptor super family
TNFSF	tumor necrosis factor super family
[redacted]	[redacted]
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background

[redacted]



[redacted]

[redacted]

1.2. Overview of INCAGN01876

INCAGN01876 is an agonistic antihuman GITR mAb, with the potential to enhance the function of tumor-specific T cells and promote antitumor immunity in cancer patients. Recent clinical success with checkpoint inhibitors has provided rationale for investigating agonists such as GITR in order to extend clinical benefit to patients.

INCAGN01876 is a human immunoglobulin G1 κ mAb that selectively binds to the extracellular domain of human GITR (CD357 or TNRSF18; Gurney et al 1999). The cytoplasmic domain of GITR shows sequence homology with other TNFRSF members, which is consistent with its ability to recruit and bind to TNFR-associated adapters and activate the NFκB signaling pathway (Melero et al 2013, Xie 2013). INCAGN01876 binds to human GITR and cross-reacts with AGM GITR but does not recognize cynomolgus monkey, mouse, or rat GITR. INCAGN01876 selectively recognizes GITR and does not bind to the following related TNFRSF members: OX40 (CD134), lymphotoxin beta receptor (LTBR or CD18), death receptor 6 (DR6 or CD358), TNF-related weak inducer of apoptosis (TWEAK or CD226,), 4-1BB (CD137), or B-cell activating receptor (BAFF-R or CD268).

Preclinical findings highlight the potential antitumor mechanisms of action of INCAGN01876: 1) costimulatory agonistic engagement of GITR enhancing T-effector cells, and 2) coengagement of activating FcγRs to selectively deplete immune suppressive Tregs located within the tumor (Gonzalez et al 2016). [redacted]

1.2.1. Preclinical Safety of INCAGN01876

The safety of INCAGN01876 was evaluated [redacted]

[redacted]

[redacted]

1.2.3. Clinical Safety of INCAGN01876

Study INCAGN 1876-101 is an open-label, nonrandomized, Phase 1/2 study to determine the safety and tolerability, define the MTD or PAD, and assess the preliminary efficacy of INCAGN01876 in subjects with advanced or metastatic solid tumors. Dose escalation is ongoing using a traditional 3 + 3 design with cohorts of subjects sequentially enrolled at doses of 0.03 mg/kg (n = 4), 0.1 mg/kg (n = 4), 0.3 mg/kg (n = 4), 1 mg/kg (n = 3), 3 mg/kg (n = 6), 5 mg/kg (n = 7), and 10 mg/kg (n = 6). INCAGN01876 is administered IV over 30 minutes on Day 1 Q2W (eg, 14 days), until disease progression, intolerable toxicity, or for a maximum of 26 cycles. Decisions for dose escalation are based on predetermined DLTs observed during a 28-day observation period.

[redacted]

1.3. Overview of Standard Therapies

1.3.1. Nivolumab

1.3.1.1. Nivolumab Summary

Nivolumab (OPDIVO®) is PD-1 blocking antibody that has been approved as monotherapy in the United States for the treatment of patients with unresectable or metastatic melanoma, metastatic NSCLC, advanced RCC, recurrent or metastatic SCCHN, and classical Hodgkin lymphoma. Nivolumab is also approved in combination with ipilimumab in patients with unresectable or metastatic melanoma (Opdivo 2016). Nivolumab is approved in the European Union as monotherapy or in combination with ipilimumab for advanced (unresectable or metastatic) melanoma, as monotherapy for locally advanced or metastatic NSCLC after prior chemotherapy, for advanced RCC after prior therapy, and for Hodgkin lymphoma following autologous stem cell transplant and treatment with brentuximab vedotin (Opdivo SmPC 2015). Refer to the Opdivo prescribing information and summary of product characteristics for updated information regarding approved indications (Opdivo 2016).

1.3.1.2. Risks From Nivolumab

Due to the mechanism of action of nivolumab, immune-mediated adverse reactions have been seen when used as monotherapy and in combination with ipilimumab. Guidance is provided in the package insert for the management of immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated skin adverse reactions, and immune-mediated encephalitis. Infusion reactions are also possible following administration of nivolumab. The most common adverse reactions seen in $\geq$ 20% of patients receiving nivolumab monotherapy were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenic conditions, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia. The most common adverse reactions seen in $\geq$ 20% of patients receiving nivolumab in combination with ipilimumab were fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea (Opdivo 2016). Refer to the Opdivo prescribing information and summary of product characteristics for updated information regarding safety and risks.

1.3.2. Ipilimumab

1.3.2.1. Ipilimumab Summary

Ipilimumab (YERVOY®) is a human CTLA-4–blocking antibody indicated as a monotherapy and in combination with nivolumab for the treatment of patients with advanced melanoma. Refer to the Yervoy prescribing information and summary of product characteristics for updated information regarding approved indications (Yervoy 2016).

1.3.2.2. Risks From Ipilimumab

Ipilimumab may cause immune-mediated adverse reactions including immune-mediated hepatitis, immune-mediated enterocolitis, immune-mediated dermatitis, immune-mediated neuropathies, immune-mediated endocrinopathies, and other immune-mediated adverse reactions. Guidance for the management of these events is found in the package insert. The approved dose of ipilimumab is 3 mg/kg Q3W for 4 doses. The most common AEs (≥ 5%) seen at the approved dose are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions (≥ 5%), seen in patients receiving a higher dose of 10 mg/kg, include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia (Yervoy 2016). Refer to the Yervoy prescribing information and summary of product characteristics for updated information regarding safety and risks (Yervoy 2016).

The combination of nivolumab and ipilimumab was initially explored in subjects with advanced or metastatic melanoma using doses of 1 mg/kg nivolumab and 3 mg/kg ipilimumab given Q3W for 4 doses followed by 3 mg/kg nivolumab administered Q2W. The toxicity of the combination was significantly higher than either agent alone with 36.4% of subjects discontinuing treatment due to an AE and 68.7% of subjects experiencing Grade 3 or 4 AEs (Larkin et al 2015). More recent published data have demonstrated that lower doses and less frequent administration of ipilimumab improves the toxicity profile of the combination (Antonia et al 2016, Hellmann et al 2016). In a study of 3 mg/kg nivolumab administered Q2W plus 1 mg/kg ipilimumab administered Q6W in first-line NSCLC, only 13% of subjects discontinued due to a treatment-related AE, and only 33% had a Grade 3 or 4 treatment-related AE (Hellmann et al 2016). The most common AEs seen in this treatment group were skin events (36%, 5% Grade 3 or 4), endocrine (20%, 5% Grade 3 or 4), and GI (23%, 5% Grade 3 or 4).

[redacted]

1.4. Potential Risks and Benefits of the Combination Regimens

The principle toxicities of administering agents that modulate the immune system are irAEs including skin manifestations, pneumonitis, enterocolitis, and endocrinopathies. Immune-related AEs have been reported in subjects treated with nivolumab and ipilimumab. As the use of immunotherapies become more prevalent, guidelines for the management of irAEs continue to evolve. Careful monitoring, early diagnosis, and treatment with corticosteroids for more severe events is recommended. The time of onset of irAEs varies, with skin manifestations and GI toxicity seen early and elevated liver enzymes and endocrinopathies appearing later

(Weber et al 2015). Subjects enrolled in this study will be carefully monitored for the onset of irAEs, and guidelines for the management of these toxicities are provided in the Protocol and in the prescribing information for nivolumab and ipilimumab.

[redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

Phase 1

- To evaluate the safety, tolerability, and DLTs of INCAGN01876 in combination with immune therapies and to define the RP2D(s) of INCAGN01876 when given in combination with immune therapies.

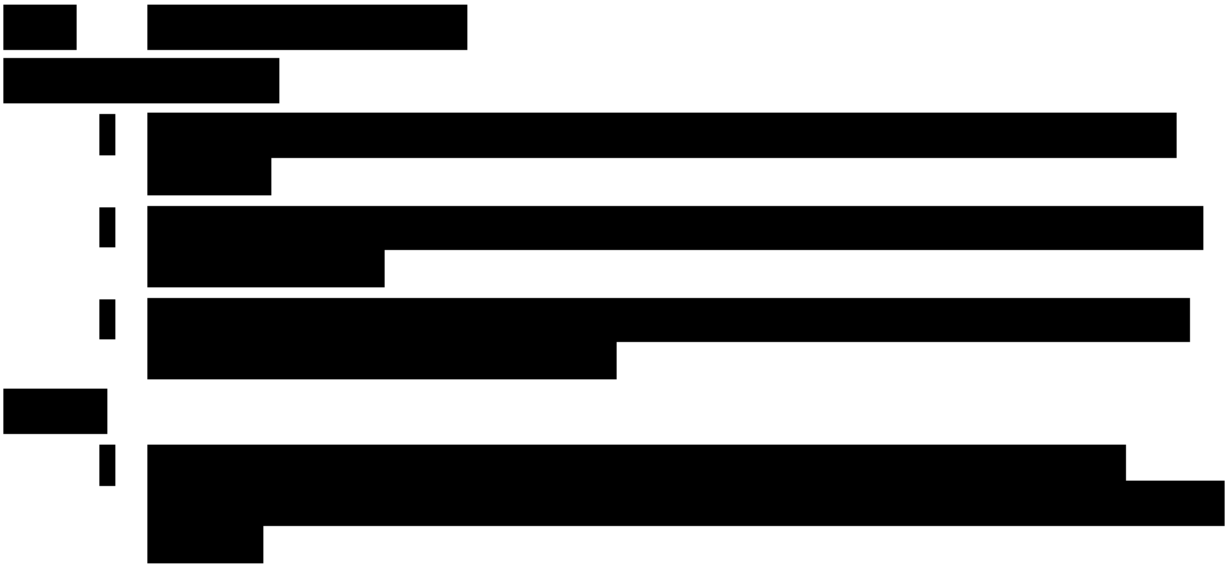
Phase 2

- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies by assessing ORR per RECIST v1.1.

2.1.2. Secondary Objectives

Phase 1 and Phase 2

- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies by assessing ORR, DOR, DCR, duration of disease control, and PFS per RECIST v1.1 and mRECIST v1.1.
- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies with respect to 1-year and 2-year OS.
- To evaluate the safety and tolerability of INCAGN01876 when given in combination with immune therapies.



2.2. Study Endpoints

2.2.1. Primary Endpoints

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs.
- ORR, defined as the percentage of subjects having CR or PR, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1.

2.2.2. Secondary Endpoints

- ORR, defined as the percentage of subjects having CR or PR, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1 and mRECIST v1.1.
- DOR, defined as the time from the earliest date of disease response (CR or PR) until earliest date of disease progression or death due to any cause, if occurring sooner than progression, will be determined by investigator assessment of radiographic disease assessment per RECIST v1.1 and mRECIST v1.1.
- DCR, defined as the percentage of subjects having CR, PR, or SD, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1 and mRECIST v1.1.
- Duration of disease control (CR, PR, and SD) as measured from first report of SD or better until disease progression or death from any cause, if occurring sooner than progression, will be determined by investigator assessment of radiographic disease per RECIST v1.1 and mRECIST v1.1.
- PFS, defined as the time from the start of combination therapy until the earliest date of disease progression or death due to any cause, if occurring sooner than progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1 and mRECIST v1.1.
- OS determined from the start of combination therapy until death due to any cause. Survival analyses will occur at 1-year, 2-years, and at the end of the study.
- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs.

[redacted]

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

1. Men and women, aged 18 or older.
2. Willingness to provide written informed consent for the study.
3. Locally advanced or metastatic disease; locally advanced disease must not be amenable to resection with curative intent.
4. Phase 1: Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach, esophageal, and GEJ), HCC, melanoma (excluding uveal melanoma), Merkel cell carcinoma, mesothelioma, MSI-H CRC, NSCLC, ovarian cancer, SCCHN, SCLC, RCC, TNBC, and urothelial carcinoma (or alternative tumor types with medical monitor approval).
5. Phase 1: Subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or who refuse standard treatment. There is no limit to the number of prior treatment regimens.
6. Phase 2: Subjects with advanced or metastatic cervical cancer, gastric cancer (including stomach, esophageal, and GEJ), SCCHN, PD-1 refractory SCCHN, or PD-1 or PD-L1 relapsed melanoma.
    a. **For subjects with cervical cancer:** should have documented histologically confirmed squamous cell carcinoma of the cervix.
    Note: Should have received up to 2 prior therapy regimens for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy). Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.
    Note: Prior therapy should **not** have included an immune therapy (eg, anti–CTLA-4, anti–PD-1, anti–PD-L1, IDO inhibitors, TNFSF agonists, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
    b. **For subjects with gastric cancer:** adenocarcinoma of the stomach, esophagus, or GEJ.
    Note: Should have received only 1 prior chemotherapy regimen for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy). Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.
    Note: Prior therapy should **not** have included an immune therapy (eg, anti–CTLA-4, anti–PD-1, anti–PD-L1, IDO inhibitors, TNFSF agonists, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
    Note: HER-2/*neu* status known and subjects with HER2/*neu* positive tumors should have documented disease progression on or after treatment containing trastuzumab or other HER2/*neu*-targeted therapy.
    c. **For subjects with SCCHN:** histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.

Note: Subjects with tumors that are adjacent to or invade major blood vessels, as shown unequivocally by imaging studies are not eligible for participation.
Note: Should consent to have tumor evaluated for HPV and EBV status of the tumor (per local institutional testing), or have documentation of HPV and EBV status.
Note: Should have received only 1 prior chemotherapy regimen for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy). Adjuvant regimens given within 6 months of screening would be counted as first-line therapy. Prior chemotherapy regimen should have been a platinum-containing regimen.
Note: Prior therapy should **not** have included an immune therapy (eg, anti–CTLA-4, anti–PD-1, anti–PD-L1, IDO inhibitors, TNFSF agonists, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
Note (Stage 2 only): Should have progressive disease per RECIST v1.1 during or within 6 months after treatment with a platinum-containing regimen. The platinum-based therapy must be the **last** therapy the subject received before enrollment.

d. **For subjects with PD-1 refractory SCCHN:** histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.
Note: Should consent to have tumor evaluated for HPV and EBV status of the tumor (per local institutional testing), or have documentation of HPV and EBV tumor status.
Note: PD-1 refractory SCCHN is defined as meeting all of the following criteria:
   i. Progressive disease per RECIST v1.1 as best overall response to treatment with an anti–PD-1 containing regimen that is confirmed at least 4 weeks (no less than 28 days) later.
   ii. Progressive disease should be at least 12 weeks from first dose of anti–PD-1 therapy and confirmed 4 weeks (no less than 28 days) later.
   iii. Should have received prior treatment with anti–PD-1 therapy for advanced or metastatic disease.
   iv. Should have received at least 2 doses of a prior anti–PD-1 containing regimen.
   v. The PD-1 therapy must be the **last** therapy the subject received before enrollment.

Note: Subjects with cervical cancer, gastric cancer, and SCCHN (excluding subjects with PD-1 refractory SCCHN) should **not** have received prior treatment with an immune therapy (eg, anti–CTLA-4, anti–PD-1, anti–PD-L1, IDO inhibitors, TNFSF agonists, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).

[redacted]

f. **For subjects with PD-1 or PD-L1 relapsed melanoma:** mucosal or cutaneous melanoma is acceptable; however, subjects with uveal melanoma are excluded. Subjects should have documented BRAF mutation status or consent to BRAF mutation testing during the screening period. BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criterion for BRAF mutation testing.
Note: PD-1 or PD-L1 relapsed melanoma is defined as progressive disease per RECIST v1.1 after an objective response (PR or CR), or SD for at least 6 months while on treatment with an anti–PD-1 or anti–PD-L1 containing regimen (administered either alone or in combination). The PD-1 or PD-L1 therapy must be the **last** therapy the subject received before enrollment.

7. Presence of measureable disease based on RECIST v1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are not considered measureable unless there has been demonstrated progression in the lesion.
8. ECOG performance status 0 to 1.
9. Willingness to avoid pregnancy or fathering children based on the criteria below:
   a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea.
   b. Woman of childbearing potential who has a negative serum pregnancy test at screening, and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up, or as required in the nivolumab and/or ipilimumab package insert, whichever is longer. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
   c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up, or as required in the nivolumab and/or ipilimumab package insert, whichever is longer. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

3.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Laboratory and medical history parameters not within the Protocol-defined range. If the screening laboratory tests below were conducted > 7 days before treatment initiation, then the tests must be repeated and eligibility confirmed before study drug administration on Cycle 1 Day 1.
   a. Absolute neutrophil count < 1.0×10^9/L.
   b. Platelets < 75×10^9/L.
   c. Hemoglobin < 9 g/dL or < 5.6 mmol/L.
   d. Serum creatinine > 1.5 × institutional ULN, OR measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or creatinine clearance) < 50 mL/min for subjects with creatinine levels > 1.5 × ULN.
   e. Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≥ 2.5 × ULN.
      Note: Subjects with 1) bone metastases and 2) no hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase is ≤ 5 × ULN. Subjects with 1) bone metastases and/or 2) hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase is ≤ 5 × ULN only with medical monitor approval.
   f. Total bilirubin ≥ 1.2 × ULN unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin.
   g. INR, PT, or activated partial thromboplastin time > 1.5 × ULN.
2. Prior treatment with any TNFSF agonist (eg, GITR, OX40, 4-1BB/CD137, CD27, etc), for any indication.
3. Transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colony–stimulating factor, granulocyte macrophage colony–stimulating factor, or recombinant erythropoietin) within 14 days before study Day 1.
4. Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study drug:
   a. ≤ 14 days for chemotherapy, targeted small molecule therapy, or radiation therapy.
      Note: Subjects must not have had radiation pneumonitis as a result of treatment. A 1-week washout is permitted for palliative radiation to non–CNS disease with medical monitor approval.
      Note: Bisphosphonates and denosumab are permitted concomitant medications.
   b. ≤ 28 days for prior immune therapy or persistence of active cellular therapy (ie, chimeric antigen receptor T-cell therapy; other cellular therapies must be discussed with medical monitor to determine eligibility).
   c. ≤ 28 days for a prior mAb used for anticancer therapy with the exception of denosumab.

d. ≤ 7 days for immune-suppressive–based treatment for any reason.
Note: Use of inhaled or topical steroids or corticosteroid use for radiographic procedures is permitted.
Note: Must not require chronic use of corticosteroids. The use of physiologic corticosteroid replacement therapy may be approved after consultation with the medical monitor.
e. ≤ 28 days or 5 half-lives (whichever is longer) before the first dose for all other investigational agents or devices. For investigational agents with long half-lives (eg, > 5 days), enrollment before the fifth half-life requires medical monitor approval.

5. Has not recovered to ≤ Grade 1 from toxic effects of prior therapy (including prior immune therapy) and/or complications from prior surgical intervention before starting therapy
Note: Subjects with stable chronic conditions (≤ Grade 2) not expected to resolve (such as neuropathy and alopecia) are exceptions and may enroll.
Note: Subjects with a history of any grade immune-related ocular AE (eg, episcleritis, scleritis, uveitis) will be excluded.
Note: Subjects with a history of a Grade 3 or higher immune-related AE from prior immunotherapies are excluded from the dose escalation portion of the study.

6. Receipt of a live vaccine within 30 days of planned start of study therapy.
Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

7. Current use of prohibited medication as described in Section 5.6.3.

8. Active autoimmune disease that required systemic treatment in the past (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
Note: Subjects who have not required systemic treatment in the past 2 years should discuss their case with medical monitor to determine eligibility.
Note: Subjects with hyper/hypothyroidism, vitiligo, controlled asthma, Type I diabetes, Graves' disease, or Hashimoto's disease are eligible to participate.
Note: Replacement and symptomatic therapies (eg, levothyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) are not considered a form of systemic treatment and are allowed.

9. Known active CNS metastases and/or carcinomatous meningitis.
Note: Subjects with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS edema, and have not required steroids for at least 7 days before the first dose of study drug.

10. Known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 2 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma *in situ* of the cervix, or other noninvasive or indolent malignancy, or cancers from which the subject has been disease-free for > 1 year, after treatment with curative intent.
11. Evidence of active, noninfectious pneumonitis or history of interstitial lung disease.
12. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia not controlled with therapy unless approved by medical monitor.
13. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Subjects with screening QTc interval > 470 milliseconds (corrected by Fridericia) are excluded, unless approved by the medical monitor. In the event that a single QTc is > 470 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 470 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with medical monitor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.
Note: QTc prolongation due to pacemaker may enroll if the JTc is normal or with medical monitor approval.
14. Evidence of HBV or HCV infection or risk of reactivation. Subjects positive for HBV DNA, HCV RNA, HBsAg, or anti-HBc antibody may be included on a case by case basis with approval from medical monitor.
Note: Subjects with no prior history of hepatitis B infection who have been vaccinated against hepatitis B and who have a positive antibody against HBsAg test as the only evidence of prior exposure may participate in the study.
15. Known history of drug-induced liver injury; alcoholic liver disease; nonalcoholic steatohepatitis; primary biliary cirrhosis; or ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver, or portal hypertension.
16. Known history of HIV; HIV 1/2 antibodies.
17. Known allergy or reaction to any component of nivolumab, ipilimumab, or study drug or formulation components.
18. Inability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
19. Women who are pregnant or breastfeeding.
20. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.

4. INVESTIGATIONAL PLAN

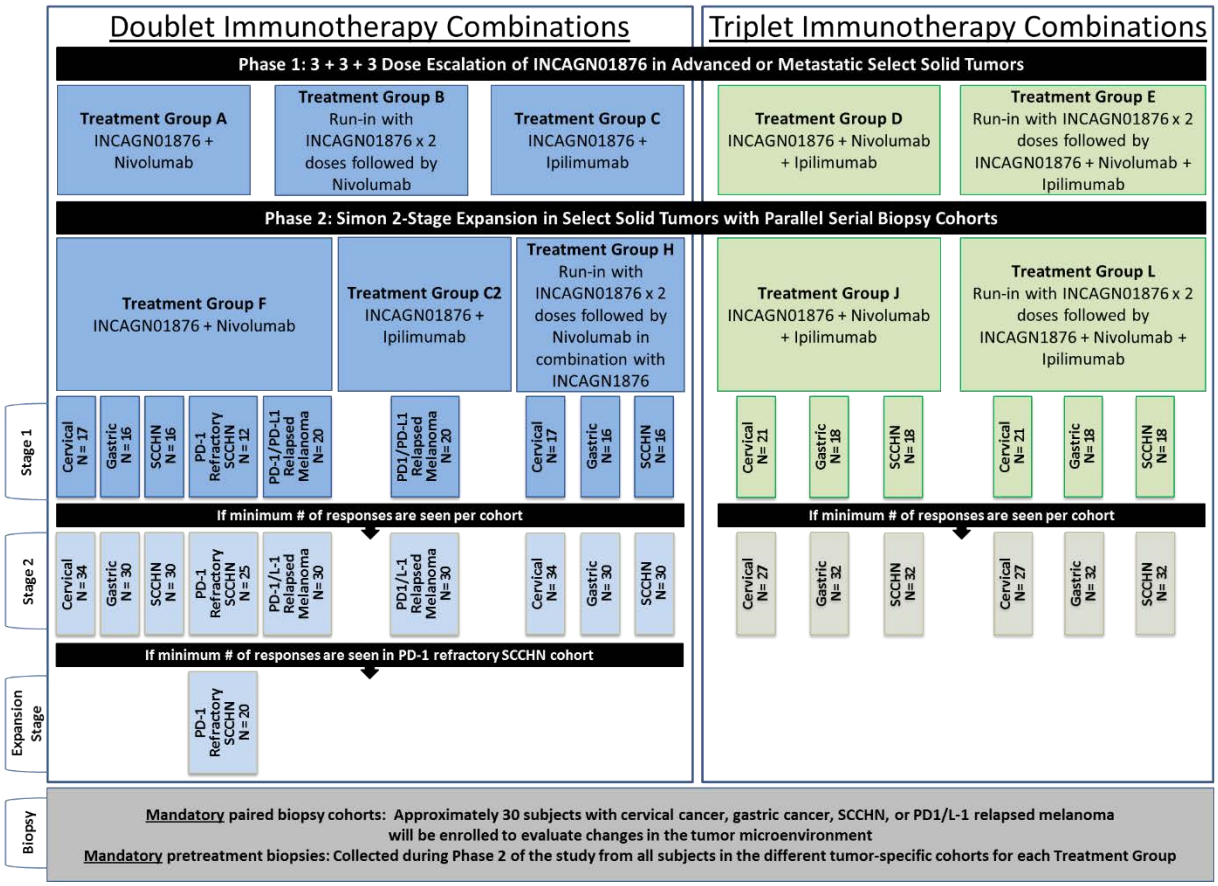
4.1. Overall Study Design

This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of INCAGN01876 when given in combination with immune therapies. Phase 1 will consist of a 3 + 3 + 3 dose escalation to determine the MTD, or PAD, defined as a dose that provides a maximal biochemical effect or an increase in biomarkers of immune activity of INCAGN01876 when given in combination with immune therapies. Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach, esophageal, and GEJ), HCC, melanoma, Merkel cell carcinoma, mesothelioma, MSI-H CRC, NSCLC, ovarian cancer, SCCHN, SCLC, RCC, TNBC, and urothelial carcinoma who have progressed after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or who refuse standard of care will be enrolled in Phase 1. The Phase 2 expansion will further evaluate the safety, tolerability, and efficacy of the recommended dose(s) of INCAGN01876 selected in Phase 1 when given in combination with immune therapies. Subjects with advanced or metastatic cervical cancer, gastric cancer (including stomach, esophageal, and GEJ), SCCHN, PD-1 refractory SCCHN, and PD-1 or PD-L1 relapsed melanoma will be enrolled in Phase 2.

The sponsor may elect to prioritize (or deprioritize) enrollment to specific treatment groups or cohorts based on emerging safety or efficacy data in collaboration with investigational sites. Additionally, alternate dose administration schedules and/or fixed doses of INCAGN01876 (comparable to or less than the highest dose levels determined to be safe or pharmacologically active) may also be explored depending on [redacted] safety results.

See Figure 1 for overall study design.

Figure 1: Overall Study Design



4.1.1. Phase 1 – Dose Escalation

A minimum of 3 evaluable subjects will be enrolled in each treatment group beginning with INCAGN01876 Dose Cohort 1 (0.1 mg/kg; starting dose). A higher starting dose of INCAGN01876 may be used if safety data are available from the monotherapy study (INCAGN 1876-101) but will not exceed 1 dose level below the highest tolerated dose of INCAGN01876 monotherapy. If a higher starting dose is used, the dose will be communicated to investigational sites with an administrative letter.

The first 3 evaluable subjects enrolled within an INCAGN01876 dose cohort will be observed for the specified DLT observation period before the next dose cohort begins enrollment. If 0 DLTs occur in a cohort of 3 evaluable subjects, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 1 of 3 evaluable subjects experience a DLT, that cohort will be expanded to 6 evaluable subjects. If 1 of 6 evaluable subjects experiences a DLT, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 2 of 6 evaluable subjects experience a DLT, that cohort will be expanded to 9 evaluable subjects. If ≥ 2 of 3, 3 of 6, or 3 of 9 evaluable subjects experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD, and the previous dose level will be considered the MTD. If only 3 evaluable subjects were treated at the MTD or PAD, then a minimum of 3 additional evaluable subjects will be enrolled before this dose is administered in Phase 2 of the study.

Additional subjects will be enrolled in a dose cohort to achieve the minimum of 3 evaluable subjects. Depending on treatment group, a subject must receive at least 2 doses of the cohort-specified dose of INCAGN01876, 2 doses of nivolumab, and 1 dose of ipilimumab, or must have had a DLT during the DLT observation period, to be considered evaluable. Subjects who dropout for reasons other than a DLT (eg, events clearly associated with the underlying disease, disease progression, concomitant medication, or comorbidity), during the DLT observation period will result in the subject being nonevaluable and the subject being replaced. The doses of INCAGN01876 to be evaluated in each treatment group are summarized in Table 2.

Table 2: INCAGN01876 Dose Cohorts

Dose Cohort	Dose of INCAGN01876
-1	0.03 mg/kg
1 (Starting Dose)	**0.1 mg/kg[a]**
2	0.3 mg/kg
3	1.0 mg/kg
4	3.0 mg/kg
5	5.0 mg/kg
6	10.0 mg/kg

[a] A higher starting dose of INCAGN01876 may be used if safety data is available from the monotherapy study (INCAGN 1876-101) but will not exceed 1 dose level below the highest tolerated dose of INCAGN01876 monotherapy. If a higher starting dose is used, the dose will be communicated to investigational sites with an administrative letter.

4.1.1.1. Doublet Immune Therapy Combinations

Phase 1 will begin with 3 doublet treatment groups, as outlined in Table 3, which will be explored in parallel.

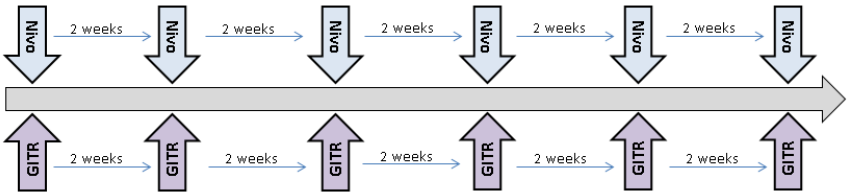
Table 3: Doublet Immune Therapy Treatment Groups

Treatment Group A	**INCAGN01876 Concurrent Dosing**	**Nivolumab**	**DLT Observation Period**
	See INCAGN01876 dose cohorts (Table 2) Q2W	240 mg Q2W	28 days
Treatment Group B	**INCAGN01876 Sequenced Dosing**	**Nivolumab**	**DLT Observation Period**
	See INCAGN01876 dose cohorts (Table 2) Run-in with INCAGN01876 Q2W for 2 doses	240 mg Q2W starting at Cycle 3	28 days from the first nivolumab dose administered at Cycle 3
Treatment Group C	**INCAGN01876 Concurrent Dosing**	**Ipilimumab**	**DLT Observation Period**
	See INCAGN01876 dose cohorts (Table 2) Q2W	1 mg/kg Q6W	28 days

4.1.1.1.1. Treatment Group A (INCAGN01876 + Nivolumab)

Treatment Group A will treat subjects with INCAGN01876 at the assigned dose level administered IV Q2W in combination with 240 mg of nivolumab administered IV Q2W (see Figure 2). **There will be a waiting period of 48 hours between dose administration of the first subject and second subject of each dosing cohort.** The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table 2 until the MTD or PAD of INCAGN01876 in combination with nivolumab is determined.

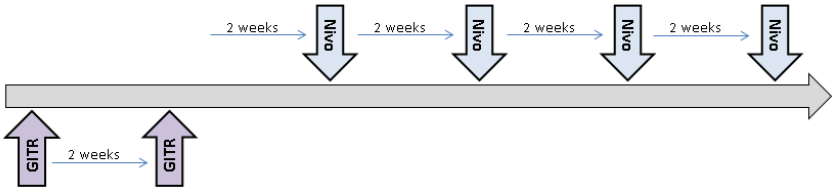
Figure 2: Dosing Figure for Treatment Group A (INCAGN01876 + Nivolumab)



4.1.1.1.2. Treatment Group B (INCAGN01876 Sequenced Dosing + Nivolumab)

Treatment Group B will treat subjects with INCAGN01876 at the assigned dose level administered IV Q2W for a total of 2 doses followed by 240 mg of nivolumab administered IV Q2W starting at Cycle 3 (see Figure 3). Alternate dose administration schedules may also be explored depending on [redacted] safety results. The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days starting after the first dose of nivolumab has been administered before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table 2 until the MTD or PAD of INCAGN01876 in combination with nivolumab sequenced dosing is determined.

Figure 3: Dosing Figure for Treatment Group B (INCAGN01876 Sequenced Dosing + Nivolumab)

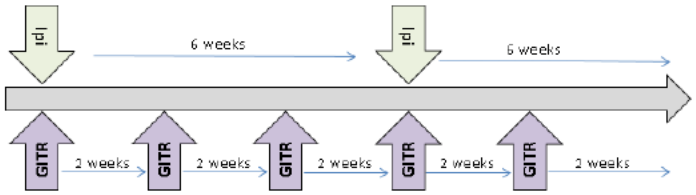


4.1.1.1.3. Treatment Group C (INCAGN01876 + Ipilimumab)

Treatment Group C will treat subjects with INCAGN01876 at the assigned dose level administered IV Q2W in combination with 1 mg/kg of ipilimumab administered IV Q6W (see Figure 4). **There will be a waiting period of 48 hours between dose administration of the first subject and second subject of each dosing cohort.** The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table 2 until the MTD or PAD of INCAGN01876 in combination with ipilimumab is determined.

At the sponsor's discretion, once the MTD or PAD of INCAGN01876 has been established with ipilimumab at 1 mg/kg Q6W, a higher dose of ipilimumab at 3 mg/kg Q6W and/or 3 mg/kg Q3W for 4 doses may be tested. If the MTD or PAD of INCAGN01876 in combination with higher doses of ipilimumab is not tolerated, dose de-escalation of INCAGN01876 will proceed as outlined in Table 2 until the MTD or PAD of INCAGN01876 is determined.

Figure 4: Dosing Figure for Treatment Group C (INCAGN01876 + Ipilimumab)



4.1.1.2. Triplet Immune Therapy Combinations

Dose escalation of the triplet immune therapy combinations will begin enrolling once all of the applicable doublet combinations have cleared 3 INCAGN01876 dose levels (see Table 2) or the MTD or PAD of INCAGN01876 has been determined (whichever occurs first). The starting dose of INCAGN01876 will be 2 dose levels below the last dose cohort deemed safe in the doublet combination. For example, if 3 mg/kg of INCAGN01876 is safe in the doublet combinations with both nivolumab and ipilimumab, then the starting dose in the triplet will be 0.3 mg/kg. If the MTD of INCAGN01876 is 1 mg/kg in the doublet combinations, then the starting dose of INCAGN01876 for the triplet immune therapy combination will be 0.1 mg/kg. If there are different MTDs of INCAGN01876 with nivolumab and ipilimumab, then the starting dose of the triplet will be 2 dose levels below the lowest MTD in the doublet. The triplet immune therapy combinations will be explored in parallel as outlined in Table 4.

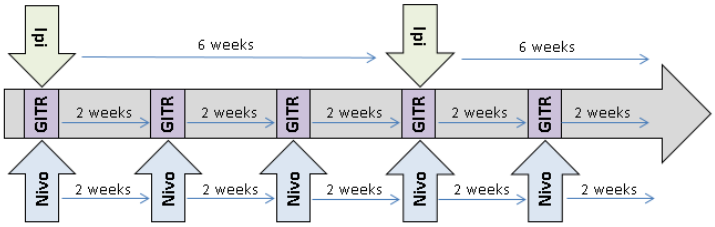
Table 4: Triplet Immune Therapy Combinations

Treatment Group D	**INCAGN01876 Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**DLT Observation Period**
	See INCAGN01876 dose cohorts (Table 2) Q2W	3 mg/kg Q2W	1 mg/kg Q6W	28 days
Treatment Group E	**INCAGN01876 Sequenced Followed by Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**DLT Observation Period**
	See INCAGN01876 dose cohorts (Table 2) Q2W Run-in with INCAGN01876 for 2 doses followed by INCAGN01876 Q2W	3 mg/kg Q2W starting at Cycle 3	1 mg/kg Q6W starting at Cycle 3	28 days from the first nivolumab/ipilimumab dose at Cycle 3

4.1.1.2.1. Treatment Group D (INCAGN01876 + Nivolumab + Ipilimumab)

Treatment Group D will treat subjects with INCAGN01876 at the assigned dose level administered IV Q2W in combination with 3 mg/kg of nivolumab administered IV Q2W and 1 mg/kg of ipilimumab administered IV Q6W (see Figure 5). **There will be a waiting period of 48 hours between dose administration of the first subject and second subject of each dosing cohort.** The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table 2 until the MTD or PAD of INCAGN01876 in combination with nivolumab and ipilimumab is determined; however, the dose of INCAGN01876 in the triplet combination will not exceed the lowest MTD of INCAGN01876 established in the applicable doublet combinations. For example, if the MTD of INCAGN01876 in combination with nivolumab is 5 mg/kg and the MTD of INCAGN01876 in combination with ipilimumab is 3 mg/kg, then the dose of INCAGN01876 would not exceed 3 mg/kg.

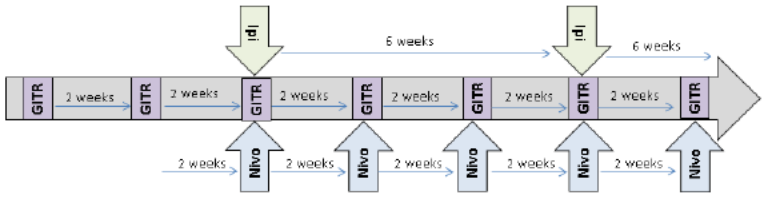
Figure 5: Dosing Figure for Treatment Group D (INCAGN01876 + Nivolumab + Ipilimumab)



4.1.1.2.2. Treatment Group E (INCAGN01876 Sequenced Followed by Concurrent Dosing + Nivolumab + Ipilimumab)

Treatment Group E will treat subjects with INCAGN01876 at the assigned dose level administered IV Q2W for 2 doses followed by INCAGN01876 at the assigned dose level Q2W in combination with 3 mg/kg of nivolumab administered IV Q2W, and 1 mg/kg of ipilimumab administered IV Q6W (see Figure 6). Alternate dose administration schedules may also be explored depending on [redacted] safety results. The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days starting after the first dose of nivolumab and ipilimumab has been administered before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table 2 until the MTD or PAD of INCAGN01876 in combination with nivolumab and ipilimumab is determined; however, the dose of INCAGN01876 in the triplet combination will not exceed the lowest MTD of INCAGN01876 established in the applicable doublet combinations. For example, if the MTD of INCAGN01876 in combination with nivolumab is 5 mg/kg and the MTD of INCAGN01876 in combination with ipilimumab is 3 mg/kg, then the dose of INCAGN01876 would not exceed 3 mg/kg.

Figure 6: Dosing Figure for Treatment Group E (INCAGN01876 Sequenced Followed by Concurrent Dosing + Nivolumab + Ipilimumab)



4.1.2. Phase 2 – Dose Expansion

Phase 2 of the study will further evaluate the safety, tolerability, efficacy, [redacted] and pharmacologic activity of the immune therapy combinations in subjects with advanced or metastatic cervical cancer, gastric cancer (including stomach, esophageal, and GEJ), SCCHN, PD-1 refractory SCCHN, and PD-1 or PD-L1 relapsed melanoma. Additional tumor-specific cohorts may be added, by protocol amendment, based on emerging data. Alternate dose administration schedules and/or fixed doses of INCAGN01876 (comparable to or less than the highest dose levels determined to be safe or pharmacologically active) may also be explored depending on [redacted] safety results.

[redacted]

The Phase 2 expansion treatment groups and tumor-specific cohorts for each treatment group are outlined in Table 5. A Simon 2-stage design will be used for the cervical cancer, gastric cancer, SCCHN, and PD-1/PD-L1 relapsed melanoma cohorts in each treatment group with a stopping rule to allow for early termination of a particular cohort at the end of Stage 1 if there are insufficient responses observed (Simon 1989). The approximate number of subjects for Stage 1 and Stage 2 for the cervical cancer, gastric cancer, SCCHN, and PD-1/PD-L1 relapsed melanoma cohorts in each treatment group is described in Table 19 and Figure 1. For the PD-1 refractory SCCHN cohort, a Simon 2-stage design with an expansion stage will be used, with stopping rules to allow for early termination if there is an insufficient number of responses observed at the end of Stage 1or Stage 2. The approximate number of subjects for Stage 1, Stage 2, and the Expansion Stage for the PD-1 refractory SCCHN cohort in Treatment Group F is described in Table 20 and Figure 1. Enrollment in Phase 2 will begin when the MTD or PAD of INCAGN01876 for a given treatment group in Phase 1 has been determined.

Table 5: Phase 2 Expansion Treatment Groups

Doublet Expansion Treatment Groups			
Treatment Group C2	**INCAGN01876 Concurrent Dosing**	**Ipilimumab**	**Tumor Cohorts**
	RP2D of INCAGN01876 Q2W	1 mg/kg Q6W	Cohort 1 – PD-1/PD-L1 relapsed melanoma [redacted]
Treatment Group F	**INCAGN01876 Concurrent Dosing**	**Nivolumab**	**Tumor Cohorts**
	RP2D of INCAGN01876 Q2W	240 mg Q2W	Cohort 1 – Cervical Cohort 2 – Gastric Cohort 3 – SCCHN Cohort 4- PD-1/PD-L1 relapsed melanoma [redacted] Cohort 6 – PD-1 refractory SCCHN
Treatment Group H	**INCAGN01876 Sequenced Followed by Concurrent Dosing**	**Nivolumab**	**Tumor Cohorts**
	RP2D of INCAGN01876 run-in Q2W for 2 doses followed by INCAGN01876 Q2W	240 mg Q2W starting at Cycle 3 in combination with INCAGN01876 Q2W	Cohort 1 –Cervical Cohort 2 – Gastric Cohort 3 – SCCHN [redacted]

Triplet Expansion Treatment Groups				
Treatment Group J	**INCAGN01876 Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**Tumor Cohorts**
	RP2D of INCAGN01876 Q2W	3 mg/kg Q2W	1 mg/kg Q6W	Cohort 1 – Cervical Cohort 2 – Gastric Cohort 3 – SCCHN [redacted]
Treatment Group L	**INCAGN01876 Sequenced Followed by Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**Tumor Cohorts**
	RP2D of INCAGN01876 run-in Q2W for 2 doses followed by INCAGN01876 Q2W	3 mg/kg Q2W starting at Cycle 3	1 mg/kg Q6W starting at Cycle 3	Cohort 1 – Cervical Cohort 2 – Gastric Cohort 3 – SCCHN [redacted]

In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of Grade 3 or higher INCAGN01876-related AEs occurs in > 40% of subjects in a particular treatment group after 6 subjects have been enrolled, then further enrollment in that treatment group will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action (eg, lower the dose of INCAGN01876, change dose frequency, etc). If a treatment group is discontinued due to toxicity, it may be re-initiated at a previously tested lower dose level and/or alternate dosing schedule. All AEs, regardless of the time of occurrence on study, may be considered for DLT determination purposes.

4.2. Measures Taken to Avoid Bias

This is an open-label study. Assessment of safety using CTCAE v4.03 and efficacy using RECIST v1.1 and mRECIST v1.1 are objective measurements, and only comparisons to pretreatment conditions will be made.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Approximately 384 to 1039 subjects may be enrolled as follows:

- Phase 1 Dose Escalation – Approximately 90 to 270 evaluable subjects.
  Note: The minimum number of subjects assumes that the starting dose is 0.1 mg/kg; however, fewer subjects would be enrolled if a higher starting dose is used based on available safety data from the monotherapy study INCAGN 1876-101.
  Note: The maximum number of subjects assumes that DLTs are observed in all dose cohorts to a maximum of 9 subjects per cohort across all treatment groups.
- Phase 2 Stage 1 – Approximately 264 evaluable subjects.
- [redacted]
- Phase 2 Stage 2 – Approximately 455 evaluable subjects.
- Phase 2 Expansion Stage (PD-1 refractory SCCHN cohort only) – Approximately 20 evaluable subjects
  Note: Assumes that all treatment groups and all tumor types proceed to Stage 2 and Expansion Stage (for PD-1 refractory SCCHN cohort only).

4.3.2. Replacement of Subjects

Subjects may be replaced for any of the following reasons:

- In Phase 1, any subject who withdraws from treatment before the completion of the DLT observation period for any reason other than a DLT (ie, is not evaluable for DLTs; see Section 5.4.2), may be replaced to ensure a minimum number of evaluable subjects.
- [redacted].
- Subjects who do not meet the eligibility requirements of the study may be replaced.

Subjects who meet any of the criteria for replacement may remain on study for evaluation as outlined in Section 9.1 and Section 9.2.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Subjects may continue to receive study treatment as long as they are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal (see Section 5.5), or for

up to 24 months from the first dose of study treatment, whichever occurs first. If the subject discontinues study treatment, the treatment period will end and the subject will enter the follow-up period (see Section 6.4). Study participation, including post-treatment follow-up is expected to average approximately 12 to 18 months per individual subject.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have discontinued treatment and the last follow-up visit has been performed.

If there are ≤ 5 subjects on study for more than 6 months, a database lock of the study may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study treatment and be seen by the investigator per usual standard of care for this population. The investigator will be expected to monitor for and report any AEs, SAEs, pregnancies, and deaths as detailed in Section 8 and Section 6.4.3. The remaining subjects are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

4.6. 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/IEC 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 review of emerging data. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Each subject will be identified in the study by a subject ID number, which is a combination of the site ID and subject number. Site staff should contact the IRT to obtain the subject ID number and confirm a slot is available during prescreening. This subject ID number will be maintained throughout the study and will not be reassigned. Subjects who fail screening and are repeating the screening process due to a change in eligibility status will be assigned a new subject ID number. The site staff will contact the IRT to enroll the subject and obtain the study drug and treatment group assignment. All subsequent cycles will follow this process. The IRT will also be contacted for ordering study drug supplies and when subjects are discontinued from treatment. Full details will be provided in the IRT manual.

5.1.2. Randomization and Blinding

This is an open-label nonrandomized study; therefore, randomization and blinding do not apply.

5.2. Study Drugs

5.2.1. INCAGN01876

5.2.1.1. Description and Administration

The study drug (INCAGN01876) is supplied as a sterile, single-use solution for injection, in a 10 mL glass vial. Each vial contains 50 mg of INCAGN01876 in 5 mL at a concentration of 10 mg/mL in [redacted], and pH [redacted] The infusion site should not be used for blood sampling.

Study drug will be diluted in [redacted] or acceptable admixture as outlined in the Pharmacy Manual and will be administered by qualified site personnel as an IV infusion over a 30-minute (-5/+10 minutes) period on Day 1 of each cycle when INCAGN01876 is scheduled to be given. On days when INCAGN01876 will be administered along with other agents administered by infusion, INCAGN01876 will be administered first, followed by a 30-minute wait before administration of the subsequent immune therapy/therapies.

In Phase 1, subjects will be administered study drug, according to cohort enrollment (see Table 2), Q2W (14-day cycles), in combination with immune therapies. In Phase 2, subjects will be administered study drug at the recommended dose Q2W (14-day cycles), in combination with immune therapies. In Treatment Group B, INCAGN01876 is only administered on Day 1 of Cycles 1 and 2.

Subjects will continue to receive INCAGN01876 as long as they are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal (see Section 5.5), or for up to 24 months from the first dose of study treatment, whichever occurs first.

5.2.1.2. Supply, Packaging, and Labeling

Study drug will be supplied as a sterile, single-use solution for injection in 10 mL glass vials. Study drug will be packaged as open-labelled supplies; each vial will be labelled and placed in a carton. The Pharmacy Manual contains additional information regarding supply, packaging, and labeling of study drug.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study drug in accordance with the Protocol and any applicable laws and regulations.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

5.2.1.3. INCAGN01876 Storage

Study drug must be stored refrigerated (2°C-8°C) and protected from light, in a secure, limited access location. Receipt and dispensing of study drug must be recorded by an authorized person at the study site. Study drug may not be used for any purpose other than that stated in the Protocol. The Pharmacy Manual contains additional information regarding storage of study drug.

5.2.2. Standard Immune Therapies

5.2.2.1. Nivolumab

Nivolumab will be administered IV per the package insert or institutional guidelines at the site, at a dose that is dependent on the assigned treatment group as follows:

- Doublet Treatment Groups A, B, F, and H: 240 mg on Day 1 of every 2-week (ie, 14-day) cycle.
- Triplet Treatment Groups D, E, J, and L: 3 mg/kg on Day 1 of every 2-week (ie, 14-day) cycle.
- Concurrent dosing Treatment Groups A, D, F, and J: Nivolumab dosing will begin on Cycle 1 Day 1.
- Sequenced dosing Treatment Groups B, E, H, and L: Nivolumab dosing will begin on Cycle 3 Day 1.

Nivolumab will be administered at least 30 minutes after the infusion of INCAGN01876 (when applicable), and subjects will continue to receive nivolumab as long as the subject is deriving benefit and has not met any of the Protocol-defined conditions for treatment withdrawal (see Section 5.5), or for up to 24 months from the first dose of study treatment, whichever occurs first.

Nivolumab is commercially available. Investigators are responsible for ensuring that subjects receive commercially available supplies of nivolumab for the entire duration of study participation. Incyte may provide certain standard of care medications such as nivolumab where required by applicable law or specific regulation or under other circumstances when subjects may not otherwise have access to them. Nivolumab must be used in accordance with the storage conditions and shelf life in the manufacturer's approved label.

5.2.2.2. Ipilimumab

Ipilimumab will be administered IV per the package insert or institutional guidelines at the site, at a dose that is dependent on the assigned treatment group as follows:

- Doublet Treatment Group C and C2 (Phase 2 Expansion) and Triplet Treatment Groups D, E, J, and L: 1 mg/kg on Day 1 of every 6-week (eg, 42-day) cycle.
- Concurrent dosing Treatment Groups C and C2 (Phase 2 Expansion), D, and J: Ipilimumab dosing will begin on Cycle 1 Day 1.
- Sequenced dosing Treatment Groups E and L: Ipilimumab dosing will begin on Cycle 3 Day 1.

Ipilimumab will be administered at least 30 minutes after the infusion of INCAGN01876 (when administered on the same day). Ipilimumab will always be administered after INCAGN0876 and nivolumab. Subjects will continue to receive ipilimumab as long as the subject is deriving benefit and has not met any of the Protocol-defined conditions for treatment withdrawal (see Section 5.5), or for up to 24 months from the first dose of study treatment, whichever occurs first.

At the sponsor's discretion, once the MTD or PAD of INCAGN01876 has been established with ipilimumab at 1 mg/kg Q6W, a higher dose of ipilimumab at 3 mg/kg Q6W and/or 3 mg/kg Q3W for 4 doses may be tested.

Ipilimumab is commercially available. Investigators are responsible for ensuring that subjects receive commercially available supplies of ipilimumab for the entire duration of study participation. Incyte may provide certain standard of care medications such as ipilimumab where required by applicable law or specific regulation or under other circumstances when subjects may not otherwise have access to them. Ipilimumab must be used in accordance with the storage conditions and shelf life in the manufacturer's approved label.

5.3. Treatment Compliance

5.3.1. Treatment Compliance of INCAGN01876, Nivolumab, and Ipilimumab

INCAGN01876, nivolumab, and ipilimumab are administered as an IV infusion by site personnel. Receipt of infusions will be documented by the site staff and monitored by the sponsor/designee.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Selections to the study drug (INCAGN01876) are planned for dose-escalation cohorts (see Section 4.1.1). Dose interruptions of study drug may also occur for individual study subjects. The identification of DLTs will define the doses used in planned cohorts (see Section 5.4.2). Further, the occurrence of DLTs and other toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects. Intrasubject dose escalation will not be permitted.

No dose reductions of INCAGN01876 are allowed for the management of toxicities of individual subjects. Doses of INCAGN01876 may be delayed for toxicity management (see Section 5.4.6). [redacted] In the event of any significant treatment related adverse events, holding of the therapy or discontinuation as per Table 7 would be advised.

No dose reductions of nivolumab or ipilimumab are allowed for the management of toxicities of individual subjects. Doses of nivolumab and ipilimumab may be delayed for toxicity management (see Section 5.4.6). Nivolumab and ipilimumab are approved therapies and have specific subject safety management guidelines within their package insert; the treating investigator should refer to and follow the labeled guidance for both nivolumab and ipilimumab.

5.4.2. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose

The evaluation period for DLTs will begin on Cycle 1 Day 1 and will continue up to and including study Day 28 for subjects in Treatment Groups A, C, D, F, and J. In the sequenced dosing Treatment Groups B, E, H, and L, the evaluation period for DLTs will begin on Cycle 3 Day 1 (first administration of nivolumab or nivolumab/ipilimumab) and will continue up for 28 days, up to and including study Day 56. All DLTs will be assessed by the investigator using CTCAE v4.03 criteria. A DLT will be defined as the occurrence of any toxicity in Table 6, with the exception of events clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity.

Decisions for dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD of INCAGN01876 will be made based on events that are observed during the DLT evaluation period. A lower MTD may subsequently be determined based on relevant toxicities that become evident after the end of the DLT evaluation period.

Table 6: Definition of Dose-Limiting Toxicity

Nonhematologic toxicity
• Any ≥ Grade 3 nonhematologic toxicity **EXCEPT** the following: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with supportive care within 48 hours. – Changes in cholesterol and triglycerides. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Asymptomatic changes in amylase and lipase. – Single or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions). – Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids, and that resolves to Grade 1 within 14 days.
Hematologic toxicity
• Grade 3 thrombocytopenia with clinically significant bleeding (ie, requires hospitalization, transfusion of blood products, or other urgent medical intervention). • Grade 4 thrombocytopenia. • ≥ Grade 3 febrile neutropenia (absolute neutrophil count < 1.0×10^9/L and fever > 101°F/38.3°C). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 3 days after interrupting study treatment. • Grade 4 anemia not explained by underlying disease or some other concomitant disorder.
Immune-related toxicity[a]
• ≥ Grade 2 ocular irAEs will be considered a DLT. • Grade 3 irAEs that do not improve to baseline or at least Grade 1 in < 5 days with appropriate care or with corticosteroid therapy will be considered a DLT. • Grade 4 irAEs will be considered a DLT regardless of duration.
General
• Inability to receive the planned number of doses within the 28-day DLT period due to toxicity, regardless of grade, will be considered a DLT.
MTD
• In Phase 1 of the study, the MTD will be defined as 1 dose level below that at which ≥ one-third of subjects in a particular cohort have DLTs. • In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of Grade 3 or higher INCAGN01876-related AEs occurs in > 40% of subjects in a particular treatment group after 6 subjects have been enrolled, then further enrollment in that treatment group will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action (eg, lower the dose of INCAGN01876, change dose frequency, etc). If a treatment group is discontinued due to toxicity, it may be re-initiated at a previously tested lower dose level and/or alternate dosing schedule. All AEs, regardless of the time of occurrence on study, may be considered for DLT determination purposes.

[a] Immune-related AEs are a diagnosis of exclusion, after alternative etiologies have been ruled out.

5.4.3. Management of Dose-Limiting Toxicities or Other Urgent Situations

In all cases, investigators may employ any measures or concomitant medications, after discussion with the medical monitor (whenever possible), necessary to optimally treat the subject.

5.4.4. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or appears to have stabilized for a minimum of 4 weeks (eg, 28 days). During follow-up, subjects should be seen as often as medically indicated to assure safety.

5.4.5. Procedures for Cohort Review and Dose Escalation

Telephone conferences will be scheduled by the sponsor with study investigators in order to review cohort-specific data and overall safety data, to agree on dose escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

5.4.6. Criteria and Procedures for Dose Interruptions of Study Drug

Treatment with INCAGN01876 in combination with standard immune therapies may be delayed up to 4 weeks (28 days) to allow for resolution of toxicity. **If an interruption or discontinuation is necessary, all study treatments should be interrupted or discontinued.** Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the medical monitor to discuss the case of any subject whose treatment has been delayed for more than 4 weeks (28 days) before restarting treatment.

Instructions for INCAGN01876 dose interruptions are outlined in Table 7. Individual decisions regarding dose interruptions of study drug should be made using clinical judgment and in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study drug and the subject'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.

Dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks (28 days) of the scheduled interruption, unless otherwise discussed with the medical monitor. The reason for interruption should be documented in the subject's study record.

Table 7: Criteria for Interruption and Restarting of Study Treatment

CTCAE Grade/Severity	Hold Treatment (Y/N)	Timing for Restarting Treatment	Dose Level for Restarting INCAGN01876	Dose Level for Restarting Immune Therapies	Treatment Discontinuation
1-2 (Mild-Moderate)	No	Continue treatment at the discretion of the investigator.	N/A	NA	N/A
3 (Severe)	Yes	Toxicity resolves to Grade 0-1.	Restart same dose	Restart same dose	Toxicity does not resolve within 4 weeks (28 days) of last dose, except by approval of the medical monitor. OR Second occurrence of previously resolved Grade 3 AE.
4 (Life-threatening)	Yes	Permanent discontinuation, except by approval of the medical monitor. If continuing, toxicity must resolve to Grade 0-1.	Permanent discontinuation, except by approval of the medical monitor. If continuing, restart same dose.	Permanent discontinuation, except by approval of the medical monitor. If continuing, restart same dose.	Permanent discontinuation for any severe or life-threatening event, except by approval of the medical monitor.

5.4.7. Management of Immune-Related Adverse Events

INCAGN01876, nivolumab, and ipilimumab are considered immune modulators, and it is possible that irAEs (both nonserious and serious) may occur. Adverse events of a potential immunologic etiology or irAEs may be defined as an AE consistent with an immune phenomenon associated with drug exposure ***after all other etiologies have been eliminated***. Immune-related AEs may be expected based on the nature of the study treatment, their mechanism of action, and reported experience with these and other immunotherapies. 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. Suspected irAEs should be discussed with the medical monitor when possible.

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of drug-related AEs with potential immunologic etiology are outlined in Table 8. Detailed supportive care guidelines for specific irAEs can be in found in Appendix B. Nivolumab and ipilimumab are approved therapies and have specific irAE management guidelines within their package insert; the treating investigator may use labeled guidance or institutional guidelines for the management of irAEs if preferred. For each AE, attempts should be made to rule out other causes, including but not limited to metastatic disease or bacterial or viral infection, which might require specific supportive care.

Table 8: Supportive Care Guidelines for Immune-Related Adverse Events

CTCAE Grade/Severity	Supportive Care[a]
Grade 1 (mild)	• Monitor symptoms and provide symptomatic treatment.
Grade 2 (moderate)	• Monitor symptoms and provide symptomatic treatment. • Consider consultation with specialists as necessary. • Consider systemic corticosteroids per institutional standard of care.
Grade 3-4 (severe–life-threatening)	• Monitor symptoms and provide symptomatic treatment. • Consider consultation with specialists as necessary. • Administer corticosteroids per institutional standard of care. • More potent immunosuppressive therapies should be considered for events not responding to systemic steroids after discussing with the medical monitor. • Study treatment may be permanently discontinued for clinically significant or severe irAEs, or for events where steroid course cannot be tapered below 7.5 mg/day prednisone or equivalent to manage symptoms.

[a] Detailed supportive care guidelines for specific irAEs can be found in Appendix B.

5.4.8. Management of Infusion Reactions

Table 9 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of study treatment. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Nivolumab and ipilimumab are approved therapies and may have specific infusion reaction management guidelines within their package insert; the treating investigator may use labeled guidance or institutional guidelines for the management of infusion reactions if preferred.

Table 9: Infusion Reaction Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dose Administration
Grade 1: Mild reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None.
Grade 2: Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dose administration will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment.	Subject may be premedicated 1.5 h (± 30 min) before infusion with the following: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).
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. Additional appropriate medical therapy may include but is not limited to the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further study treatment.	No subsequent dose.

Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

5.4.9. Criteria for Permanent Discontinuation of Study Drug

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

- Grade 4 or life-threatening AEs, except with approval from the medical monitor.
- ≥ Grade 2 ocular irAE.
- Occurrence of an AE that is related to treatment, in the judgment of the investigator or the medical monitor, and compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Persistent AE requiring a delay of treatment for more than 4 weeks (28 days) unless a greater delay has been approved by the sponsor.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

A subject may choose to withdraw from the study treatment at any time or be withdrawn from the study treatment by the investigator or sponsor, if the subject is noncompliant with the study requirements. If permanent discontinuation of any of the study treatments is necessary (eg, INCAGN01876, nivolumab, ipilimumab), all study treatments, will be discontinued. If a subject is withdrawn from study treatment, then every reasonable effort should be made to determine the reason for withdrawal, and this information should be recorded in the eCRF.

Subjects **must** be withdrawn from **study treatment** for the following reasons:

- The subject becomes pregnant.
- Consent is withdrawn. Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled.

  Note: Consent withdrawn means that the subject can no longer be followed and no additional data can be collected. Subjects may choose to discontinue study treatment and remain in the study to be followed for progression and survival.

  Note: As of Protocol Amendment 5, subjects who withdraw consent will no longer be followed for progression and survival beyond the last safety follow-up visit.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity (see Section 5.4.9). Subjects with unacceptable toxicities must be withdrawn from study treatment but will continue in the follow-up phase of the study (see Section 6.4).
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- Confirmed radiographic progression of disease per RECIST v1.1 (see Section 7.7.1). A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved (see Section 7.7.1).

  ***Note*:** For unconfirmed progression see Section 7.7.1.

- If, during the course of the study, a subject is found not to have met eligibility criteria (see Section 3), the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is lost-to-follow-up or noncompliant with study procedures or study treatment in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study treatment, the subject will be withdrawn, and the EOT visit should be conducted. Reasonable efforts should be made to have the subject return for all applicable follow-up visits (safety and efficacy; see Section 6.4). The last date of the last dose of study treatment and the reason for subject withdrawal will be recorded in the eCRF.

If a subject is withdrawn from the study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal from treatment must be documented in the subject's medical record and in the eCRF.

  Note: The reason for withdrawal from treatment may be different than the reason for withdrawal from study. For example, subjects can discontinue treatment for disease progression or toxicity, but remain in the study for safety and survival follow-up.

  Note: As of Protocol Amendment 5, subjects who discontinue treatment will no longer be followed for progression and survival beyond the last safety follow-up visit.

- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the eCRF and IRT.
- Subjects 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, or until the subject begins new anticancer therapy, whichever is longest.
- Subjects who discontinue for reasons other than disease progression will continue to be followed for disease status as outlined in Section 6.4.2.

  Note: As of Protocol Amendment 5, subjects who discontinue for reasons other than disease progression will no longer be followed for disease status beyond the last safety follow-up visit.

- All subjects who discontinue study treatment will continue to be followed for OS as outlined in Section 6.4.3.

  Note: As of Protocol Amendment 5, subjects who discontinue study treatment will no longer be followed for survival beyond the last safety follow-up visit.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up, disease assessments, or survival follow-up), then no additional data collection should occur; however, **subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety, efficacy, and survival assessments**.

Note: As of Protocol Amendment 5, subjects who withdraw consent but continue in the follow-up period will be followed for efficacy and survival until the last safety follow-up visit.

5.6. Concomitant Medications

All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 28 days before the first dose of study treatment and 60 days after the last dose of study treatment, or until the subject begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant treatments/procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

5.6.1. Permitted Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug regimen, frequency, route, and date may also be included on the eCRF. ***Note***: The use of bisphosphonates and denosumab are permitted in this study.

5.6.2. Restricted Medications

Systemic glucocorticoids for any purpose other than prophylaxis for contrast allergies for radiographic procedures, or to modulate symptoms or treat an AE of suspected immunologic etiology, are restricted and require medical monitor approval. The use of physiologic corticosteroid replacement therapy may be approved after consultation with the medical monitor.

Note: Inhaled and topical steroids are allowed. A short course of steroids (prednisone or equivalent) ≤ 10 mg/day may be permitted with medical monitor approval.

5.6.3. Prohibited Medications

Medications or vaccinations specifically prohibited in the exclusion criteria (see Section 3.2) are not allowed during the study. If there is a clinical indication for one of these medications or vaccinations 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 subject's primary physician. However, the decision to continue the subject on study treatment requires the mutual agreement of the investigator, the sponsor, and the subject.

Subjects are prohibited from receiving the following therapies during the screening and treatment periods of this study, unless otherwise indicated:

- Any anticancer medications, including chemotherapy or biologic therapy other than study treatment.
- Any immunological-based treatment for any reason from screening through the safety follow-up visit is prohibited.

  Note: Completed adjuvant therapy (eg, vaccines) with medical monitor approval, inhaled or topical steroids, systemic steroids at doses ≤ 10 mg/day prednisone or equivalents, and immune suppressants are allowed for treatment for immune toxicities as described in Section 5.4.7 and Appendix B, or as prophylaxis for contrast allergy for imaging procedures.

  Note: Allergy shots may be permitted after consultation with the medical monitor.
- Investigational agents other than study treatment. Use of such medications from screening through the safety follow-up visit is prohibited.
- Concomitant radiation therapy.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the medical monitor. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- Live vaccines within 30 days before the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid (oral) 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.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Subjects may receive other medications that the investigator deems to be medically necessary. The exclusion criteria describe other medications that are prohibited in this study. There are no prohibited therapies during the post-treatment follow-up period.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of clinical assessments (Table 10), and all laboratory assessments will be performed as indicated in Table 11. Table 12 presents a summary of clinical laboratory analytes to be assessed. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual or applicable procedural documentation.

Table 10: Schedule of Clinical Assessments

Visit Day (Range)		Screening	Treatment[a]				Post-Treatment[b]			
			Cycles 1 and 6		All Other Cycles	Every 8 weeks				
			Day 1	Day 8	Day 1	Disease Status	EOT	Safety Follow-Up Visit 1[c]	Safety Follow-Up Visit 2[c]	Survival Follow-Up[d]
Evaluation/Window	**Protocol Section**	**Day -28 to -1**	**± 3 days[e]**	**± 1 day**	**± 3 days**	**± 7 days**	**± 3 days**	**30 days (+ 7 days)**	**60 days (+ 7 days)**	**Every 12 weeks (± 7 days)**
Administrative procedures										
Informed consent	7.1	X								
Inclusion/exclusion criteria	3.1, 3.2	X	X							
Contact IRT	7.2	X	X		X		X			
Medical and cancer history	7.3.1 7.3.2	X								
Prior/concomitant medications	7.4	X	X	X	X		X	X	X	
Administer INCAGN01876	5.2.1.1		X[f]		X[f]					
Administer nivolumab	5.2.2.1		X[g]		X[g]					
Administer ipilimumab	5.2.2.2		X[h]		X[h]					
Poststudy anticancer therapy status	7.5							X	X	
Survival status	6.4.3									X
Clinical procedures/assessments										
Comprehensive physical examination (including height)	7.6.2.1	X								
Targeted physical assessment	7.6.2.2		X	X[i]	X		X	X	X	
Vital signs and weight	7.6.3	X	X	X[i]	X		X	X	X	
ECOG performance status	7.8.1	X	X	X[i]	X		X	X	X	
Laboratory assessments	7.6.5	X	X	X	X		X	X	X	
12-lead ECG[j]	7.6.4	X				X	X	X		
AE assessment	7.6.1	X	X	X[i]	X		X	X	X	
Efficacy measurements										
Radiologic tumor assessments	7.7	X[k]				X[l]	X[m]	X[n]		

[a] Treatment cycles will be Q2W (14 days ± 3 days). Alternate dose administration schedules and/or fixed doses of INCAGN01876 (comparable to or less than the highest dose levels determined to be safe or pharmacologically active), may also be explored depending on [redacted] safety results.

[b] The mandatory safety follow-up visits should be conducted approximately 30 days and 60 days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first.

[c] As of Protocol Amendment 5, the safety follow-up visits will include AE and concomitant medication assessment only and may be completed remotely (such as by televisit).

[d] As of Protocol Amendment 5, no further survival follow-up assessment will be required beyond the last safety follow-up visit.
[e] Evaluation window only applies to Cycle 6 Day 1.
[f] In Treatment Group B, INCAGN01876 is only administered on Day 1 of Cycles 1 and 2.
[g] In Treatment Groups B, E, H, and L, nivolumab administration begins at Cycle 3 Day 1.
[h] For subjects enrolled into Treatment Groups C and C2 (INCAGN01876 + ipilimumab) and Treatment Groups D and J (INCAGN01876 + nivolumab + ipilimumab), ipilimumab will be administered on Cycle 1 Day 1 and then Day 1 of every 3rd cycle (Cycle 1, Cycle 4, Cycle 7, etc). In Treatment Groups E and L ipilimumab administration begins at Cycle 3 Day 1 and then continues on Day 1 of every third cycle. If higher doses of ipilimumab are tested (eg, 3 mg/kg every 3 weeks [21 days] for 4 doses), then ipilimumab will be administered on Day 1 of each 3-week (21-day) cycle for a total of 4 doses. If the scheduled ipilimumab doses fall on days other than Day 1 of a cycle, the subjects will need to be present in clinic for the infusion, and any standard procedures required by the site should be performed.
[i] Applicable to all subjects at Cycle 1 Day 8. At Cycle 6 Day 8, only required if subject is experiencing AEs > Grade 2.
[j] All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest and should not be performed within 15 minutes after a blood collection. ECGs will be collected at screening and at least every 8 weeks, or as clinically indicated per prescribing instructions for nivolumab, as well as the EOT and first safety follow-up visits.
[k] The initial tumor imaging will be performed within 28 days before the first dose of study treatment. Images of the chest, abdomen, and pelvis are required for all subjects. 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. The same imaging technique should be used for a subject throughout the study. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management.
[l] On-study imaging will be performed at Week 8 and then every 8 weeks (± 7 days) for the first 12 months and then every 12 weeks (± 7 days) thereafter. Imaging should follow calendar days starting with Day 1 of INCAGN01876 treatment and should NOT be adjusted for delays in cycle starts. If imaging shows disease progression, then another imaging assessment should be performed at a minimum of 4 weeks but no later than 6 weeks later to confirm progression per mRECIST.
[m] If scan was obtained within 4 weeks before the date of discontinuation, then a scan at treatment discontinuation (EOT) is not mandatory. For subjects who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be repeated at the time of treatment discontinuation (ie, date of discontinuation ± 4 week window).
[n] For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status every 8 weeks (± 7 days) by radiographic imaging until 1) start of new anticancer therapy, 2) documented disease progression, 3) death, 4) the end of the study, or 5) withdrawal of consent, whichever occurs first.
Note: As of Protocol Amendment 5, no further disease status follow-up assessments will be required beyond the last safety follow-up visit.

Table 11: Schedule of Laboratory Assessments

Visit Day (Range) / Evaluation/Window	Protocol Section	Timing of Assess-ment	Screening Day -28 to -1	Treatment C1 D1	Treatment C1 D8 ± 1 day	Treatment C2 D1 ± 3 days	Treatment C3 D1 ± 3 days	Treatment C4 D1 ± 3 days	Treatment C6 D1 ± 3 days	Treatment C6 D8 ± 3 days	Treatment C7 D1 ± 3 days	Every 4th Cycle (C8, C12) D1 ± 3 days	All Other Cycles D1 ± 3 days	Post-Treatment EOT ± 3 days	Post-Treatment Safety Follow-Up Visit 1 30 days (+ 7 days)	Post-Treatment Safety Follow-Up Visit 2 60 days (+ 7 days)
Local laboratory tests[a]																
Comprehensive serum chemistries[b]	7.6.5	N/A	X[c]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology with differential	7.6.5	N/A	X[c]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation panel[e]	7.6.5	N/A	X[c]													
Urinalysis	7.6.5	N/A	X[c]											X		
Endocrine function tests	7.6.5	N/A	X[c]					X				X		X	X	
Hepatitis B and C	7.6.5.2	N/A	X													
Serum pregnancy test (childbearing females only)[f]	7.6.5.1	N/A	X											X		
Urine pregnancy test (childbearing females only)	7.6.5.1	N/A		X[g]												
[redacted]																

[a] All safety laboratory assessments will be performed locally.
[b] If liver chemistry tests increase in grade from baseline or are ≥ Grade 3, then liver chemistry monitoring should increase to once per week until resolved to baseline or ≤ Grade 1. Liver chemistry does not need to be monitored once per week indefinitely for persistent low grade abnormalities. Appropriate liver chemistry monitoring intervals should be discussed with the medical monitor for these circumstances.
[c] Screening laboratory tests must be performed within 7 days of Cycle 1 Day 1. If 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.
[d] Only required to be performed at Cycle 1 Day 1 if the screening assessment was not performed within 7 days.
[e] Subjects on anticoagulation treatment should have parameters monitored throughout the study as clinically indicated.
[f] A serum pregnancy test will be required for all women of childbearing potential during screening and must be within 72 hours before the first dose of study treatment.
[g] Urine pregnancy tests will be conducted as medically indicated or per country-specific requirements (see Section 7.6.5.1).
[redacted]
[i] Collected only on Cycle 8 Day 1 and Cycle 12 Day 1.
[j] [redacted]

Table 12: Local Laboratory Tests: Required Analytes

<table>
<tr><th>Serum Chemistries</th><th>Hematology</th><th>Urinalysis</th><th>Hepatitis Screening[a]</th><th>Coagulation</th></tr>
<tr><td rowspan="3">Albumin
Alkaline phosphatase
ALT
AST
Bicarbonate or CO_2
Blood urea nitrogen or urea
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein
Uric acid
Amylase
Lipase</td><td rowspan="3">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• White blood cell count

Absolute values must be provided for WBC differential laboratory results:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils</td><td rowspan="3">Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein</td><td>HBsAg
anti-HBc antibody
HBV-DNA
HCV antibody
HCV-RNA</td><td rowspan="2">PT
aPTT
INR</td></tr>
<tr><td>Pregnancy Testing</td></tr>
<tr><td>Female subjects of childbearing potential only require a serum test at screening and EOT.
Pregnancy tests (serum or urine) should be repeated if required by local regulations.</td><td>Endocrine Monitoring
Thyroid-stimulating hormone (TSH)
Free thyroxine (T4)
Total triiodothyronine (T3)/FT3[b]</td></tr>
</table>

[a] No HCV-RNA test is required in case HCV antibody test result is negative. No HBV DNA test is required in case HBsAg and anti-HBc antibody testing are negative.
[b] If considered standard by your region.

6.1. Screening

Screening is the interval between signing the ICF and the day the subject is enrolled in the study (eg, Cycle 1 Day 1). Screening may not exceed 28 days. Informed consent must be obtained before performing any study-specific procedures that are not considered standard of care; however, procedures conducted as part of the subject's routine clinical management obtained before signing of informed consent may be used for screening or baseline purposes with approval of the medical monitor, provided that the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment. 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 enrollment will be used to determine subject eligibility. Additionally, a subject who fails screening may repeat the screening process **1 time** if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection). Treatment should start as soon as possible after the date of enrollment.

6.2. Treatment

The treatment period begins on the day the subject receives the first dose of study treatment (Cycle 1 Day 1) through the point at which the investigator determines that the subject will be permanently discontinued from study treatment, or for up to 24 months from the first dose of study treatment, whichever occurs first. Cycle 1 Day 1 must be no more than 28 days after the subject has signed the ICF and should be within 3 days of enrollment in the study. Subjects will have regularly scheduled study visits as outlined in Table 10 and toxicities will be monitored continuously and will be graded using the NCI CTCAE v4.03 criteria.

6.3. End of Treatment

When the subject permanently discontinues study treatment, 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. The subject should be encouraged to return for the safety and survival follow-up visits.

Note: As of Protocol Amendment 5, subjects who permanently discontinue study treatment will no longer be followed for survival beyond the last safety follow-up visit.

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 days (+ 7 days) and 60 days (+ 7 days) after the last dose of study treatment. Monitoring for the occurrence of new AEs should be continued for at least 60 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. Reasonable efforts should be made to have the subject return for the follow-up visits and report any AEs that may occur during this period. If a subject is scheduled to begin a new anticancer therapy before the end of the 30-day or 60-day safety follow-up period, the safety follow-up visit should be performed before new anticancer therapy is started. Once new anticancer therapy has been initiated, AEs and SAEs will no longer be collected, and the subject will move into the survival follow-up period.

Note: As of Protocol Amendment 5, the safety follow-up visits will include AE and concomitant medication assessment only and may be completed remotely (such as by televisit).

Note: As of Protocol Amendment 5, if a new anticancer therapy has been initiated before the end of the safety follow-up period, no further survival follow-up assessment will be required beyond the last safety follow-up visit.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason **other than** disease progression (eg, toxicity) will move into the disease status follow-up period and should be assessed every 8 weeks (± 7 days), for 12 months. After 12 months, radiologic assessments will be performed every 12 weeks until disease progression is determined. Every effort should be made to collect information regarding disease status until:

- The start of new antineoplastic therapy.
- Disease progression.
- Death.
- The end of the study.
- Withdrawal of consent.

Note: As of Protocol Amendment 5, disease status follow-up will no longer be required beyond the last safety follow-up visit for subjects who discontinue study treatment for a reason other than disease progression. The last disease status follow-up data will be recorded in the eCRF at the time of the last safety follow-up visit. The last study visit will be the last safety follow-up visit.

6.4.3. Survival Follow-Up

Once a subject has received the last dose of study treatment, confirmed disease progression, or starts a new anticancer therapy, the subject moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 12 weeks (+ 7 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Note: As of Protocol Amendment 5, survival follow-up will no longer be required beyond the last safety follow-up visit for subjects who have confirmed disease progression or start a new anticancer therapy. The last survival follow-up data will be recorded in the eCRF at the time of the last safety follow-up visit. The last study visit will be the last safety follow-up visit.

6.5. End of Study

The end of the study will occur when all subjects have completed the last study follow-up visit or have discontinued study treatment and have completed applicable follow-up assessments. Additionally, subjects will be considered as having completed the study if they meet any of the following criteria:

- Subject dies and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained. (**NOTE**: Every effort must be made to obtain the date of death.)
- Consent is withdrawn for any further contact related to this study.
  - Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded in the eCRF.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB or IEC.

6.6. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled timepoints if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, HCV), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations. Per Section 3.1, subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study (Appendix A).

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Additional consent may also be required per local regulatory agencies. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation.

7.2. Interactive Response Technology System Procedure

The site will contact the IRT to obtain a subject identification number when a subject enters the prescreening phase. Upon determining that the subject is eligible for study entry, the IRT will be contacted to obtain the treatment group assignment. Additionally, the IRT will be contacted to update the subject's disposition, disease response, and for study drug resupply. Refer to the IRT manual for detailed instructions.

During Phase 2 of the study, the IRT system will be updated based on the PoS calculations discussed in Section 9.6. Probability of success calculations will be performed based on response data available within the IRT system and treatment groups may be closed to subject assignment if the PoS for a treatment group-tumor type combination is below the futility threshold. Subjects will be assigned sequentially to treatment groups that are open to assignment based on these PoS calculations. Periodically, the sponsor will review the disease response data within the IRT system for consistency with the clinical database and request changes to resolve discrepancies.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and a complete medical and medication history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment **within the last 10 years that are considered to be clinically significant** by the investigator.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history will be collected at screening. Details regarding the subject's malignancy under study including date of diagnosis, initial and current cancer stage, tumor histology, relevant disease characteristics, and prior treatments including systemic, radiation, and surgical procedures will be recorded.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. Any medication received or procedure performed within 28 days before the first dose of study treatment, up to the end of the safety follow-up phase, or until the subject starts a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF. See Section 5.6 for details regarding restricted and prohibited medications.

7.5. Poststudy Anticancer Therapy Status

The investigator or qualified designee will review all new anticancer therapy initiated after the last dose of study treatment. If a subject initiates a new anticancer therapy within 30 to 60 days after the last dose of study treatment, the 30-day or 60-day safety follow-up visit should occur before the first dose of the new anticancer therapy.

Note: As of Protocol Amendment 5, information on new anticancer therapy will no longer be collected beyond the last safety follow-up visit.

7.6. Safety Assessments

Nivolumab and ipilimumab are approved therapies; therefore, the investigator should refer to and follow the safety management guidelines as appropriate within the approved package insert for both compounds.

7.6.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.6.2. 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. Clinically notable abnormalities that are considered clinically significant in the judgement of the investigator are to be reported as AEs.

7.6.2.1. Comprehensive Physical Examination

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

7.6.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation conducted by the investigator or a medically qualified designee. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings.

7.6.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Weight will also be assessed at each study visit. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.6.4. Electrocardiograms

All 12-lead ECGs will be performed at the study site with the subject in a recumbent or semirecumbent position after 5 minutes of rest as outlined in Table 10.

The 12-lead ECG readings will be interpreted by the investigator at the site to be used for immediate subject management. Additional 12-lead ECGs may be performed as clinically indicated, or as per the nivolumab prescribing instructions, to manage subject safety. The decision to include or exclude a subject or withdraw a subject 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 > 470 milliseconds at screening, the subject may enroll if the average QTc for the 3 ECGs is < 470 milliseconds or with approval from the medical monitor. For subjects 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.

7.6.5. Laboratory Assessments

A certified laboratory local to the study site and subject will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. All local laboratory assessments should be performed using standard procedures on the days indicated in Table 11. Table 12 lists the specific laboratory analytes required for each test. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Screening laboratory assessments must be performed within 7 days of Cycle 1 Day 1. If performed more than 7 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study drug administration on Cycle 1 Day 1. Laboratory samples collected on study Day 1 must be performed before study drug administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study drug 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.

7.6.5.1. Pregnancy Testing

A local laboratory serum pregnancy test will be required for all women of childbearing potential during screening and at EOT. The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study drug. Urine pregnancy tests will be performed locally as outlined in Table 11, 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, then the results should be confirmed with a serum pregnancy test.

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

7.6.5.2. Hepatitis Screening Tests

Hepatitis screening assessments will be performed at the screening visit (Table 11) to rule out hepatitis infection; required analytes are shown in Table 12. Generally, hepatitis 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.

7.7. Efficacy Assessments

7.7.1. Modified RECIST v1.1 Assessment Disease

Modified RECIST will be applied by the site as the primary measure for assessment of tumor response and as a basis for Protocol guidelines related to disease status (eg, discontinuation of study therapy). As noted in Section 1.5.4.1, RECIST v1.1 has been adapted to account for the unique tumor responses seen with immunotherapy (Wolchok et al 2009).

If radiologic imaging shows progressive disease, tumor assessment should be repeated at a minimum of 4 weeks, but no later than 6 weeks later to confirm progression, with the option of continuing treatment while awaiting radiologic confirmation of progression. Table 13 provides instructions on how to proceed with treatment based on the subject's clinical status once the initial scan showing radiologic evidence of progression is observed.

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

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

Table 13: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Tumor Imaging	**Treatment**	**Tumor Imaging**	**Treatment**
First radiologic evidence of progression	Repeat imaging 4-6 weeks to confirm progression	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging	Repeat tumor imaging 4-6 weeks to confirm progression per physician discretion only	Discontinue treatment
Repeat scan **confirms** progression	No additional tumor imaging required	Discontinue treatment	No additional tumor imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled tumor imaging assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled tumor imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

As noted above, if disease progression is observed, the study site may elect to continue treatment, repeat imaging at a minimum of 4 weeks, but no later than 6 weeks later, and assess tumor response or confirmed progression per mRECIST.

In determining whether or not the tumor burden has increased or decreased, study site investigators should consider all target lesions as well as nontarget lesions. Subjects who are deemed clinically unstable are not required to have repeat tumor imaging for confirmation. If radiologic progression is confirmed by subsequent scan, then the subject should be discontinued from study treatment. If radiologic progression is not confirmed, then the subject should resume or continue study treatment and have the next tumor imaging according to the Protocol schedule (see Table 10). If progression is not confirmed and the subject continues on treatment, then the next scan that documents disease progression (and is confirmed by a second scan at least 4 weeks, but no later than 6 weeks later) will be considered the date of disease progression.

If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks, but no later than 6 weeks, apart demonstrating progression) per mRECIST, but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered after consultation with the medical monitor. Clinically stable subjects at the confirmatory scan should also have no further increase in the target lesions, no unequivocal increase in nontarget lesions, and no additional new lesions develop (nonworsening disease progression) to continue study treatment.

7.7.1.1. Tumor Imaging

The same imaging technique should be used in a subject throughout the study. The baseline scan must be a contrast 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 uses higher energy and thinner slices, it may be acceptable with medical monitor approval. **Images of the chest, abdomen, and pelvis are required for all subjects.** Additional imaging of anatomical sites (eg, head, neck, brain, etc), should be done as applicable for the cancer under study.

7.7.1.1.1. Tumor Imaging During Screening

Initial tumor imaging must be performed within 28 days before the first dose of study treatment. The site study team must review prestudy images to confirm that the subject has measurable disease per RECIST v1.1. Tumor lesions that are located in a previously irradiated area or in an area subjected to other locoregional therapy should not be selected as target lesions. If a subject only has lesions in an area previously irradiated or subjected to locoregional therapy, then the subject will be allowed to enroll. [redacted]

Computed tomography or MRI scan of the brain will be performed at screening if there are signs or symptoms suggesting that the subject has disease involvement in the CNS. An MRI of the brain will also be required at screening for all subjects with melanoma.

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.

7.7.1.1.2. Tumor Imaging During the Study

The first imaging assessment should be performed 8 weeks after the first dose of INCAGN01876 and then every 8 weeks (56 days ± 7 days), for 12 months and then every 12 weeks thereafter until disease progression is determined. Imaging assessments may be done more frequently if clinically indicated. **Imaging should not be delayed for delays in cycle starts**.

Per mRECIST v1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date 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 disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confirmed at least 4 weeks, but no later than 6 weeks, after the first scan indicating progression in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed, provided that they have met the conditions detailed in Section 7.7.1. A central imaging vendor will not be used in this study.

7.7.1.1.3. Imaging During Follow-Up

If the subject discontinues study treatment for reasons other than disease progression, imaging assessments should continue at the Protocol-specified interval until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

Note: As of Protocol Amendment 5, follow-up imaging to monitor disease status is no longer required beyond the last safety follow-up visit (see Section 6.4.2) for subjects who discontinue study treatment for reasons other than disease progression.

7.8. Performance and Quality-of-Life Assessments

7.8.1. Eastern Cooperative Oncology Group Performance Status

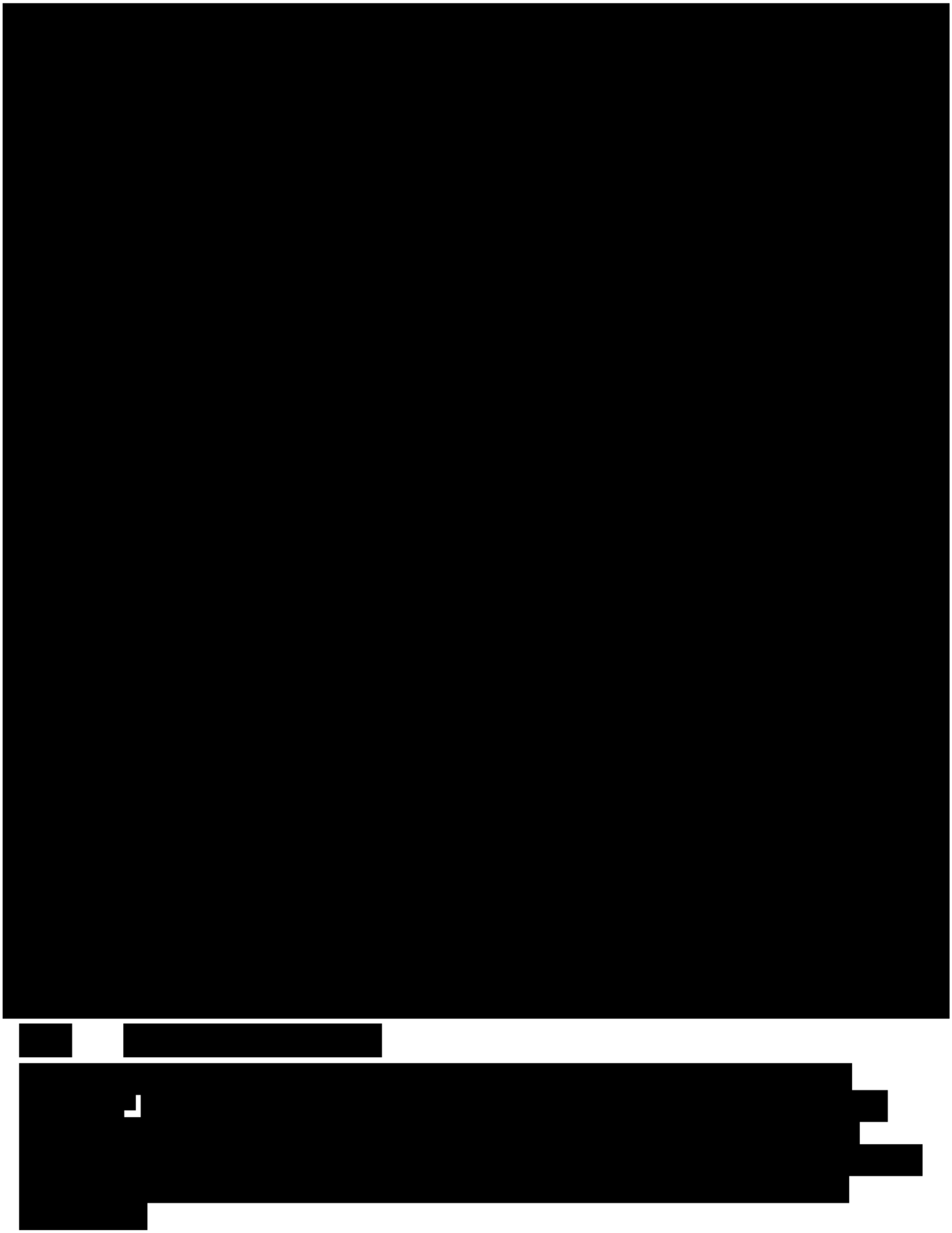
The ECOG performance status will be assessed as shown in Table 10 according to the criteria in Table 14.

Table 14: Eastern Cooperative Group Performance Status Scoring

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

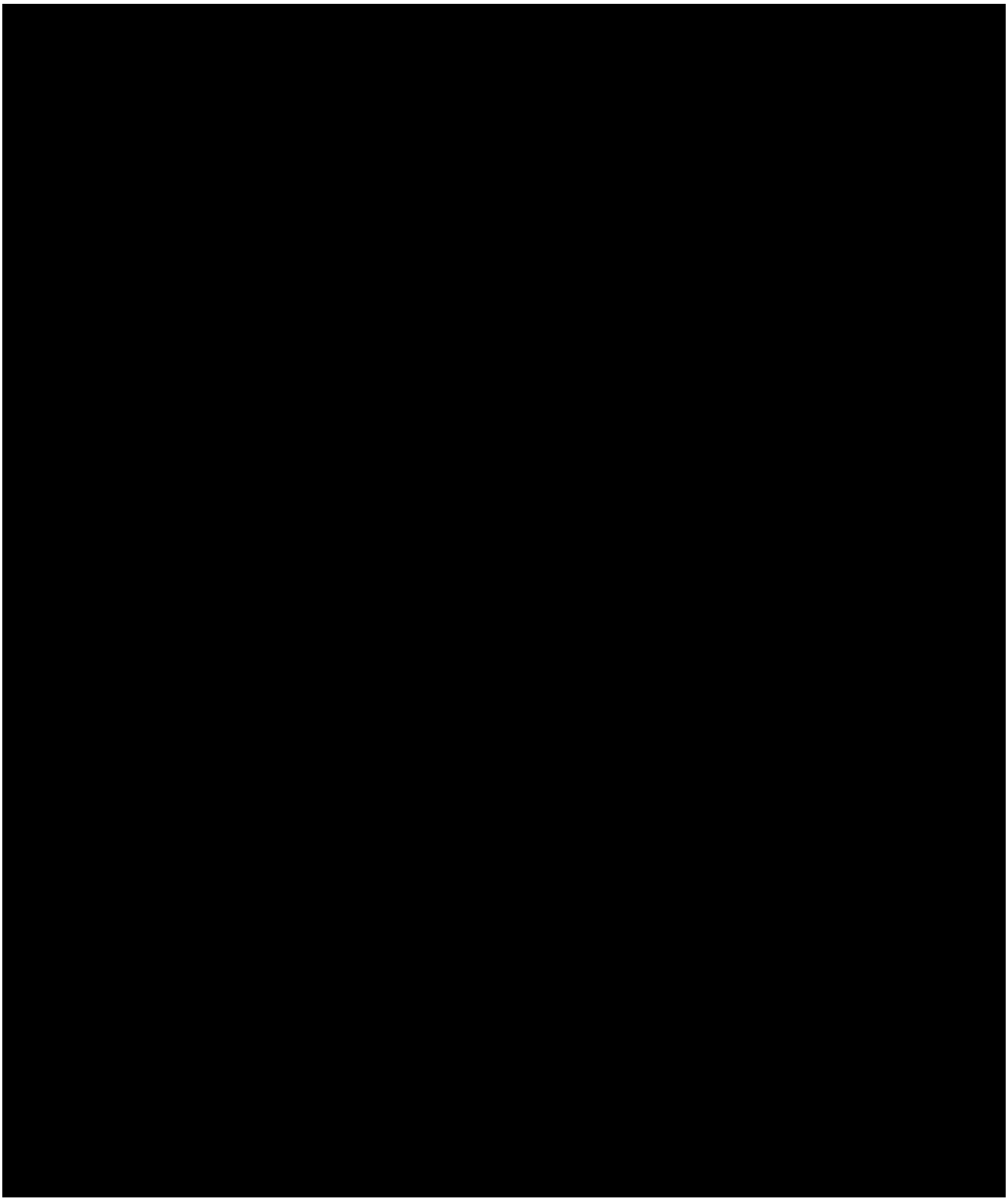
Source: Oken et al 1982.

[redacted]



[redacted]

[redacted]



7.11. Other Study Procedures

7.11.1. Distribution of Subject Reminder Cards

Subjects will be provided with a reminder card at each visit. The subject reminder cards will remind the subject of the date/time of the next visit, as well as any necessary instructions.

7.11.2. Data Collection for Survival Follow-Up

For subjects having entered the survival follow-up period of the study, the site will use continuing subject records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and OS in the eCRF. For subjects who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 12 weeks. After the final primary analysis is performed, the follow-up interval for subsequent anticancer treatments and survival may be reduced to every 16 weeks or eliminated (see Section 6.4.3).

Note: As of Protocol Amendment 5, data collection for survival follow-up is no longer required beyond the last safety follow-up visit. The last survival follow-up data will be recorded in the eCRF at the time of the last safety follow-up visit.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 60 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, should not be reported as an AE/SAE unless it is considered more severe than expected for the participant's condition or considered to be treatment-related by the investigator. Additionally, efficacy endpoints as outlined in Section 2.2 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the subjects in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

The severity of AEs will be assessed using CTCAE v4.03 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:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention 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 intervention indicated.
Grade 5	Death due to AE

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
  - ***Note*: causality assessment for each agent administered per study must be indicated.**
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per SAE definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event form and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed 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 drug, 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 until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

8.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require interruption of study treatment) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.4) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant 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 subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 60 days after the last dose of study treatment, or until the subject receives a new anticancer therapy whichever occurs earlier) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 60 days after the last dose of study treatment should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to each specific study treatment. The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the specific study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose interrupted or discontinued), or subject 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.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for 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, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

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

- The study treatment must be discontinued immediately (female subjects only).
- 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.
- A serum pregnancy test must be performed to confirm the urine pregnancy test result. If a negative serum test does not confirm the urine pregnancy result, then:
  - The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine whether it is in the subject's best interest to resume study treatment and continue participation in the study.
- The EOT visit evaluations must be performed.

Data on fetal outcome and breastfeeding 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 must be recorded on the SAE report form and submitted to the sponsor or designee.

8.6. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the Investigator's Brochure. 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 subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

Formal safety data reviews will be conducted by the study team (eg, medical monitor, clinical scientist, and biostatistician) and an independent internal review committee at least every 6 months. Details regarding data monitoring will be addressed in the Data Safety Monitoring Charter.

8.8. 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 reported as described in Section 8.1.2 of this Protocol.

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. STATISTICS

9.1. Study Populations

The full analysis set includes all subjects enrolled in the study who received at least 1 dose of study drug (INCAGN01876). This population will be used in the analyses of demographic, baseline, safety, study drug administration, and efficacy data.

[redacted]

9.2. Selection of Sample Size

9.2.1. Sample Size for Phase 1

The primary objective of Phase 1 of the study is to determine the DLTs and RP2Ds of INCAGN01876 when given in combination with immune therapies. The total number of subjects will depend on the number of dose levels tested before the RP2D(s) are established. Dose escalation will follow the 3 + 3 + 3 design algorithm. The 3 + 3 + 3 algorithm is described as follows: In each treatment group, the first 3 evaluable subjects enrolled within an INCAGN01876 dose cohort will be observed for the specified DLT observation period before the next dose cohort begins enrollment. If 0 DLTs occur in a cohort of 3 evaluable subjects, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 1 of 3 evaluable subjects experience a DLT, that cohort will be expanded to 6 evaluable subjects. If 1 of 6 subjects experiences a DLT, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 2 of 6 subjects experience a DLT, that cohort will be expanded to 9 evaluable subjects. If 2 of 9 subjects experience a DLT, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. Based on this algorithm, a minimum of 3 evaluable subjects will be enrolled in each cohort with a maximum of 9 evaluable subjects in each cohort.

A range of up to 54 evaluable subjects in each treatment group (9 subjects per dose level for 6 dose levels, if dosing begins with INCAGN01876 0.1 mg/kg), or if a higher starting dose is used based on available safety data from the monotherapy trial (INCAGN 1876-101), then up to 36 evaluable subjects in each treatment group (9 subjects per dose level for 4 dose levels, if dosing begins with 3 mg/kg) will be included based on the dose escalation.

The probabilities of dose escalation from a given dose level for the various DLT rates are provided in Table 18.

Table 18: Probability of Dose Escalation for Various DLT Rates

True DLT Rate	Probability of Dose Escalation
20%	78.4%
30%	56.1%
40%	35.0%
50%	18.9%
60%	8.8%

For example, if the true DLT rate is 50% at a given dose level, there is an 18.9% chance that the dose would be escalated. Further, if the true DLT rate is 20%, there is a 78.4% chance that the dose would be escalated. If the MTD is not determined at the highest dose level tested during the study, then the MTD is at or above the highest dose level. The MTD is below the lowest dose level of INCAGN01876 if the Cohort 1 dose is not well-tolerated.

9.2.2. Sample Size for Phase 2

Phase 2 will further evaluate the safety, tolerability, preliminary efficacy, [redacted] of the recommended dose of INCAGN01876 in combination with immune therapies as part of doublet and triplet drug expansion cohorts. In Phase 2, a Simon 2-stage design will be run for the cervical cancer, gastric cancer, SCCHN and PD-1/PD-L1 relapsed melanoma cohorts within a given doublet or triplet treatment group. A Simon 2-stage design with an expansion stage will be used for the PD-1 refractory SCCHN cohort.

The sample size for each tumor type within a given doublet or triplet expansion cohort will be guided by the Simon 2-stage design (except for the PD-1 refractory SCCHN cohort in Treatment Group F). The planned Simon 2-stage designs are summarized in Table 19. Each Simon 2-stage design will have a stopping rule to allow early termination of a particular tumor type within the given treatment combination at the end of Stage 1 if there is insufficient response observed (calculated response rate $< p_0$), while enrolling enough subjects to predict possible target responses ($\geq p_1$) worthy of cohort expansion and potentially further evaluation in future studies. The individual Simon 2-stage designs run for each tumor type within each doublet or triplet expansion cohort will have design parameters that are determined by historical response rates. The same Simon 2-stage design parameters will be used for alternative dosing sequences in the same tumor type and treatment combination. For example, the gastric cohorts in Treatment Groups F, G, and H will all use the same Simon 2-stage parameters.

In order to determine whether the target response rate (p_1) is likely, an initial number of evaluable subjects (n_1 subjects) treated at the MTD or PAD and schedule of INCAGN01876 within the corresponding doublet or triplet expansion cohort will be enrolled in a cohort (Stage 1). If there are r_1 or fewer responses in the cohort, it will be concluded that the true response rate is unlikely to be greater than or equal to the target rate, and no more subjects will be enrolled in that tumor type in Stage 2. In the cohorts in which greater than r_1 responses are observed among the Stage 1 subjects, n_2 additional evaluable subjects will be treated in Stage 2 to estimate the response rate. At the end of Stage 2, if $\leq r$ subjects have responded among the n evaluable subjects, the doublet or triplet schedule will be declared nonpromising for that cohort.

In other words, after the study is finished, if there is a sufficient number of responses in the 2 stages combined, the study doublet or triplet is considered promising; otherwise it is considered nonpromising. The detailed calculations for each tumor type-specific doublet and triplet cohort are based on a 1-sided Type I error of 0.05 and power of 85%. The individual p_0 and p_1 values for the tumor types within doublet or triplet expansion cohorts are listed in Table 19.

For the PD-1 refractory SCCHN cohort in Treatment Group F, a Simon 2-stage design with an expansion stage, as summarized in Table 20, will be used. The definitions of p_0, p_1, r_1, n_1, and n_2 are the same as those in Table 19. At the end of Stage 2, if r_2 or fewer responses are observed in $n_1 + n_2$ subjects, the PD-1 refractory SCCHN cohort will be terminated early for futility. If more than r_2 responders are observed, an additional n_3 evaluable subjects will be enrolled in the expansion stage. At the end of the expansion stage, if $\leq r$ subjects have responded among the n evaluable subjects, the concurrent dosing strategy of INCAGN01876 and nivolumab will be declared nonpromising for the PD-1 refractory SCCHN cohort. In other words, after the study is finished, if there is a sufficient number of responses in the 3 stages combined, the doublet schedule of INCAGN01876 and nivolumab will be considered promising for the PD-1 refractory SCCHN cohort; otherwise it is considered nonpromising. With this 3-stage design, the 1-sided Type I error is 0.0231, and the power is approximately 88%.

Formal quarterly safety reviews will be conducted to review efficacy and safety data with the obligation to hold a safety review meeting every 6 months.

[redacted]

Table 19: Planned Simon 2-Stage Designs for Phase 2

Indication	Combination	r_1	n_1	r	n_2	n	p_0	p_1
SCCHN	GITR + Nivo	3	16	10	30	46	15%	35%
Gastric	GITR + Nivo	3	16	10	30	46	15%	35%
Cervical	GITR + Nivo	4	17	14	34	51	20%	40%
Relapsed melanoma	GITR + Nivo	2	20	8	30	50	10%	25%
Relapsed melanoma	GITR + Ipi	2	20	8	30	50	10%	25%
SCCHN	GITR + Nivo + Ipi	5	18	17	32	50	25%	45%
Gastric	GITR + Nivo + Ipi	5	18	17	32	50	25%	45%
Cervical	GITR + Nivo + Ipi	7	21	19	27	48	30%	50%

r_1: If r_1 or fewer responses are observed during Stage 1, the study cohort is stopped early for futility.
n_1: Number of subjects initially enrolled in the Stage 1.
n_2: Number of subjects enrolled in the Stage 2.
r: If r or fewer responses are observed by the end of Stage 2, then no further investigation of the drug combination is warranted in the selected tumor type.
n: Total number of subjects.
p_0: Insufficient response rate.
p_1: Target response rate.

Table 20: Planned Simon 2-Stage Design with Expansion Stage for PD-1 Refractory SCCHN Cohort in Phase 2

Indication	Combination	r_1	n_1	r_2	n_2	r	n_3	n	p_0	p_1
PD-1 refractory SCCHN	GITR + Nivo	0	12	3	25	6	20	57	5%	20%

Note: The definitions of p_0, p_1, r_1, n, n_1, and n_2 are the same as those in Table 19.
r_2: If r_2 or fewer responses are observed by the end of Stage 2, the study cohort is stopped early for futility.
r: If r or fewer responses are observed by the end of expansion stage, then no further investigation of the drug combination is warranted in the study cohort.
n_3: Number of subjects enrolled in the expansion stage.

9.3. Level of Significance

For the primary efficacy endpoints, the 1-sided Type I error will be controlled at 0.05 for each individual cohort expansion. Note that this level of significance does not account for the multiple expansion cohorts. For other endpoints, confidence intervals will be reported at a 95% confidence level.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

In Phase 2, the proportion of subjects who meet the objective response criteria (CR + PR) per RECIST v1.1 will be summarized by tumor type.

For the cohorts using a Simon 2-stage design, if there are no responses in each tumor type–specific doublet or triplet treatment group out of the n_1 evaluable subjects specific to that tumor type–specific doublet or triplet treatment group (consistent with a calculated response rate $< p_0$) at Stage 1, then the study will be stopped for futility, and the null hypothesis is not rejected. Otherwise, in the tumor types in which greater than r_1 responses among the evaluable Stage 1 subjects is observed, where r_1 is also specific to the tumor type and doublet or triplet expansion cohort, an additional n_2 evaluable subjects will be treated in Stage 2. If there are $\leq r$ responders among the evaluable subjects at the end of Stage 2, then the drug will be declared nonpromising for that tumor type within the given doublet or triplet expansion cohort, and the null hypothesis is not rejected. Further investigation of the study drug will be considered interesting (predictive of $\geq p_1$ response rate) if $> r$ responses are observed in the first n evaluable subjects.

For the PD-1 refractory SCCHN cohort using a Simon 2-stage design with an expansion stage, if there is an insufficient number of responses observed at the end of Stage 1 or Stage 2, the cohort will be terminated early for futility. If the number of responders observed is $> r_1$ for Stage 1 and $> r_2$ for Stage 2, an additional number of evaluable subjects needed for the next stage (n_2 and n_3, respectively) will be enrolled. At the end of the expansion stage, if the number of responders observed is $\leq r$ among the n evaluable subjects, then the drug will be declared nonpromising for the PD-1 refractory SCCHN cohort. If $> r$ responders are observed, the drug will be declared promising for further investigation.

For the hypothesis tests in the Simon 2-stage design and Simon 2-stage design with expansion stage, the null response rate is p_0 and alternative response rate is p_1, where p_0 and p_1 are specific to the tumor type within a given doublet or triplet expansion cohort and are determined from historical response rates.

9.4.1.2. Secondary Efficacy Analyses

Disease control rate, defined as the proportion of subjects who have disease control (CR + PR + SD), as per RECIST v1.1 and mRECIST v1.1 will be summarized.

Progression-free survival, DOR, and duration of disease control will be estimated using the Kaplan-Meier method as per RECIST v1.1 and mRECIST v1.1. Overall survival will be estimated using the Kaplan-Meier method.

In Phase 2, the proportion of subjects who meet the objective response criteria (CR + PR) per RECIST v1.1 and mRECIST v1.1 will be summarized by tumor type.

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v4.03 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship 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 treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.2.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into Grades 1 through 5 using CTCAE v4.03. The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTCAE grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

9.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 21), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 21: Criteria for Clinically Notable Vital Sign Abnormalities

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/min	< 8/min

9.4.2.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (Table 22). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 22: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

[redacted]

[redacted]

9.5. Analyses for the Data Monitoring Committee

Formal safety data reviews will be conducted by the study team (eg, medical monitor, clinical scientist, and biostatistician) and an independent internal review committee at least every 6 months. Details regarding internal data monitoring will be addressed in the Data Safety Monitoring Charter.

9.6. Interim Analysis

9.6.1. Simon 2-Stage Design and Simon 2-Stage Design With an Expansion Stage

In Phase 2, the Simon 2-stage design will be applied for the cervical cancer, gastric cancer, SCCHN, and PD-1/L-1 relapsed melanoma cohorts within a given doublet or triplet treatment group, and the Simon 2-stage design with an expansion stage will be used for the PD-1 refractory SCCHN cohort in the doublet combination of INCAGN01876 and nivolumab (Treatment Group F). If insufficient responses are observed in any stage, then the cohort will be discontinued. As discussed in Section 9.2.2, the Simon 2-stage designs and the Simon 2-stage design with an expansion stage have design parameters that are determined by historical response rates and will have different sample sizes and different futility rules, depending on the historical response rate determined by different tumor types and different drug combinations.

As an example, the probability of early termination for Stage 1 in the head and neck tumor cohort for the doublet combination of INCAGN01876 and nivolumab is summarized in Table 23. If at least 4 responses are observed in the first evaluable 16 subjects, then 30 additional evaluable subjects will be enrolled in this cohort (Stage 2).

Table 23: Probability of Early Termination of Stage 1 for Simon 2-Stage Design

True Response Rate	Probability of Early Termination at Stage 1
15%	79.0%
20%	59.8%
25%	40.5%
30%	24.6%
35%	13.4%

9.6.2. Integrated Bayesian Futility Analysis

A second approach to determining whether the treatment is active or not across the cohorts will use an integrated Bayesian analysis of tumor and dosing strategies based on Simon et al (2016). The integrated Bayesian analysis will be used for the cervical cancer, gastric cancer, and SCCHN cohorts. Pooling is performed within dosing strategies and tumor types to determine if INCAGN01876 is active within any of the given dosing strategies, given tumor types, or given dosing strategy-tumor type combinations. The first Bayesian pooling analysis will allow sharing of information within a tumor type across dosing strategies based on a joint Bayesian prior. The joint Bayesian prior incorporates the unacceptable and target response rates from the Simon 2-stage designs with a parameter indicating the prior probability of homogeneity within the tumor types, which controls the degree of information sharing. A separate analysis will allow sharing of information for dosing strategies across tumor types using a separate joint Bayesian prior. For this analysis, the joint Bayesian prior incorporates the unacceptable and target response rates from the Simon 2-stage designs with a parameter indicating the prior probability of homogeneity within the dosing strategies, which controls the degree of information sharing.

Each time a subject with the tumor type of interest is enrolled, two PoS calculations will be performed using the evaluable subjects: the PoS in tumor type (tumor $type_i$ and dosing $strategy_j$), PoS_{1ij}, and PoS within dosing strategy (tumor $type_i$ and dosing $strategy_j$), PoS_{2ij}.

Based on the results of the 2 calculated posterior PoS values, a tumor-sequence pair ($_{i,j}$) will be considered open for enrollment if and only if either $PoS_{1ij} \geq 20\%$ or $PoS_{2ij} \geq 20\%$. Otherwise the tumor-sequence pair will be suspended.

At the end of the study, overall PoS tests will be performed using both PoS_{1ij} and PoS_{2ij}. A tumor-sequence strategy will be considered successful if either PoS_{1ij} or $PoS_{2ij} > 80\%$.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- 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 subject 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 subjects.
  - 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.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - 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 subject. 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 subject records.
- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.

  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.

- 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 subjects 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.

10.1.1. 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.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. 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 drug to the study site.
- Inventory of study drug at the site.
- Lot numbers and/or vial numbers (as applicable) of study drug used to prepare the infusion solution.

- Subject use of the study drug including pill or unit counts from each supply dispensed.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects 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 subjects.

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 study drug 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 drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. 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 drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

Data management will be performed in a validated database via an EDC system. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject. Entries made in the eCRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries, and will sign and date the designated forms in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of 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.

10.4. 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 sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Subject names will not be supplied to the sponsor or its designee. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the subject'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. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. 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 subjects, 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.

10.6. 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 and the sponsor's internal publication guidelines.

10.7. 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.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods 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.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
[4] 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 trial and the preferred and usual lifestyle of the subject.
Source: CTFG 2014.

APPENDIX B. PROCEDURES AND SUPPORTIVE CARE GUIDELINES FOR SUBJECTS EXHIBITING IMMUNE-RELATED ADVERSE EVENTS

irAE	Supportive Care
Pneumonitis	**For Grade 2 (mild to moderate new symptoms):** • Monitor symptoms daily and consider hospitalization. • Promptly start systemic steroids per institutional standard of care. • Consider adding prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration. • Reimaging as clinically indicated. • If no improvement within 3 to 5 days, additional work-up should be considered and prompt treatment with IV methylprednisolone should be started. • If still no improvement within 3 to 5 days despite IV methylprednisone, consider starting immunosuppressive therapy (eg, infliximab), after discussing with the medical monitor. ***Caution:*** Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungal, or anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections (Category 2B recommendation). • Consider pulmonary and infectious disease consult. **For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening):** • Promptly initiate empiric IV methylprednisolone or equivalent. • Carefully monitor subject, and institute medical intervention as appropriate for the management of symptoms. Consider obtaining pulmonary and infectious disease consult. • If no improvement within 3-5 days, additional work-up should be considered and prompt treatment with additional immunosuppressive therapy (eg, infliximab), after discussing with the medical monitor. ***Caution:*** Rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and in particular, anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections (Category 2B recommendation).

irAE	Supportive Care
Diarrhea/Colitis	***Note:*** Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). **For Grade 2 (mild to moderate new symptoms):** • Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. • Promptly start systemic steroids per institutional standard of care. • If event is not responsive within 3 to 5 days or worsens, gastrointestinal (GI) consult should be obtained for consideration of further work-up, and prompt treatment with IV methylprednisolone started. • If still no improvement within 3 to 5 days, consider starting immunosuppressives (eg, infliximab) after discussing with the medical monitor. ***Caution:*** Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Consult medical monitor if no resolution to ≤ Grade 1 in 3 to 4 days. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]). **For Grade 3 or 4 (severe or new symptoms, new/worsening diarrhea, life threatening):** • Treatment with systemic corticosteroids should be initiated per institutional standard of care. • Manage symptoms and consider GI consult for further work-up as appropriate. • If still no improvement within 3 to 5 days, consider starting immunosuppressives (eg, infliximab), after discussing with the medical monitor. ***Caution:*** Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

irAE	Supportive Care
Hepatitis	**For Grade 2 (mild to moderate new symptoms):** • Observe subject with regular and frequent checking of liver chemistries until improving or resolved. • Rule out non-irAE etiologies. • If event is persistent (> 3-5 days) or worsens, consider starting systemic steroids per institutional standard of care. • If still no improvement within 3 to 5 days, consider additional work-up and prompt treatment with IV methylprednisolone. • If still no improvement within 3 to 5 days, consider starting immunosuppressives (eg, mycophenolate mofetil), after discussing with the medical monitor. • **Infliximab should NOT be used.** • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]). **For Grade 3 or 4 (severe or new symptoms, new/worsening hepatitis, life threatening):** • Promptly initiate empiric IV methylprednisolone or equivalent. • If still no improvement within 3 to 5 days, consider starting treatment with immunosuppressive therapy (eg, mycophenolate mofetil), after discussing with the medical monitor. • **Infliximab should NOT be used.** • Consider hepatology consult for additional work-up, as appropriate. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

irAE	Supportive Care
Dermatitis	***Note:*** Monitor subjects for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. If there is any bullous formation, the medical monitor should be contacted, and study treatment should be discontinued. **For Grade 2 (mild to moderate new symptoms):** • Consider dermatology consult. • Consider symptomatic treatment per institutional standard of care. • Consider moderate-strength topical steroid. • If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with medical monitor and promptly start systemic steroids. **For Grade 3 or 4 (severe or new symptoms, new/worsening dermatitis, life threatening):** • Consider dermatology consult. • Promptly initiate empiric IV methylprednisolone or equivalent. • Carefully monitor subject, and institute medical intervention as appropriate for the management of symptoms. • Consider hospitalization. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]). • Discuss with medical monitor.
Renal Failure or Nephritis	***Note:*** Subjects should be monitored for signs and symptoms that may be related to changes in renal function. Subjects should be thoroughly evaluated to rule out any alternative etiology. Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2) in order to prevent potential progression to higher grade event. **For Grades 2 to 4:** • Carefully monitor subject, and institute medical intervention as appropriate for the management of symptoms. Consider consult with nephrologist, if clinically indicated. • If event is persistent (> 3-5 days) or worsens, promptly start systemic steroids per institutional standard of care. • If event is not responsive within 3-5 days or worsens despite steroids, additional work-up should be considered, and prompt treatment with IV methylprednisolone started. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

irAE	Supportive Care
Endocrinopathies	***Note:*** Subjects should be monitored for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Subjects may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated. **For Grade 2 (mild to moderate new symptoms):** • In hypophysitis, treat with systemic corticosteroids, per institutional standard of care. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered. ***Note: These suggested supportive care measures also apply to Grade 3 hypophysitis*** • In hyperthyroidism, nonselective beta-blockers (eg, propranolol) are suggested as initial therapy. • In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care. ***Note:*** Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. • Evaluate endocrine function and, as clinically indicated, consider pituitary scan. • For subjects with abnormal endocrine work-up, except for those with isolated hypothyroidism, consider short-term, high-dose corticosteroids (eg, methylprednisolone or IV equivalent) and initiate appropriate hormone replacement therapy. • For subjects with normal endocrine work-up (labs or MRI), repeat labs/MRI as clinically indicated. **For Grade 3 or 4 (severe or new symptoms, new/worsening endocrinopathies, life threatening):** • Hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. • In hyperthyroidism, treat with an initial dose of IV corticosteroid followed by oral corticosteroids. Consider initiation of systemic corticosteroids at a dose of 1-2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy. Once improving, gradually taper immunosuppressive steroids over $\geq$ 4 weeks. • In hypophysitis, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered. • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity. • Consult endocrinologist. • Consult medical monitor.

irAE	Supportive Care
Neuropathies	***Note:*** Monitor subjects for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. **For Grade 2 (mild to moderate new symptoms):** • Consider systemic corticosteroids per institutional standard of care in addition to appropriate symptomatic treatment. • If no improvement within 3-5 days, consider additional work-up and consider treating with additional immunosuppressive therapy (eg, IV IgG), after discussing with the medical monitor. **For Grade 3 or 4 (severe or new symptoms, new/worsening neuropathies, life threatening):** • Consider initiation of systemic corticosteroids (IV administration should be strongly considered) for severe neuropathies. • Institute medical intervention as appropriate for management of severe neuropathy. • If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and consider treating with additional immunosuppressants (eg, IV IgG) after discussing with the medical monitor. • Once stable, gradually taper steroids over ≥ 4 weeks.

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment (Version) 1:	12 JUN 2017
Amendment (Version) 2:	22 AUG 2017
Amendment (Version) 3:	18 DEC 2017
Amendment (Version) 4:	24 OCT 2018
Amendment (Version) 5:	22 JAN 2021

Amendment 5 (22 JAN 2021)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to provide guidance for the management of ongoing subjects, as enrollment is complete and sufficient data have been collected for primary and secondary endpoint analysis.

1. **Synopsis; Section 5.5.1, Withdrawal Criteria; Section 5.5.2, Withdrawal Procedures; Section 6, Study Assessments (Table 10: Schedule of Clinical Assessments); Section 6.3, End of Treatment; Section 6.4.1, Safety Follow-Up; Section 6.4.2, Disease Status Follow-Up; Section 6.4.3, Survival Follow-Up; Section 7.5, Poststudy Anticancer Therapy Status; Section 7.7.1.1.3, Imaging During Follow-Up; Section 7.11.2, Data Collection for Survival Follow-Up**

   Description of change: Disease status and survival follow-up data will only be collected until the last safety follow-up visit. Safety follow-up visits will only include AE and concomitant medication assessments.

   Rationale for change: To update the study assessments as enrollment is complete and all ongoing subjects have either been on study treatment for more than 15 months or are in follow-up after treatment discontinuation (for any of the treatment withdrawal criteria outlined in Section 5.5).

2. **Section 10.1.1, Identification of the Coordinating Principal Investigator; Section 10.6, Publication Policy; Section 10.7, Study and Site Closure**

   Description of change: Included the process for identification of the coordinating principal investigator and for study and site closure. Clarified the policy for study publications.

   Rationale for change: To update applicable sections as per current protocol template.

3. **Incorporation of administrative changes:** Other minor administrative changes have been incorporated throughout the Protocol to correct inadvertent inconsistencies or improve the readability and are noted in the redline version of the amendment.

Amendment 4 (24 OCT 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is (1) to introduce [redacted] and (2) to explore the combination therapy of INCAGN01876 with nivolumab in subjects with PD-1 refractory SCCHN.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 4.1.2, Phase 2 – Dose Expansion; Section 6, Study Assessments (Table 11: Schedule of Laboratory Assessments); Section 7.10.1.1, Tumor Tissue Collection Requirements; Section 7.10.1.2, Tumor Tissue Assessment**

   [redacted]

2. **Synopsis; Section 1.5.2.4, Subjects With Squamous Cell Carcinoma of the Head and Neck Who Have Progressed on Prior Treatment With an Anti–PD-1 Therapy; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design (Figure 1: Overall Study Design); Section 4.1.2, Phase 2 – Dose Expansion; Section 7.10.1.1, Tumor Tissue Collection Requirements; Section 9.2.2, Sample Size for Phase 2; Section 9.4.1.1, Primary Efficacy Analyses; Section 9.6, Interim Analysis**

   Description of change: The following changes have been made to include subjects with PD-1 refractory SCCHN in the Phase 2 portion of the study using a Simon 2-stage design with an expansion stage:

   - Addition of a new section, Section 1.5.2.4, to support inclusion of subjects with SCCHN who have progressed on prior treatment with an anti–PD-1 therapy.
   - Addition of inclusion criterion 6d to Section 3.1.
   - Update of Figure 1 and Section 4.1.2 to include a PD-1 refractory SCCHN cohort in treatment group F using a Simon 2-stage design with an expansion stage.
   - Update of statistical Sections 9.2.2, 9.4.1.1, and 9.6 to include description of analysis of the PD-1 refractory SCCHN cohort in Treatment Group F using the Simon 2-stage design with an expansion stage.

- Other relevant sections were updated accordingly and are noted in the redline version of the amendment.

Rationale for change: A large proportion of patients fail to respond to anti–PD-1 treatment; there are very limited remaining treatment options available. Combining an anti-GITR and an anti–PD-1 treatment may synergistically restore T-cell activation, enhance antitumor immunity, and overcome the resistance of tumors to the PD-1 therapy.

3. **Synopsis; Section 3.1, Subject Inclusion Criteria**

   Description of change: Addition of a note to inclusion criterion 6c that subjects with SCCHN enrolled in Stage 2 of the Phase 2 portion of the study should have progressive disease during or within 6 months after their platinum-based therapy.

   Rationale for change: To more closely define the SCCHN population to be enrolled in Stage 2 of the Phase 2 portion of the study.

4. **Synopsis; Section 4.3.1, Planned Number of Subjects**

   Description of change: The total number of subjects to be enrolled in the Phase 2 portion of the study was updated to reflect changes made to the subject population (ie, addition of subjects with PD-1 refractory SCCHN to Treatment Group F) in the Phase 2 portion of the study.

   Rationale for change: The sample size is guided by the Simon 2-stage design for cervical, gastric, SCCHN, and PD-1/L-1 relapsed melanoma tumor types within a given doublet or triplet treatment group and Simon 2-stage design with an expansion stage for the PD-1 refractory SCCHN cohort in Treatment Group F.

5. **Synopsis; Section 5.2.2, Standard Immune Therapies**

   Description of change: Update in the infusion times for nivolumab and ipilimumab.

   Rationale for change: Following recent updates to the recommended infusion times for nivolumab and ipilimumab in their respective package inserts, the recommended infusion times of nivolumab and ipilimumab have been updated in this study to allow for more flexibility with respect to nivolumab/ipilimumab infusion times as per the respective package inserts or institutional guidelines.

6. **Section 1.5.2.5, Subjects With Melanoma Who Have Relapsed After Prior Treatment With an Anti–PD-1 or Anti–PD-L1 Therapy**

   Description of change: Reference to melanoma subjects has been added to this section.

   Rationale for change: Reference to subjects with melanoma has been made to clarify that this section describes the rationale for inclusion of melanoma subjects who have relapsed after prior treatment with an anti–PD-1 or anti–PD-L1 therapy.

7. **Section 3.1, Inclusion Criteria; Section 7.10.1, Tumor Biopsies**

   Description of change: Updated the requirements for the amount of previously collected formalin-fixed paraffin embedded baseline tumor tissue material.

   Rationale for change: To allow for more flexibility with respect to the amount of available previously collected baseline tumor tissue material required for eligibility.

8. **Section 3.2, Subject Exclusion Criteria; Section 6, Study Assessments (Table 12: Local Laboratory Tests: Required Analytes)**

   Description of change: Exclusion criterion 14 was updated, and a footnote was added to Table 12 to remove the requirement for HBV-DNA and HCV-RNA negative test results prior to study enrollment in case HBsAg/anti-HBc antibody and HCV antibody test results are negative.

   Rationale for change: HBV-DNA and HCV-RNA tests are not performed as standard tests at several sites in case of negative HBsAg/anti-HBc antibody and HCV antibody test results, respectively. The requirement of HBV-DNA and HCV-RNA testing in case of negative HBsAg/anti-HBc antibody and HCV antibody test results has been removed to allow for more flexibility in testing for HBV or HCV infection or risk of reactivation.

10. **Incorporation of administrative changes:** Other minor administrative changes have been incorporated throughout the Protocol to correct inadvertent inconsistencies or improve the readability and are noted in the redline version of the amendment.

Amendment 3 (18 DEC 2017)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

[redacted]

2. **Section 1.2.3, Clinical Safety of INCAGN01876**

   Description of change: Section 1.2.3 was revised to include updated clinical safety data from the INCAGN01876 monotherapy study (INCAGN 1876-101). Clinical safety data for INCAGN018765 at doses of 0.03 mg/kg through 10 mg/kg were summarized.

   Rationale for change: To include updated clinical safety data for INCAGN01876 monotherapy.

3. **Section 1.4, Potential Risks and Benefits of the Combination Regimens**

   Description of change: Section 1.4 was revised to reflect that INCAGN01876 has been well-tolerated at doses up to 10 mg/kg, and that AEs were generally mild to moderate (ie, Grade 1 or Grade 2) and managed with supportive care.

   Rationale for change: To include current clinical safety information for INCAGN01876 monotherapy.

4. **Section 1.5.2.1, Cervical Carcinoma**

   Description of change: Section 1.5.2.1 was revised to delete the rationale for endometrial cancer and replace it with information supporting inclusion of relapsed advanced or metastatic cervical carcinoma in the Phase 2 portion of the study. References were added to support this rationale.

   Rationale for change: Subjects with recurrent advanced or metastatic cervical cancer were added to the study, as treatment options for this population are limited and clinical activity with anti–PD-1 checkpoint blockage support investigation of combination immune therapies.

5. **Section 1.5.3, Subjects Who Have Relapsed After Prior Treatment With an Anti–PD-1 or Anti–PD-L1 Therapy**

   Description of change: Section 1.5.3 was added to support inclusion of subjects who have relapsed after prior treatment with an anti–PD-1 or anti–PD-L1 therapy.

   Rationale for change: After relapsing on a PD-1– or PD-L1–containing regimen, there are few treatment options available. Combining an anti-GITR and a PD-1 inhibitor may synergistically restore T-cell activation, enhance antitumor immunity, and overcome the resistance of tumors to the PD-1/PD-L1 therapy.

6. **Section 1.5.4.1, Rationale for Fixed Dosing of INCAGN01876**

   Description of change: Section 1.5.4.1 was added to provide rationale for fixed dosing of INCAGN01876.

   Rationale for change: Research published by Wang et al (2009) and Bai et al (2012) provides rationale for using a fixed dose as opposed to weight-based dosing, which may be considered when determining the RP2D.

7. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 7.10.1.1, Tumor Tissue Collection Requirements**

   a. **Description of change to inclusion criterion number 6a:** Inclusion criteria 6a was updated to remove subjects with endometrial cancer and include subjects with cervical cancer in the Phase 2 portion of the study.

      Rationale for change: Subjects with recurrent advanced or metastatic cervical cancer were added to the Phase 2 portion of the study, as treatment options are limited and clinical activity with anti–PD-1 checkpoint blockade are encouraging further supporting investigation of combination immune therapies.

   [redacted]

   c. **Description of change to inclusion criterion number 6e:** Inclusion criteria 6e was added to include subjects with PD-1 or PD-L1 relapsed melanoma in the Phase 2 portion of the study.

      Rationale for change: Subjects with PD-1 or PD-L1 relapsed melanoma were added to the study as there are few treatment options available after relapse on checkpoint blockade. Combining an anti-GITR and a PD-1 inhibitor may synergistically restore T-cell activation, enhance antitumor immunity, and overcome the resistance of tumors to the PD-1 therapy.

8. **Synopsis; Section 4.1, Overall Study Design; Section 5.2, Study Drugs; Section 6, Study Assessments; Section 7.10.1.1, Tumor Tissue Collection Requirements**

   Description of change: Section 4.1 was updated to include the following changes; other relevant sections were updated accordingly.

   - The Phase 2 subject population was updated to remove endometrial cancer, include cervical cancer, and include PD-1 or PD-L1 relapsed melanoma.
   - Language was added to allow for alternate dose administration schedules and/or fixed doses of INCAGN01876 comparable to or less than the highest dose levels determined to be safe or pharmacologically active in the Phase 2 portion of the study.
   - Figure 1 (Overall Study Design) was updated to reflect changes made to the subject population and treatment groups.
   - Treatment Group G (run-in with INCAGN01876 × 2 doses followed by monotherapy nivolumab) and Treatment Group K (run-in with INCAGN01876 × 2 doses followed by nivolumab + ipilimumab) were removed from the study. Treatment Group E was updated from sequenced INCAGN01876 × 2 doses followed by nivolumab and ipilimumab to a run-in with INCAGN01876 × 2 doses followed by INCAGN01876 concurrent with nivolumab and ipilimumab.
   - A new Treatment Group C2 (INCAGN01876 + ipilimumab) was added to the Phase 2 portion of the study.

   Rationale for change: The rationale for the subject population and fixed dosing are described above.

   Removal of Treatment Groups G and K and revision of Treatment Group E to sequenced INCAGN01876 × 2 doses followed by concurrent nivolumab and ipilimumab dosing is based on emerging clinical and translational data from the Phase 1 portion of the study. Data thus far have not shown sufficient clinical responses or meaningful translational changes in immune markers for subjects enrolled in Treatment Group B. However, a clinical response and changes in immune markers were observed in Treatment Group A (concurrent dosing). Therefore, treatment groups investigating sequential monotherapy dosing schedule will no longer be explored in the Phase 2 portion of the study.

   Treatment Group C (INCAGN01876 + ipilimumab) will be expanded in the Phase 2 portion of the study (as Treatment Group C2). This is based on emerging clinical and translational data from the Phase 1 portion of the study showing clinical responses and meaningful translational changes in immune markers for subjects enrolled in Treatment Group C.

9. **Synopsis; Section 4.3.1, Planned Number of Subjects; Section 9.2.2, Sample Size for Phase 2**

   Description of change: The total number of subjects to be enrolled in the Phase 2 portion of the study was updated to reflect changes made to the subject population (eg, addition of cervical cancer and PD-1 or PD-L1 relapsed melanoma) and treatment groups (eg, removal of Treatment Groups G and K and addition of Treatment Group C2) in the Phase 2 portion of the study.

   Rationale for change: The sample size for each tumor type within a given treatment group is guided by the Simon 2-stage design. The individual Simon 2-stage design for each tumor type within each treatment group are based on parameters that are determined by historical response rates.

10. **Synopsis; Section 4.4, Duration of Treatment and Subject Participation; Section 5.2.1, INCAGN01876; Section 5.2.2.1, Nivolumab; Section 5.2.2.2, Ipilimumab; Section 6.2, Treatment**

    Description of change: The duration of study treatment for individual subjects was updated to allow subjects to continue treatment as long as they are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal or for up to 24 months from the first dose, whichever occurs first.

    Rationale for change: There is growing evidence that subjects may not need to be treated with immunotherapies indefinitely; rather, shorter courses of treatment may be equally effective. Additionally, shorter durations of immunotherapy reduce the risk of long-term toxicities for subjects.

11. **Synopsis; Section 4.1, Study Design, Section 5.4.1, Dose Modifications; Section 5.4.2, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose; Section 5.4.6, Criteria and Procedures for Dose Interruptions of Study Drug; Section 5.4.9, Criteria for Permanent Discontinuation of Study Drug**

    Description of change: Dose modifications of INCAGN01876 will no longer be permitted for the management of toxicities. Doses of INCAGN01876 should be delayed for toxicity management.

    Rationale for change: Anti-drug antibodies of INCAGN01876 have been observed upon repeat dosing with lower doses (≤ 1 mg/kg) of INCAGN01876, with impact on [redacted] therefore, dose reductions of INCAGN01876 are not allowed.

[redacted]

13. **Section 8.1, Adverse Events**

    Description of change: Clarification was provided regarding reporting of AEs related to study disease and/or disease progression. Adverse events related to study disease or disease progression should not be reported as an AE/SAE unless it is considered more severe than expected for the participant's condition or considered to be treatment-related by the investigator. Additionally, efficacy endpoints as outlined in Section 2.2 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study.

    Rationale for change: The original Protocol language was not clear regarding reporting of AEs related to study disease or disease progression.

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

Amendment 2 (22 AUG 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address clinical trial application review comments from the Belgian and Spanish regulatory agencies.

1. **Section 3.1, Subject Inclusion Criteria**

   Description of change: In inclusion criterion 9, clarification was provided that men and women of childbearing potential must take appropriate precautions to avoid pregnancy from screening through the safety follow-up period, or as required in the nivolumab and ipilimumab package insert, whichever is longer.

   Rationale for change: The Protocol only addressed contraceptive measures that should be adopted for the investigational product INCAGN01876 but did not include contraceptive measures for the combination drugs nivolumab and ipilimumab.

2. **Section 5.4.1, Dose Modifications; Section 7.6, Safety Assessments**

   Description of change: Clarification was added that subject safety management guidelines as outlined within the respective package inserts for nivolumab and ipilimumab should be followed as appropriate.

   Rationale for change: To ensure that the approved safety management guidelines for nivolumab and ipilimumab are being followed.

3. **Section 6, Study Assessments (Table 10, Schedule of Clinical Assessments); Section 7.6.4, Electrocardiograms**

   Description of change: A 12-lead electrocardiogram (ECG) will be collected every 8 weeks during the treatment period. Additional 12-lead ECGs may be performed as clinically indicated to manage subject safety.

   Rationale for change: Per the package insert for nivolumab in Europe, continuous monitoring for cardiac adverse reactions is recommended when nivolumab is given in combination with ipilimumab.

4. **Section 7.6.5.1, Pregnancy Testing**

   Description of change: Clarification was provided regarding when urine pregnancy testing would be medically indicated (eg, in case of loss of menstrual cycle or when pregnancy is suspected), as well as how country-specific requirements for urine pregnancy testing would be communicated to investigational sites.

   Rationale for change: To clarify when additional urine pregnancy testing would be considered medically indicated and how additional urine pregnancy testing requirements will be communicated to investigational sites.

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

Amendment 1 (12 JUN 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update the sponsor name and address to Incyte Biosciences International Sàrl.

1. **Title Page; Document Headers; Section 10.6, Publication Policy**

   Description of change: The name and address of the sponsor were updated from Incyte Europe Sàrl to Incyte Biosciences International Sàrl.

   Rationale for change: The corporate entity Incyte Europe Sàrl will be merged into Incyte Biosciences International Sàrl.

2. **Synopsis; Section 2.1.2, Secondary Objectives; Section 2.2.2, Secondary Endpoints; Section 9.4.1.2, Secondary Efficacy Analysis**

   Description of change: Added secondary objective and defined endpoint of disease control rate.

   Rationale for change: Disease control rate can be an important measure of therapeutic activity.

3. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design; Section 7.10.1.1, Tumor Tissue Collection Requirements**

   Description of change: Clarification was added to specify that only subjects with mucosal or cutaneous melanoma will be enrolled. Additionally, alternative tumor types not listed may be allowed to enroll with approval of the medical monitor.

   Rationale for change: As described in Section 1.5.1 of the Protocol, tumor types that have demonstrated clinical responses following blockage of immune checkpoint inhibitors were included in Part 1 of the study. As data in subjects treated with immune modulators continues to emerge, the list of indications provided in the Protocol may not be comprehensive; therefore, tumor types not listed may be allowed following review of the medical monitor.

4. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: The laboratory exclusion criterion for total bilirubin was updated to exclude subjects with total bilirubin $\geq 1.2 \times$ ULN.

   Rationale for change: As the safety of novel combinations of immune therapies are being assessed in this study, only subjects with sufficient liver function should be enrolled into this Phase 1/2 study.

5. **Synopsis; Section 4.1, Overall Study Design**

   Description of change: Added language to allow flexibility in prioritizing enrollment to specific treatment groups or cohorts.

   Rationale for change: Allows the sponsor and investigational sites to prioritize more promising treatment groups or cohorts (or deprioritize less promising treatment groups or cohorts) based on emerging data.

6. **Synopsis; Section 4.1.2, Phase 2 – Dose Expansion; Section 5.4.2, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose (Table 6, Definition of Dose-Limiting Toxicity)**

   Description of change: Clarification provided that the incidence of Grade 3 or higher adverse events will be considered when evaluating toxicity.

   Rationale for change: CTCAE toxicity Grade 5 is being used in this clinical study and the language was updated to include any potential Grade 5 AEs in the analysis as appropriate.

7. **Section 5.4.8, Management of Infusion Reactions**

   Description of change: Language was added to specify that investigators may use institutional guidance or labeled guidance from the nivolumab or ipilimumab package insert (as applicable) for infusion reactions subjects may experience when receiving these treatments.

   Rationale for change: To allow flexibility for treating physicians to use labeled guidance instead of Protocol guidance for commercially available nivolumab and ipilimumab.

[redacted]

9. **Section 8.7, Data Monitoring Committee; Section 9.5, Analyses for the Data Monitoring Committee**

   Description of change: Language was added to include an independent internal review committee that will review safety data at least every 6 months throughout the study.

   Rationale for change: Independent safety overview is appropriate for a clinical study of this scope.

10. **Section 4.1.2, Phase 2 – Dose Expansion; Section 9.3, Level of Significance; Section 11, References**

    Description of change: Additional language was added to describe the Simon 2-stage design for the Phase 2 analysis. The reference supporting this statistical design was also included.

    Rationale for change: The previous language did not depict the Simon 2-stage designs involved in the study.

11. **Section 10.2, Accountability, Handling, and Disposal of Study Drug**

    Description of change: Clarification was provided regarding records required for study drugs that are infused. Bullet referring to self-administered oral study drugs was removed.

    Rationale for change: Changes were applicable based on administration method of study drugs.

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

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