Official Title: **A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01949 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies**

NCT Number: NCT03241173

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Clinical Study Protocol

INCAGN 1949-201

A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01949 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies

Product:	**INCAGN01949**
IND Number:	[redacted]
EudraCT Number:	**2017-001244-35**
Phase of Study:	**1/2**
Sponsor:	**Incyte Biosciences International Sàrl** **Route de la Corniche 1** **1066 Epalinges, Switzerland**
Original Protocol (Version 0):	**06 APR 2017**
Amendment (Version) 1:	**14 JUN 2017**
Amendment (Version) 2:	**29 MAY 2018**
Amendment (Version) 3:	**05 DEC 2018**

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 INCAGN 1949-201 Protocol Amendment 3 (Version 3 dated 05 DEC 2018) 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: INCAGN01949 in combination with nivolumab and/or ipilimumab	
Title of Study: A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01949 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies	
Protocol Number: INCAGN 1949-201	**Study Phase:** 1/2
Indication: **Phase 1:** advanced or metastatic select solid tumors **Phase 2:** advanced or metastatic gastric cancer, squamous cell cancer of the head and neck, non–small cell lung cancer, and renal cell carcinoma	
Primary Objectives: Phase 1 • To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of INCAGN01949 in combination with immune therapies and to define the recommended dose(s) of INCAGN01949 when given in combination with immune therapies. Phase 2 • To evaluate the efficacy of INCAGN01949 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 INCAGN01949 when given in combination with immune therapies by assessing ORR, duration of response, disease control rate (DCR), duration of disease control, and progression-free survival (PFS), per RECIST v1.1. • To evaluate the safety and tolerability of INCAGN01949 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.
- 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.
- DCR, defined as the percentage of subjects having CR, PR, or stable disease (SD), will be determined by investigator assessment of a radiographic disease assessments per RECIST 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.
- 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.
- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs.

[redacted]

Overall Study Design:

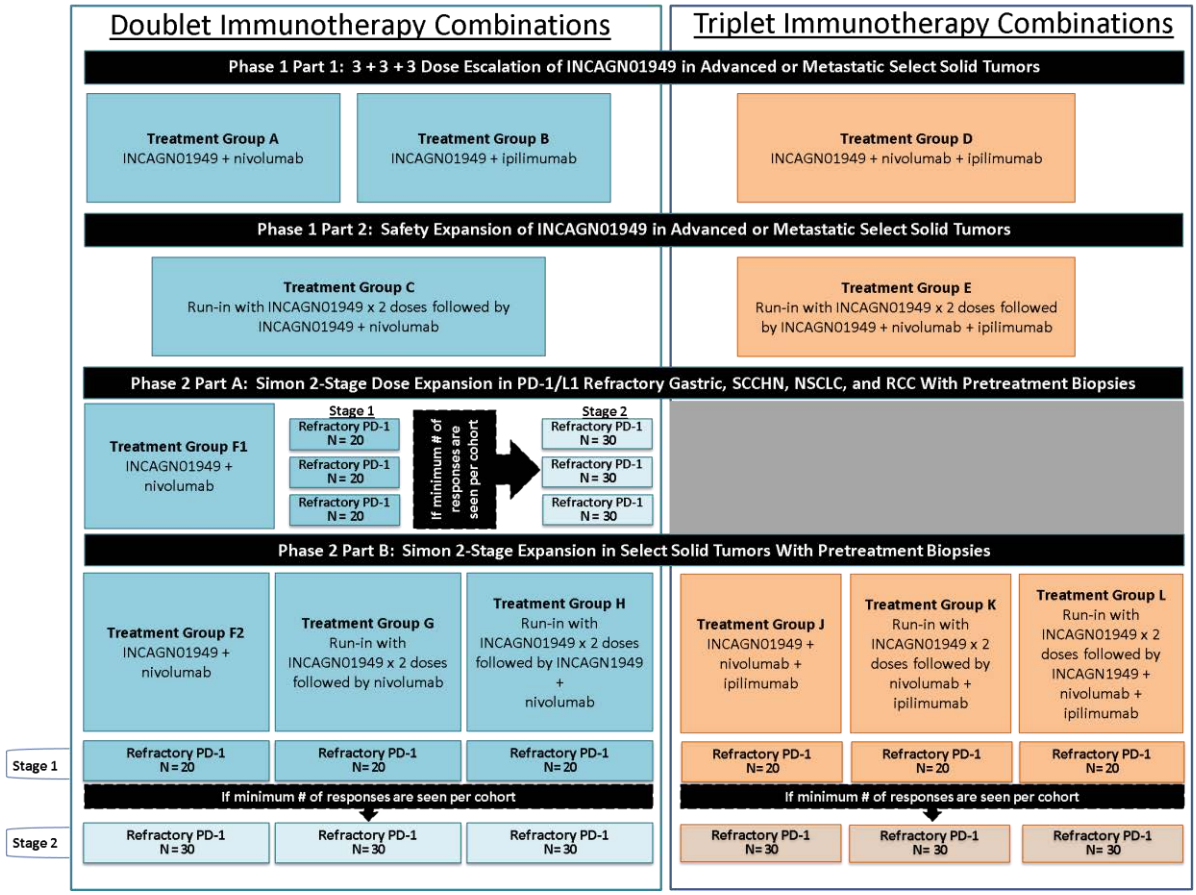
Note: Based on a change in the development plan for INCAGN01949, enrollment to the study was stopped after 52 subjects were enrolled. Phase 2 of the study will not open for enrollment. Continued study treatment will be permitted for up to 24 months at the discretion of the investigator for subjects who are considered to be obtaining ongoing clinical benefit.

This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of INCAGN01949 when given in combination with immune therapies. Phase 1 will consist of 2 parts. Dose escalation (Part 1) will consist of a 3 + 3 + 3 design to determine the maximum tolerated dose (MTD), or pharmacologically active dose (PAD), defined as a dose that provides a maximal biochemical effect [redacted] of INCAGN01949 when given in combination with immune therapies. The safety expansion (Part 2) will further explore tolerated doses of INCAGN01949 given as a run-in of 2 doses followed by concomitant immune therapies. Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach and gastroesophageal junction [GEJ] cancer), esophageal 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 who have progressed after treatment with available therapies that are known to confer clinical benefit or who are intolerant to treatment will be enrolled in both parts of Phase 1.

The Phase 2 expansion will further evaluate the safety, tolerability, and efficacy of immune therapies combined with INCAGN01949 in 2 different parts. In Phase 2 Part A, the selected doses of INCAGN01949 will be combined with nivolumab in programmed cell death protein 1 (PD-1)/programmed cell death protein ligand 1 (PD-L1) refractory subjects with gastric cancer, SCCHN, NSCLC, and RCC to further explore the safety and efficacy of different doses of INCAGN01949 in combination with nivolumab in this population. Phase 2 Part B will evaluate the recommended dose(s) of INCAGN01949 in combination with nivolumab (and ipilimumab where applicable). PD-1/L1 refractory subjects with advanced or metastatic gastric cancer, SCCHN, NSCLC, or RCC will also be enrolled in Phase 2 Part B. Pretreatment biopsies will be mandatory for subjects enrolled into either part of Phase 2. The study diagram is presented in Figure S1.

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.

Figure S1: Study Design



Phase 1 – Dose Escalation (Part 1)

A minimum of 3 evaluable subjects will be enrolled in each treatment group beginning with INCAGN01949 Dose Cohort 1 (7 mg; starting dose). A higher starting dose of INCAGN01949 may be used if safety data are available from the monotherapy study (INCAGN 1949-101) but will not exceed 1 dose level below the highest tolerated dose of INCAGN01949 monotherapy. If a higher starting dose is used, the new dose will be communicated to investigational sites with an administrative letter. The doses of INCAGN01949 to be evaluated in each treatment group are summarized in Table S1.

Table S1: INCAGN01949 Dose Cohorts

Dose Cohort	Dose of INCAGN01949
-1	2 mg
1 (Starting Dose)	**7 mg[a]**
2	20 mg
3	70 mg
4	200 mg
5	350 mg
6	700 mg

[a] A higher starting dose of INCAGN01949 may be used if safety data is available from the monotherapy study (INCAGN 1949-101) but will not exceed 1 dose level below the highest tolerated dose of INCAGN01949 monotherapy. If a higher starting dose is used, the dose will be communicated to investigational sites with an administrative letter.

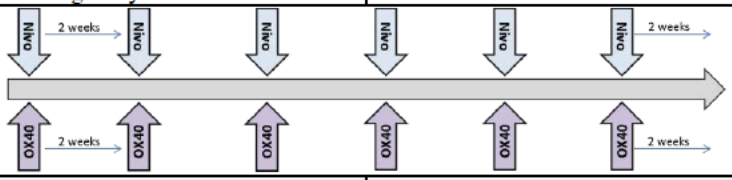
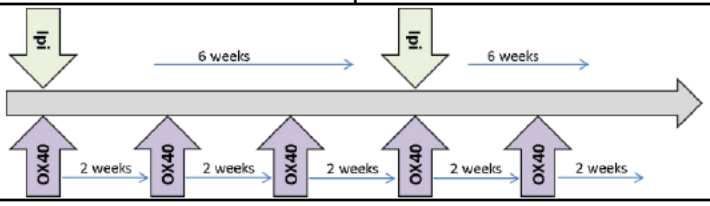
The first 3 evaluable subjects enrolled within an INCAGN01949 dose cohort will be observed for the DLT observation period of 28 days before the next dose cohort begins enrollment. If 0 DLTs occur in a cohort of 3 evaluable subjects, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 1 of 3 evaluable subjects experiences 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 $\geq$ 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 INCAGN01949, 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. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor.

Doublet Immune Therapy Combinations for Dose Escalation

Phase 1 dose escalation will begin with 2 doublet treatment groups, as outlined in Table S2, which will be explored in parallel.

Table S2: Doublet Immune Therapy Treatment Groups for Dose Escalation

Treatment Group A	**INCAGN01949 Concurrent Dosing**	**Nivolumab**
	See INCAGN01949 dose cohorts (Table S1) Q2W starting at Cycle 1	240 mg Q2W starting at Cycle 1
		
Treatment Group B	**INCAGN01949 Concurrent Dosing**	**Ipilimumab**
	See INCAGN01949 dose cohorts (Table S1) Q2W starting at Cycle 1	1 mg/kg Q6W starting at Cycle 1
		

Treatment Group A (INCAGN01949 + Nivolumab)

Treatment Group A will treat subjects with INCAGN01949 at the assigned dose level administered intravenously (IV) every 2 weeks (Q2W) in combination with nivolumab 240 mg IV Q2W (see Table S2). **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 INCAGN01949 will proceed as outlined in Table S1 until the MTD or PAD of INCAGN01949 in combination with nivolumab is determined.

Treatment Group B (INCAGN01949 + Ipilimumab)

Treatment Group B will treat subjects with INCAGN01949 at the assigned dose level administered IV Q2W in combination with ipilimumab 1 mg/kg IV every 6 weeks (Q6W; see Table S2). **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 INCAGN01949 will proceed as outlined in Table S1 until the MTD or PAD of INCAGN01949 in combination with ipilimumab is determined.

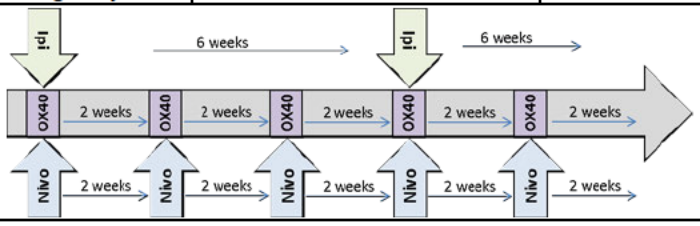
At the sponsor's discretion, once the MTD or PAD of INCAGN01949 has been established with ipilimumab at 1 mg/kg Q6W, a higher dose of ipilimumab at 3 mg/kg Q6W and/or 3 mg/kg Q3W for 4 doses may be tested. If the MTD or PAD of INCAGN01949 in combination with higher doses of ipilimumab is not tolerated, dose de-escalation of INCAGN01949 will proceed as outlined in Table S1 until the MTD or PAD of INCAGN01949 is determined.

Triplet Immune Therapy Combination for Dose Escalation

Dose escalation of the triplet immune therapy combinations will begin enrolling once all of the applicable doublet combinations in Part 1 dose escalation have cleared 3 INCAGN01949 dose levels (see Table S1), or the MTD or PAD of INCAGN01949 in combination with each component has been determined (whichever occurs first). The starting dose of INCAGN01949 will be 2 dose levels below the last dose cohort deemed safe in the doublet combination. If there are different MTDs of INCAGN01949 with nivolumab and ipilimumab, then the starting dose of the triplet will be 2 dose levels below the lowest MTD in the doublet. For example, if 200 mg of INCAGN01949 is safe in the doublet combinations with both nivolumab and ipilimumab, then the starting dose in the triplet will be 20 mg. If the MTD of INCAGN01949 is 200 mg in the nivolumab doublet combination and the MTD of INCAGN01949 in the

ipilimumab combination is 70 mg, then the starting dose of INCAGN01949 for the triplet immune therapy combination will be 7 mg. The triplet immune therapy combinations to be explored is outlined in Table S3.

Table S3: Triplet Immune Therapy Treatment Group for Dose Escalation

	INCAGN01949 Concurrent Dosing	Nivolumab	Ipilimumab
	See INCAGN01949 dose cohorts (Table S1) Q2W starting at Cycle 1	3 mg/kg Q2W starting at Cycle 1	1 mg/kg Q6W starting at Cycle 1
Treatment Group D			

Treatment Group D (INCAGN01949 + Nivolumab + Ipilimumab)

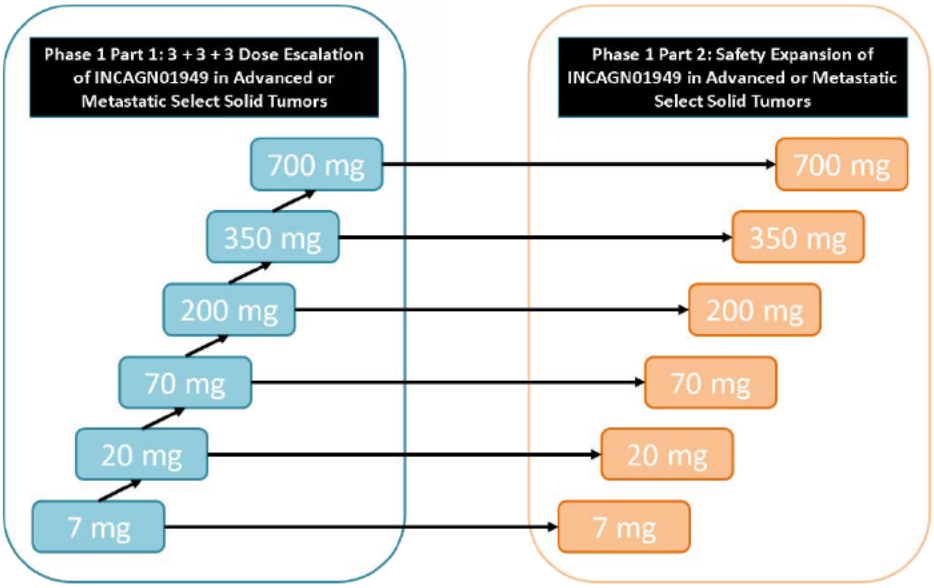
Treatment Group D will treat subjects with INCAGN01949 at the assigned dose level administered IV Q2W in combination with nivolumab 3 mg/kg IV Q2W and ipilimumab 1 mg/kg IV Q6W (see Table S3). **There will be a waiting period of 48 hours between dose administration of the first subject and second subject 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 INCAGN01949 will proceed as outlined in Table S1 until the MTD or PAD of INCAGN01949 in combination with nivolumab and ipilimumab is determined; however, the dose of INCAGN01949 in the triplet combination will not exceed the lowest MTD of INCAGN01949 established in the applicable doublet combinations. For example, if the MTD of INCAGN01949 in combination with nivolumab is 350 mg and the MTD of INCAGN01949 in combination with ipilimumab is 200 mg, then the dose of INCAGN01949 would not exceed 200 mg.

Phase 1 – Safety Expansion (Part 2)

Once an INCAGN01949 dose cohort in Treatment Group A is deemed tolerable, up to 6 subjects will be enrolled in Treatment Group C at the same dose of INCAGN01949. For example, if INCAGN01949 7 mg is tolerated in Treatment Group A, then 7 mg will be explored in up to 6 subjects in Treatment Group C. Likewise, once an INCAGN01949 dose in Treatment Group D is deemed tolerable, up to 6 subjects will be enrolled in Treatment Group E at the same dose of INCAGN01949. For example, if INCAGN01949 350 mg is tolerated in Treatment Group D, then 350 mg will be explored in up to 6 subjects in Treatment Group E. Doses of INCAGN01949 in Treatment Group C will be escalated in parallel to those explored in Treatment Group A but will not exceed the MTD of INCAGN01949 established in Treatment Group A. The same rules will apply with Treatment Group D and E. See Figure S2. Alternate dose administration schedules may also be explored depending on [redacted] safety results. The sponsor may elect to prioritize (or deprioritize) enrollment to specific dose cohorts based on emerging safety or efficacy data in collaboration with investigational sites.

If the cumulative incidence of Grade 3 or Grade 4 INCAGN01949-related AEs occurs in > 40% of subjects in a particular treatment group, then further enrollment will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action (eg, lower the dose of INCAGN01949, change dose frequency, etc).

Figure S2: Phase 1 Safety Expansion (Part 2)

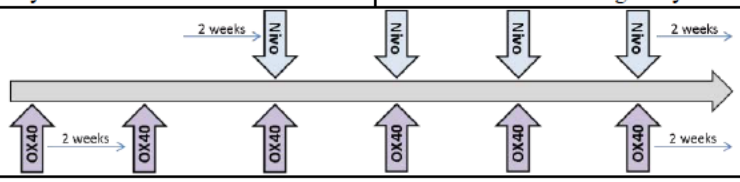


Doublet Immune Therapy Combination for Safety Expansion

Treatment Group C (INCAGN01949 Run-In Followed by Concurrent Dosing With Nivolumab)

Treatment Group C will treat subjects with a 2-dose run-in of INCAGN01949 Q2W at the assigned dose level followed by the combination of INCAGN01949 Q2W plus nivolumab 240 mg Q2W (starting at Cycle 3; see Table S4).

Table S4: Doublet Immune Therapy Treatment Group for Safety Expansion

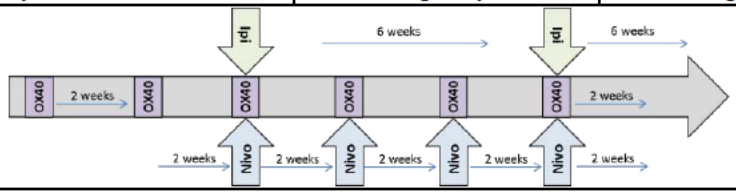
	INCAGN01949 Run-In Followed by Concurrent Dosing	Nivolumab
Treatment Group C	See INCAGN01949 dose cohorts (Table S1) Q2W starting at Cycle 1	240 mg Q2W starting at Cycle 3
		

Triplet Immune Therapy Combination for Safety Expansion

Treatment Group E (INCAGN01949 Run-In Followed by Concurrent Dosing With Nivolumab and Ipilimumab)

Treatment Group E will treat subjects with INCAGN01949 at the assigned dose level Q2W for 2 doses followed by INCAGN01949 Q2W in combination with nivolumab 3 mg/kg Q2W, and ipilimumab 1 mg/kg Q6W (starting at Cycle 3; see Table S5).

Table S5: Triplet Immune Therapy Treatment Group for Safety Expansion

	INCAGN01949 Run-In Followed by Concurrent Dosing	Nivolumab	Ipilimumab
	See INCAGN01949 dose cohorts (Table S1) Q2W starting at Cycle 1	3 mg/kg Q2W starting at Cycle 3	1 mg/kg Q6W starting at Cycle 3
Treatment Group E			

Phase 2 – Dose Expansion

Phase 2 of the study will further evaluate the safety, tolerability, efficacy, [redacted] and [redacted] in subjects with gastric cancer, SCCHN, NSCLC, and RCC. Part A of Phase 2 will enroll subjects considered PD-1/L1 refractory to further explore a range of doses of INCAGN01949 found to be safe in Phase 1 in combination with nivolumab.

Phase 2 Part B of the study will enroll subjects into different treatment groups with advanced or metastatic gastric cancer, SCCHN, NSCLC, or RCC considered PD-1/L1 refractory. Additional tumor-specific cohorts may be added, by Protocol amendment, based on emerging data. Pretreatment biopsies will be required for all subjects enrolled in Phase 2 of the study. On-study biopsies will be considered optional.

The Phase 2 expansion treatment groups and tumor-specific cohorts for each treatment group are outlined in Table S6. Treatment Groups G and K will only be administered 2 doses of INCAGN01949 followed by standard therapies. As INCAGN01949 will not be given in combination with the standard therapies for Treatment Groups G and K, the recommended dose of INCAGN01949 determined in the monotherapy study INCAGN 1949-101 will be used. A Simon 2-stage design will be used 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 in the cohorts. The approximate number of subjects for Stage 1 and Stage 2 for each treatment group and cohort is described in Table S7 and Figure S1. Enrollment in Phase 2 Part B will begin when the recommended dose of INCAGN01949 in combination with nivolumab (and ipilimumab as applicable) has been determined. The sponsor may elect to prioritize (or deprioritize) enrollment to specific dose cohorts based on emerging safety or efficacy data in collaboration with investigational sites.

Table S6: Phase 2 Expansion Treatment Groups

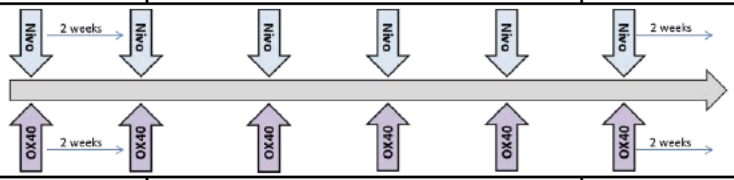
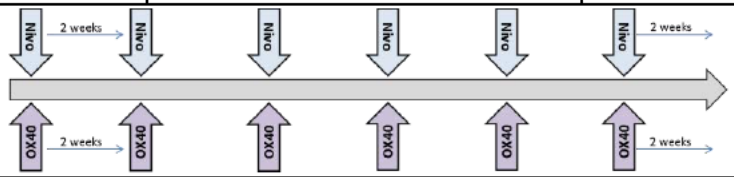
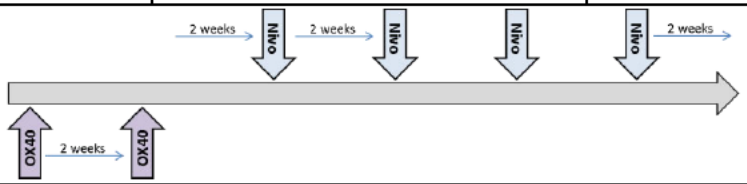
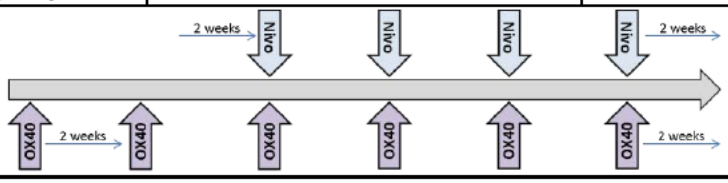
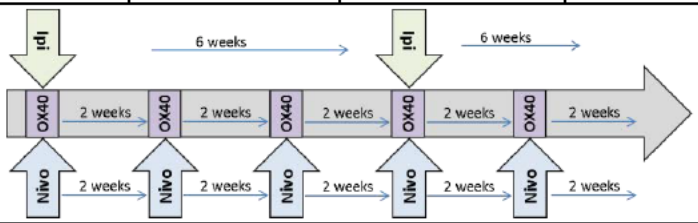
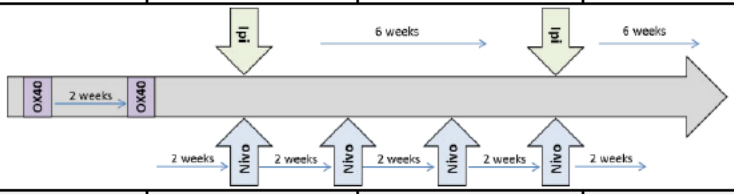
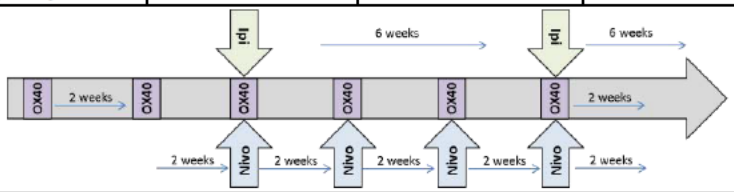
Doublet Expansion Treatment Groups			
Treatment Group F1 (Phase 2 Part A)	**INCAGN01949 Concurrent Dosing**	**Nivolumab**	**Cohorts**
	Selected doses determined to be safe in Phase 1 starting at Cycle 1	240 mg Q2W starting at Cycle 1	Cohort A1 – 70 mg[a,b] Cohort A2 – 200 mg[a,b] Cohort A3 – 350 mg[a,b]
			
Treatment Group F2 (Phase 2 Part B)	**INCAGN01949 Concurrent Dosing**	**Nivolumab**	**Cohorts**
	Recommended dose of INCAGN01949 Q2W starting at Cycle 1	240 mg Q2W starting at Cycle 1	Cohort 1 – PD-1/L1 refractory[b]
			
Treatment Group G	**INCAGN01949 Sequenced Dosing**	**Nivolumab**	**Cohorts**
	Recommended dose of monotherapy[c] INCAGN01949 run-in Q2W for 2 doses	240 mg Q2W starting at Cycle 3	Cohort 1 – PD-1/L1 refractory[b]
			
Treatment Group H	**INCAGN01949 Run-In Followed by Concurrent Dosing**	**Nivolumab**	**Cohorts**
	Recommended dose of INCAGN01949 Q2W starting at Cycle 1	240 mg Q2W starting at Cycle 3	Cohort 1 – PD-1/L1 refractory[b]
			

Table S6: Phase 2 Expansion Treatment Groups (Continued)

Triplet Expansion Treatment Groups				
Treatment Group J	**INCAGN01949 Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**Cohorts**
	Recommended dose of INCAGN01949 Q2W starting at Cycle 1	3 mg/kg Q2W starting at Cycle 1	1 mg/kg Q6W starting at Cycle 1	Cohort 1 – PD-1/L1 refractory[b]
				
Treatment Group K	**INCAGN01949 Sequenced Dosing**	**Nivolumab**	**Ipilimumab**	**Cohorts**
	Recommended dose of monotherapy[c] INCAGN01949 run-in Q2W for 2 doses	3 mg/kg Q2W starting at Cycle 3	1 mg/kg Q6W starting at Cycle 3	Cohort 1 – PD-1/L1 refractory[b]
				
Treatment Group L	**INCAGN01949 Run-In Followed by Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**Cohorts**
	Recommended dose of INCAGN01949 Q2W starting at Cycle 1	3 mg/kg Q2W starting at Cycle 3	1 mg/kg Q6W starting at Cycle 3	Cohort 1 – PD-1/L1 refractory[b]
				

[a] Doses to be explored in Treatment Group F1 Cohorts A1, A2, and A3 may be adjusted by the sponsor based on emerging data and discussed with investigators. Doses will not exceed doses determined to be tolerable in Phase 1 of the study.

[b] Subjects with PD-1/L1 refractory advanced or metastatic gastric cancer, SCCHN, NSCLC, and RCC will be enrolled.

[c] Recommended dose of INCAGN01949 monotherapy will be determined in INCAGN 1949-101.

In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of Grade 3 or Grade 4 INCAGN01949-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 INCAGN01949, 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 (Part 1 and Part 2): Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach and GEJ), esophageal cancer, HCC, melanoma (ocular melanoma excluded), 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 (Part 1 and Part 2): Subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit or who are intolerant to treatment. There is no limit to the number of prior treatment regimens.
- **Phase 2:** Subjects who have a diagnosis of advanced or metastatic gastric cancer, SCCHN, NSCLC, or RCC and are considered refractory to prior PD-1/L1 therapy. Refractory is defined as failure to achieve a CR or PR during prior treatment with an anti–PD-1/L1 agent administered either alone or in combination for advanced or metastatic disease.
  - **For subjects with gastric cancer:** Histologically confirmed adenocarcinoma of the GEJ or stomach.
  - **For subjects with SCCHN:** Histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. Subjects with nasopharyngeal and salivary gland cancer are excluded.
    ***Note*:** Should consent to have tumor evaluated for human papillomavirus (HPV) status (per local institutional testing), or have documentation of HPV status.
  - **For subjects with RCC:** Histologically confirmed diagnosis of RCC that is predominantly clear cell histology.
  - **For subjects with NSCLC:** Subjects with histologically confirmed squamous and nonsquamous histology may be enrolled.
    Note: Subjects with nonsquamous carcinoma should have documentation of driver mutation status for EGFR, ALK fusion oncogene, ROS1 rearrangement, or V600E-activated BRAF mutation status or consent to testing (per local institutional testing) for these markers during the screening period.
    [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 $< 1.0 \times 10^9$/L.
  - Platelets $< 75 \times 10^9$/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 are excluded 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 to be eligible.

- 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, OX40, 4-1BB/CD137, CD27, etc), for any indication.
- 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.
  - ≤ 14 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).

INCAGN01949, Dosage, and Mode of Administration:

Phase 1 and Phase 2: INCAGN01949 will be administered IV over a 30-minute period on Day 1 of each Q2W (ie, 14-day) cycle. INCAGN01949 will be the first drug administered, followed by a 30-minute wait before starting infusion with the next agent. Subjects can continue to receive INCAGN01949 for up to 24 months as long as the subject is considered to derive ongoing clinical benefit at the discretion of the investigator, and the subject has not met any of the Protocol-defined conditions for treatment withdrawal.

Combination Therapies, Dosage, and Mode of Administration:

Nivolumab:

In the doublet Treatment Groups A, C, F, G, and H, nivolumab will be administered IV per instructions provided in the package insert at a dose of 240 mg Q2W (eg, 14 days).

In the triplet Treatment Groups D, E, J, K, and L, nivolumab will be administered IV per instructions provided in the package insert 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/run-in dosing Treatment Groups C, E, G, H, K, and L, nivolumab dosing will begin on Cycle 3 Day 1. Alternate dose administration schedules may also be explored depending on [redacted] safety results.

Nivolumab will be administered at least 30 minutes after the end of the infusion of INCAGN01949 (when applicable), and subjects will continue to receive nivolumab for up to 24 months as long as the subject is considered to derive ongoing clinical benefit at the discretion of the investigator, and the subject has not met any of the Protocol-defined conditions for treatment withdrawal.

Ipilimumab:

Ipilimumab will be administered IV per instructions provided in the package insert to subjects in Treatment Groups B, D, E, J, K, and L, at a dose of 1 mg/kg Q6W (eg, 42 days). In the concurrent dosing Treatment Groups B, D, and J, ipilimumab dosing will begin on Cycle 1 Day 1. In the sequenced dosing Treatment Groups E, K, and L, ipilimumab dosing will begin on Cycle 3 Day 1. Alternate dose administration schedules may also be explored depending on [redacted] safety results.

Ipilimumab will be administered at least 30 minutes after the end of the infusion of INCAGN01949 (when administered on the same day). Ipilimumab will always be administered after INCAGN01949 and nivolumab. Subjects will continue to receive ipilimumab for up to 24 months as long as the subject is considered to derive ongoing clinical benefit at the discretion of the investigator, and the subject has not met any of the Protocol-defined conditions for treatment withdrawal.

At the sponsor's discretion, once the MTD or PAD of INCAGN01949 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 (or after the Week 56 scan), 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 end of treatment.

Estimated Duration of Participation: Subjects may continue on treatment as long as they are receiving benefit and do not meet withdrawal criteria. Study participation, including post-treatment follow-up is expected to average approximately 12 to 18 months per individual subject.

Estimated Number of Subjects:

Enrollment was stopped by the sponsor due to changes in the development plan of INCAGN01949 after 52 subjects were enrolled. Phase 2 of this study will not open for enrollment.

- Phase 1 Dose Escalation – Approximately 54 to 162 evaluable subjects.
  Note: The minimum number of subjects assumes that the starting dose is 7 mg; however, fewer subjects would be enrolled if a higher starting dose is used based on available safety data from the monotherapy study INCAGN 1949-101.
  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 1 Safety Expansion – Approximately 72 subjects
- Phase 2 Part A – Stage 1 – Approximately 60 evaluable subjects
- Phase 2 Part A – Stage 2 - Approximately 90 evaluable subjects
- Phase 2 Part B Stage 1 – Approximately 120 evaluable subjects.
- Phase 2 Part B Stage 2 – Approximately 180 evaluable subjects.
  Note: Assumes that all treatment groups and all cohorts proceed to Stage 2.

Principal Coordinating Investigator: [redacted], MD, [redacted], USA

Statistical Methods:

In Phase 2, a Simon 2-stage design will be run for each cohort within a given doublet or triplet drug expansion. The planned Simon 2-stage designs are summarized in Table S7. Each Simon 2-stage design will have a stopping rule to allow early termination of a particular cohort 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.

Table S7: Planned Simon 2-Stage Designs for Phase 2

Indication	Combination	Stage 1		Stage 2		n	p_0	p_1
		n_1	r_1	n_2	r			
Refractory to anti–PD-1/L1	OX40 + Nivo	20	2	30	8	50	10%	25%
Refractory to anti–PD-1/L1	OX40 + Nivo + Ipi	20	2	30	8	50	10%	25%

- 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 cohort.
- n: total number of subjects.
- p_0: insufficient response rate.
- p_1: target response rate.

The proposed designs for each cohort will be used for any planned Simon 2-stage design (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 cohort will be estimated with 95% confidence intervals. Formal safety reviews, to be held at least every 6 months during Phase 2, will be conducted to review efficacy and safety data.

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LIST OF ABBREVIATIONS

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
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
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
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
Fc	fragment, crystallizable
FcγR	Fc-gamma receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GI	gastrointestinal
GITR	glucocorticoid-induced tumor necrosis factor receptor
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HCC	hepatocellular carcinoma
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
IFN	interferon
IgG	immunoglobulin G
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
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
Nivo	nivolumab
NK	natural killer
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
OX40L	OX40 ligand
PAD	pharmacologically active dose
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
PFS	progression-free survival
PK	pharmacokinetic

Abbreviation	Definition
PoS	probability of success
PR	partial response
PT	prothrombin time
Q2W	every 2 weeks
Q6W	every 6 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	stable disease
SmPC	summary of product characteristics
TCR	T-cell receptor
TEAE	treatment emergent adverse event
Teff	effector T cells
TNBC	triple-negative breast cancer
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
TNFSF	tumor necrosis factor super family
Treg	regulatory T cell
ULN	upper limit of normal

1. INTRODUCTION

This 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 INCAGN01949 in combination with immune therapies. Phase 1 will consist of 2 parts. Dose escalation (Part 1) will use a 3 + 3 + 3 design to determine the PAD and/or MTD of INCAGN01949 in combination with immune therapies in subjects with selected immunogenic advanced or metastatic solid tumors. The safety expansion (Part 2) will further explore tolerated doses of INCAGN01949 given as a run-in of 2 doses followed by concomita[redacted]ne therapies. Phase 2 will further evaluate the safety, tolerability, preliminary efficacy [redacted] of INCAGN01949 in combination with immune therapies. Subjects with advanced or metastatic gastric cancer, SCCHN, NSCLC, and RCC considered to be refractory to PD-1/L1 will be enrolled into Phase 2. A Simon 2-stage design will be used with a stopping rule to allow for early termination of a particular cohort at the end of Stage 1 if insufficient responses are observed.

1.1. Background

1.1.1. The Role of the Immune System in Cancer

The immune system is composed of diverse sets of cells designed to protect a host from pathogens while distinguishing from host and foreign antigens. This immune response is controlled by a series of checks and balances to allow for robust immune responses to pathogens while preventing either an excessive inflammatory event or an autoimmune response. Through immune surveillance, the immune system has been shown to recognize, attack, and destroy tumor cells (Wolchok and Saenger 2008). Detailed analysis of CD8+ T cells and the ratio of CD8+ Teffs/ FoxP3+ Tregs seem to correlate with improved prognosis and long-term survival in many solid tumors (Nosho et al 2010, Chang et al 2014, Preston et al 2013). Although the immune system has been shown to recognize and reject a tumor, many tumors evade immune surveillance or develop mechanisms of resistance.

Targeting the immune system is a proven and effective approach for cancer therapies. FDA-approved checkpoint inhibitors, such as ipilimumab, nivolumab, pembrolizumab, atezolizumab, and avelumab allow for the immune response to continue to proliferate in spite of inhibitory signals. The activation of costimulatory pathways through OX40 is another promising treatment approach and is the focus of this clinical study.

1.1.2. OX40 and the Tumor Necrosis Factor Super Family

OX40 (CD134) is a member of the TNFR superfamily. Other members of the TNFR superfamily include CD40, CD27, FAS, DR3, GITR, and 4-1BB. The TNFR superfamily has been shown to play a role in the regulation of the activation, proliferation, or apoptosis of lymphocytes (Weinberg et al 2000).

OX40 is a 227 amino acid protein that has a cytoplasmic tail, a transmembrane domain, and an extracellular region that contains 3 complete and 1 truncated cysteine-rich domains (Jensen et al 2010, Croft et al 2010). OX40L (also known as CD252) is thought to be the only ligand for OX40 and is thought to only bind to OX40 (Croft et al 2010).

Expression of OX40 has been observed on activated T cells (including CD4+ T cells, CD8+ T cells, and Tregs) (Weinberg et al 2011). OX40 expression is up-regulated on the surface of T cells after TCR engagement and costimulation through CD28 or the presence of inflammatory cytokines, including IL-1, IL-2, and TNF-α (Weinberg et al 2000, Jensen et al 2010). Following antigen activation of naive T cells, OX40 expression occurs between 24 hours and 4 to 5 days following TCR engagement. The upregulation of OX40 on memory T cells after the rechallenge of antigen occurs much more rapidly (within 4 hours) compared with naive T cells (Jensen et al 2010, Croft et al 2009, Gramaglia et al 1998).

Several groups have demonstrated that OX40 is expressed on T cells in the tumor microenvironment. In samples surgically obtained from patients with breast cancer, OX40 expressing T cells were observed in areas surrounding tumor cells, and those cells were thought to be tumor-specific T cells (Weinberg et al 2000). Other groups have shown that OX40+ T cells are present in samples from patients with melanoma, head and neck cancer, breast cancer, and colon cancer (Petty et al 2002, Ladányi et al 2004, Weinberg et al 2000, Vetto et al 1997). In addition, it is thought that the proportion of OX40+ T cells may correlate with improved survival (Petty et al 2002, Ladányi et al 2004).

OX40L is mainly expressed on antigen-presenting cells that include B cells, dendritic cells, endothelial cells, and macrophages (Weinberg et al 2000). OX40L is not expressed at high levels in noninflamed tissues, but is observed at sites of active autoimmune disease. To date, OX40L has not been identified within the tumor microenvironment (Gough et al 2008, Weinberg et al 2011).

Given its role in immune activation, targeting OX40 with an agonistic antibody would be expected to enhance the response of memory and Teff to tumor-specific antigens. The use of an antibody with ADCC capabilities may also selectively deplete Tregs (Gonzalez et al 2016, Bulliard et al 2013). Therefore the use of an anti-OX40 mAb with both agonistic and ADCC properties may be beneficial in boosting the immune response to malignant cells within the body. This hypothesis will be tested in this study.

1.1.3. *In Vitro* and *In Vivo* Evaluation of OX40

Several groups have explored the function of OX40 using both *in vitro* and *in vivo* models. OX40 signaling has been shown to promote T-cell division and survival, suppress the differentiation of Tregs, and modulate cytokine production and signaling. One way this is thought to occur is that OX40L binding to the OX40 receptor results in intracellular recruitment of TNFR-associated molecules, which then activates the NF-κB pathway known to be important in cell survival (Jensen et al 2010). This is consistent with the observation that OX40 receptor engagement has been shown to increase survival, cytokine production, and migration of CD4+ T cells; increase granzyme B, IFN-γ, and perforin production of CD8+ T cells; and increase proliferation and overcome the anergic state in both CD4+ and CD8+ T cells (Moran et al 2013, Weinberg et al 2000).

Murine studies have shown that OX40 agonists promote tumor-specific memory T-cell expansion leading to rejection of tumor growth after inoculation with 4 different tumor cell lines (Weinberg et al 2000). Subsequent experiments performed in mice with established tumors showed that administration of an OX40 agonist led to an increase in the number of CD8+ T cells at the tumor site (Gough et al 2008). This combined with the lack of OX40L expression in the tumor environment indicates that there is a lack of OX40 signaling in the tumor microenvironment and provides additional rationale for OX40 agonist therapy in cancer.

While a contributing factor to the improved proportion of CD8+ T cells to Tregs is likely the activation and proliferation of CD8+ T cells after OX40 engagement, the role of Treg depletion must also be considered. Several studies have shown that OX40 expression is highest in the population of Treg cells within a tumor (Bulliard et al 2014, Marabelle et al 2013). OX40 has been shown to inhibit the suppressing ability of Tregs (Kroemer et al 2007, Valzasina et al 2005). OX40 has been shown to suppress Treg development and function *in vitro*, and in *in vivo* studies, the population of CD4+CD25+FoxP3+ Treg cells was decreased following treatment with an OX40 agonist (Gough et al 2008). Bulliard et al (2014) demonstrated that the administration of an agonistic anti-OX40 mAb induced the depletion of Tregs via an FcγR-mediated ADCC/ADCP manner. Experiments performed in mice showed that this mechanism contributed to the control of tumor growth in mice (Bulliard et al 2014).

1.1.4. Clinical Experience With OX40 Agonists

INCAGN01949 has been evaluated in a Phase 1 dose escalation study, and multiple doses have been tolerated in subjects with advanced or metastatic solid tumors. Other OX40 antibodies have been tested in humans, including a murine antibody and a humanized antibody. Curti et al (2013) developed a 9B12 murine anti-human OX40 mAb and tested this antibody in a Phase 1 dose-escalation study. Thirty subjects with metastatic solid tumors that were refractory to conventional therapy were enrolled and administered doses of anti-OX40 mAb at 0.1 mg/kg, 0.4 mg/kg, or 2 mg/kg on Days 1, 3, and 5 of the study. The murine origin of the antibody precluded further administration of this agent. Results of this study showed that the OX40 agonist was well-tolerated, with observed toxicities mostly Grade 1 or Grade 2. Events of Grade 3 and Grade 4 lymphopenia were observed; however, the lymphopenia that was seen typically resolved by Day 15 or Day 28 in a dose-dependent manner. The most common AEs reported were lymphopenia, fatigue, rash, and flu-like symptoms with fever and chills. The MTD was not reached for this mAb. Tumor shrinkage or SD was seen in subjects with melanoma, renal cell cancer, squamous cell carcinoma of the urethra, prostate cancer, and cholangiocarcinoma, including 1 subject with renal cell cancer that had SD for 470 days.

Correlative studies used Ki-67 to identify proliferating T cells after treatment with the OX40 mAb. Following treatment, the percentage of Ki-67+CD4+ T cells increased by Day 8 and Ki 67+CD8+ T cells increased by Day 15. Compared with the controls, numbers of CD4+/FoxP3- T cells, CD8+ T cells, and CD3-/NK cells were significantly increased; however, the number of CD4+/FoxP3+ Tregs was unchanged. Additional studies showed that treatment with the OX40 mAb increased proliferation and activation of CD8+ T cells. The T cell population of subjects who had some benefit (an initial decrease or stabilization of their disease) were compared with those considered initial progressors, and an increase was seen in Ki-67+ CD4+/FoxP3- and CD8+ T lymphocytes of those subjects who benefited from this treatment. This study shows evidence that OX40 agonists may provide benefit to subjects with late stage metastatic disease

and that treatment with these agents may have long term effects on the T cell population (Curti et al 2013).

Clinical data of a humanized IgG1 anti-OX40 agonistic mAb (MOXR0916) were described at the annual meeting (Hansen et al 2016). MOXR0916 was administered to 70 subjects with a variety of solid tumors within a dose-escalation study (standard 3 + 3 design with doses ranging from 0.2 to 1200 mg). No DLTs were observed; there were no study related deaths, and there were no drug-related Grade 4 AEs. On-study paired biopsies evaluating the tumor microenvironment pre- and post-treatment revealed increases in CD8 T-cell infiltration, upregulation in gene expression of T effector cells, and increased PD-L1 expression in some subjects, which may reflect an increase in IFN-γ. Two objective responses were reported, both in subjects with previously treated RCC.

MOXR0916 was also studied in combination with an anti–PD-L1 antibody, atezolizumab (Infante et al 2016). MOXR0916 was well-tolerated in combination with atezolizumab with no DLTs, deaths, or Grade 4 AEs reported. Induction of PD-L1 expression was observed in subjects who were previously treated with anti-OX40 or anti–PD-1. Partial responses were reported in subjects with RCC and urothelial carcinoma.

1.1.5. Immune Modulators

Immune cell receptors known as checkpoint modulators (collectively known as immune modulators) provide a critical mechanism for the regulation of an immune response. Checkpoint modulation can either diminish an inflammatory process or escalate an immune response. Modulation of coinhibitory and costimulatory receptors of the immune system has become a proven approach for the immunotherapy of cancer (Chen and Mellman 2013).

The development of fully human antibodies that target and modulate immune receptors in humans have led to the discovery of multiple validated targets for the immunotherapy of cancer (Chen and Mellman 2013, Leach et al 1996). Antibodies that engage the various checkpoint modulators can broadly be classified into 2 categories based on mechanism of action: antagonists (blocking the interaction between receptor and cognate ligand[s]) and agonists (inducing or facilitating receptor-forward signaling). Clinical testing of therapeutic antibodies has demonstrated their ability to influence the direction and magnitude of the immune responses, leading to tumor eradication (Yao et al 2013). The blocking of coinhibitory receptors such as CTLA-4 or PD-1 blockade are the basis of FDA-approved therapies to augment an antitumor immune response. Clinical and preclinical research has demonstrated a rationale for targeting costimulatory receptors within the TNFSF (Schaer et al 2013).

While single-agent activity has consistently been reported, combining immunotherapies that target distinct immune pathways has the potential to further enhance the depth and breadth of the antitumor immune response over single agents. Multiple immune mechanisms have been shown to be present concurrently in the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect (Quezada and Peggs 2013, Spranger et al 2014).

Blocking of immune inhibitory pathways is a proven therapeutic modality for the treatment of cancer, as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/L1. Following initial T-cell activation, CTLA-4 is upregulated on T cells and serves as a checkpoint to inhibit the pending immune response. CTLA-4 binds to B7, an inhibitor ligand, with a higher affinity than the costimulatory ligand CD28. Blocking of CTLA-4 with ipilimumab has proven to be an effective method to enhance active immune responses, including antitumor responses. As with CTLA-4, PD-1 is also an inhibitory receptor that is expressed on activated T cells and is the first indication of T-cell exhaustion. Binding of PD-1 to PD-L1 expressed on tumor cells or other immune cells is the checkpoint by which these activated T cells are programed to die and diminishes any active immune response. Blocking of PD-1 with nivolumab or pembrolizumab is proven to be an effective means to prolong antitumor immune responses and offer patients clinical benefit.

Ipilimumab is most active during the induction of antitumor immunity and promotes proliferation of T-cells earlier in the immune response. PD-1–blocking antibodies like nivolumab are more relevant during the effector phase within the tumor microenvironment. Given these unique checkpoints, it was speculated that combining these immune therapies would synergize and lead to a more robust antitumor immune response. This was proven in clinical trials evaluating patients with metastatic melanoma, and the combination of nivolumab and ipilimumab has since been approved by regulatory authorities for melanoma, and this combination continues to be investigated in a number of additional tumor types.

1.1.5.1. Combined Inhibition With Anti-OX40 and Immune Therapies

Preclinical work with anti-OX40 antibodies have elucidated at least 2 potential antitumor mechanisms of action for an agonist OX40 antibody in the clinical setting. First, effective OX40 forward signaling through the TNF receptor-associated factor NFκB signaling axis may promote enhanced T cell responsiveness under conditions of suboptimal stimulation and/or decrease the suppressive activity of intratumoral Treg. Secondly, optimal antitumor efficacy may require co-engagement of activating FcγRs on effector cells in order to selectively deplete immune suppressive Tregs located within the tumor. Therefore, an anti-OX40 mAb could support or enhance other immune therapies.

This hypothesis has been tested in preclinical models in combination with both anti–CTLA-4 and anti–PD-1. Mouse models for prostate and sarcoma tumors were treated with agonist anti-OX40 monotherapy, blocking anti–CTLA-4 monotherapy, and combined anti-OX40 and anti–CTLA-4. The combination regimen had a significant improvement in tumor regression and survival compared with the monotherapy regimens. Correlative analyses demonstrated that the combination therapy increased the proliferation of effector CD4+ T cells and showed a significant increase in IL-2 and IFN-ɣ compared to the monotherapy treatment (Redmond et al 2014). Combinatorial PD-1 blockade and OX40 agonist were studied in a murine ovarian cancer model. Again, combination treatment provided effective inhibition of tumor growth compared to each monotherapy arm. This tumor suppression correlated with significantly higher ratios of effector to Tregs (Guo et al 2014).

The mechanism of action of INCAGN01949 suggests that it may prime the tumor microenvironment in a manner that may support the additional use of an anti–PD-1 mAb either concurrently or subsequently. These combinations may lead to a more robust antitumor immune response.

A humanized OX40 antibody (MOXR0916) has been combined with an anti–PD-L1 antibody in humans and results from that clinical study are discussed above in Section 1.1.4.

1.2. Overview of INCAGN01949

INCAGN01949 is an agonistic antihuman OX40 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 OX40 in order to extend clinical benefit to patients.

1.2.1. Pharmacology of INCAGN01949

INCAGN01949 is a fully human IgG1κ mAb being developed for the treatment of advanced malignancies. INCAGN01949 binds selectively to the extracellular domain of human OX40 and does not bind to related TNFR super family members. INCAGN01949 functions as an OX40 agonist antibody in human cells by activating NF-κB signaling and providing T-cell costimulation in the context of suboptimal TCR activation.

Consistent with a human IgG1κ Fc region, INCAGN01949 binds to both recombinant and cell expressed FcγRs. Co-engagement of FcγRs by INCAGN01949-labeled target cells triggers FcγRIIA and FcγRIIIA signaling and results in FcγR-mediated effector cell activity by a NK cell line, as measured by antibody-dependent cellular cytotoxicity. Also consistent with an IgG1κ Fc region, INCAGN01949 binds to recombinant C1q, the first subcomponent of the C1 complex of the classical pathway of complement activation, and shows evidence of complement-dependent cytotoxicity of OX40-expressing target cells. A fresh human whole blood cytokine release assay was used to evaluate the potential risk of INCAGN01949 eliciting adverse proinflammatory infusion reactions in soluble and complexed (plate-bound) formats. At concentrations up to 100 μg/mL, INCAGN01949 demonstrates only modest induction of IL-6 and does not induce other cytokines in whole blood that *in vivo* would be predictive of CRS in patients. Taken together, the pharmacologic properties of INCAGN01949 illustrate its suitability for clinical development in patients with advanced malignancies.

Preclinical findings highlight the potential antitumor mechanisms of action of INCAGN01949: 1) OX40 signaling in the context of TCR activation enhances effector T-cell activation, cytokine production, and survival, which promote memory T-cell differentiation and reactivation, and 2) intratumoral depletion of T regulatory cells through ADCC (Gonzalez et al 2016). Together, this would suggest that an agonistic OX40 mAb such as INCAGN01949 would have a focused effect in the human immune response leading to the proliferation and augmentation of an ineffectually active antitumor immune response.

[redacted]

1.2.3. Preclinical Safety of INCAGN01949

The safety of INCAGN01949 was evaluated in cynomolgus monkeys that received an IV bolus injection of vehicle control or 1 of the 4 levels ([redacted] mg/kg, [redacted] mg/kg, [redacted] mg/kg, or [redacted] mg/kg) of INCAGN01949 once per week for 5 weeks followed by a 4-week recovery period (except for the [redacted] mg/kg group). INCAGN01949 was well-tolerated and did not reveal any relevant treatment-related effects up to the highest dose level ([redacted] mg/kg) at the end of the 5-week treatment period or after the 4-week recovery period. There was no evidence of tissue cross-reactivity, no evidence of INCAGN01949-induced cytokine release syndrome, and no immune-related AEs.

1.2.4. Clinical Pharmacokinetics

Subjects were administered INCAGN01949 Q2W at doses of [redacted] mg (N = 4), [redacted] mg (N = 4), [redacted] mg (N = 10), [redacted] mg (N = 9), [redacted] mg (N = 6), and [redacted] mg (N = 4) IV as monotherapy in study INCAGN 1949-101. Preliminary unaudited PK data are presented in Table 1. After a single 30-minute IV infusion of doses from [redacted] mg to [redacted] mg, the disposition of INCAGN01949 was biphasic with mean plasma half-life values of 191 to 238 hours. [redacted]

Table 1: Summary of INCAGN01949 Pharmacokinetic Parameters in Cycle 1

Cohort	Dose (N)	C_{max} (ng/mL)	T_{max} (h)[a]	AUC_{0-t} (h·µg/mL)	$AUC_{0-\infty(obs)}$ (h·µg/mL)	Cl_{obs} (mL/h)	$V_{z(obs)}$ (mL)	$t_{½}$ (h)
1	[redacted] mg (4)	1630 ± 735	0.5 (0.5, 4)	178 ± 82.1	258 ± 120	33.0 ± 17.4	5700 ± 1370	140 ± 60.4
2	[redacted] mg (4)	5820 ± 834 5770	2.25 (0.5, 4)	881 ± 213	1250 ± 451	17.2 ± 4.71	3760 ± 1360	149 ± 28.2
3	[redacted] mg (10)	14100 ± 3850	4.0 (0.5, 4)	1630 ± 764	3030 ± 1380	26.1 ± 8.60	6880 ± 1110	209 ± 115
4	[redacted] mg (9)	34700 ± 10800	0.5 (0.5, 4)	5120 ± 2520	8660 ± 6000	35.9 ± 27.2	8520 ± 5040	208 ± 132
5	[redacted] mg (6)	45400 ± 11900	0.5 (0.5, 0.5)	5690 ± 2620	12400 ± 3730	30.8 ± 11.4	10500 ± 3630	264 ± 133
6	[redacted] mg (4)	215000 ± 38800	2.25 (0.5, 4)	24300 ± 5130	31600 ± 49	22.5 ± 3.25	4900 ± 1070	150 ± 19.6

[a] Values are presented as mean ± standard deviation except t_{max}, which is presented as median with range.

1.2.5. Clinical Safety of INCAGN01949

Study INCAGN 1949-101 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 INCAGN01949 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 7 mg, 20 mg, 70 mg, 200 mg, 350 mg, 700 mg, and 1400 mg. INCAGN01949 is administered IV over 30 minutes on Day 1 of each 14-day cycle until disease progression or intolerable toxicity. Decisions for dose escalation are based on predetermined DLTs observed during a 28-day observation period.

As of 05 JAN 2018, no DLTs have been observed, and the MTD/PAD has not yet been defined. Dose expansion is ongoing. Treatment-related AEs occurring in more than 5% of subjects include events of fatigue (n = 8) and diarrhea, nausea, and rash (n = 3 each). One CTCAE Grade 3 treatment-related event of arthralgia was reported. Ten percent of subjects experienced SAEs. Serious AEs occurring in more than 1 subject were nausea, small intestinal obstruction, and dyspnea (n = 2 each, 4%).

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, locally advanced or metastatic urothelial carcinoma, classical Hodgkin lymphoma, MSI-H or dMMR metastatic CRC, and HCC. Nivolumab is also approved in combination with ipilimumab in patients with unresectable or metastatic melanoma (Opdivo 2018). 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, for advanced RCC, for Hodgkin lymphoma, for SCCHN, and for urothelial carcinoma (Opdivo SmPC 2018).

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 ≥ 20% of patients receiving nivolumab monotherapy were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia. The most common adverse reactions seen in ≥ 20% of patients receiving nivolumab in combination with ipilimumab were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory infection, pyrexia, headache, and abdominal pain (Opdivo 2018). Refer to the Opdivo prescribing information and SmPC 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.

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 2018). Refer to the Yervoy prescribing information and SmPC for updated information regarding safety and risks (Yervoy 2018).

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 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). Due to this emerging data, 1 mg/kg Q6W of ipilimumab is being used in the triplet combinations (nivolumab, ipilimumab, and INCAGN01949). Prior to initiating the triplet combinations, the safety and tolerability of ipilimumab 1 mg/kg Q6W will be tested in the doublet combination (ipilimumab and INCAGN01949).

1.4. Potential Risks of the Combination Regimens

The principal 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.

INCAGN01949 was well-tolerated in toxicology studies in cynomolgus monkeys at several doses and has been well-tolerated at doses explored so far in the Phase 1 clinical study (INCAGN 1949-101). No subjects discontinued due to a treatment-related toxicity. Adverse events were generally mild and managed with supportive care. However, as INCAGN01949 is an immune stimulator, it may enhance or exacerbate irAEs associated with any immune therapy.

The risks of nivolumab and ipilimumab are well-characterized and described in more detail in Section 1.3. Of note, a lower dose and less frequent administration of ipilimumab (1 mg/kg Q6W) was selected for the doublet and triplet combinations to minimize AEs based on emerging safety data with the nivolumab and ipilimumab combination (Antonia et al 2016, Hellmann et al 2016).

1.5. Study Rationale

1.5.1. Rationale for Phase 1 Subject Population

Most cancers exhibit genetic heterogeneity, which often translates into enhanced tumor immunogenicity. This concept of tumor immunogenicity is well-appreciated for its role in eliciting an adaptive immune response and determining the efficacy of immunotherapy. Blockade of PD-1/L1 has led to clinical responses in patients with many different types of cancer, including melanoma, NSCLC, RCC, SCCHN, gastric cancer, HCC, TNBC, cervical cancer, and bladder cancer (Hamid et al 2013, Herbst et al 2016, Powels et al 2014, Topalian et al 2014, Brahmer et al 2015, Ferris et al 2016, Melero et al 2016, Le et al 2015, Dirix et al 2016, Frenel et al 2016, Rosenberg et al 2016). The combination of PD-1 and CTLA-4 blockade has shown to significantly improve ORR, PFS, and OS compared with monotherapy PD-1/L1 in a variety of tumors, including melanoma, NSCLC, SCLC, RCC, MSI-H CRC, and gastric cancer (Antonia et al 2016, Hellmann et al 2016, Hammers et al 2016, Overman et al 2016, Janjigian et al 2016).

1.5.2. Rationale for Phase 2 Subject Population

A major difficulty in the development of new agents to treat advanced malignancy is the need to identify the appropriate dose, schedule, and combination partner particularly in settings where the combination partner has no or limited antitumor activity. The combination of nivolumab and ipilimumab has significant benefit in a number of tumor histologies, including melanoma and renal and lung cancer, although at the cost of significant toxicity. Other combinations have not been successfully developed for a variety of reasons. The combination of lenalidomide and pembrolizumab showed lower response rates and increased risk of death in patients with myeloma (FDA 2017), whereas the combination of Roche's OX40 antibody and atezolizumab was associated both with reduced clinical activity and toxicity, suggesting a possible negative effect on the tumor microenvironment (Infante et al 2016). Studies by Messeheimer et al (2016) and Shrimali et al (2017) in animal models suggest that simultaneous administration of antibodies that recognize PD-1 and OX40 provides a setting that is associated with upregulation of multiple checkpoint molecules that predispose tumor-specific T cells to undergo apoptosis upon antigen engagement. In order to identify the appropriate dose of INCAGN01949 to combine with nivolumab, we propose evaluating a population of PD-1/L1 refractory patients with a fixed dose of nivolumab and escalating doses of INCAGN01949. The best data available on response to PD-1/L1 blockade in combination with other agents in patients with no response or relapse following PD-1/L1 therapy comes from a small dataset of patients treated with nivolumab and anti-LAG3. In this study, 48 subjects with relapsed or refractory melanoma were treated. In subjects with prior response, there were 2 responses among 13 patients (15%), 1 response among 14 patients with stable disease (7%) and 2 responses in 20 patients with progressive disease (10%; Ascierto et al 2017). In this study, we will attempt to determine whether the response rate differs from the approximately 10% response rate observed in the study presented by Ascierto et al (2017). The selection of renal cell cancer, gastric cancer, SCCHN, and NSCLC for investigation is based on the immune responsiveness of these populations, the variable expression levels of OX40 in these tumor types with renal cell cancer virtually devoid of OX40 expression and gastric cancer and head and neck cancer having a significant fraction of patients with high level expression and lung cancer showing low level

expression (data on file). This will allow the assessment of a correlation between OX40 expression in the tumor and clinical response.

1.5.2.1. Renal Cell Carcinoma

Renal cell carcinoma accounts for almost 4% of all new cancer cases, with an estimated 62,700 new cases being diagnosed in 2016 (SEER 2017). The 5-year survival rate has improved to approximately 74% from the period from 2006 to 2012 (SEER 2017).

Sunitinib and pazopanib are kinase inhibitors against the vascular endothelial growth factor receptors and are commonly used for first-line treatment of metastatic clear cell RCC. Temsirolimus is used first-line for patients with poor-risk RCC. Second-line options include axitinib, cabozantinib, lenvatinib plus everolimus, and nivolumab (Choueiri and Motzer 2017). Nivolumab is approved for subjects with RCC who have received prior anti-angiogenic therapy (Opdivo 2018). In the pivotal study of nivolumab compared with everolimus, a statistically significant improvement in OS was seen in subjects randomized to nivolumab (25.0 months) versus everolimus (19.6 months). The ORR was also higher in subjects receiving nivolumab (25%) as compared with everolimus (5%; Motzer et al 2015). Nivolumab was also studied in combination with ipilimumab in subjects with metastatic RCC. Subjects were randomized to different dose groups. One group received a dose of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg Q2W (Nivo 3 + Ipi 1). Another group received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg Q2W (Nivo 1 + Ipi 3). Forty-seven subjects were enrolled into each dose group with approximately 50% of subjects having received prior systemic therapy. The ORR was 40% in each dose group (Hammers et al 2016). The combination of nivolumab and ipilimumab was recently approved by the US FDA for patients with intermediate- or poor-risk, previously untreated RCC (Opdivo 2018). Recent advances have improved treatment options for patients with metastatic RCC; however, resistance develops commonly to the treatment regimens, and further treatment options are needed for this population.

1.5.2.2. Gastric Cancer

Cancers of the upper GI tract are highly lethal malignancies. Locally advanced unresectable and metastatic gastroesophageal cancers are not curable conditions, and the goals of therapy include palliation of symptoms and prolongation of survival. Despite a large number of randomized trials, there is no consensus as to the best regimen for initial or second-line chemotherapy for advanced gastroesophageal cancer. In general, combination chemotherapy regimens provide higher response rates, but this translates into only modestly longer durations of disease control and survival.

Clinical activity with anti–PD-1 checkpoint blockade has been seen in patients with previously treated advanced gastroesophageal carcinomas. In the Checkmate-032 Phase 1/2 study, 160 subjects with gastric, esophageal, or GEJ, irrespective of PD-L1 status, who had progressed on chemotherapy (≥ 2 prior regimens) were treated with standard doses of nivolumab (N3; n = 59), nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1 + I3; n = 49), or standard doses of nivolumab + ipilimumab 1 mg/kg (N3 + I1; n = 52). The ORR was 14% (N3), 26% (N1 + I3), and 10% (N3 + I1), including 2 patients with a CR. Additionally, disease control was seen in

38% of patients. The median OS was 5 months (N3), 6.9 months (N1 + I3), and 4.8 months (N3 + I1; Kojima et al 2016, Janjigian et al 2016).

Pembrolizumab was recently approved by the US FDA for patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 as determined by an approved test (Keytruda 2018). Clinical activity and improved OS in patients with chemotherapy refractory disease are encouraging and further support investigation of combination immune therapies.

1.5.2.3. Squamous Cell Carcinoma of the Head and Neck

The prognosis of patients with recurrent or metastatic SCCHN is generally poor. The median survival in most is 6 to 9 months. Conventional cytotoxic chemotherapy, checkpoint inhibitor immunotherapy, and molecularly targeted compounds have activity in metastatic and recurrent head and neck cancer. The most widely used agents include platinum compounds (cisplatin, carboplatin), taxanes (docetaxel, paclitaxel, Abraxane®), methotrexate, fluorouracil, and cetuximab. More recently, pembrolizumab and nivolumab have shown clinically significant activity in patients who progressed on or after platinum-based chemotherapy regimens (Keytruda 2018, Mehra et al 2016, Ferris et al 2016).

Pembrolizumab was approved by the US FDA in August 2016 for patients with recurrent or metastatic SCCHN who have had progression on or after platinum-based chemotherapy. The approval was based upon results from 174 subjects in a Phase 1b study and is conditional upon the completion of randomized Phase 3 clinical studies. An ORR was seen in 28 of 174 patients (16%), including 8 CRs (5%). The median DOR was not reached, and 23 of 28 responses were longer than 6 months (Keytruda 2018). Responses were independent of HPV status. Updated results were presented at the 2016 ASCO meeting: the median OS was 8 months, and the 6- and 12-month OS rates were 58% and 38%, respectively (Mehra et al 2016).

Nivolumab was approved by the US FDA in NOV 2016 for patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy. In the Checkmate-141 Phase 3 study, 361 subjects with platinum refractory, recurrent or metastatic disease were randomly assigned to either nivolumab or a single-agent investigator's choice of therapy (methotrexate, docetaxel, or cetuximab; Ferris et al 2016). With a median follow-up of 5.1 months, OS for the entire study population was significantly longer in subjects treated with nivolumab (median 7.5 vs 5.1 months, 1-year OS rate 36% vs 17%). The ORR was also increased with nivolumab (13% versus 6%). In a prespecified exploratory analysis, OS was significantly increased with immunotherapy in patients with PD-L1 expression ≥ 1% (8.7 vs 4.6 months). In a post-hoc exploratory analysis, OS was significantly increased in subjects treated with immunotherapy with HPV positive tumors (median 9.1 vs 4.4 months). The difference in OS was not statistically significant in those with HPV-negative tumors (median 7.5 vs 5.8 months).

1.5.2.4. Non–Small Cell Lung Cancer

The treatment landscape for patients with NSCLC has been evolving rapidly with the approval of immunotherapy in this disease over the past several years. Anti–PD-1/L1 inhibitors have recently been approved in locally advanced and metastatic NSCLC in a variety of settings (Keytruda 2018, Imfinzi 2018, Opdivo 2018, Tecentriq 2018). Unfortunately, a large number of patients still do not respond to treatment, and treatment options remain limited. Recent data have shown that combining the PD-1 inhibitor, pembrolizumab, with chemotherapy can significantly improve the ORR, PFS, and OS as compared with chemotherapy alone, but the response rate was 47.6%, leaving a majority of patients seeking additional treatment (Gandhi et al 2018). Immunotherapy combinations have also been tested with the combination of PD-1 and CTLA-4 (nivolumab with ipilimumab) having been shown to improve PFS in patients with a high tumor mutational burden, but again, less than half of the patients treatment achieve an object response with an ORR of 45.3% (Hellmann et al 2018). Clearly, there remains an unmet need for effective treatment for these patients who do not respond to a PD-1/L1 inhibitor.

1.5.3. Rationale for Dose and Schedule of Combination Therapies

The proposed starting dose and schedule of INCAGN01949 (7 mg IV Q2W) in the Phase 1 portion of the study is based on preclinical data and emerging clinical data from the ongoing first in human monotherapy study (INCAGN 1949-101).

To ensure safety in combination with nivolumab and ipilimumab in this study, the starting dose of INCAGN01949 will be defined as 1 dose level below the highest tolerated dose of INCAGN01949 when given as monotherapy. Current clinical observations from study INCAGN 1949-101 have shown safety and tolerability of INCANG01949 when administered at a dose up to 1400 mg Q2W. As data emerge from Study INCAGN 1949-101, a higher starting dose of INCAGN01949 may be used but will not exceed 1 dose level below the highest tolerated monotherapy dose of INCAGN01949.

The current schedule of administration (Q2W) is based on both preclinical and clinical observations. The Q2W schedule used in Study INCAGN 1949-101 was based on the PK of INCAGN01949 determined in cynomolgus monkeys following a single and weekly IV doses. The mean estimated terminal half-life was estimated to be 11.4 days. These preclinical findings support Q2W dosing and are consistent with observations in the first-in-human study (INCAGN 1949-101).

The proposed mechanism of action of INCAGN01949 is the depletion of Tregs in the tumor microenvironment and costimulation of recently activated Teff cells. This suggests that INCAGN01949 may help prime the immune microenvironment for a more robust antitumor immune response. Preclinical models have shown that the priming of the tumor microenvironment with monotherapy anti-OX40 prior to anti–PD-1 therapy offers greater antitumor activity when compared with combining concurrently with an anti–PD-1 or anti–PD-L1 antibody (Messenheimer et al 2016). Clinical data evaluating the monotherapy activity of anti-OX40 antibodies have shown changes in the tumor microenvironment that would favor an antitumor immune response as evident by the rise of tumor infiltrating lymphocytes, T helper 1 cytokines, and a diminished Treg population (Hansen et al 2016). However, when combined concurrently with an anti–PD-L1 antibody, the response rates were lower than expected (2 PRs of 58 subjects); of note, 1 of the responders was a subject who had previously

received monotherapy anti-OX40 antibodies (Infante et al 2016). These findings suggest a rationale to evaluate INCAGN01949 as a monotherapy immune primer prior to subsequent immunotherapies as well as dosing both therapies concurrently. As more clinical data emerge from Study INCAGN 1949-101, the dosing and schedule of INCAGN01949 will be re-assessed with investigators.

The approved dose of nivolumab (240 mg Q2W) has been selected for the doublet combination (nivolumab and INCAGN01949). The approved doses of nivolumab and ipilimumab in combination are nivolumab 3 mg/kg Q2W and ipilimumab 3 mg/kg Q3W for 4 doses. Additional combination studies of nivolumab (3 mg/kg Q2W) and ipilimumab (1 mg/kg Q6W) showed similar efficacy with better tolerability. To minimize any additional risk to safety, INCAGN01949 will be combined with nivolumab (3 mg/kg Q2W) and ipilimumab (1 mg/kg Q6W) in the triplet cohorts (nivolumab, ipilimumab, and INCAGN01949; see Section 1.3 and Section 1.4; Antonia et al 2016, Hellmann et al 2016).

INCAGN01949 has been generally well-tolerated at doses ranging from 7 mg to 1400 mg as monotherapy and up to 350 mg in combination with nivolumab or ipilimumab. Preliminary data have not elucidated the appropriate pharmacologic dose for future studies. The decision for dose selection will be based on results from biopsy data from the INCAGN 1949-101 study and the efficacy of INCAGN01949 and nivolumab combination in PD-1/L1 refractory patients.

1.5.4. Rationale for the Study Endpoints

1.5.4.1. Efficacy Endpoints

Efficacy endpoints of this study include ORR, DOR, DCR, duration of disease control, and PFS by investigator assessment based on RECIST v1.1.

1.5.4.1.1. Modified RECIST

Note: Modified RECIST was removed as an endpoint in Amendment 3 of the Protocol; however, mRECIST principles may still be used to guide treatment discontinuation decisions for disease progression. RECIST v1.1 will be adapted to account for the unique tumor response characteristics seen with immunotherapy (Wolchok et al 2009). Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may cause subjects who are clinically benefiting from treatment to be discontinued from treatment prematurely. Therefore, RECIST v1.1 will be used with the following adaptations to guide treatment discontinuation decisions for disease progression:

If radiologic imaging shows initial progressive disease, tumor assessment should be repeated at least 4 weeks, but no later than 6 weeks, later in order to confirm disease progression with the option of continuing treatment while awaiting radiologic confirmation of progression.

In subjects who have initial evidence of radiological progression but are clinically stable as defined below, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of disease progression if they are clinically stable as defined by the following criteria:

- Absence of clinically significant signs and symptoms 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.

If repeat imaging shows < 20% tumor burden compared with nadir, stable or improved previous new lesion (if identified as cause for initial disease progression), and stable/improved nontarget disease (if identified as cause for initial disease progression), then treatment may be continued or resumed. If repeat imaging confirms disease progression due to any of the scenarios listed below, subjects will be discontinued from study therapy. However, 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 (see Section 7.7.1).

In determining whether or not the tumor burden has increased or decreased, the site study team should consider all target lesions, as well as nontarget lesions (refer to RECIST v1.1 guidelines).

Scenarios where disease progression is confirmed at repeat imaging include the following:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared with nadir.
- Nontarget disease resulting in initial disease progression is worse (qualitative).
- New lesion resulting in initial disease progression is worse (qualitative).
- Additional new lesion(s) since last evaluation.

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy but with subsequent disease response. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation of disease progression.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

Phase 1

- To evaluate the safety, tolerability, and DLTs of INCAGN01949 in combination with immune therapies and to define the recommended dose(s) of INCAGN01949 when given in combination with immune therapies.

Phase 2

- To evaluate the efficacy of INCAGN01949 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 INCAGN01949 when given in combination with immune therapies by assessing ORR, DOR, DCR, duration of disease control, and PFS per RECIST v1.1.
- To evaluate the safety and tolerability of INCAGN01949 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.
- 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 assessments per RECIST v1.1.
- DCR, defined as the percentage of subjects having CR, PR, or SD, will be determined by investigator assessment of a radiographic disease assessments per RECIST 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.
- 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.
- 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 (Part 1 and Part 2): Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach and GEJ), esophageal cancer, HCC, melanoma (ocular melanoma excluded), 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 (Part 1 and Part 2): Subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit or who are intolerant to treatment. There is no limit to the number of prior treatment regimens.
6. **Phase 2:** Subjects who have a diagnosis of advanced or metastatic gastric cancer, SCCHN, NSCLC, or RCC and are considered refractory to prior PD-1/L1 therapy. Refractory is defined as failure to achieve a CR or PR during prior treatment with an anti–PD-1/L1 agent administered either alone or in combination for advanced or metastatic disease.
    a. **For subjects with gastric cancer:** Histologically confirmed adenocarcinoma of the GEJ or stomach.
    b. **For subjects with SCCHN:** Histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. Subjects with nasopharyngeal and salivary gland cancer are excluded.
    Note: Should consent to have tumor evaluated for HPV status (per local institutional testing), or have documentation of HPV status.
    c. **For subjects with RCC:** Histologically confirmed diagnosis of RCC that is predominantly clear cell histology.
    d. **For subjects with NSCLC:** Subjects with histologically confirmed with squamous and nonsquamous histology may be enrolled.
    Note: Subjects with nonsquamous carcinoma should have documentation of driver mutation status for EGFR, ALK fusion oncogene, ROS1 rearrangement, V600E-activated BRAF mutation status or consent to testing (per local institutional testing) for these markers during the screening period.

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. 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. 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. AST, ALT, 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 are excluded 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 to be eligible.
g. INR, PT, or aPTT > 1.5 × ULN.

2. Prior treatment with any TNFSF agonist (eg, GITR, OX40, 4-1BB/CD137, CD27, etc), for any indication.
3. 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. ≤ 14 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. Hepatitis B virus DNA and HCV RNA must be undetectable. Subjects cannot be positive for HBV DNA, HCV RNA, hepatitis B surface antigen, or anti–hepatitis B core antibody, without approval from the 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 hepatitis B surface antigen 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

Based on a change in the development plan for INCAGN01949, enrollment to the study was stopped after 52 subjects were enrolled. Phase 2 of this study will not open for enrollment. Continued study treatment will be permitted for up to 24 months at the discretion of the investigator for subjects who are considered to be obtaining ongoing clinical benefit.

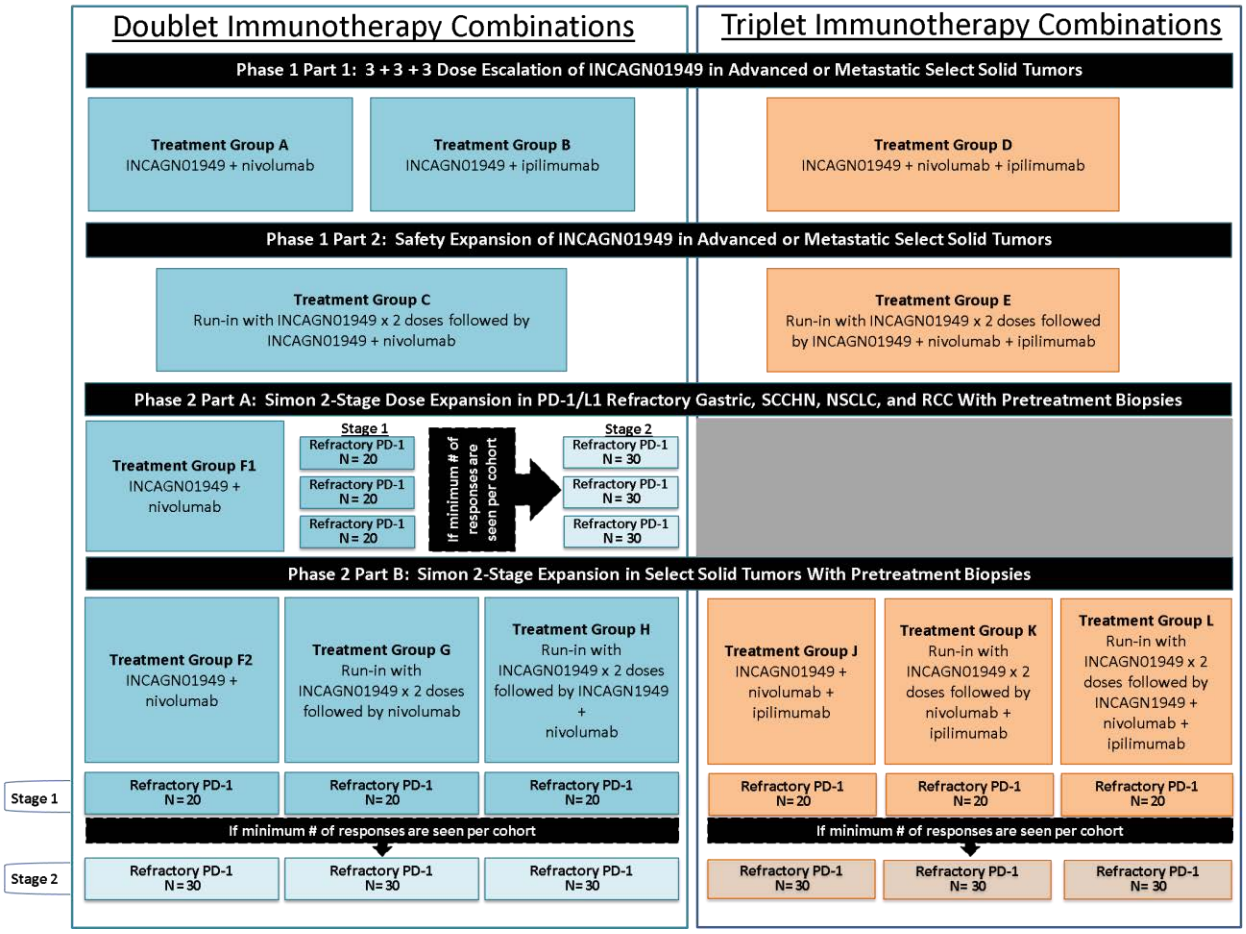
This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of INCAGN01949 when given in combination with immune therapies. Phase 1 will consist of 2 parts. Dose escalation (Part 1) will consist of a 3 + 3 + 3 design to determine the MTD, or PAD, defined as a dose that provides a maximal biochemical effect [redacted] of INCAGN01949 when given in combination with immune therapies. The safety expansion (Part 2) will further explore tolerated doses of INCAGN01949 given as a run-in of 2 doses followed by concomitant immune therapies. Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach and GEJ), esophageal cancer, 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 will be enrolled in both parts of Phase 1.

The Phase 2 expansion will further evaluate the safety, tolerability, and efficacy of immune therapies combined with INCAGN01949 in 2 different parts. In Phase 2 Part A, the selected doses of INCAGN01949 will be combined with nivolumab in PD-1/L1 refractory subjects with advanced or metastatic gastric cancer, SCCHN, NSCLC, and RCC to further explore the safety and efficacy of different doses of INCAGN01949 in combination with nivolumab in this population. Phase 2 Part B will evaluate the recommended dose(s) of INCAGN01949 in combination with nivolumab (and ipilimumab where applicable). PD-1/L1 refractory subjects with advanced or metastatic gastric cancer, SCCHN, NSCLC, or RCC will also be enrolled in Phase 2 Part B. Pretreatment biopsies will be mandatory for subjects enrolled into either part of Phase 2. On-treatment biopsies will be optional.

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.

See Figure 1 for overall study design.

Figure 1: Overall Study Design



4.1.1. Phase 1 Part 1 – Dose Escalation

A minimum of 3 evaluable subjects will be enrolled in each treatment group beginning with INCAGN01949 Dose Cohort 1 (7 mg; starting dose). A higher starting dose of INCAGN01949 may be used if safety data are available from the monotherapy study (INCAGN 1949-101) but will not exceed 1 dose level below the highest tolerated dose of INCAGN01949 monotherapy. If a higher starting dose is used, the new dose will be communicated to investigational sites with an administrative letter. The doses of INCAGN01949 to be evaluated in each treatment group are summarized in Table 2.

Table 2: INCAGN01949 Dose Cohorts

Dose Cohort	Dose of INCAGN01949
-1	2 mg
1 (Starting dose)	**7 mg**[a]
2	20 mg
3	70 mg
4	200 mg
5	350 mg
6	700 mg

[a] A higher starting dose of INCAGN01949 may be used if safety data is available from the monotherapy study (INCAGN 1949-101) but will not exceed 1 dose level below the highest tolerated dose of INCAGN01949 monotherapy. If a higher starting dose is used, the dose will be communicated to investigational sites with an administrative letter.

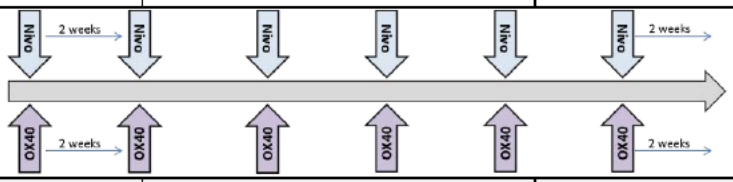
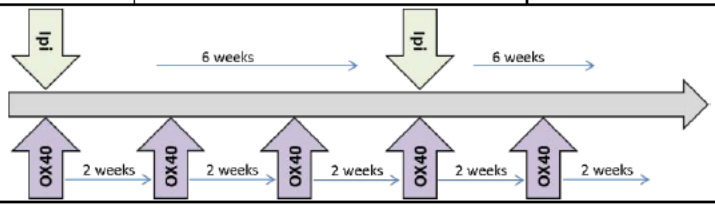
The first 3 evaluable subjects enrolled within an INCAGN01949 dose cohort will be observed for the specified DLT observation period before the next dose cohort begins enrollment. If 0 DLTs occur in a cohort of 3 evaluable subjects, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 1 of 3 evaluable subjects experiences 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 $\geq$ 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 INCAGN01949, 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. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor.

4.1.1.1. Doublet Immune Therapy Combinations

Phase 1 dose escalation will begin with 2 doublet treatment groups, as outlined in Table 3, which will be explored in parallel.

Table 3: Doublet Immune Therapy Treatment Groups for Dose Escalation

Treatment Group A	**INCAGN01949 Concurrent Dosing**	**Nivolumab**	**DLT Observation Period**
	See INCAGN01949 dose cohorts (Table 2) Q2W starting at Cycle 1	240 mg Q2W starting at Cycle 1	28 days
			
Treatment Group B	**INCAGN01949 Concurrent Dosing**	**Ipilimumab**	**DLT Observation Period**
	See INCAGN01949 dose cohorts (Table 2) Q2W starting at Cycle 1	1 mg/kg Q6W starting at Cycle 1	28 days
			

4.1.1.1.1. Treatment Group A (INCAGN01949 + Nivolumab)

Treatment Group A will treat subjects with INCAGN01949 at the assigned dose level administered IV Q2W in combination with nivolumab 240 mg IV Q2W (see Table 3). **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 INCAGN01949 will proceed as outlined in Table 2 until the MTD or PAD of INCAGN01949 in combination with nivolumab is determined.

4.1.1.1.2. Treatment Group B (INCAGN01949 + Ipilimumab)

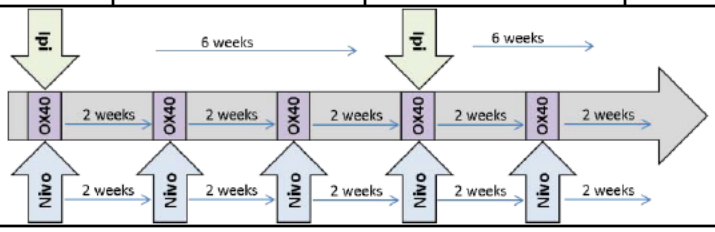
Treatment Group B will treat subjects with INCAGN01949 at the assigned dose level administered IV Q2W in combination with ipilimumab 1 mg/kg IV Q6W (see Table 3). **There will be a waiting period of 48 hours between dose administration of the first subject and second subject of each dosing cohort.** The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days before the next cohort begins enrollment. Dose escalation of INCAGN01949 will proceed as outlined in Table 2 until the MTD or PAD of INCAGN01949 in combination with ipilimumab is determined.

At the sponsor's discretion, once the MTD or PAD of INCAGN01949 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 INCAGN01949 in combination with higher doses of ipilimumab is not tolerated, dose de-escalation of INCAGN01949 will proceed as outlined in Table 2 until the MTD or PAD of INCAGN01949 is determined.

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 in Part 1 dose escalation have cleared 3 INCAGN01949 dose levels (see Table 2) or the MTD or PAD of INCAGN01949 in combination with each component has been determined (whichever occurs first). The starting dose of INCAGN01949 will be 2 dose levels below the last dose cohort deemed safe in the doublet combination. If there are different MTDs of INCAGN01949 with nivolumab and ipilimumab, then the starting dose of the triplet will be 2 dose levels below the lowest MTD in the doublet. For example, if 200 mg of INCAGN01949 is safe in the doublet combinations with both nivolumab and ipilimumab, then the starting dose in the triplet will be 20 mg. If the MTD of INCAGN01949 is 200 mg in the nivolumab doublet combination and the MTD of INCAGN01949 in the ipilimumab combination is 70 mg, then the starting dose of INCAGN01949 for the triplet immune therapy combination will be 7 mg. The triplet immune therapy combinations will be explored in parallel as outlined in Table 4.

Table 4: Triplet Immune Therapy Treatment Group for Dose Escalation

	INCAGN01949 Concurrent Dosing	Nivolumab	Ipilimumab	DLT Observation Period
	See INCAGN01949 dose cohorts (Table 2) Q2W starting at Cycle 1	3 mg/kg Q2W starting at Cycle 1	1 mg/kg Q6W starting at Cycle 1	28 days
Treatment Group D				

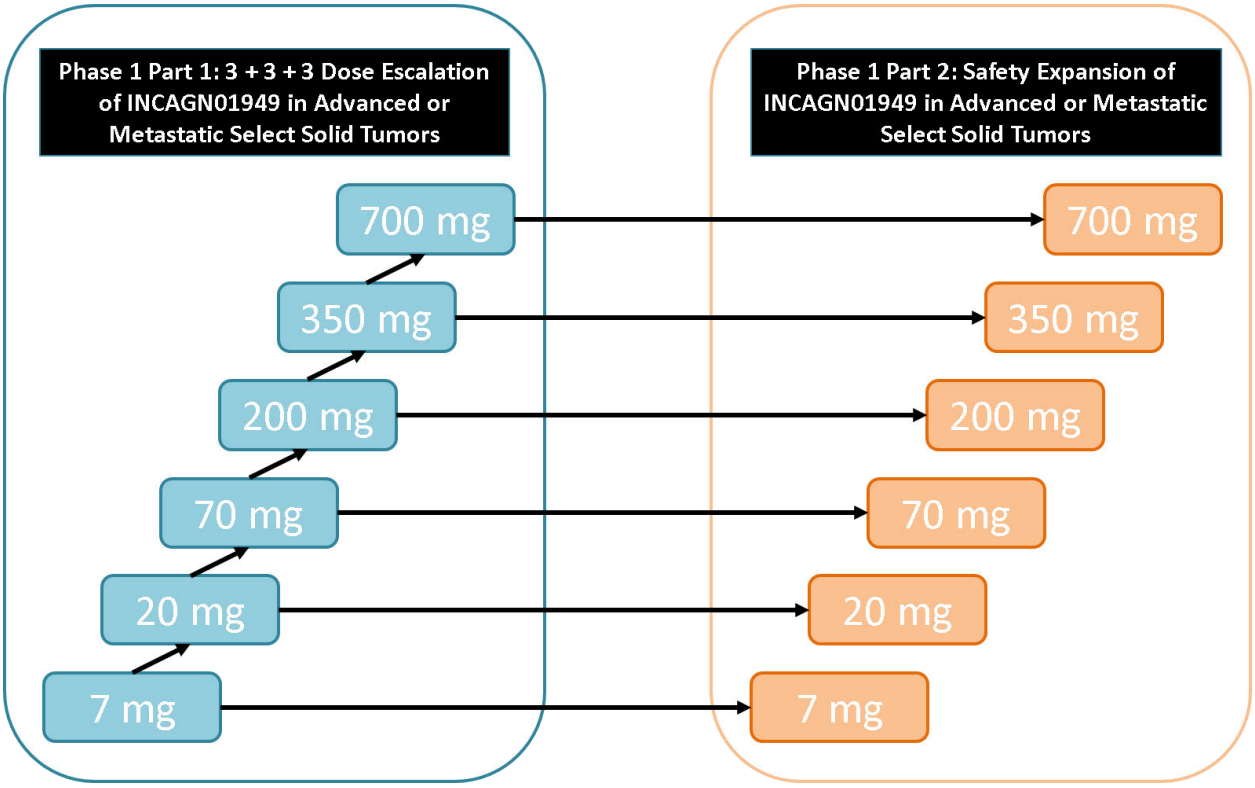
4.1.1.2.1. Treatment Group D (INCAGN01949 + Nivolumab + Ipilimumab)

Treatment Group D will treat subjects with INCAGN01949 at the assigned dose level administered IV Q2W in combination with nivolumab 3 mg/kg IV Q2W and ipilimumab 1 mg/kg IV Q6W (see Table 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 INCAGN01949 will proceed as outlined in Table 2 until the MTD or PAD of INCAGN01949 in combination with nivolumab and ipilimumab is determined; however, the dose of INCAGN01949 in the triplet combination will not exceed the lowest MTD of INCAGN01949 established in the applicable doublet combinations. For example, if the MTD of INCAGN01949 in combination with nivolumab is 350 mg and the MTD of INCAGN01949 in combination with ipilimumab is 200 mg, then the dose of INCAGN01949 would not exceed 200 mg.

4.1.2. Phase 1 Part 2 – Safety Expansion

Once an INCAGN01949 dose cohort in Treatment Group A is deemed tolerable, up to 6 subjects will be enrolled in Treatment Group C at the same dose of INCAGN01949. For example, if INCAGN01949 7 mg is tolerated in Treatment Group A, then 7 mg will be explored in up to 6 subjects in Treatment Group C. Likewise, once an INCAGN01949 dose in Treatment Group D is deemed tolerable, up to 6 subjects will be enrolled in Treatment Group E at the same dose of INCAGN01949. For example, if INCAGN01949 350 mg is tolerated in Treatment Group D, then 350 mg will be explored in up to 6 subjects in Treatment Group E. Doses of INCAGN01949 in Treatment Group C will be escalated in parallel to those explored in Treatment Group A but will not exceed the MTD of INCAGN01949 established in Treatment Group A. The same rules will apply with Treatment Group D and E. See Figure 2 below. Alternate dose administration schedules may also be explored depending on [redacted] safety results. The sponsor may elect to prioritize (or deprioritize) enrollment to specific dose cohorts based on emerging safety or efficacy data in collaboration with investigational sites.

Figure 2: Phase 1 Safety Expansion (Part 2)



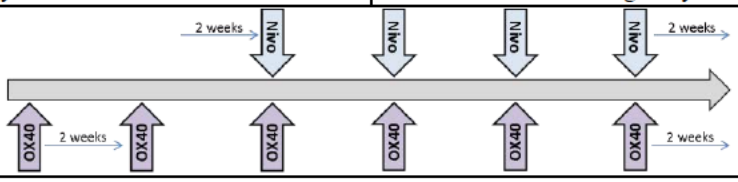
If the cumulative incidence of Grade 3 or Grade 4 INCAGN01949-related AEs occurs in > 40% of subjects in a particular treatment group, then further enrollment will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action (eg, lower the dose of INCAGN01949, change dose frequency, etc).

4.1.2.1. Doublet Immune Therapy Combination for Safety Expansion

4.1.2.1.1. Treatment Group C (INCAGN01949 Run-In Followed by Concurrent Dosing With Nivolumab)

Treatment Group C will treat subjects with a 2-dose run-in of INCAGN01949 Q2W at the assigned dose level followed by the combination of INCAGN01949 Q2W plus nivolumab 240 mg Q2W (starting at Cycle 3, see figure in Table 5).

Table 5: Doublet Immune Therapy Treatment Group for Safety Expansion

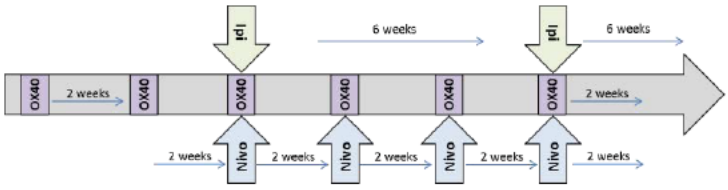
	INCAGN01949 Run-In Followed by Concurrent Dosing	Nivolumab
Treatment Group C	See INCAGN01949 dose cohorts (Table 2) Q2W starting at Cycle 1	240 mg Q2W starting at Cycle 3
		

4.1.2.2. Triplet Immune Therapy Combination for Safety Expansion

4.1.2.2.1. Treatment Group E (INCAGN01949 Run-In Followed by Concurrent Dosing With Nivolumab and Ipilimumab)

Treatment Group E will treat subjects with INCAGN01949 at the assigned dose level Q2W for 2 doses followed by INCAGN01949 Q2W in combination with nivolumab 3 mg/kg Q2W, and ipilimumab 1 mg/kg Q6W (starting at Cycle 3; see figure in Table 6).

Table 6: Triplet Immune Therapy Treatment Group for Safety Expansion

	INCAGN01949 Run-In Followed by Concurrent Dosing	Nivolumab	Ipilimumab
Treatment Group E	See INCAGN01949 dose cohorts (Table 2) Q2W starting at Cycle 1	3 mg/kg Q2W starting at Cycle 3	1 mg/kg Q6W starting at Cycle 3
			

4.1.3. Phase 2 – Dose Expansion

Phase 2 of the study will further evaluate the safety, tolerability, efficacy, [redacted], and [redacted] in subjects with gastric cancer, SCCHN, NSCLC, and RCC. Part A of Phase 2 will enroll subjects considered PD-1/L1 refractory to further explore a range of doses of INCAGN01949 found to be safe in Phase 1 in combination with nivolumab given concurrently. Enrollment of the selected tumor types within each dose cohort may be managed by the sponsor in an administrative manner.

Phase 2 Part B of the study will enroll advanced or metastatic gastric cancer, SCCHN, NSCLC, or RCC considered to be PD-1/L1 refractory. Additional tumor-specific cohorts may be added, by Protocol amendment, based on emerging data. [redacted]

The Phase 2 expansion treatment groups and tumor-specific cohorts for each treatment group are outlined in Table 7. Treatment Groups G and K will only be administered 2 doses of INCAGN01949 followed by standard therapies. As INCAGN01949 will not be given in combination with the standard therapies for Treatment Groups G and K, the recommended dose of INCAGN01949 determined in the monotherapy study INCAGN 1949-101 will be used. A Simon 2-stage design will be used 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 in the cohorts. The approximate number of subjects for Stage 1 and Stage 2 for each treatment group and cohort is described in Table 21 and Figure 1. Enrollment in Phase 2 Part B will begin when the recommended dose of INCAGN01949 in combination with nivolumab (and ipilimumab as applicable) has been determined. The sponsor may elect to prioritize (or deprioritize) enrollment to specific dose cohorts based on emerging safety or efficacy data in collaboration with investigational sites.

Table 7: Phase 2 Expansion Treatment Groups

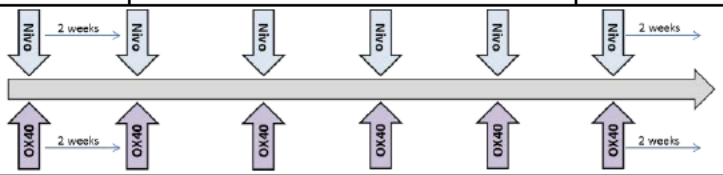
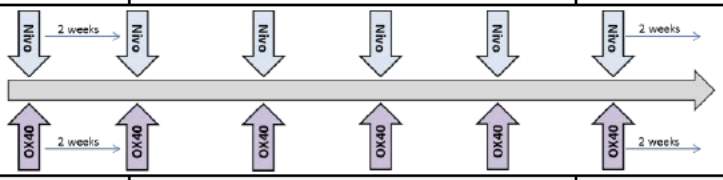
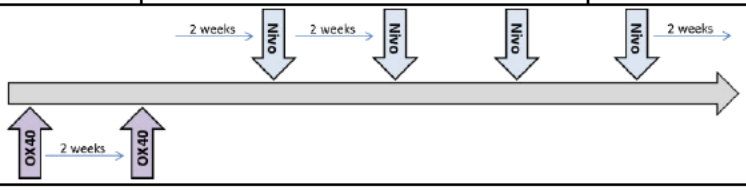
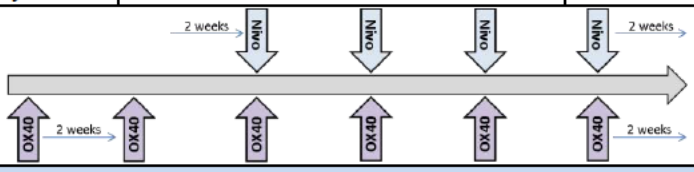
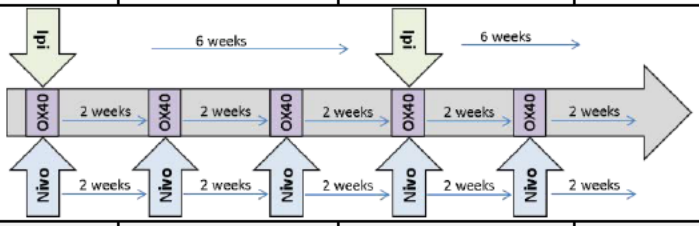
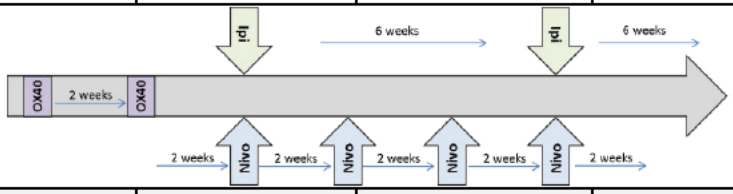
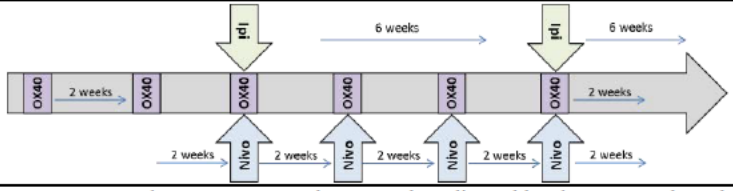
Doublet Expansion Treatment Groups			
Treatment Group F1 (Phase 2 Part A)	**INCAGN01949 Concurrent Dosing**	**Nivolumab**	**Cohorts**
	Selected doses determined to be safe in Phase 1 starting at Cycle 1	240 mg Q2W starting at Cycle 1	Cohort A1 – 70 mg[a,b] Cohort A2 – 200 mg[a,b] Cohort A3 – 350 mg[a,b]
			
Treatment Group F2 (Phase 2 Part B)	**INCAGN01949 Concurrent Dosing**	**Nivolumab**	**Cohorts**
	Recommended dose of INCAGN01949 Q2W starting at Cycle 1	240 mg Q2W starting at Cycle 1	Cohort 1 – PD-1/L1 refractory[b]
			
Treatment Group G	**INCAGN01949 Sequenced Dosing**	**Nivolumab**	**Cohorts**
	Recommended dose of monotherapy[c] INCAGN01949 run-in Q2W for 2 doses	240 mg Q2W starting at Cycle 3	Cohort 1 – PD-1/L1 refractory[b]
			

Table 7: Phase 2 Expansion Treatment Groups (Continued)

Doublet Expansion Treatment Groups			
Treatment Group H	**INCAGN01949 Run-In Followed by Concurrent Dosing**	**Nivolumab**	**Cohorts**
	Recommended dose of INCAGN01949 Q2W starting at Cycle 1	240 mg Q2W starting at Cycle 3	Cohort 1 – PD-1/L1 refractory[b]
			
Triplet Expansion Treatment Groups			
Treatment Group J	**INCAGN01949 Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**Cohorts**
	Recommended dose of INCAGN01949 Q2W starting at Cycle 1	3 mg/kg Q2W starting at Cycle 1	1 mg/kg Q6W starting at Cycle 1	Cohort 1 – PD-1/L1 refractory[b]
				
Treatment Group K	**INCAGN01949 Sequenced Dosing**	**Nivolumab**	**Ipilimumab**	**Cohorts**
	Recommended dose of monotherapy[c] INCAGN01949 run-in Q2W for 2 doses	3 mg/kg Q2W starting at Cycle 3	1 mg/kg Q6W starting at Cycle 3	Cohort 1 – PD-1/L1 refractory[b]
				
Treatment Group L	**INCAGN01949 Run-In Followed by Concurrent Dosing**	**Nivolumab**	**Ipilimumab**	**Cohorts**
	Recommended dose of INCAGN01949 Q2W starting at Cycle 1	3 mg/kg Q2W starting at Cycle 3	1 mg/kg Q6W starting at Cycle 3	Cohort 1 – PD-1/L1 refractory[b]
				

[a] Doses to be explored in Treatment Group F1 Cohorts A1, A2, and A3 may be adjusted by the sponsor based on emerging data and discussed with investigators. Doses will not exceed doses determined to be tolerable in Phase 1 of the study.
[b] Subjects with PD-1/L1 refractory advanced or metastatic gastric cancer, SCCHN, NSCLC, and RCC will be enrolled.
[c] Recommended dose of INCAGN01949 monotherapy will be determined in INCAGN 1949-101.

In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of Grade 3 or Grade 4 INCAGN01949-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 INCAGN01949, 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 are objective measurements, and only comparisons with pretreatment conditions will be made.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Enrollment was stopped by the sponsor following a change in the development plan of INCAGN01949 after 52 subjects were enrolled. Phase 2 of this study will not open for enrollment.

Approximately 306 to 684 subjects may be enrolled as follows:

- Phase 1 Dose Escalation – Approximately 54 to 162 evaluable subjects.
  Note: The minimum number of subjects assumes that the starting dose is 7 mg; however, fewer subjects would be enrolled if a higher starting dose is used based on available safety data from the monotherapy study INCAGN 1949-101.
  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 1 Safety Expansion – Approximately 72 subjects.
- Phase 2 Part A – Stage 1 – Approximately 60 evaluable subjects.
- Phase 2 Part A – Stage 2 – Approximately 90 evaluable subjects.
- Phase 2 Part B – Stage 1 – Approximately 120 evaluable subjects.
- Phase 2 Part B – Stage 2 – Approximately 180 evaluable subjects.
  Note: Assumes that all treatment groups and all cohorts proceed to Stage 2.

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). 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. 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. INCAGN01949

5.2.1.1. Description and Administration

The study drug (INCAGN01949) is in liquid form in the formulation buffer of 20 mM histidine, 250 mM sorbitol, pH 6.5 at a strength of 10 mg/mL to be used for IV infusion. The infusion site should not be used for blood sampling.

Study drug will be diluted in 0.9% normal saline or acceptable admixture as outlined in the Pharmacy Manual and will be administered by qualified personnel as an IV infusion over a 30-minute (-5/+10 minutes) period on Day 1 of each cycle when INCAGN01949 is scheduled to be given. On days when INCAGN01949 will be administered along with other agents administered by infusion, INCAGN01949 will be administered first, and subsequent immune therapy/therapies will be administered at least 30 minutes after the end of the infusion of INCAGN01949.

In Phase 1, subjects will be administered study drug, according to cohort enrollment (Table 2). In Phase 2, subjects will be administered study drug at the recommended dose and schedule. Subjects can continue to receive INCAGN01949 for up to 24 months as long as the subject is considered to derive ongoing clinical benefit at the discretion of the investigator, and the subject has not met any of the Protocol-defined conditions for treatment withdrawal (see Section 5.5).

In Treatment Groups G and K, INCAGN01949 is only administered on Day 1 of Cycles 1 and 2.

5.2.1.2. Supply, Packaging, and Labeling

Study drug will be supplied as 5 mL of aqueous solution in 10 mL glass vials with 10 mg/mL of INCAGN01949. Study drug will be packaged as open-labeled supplies, and each vial will be labeled 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. INCAGN01949 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 instructions in the package insert at the site, at a dose that is dependent on the assigned treatment group as follows:

- Doublet Treatment Groups A and F: 240 mg on Day 1 of every 2-week (ie, 14-day) cycle.
- Doublet Treatment Groups C, G, and H: 240 mg on Day 1 of every 2-week (ie, 14-day) cycle beginning on Cycle 3 Day 1.
- Triplet Treatment Groups D and J: 3 mg/kg on Day 1 of every 2-week (ie, 14-day) cycle.
- Triplet Treatment Groups E, K, and L: 3 mg/kg on Day of every 2-week (ie, 14-day) cycle beginning on Cycle 3 Day 1.

Alternate dose administration schedules may also be explored depending on [redacted] safety results.

Nivolumab will be administered at least 30 minutes after the end of the infusion of INCAGN01949 (when applicable), and subjects will continue to receive nivolumab for up to 24 months as long as the subject is considered to derive ongoing clinical benefit at the discretion of the investigator, and the subject has not met any of the Protocol-defined conditions for treatment withdrawal.

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 instructions provided in the package insert at the site, at a dose that is dependent on the assigned treatment group as follows:

- Doublet Treatment Group B and Triplet Treatment Group D: 1 mg/kg administered every 6 weeks (eg, 42 days) beginning on Cycle 1 Day 1.
- Triplet Treatment Group J: 1 mg/kg administered every 6 weeks (eg, 42 days) beginning on Cycle 1 Day 1.
- Triplet Treatment Groups E, K, and L: 1 mg/kg administered every 6 weeks (eg, 42 days) beginning on Cycle 3 Day 1.

Alternate dose administration schedules may also be explored depending on [redacted] safety results.

Ipilimumab will be administered at least 30 minutes after the end of the infusion of INCAGN01949 (when administered on the same day). Ipilimumab will always be administered after INCAGN01949 and nivolumab. Subjects will continue to receive ipilimumab for up to 24 months as long as the subject is considered to derive ongoing clinical benefit at the discretion of the investigator, and the subject has not met any of the Protocol-defined conditions for treatment withdrawal.

At the sponsor's discretion, once the MTD or PAD of INCAGN01949 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 INCAGN01949, Nivolumab, and Ipilimumab

INCAGN01949, 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 and modifications to the study drug (INCAGN01949) 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 of INCAGN01949 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. Dose interruptions of INCAGN01949 should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation will not be permitted.

No dose reductions of INCAGN01949, nivolumab, or ipilimumab are allowed for the management of toxicities of individual subjects. Doses of INCAGN01949, nivolumab, and ipilimumab may be delayed for toxicity management (see Section 5.4.6).

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 Phase 1 Part 1 (Treatment Groups A, B, and D). 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 8, except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

Individual subject dose interruptions of study drug may be made based on events observed at any time during treatment; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD of INCAGN01949, decisions 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 8: Definition of Dose-Limiting Toxicity

Nonhematologic toxicity
• Any liver function abnormalities that meet the definition of Hy's law[a]. • Any grade encephalopathy. • Any ≥ Grade 3 nonhematologic toxicity **EXCEPT** the following: – Transient (≤ 72 hours) abnormal electrolyte values, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions. – Nausea, vomiting, and diarrhea adequately controlled with supportive care within 48 hours. – Changes in cholesterol and triglycerides. An event clearly and incontrovertibly due to disease progression or extraneous causes. – Grade ≥ 3 changes in amylase and lipase that is not associated with symptoms or clinical manifestations of pancreatitis. – Grade 3 fatigue < 1 week. – 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 neutropenia or thrombocytopenia lasting > 7 days. • Any grade febrile neutropenia (fever > 101°F/38.3°C). • Grade 4 anemia not explained by underlying disease or some other concomitant disorder.
Immune-related toxicity[b]
• ≥ 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. • ≥ Grade 2 pneumonitis
General
• Any death not clearly due to the underlying disease or extraneous causes. • 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 Part 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 Grade 4 INCAGN01949-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 INCAGN01949, 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] Hy's law is defined as 1) ALT or AST elevation ≥ 3 times ULN AND 2) total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND 3) no other apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

[b] 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 INCAGN01949 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 dose interruptions are outlined in Table 9. 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 9: Criteria for Interruption and Restarting of Study Treatment

CTCAE Grade/Severity	Hold Treatment (Y/N)	Timing for Restarting Treatment	Dose Level for Restarting INCAGN01949	Dose Level for Restarting Immune Therapies	Treatment Discontinuation
1-2 (Mild to 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

Nivolumab and ipilimumab are immune checkpoint inhibitors and are known to induce irAEs. INCAGN01949 is an immune modulator that may enhance the activity of other immunotherapies and therefore may also exacerbate any irAEs associated nivolumab and ipilimumab. 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 ruled out.** 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 10. 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 10: Supportive Care Guidelines for Immune-Related Adverse Events

CTCAE Grade/Severity	Supportive Care[a]
1 (Mild)	• Monitor symptoms and provide symptomatic treatment.
2 (Moderate)	• Monitor symptoms and provide symptomatic treatment. • Consider consultation with specialists as necessary. • Consider systemic corticosteroids per institutional standard of care.
3-4 (Severe to 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 11 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 11: 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 hours (± 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 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 safety through the safety follow-up period.
- 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.
- The subject has received 24 months of treatment with study drug.

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 follow-up visits (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 follow-up.
- 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.

If the subject discontinues study treatment and actively withdraws consent for collection of safety follow-up data, 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 assessments**.

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 medications administered after 60 days after the last dose of study treatment should be recorded for SAEs as defined in Section 8. 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:

- 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 12), and all laboratory assessments will be performed as indicated in Table 13. Table 14 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 12: Schedule of Clinical Assessments

Visit Day (Range) / Evaluation/Window	Protocol Section	Screening	Treatment[a]					Post-Treatment[b]		
			Cycles 1 and 6		Cycles ≥ 10 Weeks	All Other Cycles	Every 8 Weeks			
			Day 1	Day 8	Day 1	Day 1	Disease Status	EOT	Safety Follow-Up Visit 1	Safety Follow-Up Visit 2
		Day -28 to -1		± 1 day	± 3 days	± 3 days	± 7 days	± 3 days	30 days (+ 7 days)	60 days (+ 7 days)
Administrative procedures										
Informed consent	7.1	X								
Inclusion/exclusion criteria	3.1, 3.2	X	X[c]							
Contact IRT	7.2	X	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	X
Administer INCAGN01949	5.2.1.1		X[d]		X[d]	X[d]				
Administer nivolumab	5.2.2.1		X[e]		X[e]	X[e]				
Administer ipilimumab	5.2.2.2		X[f]		X[f]	X[f]				
Poststudy anticancer therapy status	7.5								X	X
Clinical procedures/assessments										
Comprehensive physical examination (including height)	7.6.2.1	X								
Targeted physical assessment	7.6.2.2		X	X[g]	X	X		X	X	X
Vital signs and weight	7.6.3	X	X	X[g]	X	X		X	X	X
ECOG performance status	7.8.1	X	X	X[g]		X				
Laboratory assessments	7.6.5	X	X	X	X	X		X	X	X
12-lead ECG[h]	7.6.4	X								
AE assessment	7.6.1	X	X	X[g]	X	X		X	X	X
Efficacy measurements										
Radiologic tumor assessments	7.7	X[i]					X[j]	X[k]		

[a] Treatment cycles will be Q2W (14 days ± 3 days).

[b] The safety follow-up visits should be conducted approximately 30 days and 60 days after the EOT visit (or after the last dose of study treatment if the EOT visit was not performed) or before the initiation of a new anticancer treatment, whichever comes first.

[c] Assessment of inclusion/exclusion criteria is only required at Cycle 1 Day 1.

[d] In Treatment Groups G and K, INCAGN01949 is only administered on Day 1 of Cycles 1 and 2.

[e] In Treatment Groups C, E, G, H, K, and L, nivolumab administration begins at Cycle 3 Day 1.

[f] For subjects enrolled into Treatment Group B (INCAGN01949 + ipilimumab) and Treatment Groups D and J (INCAGN01949 + nivolumab + ipilimumab), ipilimumab will be administered on Cycle 1 Day 1 and then Day 1 of every third cycle (Cycle 1, Cycle 4, Cycle 7, etc). In Treatment Groups E, K, 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 every 3 weeks 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.

[g] Only required for Cycle 6 Day 8 if subject is experiencing AEs > Grade 2.

[h] 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.

[i] 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.

[j] On-study imaging will be performed at Week 8 and then every 8 weeks (± 7 days) for the first 12 months (until the Week 56 scan) and then every 12 weeks (± 7 days) thereafter. Imaging should follow calendar days starting with Day 1 of INCAGN01949 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.

[k] If scan was obtained within 4 weeks before the date of treatment 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).

Table 13: Schedule of Laboratory Assessments

Visit Day (Range) / Evaluation/Window	Protocol Section	Timing of Assessment	Screening	Treatment									Post-Treatment		
				C1		C2	C4	C6		C7	Every 4th Cycle (C8, C12)	All Other Cycles			
				D1	D8	D1	D1	D1	D8	D1	D1	D1	EOT	Safety Follow-Up Visit 1	Safety Follow-Up Visit 2
			Day -28 to -1		± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	30 days (+ 7 days)	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
Hematology with differential	7.6.5	N/A	X[c]	X[d]	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]												
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.

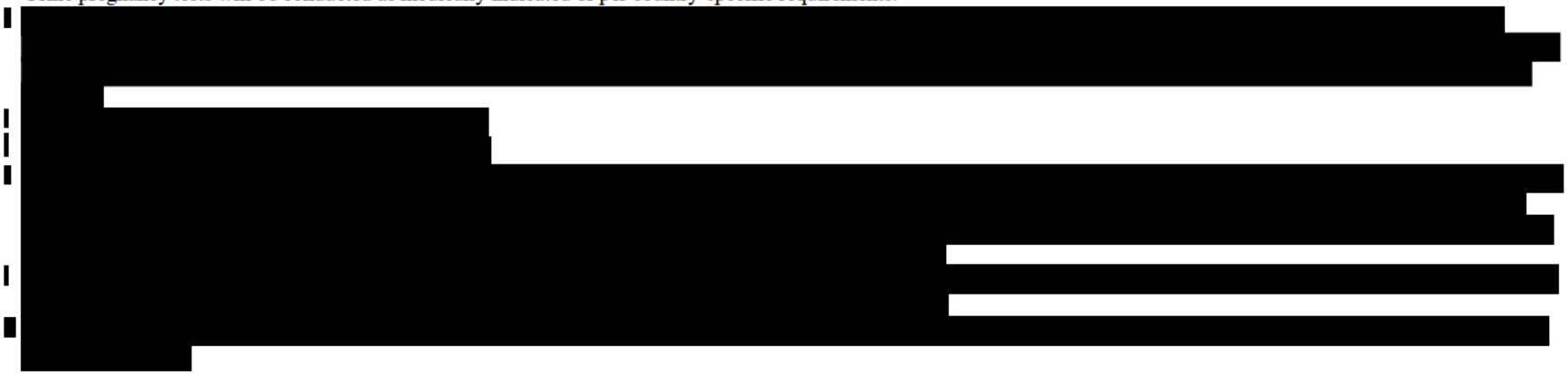


Table 14: Local Laboratory Tests: Required Analytes

<table>
<tr><th>Serum Chemistries</th><th>Hematology</th><th>Urinalysis</th><th>Hepatitis Screening</th><th>Coagulation</th></tr>
<tr><td rowspan="2">Albumin
Alkaline phosphatase
ALT
AST
Bicarbonate
Blood urea nitrogen
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="2">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• White blood cell count

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

Absolute values must be provided for:
White blood cell differential laboratory results:
• Lymphocytes
• Neutrophils</td><td rowspan="2">Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein</td><td>Hepatitis B surface antigen
Hepatitis B core antibody
HBV-DNA
HCV antibody
HCV-RNA</td><td>PT
aPTT
INR</td></tr>
<tr><td>Pregnancy Testing</td><td>Endocrine Monitoring</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>Thyroid-stimulating hormone (TSH)
Free thyroxine (T4)
Total triiodothyronine (T3)/FT3[a]</td></tr>
</table>

[a] 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. 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 12, 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 follow-up visits.

6.4. 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 be considered to have completed the study.

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. 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. 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 subject number and treatment group assignment. Additionally, the IRT will be contacted to update the subject's disposition and disease response and for study drug resupply. Refer to the IRT manual for detailed instructions.

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.

7.6. Safety Assessments

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.

The 12-lead ECG readings will be interpreted by the investigator at the site to be used for immediate subject management. 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 13. Table 14 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 13, as medically indicated, or per country-specific requirement. 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 13) to rule out hepatitis infection; required analytes are shown in Table 14. 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 Assessment Disease

Modified RECIST will be applied by the site 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 may 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 15 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 15: 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 12). 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 performed 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 INCAGN01949 and then every 8 weeks (56 days ± 7 days) for 12 months (until the Week 56 scan) 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, response may 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 may 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.

7.8. 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 12 according to the criteria in Table 16.

Table 16: 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]

[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.

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 term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

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 changes in study drug) 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 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, regardless of when it occurs.

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 (INCAGN01949 IB). 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 reviews will be conducted by the study team and an independent internal review committee, at least every 6 months during Phase 2, to review safety data. Details regarding internal data monitoring will be addressed in the Data 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

Based on a change in the development plan for INCAGN01949, enrollment to the study was stopped after 52 subjects were enrolled into Phase 1. Therefore, only Phase 1 statistical analyses will be performed.

9.1. Study Populations

The full analysis set includes all subjects enrolled in the study who received at least 1 dose of study drug (INCAGN01949). This population will be used in the analyses of demographic, baseline, safety, study drug administration, and efficacy data.

9.2. Selection of Sample Size

9.2.1. Sample Size for Phase 1

9.2.1.1. Sample Size for Phase 1 Part 1

The primary objective of Phase 1 of the study is to determine the DLTs and the recommended dose of INCAGN01949 when given in combination with immune therapies. The total number of subjects will depend on the number of dose levels tested before the recommended dose(s) are established. Dose escalation will follow the 3 + 3 + 3 design algorithm (see Section 4.1.1). 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 will be enrolled in each treatment group (9 subjects per dose level for 6 dose levels, if dosing begins with INCAGN01949 7 mg), or if a higher starting dose is used based on available safety data from the monotherapy trial (INCAGN 1949-101), then up to 36 evaluable subjects in each treatment group (9 subjects per dose level for 4 dose levels, if dosing begins with 70 mg) 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 20.

Table 20: 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 INCAGN01949 if the Cohort 1 dose is not well-tolerated.

9.2.1.2. Sample Size for Phase 1 Part 2

Once an INCAGN01949 dose cohort in Treatment Group A is deemed tolerable, 6 subjects will be enrolled in Treatment Group C at the same dose of INCAGN01949. For example, if INCAGN01949 7 mg is tolerated in Treatment Group A, then 7 mg will be explored in 6 subjects in Treatment Group C. Likewise, once an INCAGN01949 dose cohort in Treatment Group D is deemed tolerable, 6 subjects will be enrolled in Treatment Group E at the same dose of INCAGN01949. For example, if 350 mg of INCAGN01949 is tolerated in Treatment Group D then 350 mg will be explored in 6 subjects in Treatment Group E.

9.2.2. Sample Size for Phase 2

Phase 2 will further evaluate the safety, tolerability, preliminary efficacy, [redacted] and [redacted] of the recommended dose of INCAGN01949 in combination with immune therapies as part of doublet and triplet drug expansion cohorts. In Phase 2 Part A, a Simon 2-stage design will be run for each dose expansion cohort. In Phase 2 Part B, a Simon 2-stage design will be run for each cohort within a given doublet or triplet drug expansion cohort.

The sample size for each cohort within a given doublet or triplet expansion cohort will be guided by the Simon 2-stage design. The planned Simon 2-stage designs are summarized in Table 21. Each Simon 2-stage design will have a stopping rule to allow early termination of a cohort 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 Simon 2-stage designs run for each cohort within each doublet or triplet expansion cohort will have design parameters that are determined by historical response rates. As all cohorts are being run in subjects determined to be PD-1/L1 refractory, the same Simon 2-stage parameters will be used for all cohorts.

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 INCAGN01949 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 cohort 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 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 21.

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 during Phase 2.

Table 21: Planned Simon 2-Stage Designs for Phase 2

Indication	Combination	r_1	n_1	r	n_2	n	p_0	p_1
Refractory to anti–PD-1/L1	OX40 + Nivo	2	20	8	30	50	10%	25%
Refractory to anti–PD-1/L1	OX40 + Nivo + Ipi	2	20	8	30	50	10%	25%

9.3. Level of Significance

This is an exploratory study and no formal statistical tests will be performed. All confidence intervals will be 95%.

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 dose and tumor type.

If there are $\leq r_1$ responses in each doublet or triplet expansion out of the n_1 evaluable subjects specific to that cohort (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 cohorts in which greater than r_1 responses among the evaluable Stage 1 subjects is observed, where r_1 is also specific to the 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 cohort 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 hypothesis tests in the Simon 2-stage design, the null response rate is p_0% and alternative response rate is p_1%, where p_0 and p_1 are specific to the cohort 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 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.

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.

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 4 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 22), 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 22: 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	> 38ºC	< 35.5ºC
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 23). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 23: 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]

9.5. Analyses for the Data Monitoring Committee

Formal safety reviews will be conducted by the study team and an independent internal review committee, at least every 6 months during the Phase 2 portion of the study, to review safety data. Details regarding internal data monitoring will be addressed in the Data Monitoring Charter.

9.6. Interim Analysis

9.6.1. Simon 2-Stage Design

In Phase 2, the Simon 2-stage design will be applied for each cohort within a given doublet or triplet expansion cohort (Simon 1989). During Stage 1, n_1 evaluable subjects treated at the recommended dose and schedule will be enrolled, and if r_1 or fewer responses are observed, then the cohort will be discontinued. As discussed in Section 9.2.2, the Simon 2-stage designs run for each doublet or triplet expansion cohort have design parameters that are determined by historical response rates and will different sample sizes and different futility rules, depending on the historical response rate.

The probability of early termination for Stage 1 for both doublet and triplet expansion cohorts is summarized in Table 24. If at least 3 responses are observed in the first evaluable 20 subjects, then 30 additional evaluable subjects will be enrolled in this cohort (Stage 2).

Table 24: Probability of Early Termination of Stage 1 for Simon 2-Stage Design

True Response Rate	Probability of Early Termination at Stage 1
5%	92.5%
10%	67.7%
15%	40.5%
20%	20.6%
25%	9.1%

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.

10.2. 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.
- Return of study drug to the investigator or designee by subjects.

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 privacy laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject names will not be supplied to the sponsor or its designee, if applicable. 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 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 or 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.

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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 provided of avoiding pregnancy 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 2017 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 pneumonitis, 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 2017 for treatment of cancer-related infections (Category 2B recommendation).

irAE	Supportive Care
Diarrhea/Colitis (continued)	***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 2017 for treatment of cancer-related infections [Category 2B recommendation]). **For Grade 3 or 4 (severe or new symptoms, new/worsening diarrhea/colitis, 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 2017 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 2017 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 2017 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 2017 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 2017 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 ≥ 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	Date
Amendment (Version) 1:	14 JUN 2017
Amendment (Version) 2:	29 MAY 2018
Amendment (Version) 3:	05 DEC 2018

Amendment 3 (05 DEC 2018)

Overall Rationale for the Amendment: The primary purpose of the amendment is to decrease procedures, including the removal of disease and survival follow-up, for subjects remaining on the study.

1. **Synopsis; Section 1.5.4.1, Efficacy Endpoints; Section 2.1.2, Secondary Objectives; Section 2.2.2, Secondary Endpoints; Section 5.5.1, Withdrawal Criteria; Section 5.5.2, Withdrawal Procedures; Section 6, Study Assessments (Table 12 and Table 13); Section 6.3, End of Treatment; Section 6.4, Safety Follow-Up; Section 7.9.1.1, Blood Sample Collection (Table 17and Table 18); Section 9.4.1.2, Secondary Efficacy Analyses**

   Description of change: The disease follow-up and survival follow-up periods, as well as some study procedures and laboratory assessments during the EOT and safety follow-up visits, were removed. Overall survival was removed as an endpoint for the study.

   Rationale for change: Enrollment to the study was stopped due to changes in the development plan of INCAGN01949. Therefore, disease and survival follow-up data would not add significant value to the study at this point in the clinical development program.

2. **Synopsis; Section 5.2.1.1, Description and Administration; Section 5.2.2.1, Nivolumab; Section 5.2.2.2, Ipilimumab; Section 5.5.1, Withdrawal Criteria**

   Description of change: Study treatment (including INCAGN01949, nivolumab, and ipilimumab) will be limited to 24 months of treatment with INCAGN01949.

   Rationale for change: There have been several reports that continued treatment with immunotherapy does not provide additional benefit.

   Another approved anti–PD-1 agent, pembrolizumab, is administered for a maximum of 2 years for all FDA-approved indications with the exception of melanoma (Keytruda 2018). Recent follow-up data were published for subjects with NSCLC who received nivolumab. This study limited nivolumab treatment to 96 weeks and the 5-year OS was reported to be 16%. Of the subjects who survived for 5 years, 75% received no further cancer treatment after discontinuing nivolumab and had no evidence of progressive disease at the time the data were prepared for publishing.

The authors concluded that these data suggest that long-term survival may be achieved after nivolumab treatment of 2 years or less (Gettinger S, Horn L, Jackman D, et al. Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: results from the CA209-003 study. J Clin Oncol 2018;17:1675-1684.).

Additional studies have come to similar conclusions. Hodi et al presented data that compared OS in subjects who discontinued nivolumab + ipilimumab combination treatment due to toxicity versus the overall combination treatment group. The OS at 18 months in the group that discontinued due to toxicity was 79.5 months compared with 73.2 months in the overall population. These data also suggest that a shorter treatment duration of immunotherapy may be sufficient to provide an OS benefit (Hodi F, Postow M, Chesney J, et al. Overall survival in patients with advanced melanoma [MEL] who discontinued treatment with nivolumab [NIVO] plus ipilimumab [IPI] due to toxicity in a phase II trial [CHECKMATE 069]. J Clin Oncol 2016;34[suppl]:Abstract 9518.).

Another recent data update provides long-term information on the KEYNOTE-010 study, in which subjects were treated for up to 2 years with pembrolizumab. Most of the subjects had a durable response even after discontinuing therapy after the 2-year treatment period, with the response ongoing in 64% of those subjects at a median follow-up of 43.4 months (Herbst RS, Garon EB, Kim D-W, et al. Long-term survival in patients with advanced NSCLC in the KEYNOTE-010 study overall and in patients who completed 2 years of pembrolizumab. Ann Oncol 2018;29[suppl 8]:Abstract LBA63.). These data collectively suggest that treatment beyond 24 months with an immunotherapy may not provide additional benefit to oncology patients.

3. **Synopsis; Section 4.1, Overall Study Design; Section 4.3.1, Planned Number of Subjects; Section 9, Statistics**

   Description of change: Text was revised to indicate that enrollment was stopped at 52 subjects.

   Rationale for change: Enrollment to the study was stopped after 52 subjects were enrolled in Phase 1 due to changes in the development plan of INCAGN01949. No subjects were enrolled in Phase 2; therefore, only Phase 1 statistical analyses will be performed.

4. **Synopsis; Section 1.5.4.1, Efficacy Endpoints; Section 2.1.2, Secondary Objectives; Section 2.2.2, Secondary Endpoints; Section 4.2, Measures Taken to Avoid Bias; Section 7.7.1, Modified RECIST Assessment Disease; Section 7.7.1.12, Tumor Imaging During the Study; Section 9.4.1.2, Secondary Efficacy Analyses**

   Description of change: Efficacy evaluation per modified RECIST (mRECIST) was removed as an endpoint for the study. mRECIST may continue to be used guide treatment decisions for disease progression.

   Rationale for change: Efficacy will continue to be analyzed using RECIST v1.1. The additional analysis of mRECIST would not add significant value to the study at this point in the clinical development program.

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

Amendment 2 (29 MAY 2018)

Overall Rationale for the Amendment: The primary purpose of the amendment is to add cohorts to Phase 2 Part A that will allow further exploration of the dose of INCAGN01949 in combination with nivolumab in subjects considered refractory to prior PD-1/L1 therapy. Other cohorts were removed from Phase 2 so that the overall estimated number of subjects decreased significantly.

1. **Synopsis; Section 4.1, Overall Study Design; Section 4.1.3, Phase 2 – Dose Expansion; Section 4.3.1, Planned Number of Subjects; Section 9.2.2, Sample Size for Phase 2; Section 9.4.1.1, Primary Efficacy Analysis; Section 9.6.1, Simon 2-Stage Design**

   Description of change: Dose expansion cohorts were added as Treatment Group F1 in Phase 2 Part A to explore doses of INCAGN01949 in a larger number of subjects.

   Rationale for change: To further explore the activity of three tolerated doses of INCAGN01949 in combination with nivolumab.

2. **Synopsis; Section 1, Introduction; Section 1.5.2, Rationale for Phase 2 Subject Population; Section 1.5.2.2, Gastric Cancer; Section 1.5.2.3, Squamous Cell Carcinoma of the Head and Neck; Section 1.5.2.4, Non–Small Cell Lung Cancer; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design; Section 4.1.3, Phase 2 – Dose Expansion; Section 4.3.1, Planned Number of Subjects; Section 9.2.2, Sample Size for Phase 2; Section 9.4.1.1, Primary Efficacy Analysis; Section 9.6.1, Simon 2-Stage Design**

   Description of change: Phase 2 population was adjusted to only include subjects with gastric cancer, SCCHN, NSCLC, and RCC who are considered refractory to PD-1/L1 therapy.

   Rationale for change: To include subjects considered PD-1/L1 refractory where there is a clear unmet medical need. Gastric cancer, SCCHN, NSCLC, and RCC were chosen based on the availability of PD-1/L1 therapies for these indications and the varying levels of OX40 expression on tumor samples.

[redacted]

4. **Section 1.2.4, Clinical Pharmacokinetics**; **Section 1.2.5, Clinical Safety of INCAGN01949; Section 1.4, Potential Risks of the Combination Regimens; Section 1.5.3, Rationale for Dose and Schedule of Combination Therapies**

   Description of change: Added preliminary data from the INCAGN 1949-101 study.

   Rationale for change: Provide available information to investigators.

5. **Section 1.3, Overview of Standard Therapies; Section 1.5.2.1, Renal Cell Carcinoma; Section 11, References**

   Description of change: Included updated information on nivolumab and ipilimumab from package inserts.

   Rationale for change: Provide updated information on nivolumab and ipilimumab so that the information in the Protocol was consistent with the currently approved package inserts.

6. **Synopsis; Section 3.2, Subject Exclusion Criteria (Exclusion Criterion #3)**

   Description of change: Removed transfusion of blood products within 14 days of Cycle 1 Day 1 from exclusion criterion.

   Rationale for change: Early safety data have shown that INCAGN01949 does not cause myelosuppression, and therefore, the removal of this exclusion criterion will allow subjects to receive transfusions as necessary to address chemotherapy-induced hematologic abnormalities without delaying the start of study treatment.

7. **Synopsis; Section 3.2, Subject Exclusion Criteria (Exclusion Criterion #4)**

   Description of change: Adjusted washout period for prior immune therapies from 28 days to 14 days of Cycle 1 Day 1.

   Rationale for change: Treatment with immune therapies including PD-1/L1 antibodies have become standard of care in a number of indications. Subjects in Phase 2 will be required to have received these therapies and will receive INCAN01949 in combination with nivolumab, therefore, a 14-day washout period is sufficient and will allow subjects to start study therapy as soon as possible.

8. **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 and Adjustments of Study Drug; Section 5.4.9, Criteria for Permanent Discontinuation of Study Drug; Section 8.3.2, Reporting**

   Description of change: Requirement for dose reduction of INCAGN01949 was eliminated.

   Rationale for change: Dose reduction is not a common method of managing toxicities in patients treated with immune therapies, and dose interruption or treatment discontinuation is felt to be a more appropriate method of managing treatment-related toxicities. Dose reductions have not been required to manage toxicity so far in the INCAGN01949 development program.

9. **Section 6.4.1, Safety Follow-Up**

   Description of change: Added language to clarify that subjects should be monitored for the occurrence of new AEs until the end of safety follow-up or the start of new anticancer therapy, whichever occurs first.

   Rationale for change: Clarification was required to alleviate confusion regarding AE reporting.

10. [redacted]

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

Amendment 1 (14 JUN 2017)

Overall Rationale for the Amendment: The primary purpose of this amendment is to address comments from the United States FDA review and to update the sponsor name and address to Incyte Biosciences International Sarl.

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

   Description of change: The definition for platinum-ineligible was provided in the inclusion criteria for subjects with urothelial carcinoma.

   Rationale for change: To provide additional guidance to the sites.

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

   Description of change: Subjects who refuse standard treatment will no longer be eligible for participation in Phase 1 (Parts 1 and 2) of the study.

   Rationale for change: Change was made upon request from the FDA. The concern is that patients will forgo standard therapy with a proven clinical benefit to participate in an investigational study.

3. **Section 5.4.2, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose**

   Description of change: The definition of dose-limiting toxicity has been updated in Table 8 of the protocol.

   Rationale for change: To incorporate requested changes from the FDA.

4. **Title Page; Synopsis; 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.