Clinical Study Protocol

INCAGN 1949-101 / NCT02923349

A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCAGN01949 in Subjects With Advanced or Metastatic Solid Tumors

Product:	**INCAGN01949**
IND Number:	**129,838**
EudraCT Number:	**2016-002079-93**
Phase of Study:	**1/2**
Sponsor:	**Incyte Biosciences International Sàrl** **Route de la Corniche 1** **1066 Epalinges, Switzerland**
Date of Protocol:	**07 JUN 2016**
Date of Amendment 1:	**26 APR 2017**
Date of Amendment 2:	**15 AUG 2017**

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

INVESTIGATOR'S AGREEMENT

I have read the INCAGN 1949-101 Protocol Amendment 2 (dated 15 AUG 2017) 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	
Title of Study: A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCAGN01949 in Subjects With Advanced or Metastatic Solid Tumors	
Protocol Number: INCAGN 1949-101	**Study Phase:** 1/2

Indication:

Part 1: advanced or metastatic solid tumors

Part 2: advanced or metastatic adenocarcinoma of the endometrium, ovarian cancer, renal cell carcinoma (RCC), melanoma, and non–small cell lung cancer (NSCLC)

Primary Objective:

- To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of INCAGN01949 and to define a maximum tolerated dose (MTD) or pharmacologically active dose (PAD) of INCAGN01949 in subjects with metastatic or advanced solid tumors.

Secondary Objectives:

- To evaluate the pharmacokinetics (PK) of INCAGN01949 in subjects with advanced or metastatic solid tumors.
- To evaluate the preliminary efficacy of INCAGN01949 by assessing the objective response rate, duration of response, progression-free survival, and duration of disease control per RECIST v1.1 and modified RECIST v1.1 (mRECIST v1.1).

[redacted]

Primary Endpoint:

- Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of adverse events (AEs).

Secondary Endpoints:

- The PK of INCAGN01949, including C_{max}, T_{max}, C_{min}, and AUC_{0-t} for subjects in Parts 1 and 2 will be summarized.
- Objective response rate, defined as the percentage of subjects having complete response (CR) or partial response (PR), will be determined by investigator assessment of radiographic disease per RECIST v1.1 and mRECIST v1.1.
- Duration of response, defined as the time from earliest date of disease response (CR or PR) until earliest date of disease progression, will be determined by investigator assessment of radiographic disease per RECIST v1.1 and mRECIST v1.1, or death from any cause, if occurring sooner than progression.
- Progression-free survival, defined as the time from date of first dose of study drug until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease per RECIST v1.1 and mRECIST v1.1, or death from any cause if occurring sooner than progression.

- Duration of disease control (CR, PR, and stable disease [SD]) as measured from first report of SD or better until disease progression, will be determined by investigator assessment of radiographic disease per RECIST v1.1 and mRECIST v1.1, or death from any cause, if occurring sooner than progression.

[redacted]

Overall Study Design:

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 subjects with advanced or metastatic solid tumors. Subjects will receive INCAGN01949 on Day 1 of each cycle. Part 1 of the study will begin with 14-day cycles; however, alternate dose administration schedules may also be explored depending on PK, [redacted], and safety results. The study will be conducted in 2 parts:

- Part 1 – Dose Escalation and Safety Expansion will determine the PAD, defined as a dose that provides a maximal biochemical effect, or an increase in [redacted] immune activity, and/or the MTD of INCAGN01949, which includes defining the optimal dose administration schedule and the maximum number of tolerated doses (MNTD).
- Part 2 – Dose Expansion will evaluate the recommended dose and administration schedule determined in Part 1 in subjects with select tumor types [redacted] including adenocarcinoma of endometrium, ovarian cancer, RCC, melanoma, and NSCLC.

Part 1

In Part 1, subjects with advanced or metastatic solid tumors who progressed after treatment with available therapies that are known to confer clinical benefit, who are intolerant to treatment, or refuse standard treatment will be enrolled.

Dose Escalation

A 3 + 3 design will be utilized to determine the MTD or PAD of INCAGN01949. A minimum of 3 evaluable subjects will be enrolled in each cohort beginning with Cohort 1 (7 mg; starting dose). There will be a waiting period of 48 hours between dose administration to the first subject and second subject of each dose cohort. The first 3 subjects enrolled within a cohort will be observed for a DLT observation period of 28 days before the next cohort begins enrollment. The dose will be escalated if 0 of the first 3 evaluable subjects enrolled has a DLT. If 1 of the first 3 evaluable subjects enrolled has a DLT, then the cohort will be expanded to include 3 additional evaluable subjects, and if no DLT occurs in the additional 3 subjects, then the dose will be escalated. If a DLT occurs in one-third or more of the

expanded cohort, then the MTD will be deemed to be exceeded, and the previous dose level will be considered the MTD. If only 3 subjects were treated at the MTD or PAD, then a minimum of 3 additional subjects will be enrolled before this dose is administered in Part 2 of the study.

If Cohort 1 (7 mg; starting dose) exceeds the MTD, then the sponsor and investigators will consider administering INCAGN01949 at 2 mg (Cohort -1) and/or investigate 7 mg at alternate dose schedules (eg, every 3 weeks administration), based on available safety, PK, [redacted] data. If an alternate schedule is tested and determined to be safe, re-escalation of INCAGN01949 will proceed according to the table below.

Throughout the treatment period, if > 33% of subjects (a minimum of 6 subjects) experience a ≥ Grade 3 toxicity related to study drug after completing ≥ 4 cycles, then dose administration will be stopped, and the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

Additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects. Subjects who drop out for reasons other than a DLT (eg, events clearly associated with the underlying disease, disease progression, concomitant medication, or comorbidity) during the 28-day DLT observation period will be considered nonevaluable and will be replaced. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation is not permitted; however, once the recommended dose has been determined, ongoing subjects in Part 1 may be permitted to escalate the dose to the recommended level with approval of the medical monitor. The cohorts and dose levels are shown in the table below.

Cohort	Dose of INCAGN01949[a]
-1	2 mg[b]
1 (starting dose)	**7 mg**
2	20 mg
3	70 mg
4	200 mg
5	350 mg
6	700 mg
7	1400 mg[c]

[a] Additional dose schedules may be explored that would depend on PK, [redacted], and safety results.
[b] Subjects who require a dose reduction below 2 mg should be discontinued from study drug.
[c] Cohort 7 may be evaluated if the MTD has not been established and translational data indicate that a higher dose of INCAGN01949 may be necessary to confirm the optimal PAD.

Safety Expansion

In order to evaluate additional [redacted] activity of INCAGN01949 and confirm the preliminary safety of the dose-escalation cohorts, Part 1 of the study may include safety expansion cohorts evaluating doses and schedules equivalent to or lower than the highest dose levels determined to be safe and/or doses determined to be pharmacologically active. The alternative dose administration schedules and fixed doses (equivalent to or less than the MTD determined during dose escalation) that may be explored during the safety expansion would depend on PK, [redacted], and safety results.

A maximum of 36 subjects will be enrolled into the Part 1 safety expansion, and each Part 1 safety expansion cohort will enroll up to 9 evaluable subjects. If < 3 of 9 evaluable subjects have a DLT, then the cohort will be deemed safe. If > 1 safety expansion cohort is deemed safe, then a recommended dose and schedule will be determined in conjunction with the investigators and sponsor based on all available safety, PK, [redacted] results. The safety expansion cohorts may be run in parallel to Part 2 and may be limited by the sponsor to subjects with specific tumor types to achieve a balance across cohorts.

Part 2

Part 2 of the study will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the recommended dose of INCAGN01949 in subjects with advanced or metastatic adenocarcinoma of the endometrium, ovarian cancer, RCC, melanoma, and NSCLC (squamous and nonsquamous). Each cohort will consist of an individual tumor type. 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. During Stage 1, 9 subjects will be enrolled into each cohort; if no responses are observed within a cohort, then the cohort will be discontinued. If at least 1 response is observed, then 8 additional subjects will be enrolled into that cohort (Stage 2), for a maximum of 17 subjects per cohort.

Subjects will continue to receive INCAGN01949 until Protocol-defined withdrawal criteria are met. Continuous evaluation of toxicity events will be performed throughout enrollment in Part 2 of the study. If the cumulative incidence of DLTs occurs in > 33% of subjects after 6 subjects have been observed for at least 28 days, further enrollment may be interrupted until the sponsor has determined the appropriate course of action (eg, the MNTD may be determined). All AEs, regardless of the time of occurrence on study, may be considered in determining of the appropriate dose, schedule, and MNTD.

Toxicity will continue to be monitored throughout the treatment period. If > 33% of subjects (minimum of 6 subjects) experience a Grade ≥ 3 toxicity related to study drug after completing ≥ 4 cycles, then the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

Study Population: Enrollment in Part 1 will include subjects with advanced or metastatic solid tumors who have disease progression after prior treatment. Enrollment in Part 2 will be limited to subjects with advanced or metastatic adenocarcinoma of the endometrium, ovarian cancer, RCC, melanoma, and NSCLC (squamous and nonsquamous).

Key Inclusion Criteria:

- Men and women, aged 18 or older.
- Willingness to provide written informed consent for the study.
- Locally advanced or metastatic disease; locally advanced disease must not be amenable to resection with curative intent.
- Subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or who refuse standard treatment. There is no limit to the number of prior treatment regimens.
- Part 1: Subjects with advanced or metastatic solid tumors.
- Part 2: Subjects with advanced or metastatic adenocarcinoma of the endometrium, ovarian cancer, RCC, melanoma, and NSCLC.
  - **For subjects with adenocarcinoma of the endometrium**: should have documented microsatellite instability (MSI) status (eg, MSI-high, MSI-low, microsatellite stable), or consent to MSI status testing during the screening period.
    Note: MSI-high is defined by instability in ≥ 30% of examined microsatellites. MSI-low is defined by instability of < 30% of examined microsatellites. Microsatellite stable is defined by no instability.
  - **For subjects with ovarian cancer**: histologically confirmed diagnosis of ovarian, fallopian, or primary peritoneal carcinoma of epithelial origin.
  - **For subjects with NSCLC (squamous and nonsquamous)**: should have documentation of driver mutation testing for anaplastic lymphoma kinase, epidermal growth factor receptor status, BRAF mutation status, or consent to testing for these markers during the screening period.
  - **For subjects with RCC**: must have histologically confirmed diagnosis of RCC that is predominantly clear cell histology.

- **For subjects with melanoma**: mucosal or cutaneous melanoma is acceptable; however, subjects with ocular melanoma are excluded. Subjects should have documented BRAF mutation status or consent to BRAF mutation testing during the screening period.
  Note: BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criterion for BRAF mutation testing.

- 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.
- Part 1 Safety Expansion and Part 2: Willingness to undergo pretreatment and on-treatment tumor biopsies (core or excisional).
  Note: A baseline biopsy obtained for other purposes (ie, not a protocol-defined procedure) before signing consent may be utilized if the subject has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (ie, Cycle 1 Day 1), and if a minimum of 20 slides or preferably 1 tissue block can be submitted.
  Note: If a subject is scheduled to have a tumor biopsy for the purposes of this study and it is subsequently determined that tumor tissue cannot safely be obtained, then the subject may still enroll on the study. The subject may be replaced within the cohort.
  Note: For Part 1 Dose Escalation, pretreatment tumor biopsies are optional.
- ECOG performance status 0 or 1.

Key Exclusion Criteria (refer to full Protocol for full exclusion criteria):

- Laboratory and medical history parameters not within the Protocol-defined range. If the screening laboratory tests below were conducted > 7 days before treatment initiation, they will need to be repeated on Day 1 before initiation of treatment.
  - Absolute neutrophil count $< 1.5 \times 10^9$/L.
  - Platelets $< 100 \times 10^9$/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 (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.
  - Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≥ 2.5 × ULN.
    Note: Subjects with 1) bone metastases and 2) no hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase ≤ 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.
  - Total bilirubin ≥ 1.2 × ULN unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin.
  - International normalized ratio, prothrombin time, or activated partial thromboplastin time > 1.5 × ULN.
- Transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colony–stimulating factor, granulocyte macrophage colony–stimulating factor, or recombinant erythropoietin) within 14 days before study Day 1.
- 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. Subjects must also not require chronic use of corticosteroids and 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 sponsor approval.

Note: There is no washout period required between radiation therapy and the first administration of study drug in Part 2 of the study.

Note: Bisphosphonates and denosumab are permitted concomitant medications.

- ≤ 28 days for prior immunotherapy 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: 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 immunotherapy) and/or complications from prior surgical intervention before starting therapy.
  Note: Subjects with stable chronic AEs (≤ 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 AEs 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.
- Receipt of a live vaccine within 30 days of planned start of study drug.
  Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
- 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 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 14 days before the first dose of study drug.
- 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.
- Evidence of active, noninfectious pneumonitis or history of interstitial lung disease.

- History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 470 milliseconds is excluded (corrected by Fridericia). 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 sponsor 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.
- Active infection requiring systemic therapy.
- Evidence of hepatitis B virus (HBV) or hepatitis C virus (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.
- Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies).
- Known allergy or reaction to any component of study drug or formulation components.
- Prior treatment with an OX40 agonist for any indication.
- Is a female who is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 60 days after the last dose of study drug.
- Is a male who is expected to father children within the duration of the study, starting with the screening visit through 90 days after the last dose of study drug.

INCAGN01949 Dosage, and Mode of Administration:

INCAGN01949 will be administered intravenously over a 30-minute period on Day 1 of each cycle. Subjects will continue to receive INCAGN01949 as long as the subject is deriving benefit, has not met any of the Protocol-defined conditions for treatment withdrawal, or has not exceeded the MNTD. The MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

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, or for PK/[redacted] evaluations. 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:** Day 1, Day 2, and Day 7 (± 1 day).
- **Cycle 2:** Day 1 (± 1 days) and Day 7 (± 1 day).
- **Cycle 6:** Day 1 (± 3 days), Day 2, and Day 7 (± 1 day).
- **All other treatment cycles:** Day 1 (± 3 days).
- **Efficacy assessments:** Every 8 weeks (± 7 days) for 12 months, and every 12 weeks (± 7 days) thereafter 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.

Safety Assessments:

Subjects will have regularly scheduled study visits at the clinical site on Day 1 of every cycle where targeted physical examinations, vital sign collection, ECOG performance status, collection of concomitant medications, and AE assessments will be performed. A 12-lead ECG will be performed at screening, Cycle 1 Day 1, Cycle 2 Day 1, and then Day 1 of ***every other cycle*** after Cycle 2 (eg, Cycle 4, Cycle 6, Cycle 8). Triplicate ECG measurements will be performed at screening, Cycle 1 Day 1, and Cycle 6 Day 1, in conjunction with PK assessments. Laboratory assessments will be collected on Day 1 of each cycle, with more frequent blood sample collection during the first and second cycles (Day 1 and Day 7) to evaluate for DLTs. Toxicities will be monitored continuously and will be graded using the NCI CTCAE v4.03 criteria.

On Day 1 of the first 4 cycles (Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1), subjects will be required to stay at the study site for at least 4 hours after infusion of study drug for safety observation. It is recommended that the subject does not leave the site for any reason during the safety observation period. During the safety observation period, subjects will be assessed for the onset of acute AEs.

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

Efficacy Assessments:

Disease assessments will be performed based on RECIST v1.1 and also on mRECIST to account for the unique tumor response characteristics seen with immunotherapy. Modified RECIST will be defined as RECIST v1.1 with required confirmation of disease progression in the absence of clinical deterioration. The best overall response for subjects will be defined as the best overall response occurring during treatment, even if this assessment occurs after an initial assessment of progressive disease.

Assessment of tumor size (by magnetic resonance imaging or computed tomography scan) will be performed at screening or baseline (before beginning therapy) and every 8 weeks for 12 months and then every 12 weeks thereafter until disease progression is determined. Disease progression is defined as progression confirmed by a second consecutive assessment at least 4 weeks but no later than 6 weeks apart with the option for continuing treatment while awaiting radiographic confirmation of progression where feasible, provided that the subject meets the following definition of clinical stability:

- 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 tumors at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

Subjects who discontinue study drug for a reason other than disease progression will continue to be assessed for their disease status during the follow-up phase and should continue to have tumor assessments every 8 weeks for the first 12 months and then every 12 weeks thereafter until a new cancer therapy is started, disease progression, death, or the end of the study, whichever occurs first.

Pharmacokinetic Assessments:

Serum PK samples will be obtained at Cycle 1 (Day 1, Day 2, and Day 7), Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 6 (Day 1, Day 2, and Day 7), and Cycle 7 Day 1. [redacted] Adjustments to the timing of blood sample

collection after dose administration may be made based on emerging PK data.

[redacted]

Estimated Duration of Participation:

Each subject will be expected to participate for up to 14 months.

Estimated Number of Subjects:

Up to approximately 163 subjects may be enrolled in the study.

- Part 1 Dose Escalation – Approximately 18 to 42 evaluable subjects.
- Part 1 Safety Expansion – Approximately 18 to 36 evaluable subjects.
- Part 2 – Up to 85 evaluable subjects (up to 45 in Stage 1 and up to 40 in Stage 2).

Statistical Methods:

This is an open-label, nonrandomized, multicenter, dose-escalation Phase 1/2 study. The primary objective of Part 1 of the study is to determine the MTD and/or PAD of INCAGN01949. The total number of subjects will depend on the number of dose levels tested before the MTD or PAD is established. Dose escalation will follow a 3 + 3 design algorithm.

A Simon 2-stage design will be used in Part 2 with a stopping rule to allow early termination of a particular cohort at the end of Stage 1 if insufficient response is observed (calculated response rate < 5%), while enrolling enough subjects to predict possible target responses (≥ 25%) worthy of cohort expansion and potentially further evaluation in future studies. Part 2 will include 5 cohorts, one for each of the tumor types to be studied (ie, adenocarcinoma of the endometrium, ovarian cancer, RCC, melanoma, and NSCLC). The response rates for each tumor type will be estimated with 95% confidence intervals. Other efficacy variables will be summarized with descriptive statistics.

With a 1-sided Type I error of 0.05 and power of 80%, 9 subjects will initially be enrolled in the first stage. If no responses are observed within a cohort (consistent with a calculated response rate < 5%), the cohort will be discontinued. If at least 1 response is observed within a cohort, then 8 additional subjects will be enrolled in the appropriate cohort to a maximum of 17 subjects per cohort. Investigation of the study drug will be considered interesting (predictive of a 25% response rate) if ≥ 3 responses are observed in the first 17 subjects.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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
aPTT	activated partial thromboplastin time
CA-125	cancer antigen 125
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRA	cytokine release assays
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte–associated protein 4
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
FcγR	Fc-gamma receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony–stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
ICF	informed consent form

Abbreviation	Definition
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	interferon
IgG	immunoglobulin G
IL	interleukin
IN	Investigator Notification
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LDL	low-density lipoprotein
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
MNTD	maximum number of tolerated doses
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
PAD	pharmacologically active dose
PCP	pneumocystis pneumonia
[redacted]	[redacted]
PD-1	programmed cell death protein
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
RCC	renal cell carcinoma

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SSD	safe starting dose
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
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 maximum tolerated dose (MTD) or pharmacologically active dose (PAD), and assess the preliminary efficacy of INCAGN01949. Part 1 will utilize a 3 + 3 design to determine the PAD and/or MTD of INCAGN01949 in subjects with advanced or metastatic solid tumors. An optional safety expansion may also be initiated in Part 1, which would enroll cohorts to evaluate dose(s) and schedule(s) equivalent to or less than the highest dose determined to be safe in the Part 1 dose escalation. Part 2 will further evaluate the safety, tolerability, preliminary efficacy, pharmacokinetics (PK), and pharmacologic activity of INCAGN01949 in subjects with advanced or metastatic adenocarcinoma of the endometrium, ovarian cancer, renal cell carcinoma (RCC), melanoma, or non–small cell lung cancer (NSCLC). 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 observed.

1.1. Background

1.1.1. The Role of the Immune System in Cancer

The immune system comprises diverse sets of cells designed to protect a host from pathogens while distinguishing host from 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). The presence of tumor-infiltrating lymphocytes in cancer tissue among various malignancies has been shown to confer a more favorable prognosis (Mei et al 2014, Salgado et al 2015, Gooden et al 2011, Schreiber et al 2011, Bremnes et al 2011, Talmadge 2011, Shirabe et al 2010, Nosho et al 2010, Bellati et al 2009, Oble et al 2009, Uppaluri et al 2008). Detailed analysis of CD8+ T cells and the ratio of CD8+ effector T cells/forkhead box P3 (FoxP3)+ regulatory T cells (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, Yoon et al 2012, Kim et al 2013, Mathai et al 2012, Liu et al 2011, Kirk 2010). Although the immune system has been shown to recognize and reject a tumor, many tumors evade immune surveillance or develop mechanisms of resistance.

Histologic evaluation of multiple human cancers show extensive infiltration by inflammatory and immune cells (Galon et al 2006), suggesting that the immune system responds less effectively to malignancy. As tumors grow, an "equilibrium" is reached where tumor growth is matched by immune-mediated tumor destruction. Eventually, malignant cells either accumulate mutations, making them nonimmunogenic, or immunosuppressive pathways become activated, allowing the tumor to escape immune recognition (DuPage et al 2012, Schreiber et al 2011, Dunn et al 2002, Matsushita et al 2012). The accumulation of suppressive cells and an inhibitory cytokine milieu in and around a tumor can form an immunosuppressive environment that prevents successful T-cell–mediated destruction of malignant cells (Schaer et al 2011). Overcoming tumor resistance to immune surveillance either through stimulating the immune response or preventing inhibition is the basic rationale for the development of immunotherapies.

Targeting the immune system is a proven and effective approach for cancer therapies. Food and Drug Administration– and EU-approved checkpoint inhibitors, such as ipilimumab, nivolumab, and pembrolizumab, 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 trial.

1.1.2. 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 cytotoxic T lymphocyte–associated protein 4 (CTLA-4) or programmed cell death protein 1 (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 tumor necrosis factor super family (Schaer et al 2013).

1.1.3. OX40 and the Tumor Necrosis Factor Super Family

OX40 (CD134) is a member of the tumor necrosis factor receptor (TNFR) superfamily. Other members of the TNFR superfamily include CD40, CD27, FAS, DR3, GITR, and 4-1BB. The regulation of the activation, proliferation, or apoptosis of lymphocytes is a common function of members of this family (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 T-cell receptor (TCR) engagement and costimulation through CD28 or the presence of inflammatory cytokines, including interleukin (IL) 1, IL-2, and tumor necrosis factor (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 to 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 effector T cells to tumor-specific antigens. The use of an antibody with antibody-dependent cell-mediated cytotoxicity (ADCC) capabilities may also selectively deplete Tregs (Gonzalez et al 2016, Bulliard et al 2013). Therefore the use of an anti-OX40 monoclonal antibody (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.

1.1.4. *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 nuclear factor kappa-light-chain-enhancer of activated B cells (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, interferon (IFN) γ, 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 Fc gamma receptor (FcγR)-mediated ADCC/antibody-dependent cell-mediated phagocytosis (ADCP) manner. Experiments performed in mice showed that this mechanism contributed to the control of tumor growth in mice (Bulliard et al 2014).

1.1.5. Clinical Experience With OX40 Agonists

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 adverse events (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 stable disease (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-/natural killer (NK) cells were significantly increased; however, the number of CD4+/FoxP3+ Treg 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 AACR 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 dose-limiting toxicities (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.

1.2. Overview of INCAGN01949

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 with an estimated affinity (K_D) of 0.12 nM and does not bind to related TNFR super family members. INCAGN01949 functions as an OX40 agonist antibody in human cells, activating NF-κB signaling, and providing T-cell costimulation in the context of suboptimal TCR activation. Similar to its effects on human T cells, INCAGN01949 binds to cynomolgus monkey OX40 with less than 2-fold difference in relative affinity and enhances cynomolgus monkey T-cell function under suboptimal TCR stimulatory conditions in cell-based assays. INCAGN01949 does not cross-react with rodent OX40. Therefore, the cynomolgus monkey nonhuman primate was considered a relevant species to evaluate the pharmacological and toxicological impact of INCAGN01949.

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 (CRA) 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 cytokine release syndrome (CRS) in patients. Taken together, the pharmacologic properties of INCAGN01949 illustrate its suitability for clinical development in patients with advanced malignancies.

1.2.2. Pharmacokinetics of INCAGN01949

The PK of INCAGN01949 was characterized in cynomolgus monkeys after intravenous (IV) administration. Following a single IV dose, the mean estimated terminal half-life was estimated to be 11.4 days; the mean clearance was estimated to be 0.23 mL/h/kg, and the mean volume of distribution was estimated to be 90.3 mL/kg. In monkeys, exposures (AUC and C_{max}) demonstrated a linear and dose-proportional increase. No sex differences in the PK of INCAGN01949 were noted.

Following weekly repeat dose administration from 0.5 to 100 mg/kg in monkeys, the mean C_{max} and AUC values after the fourth dose were higher than after the first dose, reflecting accumulation of INCAGN01949. The observed incidence of immunogenicity was low, with 5 out of 46 monkeys with confirmed antidrug antibodies (ADA). Monkeys with confirmed ADA exhibited decreased systemic exposures after repeated dosing. However, the high plasma concentrations of INCAGN01949, especially at the higher dose levels, may have confounded the detection of ADA.

1.2.3. Preclinical Safety and Potential Risks of INCAGN01949

A non-GLP repeated dose range finding toxicity study was conducted in cynomolgus monkeys (1 male/1 female) given weekly IV doses of INCAGN01949 (0 mg/kg, 0.5 mg/kg, 5 mg/kg, 20 mg/kg, or 100 mg/kg) for 4 weeks (29 days). There were no adverse treatment-related changes in clinical observations, body weight, food consumption, serum proinflammatory cytokines, peripheral blood immunophenotypes, immune cell activation markers, or clinical or anatomic pathology. Thus, the no-observed-adverse-effect level (NOAEL) for this non-GLP dose range finding study was determined to be 100 mg/kg.

A GLP repeat-dose toxicity study was conducted in cynomolgus monkeys that received an IV bolus injection of vehicle control or 1 of the 4 levels (0.5 mg/kg, 5 mg/kg, 20 mg/kg, or 100 mg/kg) of INCAGN01949 once per week for 5 weeks followed by a 4-week recovery period (except for 0.5 mg/kg group). There were no adverse treatment-related changes in physical examinations, ophthalmologic examinations, clinical observations, neurologic examinations, body weights, food consumption, electrocardiogram (ECG), clinical pathology (hematology, clinical chemistry, and urinalysis) serum proinflammatory cytokines, peripheral blood immunophenotypes, immune cell activation markers, or anatomic pathology.

The NOAEL for this 4-week GLP repeat dose study with a 4-week recovery period was determined to be 100 mg/kg per dose. This dose level corresponded to mean C_{max} and $AUC_{0\text{-}168h}$ values of 2980 µg/mL and 221,000 µg·hr/mL, respectively, after the first dose in this study; and C_{max} and AUC values of 4360 µg/mL and 457,000 µg·hr/mL, respectively, following the fourth dose (Day 22). The estimated half-life was approximately 15 days.

Antidrug antibodies were detected in 5 of 46 treated monkeys. However, the high circulating plasma concentrations of INCAGN01949 at the time of the collection of the ADA samples may have confounded detection of ADA, as the bridging ELISA method had a plasma drug tolerance limit of 200 µg/mL. Consequently, the negative ADA results at the higher INCAGN01949 dose levels (20 and 100 mg/kg) should be considered inconclusive.

In a GLP tissue cross-reactivity study of the INCAGN01949 mAb, expected cell membrane and cytoplasmic staining was observed in resident, migrating, and/or infiltrating mononuclear cells in colon, esophagus, spleen, thymus, tonsil, ureter, and cervix.

In summary, in the pivotal toxicity study, treatment of cynomolgus monkeys with 5 weekly doses of INCAGN01949 (at 0.5 mg/kg, 5 mg/kg, 20 mg/kg, or 100 mg/kg) was well-tolerated and did not reveal any relevant treatment-related effects up to the highest dose level (100 mg/kg), at the end of the 5-week treatment period, or after the 4-week recovery period. Although not observed in the preclinical toxicology studies, INCAGN01949 is a potential moderator of the immune system, and although no immune-related adverse events (irAEs) were observed in preclinical toxicology studies, investigative sites will be instructed to monitor for irAEs, which have been previously observed with other immunotherapies (see Section 5.4.7, Section 5.4.8, and Appendix B).

In *in vitro* CRA, INCAGN01949 at concentrations up to 100 µg/mL did not induce the classic signature of CRS, which consists of the proinflammatory cytokines TNF-α, IFN-γ, and IL-6. Only modest increases in median IL-6 levels were observed at the highest concentrations of INCAGN01949 tested. Interleukin 4, which has not been associated with CRS, was also modestly increased (median levels) but not related to dose. These effects demonstrated

donor-to-donor variability, and the levels were lower than the comparator antibody alemtuzumab, an antibody previously associated with CRS in patients, suggesting that the changes may have limited value in predicting a potential safety risk for patients. Increases in IL-8, IL-10, IFN-γ and TNF-α occurred in only a subset of donors (median values were 0) and were not related to dose; and thus, these too were considered to have limited value in predicting a potential safety risk for patients. Given the variability in human donor-to-donor response in the CRA, these data must be interpreted with caution and may not be representative of CRS in patients administered INCAGN01949.

Safety pharmacology assessments were incorporated into the 4-week GLP toxicity study in cynomolgus monkeys. There were no INCAGN01949-related effects on clinical observations; physical examinations (abdominal palpation, observation of the integument, body temperature, heart rate, and respiratory rate); or neurologic (behavior, evaluation of motor function, cranial nerves, proprioception, postural reactions, and spinal nerves), ophthalmologic, or ECG parameters.

1.3. Study Rationale

1.3.1. Rationale for the Safe Starting Dose of INCAGN01949

INCAGN01949 was characterized in a series of *in vitro* pharmacology assays. The assays considered most physiologically relevant in the assessment of potential safety signals in humans, and to the determination of the safe starting dose (SSD), were those that assessed the impact of INCAGN01949 agonist activity using primary human T cells. Similarly, the assays that evaluated the potential of INCAGN01949 to enhance T-cell cytokine modulation were considered to be most relevant to the assessment of proinflammatory cytokines in relation to potential CRS (Table 1).

A minimum anticipated biological effect level (MABEL)-based approach is the basis for the determination of the SSD, and the EC_{30} closely approximates the MABEL. Using the potency values obtained experimentally in the cytokine assays shown (Table 1), the mean EC_{30} is calculated to be 1.7 µg/mL. [redacted]

Table 1: Summary of *In Vitro* Pharmacology Data to Support the Safe Starting Dose of INCAGN01949

Assays	n	EC_{50} (µg/mL)
INCAGN01949-induced IL-2 secretion (with SEA antigen)	5	2.9
INCAGN01949-induced human T cell IFN-γ and/or TNF-α production (with TCR)	14	6.1
INCAGN01949-induced human TNF-β (supernatant; with TCR)	9	2.0
INCAGN01949-induced human IL-2 (supernatant; with TCR)	9	6.7
INCAGN01949-induced human GM-CSF (supernatant; with TCR)	9	2.0
	Average	**3.9**
	Standard Deviation	**2.3**
Calculated EC_{30} (assuming slope of 1)[a]		**1.7**
EC_{30} value converted to dose (mg/kg)		**0.13**

GM-CSF = granulocyte macrophage colony–stimulating factor.
[a] Based on TK (C_{ave}) from 4-week study in cynomolgus monkeys - Steady state $AUC_{0\text{-}168h}$ (Day 22) = 1120 µg·hr/mL at 0.5 mg/kg (male); average concentration (C_{ave}) = 1120 / (7 × 24 h) = 6.67 µg/mL. Calculation based on male AUC only due to the impact of high ADA in females at 0.5 mg/kg (low AUC).

The MABEL-based SSD of 0.1 mg/kg is approximately 300-fold lower than the NOAEL determined for the cynomolgus monkey and approximately 4.4-fold lower than an estimated PAD of 0.44 mg/kg (based on a mean EC_{50} for cytokine release of 3.9 µg/mL).

The proposed SSD attempts to balance potential safety risks with the recognized obligation to provide an effective therapeutic dose to a patient with advanced malignancy. This proposed SSD is expected to pose a low safety risk to humans based on the following key observations:

- An absence of target organ toxicity, cytokine release or changes in immune cell populations in the 4-week GLP toxicity study in cynomolgus monkeys.
- Absence of evidence for potential infusion reactions; assay of cytokine release without T-cell activation.
- Absence of evidence for specific off-target tissue cross-reactivity in human tissues.
- OX40 expression is restricted to activated T cells, with minimal to no detectable expression on peripheral T cell subsets. Related to this, INCAGN01949 modulates T-cell function (e.g. cytokine responses) only in the context of TCR stimulation.

Fixed dosing has several advantages over weight-based dosing, including convenience of preparation and administration, reducing errors in preparation calculations, and minimization of drug waste. Body size–based dosing and fixed dosing of monoclonal antibodies have been evaluated with the 2 dosing approaches performing similarly, with body size–based dosing not always offering an advantage in reducing variability of exposure. The authors of these studies concluded that either approach may be used in first-in-human studies and that fixed dosing is recommended in these studies due to the advantages discussed above (Wang et al 2009,

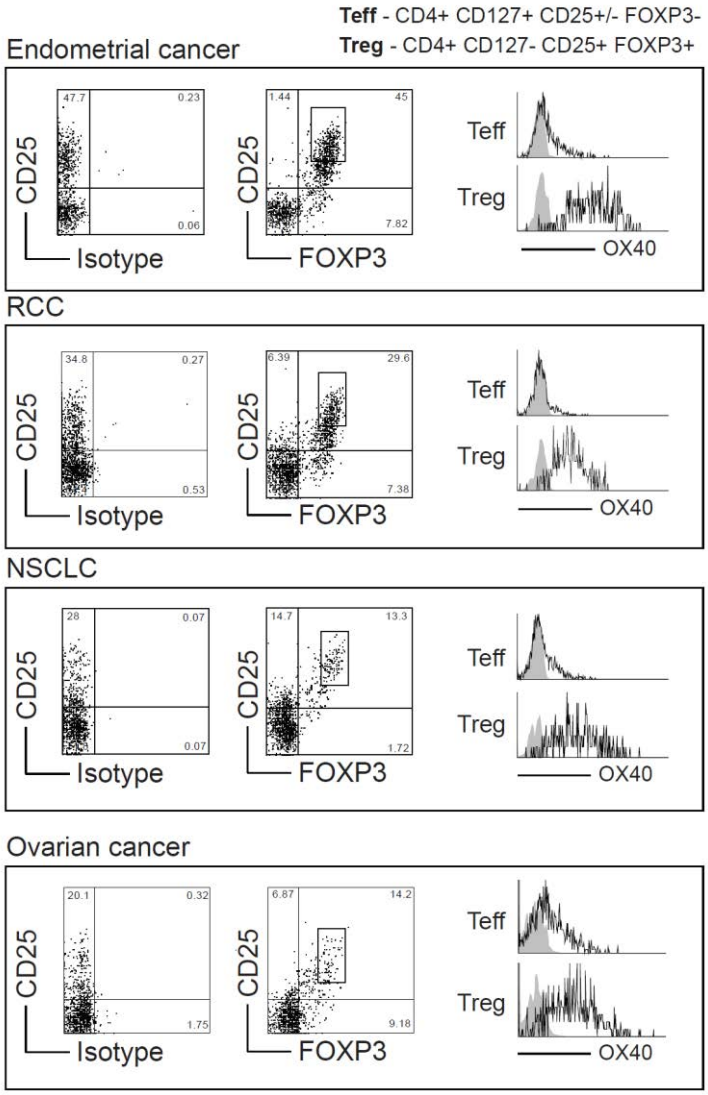
Bai et al 2012). An average adult weight of 70 kg was used to convert weight-based dose levels to fixed doses. The MABEL-based SSD of 0.13 mg/kg is rounded down to 0.1 mg/kg to achieve a starting dose of 7 mg (0.1mg/kg · 70 kg = 7 mg).

1.3.2. Rationale for Subject Population in Part 2

To further elucidate the effects of INCAGN01949, 5 different tumor types have been selected for investigation in Part 2. Melanoma and NSCLC will be evaluated, because they are both immunogenic histologies that have been proven to respond to checkpoint inhibitors (CTLA-4 and PD-1). Experiments looked at the expression of OX40 on T effector cells and Tregs in samples from patients with endometrial cancer, RCC, ovarian cancer, and NSCLC. Intratumoral Tregs had elevated OX40 expression, and to a lesser extent, T effector cells had elevated OX40 expression as well. Dissociated (frozen) primary tumor samples were analyzed by flow cytometry. After gating on either CD4+CD25-Foxp3- (T effector cells) and CD4+CD25+Foxp3+ (Tregs), OX40 expression was analyzed, and a few representative experiments are shown in Figure 1.

Based on these data, ovarian cancer, endometrial cancer, RCC, NSCLC, and melanoma will be further evaluated in disease-specific cohorts in Part 2 of this study. A Simon 2-stage design will be used with a stopping rule to allow early termination of a particular cohort at the end of Stage 1 if insufficient response is observed, and enough subjects will be enrolled to predict possible target responses (≥ 25%) worthy of cohort expansion and potentially for further evaluation in future studies (see Section 9.2.2).

Figure 1: Tumor-Infiltrating Lymphocytes Expression of OX40



1.3.3. Rationale for the Study Endpoints

1.3.3.1. Efficacy Endpoints

Efficacy endpoints of this study are secondary and include objective response rate, duration of response, duration of disease control, and progression-free survival (PFS) by investigator assessment based on RECIST v1.1 and modified RECIST (mRECIST).

1.3.3.1.1. Modified RECIST

RECIST v1.1 will be adapted to account for the unique tumor response characteristics seen with immunotherapy (Chiou and Burotto 2015). 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 not provide an accurate response

assessment of immunotherapeutic agents. Therefore, RECIST v1.1 will be used with the following adaptations:

If radiologic imaging shows initial progressive disease, then 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 drug 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, then 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, then 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, site study teams 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) are found 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 Objective

- To evaluate the safety, tolerability, and DLTs of INCAGN01949 and to define a MTD or PAD of INCAGN01949 in subjects with metastatic or advanced solid tumors.

2.1.2. Secondary Objectives

- To evaluate the PK of INCAGN01949 in subjects with advanced or metastatic solid tumors.
- To evaluate the preliminary efficacy of INCAGN01949 by assessing the objective response rate, duration of response, PFS, and duration of disease control per RECIST v1.1 and mRECIST v1.1.

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of AEs.

2.2.2. Secondary Endpoints

- The PK of INCAGN01949, including C_{max}, T_{max}, C_{min}, and AUC_{0-t} for subjects in Parts 1 and 2 will be summarized.
- Objective response rate, defined as the percentage of subjects having complete response (CR) or PR, will be determined by investigator assessment of radiographic disease per RECIST v1.1 and mRECIST v1.1.

- Duration of response, defined as the time from earliest date of disease response (CR or PR) until earliest date of disease progression, will be determined by investigator assessment of radiographic disease per RECIST v1.1 and mRECIST v1.1, or death from any cause, if occurring sooner than progression.
- Progression-free survival, defined as the time from date of first dose of study drug until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease per RECIST v1.1 and mRECIST v1.1, or death from any cause if occurring sooner than progression.
- Duration of disease control, (CR, PR, and SD), as measured from first report of SD or better until disease progression, will be determined by investigator assessment of radiographic disease per RECIST v1.1 and mRECIST v1.1, or death from any cause, if occurring sooner than progression.

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. Subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or who refuse standard treatment. There is no limit to the number of prior treatment regimens.
5. Part 1: Subjects with advanced or metastatic solid tumors.
6. Part 2: Subjects with advanced or metastatic adenocarcinoma of the endometrium, ovarian cancer, RCC, melanoma, and NSCLC.
    a. For subjects with adenocarcinoma of the endometrium: should have documented microsatellite instability (MSI) status (eg, MSI-high, MSI-low, microsatellite stable), or consent to MSI status testing during the screening period.
    Note: MSI-high is defined by instability in ≥ 30% of examined microsatellites. MSI-low is defined by instability of < 30% of examined microsatellites. Microsatellite stable is defined by no instability.
    b. For subjects with ovarian cancer: histologically confirmed diagnosis of ovarian, fallopian, or primary peritoneal carcinoma of epithelial origin.
    c. For subjects with NSCLC (squamous and nonsquamous): should have documentation of driver mutation testing for anaplastic lymphoma kinase, epidermal growth factor receptor status, BRAF mutation status, or consent to testing for these markers during the screening period.
    d. For subjects with RCC: must have histologically confirmed diagnosis of RCC that is predominantly clear cell histology.
    e. For subjects with melanoma: mucosal or cutaneous melanoma is acceptable; however, subjects with ocular melanoma are excluded. Subjects should have documented BRAF mutation status or consent to BRAF mutation testing during the screening period.
    Note: BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criterion for BRAF mutation testing.

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. Part 1 Safety Expansion and Part 2: Willingness to undergo pretreatment and on-treatment tumor biopsies (core or excisional).
   Note: A baseline biopsy obtained for other purposes (ie, not a Protocol-defined procedure) before signing consent may be utilized if the subject has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (ie, Cycle 1 Day 1), and if a minimum of 20 slides or preferably 1 tissue block can be submitted.
   Note: If a subject is scheduled to have a tumor biopsy for the purposes of this study and it is subsequently determined that tumor tissue cannot safely be obtained, then the subject may still enroll on the study. The subject may be replaced within the cohort.
   Note: For Part 1 Dose Escalation, pretreatment tumor biopsies are optional.
9. ECOG performance status 0 or 1.
10. Female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy and are not postmenopausal, defined as ≥ 12 months of amenorrhea) must have a negative serum pregnancy test at screening. All female subjects of childbearing potential must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 60 days after the last dose of study drug. All male subjects must agree to take appropriate precautions to avoid pregnancy with a partner (with at least 99% certainty) from screening through 90 days after the last dose of study drug. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subjects 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, they will need to be repeated on Day 1 before initiation of treatment.
   a. Absolute neutrophil count < 1.5×10^9/L.
   b. Platelets < 100×10^9/L.
   c. Hemoglobin < 9 g/dL or < 5.6 mmol/L.
   d. Serum creatinine > 1.5 × institutional upper limit of normal (ULN), OR measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or creatinine clearance) < 50 mL/min for subjects with creatinine levels > 1.5 × ULN.
   e. Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≥ 2.5 × ULN.
      Note: Subjects with 1) bone metastases and 2) no hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase ≤ 5 × ULN. Subjects with 1) bone metastases and/or 2) hepatic parenchymal

metastases on screening radiographic examinations may enroll if the alkaline phosphatase is ≤ 5 × ULN only with medical monitor approval.

f. Total bilirubin ≥ 1.2 × ULN unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin.
g. International normalized ratio, prothrombin time (PT), or activated partial thromboplastin time > 1.5 × ULN.

2. Transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte colony–stimulating factor, granulocyte macrophage colony–stimulating factor, or recombinant erythropoietin) within 14 days before study Day 1.

3. 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. Subjects must also not require chronic use of corticosteroids and 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 sponsor approval.
      Note: There is no washout period required between radiation therapy and the first administration of study drug in Part 2 of the study.
      Note: Bisphosphonates and denosumab are permitted concomitant medications.
   b. ≤ 28 days for prior immunotherapy 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: 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.

4. Has not recovered to ≤ Grade 1 from toxic effects of prior therapy (including prior immunotherapy) and/or complications from prior surgical intervention before starting therapy.
   Note: Subjects with stable chronic AEs (≤ 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 will be excluded.
   Note: Subjects with a history of a Grade 3 or higher irAE from prior immunotherapies are excluded from the dose escalation portion of the study.

5. Receipt of a live vaccine within 30 days of planned start of study drug.
   Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live-attenuated vaccines and are not allowed.
6. Active autoimmune disease that required systemic treatment in the past (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs).
   ***Note*:** For subjects who have not required systemic treatment in the past 2 years, the investigator should discuss the case with medical monitor to determine eligibility.
   Note: Subjects with hyper/hypothyroidism 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.
7. 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 14 days before the first dose of study drug.
8. 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.
9. Evidence of active, noninfectious pneumonitis or history of interstitial lung disease.
10. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 470 milliseconds is excluded (corrected by Fridericia). 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 sponsor 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.
11. Active infection requiring systemic therapy.

12. Evidence of hepatitis B virus (HBV) or hepatitis C virus (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.
13. Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies).
14. Known allergy or reaction to any component of study drug or formulation components.
15. Prior treatment with an OX40 agonist for any indication.
16. Is a female who is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 60 days after the last dose of study drug OR is a male who is expected to father children within the duration of the study, starting with the screening visit through 90 days after the last dose of study drug.
17. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study.
18. Inability to comprehend or unwillingness to sign the informed consent form (ICF).

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

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 subjects with advanced or metastatic solid tumors. Subjects will receive INCAGN01949 on Day 1 of each cycle. Part 1 of the study will begin with 14-day cycles; however, alternate dose administration schedules may also be explored depending on PK, [redacted], and safety results. The study will be conducted in 2 parts:

- Part 1 – Dose Escalation and Safety Expansion will determine the PAD, defined as a dose that provides a maximal biochemical effect [redacted], and/or the MTD of INCAGN01949, which includes defining the optimal dose administration schedule and the maximum number of tolerated doses (MNTD).
- Part 2 – Dose Expansion will evaluate the recommended dose and administration schedule determined in Part 1 in subjects with select tumor types [redacted] including adenocarcinoma of the endometrium, ovarian cancer, RCC, melanoma, and NSCLC.

See Figure 2 for overall study design.

4.1.1. Part 1

In Part 1, subjects with advanced or metastatic solid tumors who progressed after treatment with available therapies that are known to confer clinical benefit, who are intolerant to treatment, or who refuse standard treatment will be enrolled.

4.1.1.1. Dose Escalation

In the dose-escalation part of the study, a 3 + 3 design will be utilized to determine the MTD or PAD of INCAGN01949. A minimum of 3 evaluable subjects will be enrolled in each cohort beginning with Cohort 1 (7 mg; starting dose). There will be a waiting period of 48 hours between dose administration to the first subject and second subject of each dose cohort. The first 3 subjects enrolled within a cohort will be observed for a DLT observation period of 28 days before the next cohort begins enrollment. The dose will be escalated if 0 of the first 3 evaluable subjects enrolled has a DLT. If 1 of the first 3 evaluable subjects enrolled has a DLT, then the cohort will be expanded to include 3 additional evaluable subjects, and if no DLT occurs in the additional 3 subjects, then the dose will be escalated. If a DLT occurs in one-third or more of the expanded cohort, then the MTD will be deemed to be exceeded, and the previous dose level will be considered the MTD. If only 3 subjects were treated at the MTD or PAD, then a minimum of 3 additional subjects will be enrolled before this dose is administered in Part 2 of the study.

If Cohort 1 (7 mg; starting dose) exceeds the MTD, then the sponsor and investigators will consider administering INCAGN01949 at 2 mg (Cohort -1) and/or investigate 7 mg at alternate dose schedules (eg, every 3 week administration), based on available safety, PK, [redacted] data. If an alternate schedule is tested and determined to be safe, then re-escalation of INCAGN01949 will proceed according to Table 2.

Throughout the treatment period, if > 33% of subjects (a minimum of 6 subjects) experience a Grade ≥ 3 toxicity related to study drug after completing ≥ 4 cycles, then dose administration will be stopped, and the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

Additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects. Subjects who drop out for reasons other than a DLT (eg, events clearly associated with the underlying disease, disease progression, concomitant medication, or comorbidity) during the 28-day DLT observation period will be considered nonevaluable and will be replaced. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation is not permitted; however, once the recommended dose has been determined, ongoing subjects in Part 1 may be permitted to escalate the dose to the recommended level with approval of the medical monitor. The cohorts and dose levels are shown in Table 2.

Table 2: INCAGN01949 Dose Levels and Cohort

Cohort	Dose of INCAGN01949[a]
-1	2 mg[b]
1 (starting dose)	**7 mg**
2	20 mg
3	70 mg
4	200 mg
5	350 mg
6	700 mg
7	1400 mg[c]

[a] Additional dose schedules may be explored that would depend on PK, [redacted], and safety results.
[b] Subjects who require a dose reduction below 2 mg should be discontinued from study drug.
[c] Cohort 7 may be evaluated if the MTD has not been established and translational data indicate that a higher dose of INCAGN01949 may be necessary to confirm the optimal PAD.

4.1.1.2. Safety Expansion

In order to evaluate additional [redacted] activity of INCAGN01949 and confirm the preliminary safety of the dose-escalation cohorts, Part 1 of the study may include safety expansion cohorts evaluating doses and schedules equivalent to or lower than the highest dose levels determined to be safe and/or doses determined to be pharmacologically active. The alternative dose administration schedules and fixed doses (equivalent to or less than the MTD determined during dose escalation) that may be explored during the safety expansion would depend on PK, [redacted] and safety results.

A maximum of 36 subjects will be enrolled into the Part 1 safety expansion, and each Part 1 safety expansion cohort will enroll up to 9 evaluable subjects. If < 3 of 9 evaluable subjects have a DLT, then the cohort will be deemed safe. If > 1 safety expansion cohort is deemed safe, then a recommended dose and schedule will be determined in conjunction with the investigators and sponsor based on all available safety, PK, [redacted] results. The safety expansion cohorts may be run in parallel to Part 2 and may be limited by the sponsor to subjects with specific tumor types to achieve a balance across cohorts.

4.1.2. Part 2

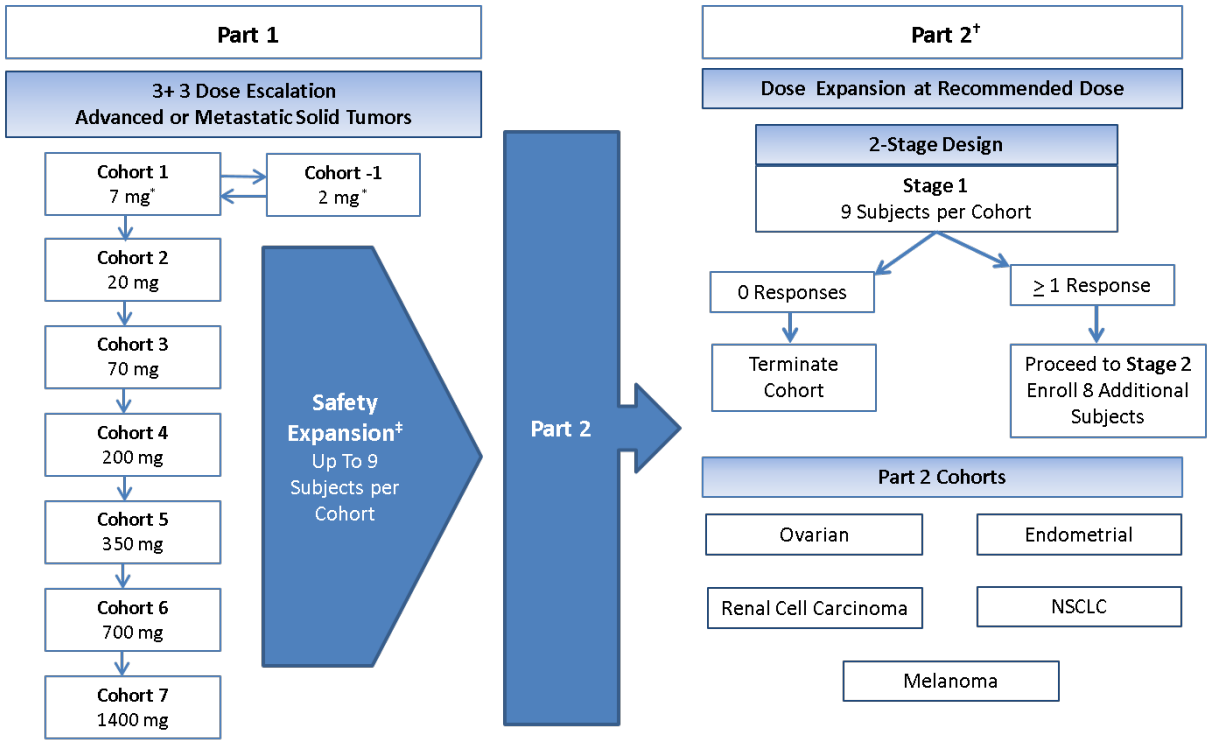
Part 2 of the study will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the recommended dose of INCAGN01949 in subjects with advanced or metastatic adenocarcinoma of the endometrium, ovarian cancer, RCC, melanoma, and NSCLC (squamous and nonsquamous). Each cohort will consist of an individual tumor type. 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. During Stage 1, 9 subjects will be enrolled into each cohort; if no responses are observed within a cohort, then the cohort will be discontinued. If at least 1 response is observed, then 8 additional subjects will be enrolled into that cohort (Stage 2), for a maximum of 17 subjects per cohort.

Subjects will continue to receive INCAGN01949 until Protocol-defined withdrawal criteria are met. Continuous evaluation of toxicity events will be performed throughout enrollment in Part 2

of the study. If the cumulative incidence of DLTs occurs in > 33% of subjects after 6 subjects have been observed for at least 28 days, then further enrollment may be interrupted until the sponsor has determined the appropriate course of action (eg, the MNTD may be determined). All AEs, regardless of the time of occurrence on study, may be considered in determining the appropriate dose, schedule, and MNTD.

Toxicity will continue to be monitored throughout the treatment period. If > 33% of subjects (minimum of 6 subjects) experience a Grade ≥ 3 toxicity related to study drug after completing ≥ 4 cycles, then the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

Figure 2: Study Design



* If Cohort 1 (7 mg) ***exceeds*** the MTD, Cohort -1 (2 mg) may be tested and/or Cohort 1 (7 mg) will be tested at alternate dose schedules based on available safety, PK, [redacted] data. If an alternate schedule is tested and determined to be safe, re-escalation of INCAGN01949 will proceed as outlined above.

‡ The safety expansion cohorts may evaluate dose(s) and schedule(s) equivalent to or less than the highest dose levels determined to be safe or doses determined to be pharmacologically active. Alternate dose schedules may also be tested depending on PK, [redacted] and safety results.

†Subjects in Part 2 will receive the recommended dose determined in Part 1.

4.2. Measures Taken to Avoid Bias

This is an open-label study; no formal comparisons will be made between subjects or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Up to approximately 163 subjects may be enrolled in the study:

- Part 1 Dose Escalation – Approximately 18 to 42 evaluable subjects.
- Part 1 Safety Expansion – Approximately 18 to 36 evaluable subjects.
- Part 2 – Up to 85 evaluable subjects (up to 45 in Stage 1 and up to 40 in Stage 2).

4.3.2. Replacement of Subjects

Subjects may be replaced for any of the following reasons:

- Subject is not evaluable for DLTs (see Section 5.4.2).
- In Part 1 Safety Expansion and Part 2, subject has not met the biopsy requirements for the study (ie, pre- and on-treatment samples).
- Subject does not meet the eligibility requirements of the study (eg, accidental enrollment).

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. Each subject enrolled in the study may continue to receive INCAGN01949 as long as the subject is deriving benefit and has not met any of the Protocol-defined conditions for treatment withdrawal (see Section 5.5). If the subject discontinues treatment with INCAGN01949, then the treatment period will end, and the subject will enter the follow-up period (see Section 6.4). Subjects are expected to participate in the study for a maximum of 14 months.

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 completed the last study follow-up visit or have discontinued study drug and have completed applicable follow-up assessments.

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 institutional review board (IRB)/independent ethics committee (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, then the sponsor or designee 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

All subject numbers will be 6 digits; the first 3 digits will be the site number, and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their number.

This is a nonrandomized study, in which subjects will be enrolled into either Part 1 or Part 2 as described previously, with all subjects receiving INCAGN01949 (herein referred to as study drug). Site staff will contact the interactive response technology (IRT) at the time of screening, when enrolling subjects, and when ordering study drug for all treatment cycles, as well as to discontinue subjects from treatment. Refer to the IRT manual for detailed information.

5.1.2. Randomization and Blinding

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

5.2. INCAGN01949

5.2.1. 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 30 minutes (-5/+10 minutes) on Day 1 of each cycle. In Part 1, subjects will be administered study drug, according to cohort enrollment (Table 2). In Part 2, subjects will be administered study drug at the recommended dose and schedule. Subjects will continue to receive INCAGN01949 as long as the subject is deriving benefit and has not met any of the Protocol-defined conditions for treatment withdrawal (see Section 5.5).

The Pharmacy Manual contains additional information and instructions for study drug preparation and infusion.

5.2.2. 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 protective packaging. The Pharmacy Manual contains additional information regarding supply, packaging, and labeling of study drug.

The investigator will take responsibility for and 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.

5.2.3. 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.

5.3. Treatment Compliance

INCAGN01949 is 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 regimen are planned for dose-escalation cohorts. Dose interruptions and modifications also may occur for individual study subjects. The identification of DLTs will define the doses used in planned cohorts (see Section 5.4.2). Further, the occurrence of DLTs and other toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects.

Intrasubject dose escalation is not permitted; however, once the recommended dose has been determined, ongoing subjects in Part 1 may be permitted to dose escalate to the recommended dose and schedule with approval of the medical monitor.

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. All DLTs will be assessed by the investigator using CTCAE v4.03. A DLT will be defined as the occurrence of any toxicity in Table 3, with the exception of events clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity.

Individual subject dose reductions may be made based on events observed at any time during treatment with study drug; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD/PAD of study drug, decisions will be made based on events that are observed from the first day of study drug administration through and including study Day 28. A lower MTD may subsequently be determined based on relevant toxicities that become evident after Day 28.

Table 3: Definition of Dose-Limiting Toxicity

Nonhematologic toxicity
• Any ≥ Grade 3 nonhematologic toxicity EXCEPT the following: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with supportive care within 48 hours. – Changes in cholesterol and triglycerides. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Asymptomatic changes in lipid profiles. – Asymptomatic changes in amylase and lipase. – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions).
Hematologic toxicity
• Grade 3 thrombocytopenia with clinically significant bleeding (ie, requires hospitalization, transfusion of blood products, or other urgent medical intervention). • Grade 4 thrombocytopenia. • ≥ Grade 3 febrile neutropenia (absolute neutrophil count < 1.0×10^9/L and fever > 101°F/38.3°C). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 3 days after interrupting study drug. • Grade 4 anemia not explained by underlying disease or some other concomitant disorder.
Immune-related toxicity[a]
• ≥ Grade 2 ocular irAEs will be considered a DLT. • Grade 3 irAEs that do not improve to baseline or at least Grade 1 in < 5 days with appropriate care or with corticosteroid therapy will be considered a DLT. • Grade 4 irAEs will be considered a DLT regardless of duration.
General
• Inability to receive the planned number of doses within the 28-day DLT period due to toxicity, regardless of grade, will be considered a DLT.
MTD
• In 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 Part 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of DLTs occurs in ≥ 33% of subjects after 6 subjects have been observed for at least 28 days, further enrollment may be interrupted, and the investigators and sponsor will meet and reassess the MTD. All AEs, regardless of the time of occurrence on study, may be considered in DLT determination purposes.
MNTD
• For each dose and schedule explored, if > 33% of subjects (minimum of 6 subjects) experience a ≥ Grade 3 toxicity related to study drug after completing ≥ 4 cycles, then treatment will be stopped, and the MNTDs will be determined in conjunction with the investigators and sponsor based on all available safety data. All AEs, regardless of the time of occurrence on study, may be considered in DLT determination decisions.

Note: Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination will not be considered DLTs.

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

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

In all cases, investigators may employ any measures or concomitant medications, after discussion with the sponsor (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 (ie, 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, 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 and Adjustments of Study Drug

Treatment with study drug may be delayed to allow for resolution of toxicity. 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. For toxicities that occur outside of the 28-day DLT period, 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 with study drug.

Instructions for dose modifications and interruptions are outlined in Table 4. Individual decisions regarding dose interruptions and reductions should be made using appropriate clinical judgment in consultation with the medical monitor, 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-reduction 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, holidays). Subjects should be placed back on study therapy within 4 weeks (28 days) of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the subject's study record.

Table 4: Rules for Interruption and Restarting of Study Drug

CTCAE Grade or Severity	Timing for Restarting Treatment	Dose Level for Restarting Treatment	Treatment Discontinuation[a]
1-2 (mild-moderate)	Continue treatment at the discretion of the investigator.	N/A	N/A
3 (severe)	Toxicity resolves to Grade 0-1.	Reduce by 1 dose level.[b]	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)	Permanently discontinue.	N/A	Permanently discontinue.

[a] Permanently discontinue for any severe or Grade 3 AE that recurs or any life-threatening event.
[b] No more than 2 dose reductions of study drug are permitted, or 1 dose reduction of study drug if the starting dose is 7 mg (see Table 2). Subject should be permanently discontinued from study drug if they have AEs requiring more than 2 dose reductions of study drug.

5.4.7. Definition, Procedures, and Supportive Care Guidelines for Immune-Related Adverse Events

INCAGN01949 is an immune modulator, and although no toxicities were identified in preclinical models, it is possible that irAEs (both nonserious and serious) similar to those described with approved immunotherapies may occur. Adverse events of a potential immunologic etiology or irAEs may be defined as an AE consistent with an immune phenomenon associated with drug exposure ***after all other etiologies have been eliminated*** (see Section 8.8). Immune-related AEs may be expected based on the nature of INCAGN01949, its mechanism of action, and reported experience with 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 5. Detailed supportive care guidelines for specific irAEs can be in found in Appendix B. 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 5: Supportive Care Guidelines for Subjects Exhibiting Immune-Related Adverse Events

CTCAE Grade/Severity	Supportive Care[a]
Grade 1 (mild)	• Monitor symptoms and provide symptomatic treatment.
Grade 2 (moderate)	• Monitor symptoms and provide symptomatic treatment. • Consider consultation with specialists as necessary. • Consider systemic corticosteroids per institutional standard of care.
Grade 3-4 (severe–life-threatening)	• Monitor symptoms and provide symptomatic treatment. • Consider consultation with specialists as necessary. • Administer corticosteroids per institutional standard of care. • More potent immunosuppressive therapies should be considered for events not responding to systemic steroids after discussing with the medical monitor. • Study drug should 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 6 shows treatment guidelines for subjects who experience an infusion reaction associated with study drug administrative procedures. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 6: INCAGN01949 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 interrupted 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 drug administration.	Subject may be premedicated 1.5 h (± 30 min) before infusion with the following: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).
Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated.	Stop infusion. Additional appropriate medical therapy may include but not be 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 drug administration.	No subsequent dose.

NSAID = nonsteroidal anti-inflammatory drug.
Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during study drug infusion.

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 drug treatment and will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Grade 4 or life-threatening AEs (see Table 4 and Table 6).
- ≥ Grade 2 ocular irAE.
- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- An AE requiring more than 2 dose reductions of study drug, or more than 1 dose reduction if the starting dose is 7 mg (see Table 2).
- Persistent AE requiring a delay of therapy for more than 4 weeks (28 days), unless a greater delay has been approved by the sponsor.

5.4.10. Treatment After Initial Evidence of Radiologic Disease Progression

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 may manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows disease progression, then subjects have the option to continue treatment while awaiting radiographic confirmation of progression as outlined in Section 7.7.1.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

A subject may choose to withdraw from the study at any time or be withdrawn by the investigator or sponsor, if the subject is noncompliant with the study requirements. Subjects may also be withdrawn at the discretion of the FDA or health authorities. If a subject is withdrawn, then every reasonable effort should be made to determine the reason for withdrawal, and this information should be recorded in the electronic case report form (eCRF).

Subjects **must** be withdrawn from **study drug** 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.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The subject is lost to follow-up.

- Unacceptable toxicity (see Section 5.4). Subjects with unacceptable toxicities must be withdrawn from study drug but will continue to be followed during the safety follow-up visits as specified in Section 6.4.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- Confirmed radiographic progression of disease per mRECIST v1.1. See Section 7.7.1.

  Note: For unconfirmed progression, see Section 7.7.1.

  Note: 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.
- If, during the course of the study, a subject is found not to have met eligibility criteria (see Section 3), then the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, then 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 drug, the subject will be withdrawn from the study, and the end-of-treatment (EOT) visit should be conducted. Reasonable efforts should be made to have the subject return for follow-up visits. These visits are described in Section 6. The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF.

If a subject is withdrawn from the study:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the IRT.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy 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 drug and 60 days after the last dose of study drug 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 drug should be recorded for serious adverse events (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 and over-the-counter medications, herbal supplements, and IV medications and fluids. If changes occur during the study period, then 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

Use of systemic glucocorticoids is restricted to prophylaxis for contrast allergies for radiographic procedures or to modulate symptoms or treat an AE of suspected immunologic etiology. The use of physiologic corticosteroid replacement therapy may be approved after consultation with the sponsor.

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

5.6.3. Prohibited Medications

Medications or vaccinations specifically prohibited in the exclusion criteria (see Section 3.2) are not allowed during the ongoing study. If there is a clinical indication for one of these medications or vaccinations specifically prohibited during the study, discontinuation from study drug or vaccination may be required. The investigator should discuss any questions regarding this with the sponsor. 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 drug or vaccination schedule 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 the study drug.
- Any immunological-based treatment for any reason from screening through follow-up visit.

  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 of immune toxicities as described in Section 5.4.7 and Appendix B.

  Note: Allergy shots may be permitted after consultation with the medical monitor.
- Investigational agents other than the study drug from screening through the follow-up visit.
- Concomitant radiation therapy.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on a 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 drug and while participating in the study. Examples of live vaccines include, but are not limited to, 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 assessments (Table 7), and all laboratory assessments will be performed as indicated in Table 8 and Table 9. Table 10 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 7: Schedule of Assessments

Visit Day (Range)	Protocol Section	Screening	Treatment[a]				Post-Treatment[b]		
			C1 and C2		All Subsequent Cycles	Every 8 weeks	EOT	Safety Follow-Up Visit 1	Safety Follow-Up Visit 2
			D1	D7	D1	Disease Status			
Evaluation/Window		**Day -28 to -1**		**± 1 day**	**± 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						
Contact IRT	7.2	X	X		X		X		
Medical and cancer history	7.3	X							
Prior/concomitant medications	7.4	X	X	X	X		X	X	X
Administer INCAGN01949	5.2.1		X		X				
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	X		X	X	X
Vital signs and weight	7.6.3	X	X[c]	X	X[c]		X	X	X
ECOG performance status	7.8	X	X	X	X		X	X	X
Laboratory assessments	7.6.5	X	X[d]	X	X		X	X	X
12-lead ECG[e]	7.6.4	X[f,g]	X[g]		X[g,h]		X	X	
AE assessment	7.6.1	X	X	X	X		X	X	X
Efficacy measurements									
Radiologic tumor assessments	7.7	X[i]				X[j]	X[k]	X[k]	

[a] Treatment cycles will begin every 14 days (± 3 days). Alternate dose schedules may also be explored based on emerging safety, PK, [redacted] data.

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

[c] On Day 1 of the first 4 cycles (C1D1, C2D1, C3D1, and C4D1), subjects will be required to stay at the study site for safety observation for up to 4 hours postinfusion. It is recommended that the subject does not leave the site for any reason during the safety observation period. During the safety observation period, vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be assessed every 60 minutes ± 10 minutes (eg, 1 hour postinfusion, 2 hours postinfusion, 3 hours postinfusion, and 4 hours postinfusion). Subjects will also be assessed for the onset of acute AEs.

[d] Laboratory assessments may also be required on additional visit days as described in Table 8 and Table 9.

[e] 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.

[f] 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.

[g] **Triplicate ECG measurements are required at screening, C1D1 (in conjunction with PK samples), and C6D1 (in conjunction with PK samples).** Other ECGs only need to be performed in triplicate if there has been a QT prolongation on study or if the ECG shows a clinically significant abnormality not present at baseline. Triplicate ECG measurements should be performed predose and within 1 hour postdose. Measurements should be taken in triplicate (separated by 5 minutes ± 5 minutes).

[h] A 12-lead ECG should be performed on Day 1 of every other cycle after C2 (eg, C4, C6, C8, C10).

[i] The initial tumor imaging will be performed within 28 days before the first dose of study drug. 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 drug. 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, every 8 weeks (± 7 days) for the first 12 months, and then every 12 weeks (± 7 days) thereafter. Imaging should follow calendar days 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 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). For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status every 8 weeks (± 7 days) by radiographic imaging until 1) start of new cancer therapy, 2) documented disease progression, 3) death, 4) withdrawal of consent or 5) the end of the study, whichever occurs first.

Table 8: Schedule of Laboratory Assessments

Visit Day (Range)	Protocol Section	Screening	Treatment				Post-Treatment		
			C1 and C2		Odd Numbered Cycles (C3, C5, C7, etc)	Even Numbered Cycles (C4, C6, C8, etc)	EOT	Safety Follow-Up Visit 1	Safety Follow-Up Visit 2
			D1	D7	D1	D1			
Evaluation/Window		**Day -28 to -1**	**Predose**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**30 days (+ 7 days)**	**60 days (+ 7 days)**
Local laboratory tests[a]									
Comprehensive serum chemistries[b] and lipid panel	7.6.5	X[c]	X[d]	X	X	X	X	X	X
Hematology with differential	7.6.5	X[c]	X[d]	X	X	X	X	X	X
Coagulation panel	7.6.5	X[c]	X[d]	X	X		X	X	X
Urinalysis	7.6.5	X	X[d]	X	X		X		
Endocrine function tests	7.6.5	X[c]	X[d]	X	X		X	X	X
Hepatitis B and C	7.6.5.2	X							
Serum pregnancy test (childbearing females only)[e]	7.6.5.1	X					X		
Urine pregnancy test (childbearing females only)[f]	7.6.5.1				X	X			
CA-125 (subjects with ovarian cancer only)			X[g]			X[g]	X		

[a] All safety laboratory assessments will be performed locally.
[b] If liver chemistry tests are abnormal (eg, change in grade from baseline), then liver chemistry monitoring should increase to once per week until resolved to baseline. 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 those 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 drug 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] A serum pregnancy test will be required for all women of childbearing potential during screening and must be performed within 72 hours before the first dose of study drug.
[f] Urine pregnancy tests will be conducted as medically indicated or per country-specific requirements.
[g] CA-125 should be performed at Cycle 1 Day 1 and with the radiographic tumor assessment (± 7 days).

Table 9: Schedule of Pharmacokinetic and Pharmacodynamic Assessments

				Treatment											Post-Treatment	
				C1			C2	C3	C4	C6			C7	C8 and C12		
Visit Day (Range)	**Protocol Section**	**Timing of Assessment**	**Screening**	**D1**	**D2**	**D7**	**D1**	**D1**	**D1**	**D1**	**D2**	**D7**	**D1**	**D1**	**EOT**	**Safety Follow-Up Visit 1**
Evaluation/Window			**Day -28 to -1**			**± 1 day**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**		**± 1 day**	**± 3 days**	**± 3 days**		**30 days (+ 7 days)**
Pharmacokinetics Assessments[a]																
Serum sample for PK[b]	7.9	Table 13		X	X	X	X	X	X	X	X	X	X			
[redacted]																

[a] All PK [redacted] assessments will be performed by a central laboratory. Details regarding PK [redacted] samples including specimen handling, processing, and shipping will be outlined in the laboratory manual.

[b] Adjustments to the time of PK [redacted] blood sampling postdose may be made based on emerging PK data; however, no additional postdose timepoints will be used, and the maximum scheduled timepoints will be not greater than 6 hours postdose on the day of infusion.

[redacted]

Table 10: Local Laboratory Tests: Required Analytes

Serum Chemistries	Hematology	Urinalysis	Hepatitis Screening	Coagulation
Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphorus Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid Amylase Lipase	Complete blood count, including: Hemoglobin Hematocrit Platelet count Red blood cell count White blood cell count Mean corpuscular volume Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for the following WBC differential laboratory results: White blood cells Lymphocytes Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen	Hepatitis B surface antigen Hepatitis B core antibody HBV-DNA HCV antibody HCV-RNA	PT aPTT INR
		Lipid Panel	**Endocrine Monitoring**	**Pregnancy Testing**[a]
		Total Cholesterol Triglycerides LDL HDL	Thyroid-stimulating hormone Free thyroxine Total triiodothyronine/free triiodothyronine[b]	Female subjects of childbearing potential only require a serum test at screening. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

aPTT = activated partial thromboplastin time; HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein.
Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.
[a] Urine pregnancy tests are only required if medically indicated or a country-specific requirement.
[b] If considered standard depending on region.

6.1. Screening

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

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided that the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study. All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

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 that the subject receives the first dose of study drug (Cycle 1 Day 1) through the point at which the investigator determines that the subject will be permanently discontinued from study drug. Cycle 1 Day 1 must be no more than 28 days after the subject has signed the ICF.

Subjects will have regularly scheduled study visits on Day 1 of every cycle ± 3 days. Additional visits will be required on Day 7 of Cycles 1 and 2. During study visits, the subject will have clinical and laboratory assessments as outlined in Table 7 and Table 8. At certain study visits as indicated in Section 7.9 and Section 7.10, subjects will have PK, [redacted] samples obtained (see Table 9). Toxicities will be monitored continuously and will be graded using the National Cancer Institute (NCI) CTCAE v4.03 criteria.

One Day 1 of the first 4 cycles (Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1), subjects will be required to stay at the study site for safety observation for up to 4 hours postinfusion. It is recommended that the subject does not leave the site for any reason during the safety observation period. During the safety observation period, subjects will be assessed for the onset of acute AEs.

6.3. End of Treatment

When the subject permanently discontinues study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, then 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 follow-up visit(s).

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 days (+ 7 days) and 60 days (+ 7 days) after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 60 days after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. If a subject is scheduled to begin a new anticancer therapy before the end of the 30-day or the 60-day safety follow-up period, then the safety follow-up visit should be performed before new anticancer therapy is started.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason **other than** disease progression will move into the disease status follow-up period and should continue to be assessed every 8 weeks (± 7 days) for the first 12 months and then every 12 weeks thereafter by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the earliest of the following:

- The start of new antineoplastic therapy.
- Disease progression.
- Death.
- The end of 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 drug 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 Procedure

The investigator or designee will assign a subject number when a subject enters the screening phase (see Section 5.1.1). Upon determining that the subject is eligible for study entry (see Section 3), the subject will be entered into the IRT. Additionally, the IRT will be contacted to update the subject's status and for study drug supply. 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 general medical 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 illness. 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, primary tumor histology, 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. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within 28 days before the first dose of study drug and up to the end of the safety follow-up phase of the study 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 drug. If a subject initiates a new anticancer therapy within 30 to 60 days after the last dose of study drug, 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

7.6.2.1. Comprehensive Physical Examination

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.

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

7.6.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation conducted by the investigator or 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. Clinically notable abnormalities that are considered clinically significant in the judgement of the investigator are to be reported as AEs.

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 with the subject in a recumbent or semirecumbent position after 5 minutes of rest and should not be performed within 15 minutes of a blood collection. All 12-lead ECGs will be acquired using an ECG analysis system with analysis and printing capabilities, as well as digital transmission capabilities to a central capture module at the central ECG laboratory.

Timed triplicate ECGs (separated by 5 minutes ± 5 minutes) will be conducted at screening and in conjunction with the pre- and postinfusion PK timepoints on C1D1 and C6D1 (see Table 11). The specified postdose timepoint may be adjusted based on emerging PK data.

A 12-lead ECG should be performed on Day 1 of every other cycle after Cycle 2 (eg, Cycle 4, Cycle 6, Cycle 8, Cycle 10). Subsequent ECGs only need to be performed in triplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnormality not present at baseline.

The 12-lead ECGs will be interpreted by the investigator or qualified designee at the site to be used for immediate subject management. The decision to include, exclude, or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the medical monitor, as appropriate. Clinically significant abnormal findings before signing consent should be recorded as medical history. Clinically significant abnormal findings after signing consent should be recorded as an AE. 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. 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 sponsor approval. In addition, the JTc interval should be used for all subsequent assessments.

Table 11: Timing of Triplicate Electrocardiograms

Study Visit	Timing of Sample			
	Any Time	Preinfusion	Postinfusion PK Timepoint	4-Hr Postinfusion PK Timepoint
Screening	X			
C1D1		X[a]	X[b]	X[a]
C6D1		X[a]	X[b]	X[a]

[a] Electrocardiograms should be conducted before but within 30 minutes of the PK blood draw at the corresponding timepoint.
[b] Electrocardiograms should be performed 15 to 30 minutes (+ 10 minutes) after corresponding PK sample is drawn.

7.6.5. Laboratory Assessments

A 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 8. Table 10 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.

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 the EOT visit. 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 conducted as outlined in Table 8, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. 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 drug and continue participation in the study.

7.6.5.2. Hepatitis Screening Tests

Hepatitis screening assessments will be performed at the screening visit (Table 8) to rule out hepatitis infection; required analytes are shown in Table 10. 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 in clinically indicated.

7.7. Efficacy Assessments

7.7.1. Modified RECIST v1.1 Assessment of Disease

Modified RECIST will be applied by the site as the primary measure for assessment of tumor response and as a basis for Protocol guidelines related to disease status (eg, discontinuation of study therapy). Unique tumor responses have been noted with immunotherapy treatment (Chiou and Burotto 2015); therefore, RECIST v1.1 has been adapted for use in this study and referred to as mRECIST (see Section 1.3.3.1).

If radiologic imaging shows progressive disease, then tumor assessment should be repeated at a minimum of 4 weeks, but no later than 6 weeks later to confirm progression, with the option of continuing treatment while awaiting radiologic confirmation of progression. Table 12 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 12: 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, then 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 that 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 7). 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 for a subject throughout the study. The baseline scan must be a contrast computed tomography (CT) or magnetic resonance imaging (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 and abdomen are required for all subjects.

7.7.1.1.1. Tumor Imaging During Screening

Initial tumor imaging must be performed within 28 days before the first dose of study drug. 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. Additionally, it is recommended that tumor lesions selected for biopsy **not** be selected as target lesions.

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 drug.

7.7.1.1.2. Tumor Imaging During the Study

The first imaging assessment should be performed 8 weeks after the first dose of study drug, every 8 weeks (56 days ± 7 days) for 12 months, and then every 12 weeks (84 days ± 7 days) thereafter until disease progression is determined. Imaging assessments may be performed more frequently if clinically indicated. **Imaging should not be adjusted for delays in cycle starts**.

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

Imaging should continue to be performed until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confirmed at least 4 weeks, but no later than 6 weeks after the first scan indicating progression in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed, provided that they have met the conditions detailed in Section 7.7.1. A central imaging vendor will not be used in this study.

7.7.1.1.3. Imaging During Follow-Up

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

7.8. Performance and Quality-of-Life Assessments

Eastern Cooperative Oncology Group performance status (Appendix C) must be assessed by a medically qualified individual and recorded in the CRF at visits indicated in Table 7.

7.9. Pharmacokinetic Assessments

7.9.1. Blood Sample Collection

Pharmacokinetics [redacted] samples will be obtained at the visits indicated in Table 9. Timing of PK [redacted] assessments are outlined in Table 13. After the predose PK sample is drawn, subjects will begin the study drug infusion. Predose is defined as within 24 hours before administration of study drug. Adjustments to the timing of blood sampling may be made based on emerging PK data. The exact dates and times of the PK blood collection will be recorded in the eCRF. Instructions for sample preparation and shipping will be provided in the Laboratory Manual.

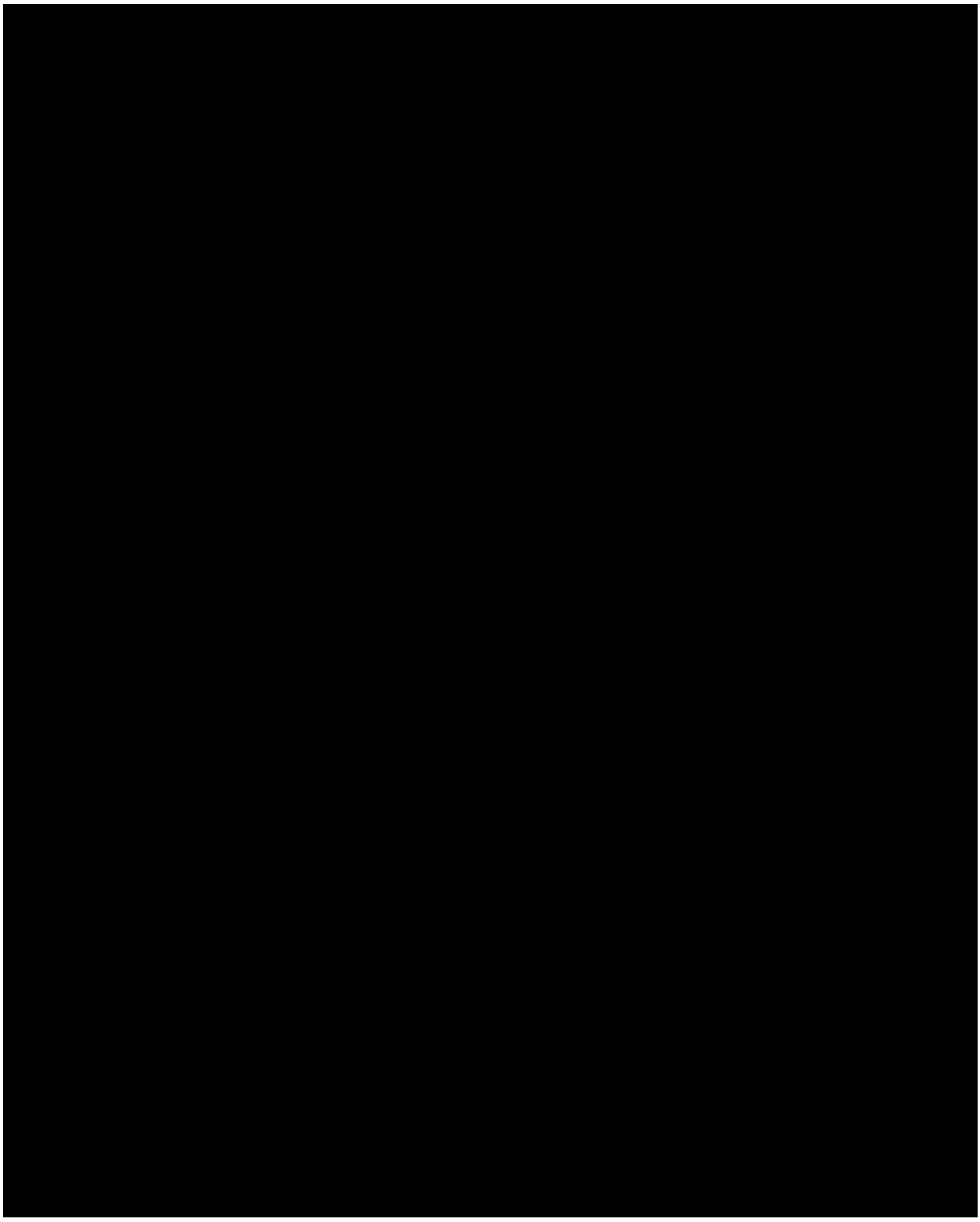
Table 13: Timing of Pharmacokinetic [redacted] Sample Collection

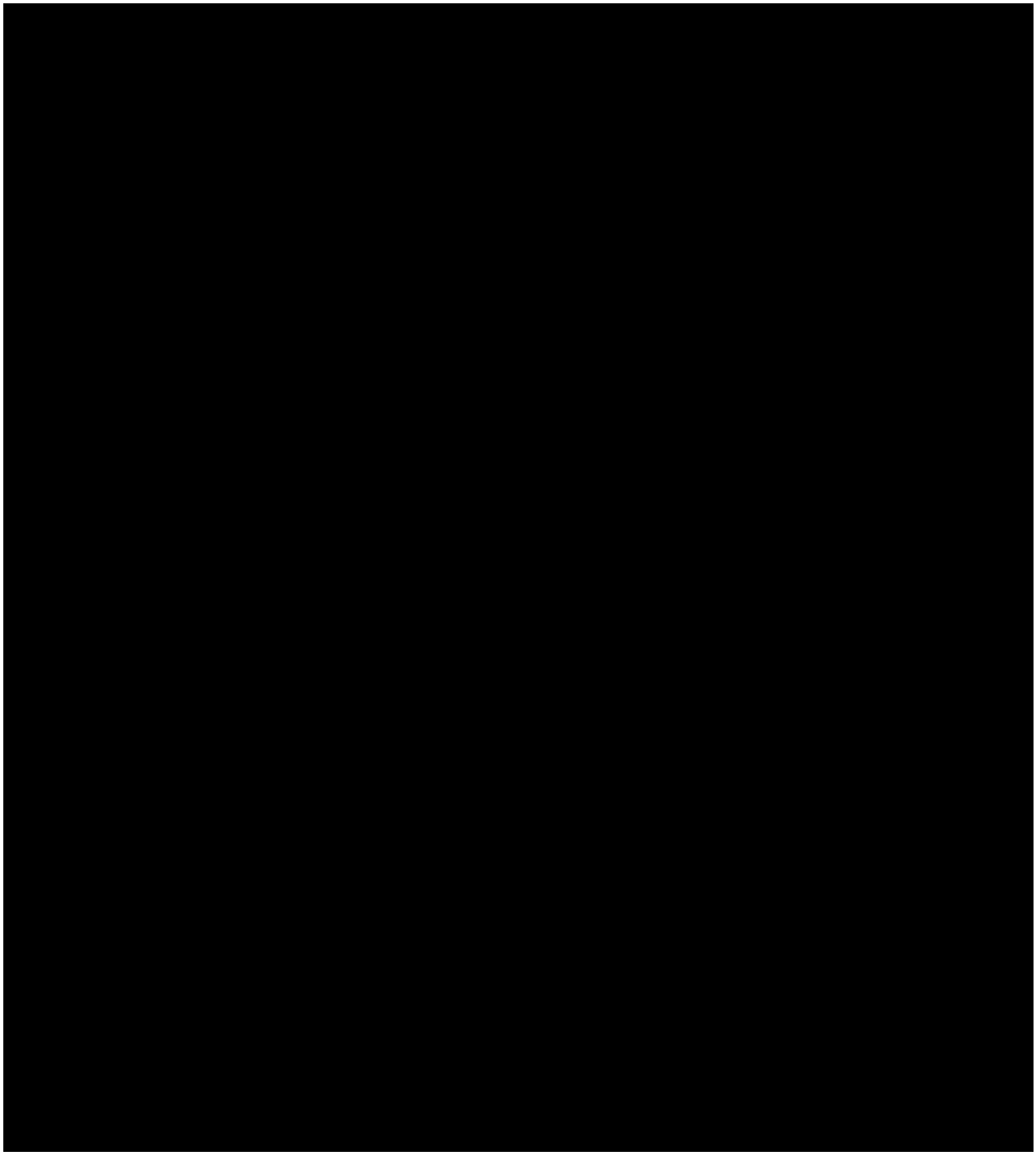
Study Visit	Assessment	Timing of Sample Collection
Cycle 1 Day 1	PK [redacted]	• Preinfusion
	PK	• Postinfusion (± 10 min) • 4 h (± 30 min) postinfusion
Cycle 1 Day 2	PK	• 24 h (± 60 min) postinfusion
Cycle 1 Day 7	PK	• Untimed PK sample
Cycle 2 Day 1	PK [redacted]	• Preinfusion
Cycle 3 Day 1	PK [redacted]	• Preinfusion
Cycle 4 Day 1	PK	• Preinfusion
Cycle 6 Day 1	PK [redacted]	• Preinfusion
	PK	• Postinfusion (± 10 min) • 4 h (± 30 min) postinfusion
Cycle 6 Day 2	PK	• 24 h (± 60 min) postinfusion
Cycle 6 Day 7	PK	• Untimed PK sample
Cycle 7 Day 1	PK	• Preinfusion
[redacted]	[redacted]	[redacted]

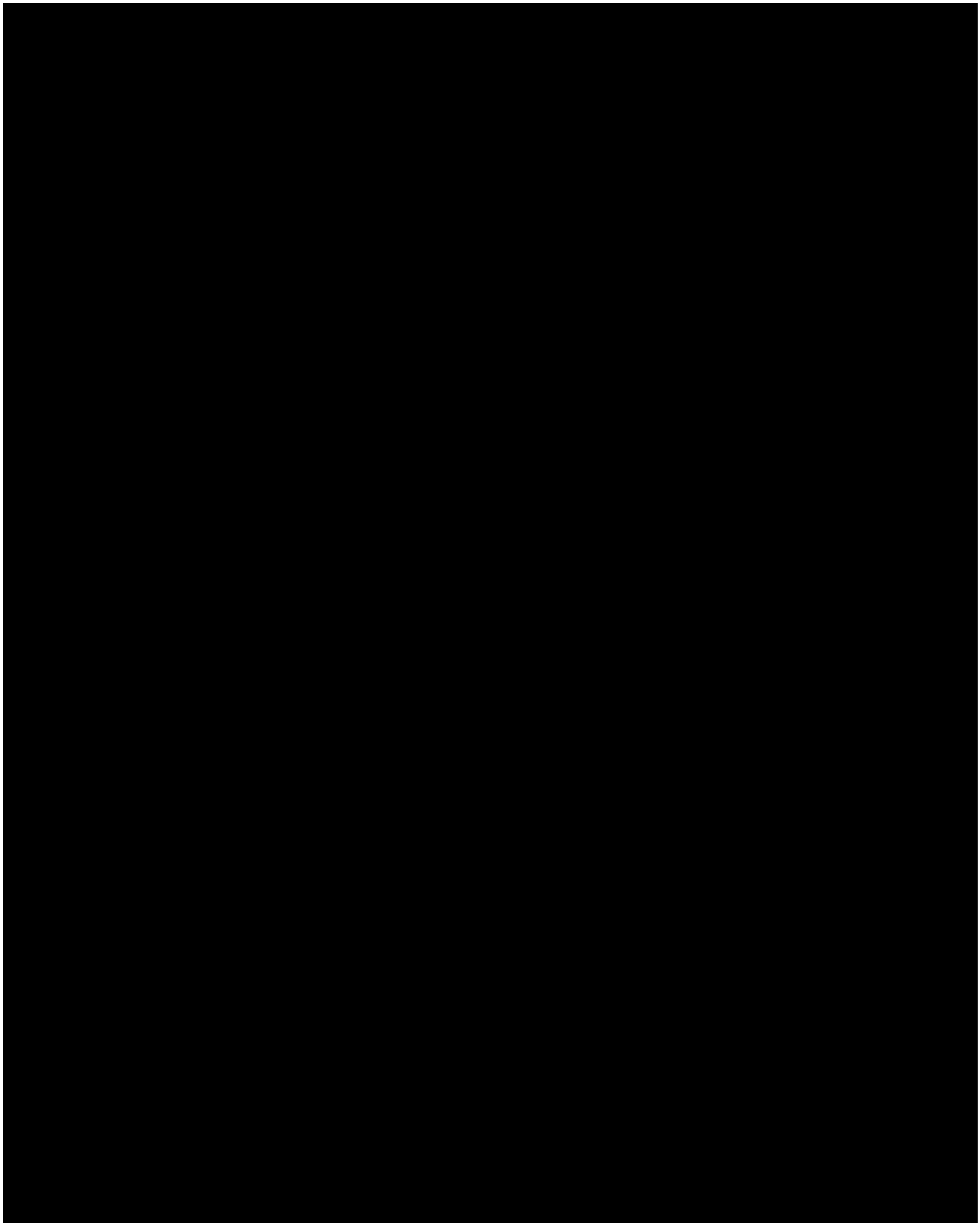
7.9.2. Pharmacokinetic Analysis

The PK calculations will be performed, if appropriate, using commercial software such as WinNonlin® (Pharsight Corporation, Mountain View, CA). Nominal times will be used in all cases, except when the difference between the actual time and nominal time is greater than 5 minutes for samples collected up to 4 hours after administration; in these cases, actual times will be used for PK analysis. Additional details of analyses will be described in the Statistical Analysis Plan.

[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.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (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 drug 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 4. The CTCAE v4.03 severity of Grade 5 will not be used; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. 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.

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 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- 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 serious adverse event (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 (severe) AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.4) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

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

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

- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 60 days after the last dose of study drug, whichever is later) 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 drug 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 the 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 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 reduced, 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 (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) 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, a) within 60 days of the last dose of study drug for maternal exposure, b) within 90 days of the last dose for paternal exposure, or c) within 30 days after cessation of treatment if the subject initiates new anticancer therapy, the following procedures should be followed in order to ensure subject safety:

- The study drug 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 test 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 drug 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 (IB). Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). 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

There will be no formal Data Monitoring Committee for this open-label study. For Part 1, the sponsor will conduct telephone conferences with investigators in order to review cohort-specific data, to review overall safety data from previous cohorts (if applicable), and to agree on dose escalation, de-escalation, and cohort expansion decisions on a regular basis (ie, approximately weekly). For Part 2, safety and tolerability will be carefully monitored throughout the study by the sponsor on a regular basis (ie, approximately monthly).

8.8. Immune-Related Adverse Events

Adverse events of a potential immunologic etiology or irAEs may be defined as an AE consistent with an immune phenomenon associated with drug exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on the nature of INCAGN01949, its mechanism of action, and reported experience with 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. Guidance for the assessment, diagnosis, and management of irAEs is provided in Section 5.4.7 and Appendix B. Suspected irAEs should be discussed with the medical monitor when possible.

8.9. Product Complaints

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

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

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.1.2 of this Protocol.

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

9. STATISTICS

9.1. Study Populations

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

The PK/[redacted] evaluable population includes subjects having received at least 1 dose of study drug and had at least 1 PK/[redacted] sample collected and analyzed.

9.2. Selection of Sample Size

9.2.1. Sample Size in Part 1

The primary objective of Part 1 of the study is to determine the PAD or the MTD of INCAGN01949. The total number of subjects will depend on the number of dose levels tested before the PAD or MTD is established. Approximately 18 to 42 subjects (6 subjects per dose level for 7 dose levels) will be included based on the dose escalation. Dose escalation will follow the 3 + 3 design algorithm. Based on this algorithm, a minimum of 3 evaluable subjects will be enrolled in each cohort beginning with Cohort 1 (7 mg; starting dose) and a maximum of 6 subjects for each cohort.

Part 1 of the study may also include safety expansion cohorts evaluating dose(s) and schedule(s) equivalent to or lower than the highest dose levels determined to be safe and/or doses determined to be pharmacologically active. Each safety expansion cohort will enroll 9 evaluable subjects. Up to 36 subjects will be enrolled in Part 1 safety expansion. If < 3 of 9 evaluable subjects experience a DLT, then the cohort will be deemed safe. If more than 1 safety expansion cohort is deemed safe, then a recommended dose and schedule will be determined in conjunction with the investigators and sponsor based on all available safety, PK, [redacted] results.

9.2.2. Sample Size in Part 2

Part 2 of the study will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the recommended dose of INCAGN01949. The sample size for each tumor type will be guided by the Simon 2-stage design (Simon 1989). Let 5% be a clinically insignificant response rate for all tumor types. During Stage 1, 9 subjects will be enrolled; if no responses are observed, then the cohort will be discontinued. If at least 1 response is observed, then 8 additional subjects will be enrolled (Stage 2), for a maximum of 17 subjects per tumor type in Part 2. The detailed calculation is based on a 1-sided Type I error of 0.05 and power of 80% to detect a 25% response rate for each of the tumor types.

9.3. Level of Significance

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

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

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

If there are no responses with each tumor type out of 9 subjects (consistent with a calculated response rate < 5%) at Stage 1, then the study will be stopped for futility, and the null hypothesis is not rejected. Otherwise, in the tumor types in which at least 1 response among the Stage 1 subjects is observed, 8 additional subjects will be treated in Stage 2. If there are ≤ 2 responders among 17 subjects at the end of Stage 2, then the drug will be declared nonpromising for that tumor type, and the null hypothesis is not rejected. Further investigation of the study drug will be considered interesting (predictive of ≥ 25% response rate) if ≥ 3 responses are observed in the first 17 subjects. For the hypothesis test in the Simon 2-stage design, the null response rate is 5% and alternative response rate is 25%.

9.4.1.2. Secondary Efficacy Analyses

The PK of INCAGN01949 will be summarized.

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

Progression-free survival and duration of response will be estimated using the Kaplan-Meier method as per RECIST v1.1 and mRECIST v1.1.

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

A treatment-emergent adverse event (TEAE) is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation 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 4.

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, then 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 of 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 15), 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 15: 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 16). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 16: 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.

9.4.3. Pharmacokinetic Analysis

The PK parameters of C_{max}, T_{max}, C_{min}, and AUC_{0-t} (INCAGN01949) will be summarized by part, dose, and study cycle. The log-transformed PK parameters will be compared among dose levels by using a 1-factor analysis of variance. Dose-dependent parameters (C_{max} and AUC) will be normalized to the lowest common dose before statistical comparisons. Additionally, if sufficient data are available, then the dose proportionality of INCAGN01949 C_{max} and AUC will be evaluated statistically by using a power model (eg, $AUC = \alpha \cdot [dose^{\beta}]$) or equivalently log $(AUC) = \log(\alpha) + \beta \cdot \log(dose)$, where linear dose proportionality is accepted if β is not significantly different from 1).

If there is a sufficient amount of plasma concentration data from this study, then the data will be analyzed by standard population PK methods using appropriate software (eg, NONMEM).

[redacted]

[redacted]

9.5. Analyses for the Data Monitoring Committee

Not applicable.

9.6. Interim Analysis

Part 1 of the study will use a standard 3 + 3 dose-escalation design. Each Part 1 safety expansion cohort will enroll up to 9 additional evaluable subjects. If < 3 of 9 additional evaluable subjects has a DLT, then the cohort will be deemed safe. If more than 1 safety expansion cohort is deemed safe, then a recommended dose and schedule will be determined in conjunction with the investigators and sponsor based on all available safety, PK, [redacted] results. The probability of declaring a dose cohort as safe for various DLT rates in the 3 + 3 and the safety expansion is summarized in Table 17.

Table 17: Probability of Dose Escalation by DLT Rate for 3 + 3 Design and Safety Expansion

True DLT Rate	Probability of Declaring Dose Cohort as Safe	
	3 + 3 Design	In BOTH 3 + 3 Design and Safety Expansion
10%	90.6%	85.8%
20%	70.9%	52.3%
30%	49.4%	22.9%
40%	30.9%	7.2%
50%	17.2%	1.5%
60%	8.2%	0.2%

In Part 2, the Simon 2-stage design will be applied. During Stage 1, 9 subjects will be enrolled, and if no responses are observed, then the cohort will be discontinued. The probability of early termination for Stage 1 is summarized in Table 18. If at least 1 response is observed, then 8 additional subjects will be enrolled (Stage 2).

Table 18: Probability of Early Termination at Stage 1 for Simon 2-Stage Design

True Response Rate	Probability of Early Termination at Stage 1
15%	23.2%
20%	13.4%
25%	7.5%
30%	4.0%
35%	2.1%

Subjects will continue to receive INCAGN01949 until Protocol-defined withdrawal criteria are met. Continuous evaluation of toxicity events will be performed throughout enrollment in Part 2 of the study. If the cumulative incidence of DLTs occurs in ≥ 33% of subjects after 6 subjects have been observed for at least 28 days, further enrollment may be interrupted until the sponsor has determined the appropriate course of action. All AEs, regardless of the time of occurrence on study may be considered in determination of the appropriate dose, schedule, and MNTD.

Toxicity will continue to be monitored throughout the treatment period. If > 33% of subjects (minimum of 6 subjects) experience a Grade ≥ 3 toxicity related to study drug after completing ≥ 4 cycles, then dose administration will be stopped, and the MNTD will be determined in conjunction with the investigators and sponsor based on all available safety data.

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.
- 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 Electronic Data Capture (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 Code of Federal Regulations (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]
- Vasectomised 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 vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: CTFG 2014.

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

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

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

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

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

irAE	Supportive Care
Endocrinopathies	***Note:*** Subjects should be monitored for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Subjects may report fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension or report nonspecific symptoms that 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 (laboratory assessments or MRI), repeat laboratory assessments/MRI as clinically indicated. • For Grade 3 or 4 (severe or new symptoms**, new/worsening endocrinopathies, life threatening):** • Hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. • In hyperthyroidism, treat with an initial dose of IV corticosteroid followed by oral corticosteroids. Consider initiation of systemic corticosteroids at a dose of 1-2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy. Once improving, gradually taper immunosuppressive steroids over $\geq$ 4 weeks. • In hypophysitis, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered. • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate IV 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.

GI = gastrointestinal; IgG = immunoglobulin G; irAE = immune-related adverse event; IV = intravenous; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PCP = pneumocystis pneumonia.

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	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.

Signature Manifest

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