Official Title:	**A Phase 1/2 Safety and Efficacy Study of INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies**
NCT Number:	NCT03277352
Document Date:	Clinical Study Protocol: 24 August 2017

Clinical Study Protocol

INCAGN 1876-202

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

Product:	**INCAGN01876**
IND Number:	[redacted]
EudraCT Number:	**2017-001951-29**
Phase of Study:	**1/2**
Sponsor:	**Incyte Biosciences International Sàrl** **Route de la Corniche 1** **1066 Epalinges, Switzerland**
Date of Protocol:	**23 JUN 2017**
Date of Amendment 1:	**24 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 1876-202 Protocol Amendment 1 (dated 24 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: INCAGN01876, epacadostat (INCB024360), pembrolizumab	
Title of Study: A Phase 1/2 Safety and Efficacy Study of INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies	
Protocol Number: INCAGN 1876-202	**Study Phase:** 1/2

Indication:

Phase 1: advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach and gastroesophageal junction [GEJ] cancer), esophageal, hepatocellular carcinoma (HCC), melanoma (mucosal or cutaneous), Merkel cell carcinoma, mesothelioma, microsatellite instability-high (MSI-H) solid tumors, non-small cell lung cancer (NSCLC), ovarian cancer, squamous cell carcinoma of the head and neck (SCCHN), small cell lung cancer (SCLC), renal cell carcinoma (RCC), triple-negative breast cancer (TNBC), and urothelial carcinoma (UC)

Phase 2: advanced or metastatic melanoma, RCC, and UC

Primary Objectives:

Phase 1

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

Phase 2

- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies by assessing objective response rate (ORR) or complete response rate (CRR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary Objectives:

Phase 1 and Phase 2

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

Exploratory Objectives:

[redacted]

Primary Endpoints:

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

Secondary Endpoints:

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

Exploratory Endpoints:

[redacted]

Overall Study Design:

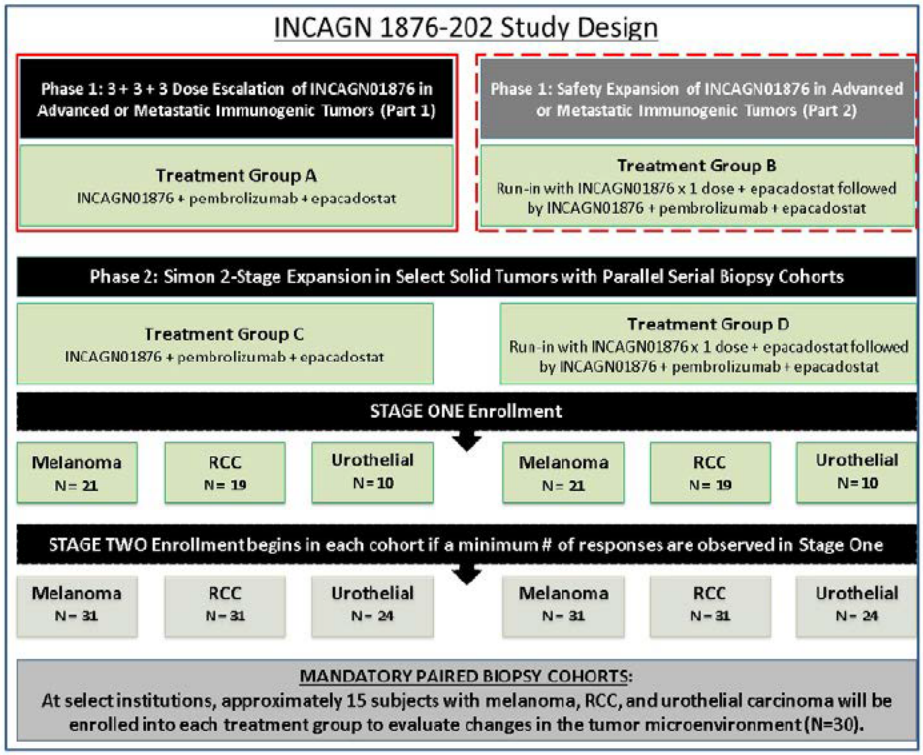
This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of INCAGN01876 when given in combination with immune therapies. Phase 1 will consist of 2 parts. Dose Escalation (Part 1), will consist of a 3 + 3 + 3 design to determine the maximum tolerated dose (MTD) [redacted] The Safety Expansion (Part 2) will further explore tolerated doses of INCAGN01876 from Part 1 given as a single-dose run-in followed by concomitant immune therapy. Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach and GEJ), esophageal cancer, HCC, melanoma (mucosal or cutaneous), Merkel cell carcinoma, mesothelioma, MSI-H solid tumors, NSCLC, ovarian cancer, SCCHN, SCLC, RCC, TNBC, and UC who have progressed after treatment with available therapies that are known to confer clinical benefit, who are

intolerant to treatment, or who refuse standard of care will be enrolled in both parts of Phase 1.

The Phase 2 Dose Expansion will further evaluate the safety, tolerability, and efficacy of the recommended dose(s) of INCAGN01876 selected in Phase 1 when given in combination with immune therapies. Subjects with advanced or metastatic melanoma, RCC, and UC will be enrolled in Phase 2. The study diagram is presented in Figure SF1.

The sponsor may elect to prioritize (or deprioritize) enrollment to specific treatment groups or cohorts based on emerging safety or efficacy data in collaboration with investigational sites.

Figure SF1: Overall Study Design



Phase 1 – Dose Escalation (Part 1)

A minimum of 3 evaluable subjects will be enrolled in Treatment Group A (see Table S2), beginning with INCAGN01876 Dose Cohort 1 (1.0 mg/kg; starting dose; see Table S1). A higher starting dose of INCAGN01876 may be used if safety data are available from the monotherapy study (INCAGN 1876-101), but it will not exceed 1 dose level below the highest tolerated dose of INCAGN01876 monotherapy. If a higher starting dose is used, the dose will be communicated to investigational sites with an administrative letter. The first 3 evaluable subjects enrolled within an INCAGN01876 dose cohort will be observed for a minimum of 28 days before the next dose cohort begins enrollment. If 0 DLTs occur in a cohort of 3 evaluable subjects, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 1 of 3 evaluable subjects experiences a DLT, that cohort will be expanded to 6 evaluable subjects. If 1 of 6 evaluable subjects experiences a DLT, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 2 of 6 evaluable subjects experience a DLT, that cohort will be expanded to 9 evaluable subjects. If $\geq$ 2 of 3, 3 of 6, or 3 of 9 evaluable subjects experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD, and the previous dose level will be considered the MTD. If only 3 evaluable subjects were treated at the MTD [redacted], then a minimum of 3 additional evaluable subjects will be enrolled before this dose is administered in Phase 2 of the study.

Additional subjects will be enrolled in a dose cohort to achieve the minimum of 3 evaluable subjects. 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 DLT observation period will result in the subjects being nonevaluable and replaced. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. The doses of INCAGN01876 to be evaluated in each treatment group are summarized in Table S1.

Table S1: INCAGN01876 Dose Cohorts

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

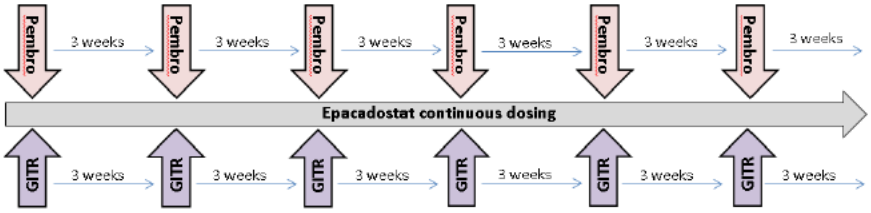
[a] A higher starting dose of INCAGN01876 may be used if safety data are available from the monotherapy study (INCANG 1876-101), but it will not exceed 1 dose level below the highest tolerated dose of INCAGN01876 monotherapy. If a higher starting dose is used, the dose will be communicated to investigational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

Treatment Group A (INCAGN01876 + Pembrolizumab + Epacadostat)

Treatment Group A will treat subjects with INCAGN01876 at the assigned dose level administered every 3 weeks (Q3W) in combination with 200 mg of pembrolizumab administered Q3W and [redacted] of epacadostat administered orally twice a day (BID; see Table S2). **There will be a waiting period of 48 hours between dose administration of the first subject and second subject of each dosing cohort.** The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table S1 until the MTD [redacted] of INCAGN01876 in combination with pembrolizumab and epacadostat is determined. Subjects must receive at least 1 dose of the cohort-specified dose of INCAGN01876, 1 dose of pembrolizumab, and at least 75% of planned doses of epacadostat (42 doses) or have had a DLT during the DLT observation period considered to be evaluable.

Table S2: Phase 1 Dose Escalation of Treatment Group A

Treatment Group A	INCAGN01876 Concurrent Dose Administration	Pembrolizumab	Epacadostat
	See INCAGN01876 dose cohorts (Table S1) Q3W starting at Cycle 1	200 mg Q3W starting at Cycle 1	[redacted] starting at Cycle 1



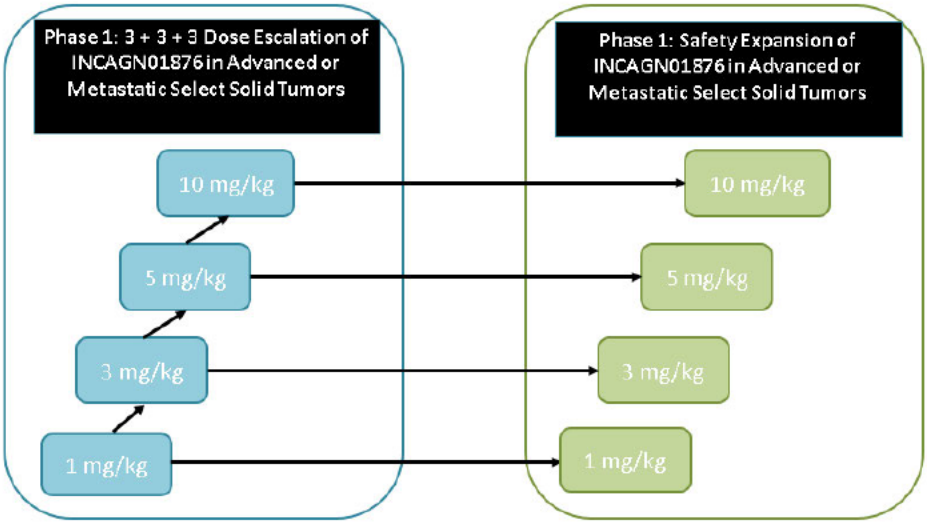
Phase 1 – Safety Expansion (Part 2)

Once an INCAGN01876 dose cohort in Treatment Group A is deemed tolerable (ie, no DLTs or unacceptable toxicities were observed within the defined DLT observation period of at least 28 days), up to 6 subjects will be enrolled in Treatment Group B at the same dose of INCAGN01876 (see Figure SF2). For example, if 3.0 mg/kg of INCAGN01876 is tolerated in Treatment Group A, then 3.0 mg/kg will be explored in up to 6 subjects in Treatment Group B. Doses of INCAGN01876 in Treatment Group B will be escalated in parallel to those explored in Treatment Group A, but will not exceed the MTD of INCAGN01876 established in Treatment Group A. Alternate dose administration schedules may also be explored, depending o [redacted] safety results. The sponsor may elect to

prioritize (or deprioritize) enrollment into specific dose cohorts based on emerging safety or efficacy data in collaboration with investigational sites.

If the cumulative incidence of Grade 3 or higher INCAGN01876-related AEs occurs in > 40% of subjects enrolled in a particular treatment group, then further enrollment will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action (eg, lower the dose of INCAGN01876, change dose frequency, etc).

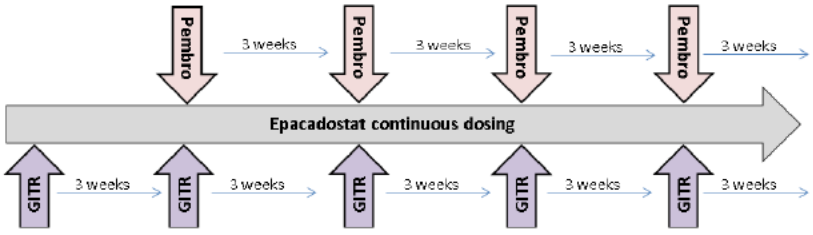
Figure SF2: Phase 1 Safety Expansion (Part 2)



Treatment Group B (INCAGN01876 + Epacadostat Run-In Followed by INCAGN01876 + Pembrolizumab + Epacadostat)

Treatment Group B will treat subjects with a single-dose run-in of INCAGN01876 at the assigned dose level in combination with [redacted] of epacadostat administered orally BID, followed by the combination of INCAGN01876 Q3W, 200 mg of pembrolizumab Q3W starting at Cycle 2, and [redacted] of epacadostat administered orally BID (see Table S3).

Table S3: Phase 1 Safety Expansion of Treatment Group B

Treatment Group B	INCAGN01876 Run-In Followed by Concurrent Dose Administration	Pembrolizumab	Epacadostat
	See INCAGN01876 dose cohorts (Table S1) Q3W starting at Cycle 1	200 mg Q3W starting at Cycle 2	[redacted] starting at Cycle 1
			

Phase 2 – Dose Expansion

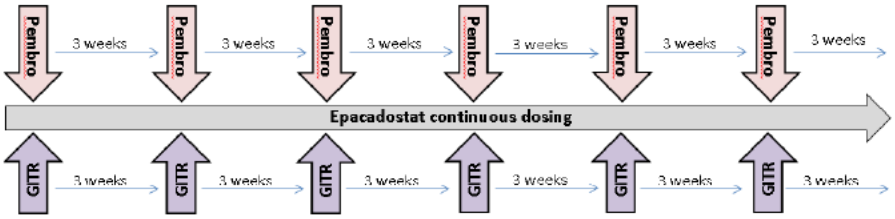
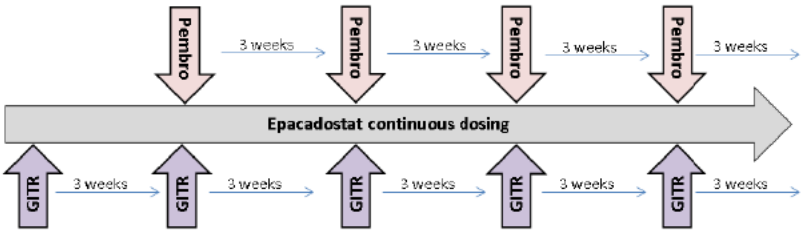
Phase 2 of the study will further evaluate the safety, tolerability, efficacy [redacted] of the immune therapy combination in subjects with advanced or metastatic melanoma, RCC, and UC. Additional tumor-specific cohorts may be added, by protocol amendment, based on emerging data.

Biopsy cohorts [redacted]

[redacted]. Approximately 15 evaluable subjects who have tumor lesions that are amenable to percutaneous biopsy will be enrolled in each biopsy cohort. The biopsy-specific cohorts will be limited to subjects with melanoma (mucosal or cutaneous), RCC, and UC.

The Phase 2 expansion treatment groups and tumor-specific cohorts for each treatment group are outlined in Table S4. A Simon 2-stage design will be used with a stopping rule to allow for early termination of a particular cohort at the end of Stage 1 if there are insufficient responses observed. The approximate number of subjects for Stage 1 and Stage 2 for each treatment group and tumor type is described in Table S5. Enrollment in Phase 2 will begin when the MTD [redacted] of INCAGN01876 for a given treatment group in Phase 1 has been determined.

Table S4: Phase 2 Dose Expansion Treatment Groups

Expansion Treatment Groups				
	INCAGN01876 Concurrent Dose Administration	**Pembrolizumab**	**Epacadostat**	**Tumor Cohorts**
Treatment Group C	MTD [redacted] of Treatment Group A Q3W starting at Cycle 1	200 mg Q3W starting at Cycle 1	[redacted] starting at Cycle 1	Cohort 1 – Biopsy Cohort 2 – Melanoma Cohort 3 – RCC Cohort 4 – UC
				
Treatment Group D	**INCAGN01876 Run-In Followed by Concurrent Dose Administration**	**Pembrolizumab**	**Epacadostat**	**Tumor Cohorts**
	MTD [redacted] of Treatment Group A Q3W starting at Cycle 1	200 mg Q3W starting at Cycle 2	[redacted] starting at Cycle 1	Cohort 1 – Biopsy Cohort 2 – Melanoma Cohort 3 – RCC Cohort 4 – UC
				

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

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

Key Inclusion Criteria:

- Locally advanced or metastatic disease; locally advanced disease must not be amenable to resection with curative intent.
- Phase 1 (Part 1 and Part 2): Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach and GEJ), esophageal cancer, HCC, melanoma (mucosal or cutaneous), Merkel cell carcinoma, mesothelioma, MSI-H solid tumors, NSCLC, ovarian cancer, SCCHN, SCLC, RCC, TNBC, and UC (or alternative tumor types with medical monitor approval).
- Phase 1 (Part 1 and Part 2): Subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit or who are intolerant to treatment. There is no limit to the number of prior treatment regimens.
- Phase 2: Subjects with advanced or metastatic melanoma, RCC, and UC.
  - **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. BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criterion for BRAF mutation testing.
    Note: Should **not** have received prior therapy for advanced or metastatic disease. Adjuvant regimens given within 6 months of screening will be counted as first-line therapy.
    Note: Should **not** have received prior therapy that included an immune therapy (eg, anti-cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) or programmed cell death protein 1 (PD-1)/ programmed cell death protein ligand 1 (PD-L1) inhibitor, indoleamine 2,3-dioxygenase (IDO) inhibitor, tumor necrosis factor super family (TNFSF) agonist, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
  - **For subjects with RCC:** histologically confirmed RCC that is predominantly clear-cell.
    Note: Should **not** have received prior therapy for advanced or metastatic disease. Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.
    Note: Should **not** have received prior therapy that included an immune therapy (eg, anti–CTLA-4 or PD-1/PD-L1 inhibitor, IDO inhibitor, TNFSF agonist, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
  - **For subjects with UC:** histologically confirmed UC of the renal pelvis, ureter, bladder, or urethra that is transitional cell type or mixed histology (predominantly transitional cell) type.
    Note: Should **not** have received prior therapy for advanced or metastatic disease. Adjuvant regimens given within 6 months of screening will be counted as first-line therapy.
    Note: Should **not** have received prior therapy that included an immune therapy (eg, anti–CTLA-4 or PD-1/PD-L1 inhibitor, IDO inhibitor, TNFSF agonist, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
  - **For subjects in the biopsy cohort:** willingness to undergo pretreatment and on treatment tumor biopsies (core or excisional). Must have melanoma (mucosal or cutaneous), RCC, or UC.
    Note: A baseline biopsy obtained for other purposes (ie, not an INCAGN 1876-202 procedure) before signing the informed consent form (ICF) may be used if the subject has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (ie, Cycle1 Day 1) and if a minimum of 20 slides or preferably 1 tissue block can be submitted.
- Presence of measureable disease based on RECIST v1.1.
- Eastern Cooperative Oncology Group performance status of 0 or 1.

Key Exclusion Criteria:

- Laboratory and medical history parameters not within the Protocol-defined range.
  - Absolute neutrophil count < 1.0×10^9/L.
  - Platelets < 75×10^9/L.
  - Hemoglobin < 9 g/dL or < 5.6 mmol/L.
  - Serum creatinine > 1.5 × institutional upper limit of normal (ULN) OR measured or calculated creatinine clearance < 50 mL/min for subjects with creatinine levels > 1.5 × ULN.
  - Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≥ 2.5 × ULN.
  - Total bilirubin ≥ 1.2 × ULN is excluded unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin to be eligible.
  - International normalized ratio, prothrombin time, or activated partial thromboplastin time > 1.5 × ULN.
- Prior treatment with any TNFSF agonist (eg, glucocorticoid-induced tumor necrosis factor receptor [GITR], OX40, 4-1BB/CD137, CD27, etc) for any indication.
- Transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors within 14 days before study Day 1.
- Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study treatment:
  - ≤ 14 days for chemotherapy, targeted small molecule therapy, or radiation therapy.
    Note: Subjects must not have had radiation pneumonitis as a result of treatment. A 1-week washout is permitted for palliative radiation to non-central nervous system (CNS) disease with medical monitor approval.
    Note: Bisphosphonates and denosumab are permitted concomitant medications.
  - ≤ 28 days for prior immune therapy or persistence of active cellular therapy (ie, chimeric antigen receptor T-cell therapy; other cellular therapies must be discussed with the medical monitor to determine eligibility).
  - ≤ 28 days for a prior monoclonal antibody used for anticancer therapy, with the exception of denosumab.
  - ≤ 7 days for immune-suppressive–based treatment for any reason.
    Note: Use of inhaled or topical steroids or corticosteroid use for radiographic procedures is permitted.
    Note: Must not require chronic use of corticosteroids. The use of physiologic corticosteroid replacement therapy may be approved after consultation with the medical monitor.
  - ≤ 28 days or 5 half-lives (whichever is longer) before the first dose for all other investigational agents or devices. For investigational agents with long half-lives (eg, > 5 days), enrollment before the fifth half-life requires medical monitor approval.
- Has not recovered to ≤ Grade 1 from toxic effects of prior therapy (including prior immune therapy) and/or complications from prior surgical intervention before starting therapy
  Note: Subjects with stable chronic conditions (≤ Grade 2) that are not expected to resolve (such as neuropathy and alopecia) are exceptions and may enroll.
  Note: Subjects with a history of any grade immune-related ocular AE (eg, episcleritis, scleritis, uveitis) will be excluded.
  Note: Subjects with a history of a Grade 3 or higher immune-related AE from prior immunotherapies are excluded from the dose-escalation portion of the study.
- Active autoimmune disease that required systemic treatment in the past (ie, 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 the medical monitor to determine eligibility.

Note: Subjects with hyper/hypothyroidism, vitiligo, controlled asthma, Type I diabetes, Graves' disease, or Hashimoto's disease are eligible to participate.
Note: Replacement and symptomatic therapies (eg, levothyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) are not considered a form of systemic treatment and are allowed.

- Known active CNS metastases and/or carcinomatous meningitis.
  Note: Subjects with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS edema, and have not required steroids for at least 7 days before the first dose of study treatment.
- 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.
- Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or risk of reactivation.
- Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies).

INCAGN01876, Dosage, and Mode of Administration:

INCAGN01876 will be administered intravenously (IV) over a 30-minute period (-5 to +10 minutes) on Day 1 of each Q3W (ie, 21 days) cycle. On days when epacadostat is administered in the clinic, INCAGN01876 will be administered after the epacadostat dose but before the pembrolizumab infusion. INCAGN01876 will always be the first infusion, followed by a 30-minute wait before starting the pembrolizumab infusion. Subjects will continue to receive INCAGN01876 as long as they are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal or for up to 24 months from the first dose of study treatment, whichever occurs first.

Epacadostat, Dosage, and Mode of Administration:

Epacadostat (INCB024360) is provided as tablets and will be self-administered orally [redacted] without regard to food, continuously, [redacted]. Treatment will continue as long as subjects are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal or for up to 24 months from the first dose of study treatment, whichever occurs first. Epacadostat will be administered at the site before the INCAGN01876 infusion on Day 1 of Cycle 1 and Cycle 2. All BID doses will be taken in the morning and the evening, approximately 12 hours apart. If a dose is missed by more than 4 hours, then that dose should be skipped, and the next scheduled dose should be taken at the usual time.

Reference Therapies, Dosage, and Mode of Administration:

Pembrolizumab will be administered IV as per the prescribing information at a dose of 200 mg Q3W (eg, 21 days).

In the concurrent dose administration Treatment Groups A and C, pembrolizumab dosing will begin on Cycle 1 Day 1. In the run-in dosing, Treatment Groups B and D, pembrolizumab dosing will begin on Cycle 2 Day 1. Alternate dose administration schedules may also be explored depending on [redacted]

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

Study Schedule/Procedures:

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

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

Cycle 1 and Cycle 6: Day 1, Day 8, and Day 15 (± 1 day).

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

Efficacy assessments: Every 9 weeks (± 7 days). After 12 months, efficacy assessments will occur every 12 weeks (± 7 days) until disease progression is determined.

End of treatment (EOT): ± 3 days of withdrawal from study.

Safety follow-up: 30 days (+ 7 days) and 60 days (+ 7 days) after EOT.

Disease status follow-up: Subjects who discontinue treatment for reasons other than disease progression will continue to be assessed every 9 weeks (± 7 days) for their disease status for 12 months. After 12 months, radiologic assessments will be performed every 12 weeks and should continue until a new anticancer therapy is started, documented disease progression, death, the end of the study, or withdrawal of consent.

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

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

Estimated Number of Subjects:

- Phase 1 Dose Escalation (Part 1) – Approximately 12 to 36 evaluable subjects.
  Note: The minimum number of subjects assumes that the starting dose is 1.0 mg/kg.
  Note: The maximum number of subjects assumes that DLTs are observed in all dose cohorts to a maximum of 9 subjects per cohort across all treatment groups.
- Phase 1 Safety Expansion (Part 2) – Approximately 24 evaluable subjects.
- Phase 2 Stage 1 – Approximately 100 evaluable subjects.
- Biopsy cohorts – Approximately 30 evaluable subjects.
- Phase 2 Stage 2 – Up to 172 evaluable subjects.
  Note: The maximum number of subjects assumes that all treatment groups and all tumor types proceed to Stage 2.

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

Statistical Methods:

Primary Endpoint: In Phase 2, a Simon 2-stage design will be applied for each tumor type within a treatment group. The planned Simon 2-stage designs are summarized in Table S5. Each Simon 2-stage design will have a stopping rule to allow for early termination of a particular cohort at the end of Stage 1 if there are insufficient responses observed while enrolling enough subjects to predict possible target responses worthy of cohort expansion and potential further evaluation in future studies. For the RCC and

UC cohorts, the insufficient response rates are obtained from historical data, and the Simon 2-stage designs allowing early termination are based on ORR. For the melanoma cohort, the insufficient response rate is obtained from historical data, and the primary endpoint for the Simon 2-stage design allows for early termination based on CRR.

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

Indication	Combination	r_1	n_1	r	n_2	n	p_0	p_1
Melanoma (CRR)	GITR + Pembro + Epacadostat	6	21	18	31	52	26%	45%
RCC (ORR)	GITR + Pembro + Epacadostat	8	19	25	31	50	40%	60%
UC (ORR)	GITR + Pembro + Epacadostat	3	10	14	24	34	30%	55%

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

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

Secondary Endpoints:

Objective response rate as assessed by RECIST v1.1 and mRECIST will be summarized for the RCC and UC cohorts. Disease control rate as assessed by RECIST v1.1 and mRECIST will be summarized for each cohort. Duration of response as assessed by RECIST v1.1 and mRECIST, PFS as determined by RECIST v1.1 and mRECIST, and OS will be analyzed by the Kaplan-Meier method for each cohort. Duration of disease control as assessed by RECIST v1.1 and mRECIST will be estimated with 95 % confidence intervals in each cohort.

Integrated Bayesian Futility Analysis:

When each subject enrolls in Phase 2, an integrated analysis of tumor and dosing strategies specific to Treatment Groups C and D will be conducted. Tumor types within a treatment group will be jointly analyzed using a Bayesian model, allowing sharing of information across tumor types. Similar sharing will be applied separately for tumor types across treatment groups. The integrated Bayesian analysis will terminate a cohort within a treatment group if the cohort appears unlikely to achieve higher response rates with INCAGN01876 than with the background therapy alone. Enrollment in a treatment group-tumor type combination may be suspended if the maximum of the 2 probabilities of success calculated using the integrated Bayesian approach with sharing based on tumor types and sharing based on treatment group is less than 20%. Collection of response data will be based on investigator assessments entered into an interactive response technology system and analyzed separately from the clinical database. Additional information regarding the futility analysis is detailed in the full Protocol.

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LIST OF ABBREVIATIONS

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

Abbreviation	Definition
[redacted]	[redacted]
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
AGM	African green monkey
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
BID	twice a day
CFR	Code of Federal Regulations
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRR	complete response rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte–associated protein 4
DCR	disease control rate
DLT	dose-limiting toxicity
[redacted]	[redacted]
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
Fc	fragment, crystallizable
FcγR	Fc-gamma receptor
FDA	Food and Drug Administration
[redacted]	[redacted]
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GI	gastrointestinal

Abbreviation	Definition
GITR	glucocorticoid-induced tumor necrosis factor receptor
GITRL	glucocorticoid-induced tumor necrosis factor receptor ligand
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDO	indoleamine 2,3-dioxygenase
IEC	independent ethics committee
IgG	immunoglobulin G
IL	interleukin
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
mAb	monoclonal antibody
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
[redacted]	[redacted]
PCP	pneumocystis pneumonia
[redacted]	[redacted]
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1

Abbreviation	Definition
PFS	progression-free survival
[redacted]	[redacted]
PoS	probability of success
PR	partial response
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	stable disease
SNRI	serotonin/norepinephrine reuptake inhibitors
SS	serotonin syndrome
SSRI	selective serotonin reuptake inhibitors
T1DM	type I diabetes mellitus
TCR	T-cell receptor
Teff	effector T cells
TNBC	triple-negative breast cancer
TNFRSF	tumor necrosis factor receptor super family
TNFSF	tumor necrosis factor super family
Treg	regulatory T cell
Trp	tryptophan
UC	urothelial carcinoma
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background

1.1.1. The Role of the Immune System in Cancer

The immune system is comprised of diverse sets of cells designed to protect a host from pathogens while distinguishing from host and foreign antigens. This immune response is controlled by a series of checks and balances to allow for robust immune responses to pathogens while preventing either an excessive inflammatory event or an autoimmune response. Through immune surveillance, the immune system has been shown to recognize, attack, and destroy tumor cells (Wolchok and Saenger 2008). [redacted] lthough the immune system has been shown to recognize and reject a tumor, many tumors evade immune surveillance or develop mechanisms of resistance.

[redacted]

1.1.2. Glucocorticoid-Induced Tumor Necrosis Factor Receptor and the Tumor Necrosis Factor Super Family

Glucocorticoid-induced tumor necrosis factor receptor belongs to the TNFSF and is activated by its cognate ligand, GITRL. Glucocorticoid-induced tumor necrosis factor receptor regulates a variety of immune cell functions including T-cell proliferation, differentiation, cytokine production, and survival (Smith et al 1994). Glucocorticoid-induced tumor necrosis factor receptor expression is generally restricted to normal tissues with high immune cell composition, including the peripheral blood, bone marrow, spleen, and thymus (Gurney et al 1999). Glucocorticoid-induced tumor necrosis factor receptor is expressed on some Tregs, is upregulated upon T-cell activation of both CD4+ and CD8+ T cells, and is a costimulator in the activation of these T cells (Allan et al 2007, Bianchini et al 2011, Schaer et al 2012).

In mice, the GITR-GITRL system is implicated in development of autoimmune and inflammatory responses, as well as promoting protective immunity to pathogens and tumors (Nocentini et al 2012). Animals treated with a GITR-Fc fusion protein leading to an attenuated GITR signaling showed signs of ameliorated autoimmunity. By contrast, an agonist anti-GITR antibody augmented an immune response to viral, bacterial, and parasitic infections. [redacted]

[redacted]

1.1.3. Glucocorticoid-Induced Tumor Necrosis Factor Receptor and Activated T Cells

During T-cell priming, peptide-loaded major histocompatibility complex molecules expressed by antigen-presenting cells are recognized by T cells through the TCR (Wilson and Villadangos 2005). Signaling through the TCR leads to rapid GITR upregulation on human T cells (Ronchetti et al 2015). In the context of major histocompatibility complex-mediated TCR activation, the GITR pathway provides an important costimulatory signal leading to enhanced T-cell proliferation and survival and cytokine function (Tone et al 2003). These outcomes are mediated by signaling via the NFκB pathway, which can promote T-cell survival in response to weak, rather than strong, TCR signals (Zhan et al 2008, Gerondakis et al 2014). In addition to the costimulatory function of the GITR pathway within the antigen-presenting cell T-cell synapse, GITRL/GITR interactions on endothelial cells may also contribute to leukocyte adhesion and transmigration at sites of infection or into tumors (Lacal et al 2013). Modulation of the GITR costimulatory pathway may therefore provide a therapeutically tractable strategy for increasing T-cell responsiveness against relatively weak antigens, such as those expressed by tumor cells. This possibility is further supported by the observation that ectopic expression of GITRL on tumor cells results in rapid tumor regression following a period of transient growth (Piao et al 2009). In this example, antitumor efficacy was mediated by enhanced T-cell function, a finding that established a link between tumor regression and GITR dependent T-cell costimulation within the tumor microenvironment. Modulation of GITR signaling in T cells using a murine mAb GITR agonist, DTA-1, has similarly been shown to enhance T-cell-mediated immune responses, leading to convincing single-agent antitumor activity in a range of syngeneic mouse tumor models (Turk et al 2004, Ko et al 2005).

1.1.4. Glucocorticoid-Induced Tumor Necrosis Factor Receptor and T Regulatory Cells

Glucocorticoid-induced tumor necrosis factor receptor expression has been observed on Tregs within the tumor microenvironment, which may play a role in suppressing an antitumor immune response (Wing et al 2008, Zou et al [redacted]

1.1.5. Immune Modulators

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

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

1.1.6. Programmed Cell Death Protein 1 and Indoleamine 2,3-Dioxygenase 1 Inhibition in Advanced or Metastatic Cancers

The goal of cancer immunotherapy is to initiate or reinitiate a self-sustaining cycle of cancer immunity, enabling it to amplify and propagate. Cancer immunotherapies must overcome the negative feedback mechanisms inherent in most cancers. The current approach will attempt to further amplify an immune response by targeting multiple nonredundant immune checkpoints.

Expression of IDO1 represents an early checkpoint that results in a diminished immune response and tolerance to tumor antigen. Many recent clinical results suggest that another common rate-limiting step is the expression of PD-L1 as a distal immune modulator expressed in 20% to 50% of human cancer (Herbst et al 2013). [redacted]

1.1.7. Combined Inhibition With Anti–Glucocorticoid-Induced Tumor Necrosis Factor Receptor and Immune Therapies

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

The GITR pathway provides an important costimulatory signal leading to enhanced T-cell proliferation and survival and cytokine function (Tone et al 2003). Monoclonal antibodies

directed to the GITR receptor on Tregs have been shown to deplete Tregs in the tumor microenvironment and ultimately confer a modest delay in tumor growth (Kim et al 2015). The proposed mechanisms of an anti-GITR mAb could support or enhance other immune therapies, and preclinical models suggest a synergistic effect if given with a PD-1 blocking mAb.

Murine tumor xenograft models demonstrate that an agonist mAb directed to GITR in combination with an anti–PD-1 blocking mAb leads to a potent antitumor immune response (Lu et al 2014). [redacted]

Preclinical models have also been used to explore the synergistic effect of an anti-GITR mAb and epacadostat. Clear combinatorial effects were seen with anti-GITR and epacadostat in the more inflamed, IDO1-expressing PAN02 pancreatic cancer model. These data suggest that IDO1 inhibition can be effective in combination with agents that agonize T cell costimulatory receptors as well as with agents that block coinhibitory receptors (Koblish et al 2017).

[redacted]

1.2. Overview of INCAGN01876

INCAGN01876 is an agonistic antihuman GITR mAb with the potential to enhance the function of tumor-specific T cells and to promote antitumor immunity in cancer patients. [redacted]

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

[redacted]

[redacted]

1.2.1. Preclinical Safety of INCAGN01876

The safety of INCAGN01876 was evaluated [redacted] (see the INCAGN01876 Investigator's Brochure [IB]).

1.2.2. Clinical Pharmacology

Repeat doses [redacted]

1.2.3. Clinical Safety of INCAGN01876

Study INCAGN 1876-101 is an open-label, nonrandomized, Phase 1/2 study to determine the safety and tolerability, define the MTD [redacted] and assess the preliminary efficacy of INCAGN01876 in subjects with advanced or metastatic solid tumors. Dose escalation is ongoing using a traditional 3 + 3 design with cohorts of subjects sequentially enrolled at doses of [redacted] INCAGN01876 is administered [redacted] until disease progression, intolerable toxicity, or for a maximum of 26 cycles. Decisions for dose escalation are based on predetermined DLTs observed during a 28-day observation period.

[redacted]

1.3. Overview of Epacadostat

Epacadostat (INCB024360) is an inhibitor of the enzyme IDO1. Indoleamine 2,3-dioxygenase 1 mediates the catabolism of the essential amino acid Trp to kynurenine within immune cells and a subset of tumor cells. This catabolism of Trp results in the inhibition of antitumor cell-mediated immune responses. Histologic evaluation of most human cancers shows extensive infiltration by inflammatory and immune cells, suggesting that the immune system does recognize and respond to the presence of the malignancy (Galon et al 2006); but in most cases, the immune response is ineffective in inhibiting or eradicating tumor growth. Many tumor cells or the infiltrating immune cells overexpress IDO1, and there have been multiple lines of evidence to suggest that IDO1 is a key regulator in the immunosuppressive mechanisms responsible for tumor escape from immune surveillance (Liu et al 2009). Therefore, inhibition of this enzyme may provide a unique method to treat malignancies, either alone or in combination with chemotherapeutics or other immune-based therapies.

1.3.1. Clinical Summary of Epacadostat

Twelve Incyte-sponsored clinical studies have either been completed or are ongoing (11 Phase 1/2 studies and 1 Phase 3 study). Three clinical studies have been completed (INCB 24360-101, INCB 24360-102, and INCB 24360-210). Seven ongoing studies (INCB 24360-110, INCB 24360-201, INCB 24360-202, INCB 24360-203, INCB 24360-204, INCB 24360-301, and INCB 39110-106) are combination therapy studies. Two ongoing studies (INCB 24360-103 and INCB 24360-104) are monotherapy studies. As of 29 OCT 2016, 898 unique subjects have been exposed to INCB024360 in Incyte-sponsored studies as monotherapy (149 subjects) and/or in combination with CPI anti−PD-1 targeted therapy (543 subjects), anti−PD-L1 targeted therapy (124 subjects), anti−CTLA-4 targeted therapy (50 subjects), and a Janus kinase 1 inhibitor (32 subjects). For a thorough overview of the pharmacology of epacadostat and ongoing clinical studies, refer to the INCB024360 IB.

There are currently 2 ongoing studies evaluating the combination of epacadostat and pembrolizumab: INCB 24360-202 is an ongoing Phase 1/2 study, and INCB 24360-301 (KEYNOTE-252) is an ongoing Phase 3 study. In the INCB 24360-202 study, Phase 1 consists of a dose-escalation phase followed by Phase 2, which is an open-label, single-arm, cohort expansion phase. The tumor types evaluated in the expansion phase included NSCLC, melanoma, transition cell carcinoma of the genitourinary tract, TNBC, SCCHN, ovarian cancer, diffuse large B-cell lymphoma, RCC, and MSI-H colorectal cancer.

Study INCB 24360-301 (KEYNOTE-252) is an ongoing, Phase 3, randomized, double-blind, placebo-controlled study of pembrolizumab in combination with epacadostat or placebo in subjects with unresectable or metastatic melanoma. Subjects are randomized 1:1 (active:placebo) to pembrolizumab plus epacadostat or pembrolizumab plus placebo and stratified by PD-L1 expression (positive vs negative/indeterminate) and BRAF mutation status (BRAF mutant and received prior BRAF-directed treatment, BRAF mutant with no prior BRAF-directed treatment, and BRAF wild type). Additional Phase 3 studies with epacadostat in combination with pembrolizumab are scheduled to open in 2017.

1.3.2. Clinical Safety and Potential Risks of Epacadostat in Combination With Pembrolizumab

Phase 1 of Study INCB 24360-202 has completed enrollment with a total of 62 subjects. Epacadostat [redacted] were tolerated in combination with pembrolizumab 2 mg/kg or 200 mg IV Q3W. Preliminary safety results for subjects receiving [redacted] of epacadostat in combination with 200 mg Q3W pembrolizumab in the Phase 2 portion of Study INCB 24360-202 were presented at the 2017 ASCO annual meeting. The most frequently reported treatment-related AEs were fatigue (29%), rash (17%), nausea (11%), and pruritus (10%). Rash includes the preferred terms rash, rash generalized, rash macular, rash maculopapular, and rash pruritic. Adverse events of special interest occurred infrequently, with only hypothyroidism (5%) and severe skin reaction (3%) occurring in ≥ 3 subjects. Treatment-related AEs leading to treatment discontinuation occurred in 4% of subjects, with only arthralgia and rash (n = 2 each) occurring in more than 1 subject. There was 1 treatment-related death due to respiratory failure secondary to aspiration pneumonia; however, pneumonitis could not be ruled out (Hamid et al 2017b).

An uncommon risk of IDO1 inhibition is an increase in serotonin levels that could precipitate a cluster of AEs termed SS when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some MAOIs and combinations of serotonergic drugs (Boyer and Shannon 2005). The clinical manifestations of SS range from barely perceptible to lethal; onset is rapid (within 12 hours of drug[s] administration). As of 27 FEB 2017, 2 subjects across the epacadostat program (958 subjects treated) have reported SS or symptoms of SS, and both were mild in their severity and resolved (refer to the INCB024360 IB). Although this incidence is uncommon, use of MAOIs will be prohibited during the study, and all subjects will be assessed for SS symptoms at an appropriate timeframe after dosing. Subjects will be provided with an informative subject leaflet describing the signs and symptoms of the syndrome, along with instructions to seek immediate medical care if any of these signs or symptoms are observed.

1.4. Overview Pembrolizumab

1.4.1. Pembrolizumab Summary

Pembrolizumab (KEYTRUDA®) is a PD-1 blocking antibody that has been approved as monotherapy in the United States for the treatment of patients with unresectable or metastatic melanoma, metastatic NSCLC whose tumors have PD-L1 expression, recurrent or metastatic SCCHN, and refractory classical Hodgkin lymphoma (Keytruda 2017).

1.4.2. Risks From Pembrolizumab

Due to the effects of pembrolizumab on the immune system, immune-mediated adverse reactions have been observed in patients treated with this agent. Guidance is provided in the prescribing information for immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, and immune-mediated nephritis and renal dysfunction. Infusion reactions are also possible following administration of pembrolizumab. The most common adverse reactions seen in ≥ 20% of patients were fatigue, pruritis, diarrhea,

decreased appetite, rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation, and nausea (Keytruda 2017).

1.5. Study Rationale

1.5.1. Rationale for the Study Population

Most cancers exhibit genetic heterogeneity, which often translates into enhanced tumor immunogenicity. This concept of tumor immunogenicity is well-appreciated for its role in eliciting an adaptive immune response and determining the efficacy of immunotherapy. Blockade of PD-1/PD-L1 has led to clinical responses in patients with many different types of cancer, including melanoma, NSCLC, RCC, SCCHN, gastric cancer, HCC, TNBC, cervical cancer, and bladder (Hamid et al 2013, Powels et al 2014, Topalian et al 2014, Brahmer et al 2015, Dirix et al 2015, Ferris et al 2016, Frenel et al 2016, Herbst et al 2016, Le et al 2016, Melero et al 2016, Rosenberg et al 2016). The combination of pembrolizumab and epacadostat has also demonstrated improved ORR compared with monotherapy PD-1/PD-L1 in a variety of tumor types, including melanoma, NSCLC, RCC, SCCHN, and UC (Gangadhar et al 2017, Lara et al 2017, Hamid et al 2017a, Smith et al 2017); however, further clinical improvement is warranted.

The Phase 2 portion of this study (INCAGN 1876-202) will utilize a Simon 2-stage design to evaluate the benefit of the combination of pembrolizumab, epacadostat, and INCAGN01876 (Simon 1989). The approximate number of subjects for Stage 1 and Stage 2 for each treatment group and tumor type was determined based on an observed improvement in the ORR from the INCB 24360-202 study, as outlined below.

Epacadostat and Pembrolizumab in Melanoma

Preliminary efficacy results for subjects with melanoma enrolled in the Phase 1 portion of Study INCB 24360-202 was presented at the 2016 European Society for Medical Oncology annual meeting (Gangadhar et al 2016). Twenty-two subjects with advanced melanoma were enrolled in Phase 1; of the 19 treatment-naive melanoma subjects, 11 subjects (58%) achieved an objective response (CR or PR) by RECIST v1.1, with 5 of 19 subjects (26%) achieving a CR. [redacted]. The combination of INCAGN01876, pembrolizumab, and epacadostat will be evaluated to determine if the combination regimen can improve the CRR of 26% in this setting.

Epacadostat and Pembrolizumab in Renal Cell Carcinoma

Subjects with RCC enrolled in the INCB 24360-202 study showed improved ORR and DCR compared with pembrolizumab monotherapy. Of 30 efficacy-evaluable subjects, 63% (n = 19) had 0 to 1 prior line of therapy, and 37% (n = 11) had ≥ 2 prior lines of therapy for advanced disease. The ORR (CR + PR) and DCR (CR + PR + SD) for subjects with 0 to1 prior line of therapy were 47% (9/19; 1 CR, 8 PR) and 58% (11/19; 1 CR, 8 PR, 2 SD), respectively. For subjects with ≥ 2 prior lines of therapy, ORR and DCR were 0% and 36% (4/11; all SD), respectively. At the time of the data cutoff, 9/9 responses were ongoing (range, 1+ to 372+ days; Lara et al 2017).

Epacadostat and Pembrolizumab in Urothelial Carcinoma

Responses by RECIST v1.1 were also observed in subjects with UC enrolled in the INCB 24360-202 study. In the UC group, a total of 37 subjects were considered efficacy evaluable. Preliminary ORR (CR + PR) and DCR (CR + PR + SD) for all urothelial efficacy-evaluable subjects were 35% (13/37; all PR) and 57% (21/37; 13 PR, 8 SD), respectively. At the time of the data cutoff, 12/13 responses were ongoing (range, 1+ to 652+ days; Smith et al 2017).

1.5.2. Rationale for the Dose and Schedule of Combination Therapies

The proposed starting dose and schedule o

.

The current schedule of administratio

1.5.3. Rationale for the Dose of Epacadostat

The safety and tolerability of the pembrolizumab and epacadostat combination is currently being evaluated in the ongoing Phase 1/2 INCB 24360-202 study. In Phase 1 of the study, the established regimen of pembrolizumab 2 mg/kg Q3W and 200 mg Q3W was evaluated with epacadostat [redacted] In 294 subjects enrolled in Phase 2, the most frequent treatment-related AEs were fatigue (29%), rash (17%), nausea (11%), and pruritus (10%; Hamid et al 2017b).

Selection of the epacadostat [redacted]
Using an *ex vivo* assay optimized for determining the inhibition of the metabolism of tryptophan [redacted].

The epacadostat dose selected for the current study was determined on the basis of having a well-tolerated safety profile as monotherapy and in combination with [redacted]. In general, as single agents, epacadostat and pembrolizumab have been well-tolerated in a study population that has significant comorbidities.

1.5.4. Rationale for the Study Endpoints

1.5.4.1. Efficacy Endpoints

Efficacy endpoints of this study include ORR, DOR, duration of disease control, and PFS by investigator assessment based on RECIST v1.1 and mRECIST (a modified version of RECIST v1.1). Additionally, 1-year and 2-year OS will also be assessed.

1.5.4.1.1. Modified Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors v1.1 will be modified to account for the unique tumor response characteristics seen with immunotherapy (Wolchok et al 2009). Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST v1.1 may not provide an accurate response assessment of immunotherapeutic agents. Therefore, RECIST v1.1 will be used with the following modifications:

If radiologic imaging shows initial progressive disease, tumor assessment should be repeated at least 4 weeks, but no more than 6 weeks, later in order to confirm disease progression, with the option of continuing treatment while awaiting radiologic confirmation of disease 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 them on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on subjects' overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of disease progression if they are clinically stable, as defined by the following criteria:

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

If repeat imaging shows < 20% tumor burden compared with nadir, stable or improved previous new lesion (if identified as cause for initial disease progression), and stable/improved nontarget disease (if identified as cause for initial disease progression), then treatment may be continued or resumed. If repeat imaging confirms disease progression due to any of the scenarios listed below, subjects will be discontinued from study treatment. However, if a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks, but no more than 6 weeks, apart demonstrating disease progression) per mRECIST, but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered after consultation with the medical monitor. Clinically stable subjects at the confirmatory scan should also have no further increase in the target lesions, no unequivocal increase in nontarget lesions, and no additional new lesions develop (nonworsening disease progression) to continue study treatment (see Section 7.7.1).

When feasible, subjects should not be discontinued until disease progression is confirmed. This allowance to continue treatment despite initial radiographic 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 radiographic confirmation of disease progression.

1.6. Risks and Benefits of Combination Immunotherapy

The principal toxicities of administering agents that modulate the immune system are irAEs, including skin manifestations, pneumonitis, enterocolitis, and endocrinopathies. The time of onset of irAEs varies, with skin manifestations and GI toxicity seen early and elevated liver enzymes and endocrinopathies appearing later (Weber et al 2015). Immune-related AEs have been reported in subjects treated with pembrolizumab and epacadostat. As the use of immunotherapies becomes more prevalent, guidelines for the management of irAEs continue to evolve. Careful monitoring, early diagnosis, and treatment with corticosteroids for more severe events is recommended. Subjects enrolled in this study will be carefully monitored for the onset of irAEs, and guidelines for the management of these toxicities are provided in both the Protocol (see Section 5.4.7 and Appendix B) and in the prescribing information for pembrolizumab (Keytruda 2017).

The combination of INCAGN01876, pembrolizumab, and epacadostat will be administered in Phase 1 to subjects who have exhausted options for treatments that have demonstrated clinical benefit. The combination of pembrolizumab and epacadostat has been shown to be active in a number of different types of cancer. Preclinical studies have shown a benefit in adding INCAGN01876 to an anti–PD-1 antibody and epacadostat. Therefore, it is reasonable to test this triplet combination in subjects who have limited options for further treatment. Subjects with melanoma, RCC, and UC will be enrolled in Phase 2 earlier in their course of disease. The doublet therapy of pembrolizumab and epacadostat has already shown clinical benefit in these indications, and the safety of the triplet combination would have been assessed in Phase 1 of the study prior to enrolling these subjects.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

Phase 1

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

Phase 2

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

2.1.2. Secondary Objectives

Phase 1 and Phase 2

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

- To evaluate the efficacy of INCAGN01876 when given in combination with immune therapies with respect to 1-year and 2-year OS.
- To evaluate the safety and tolerability of INCAGN01876 when given in combination with immune therapies.

[redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoints

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

2.2.2. Secondary Endpoints

- ORR, defined as the percentage of subjects having CR or PR, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1 and mRECIST.
- DCR, defined as the percentage of subjects having CR, PR, or SD, will be determined by investigator assessment of a radiographic disease assessments per RECIST v1.1 and mRECIST.
- DOR, defined as the time from the earliest date of disease response (CR or PR) until earliest date of disease progression or death due to any cause, if occurring sooner than progression, will be determined by investigator assessment of radiographic disease assessment per RECIST v1.1 and mRECIST.

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

[redacted]

3. SUBJECT ELIGIBILITY

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

3.1. Subject Inclusion Criteria

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

1. Men and women, aged 18 years or older.
2. Willingness to provide written informed consent for the study.
3. Locally advanced or metastatic disease; locally advanced disease must not be amenable to resection with curative intent.
4. Phase 1 (Part 1 and Part 2): Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach and GEJ), esophageal cancer, HCC, melanoma (mucosal or cutaneous), Merkel cell carcinoma, mesothelioma, MSI-H solid tumors, NSCLC, ovarian cancer, SCCHN, SCLC, RCC, TNBC, and UC (or alternative tumor types with medical monitor approval).

5. Phase 1 (Part 1 and Part 2): Subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit or who are intolerant to treatment. There is no limit to the number of prior treatment regimens.
6. Phase 2: Subjects with advanced or metastatic melanoma, RCC, and UC.
    a. **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. BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criterion for BRAF mutation testing.
    Note: Should **not** have received prior therapy for advanced or metastatic disease. Adjuvant regimens given within 6 months of screening will be counted as first-line therapy.
    Note: Should **not** have received prior therapy that included an immune therapy (eg, anti–CTLA-4 or PD-1/PD-L1 inhibitor, IDO inhibitor, TNFSF agonist, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
    b. **For subjects with RCC:** histologically confirmed RCC that is predominantly clear-cell.
    Note: Should **not** have received prior therapy for advanced or metastatic disease. Adjuvant regimens given within 6 months of screening will be counted as first-line therapy.
    Note: Should **not** have received prior therapy that included an immune therapy (eg, anti–CTLA-4 or PD-1/PD-L1 inhibitor, IDO inhibitor, TNFSF agonist, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
    c. **For subjects with UC:** histologically confirmed UC of the renal pelvis, ureter, bladder, or urethra that is transitional cell type or mixed histology (predominantly transitional cell) type.
    Note: Should **not** have received prior therapy for advanced or metastatic disease. Adjuvant regimens given within 6 months of screening will be counted as first-line therapy.
    Note: Should **not** have received prior therapy that included an immune therapy (eg, anti–CTLA-4 or PD-1/PD-L1 inhibitor, IDO inhibitor, TNFSF agonist, or other antibodies or drugs specifically targeting T-cell costimulation or checkpoint pathways, etc).
    d. **For subjects in the biopsy cohort:** willingness to undergo pretreatment and on treatment tumor biopsies (core or excisional; see Section 7.10.4). Must have melanoma (mucosal or cutaneous), RCC, or UC.
    Note: A baseline biopsy obtained for other purposes (ie, not an INCAGN 1876-202 procedure) before signing the ICF may be used 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.

7. Presence of measureable disease based on RECIST v1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are not considered measureable unless there has been demonstrated progression in the lesion.
8. ECOG performance status of 0 or 1.
9. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea).
    b. Woman of childbearing potential who has a negative serum pregnancy test at screening and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up, or as required in the pembrolizumab prescribing information, whichever is longer. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject, and her understanding should be confirmed.
    c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study treatment, or as required in the pembrolizumab prescribing information, whichever is longer. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject, and his understanding should be confirmed.

3.2. Subject Exclusion Criteria

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

1. Laboratory and medical history parameters not within the Protocol-defined range. If the screening laboratory tests below were conducted > 7 days before treatment initiation, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1.
    a. Absolute neutrophil count < 1.0×10^9/L.
    b. Platelets < 75×10^9/L.
    c. Hemoglobin < 9 g/dL or < 5.6 mmol/L.
    d. Serum creatinine > 1.5 × institutional ULN OR measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or creatinine clearance) < 50 mL/min for subjects with creatinine levels > 1.5 × ULN.
    e. Aspartate aminotransferase, ALT, and alkaline phosphatase ≥ 2.5 × ULN.
    Note: Subjects with 1) bone metastases and 2) no hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase is ≤ 5 × ULN. Subjects with 1) bone metastases and/or 2) hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase is ≤ 5 × ULN only with medical monitor approval.
    f. Total bilirubin ≥ 1.2 × ULN is excluded unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin to be eligible.
    g. International normalized ratio, PT, or aPTT > 1.5 × ULN.

2. Prior treatment with any TNFSF agonist (eg, GITR, OX40, 4-1BB/CD137, CD27, etc) for any indication.
3. Transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) within 14 days before study Day 1.
4. Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study treatment:
   a. ≤ 14 days for chemotherapy, targeted small molecule therapy, or radiation therapy.
      Note: Subjects must not have had radiation pneumonitis as a result of treatment. A 1-week washout is permitted for palliative radiation to non-CNS disease with medical monitor approval.
      Note: Bisphosphonates and denosumab are permitted concomitant medications.
   b. ≤ 28 days for prior immune therapy or persistence of active cellular therapy (ie, chimeric antigen receptor T-cell therapy; other cellular therapies must be discussed with the medical monitor to determine eligibility).
   c. ≤ 28 days for a prior mAb used for anticancer therapy, with the exception of denosumab.
   d. ≤ 7 days for immune-suppressive–based treatment for any reason.
      Note: Use of inhaled or topical steroids or corticosteroid use for radiographic procedures is permitted.
      Note: Must not require chronic use of corticosteroids. The use of physiologic corticosteroid replacement therapy may be approved after consultation with the medical monitor.
   e. ≤ 28 days or 5 half-lives (whichever is longer) before the first dose for all other investigational agents or devices. For investigational agents with long half-lives (eg, > 5 days), enrollment before the fifth half-life requires medical monitor approval.
5. Has not recovered to ≤ Grade 1 from toxic effects of prior therapy (including prior immune therapy) and/or complications from prior surgical intervention before starting therapy.
   Note: Subjects with stable chronic conditions (≤ Grade 2) that are not expected to resolve (such as neuropathy and alopecia) are exceptions and may enroll.
   Note: Subjects with a history of any grade immune-related ocular AE (eg, episcleritis, scleritis, uveitis) will be excluded.
   Note: Subjects with a history of a Grade 3 or higher immune-related AE from prior immunotherapies are excluded from the dose-escalation portion of the study.
6. Receipt of a live vaccine within 30 days of planned start of study treatment.
   Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccines. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
7. Current use of prohibited medication as described in Section 5.6.3.

8. Active autoimmune disease that required systemic treatment in the past (ie, 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 the medical monitor to determine eligibility.
   Note: Subjects with hyper/hypothyroidism, vitiligo, controlled asthma, Type I diabetes, Graves' disease, or Hashimoto's disease are eligible to participate.
   Note: Replacement and symptomatic therapies (eg, levothyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) are not considered a form of systemic treatment and are allowed.
9. Known active CNS metastases and/or carcinomatous meningitis.
   Note: Subjects with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS edema, and have not required steroids for at least 7 days before the first dose of study treatment.
10. Known additional malignancy that is progressing or requires active treatment or history of other malignancy within 2 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma *in situ* of the cervix, other noninvasive or indolent malignancies, or cancers from which the subject has been disease-free for > 1 year after treatment with curative intent.
11. Evidence of active noninfectious pneumonitis or history of interstitial lung disease.
12. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study treatment administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia not controlled with therapy unless approved by the medical monitor.
13. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Subjects with screening QTc interval > 470 milliseconds (corrected by Fridericia) are excluded, unless approved by the medical monitor. In the event that a single QTc is > 470 milliseconds, the subject may enroll if the average QTc for 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 medical monitor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.
    Note: QTc prolongation due to pacemaker may enroll if the JTc is normal or with medical monitor approval.
14. Evidence of HBV or HCV infection or risk of reactivation. Hepatitis B virus DNA and HCV RNA must be undetectable. Subjects cannot be positive for HBV DNA, HCV RNA, hepatitis B surface antigen, or anti-hepatitis B core antibody without approval from the medical monitor.
    Note: Subjects with no prior history of HBV infection who have been vaccinated against HBV and who have a positive antibody against hepatitis B surface antigen test as the only evidence of prior exposure may participate in the study.

15. Known history of drug-induced liver injury; alcoholic liver disease; nonalcoholic steatohepatitis; primary biliary cirrhosis; or ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver, or portal hypertension.
16. Known history of HIV (HIV 1/2 antibodies).
17. For cohorts where subjects receive epacadostat, subjects should not receive MAOIs or drugs that have significant MAOI activity (eg, meperidine, linezolid, methylene blue) within the 21 days before screening. See Appendix C for prohibited medications associated with MAO inhibition.
18. For cohorts where subjects receive epacadostat, any history of SS after receiving serotonergic drugs.
19. For cohorts where subjects receive epacadostat, use of any UGT1A9 inhibitor from screening through the safety follow-up, including the following: diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid. See Section 5.6.3 for more details.
20. History of a GI condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) that may affect drug absorption.
21. Known allergy or reaction to any component of pembrolizumab, epacadostat, or INCAGN01876.
22. Inability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
23. Women who are pregnant or breastfeeding.
24. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.

4. INVESTIGATIONAL PLAN

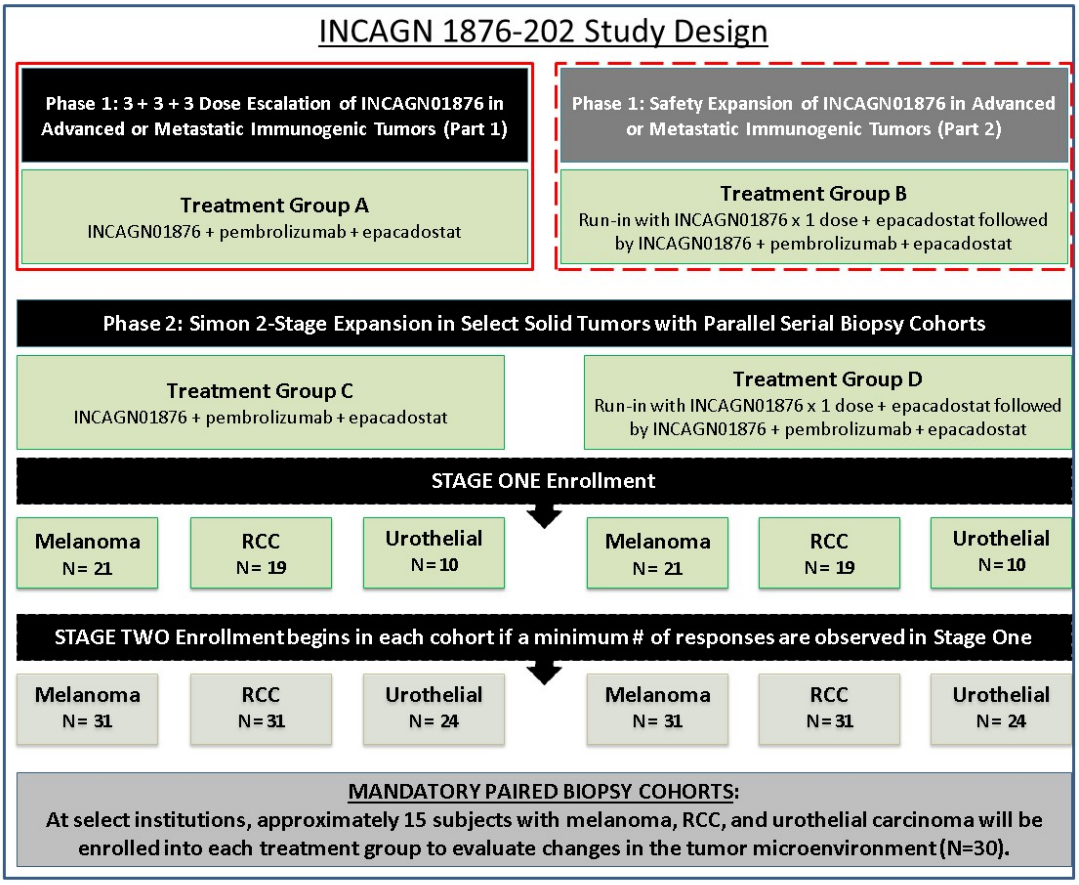
4.1. Overall Study Design

This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of INCAGN01876 when given in combination with immune therapies. Phase 1 will consist of 2 parts. Dose Escalation (Part 1) will consist of a 3 + 3 + 3 design to determine the MTD [redacted] The Safety Expansion (Part 2) will further explore tolerated doses of INCAGN01876 from Part 1 given as a single-dose run-in followed by concomitant immune therapy. Subjects with advanced or metastatic cervical cancer, endometrial cancer, gastric cancer (including stomach and GEJ), esophageal cancer, HCC, melanoma (mucosal or cutaneous), Merkel cell carcinoma, mesothelioma, MSI-H solid tumors, NSCLC, ovarian cancer, SCCHN, SCLC, RCC, TNBC, and UC who have progressed after treatment with available therapies that are known to confer clinical benefit, who are intolerant to treatment, or who refuse standard of care will be enrolled in both parts of Phase 1.

The Phase 2 Dose Expansion will further evaluate the safety, tolerability, and efficacy of the recommended dose(s) of INCAGN01876 selected in Phase 1 when given in combination with immune therapies. Subjects with advanced or metastatic melanoma, RCC, and UC will be enrolled in Phase 2. See Figure 1 for overall study design.

The sponsor may elect to prioritize (or deprioritize) enrollment to specific treatment groups or cohorts based on emerging safety or efficacy data in collaboration with investigational sites.

Figure 1: Overall Study Design



4.1.1. Phase 1 – Dose Escalation (Part 1)

A minimum of 3 evaluable subjects will be enrolled in Treatment Group A (see Table 2), beginning with INCAGN01876 Dose Cohort 1 (1.0 mg/kg; starting dose; see Table 1). A higher starting dose of INCAGN01876 may be used if safety data are available from the monotherapy study (INCANG 1876-101), but it will not exceed 1 dose level below the highest tolerated dose of INCAGN01876 monotherapy. If a higher dose is used, the dose will be communicated to investigational sites with an administrative letter. The first 3 evaluable subjects enrolled within an INCAGN01876 dose cohort will be observed for a minimum of 28 days before the next dose cohort begins enrollment. If 0 DLTs occur in a cohort of 3 evaluable subjects, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 1 of 3 evaluable subjects experiences a DLT, that cohort will be expanded to 6 evaluable subjects. If 1 of 6 evaluable

subjects experiences a DLT, a new cohort of 3 evaluable subjects will be treated at the next higher dose level. If 2 of 6 evaluable subjects experience a DLT, that cohort will be expanded to 9 evaluable subjects. If ≥ 2 of 3, 3 of 6, or 3 of 9 evaluable subjects experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD, and the previous dose level will be considered the MTD. If only 3 evaluable subjects were treated at the MTD [redacted] then a minimum of 3 additional evaluable subjects will be enrolled before this dose is administered in Phase 2 of the study.

Additional subjects will be enrolled in a dose cohort to achieve the minimum of 3 evaluable subjects. 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 DLT observation period will result in the subjects being nonevaluable and replaced. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. The doses of INCAGN01876 to be evaluated in each treatment group are summarized in Table 1.

Table 1: INCAGN01876 Dose Cohorts

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

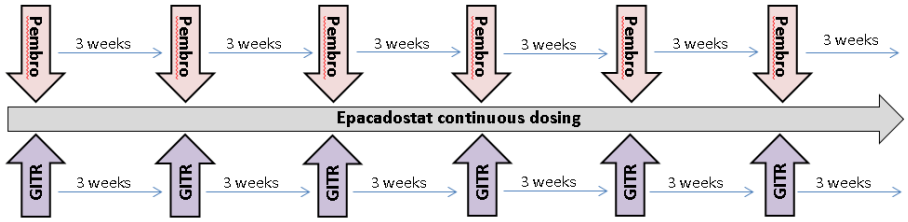
[a] A higher starting dose of INCAGN01876 may be used if safety data are available from the monotherapy study (INCAGN 1876-101), but it will not exceed 1 dose level below the highest tolerated dose of INCAGN01876 monotherapy. If a higher dose is used, the dose will be communicated to investigational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

4.1.1.1. Treatment Group A (INCAGN01876 + Pembrolizumab)

Treatment Group A will treat subjects with INCAGN01876 at the assigned dose level administered Q3W in combination with 200 mg of pembrolizumab administered Q3W and [redacted] epacadostat administered orally BID (see Table 2). **There will be a waiting period of 48 hours between dose administration of the first subject and second subject of each dosing cohort.** The first 3 evaluable subjects enrolled within a cohort will be observed for 28 days before the next cohort begins enrollment. Dose escalation of INCAGN01876 will proceed as outlined in Table 1 until the MTD [redacted] of INCAGN01876 in combination with pembrolizumab and epacadostat is determined. Subjects must receive at least 1 dose of the cohort-specified dose of INCAGN01876, 1 dose of pembrolizumab, and at least 75% of planned doses of epacadostat (42 doses) or have had a DLT during the DLT observation period to be considered evaluable.

Table 2: Phase 1 Dose Escalation of Treatment Group A

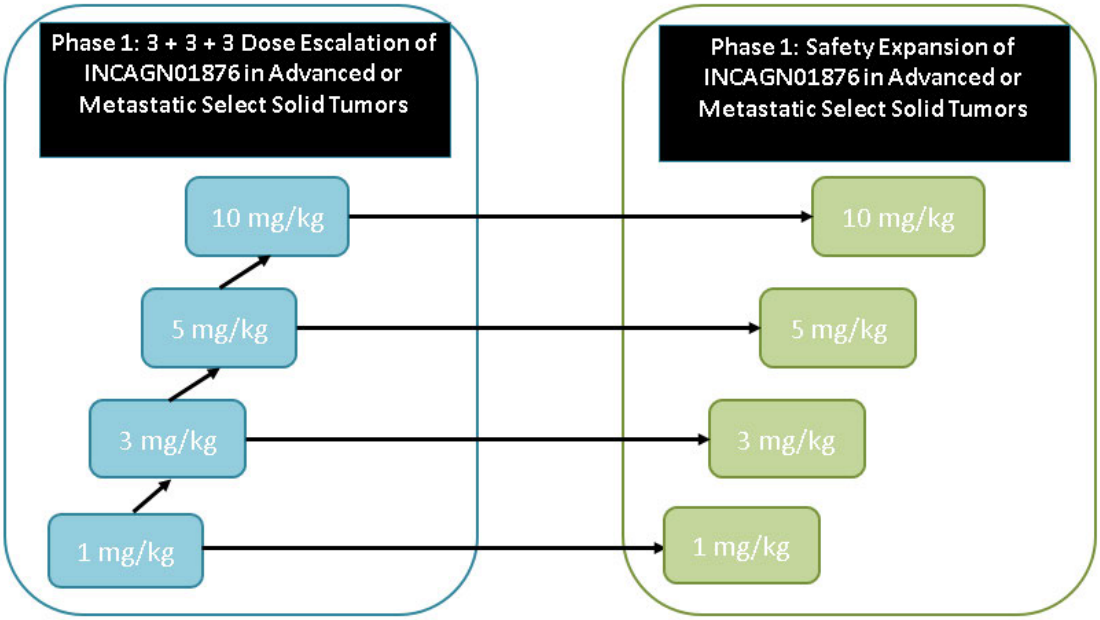
Treatment Group A	INCAGN01876 Concurrent Dose Administration	Pembrolizumab	Epacadostat
	See INCAGN01876 dose cohorts (Table 1) Q3W starting at Cycle 1	200 mg Q3W starting at Cycle 1	[redacted] starting at Cycle 1



4.1.2. Phase 1 – Safety Expansion (Part 2)

Once an INCAGN01876 dose cohort in Treatment Group A is deemed tolerable (ie, no DLTs or unacceptable toxicities were observed within the defined DLT observation period of at least 28 days), up to 6 evaluable subjects will be enrolled in Treatment Group B at the same dose of INCAGN01876 (see Figure 2). For example, if 3.0 mg/kg of INCAGN01876 is tolerated in Treatment Group A, then 3.0 mg/kg will be explored in up to 6 evaluable subjects in Treatment Group B. Doses of INCAGN01876 in Treatment Group B will be escalated in parallel to those explored in Treatment Group A, but will not exceed the MTD of INCAGN01876 established in Treatment Group A. Alternate dose administration schedules may also be explored depending on [redacted] safety results. The sponsor may elect to prioritize (or deprioritize) enrollment to specific dose cohorts based on emerging safety or efficacy data in collaboration with investigational sites.

Figure 2: Phase 1 Safety Expansion (Part 2)



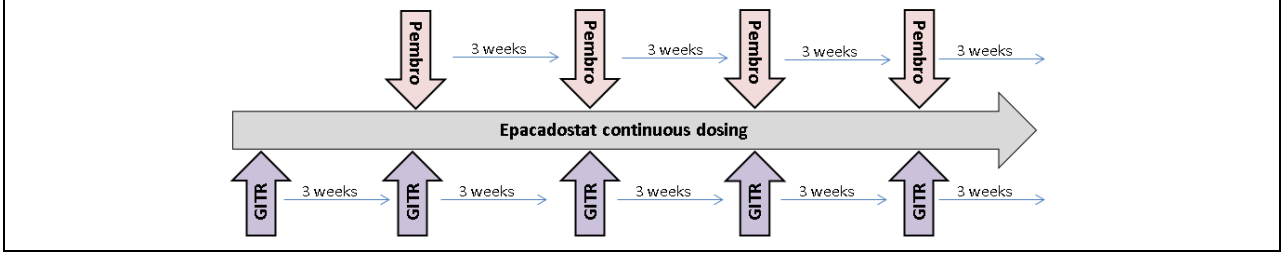
If the cumulative incidence of Grade 3 or higher INCAGN01876-related AEs occurs in > 40% of subjects in a particular treatment group, then further enrollment will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action (eg, lower the dose of INCAGN01876, change dose frequency, etc).

4.1.2.1. Treatment Group B (INCAGN01876 + Epacadostat Run-In Followed by INCAGN01876 + Pembrolizumab + Epacadostat)

Treatment Group B will treat subjects with a single-dose run-in of INCAGN01876 at the assigned dose level in combination with [redacted] epacadostat administered orally BID, followed by the combination of INCAGN01876 Q3W, 200 mg of pembrolizumab Q3W starting at Cycle 2, and [redacted] epacadostat administered orally BID (see Table 3).

Table 3: Phase 1 Safety Expansion of Treatment Group B

Treatment Group B	INCAGN01876 Run-In Followed by Concurrent Dose Administration	Pembrolizumab	Epacadostat
	See INCAGN01876 dose cohorts (Table 1) Q3W starting at Cycle 1	200 mg Q3W starting at Cycle 2	[redacted] starting at Cycle 1



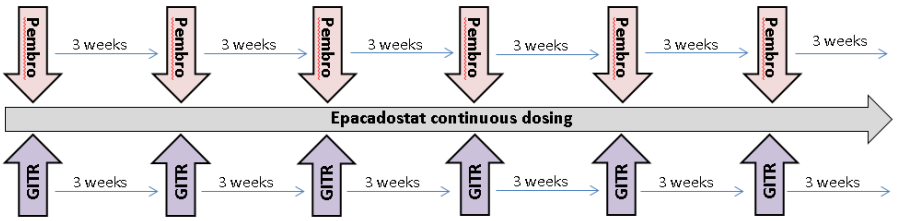
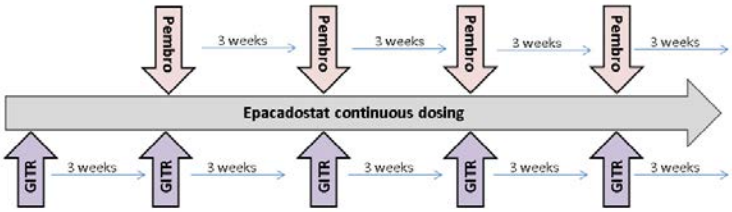
4.1.3. Phase 2 – Dose Expansion

Phase 2 will further evaluate the safety, tolerability, efficacy, [redacted] of the immune therapy combinations in subjects with advanced or metastatic melanoma, RCC, and UC. Additional tumor-specific cohorts may be added, by protocol amendment, based on emerging data.

Biopsy cohorts will be added at specific institutions for each treatment group (C and D), where serial mandatory pretreatment and on-treatment biopsies will be collected to evaluate changes in the tumor microenvironment. Approximately 15 evaluable subjects who have tumor lesions that are amenable to percutaneous biopsy will be enrolled in each biopsy cohort. The biopsy-specific cohorts will be limited to subjects with melanoma (mucosal or cutaneous), RCC, and UC (see Section 7.10.4).

The Phase 2 dose expansion treatment groups and tumor-specific cohorts for each treatment group are outlined in Table 4. 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. The approximate number of subjects for Stage 1 and Stage 2 for each treatment group and tumor type is described in Table 21. Enrollment in Phase 2 will begin when the MTD [redacted] of INCAGN01876 for a given treatment group in Phase 1 has been determined.

Table 4: Phase 2 Dose Expansion Treatment Groups

Dose Expansion Treatment Groups				
Treatment Group C	**INCAGN01876 Concurrent Dose Administration**	**Pembrolizumab**	**Epacadostat**	**Tumor Cohorts**
	MTD [redacted] of Treatment Group A Q3W starting at Cycle 1	200 mg Q3W starting at Cycle 1	[redacted] starting at Cycle 1	Cohort 1 – Biopsy Cohort 2 – Melanoma Cohort 3 – RCC Cohort 4 – UC
				
Treatment Group D	**INCAGN01876 Run-In Followed by Concurrent Dose Administration**	**Pembrolizumab**	**Epacadostat**	**Tumor Cohorts**
	MTD [redacted] of Treatment Group A Q3W starting at Cycle 1	200 mg Q3W starting at Cycle 2	[redacted] starting at Cycle 1	Cohort 1 – Biopsy Cohort 2 – Melanoma Cohort 3 – RCC Cohort 4 – UC
				

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

4.2. Measures Taken to Avoid Bias

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

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Approximately 166 to 362 subjects may be enrolled as follows:

- Phase 1 Dose Escalation (Part 1) – Approximately 12 to 36 evaluable subjects.
  Note: The minimum number of subjects assumes that the starting dose is 1.0 mg/kg.
  Note: The maximum number of subjects assumes that DLTs are observed in all dose cohorts to a maximum of 9 subjects per cohort across all treatment groups.
- Phase 1 Safety Expansion (Part 2) – Approximately 24 evaluable subjects.
- Phase 2 Stage 1 – Approximately 100 evaluable subjects.
- Biopsy cohorts – Approximately 30 evaluable subjects.
- Phase 2 Stage 2 – Up to 172 evaluable subjects.
  Note: The maximum number of subjects assumes that all treatment groups and all tumor types proceed to Stage 2.

4.3.2. Replacement of Subjects

Subjects may be replaced for any of the following reasons:

- In Phase 1, any subject who withdraws from treatment before the completion of the DLT observation period for any reason other than a DLT (ie, is not evaluable for DLTs; see Section 5.4.2) may be replaced to ensure a minimum number of evaluable subjects.
- In the Phase 2 biopsy cohorts, a subject who has not met the biopsy requirements for the study (ie, pre- and on-treatment samples; see Section 7.10.4) may be replaced to allow for a minimum number of evaluable biopsied subjects.
- Subjects who do not meet the eligibility requirements of the study may be replaced (see Section 3).

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

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Subjects may continue to receive study treatment as long as they are deriving benefit and have not met any of the Protocol-defined criteria for treatment withdrawal (see Section 5.5), or for up to 24 months from the first dose of study treatment, whichever occurs first. If the subject discontinues study treatment, then the treatment period will end, and the subject will enter the follow-up period (see Section 6.4), for safety and survival. Study participation, including post-treatment follow-up, is expected to average approximately 12 to 18 months per individual subject.

4.5. Overall Study Duration

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

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

4.6. Study Termination

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

The sponsor may terminate the study electively, if required by regulatory decision, or upon review of emerging data. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Each subject will be identified in the study by a subject ID number, which is a combination of the site ID and subject number. Site personnel should contact IRT to obtain the subject ID number and to confirm that a slot is available during prescreening. This subject ID number will be maintained throughout the study and will not be reassigned. Subjects who fail screening and repeat the screening process due to a change in eligibility status will be assigned a new subject ID number. Site personnel will contact IRT to enroll the subject and to obtain the study drugs and treatment group assignment. All subsequent cycles will follow this process. Interactive Response Technology will also be contacted to order study drug supplies and when subjects are discontinued from treatment. Full details will be provided in the Cohort Management Plan and the IRT Manual.

5.1.2. Randomization and Blinding

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

5.2. Study Drugs

5.2.1. INCAGN01876

5.2.1.1. Description and Administration

INCAGN01876 is supplied as [redacted] The infusion site should not be used for blood sampling.

INCAGN01876 will be diluted in [redacted] when INCAGN01876 is scheduled to be given. **On days when epacadostat is administered in the clinic, INCAGN01876 will be administered after the epacadostat dose but before the pembrolizumab infusion.** INCAGN01876 will always be the first infusion, followed by a 30-minute wait before starting the pembrolizumab infusion. Subjects should be monitored for signs and symptoms of infusion-related reactions, including rigors, chills, wheezing, pruritus, flushing, rash, hyper/hypotension, hypoxemia, and fever (see Section 5.4.8 for information regarding infusion-related reactions). Alternate dose administration schedules may also be explored depending on [redacted] safety results.

In Phase 1, subjects will be administered INCAGN01876 according to cohort enrollment (see Table 1). In Phase 2, subjects will be administered INCAGN01876 at the recommended dose and schedule.

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

5.2.1.2. Supply, Packaging, and Labeling

INCAGN01876 will be supplied as a sterile, single-use solution for injection in 10 mL glass vials. INCAGN01876 will be packaged as open-labelled supplies; each vial will be labelled and placed in a carton. The Pharmacy Manual contains additional information regarding supply, packaging, and labeling of study drug.

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

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

5.2.1.3. Storage

INCAGN01876 must be stored refrigerated (2°C-8°C) and protected from light in a secure, limited access location. Receipt and dispensing of INCAGN01876 must be recorded by an authorized person at the study site. INCAGN01876 may not be used for any purpose other than

that stated in the Protocol. The Pharmacy Manual contains additional information regarding storage of study drug.

5.2.2. Epacadostat

5.2.2.1. Description and Administration

Epacadostat will be self-administered orally [redacted] without regard to food. Doses will be taken in the morning and evening, approximately 12 hours apart. If a dose is missed by more than 4 hours, then the dose should be skipped, and the next dose should be taken at the usual time.

For subjects enrolled in Phase 1 and Phase 2, Treatment Groups A through D, epacadostat will begin on Cycle 1 Day 1 and will be self-administered continuously, [redacted] (see Table 18). [redacted] epacadostat will be administered at the clinic and should be taken before the INCAGN01876 infusion. Treatment will continue as long as subjects are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal (see Section 5.5) or for up to 24 months from the first dose of study treatment, whichever occurs first.

5.2.2.2. Supply, Packaging, and Labeling

Epacadostat will be available [redacted]. In Phase 1, Treatment Groups A and B subjects will receive epacadostat according to Table 2 and Table 3, respectively. In Phase 2, Treatment Groups C and D subjects will receive epacadostat according to Table 4. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph. Eur., USP/NF; refer to the INCB024360 IB).

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

5.2.2.3. Storage

Bottles should be stored at room temperature (15°C-30°C) and closed tightly to protect the tablets from humidity.

5.2.3. Pembrolizumab

5.2.3.1. Description and Administration

Pembrolizumab will be administered IV as per the prescribing information at a dose of 200 mg Q3W (eg, 21 days).

In the concurrent dose administration, Treatment Groups A and C, pembrolizumab will begin on Cycle 1 Day 1. In the run-in dose administration, Treatment Groups B and D, pembrolizumab will begin on Cycle 2 Day 1. Alternate dose administration schedules may also be explored depending on [redacted] safety results.

Pembrolizumab will be administered at least 30 minutes after the end of the INCAGN01876 infusion (when applicable), and subjects will continue to receive pembrolizumab as long as they

are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal or for up to 24 months from the first dose of study treatment, whichever occurs first.

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

5.3. Treatment Compliance

5.3.1. Treatment Compliance of INCAGN01876, Pembrolizumab, and Epacadostat

INCAGN01876 and pembrolizumab are administered as IV infusions by site personnel. Receipt of infusions will be documented by the site personnel and monitored by the sponsor or the sponsor's designee.

Epacadostat is an oral medication, and compliance will be calculated based on the drug accountability documented by the site personnel and monitored by the sponsor/designee (tablet counts). The objective is 100% compliance, and site personnel should evaluate compliance at each visit to take appropriate steps to optimize compliance.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Selections and modifications to INCAGN01876 are planned for dose-escalation cohorts (see Section 4.1.1). Treatment interruptions and dose modifications of INCAGN01876 and epacadostat may also occur for individual study subjects. The identification of DLTs will define the doses of INCAGN01876 used in planned cohorts (see Section 5.4.2). Further, the occurrence of DLTs and other toxicities (related or unrelated to INCAGN01876) will guide decisions for treatment interruptions and discontinuations for individual subjects. Dose modifications of INCAGN01876 and epacadostat should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation will not be permitted.

No dose reductions of pembrolizumab are allowed for the management of toxicities of individual subjects. Doses of pembrolizumab may be delayed for toxicity management (see Section 5.4.6). Pembrolizumab is an approved therapy and has specific subject safety management guidelines within the prescribing information; the treating investigator should refer to and follow the labeled guidance for pembrolizumab.

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

The observation period for DLTs will begin on Cycle 1 Day 1 and will continue up to and including study Day 28 for subjects in Phase 1 Part 1 (Treatment Group A). All DLTs will be assessed by the investigator using CTCAE v4.03 criteria. A DLT will be defined as the occurrence of any toxicity in Table 5, except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

Individual subject dose reductions of INCAGN01876 and epacadostat may be made based on events observed at any time during treatment; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD of INCAGN01876, decisions will be made based on events that are observed during the DLT observation period. A lower MTD may subsequently be determined based on relevant toxicities that become evident after the end of the DLT observation period.

Table 5: Definition of Dose-Limiting Toxicity

Nonhematologic toxicity
• Any liver function abnormalities that meet the definition of Hy's law.[a] • Any grade encephalopathy. • Any ≥ Grade 3 nonhematologic toxicity **EXCEPT** for the following: – Transient (≤ 72 hours) abnormal electrolyte values, not clinically complicated, and resolved spontaneously or responded to conventional medical interventions. – Nausea, vomiting, and diarrhea adequately controlled with supportive care within 48 hours. – Changes in cholesterol and triglycerides. – An event clearly and incontrovertibly due to disease progression or extraneous causes. – ≥ Grade 3 changes in amylase and lipase that are not associated with symptoms or clinical manifestations of pancreatitis. – Grade 3 fatigue < 1 week. – 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). – Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids and that resolves to Grade 1 within 14 days.
Hematologic toxicity
• Grade 3 thrombocytopenia with clinically significant bleeding (ie, requires hospitalization, transfusion of blood products, or other urgent medical intervention). • Grade 4 neutropenia or thrombocytopenia lasting > 7 days. • Any grade febrile neutropenia (fever > 101°F/38.3°C). • Grade 4 anemia not explained by underlying disease or some other concomitant disorder.
Immune-related toxicity[b]
• ≥ Grade 2 ocular irAEs. • Grade 3 irAEs that do not improve to baseline or at least Grade 1 in < 5 days with appropriate care or with corticosteroid therapy. • Grade 4 irAEs, regardless of duration. • ≥ Grade 2 pneumonitis.
General
• Any death not clearly due to the underlying disease or extraneous causes. • Inability to receive the planned number of doses within the 28-day DLT observation period due to toxicity, regardless of grade.

Table 5: Definition of Dose-Limiting Toxicity (Continued)

MTD
• In Phase 1 Part 1(Dose Escalation), the MTD will be defined as 1 dose level below that at which ≥ one-third of subjects in a particular cohort have DLTs. • In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of Grade 3 or higher INCAGN01876-related AEs occurs in > 40% of subjects in a particular treatment group after 6 subjects have been enrolled, then further enrollment in that treatment group will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action (eg, lower the dose of INCAGN01876, change dose frequency, etc). If a treatment group is discontinued due to toxicity, it may be re-initiated at a previously tested lower dose level and/or alternate dosing schedule. All AEs, regardless of the time of occurrence on study, may be considered for DLT determination purposes.

[a] Hy's law is defined as 1) ALT or AST elevation > 3 × ULN, 2) total bilirubin > 2 × ULN without initial findings of cholestasis (elevated serum alkaline phosphatase), AND 3) no other apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.
[b] Immune-related AEs are a diagnosis of exclusion, after alternative etiologies have been ruled out.

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

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

5.4.4. Follow-Up of Dose-Limiting Toxicities

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

5.4.5. Procedures for Cohort Review and Dose Escalation

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

5.4.6. Criteria and Procedures for Dose Interruptions and Adjustments

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

Instructions for dose interruptions and modifications for INCAGN01876 are outlined in Table 7. Doses of epacadostat may be modified according to the guidelines and dose levels described in Table 6. Individual decisions regarding dose interruptions and modifications of INCAGN01876 and epacadostat should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the 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 treatment (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study treatment within 4 weeks (28 days) of the scheduled interruption, unless otherwise discussed with the medical monitor. The reason for interruption should be documented in the subject's source documentation.

Table 6: Dose Modifications for Epacadostat

	Dose Level -1	**Dose Level -2**[a]
Dose of Epacadostat	First Reduction of Epacadostat	Second Reduction of Epacadostat
[redacted] BID	[redacted] BID	[redacted] BID

[a] No more than 2 dose reductions are permitted for epacadostat.

Table 7: Criteria for Interruption and Restarting of Study Treatment

Toxicity	Hold Treatment for Grade	Agent	Timing for Restarting Treatment	Dose Level for Restarting Treatment	Treatment Discontinuation
Diarrhea/colitis	2-3	Pembrolizumab	Toxicity resolves to Grade 0-1.	N/A	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		INCAGN01876		**Grade 2:** N/A **Grade 3:** Reduce by 1 dose level.	
		Epacadostat		**Related:** Reduce by 1 dose level. **Not Related:** Same dose level.	
	4	Pembrolizumab	Permanently discontinue.	N/A	Permanently discontinue.
		INCAGN01876			
		Epacadostat			
AST, ALT, or increased bilirubin	2	Pembrolizumab	Toxicity resolves to Grade 0-1.	N/A	Toxicity does not resolve within 12 weeks of last dose.
		INCAGN01876		N/A	
		Epacadostat		**Related:** Reduce by 1 dose level. **Not Related:** Same dose level.	
	3-4	Pembrolizumab	Permanently discontinue (see exception below)[a].	N/A	Permanently discontinue (see exception below)[a].
		INCAGN01876			
		Epacadostat			
T1DM (if new onset) or hyperglycemia	T1DM or 3-4	Pembrolizumab	Hold pembrolizumab, INCAGN01876, and epacadostat for new onset T1DM or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	N/A	Resume study medications when subjects are clinically and metabolically stable.
		INCAGN01876		**Grade 2:** N/A **Grade 3-4:** Reduce by 1 dose level.	
		Epacadostat		**Related:** Reduce by 1 dose level. **Not Related:** Same dose level.	

Table 7: Criteria for Interruption and Restarting of Study Treatment (Continued)

Toxicity	Hold Treatment for Grade	Agent	Timing for Restarting Treatment	Dose Level for Restarting Treatment	Treatment Discontinuation
Hypophysitis	2-4	Pembrolizumab	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab, INCAGN01876, and epacadostat can be continued while endocrine replacement therapy is instituted.	N/A	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		INCAGN01876		**Grade 2:** N/A **Grade 3:** Reduce by 1 dose level.	
		Epacadostat		**Related:** Reduce by 1 dose level. **Not Related:** Same dose level.	
Hyperthyroidism	3	Pembrolizumab	Toxicity resolves to Grade 0-1.	N/A	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		INCAGN01876		Reduce by 1 dose level.	
		Epacadostat		**Related:** Reduce by 1 dose level. **Not Related:** Same dose level.	
	4	Pembrolizumab	Permanently discontinue.	N/A	Permanently discontinue.
		INCAGN01876			
		Epacadostat			
Hypothyroidism	N/A	Pembrolizumab	Therapy with pembrolizumab, INCAGN01876, and epacadostat can be continued while thyroid replacement therapy is instituted.	N/A	Therapy with pembrolizumab and epacadostat can be continued while thyroid replacement therapy is instituted.
		INCAGN01876			
		Epacadostat			
Infusion reaction	2	Pembrolizumab[b]	Toxicity resolves to Grade 0-1.	N/A	N/A
		INCAGN01876[b]		Same dose level.	N/A
		Epacadostat		Same dose level.	N/A
	3-4	Pembrolizumab	Permanently discontinue.	N/A	Permanently discontinue.
		INCAGN01876			
		Epacadostat			

Table 7: Criteria for Interruption and Restarting of Study Treatment (Continued)

Toxicity	Hold Treatment for Grade	Agent	Timing for Restarting Treatment	Dose Level for Restarting Treatment	Treatment Discontinuation
Pneumonitis	2	Pembrolizumab	Toxicity resolves to Grade 0-1.	N/A	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		INCAGN01876		Reduce by 1 dose level	
		Epacadostat		**Related:** Reduce by 1 dose level. **Not Related:** Same dose level.	
	3-4 (or recurrent Grade 2)	Pembrolizumab	Permanently discontinue.	N/A	Permanently discontinue.
		INCAGN01876			
		Epacadostat			
Renal failure or nephritis	2	Pembrolizumab	Toxicity resolves to Grade 0-1.	N/A	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		INCAGN01876		N/A	
		Epacadostat		**Related:** Reduce by 1 dose level. **Not Related:** Same dose level.	
	3-4	Pembrolizumab	Permanently discontinue.	N/A	Permanently discontinue.
		INCAGN01876			
		Epacadostat			
Rash	3[c]	Pembrolizumab	Toxicity resolves to Grade 0-1.	Same dose level.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		INCAGN01876		Reduce by 1 dose level.	
		Epacadostat		**Related:** Reduce by 1 dose level. **Not Related:** Same dose level.	
	4	Pembrolizumab	Permanently discontinue.	N/A	Permanently discontinue.
		INCAGN01876			
		Epacadostat			

Table 7: Criteria for Interruption and Restarting of Study Treatment (Continued)

Toxicity	Hold Treatment for Grade	Agent	Timing for Restarting Treatment	Dose Level for Restarting Treatment	Treatment Discontinuation
All other drug-related toxicity	3 or Severe[d]	Pembrolizumab	Toxicity resolves to Grade 0-1.	N/A	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		INCAGN01876		Reduce by 1 dose level	
		Epacadostat		**Related:** Reduce by 1 dose level. **Not Related:** Same dose level.	
	4	Pembrolizumab	Permanently discontinue.	N/A	Permanently discontinue.
		INCAGN01876			
		Epacadostat			

[a] For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week, then subjects should be discontinued. The dose of INCAGN01876 and epacadostat should also be reduced by 1 dose level for subjects with liver metastasis that have Grades 3 to 4 AST or ALT elevations.
[b] If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose; see Table 9 for further management details.
[c] Subjects with Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids, and that resolves to Grade 1 within 14 days do not have to hold study treatment.
[d] Subjects with intolerable or persistent Grade 2 treatment-related toxicities may hold study treatment at the discretion of the investigator.

5.4.7. Management of Immune-Related Adverse Events

INCAGN01876, pembrolizumab, and epacadostat are considered immune modulators, and it is possible that irAEs (both nonserious and serious) may occur. Adverse events of a potential immunologic etiology, or irAEs, may be defined as AEs consistent with an immune phenomenon associated with drug exposure ***after all other etiologies have been eliminated.*** Immune-related AEs may be expected based on the nature of the study treatment, their mechanisms of action, and reported experience with these and other immunotherapies. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Suspected irAEs should be discussed with the medical monitor when possible.

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

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

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

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

5.4.8. Management of Infusion Reactions

Table 9 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of study treatment. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of the infusion. Pembrolizumab is an approved agent and has specific infusion reaction management guidelines within the prescribing information; the treating investigator may use labeled guidance or institutional guidelines for the management of infusion reactions if preferred.

Table 9: Infusion Reaction Treatment Guidelines for Pembrolizumab and INCAGN01876

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 clinically 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 clinically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dose administration will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment.	Subject may be premedicated 1.5 h (± 30 min) before infusion with the following: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).
Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated.	Stop infusion. Additional appropriate medical therapy may include, but is not limited to, the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as clinically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further study treatment.	No subsequent dose.

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

5.4.9. Procedure for Subjects Exhibiting Serotonin Syndrome

As noted in Section 1.3, there is a chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger SS (Boyer and Shannon 2005) when administered in combination with other serotonergic agents. This syndrome has been most closely associated with use of MAOIs, meperidine, linezolid, or methylene blue; all of these agents are prohibited during the study. Selective serotonin reuptake inhibitors and SNRIs are permitted in the study. The following procedures will be implemented if subjects exhibit the signs/symptoms of SS described in Table 10, including tremor; hyperreflexia; and spontaneous, ocular, or inducible clonus, together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt epacadostat, pembrolizumab, and INCAGN01876 administration.
- Immediately interrupt any SSRI or SNRI administration.
- Provide appropriate medical management of the subject until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists, such as cyproheptadine).
- If subject chooses to remain in the study, restart treatment with all study medications after the SSRI or SNRI has been discontinued and no sooner than when 5 half-lives have elapsed for the specific SSRI or SNRI in question and after resolution of signs/symptoms of SS. The SSRI or SNRI treatment MAY NOT be restarted.
- If subject chooses to withdraw from the study or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit (see Section 6.4). Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.

Table 10: Signs and Symptoms of Serotonin Syndrome

Tremor and hyperreflexia
Spontaneous clonus
Muscle rigidity, temperature > 38°C (100.4°F), and either ocular clonus or inducible clonus
Ocular clonus and either agitation or diaphoresis
Inducible clonus and either agitation or diaphoresis

5.4.10. Criteria for Permanent Discontinuation of Study Treatment

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

- Grade 4 or life-threatening AEs, except with approval from the medical monitor.
- Toxicity requiring more than 2 dose reductions of INCAGN01876 (see Table 1) or epacadostat (see Table 6).
- ≥ Grade 2 ocular irAE.

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

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

A subject may choose to withdraw from the study treatment at any time or be withdrawn from the study treatment by the investigator or sponsor if the subject is noncompliant with the study requirements. If a subject is withdrawn from study treatment, then every reasonable effort should be made to determine the reason for withdrawal, and this information should be recorded in the eCRF.

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

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

  Note: Consent withdrawn means that the subject can no longer be followed and no additional data can be collected. Subjects may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity (see Section 5.4) occurs. Subjects with unacceptable toxicities must be withdrawn from study treatment but will continue in the follow-up phase of the study (see Section 6.4).
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

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

  Note: For unconfirmed progression, see Section 7.7.1.
- If, during the course of the study, a subject is found not to have met eligibility criteria (see Section 3), the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from study treatment.
- If a subject is lost to follow-up or noncompliant with study procedures or study treatment in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

5.5.2. Withdrawal Procedures

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

If a subject is withdrawn from the study treatment:

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

  Note: The reason for withdrawal from treatment may be different than the reason for withdrawal from study. For example, subjects can discontinue treatment for disease progression or toxicity but remain in the study for safety and survival follow-up.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the eCRF and the IRT system.
- Subjects must be followed for safety until the time of the follow-up visit or until study treatment-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.
- Subjects who discontinue for reasons other than disease progression will continue to be followed for disease status as outlined in Section 6.4.2.
- All subjects who discontinue study treatment will continue to be followed for survival as outlined in Section 6.4.3.

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

5.6. Concomitant Medications

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

5.6.1. Permitted Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded in the eCRF, including all

prescription and over-the-counter medications, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug regimen, frequency, route, and date may also be included in the eCRF. ***Note:*** The use of bisphosphonates and denosumab are permitted in this study.

5.6.2. Restricted Medications

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

  Note: Inhaled and topical steroids are allowed. A short course of steroids (eg, prednisone or equivalent) at doses ≤ 10 mg/day may be permitted with medical monitor approval.
- Use of the anticonvulsant carbamazepine (a UGT1A9 inducer) is discouraged. Because there is a potential interaction that could result in lower epacadostat exposures, an alternative to carbamazepine should be used, if possible.
- Use of coumarin-based anticoagulants (eg, warfarin) with epacadostat is discouraged. Low-dose warfarin (1 mg) is acceptable; however, other higher doses are discouraged. If an alternative to coumarin-based anticoagulants cannot be used, the INR should be monitored closely per standards of care when epacadostat is started.

5.6.3. Prohibited Medications

Medications or vaccinations specifically prohibited in the exclusion criteria (see Section 3.2) are not allowed during the study. If there is a clinical indication for one of these medications or vaccinations specifically prohibited during the study, discontinuation from study treatment may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study treatment requires the mutual agreement of the investigator, the sponsor, and the subject.

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

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

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

  Note: Allergy shots may be permitted after consultation with the medical monitor.

- Investigational agents other than study treatment. Use of such medications from screening through the safety follow-up visit is prohibited.
- Concomitant radiation therapy.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the medical monitor. The subject must have clear measurable disease outside of the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- Live vaccines within 30 days before the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
- For cohorts where subjects receive epacadostat, use of any melatonin supplements.
- For cohorts where subjects receive epacadostat, use of any MAOI or drug associated with significant MAOI activity agents is prohibited from 21 days before study Day 1 through 14 days after the final dose of epacadostat has been administered (refer to Appendix C).
- For cohorts where subjects receive epacadostat, any UGT1A9 inhibitor from screening through the safety follow-up, including acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole, linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid propofol*, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

  Note: Propofol, when used for short-term sedation during surgical/biopsy procedures, is allowed after consultation with the sponsor. The epacadostat dose may be taken on the morning of the procedure and the evening dose held following the procedure. Epacadostat may be resumed the next day.

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 (see Section 3.2). There are no prohibited therapies during the post-treatment follow-up period.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of clinical assessments (Table 11), and all laboratory assessments will be performed as indicated in Table 12. Table 13 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 11: Schedule of Assessments

Visit Day (Range) / Evaluation/Window	Protocol Section	Screening	Treatment[a]						Post-Treatment[b]			
			Cycles 1 and 6			Cycle 2	All Other Cycles	Every 9 Weeks		Safety Follow-Up Visit 1	Safety Follow-Up Visit 2	Survival Follow-Up
			D1	D8	D15	D1	D1	Disease Status	EOT			Every 12 weeks
		Days -28 to -1		± 1 day	± 3 days	± 3 days	± 3 days	± 7 days	± 3 days	30 days (+ 7 days)	60 days (+ 7 days)	± 7 days
Informed consent	7.1	X										
Inclusion/exclusion criteria	3.1, 3.2	X	X[c]									
Contact IRT	7.2	X	X			X	X		X			
Medical and cancer history	7.3.1, 7.3.2	X										
Prior/concomitant medications	7.4	X	X	X	X	X	X		X	X	X	
Administer INCAGN01876	5.2.1.1		X			X	X					
Administer pembrolizumab	5.2.3.1		X[d]			X	X					
Administer/dispense epacadostat at site	5.2.2.1		X[e]			X[e]	X[e]					
Poststudy anticancer therapy status	7.5									X	X	X
Survival status	6.4.3											X
Comprehensive physical examination (including height)	7.6.2.1	X										
Targeted physical examination	7.6.2.2		X	X[f]	X[f]	X	X		X	X	X	
Vital signs and weight	7.6.3	X	X	X[f]	X[f]	X	X		X	X	X	
ECOG performance status	7.8.1	X	X	X[f]	X[f]	X	X		X	X	X	
Laboratory assessments	7.6.5	X	X	X	X	X	X		X	X	X	
12-Lead ECG[g]	7.6.4	X	X[h]			X[h]			X	X		
AE assessment	7.6.1	X	X	X[f]	X[f]	X	X		X	X	X	
Distribute subject reminder cards	7.11.1		X	X	X	X	X		X	X		
Radiologic tumor assessments	6.4.2, 7.7	X[i]						X[j]	X[k]	X[l]		

[a] Treatment cycles will be every 3 weeks (21 ± 3 days).
[b] The mandatory safety follow-up visits should be conducted approximately 30 days and 60 days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first.

[c] Screening laboratory tests performed more than 7 days before Cycle 1 Day 1 must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1.
[d] In Treatment Groups B and D, pembrolizumab administration begins at Cycle 2 Day 1.
[e] Epacadostat is only required to be dosed at the site on Day 1 of Cycle 1 and Cycle 2.
[f] Only required for Cycle 6 Day 8 and Cycle 6 Day 15 if the subject is experiencing an AE > Grade 2.
[g] All 12-lead ECGs will be performed at the study site with the subject in a recumbent or semirecumbent position after 5 minutes of rest and should not be performed within 15 minutes after a blood sample collection.
[h] A 12-lead ECG will be collected before the morning dose of epacadostat on Cycle 1 Day 1 and Cycle 2 Day 1, and 2 hours (± 15 minutes) after the morning dose of epacadostat on Cycle 1 Day 1 and Cycle 2 Day 1 (see Table 14).
[i] The initial tumor imaging will be performed within 28 days before the first dose of study treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study treatment. The same imaging technique should be used for a subject throughout the study. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management.
[j] On-study imaging will be at Week 9 and then every 9 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 more than 6 weeks, later to confirm disease progression per mRECIST.
[k] If a scan was obtained within 4 weeks prior to the date of treatment discontinuation, then a scan at treatment discontinuation (EOT) is not mandatory. For subjects who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be repeated at the time of treatment discontinuation (ie, date of discontinuation ± 4 week window).
[l] For subjects who discontinue treatment for a reason other than disease progression (eg, toxicity), every effort should be made to collect information regarding disease status every 9 weeks (± 7 days) for 12 months and then every 12 weeks (± 7 days) thereafter by radiographic imaging until 1) the start of new anticancer therapy, 2) documented disease progression, 3) death, 4) the end of the study, or 5) withdrawal of consent, whichever occurs first.

Table 12: Schedule of Laboratory Assessments

Visit Day (Range)			Screening	Treatment										Post-Treatment		
				C1			C2	C4	C6			C7	C8 and Every 4th Cycle	All Other Cycles	EOT	Safety Follow-Up Visit 1	Safety Follow-Up Visit 2
				D1	D8	D15	D1	D1	D1	D8	D15	D1	D1	D1			
Evaluation/Window	**Protocol Section**	**Timing of Assessment**	**Days -28 to -1**	**Predose**	**± 1 day**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 1 day**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**30 days (+ 7 days)**	**60 days (+ 7 days)**
Local laboratory tests[a]																	
Comprehensive serum chemistries[b]	7.6.5	N/A	X[c]	X[d]	X	X	X	X	X			X	X		X	X	X
Hematology with differential	7.6.5	N/A	X[c]	X[d]	X	X	X	X	X			X	X		X	X	X
Coagulation panel[e]	7.6.5	N/A	X[c]														
Urinalysis	7.6.5	N/A	X[c]												X		
Endocrine function tests	7.6.5	N/A	X[c]					X					X		X	X	
HBV and HCV tests	7.6.5.2	N/A	X														
Serum pregnancy test (childbearing females only)[f]	7.6.5.1	N/A	X												X		
Urine pregnancy test (childbearing females only)	7.6.5.1	N/A		X[g]													
[redacted]																	

[redacted]

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 or ≤ Grade 1. Liver chemistry does not need to be monitored once per week indefinitely for persistent low grade abnormalities. Appropriate liver chemistry monitoring intervals should be discussed with the medical monitor for these circumstances.

[c] Screening laboratory tests must be performed within 7 days of Cycle 1 Day 1. If performed more than 7 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1.

[d] Only required to be performed at Cycle 1 Day 1 if the screening assessment was not performed within 7 days prior.

[e] Subjects on anticoagulation treatment should have parameters monitored throughout the study as clinically indicated.

[f] A serum pregnancy test will be required for all females of childbearing potential during screening and at EOT. The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study treatment.

[g] Urine pregnancy tests will be performed locally as clinically indicated or per country-specific requirements (see Section 7.6.5.1).

[redacted]

Table 13: Local Laboratory Tests: Required Analytes

<table>
<tr><th>Serum Chemistries</th><th>Hematology</th><th>Urinalysis</th><th>Hepatitis Screening</th><th>Coagulation</th></tr>
<tr><td rowspan="2">Albumin
Alkaline phosphatase
ALT
AST
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein
Uric acid
Amylase
Lipase</td><td rowspan="2">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• White blood cell count

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

[a] If considered standard by your region.

6.1. Screening

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

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment. Tests with results that fail eligibility requirements may be repeated **once** during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before enrollment will be used to determine subject eligibility. Additionally, a subject who fails screening may repeat the screening process **1 time** if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection). Treatment should start as soon as possible after the date of enrollment.

6.2. Treatment

The treatment period begins on the day the subject receives the first dose of study treatment (eg, Cycle 1 Day 1) through the point at which the investigator determines that the subject will be permanently discontinued from study treatment. Cycle 1 Day 1 must be no more than 28 days after the subject has signed the ICF and should be within 3 days of enrollment in the study. Subjects will have regularly scheduled study visits as outlined in Table 11, and toxicities will be monitored continuously and graded using the CTCAE v4.03 criteria.

6.3. End of Treatment

When the subject permanently discontinues study treatment, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the safety and survival follow-up visits.

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 treatment 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 treatment, until the subject starts a new anticancer therapy, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the subject return for the follow-up visits and report any AEs that may occur during this period. If a subject is scheduled to begin a new anticancer therapy before the end of the 30-day or 60-day safety follow-up period, the safety follow-up visit should occur before the new anticancer therapy is

started. Once the new anticancer therapy has been initiated, AEs and SAEs will no longer be collected, and the subject will move into the survival follow-up period.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason **other than** disease progression (eg, toxicity) will move into the disease status follow-up period and should be assessed every 9 weeks (± 7 days), for 12 months. After 12 months, radiologic assessments will be performed every 12 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the first occurrence of any of the following:

- The start of new anticancer therapy.
- Documented disease progression.
- Death.
- The end of the study.
- Withdrawal of consent.

6.4.3. Survival Follow-Up

Once a subject has received the last dose of study treatment, confirmed disease progression, or starts a new anticancer therapy, the subject moves into the survival follow-up period and should be contacted by telephone, email, or visit by the subject or the subject's caregiver at least every 12 weeks (± 7 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. After the final primary analysis is performed, the follow-up interval for subsequent anticancer treatments and survival may be reduced to every 16 weeks (± 7 days) or eliminated.

6.5. End of Study

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

- Subject dies, and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained.

  Note: Every effort must be made to obtain the date of death.
- Consent is withdrawn for any further contact related to the 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, IRB, or IEC.

6.6. Unscheduled Visits

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

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

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

7.2. Interactive Response Technology System Procedure

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

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

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

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

7.3.2. Disease Characteristics and Treatment History

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

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. Any medication received or procedure performed within 28 days before the first dose of study treatment, up to the end of the safety follow-up period, or until the subject starts a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, natural/herbal preparations, and IV medications and fluids 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 permitted, restricted, and prohibited medications.

7.5. Poststudy Anticancer Therapy Status

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

7.6. Safety Assessments

Pembrolizumab is an approved therapy; therefore, the investigator should refer to and follow the safety management guidelines as appropriate within the approved prescribing information.

7.6.1. Adverse Events

Adverse events will be monitored from the time subjects sign 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 treatment. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.6.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. Clinically notable abnormalities that are considered clinically significant in the judgement of the investigator are to be reported as AEs (see Section 8.1.2).

7.6.2.1. Comprehensive Physical Examination

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

7.6.2.2. Targeted Physical Examination

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

7.6.3. Vital Signs and Weight

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and pulse oximetry. 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 (see Section 8.1.2).

7.6.4. Electrocardiograms

All 12-lead ECGs will be performed at the study site as outlined in Table 14 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 sample collection.

Table 14: Schedule of ECG Assessments

Visit	Anytime	Before the Morning Dose of Epacadostat	2 Hours (± 15 minutes) After the Morning Dose of Epacadostat
Screening	X		
Cycle 1 Day 1		X	X
Cycle 2 Day 1		X	X
EOT	X		
Safety Follow-up Visit 1	X		

The 12-lead ECG readings will be interpreted by the investigator at the site to be used for immediate subject management. Additional 12-lead ECGs may be performed as clinically indicated to manage subject safety. The decision to include or exclude a subject or to withdraw a subject from study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator in consultation with the medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs (see Section 8.1.2).

In the event that a single QTc is > 470 milliseconds at screening (corrected by Fridericia), the subject may enroll if the average QTc for 3 ECGs is < 470 milliseconds or with approval from the medical monitor. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. 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. In addition, the JTc interval should be used for all subsequent assessments.

7.6.5. Laboratory Assessments

A certified laboratory local to the study site and subject will perform all clinical laboratory assessments for safety (ie, serum 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 12. Table 13 lists the specific laboratory analytes required for each test. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Screening laboratory assessments must be performed within 7 days of Cycle 1 Day 1. If performed more than 7 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1. Laboratory samples collected on Study Day 1 must be performed before study treatment administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration (within the 3-day study window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

7.6.5.1. Pregnancy Testing

A local laboratory serum pregnancy test will be required for all females of childbearing potential during screening and at EOT. The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study treatment. Urine pregnancy tests will be performed locally as outlined in Table 12, as clinically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirements (note that country-specific requirements for urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, then the results should be confirmed with a serum pregnancy test.

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

7.6.5.2. Hepatitis Screening Tests

Hepatitis (HBV and HCV) screening assessments will be performed at the screening visit (Table 12) to rule out hepatitis infection; required analytes are shown in Table 13. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

7.7. Efficacy Assessments

7.7.1. Modified Response Evaluation Criteria in Solid Tumors

Modified response evaluation criteria in solid tumors will be applied by the site as the primary measure for assessment of tumor response and as a basis for Protocol guidelines related to disease status (eg, discontinuation of study therapy). As noted in Section 1.5.4.1 , RECIST v1.1 will be modified to account for the unique tumor responses seen with immunotherapy (Wolchok et al 2009). Therefore, RECIST v1.1 will be used with the following modifications:

If radiologic imaging shows progressive disease, tumor assessment should be repeated at a minimum of 4 weeks, but no more than 6 weeks, later to confirm disease progression, with the option of continuing treatment while awaiting radiologic confirmation of disease progression. Table 15 provides instructions on how to proceed with treatment based on subjects' clinical statuses once the initial scan showing radiologic evidence of disease progression is observed.

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

Table 15: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

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

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

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

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

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

Subjects who are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of disease progression. 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 11). If disease 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 more 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 more than 6 weeks, apart demonstrating disease 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.

7.7.2. Response Evaluation Criteria in Solid Tumors Version 1.1 Tumor Imaging

The same imaging technique should be used for a subject throughout the study. The baseline scan must be a contrast CT or MRI, except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a positron emission tomography/CT scan uses higher energy and thinner slices, it may be acceptable with medical monitor approval. **Images of the chest, abdomen, and pelvis are required for all subjects.** Additional imaging of anatomical sites (eg, head, neck, brain, etc) should be done as applicable for the malignancy under study.

A CT 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.**

7.7.2.1. Response Evaluation Criteria in Solid Tumors Version 1.1 Tumor Imaging During Screening

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

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

7.7.2.2. Response Evaluation Criteria in Solid Tumors Version 1.1 Tumor Imaging During Treatment

The first imaging assessment should be performed 9 weeks after the first dose of INCAGN01876 and then every 9 weeks (± 7 days) for the first 12 months and then every 12 weeks (± 7 days) thereafter until disease progression is determined. Imaging assessments may be done more frequently if clinically indicated. **Imaging should follow calendar days and should NOT be delayed for delays in cycle starts**.

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

Imaging should continue to be performed until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confirmed at least 4 weeks, but no more than 6 weeks, later after the first scan indicating disease 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.

7.7.2.3. Response Evaluation Criteria in Solid Tumors Version 1.1Tumor Imaging During Follow-Up

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

7.8. Performance and Quality-of-Life Assessments

7.8.1. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be assessed as shown in Table 11 according to the criteria in Table 16.

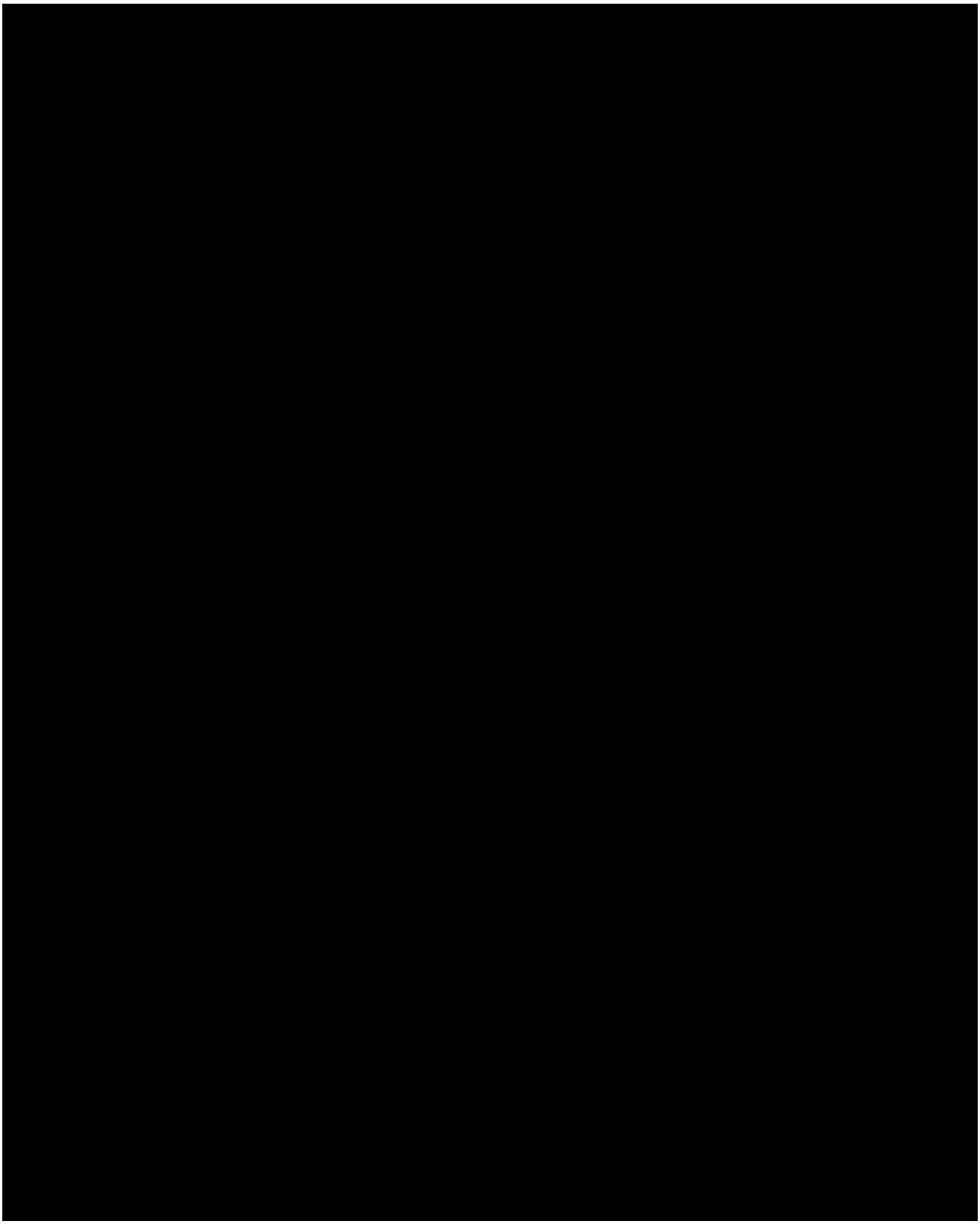
Table 16: Eastern Cooperative Group Performance Status Scoring

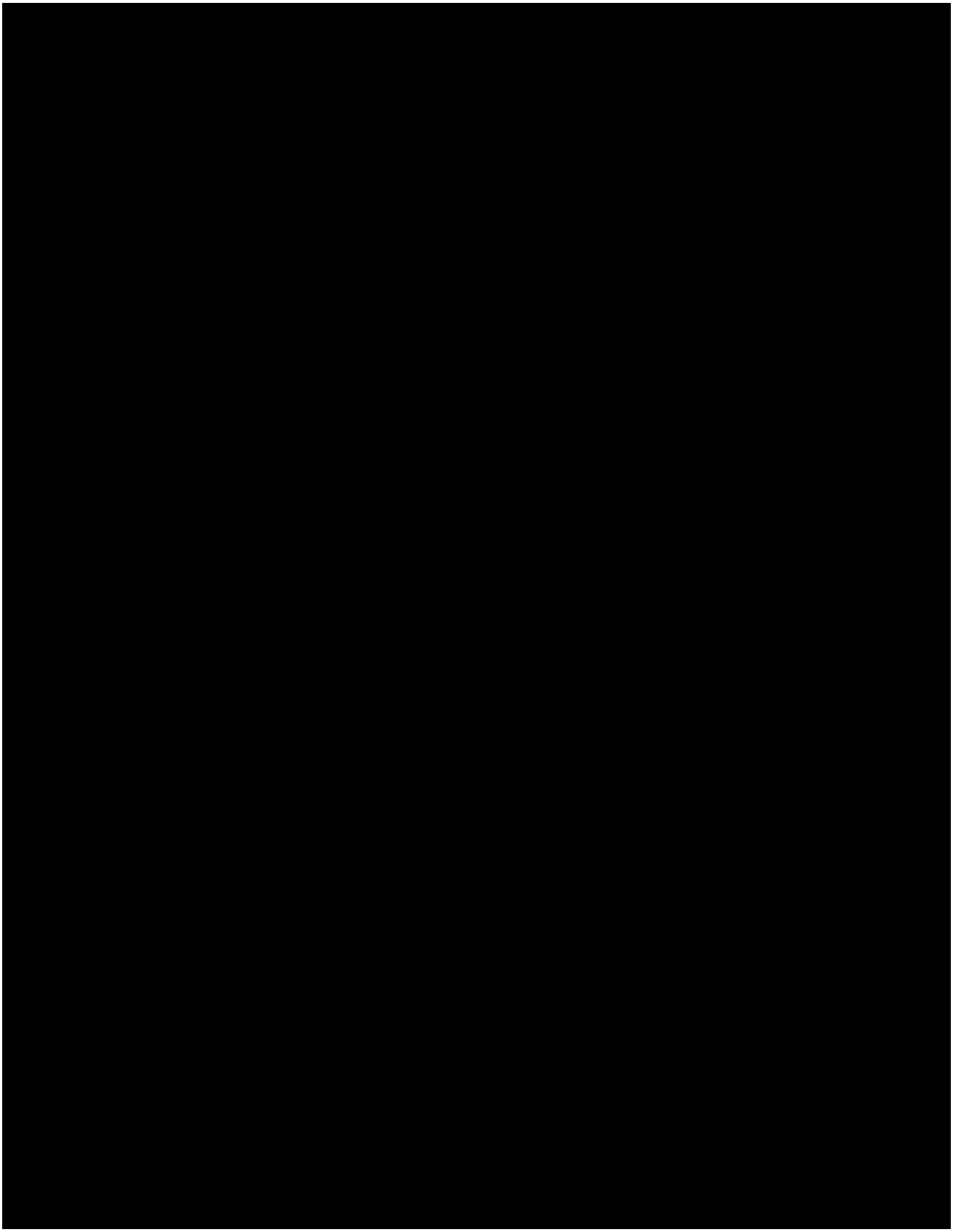
Grade	ECOG Performance Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care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

Source: Oken et al 1982.

7.9. Pharmacokinetic Assessments

[redacted]





7.10.4. Tumor Biopsies

7.10.4.1. Tumor Tissue Collection Requirements

During Phase 2 of the study, biopsy cohorts will be added **at specific institutions** for each treatment group, where serial mandatory pretreatment (before Day 1 dose administration) and on-treatment biopsies will be collected to evaluate changes in the tumor microenvironment. Approximately 15 evaluable subjects who have tumor lesions that are amenable to percutaneous biopsy will be enrolled in each biopsy cohort. The biopsy-specific cohorts will be limited to melanoma (mucosal or cutaneous), RCC, and UC. Detailed instructions for tissue collection, processing, and storage can be found in the Laboratory Manual. Fine- needled aspirates are not acceptable. Mandatory tumor biopsies will be collected as specified below:

- **Screening:** Tumor tissue will be collected during screening. A fresh biopsy at screening is preferred; however, formalin-fixed paraffin embedded tissue is acceptable as long as the sample has been collected after the completion of the most recent prior systemic therapy. A minimum of 20 slides or preferably 1 tissue block should be submitted before Day 1 dosing. Biopsies should be performed on lesions that have not been exposed to prior radiation (exceptions may be granted with sponsor approval).

  Note: Fresh tumor biopsies should be taken from **nontarget lesions** when possible.

- **On-treatment:** An on-treatment biopsy will be collected any time between the start of Cycle 3 and the end of Cycle 4.
  Note: On-treatment biopsies should be taken from the same site as the screening biopsy whenever possible.
- **After the first on-treatment imaging assessment (optional):** A third optional biopsy, referred to as the disease assessment biopsy, may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. [redacted]

If a subject is selected for inclusion in the biopsy cohort, and it is subsequently determined that tissue cannot safely be obtained, the subject may still enroll for evaluation of efficacy; however, the subject may be replaced in the biopsy cohort.

Tumor biopsy samples are ***optional*** for the Phase 1 dose-escalation portion of the study **at specific institutions**. If a subject consents to provide a tumor biopsy, then samples will be collected as outlined below:

- **Screening:** Tumor tissue will be collected during screening (see details above).
- **On-treatment:** An on-treatment biopsy will be collected any time between the start of Cycle 3 and the end of Cycle 4.

  Note: On-treatment biopsies should be taken from the same site as the screening biopsy whenever possible.
- **After the first on-treatment imaging assessment (optional):** A third optional biopsy, referred to as the disease assessment biopsy, may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment.

7.11. Other Study Procedures

7.11.1. Distribution of Subject Reminder Cards

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

7.11.2. Data Collection for Survival Follow-Up

For subjects having entered the survival follow-up period of the study, the site will use continuing subject records to supply data on subsequent treatment regimens, tumor assessments (if they discontinued treatment for a reason other than progression), and OS in the eCRF. For subjects who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 12 weeks (± 7 days). After the final primary analysis is performed, the follow-up interval for subsequent anticancer treatments and survival may be reduced to every 16 weeks (± 7 days) or eliminated (see Section 6.4.3).

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

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

8.1.2. Reporting

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

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

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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

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

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

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

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

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to study treatment, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE 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 treatment) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low

hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs (see Section 8.1.2). A Grade 3 or 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.4) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

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

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an 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 treatment or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 60 days after the last dose of study treatment or until the subject receives a new anticancer therapy, whichever occurs earlier) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any

SAEs occurring more than 60 days after the last dose of study treatment should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study treatment.

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

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

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study treatment 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 drugs (new occurrence) and is thought to be related to the sponsor's study drugs, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study treatment 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 treatment, the following procedures should be followed in order to ensure subject safety:

- The study treatment must be discontinued immediately (female subjects only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.
- A serum pregnancy test must be performed to confirm the urine pregnancy test result. If a negative serum test does not confirm the urine pregnancy result, then:
  - The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine whether it is in the subject's best interest to resume study treatment and continue participation in the study.
- The EOT visit evaluations must be performed.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drugs 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 drugs (INCAGN01876 and epacadostat), derived from safety information collected by the sponsor or its designee, and are presented in the INCAGN01876 IB and the INCB024360 IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

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

8.8. Product Complaints

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

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

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

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

9. STATISTICS

9.1. Study Populations

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

[redacted]

The biopsy evaluable population includes subjects who received at least 1 dose of study treatment (INCAGN01876, pembrolizumab, or epacadostat) and had at least 1 biopsy sample collected and analyzed. During Phase 2 of the study, biopsy cohorts will be added for each treatment group (C and D). A subject who does not meet the biopsy requirements for the study will be replaced within the biopsy cohort.

9.2. Selection of Sample Size

9.2.1. Sample Size for Phase 1 (Part 1)

The primary objective of Phase 1 of the study is to evaluate the safety, tolerability, and DLTs of INCAGN01876 in combination with immune therapies and to determine the recommended Phase 2 dose(s) of INCAGN01876 when given in combination with immune therapies. The total number of subjects will depend on the number of dose levels tested before the recommended dose(s) are established. Dose escalation will follow the 3 + 3 + 3 design algorithm

(see Section 4.1.1). Based on this algorithm, a minimum of 3 evaluable subjects will be enrolled in each cohort with a maximum of 9 evaluable subjects in each cohort.

The probabilities of dose escalation from a given dose level for the various DLT rates are provided in Table 20.

Table 20: Probability of Dose Escalation for Various Dose-Limiting Toxicity Rates

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

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

9.2.2. Sample Size for Phase 1 (Part 2)

Once an INCAGN01876 dose cohort in Treatment Group A is deemed tolerable, up to 6 evaluable subjects will be enrolled in Treatment Group B at the same dose of INCAGN01876. For example, if 3 mg/kg of INCAGN01876 is tolerated in Treatment Group A, then 3.0 mg/kg will be explored in up to 6 evaluable subjects in Treatment Group B.

9.2.3. Sample Size for Phase 2

Phase 2 will further evaluate the safety, tolerability, preliminary efficacy, [redacted] of the immune therapy combinations as part of dose expansion cohorts in Treatment Groups C and D. In Phase 2, a Simon 2-stage design will be run for each tumor type within a given treatment group.

The sample size for each tumor type within a given treatment group will be guided by the Simon 2-stage design. The planned Simon 2-stage designs are summarized in Table 21. Each Simon 2-stage design will have a stopping rule to allow early termination of a particular cohort at the end of Stage 1 if there are insufficient responses observed, while enrolling enough subjects to predict possible target responses worthy of cohort expansion and potentially further evaluation in future studies.

The individual Simon 2-stage designs run for each tumor type within each treatment group will have design parameters that are determined by historical response rates. For the RCC and UC cohorts, the insufficient response rates are obtained from historical data, and the Simon 2-stage designs allowing early termination are based on ORR. For the melanoma cohort, the insufficient response rate is obtained from historical data, and the primary endpoint for the Simon 2-stage design allows for early termination based on CRR. The same Simon 2-stage design parameters will be used for the alternative dosing sequences represented by Treatment Groups C and D in

the same tumor type. For example, the RCC cohorts in Treatment Groups C and D will use the same Simon 2-stage parameters.

In order to determine whether the target response rate (p_1%) is likely, an initial number of evaluable subjects (n_1 subjects) will be treated at the MTD [redacted] and schedule of INCAGN01876 within the corresponding tumor type and treatment group and will be enrolled in a cohort (Stage 1). If there are r_1 or fewer responses in the cohort, it will be concluded that the true response rate is unlikely to be greater than or equal to the target rate, and no more subjects will be enrolled in that tumor type cohort for that treatment group in Stage 2. In the cohorts in which greater than r_1 responses are observed among the Stage 1 subjects, n_2 additional evaluable subjects will be treated in Stage 2 to estimate the response rate. At the end of Stage 2, if $\leq r$ subjects have responded among the n evaluable subjects, the triplet combination dosing sequence will be declared nonpromising for that cohort. In other words, after the study is finished, if there is a sufficient number of responses in the 2 stages combined, the triplet combination dosing sequence is considered promising; otherwise it is considered nonpromising. The detailed calculations for each tumor-specific cohort are based on a 1-sided Type I error of 0.05 and power of 85%. The individual p_0 and p_1 values for the tumor types are listed in Table 21.

A second approach to determining whether the treatment is active across the cohorts will use an integrated Bayesian futility analysis of tumor and dosing strategies specific to Treatment Groups C and D (see Section 9.6.2).

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

[redacted]

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

Indication	Combination	r_1	n_1	r	n_2	n	p_0	p_1
Melanoma (CRR)	GITR + Pembro + Epacadostat	6	21	18	31	52	26%	45%
RCC (ORR)	GITR + Pembro + Epacadostat	8	19	25	31	50	40%	60%
UC (ORR)	GITR + Pembro + Epacadostat	3	10	14	24	34	30%	55%

9.3. Level of Significance

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

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

In Phase 2, ORR, defined as the percentage of subjects having CR or PR per RECIST v1.1 will be summarized by tumor type. For CPI-naive melanoma subjects, CRR, defined as the percentage of subjects who have a CR per RECIST v1.1, will be summarized.

9.4.1.2. Secondary Efficacy Analyses

Disease control rate, defined as the percentage of subjects having CR, PR, or SD, as per RECIST v1.1 and mRECIST.

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

In Phase 2, ORR, defined as the percentage of subjects having CR or PR per RECIST v1.1 and mRECIST will be summarized by tumor type.

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

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

The subset of AEs considered by the investigator to have a relationship to study treatment will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study treatment, the AE will be considered treatment-related. The incidences 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, body temperature, and pulse oximetry) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 22), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 22: Criteria for Clinically Notable Vital Sign Abnormalities

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

9.4.2.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (see Table 23). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 23: Criteria for Clinically Notable Electrocardiogram Abnormalities

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

QTcF = Fridericia correction.

[redacted]

[redacted]

9.5. Analyses for the Data Monitoring Committee

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

9.6. Interim Analysis

9.6.1. Simon 2-Stage Design

In Phase 2, the Simon 2-stage design will be applied for each tumor within a given treatment group (Simon 1989). During Stage 1, n_1 evaluable subjects treated at the recommended dose and schedule will be enrolled, and if r_1 or fewer responses are observed, then the cohort will be discontinued. As discussed in Section 9.2.3, the Simon 2-stage designs run for each tumor type within each treatment group will have design parameters that are determined by historical response rates and will have different sample sizes and different futility rules, depending on the historical response rate.

As an example, the probability of early termination for Stage 1 in the NSCLC tumor cohort for the triplet combination of INCAGN01876, pembrolizumab, and epacadostat is summarized in Table 24. If at least 4 responses are observed in the first evaluable 15 subjects, then 32 additional evaluable subjects would be enrolled in this cohort in Stage 2.

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

True Response Rate	Probability of Early Termination at Stage 1
15%	82.3%
20%	64.8%
25%	46.1%
30%	29.7%
35%	17.3%

9.6.2. Integrated Bayesian Futility Analysis

Treatment Groups C (concurrent dose administration) and D (run-in with INCAGN01876 × 1 dose followed by concurrent dose administration with immune therapies) represent different dosing strategies of the triplet combination of INCAGN01876, pembrolizumab, and epacadostat.

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

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

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

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

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

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

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drugs

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 drugs to the study site.
- Inventory of study drugs at the site.
- Lot numbers and/or vial numbers (as applicable) of study drug used to prepare the infusion solution.
- Subject use of the study drugs including pill or unit counts from each supply dispensed.
- Return of study drugs 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 drugs. 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 drugs until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drugs back to the sponsor or its designee for destruction according to institutional 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 drugs is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

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

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

Protocol deviations will be identified and recorded in the Protocol Deviation form of the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data privacy laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, Health Insurance Portability and Accountability Act of 1996). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in

accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. Financial Disclosure

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

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

10.6. Publication Policy

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

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

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method of avoiding pregnancy, provided that partner is the sole sexual partner of the female of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: CTFG 2014.

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

Immune-Related Adverse Event (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. • Re-imaging 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 to refer to the infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungal, or anti-pneumocystis pneumonia (PCP) treatment (refer to current National Comprehensive Cancer Network [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 to 5 days, additional work-up should be considered, and prompt treatment with additional immunosuppressive therapy (eg, infliximab) should be started 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]).

Immune-Related Adverse Event (irAE)	**Supportive Care**
Diarrhea/Colitis	***Note:*** Subjects should be carefully monitored for signs and symptoms of enterocolitis (eg, diarrhea, abdominal pain, and blood or mucus in stool, with or without fever) and of bowel perforation (eg, 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 should be started. • If still no improvement within 3 to 5 days, consider starting immunosuppressive therapy (eg, infliximab) after discussing with the medical monitor. ***Caution:*** Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Consult medical monitor if no resolution to ≤ Grade 1 in 3 to 4 days. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]). **For Grade 3 or 4 (severe or new symptoms, new/worsening diarrhea, life threatening):** • Treatment with systemic corticosteroids should be initiated per institutional standard of care. • Manage symptoms and consider GI consult for further work-up as appropriate. • If still no improvement within 3 to 5 days, consider starting immunosuppressive therapy (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]).

Immune-Related Adverse Event (irAE)	**Supportive Care**
Hepatitis	**For Grade 2 (mild to moderate new symptoms):** • Observe subject with regular and frequent checking of liver chemistries until improving or resolved. • Rule out non-irAE etiologies. • If event is persistent (> 3-5 days) or worsens, consider starting systemic steroids per institutional standard of care. • If still no improvement within 3 to 5 days, consider additional work-up and prompt treatment with IV methylprednisolone. • If still no improvement within 3 to 5 days, consider starting immunosuppressive therapy (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]).

Immune-Related Adverse Event (irAE)	**Supportive Care**
Dermatitis	***Note:*** Monitor subjects for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. If there is any bullous formation, the medical monitor should be contacted, and study treatment should be discontinued. **For Grade 2 (mild to moderate new symptoms):** • Consider dermatology consult. • Consider symptomatic treatment per institutional standard of care. • Consider moderate-strength topical steroid. • If no improvement of rash/skin lesions occurs within 3 to 5 days, or rash/skin lesions are 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.

Immune-Related Adverse Event (irAE)	**Supportive Care**
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 (eg, 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 to 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]).

Immune-Related Adverse Event (irAE)	**Supportive Care**
Endocrinopathies	***Note:*** Subjects should be monitored for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyperthyroidism or hypothyroidism. Subjects may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or 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, steroid taper should be started and continued over ≥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 (eg, labs or magnetic resonance imaging [MRI]), repeat labs or 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 corticosteroids followed by oral corticosteroids. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy. Once improving, gradually taper immunosuppressive steroids over ≥ 4 weeks. • In hypophysitis, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to ≤ Grade 1, steroid taper should be started and continued over ≥ 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.

Immune-Related Adverse Event (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 to 5 days, consider additional work-up and treating with additional immunosuppressive therapy (eg, IV immunoglobulin G [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 to 5 days despite IV corticosteroids, consider additional workup and treating with additional immunosuppressive therapy (eg, IV IgG) after discussing with the medical monitor. • Once stable, gradually taper steroids over ≥ 4 weeks.

APPENDIX C. PROHIBITED MONOAMINE OXIDASE INHIBITORS AND DRUGS ASSOCIATED WITH SIGNIFICANT MONOAMINE OXIDASE INHIBITORY ACTIVITY

Monoamine Oxidase Inhibitors	Drugs Associated With Significant Monoamine Oxidase Inhibitory Activity
Hydrazines (eg, phenelzine)	Meperidine
Caroxazone	Linezolid
Echinopsidine	Methylene blue
Furazolidone	
Tranylcypromine	
Brofaromine	
Metralindole	
Minaprine	
Moclobemide	
Pirlindole	
Toloxatone	
Lazabemide	
Pargyline	
Rasagiline	
Selegiline	