Clinical Study Protocol

INCB 01158-202

An Open-Label, Multicenter, Nonrandomized, Dose-Escalation, and Tumor-Expansion Phase 1/2 Study to Evaluate the Safety, Tolerability, and Antitumor Activity of INCB001158 Plus Epacadostat (INCB024360), With or Without Pembrolizumab, in Subjects With Advanced Solid Tumors

Product:	**INCB001158**
IND Number:	**136,524**
EudraCT Number:	**2017-002716-13**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**02 OCT 2017**
Date of Amendment (Version) 1:	**27 OCT 2017**
Date of Amendment (Version) 2:	**01 JUN 2018**

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

INVESTIGATOR'S AGREEMENT

I have read the INCB 01158-202 Protocol Amendment 2 (Version 2 dated 01 JUN 2018) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

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(Printed Name of Investigator)

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(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB001158 (formerly known as CB-1158)

Title of Study: An Open-Label, Multicenter, Nonrandomized, Dose-Escalation and Tumor-Expansion Phase 1/2 Study to Evaluate the Safety, Tolerability, and Anti-Tumor Activity of INCB001158 plus Epacadostat (INCB024360), with or without Pembrolizumab, in Subjects With Advanced or Metastatic Solid Tumors

Protocol Number: INCB 01158-202 **Study Phase:** 1/2

Indication: Any advanced or metastatic solid tumors in Phase 1 Dose Escalation and selected, advanced or metastatic solid tumors in Phase 2 Parts A and B Tumor Expansion cohorts.

As of this Protocol Amendment (Version) 2, enrollment of subjects into any part of Study INCB 01158-202 is halted. This is based on the results from the ECHO-301/KEYNOTE-252 melanoma clinical study. In an interim analysis, the study did not meet the prespecified endpoint of improvement in progression-free survival (PFS) for the combination of pembrolizumab and epacadostat compared with pembrolizumab and placebo. The overall survival endpoint was also not expected to reach statistical significance. There were no safety concerns with the treatment (pembrolizumab + epacadostat) arm compared with the control (pembrolizumab + placebo) arm.

Given the outcome of study ECHO-301/KEYNOTE-252, the changes to the INCB 01158-202 study design are summarized below:

- **The ongoing Phase 1 portion (dose escalation and safety evaluation of INCB001158 in combination with epacadostat and pembrolizumab) will stop further enrollment, except for subjects who have consented and are in screening as of 08 MAY 2018. These subjects will be permitted to enroll if eligibility is determined as outlined per the Protocol.**
- **The Phase 1 backfill cohorts and the Phase 2 portion of the study (Part A – tumor expansion of INCB001158 + epacadostat + pembrolizumab and Part B – tumor expansion of INCB001158 + epacadostat) will not be opened.**
- **Phase 1 subjects may continue treatment with INCB001158 + epacadostat + pembrolizumab as long as, per the Protocol, they are deriving clinical benefit, tolerating the treatment, and do not meet any withdrawal criteria.**

Sections of the Protocol relating to the parts of the study that will no longer be conducted are now not applicable and should be ignored.

Objectives and Endpoints:

Primary Objectives	Primary Endpoints
Phase 1 only: To assess the safety and tolerability, and to determine the recommended Phase 2 dose (RP2D) of INCB001158 in combination with epacadostat ± pembrolizumab.	Safety, tolerability, dose-limiting toxicities (DLTs), and RP2D of INCB001158 in combination with epacadostat ± pembrolizumab, as assessed by adverse events (AEs), clinical laboratory assessments, physical examination results, and 12-lead electrocardiogram (ECG) results.
Phase 2 only: To evaluate the objective response rate (ORR) of INCB001158 in combination with epacadostat ± pembrolizumab.	ORR, defined as the percentage of subjects having a complete response (CR) or partial response (PR), as determined by investigator assessment of radiographic disease as per RECIST v1.1.

Secondary Objectives	Secondary Endpoints
Phase 2 only: To assess the safety, tolerability, and RP2D of INCB001158 in combination with epacadostat ± pembrolizumab.	Safety, tolerability, and RP2D of INCB001158 in combination with epacadostat ± pembrolizumab, as assessed by AEs, clinical laboratory assessments, physical examination results, and 12-lead ECG results.
To evaluate the antitumor effect of INCB001158 in combination with epacadostat ± pembrolizumab by RECIST v1.1.	• ORR, defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 (Phase 1 only). • Disease control rate (DCR), defined as the percentage of subjects having CR, PR, or stable disease (SD) for at least 56 days, as determined by investigator assessment of radiographic disease as per RECIST v1.1. • Duration of response (DoR), determined by radiographic disease assessment, defined as the time from earliest date of disease response until the earliest date of disease progression per RECIST v1.1, or death due to any cause, if occurring sooner than progression. • PFS, defined as the time from date of first dose of study treatment until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1, or death due to any cause, if occurring sooner than progression.
To determine the pharmacokinetics (PK) of each of INCB001158 and epacadostat in subjects treated with INCB001158 in combination with epacadostat ± pembrolizumab.	The PK of INCB001158 and epacadostat will be assessed by summarizing C_{min}, C_{max}, t_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\tau}$.
[redacted]	

[redacted]

Overall Study Design: This is a Phase 1/2 study, with Phase 1 being a dose-escalation of the triplet combination of INCB001158 plus epacadostat and pembrolizumab, and with Phase 2 consisting of tumor expansion cohorts to study the RP2D of the triplet combination of INCB001158 plus epacadostat and pembrolizumab in Part A and the RP2D of the doublet combination of INCB001158 plus epacadostat in Part B. The figure below shows a schematic of the study design.

Subjects with advanced or metastatic solid tumors will be enrolled in Phase 1. Subjects with select advanced or metastatic solid tumors will be enrolled in Phase 2 Parts A (non–small cell lung cancer [NSCLC], melanoma, urothelial carcinoma, squamous cell carcinoma of the head and neck [SCCHN], and small cell lung cancer [SCLC]) and B (urothelial carcinoma, SCCHN, and colorectal cancer [CRC]).

Phase 1: Dose Escalation:

In this study, the RP2D of both the triplet (INCB001158 + epacadostat + pembrolizumab) and doublet (INCB001158 + epacadostat) will be determined from the dose escalation of the triplet combination in Phase 1. The INCB001158 dose will be escalated while keeping the epacadostat (100 mg twice daily [BID]) and pembrolizumab (200 mg once every 3 weeks [Q3W]) doses fixed at the levels used to study this doublet in Phase 3. INCB001158 is not expected to have overlapping toxicity with either of these molecules, based on their respective mechanisms and on the available safety data from the first-in-human study, INCB 01158-101 and the epacadostat + pembrolizumab INCB 24360-202 Phase 2 study. In the ongoing INCB 01158-101 study, INCB001158 doses have been identified that are pharmacologically active and well-tolerated. Thus, it is hypothesized that when INCB001158 is escalated with the Phase 3 doses of epacadostat plus pembrolizumab, an RP2D will be identified based on an INCB001158 pharmacologically active dose (PAD) and before a maximum tolerated dose (MTD) is reached. In that case, the INCB001158 and epacadostat doses in the triplet RP2D would be

appropriate to also use as the RP2D for the INCB001158 + epacadostat doublet in Phase 2 Part B. Hence, no separate dose escalation of INCB001158 with epacadostat 100 mg BID will be conducted in this study.

An open-label, Bayesian Optimal Interval (BOIN) design will be used to determine the RP2D of the triplet combination of INCB001158, epacadostat, and pembrolizumab in 21-day treatment cycles in subjects with advanced or metastatic solid tumors. Given the target DLT rate of 33% for the INCB001158 plus epacadostat and pembrolizumab combination, the dose escalation and de-escalation rules are shown in the table below. The BOIN design also includes an elimination rule. When ≥ 3 subjects have been treated, if the probability that the estimated toxicity rate that is above the target DLT rate is > 95% at a certain dose level, then this dose level and higher dose levels are assumed too toxic and will be eliminated. If the lowest dose level is eliminated, the whole dose escalation will be terminated. The table below (in the bottom row) provides the elimination rules. Based on this algorithm, a minimum of 3 evaluable subjects and a maximum of 9 evaluable subjects will be enrolled at each tested dose level. The dose escalation will continue, based on the rules in the table, until the rules require at least 1 of the following:

- Enrollment of additional subjects in a cohort that already has 9 evaluable subjects, or
- Dose escalation to a dose level that has already been eliminated, or
- Dose escalation above the maximum allowable dose level identified in the INCB 01158-101 study.

At that point, the dose escalation will be stopped.

Dose Escalation, De-Escalation, and Elimination Boundaries for Target DLT Rate = 33% in Phase 1

	The Number of Subjects Treated at the Current Dose								
Action	1	2	3	4	5	6	7	8	9[a]
Escalate if # of DLTs ≤	NA	NA	0	1	1	1	1	2	2
De-escalate if # of DLTs ≥	1	1	2	2	2	3	3	4	4
Elimination if # of DLTs ≥	NA	NA	3	3	4	4	5	5	6

DLT = dose-limiting toxicity; NA = not applicable.

[a] If 9 evaluable subjects are enrolled in a cohort and 3 of those subjects experience a DLT, the medical monitor and the investigators will review the entirety of the data and decide whether to dose-escalate, dose de-escalate, or to stop at that dose level.

Dose escalation will begin with starting doses of INCB001158 at least 2 dose levels below the maximum tolerated and tested dose from the INCB 01158-101 study (likely to be 50 mg BID or 75 mg BID – see tables below) and epacadostat 100 mg orally (PO) BID continuous dose administration, and pembrolizumab 200 mg IV Q3W. Epacadostat 100 mg BID was selected as the starting dose because it has been shown to be active and tolerable in several epacadostat combination clinical studies, including with pembrolizumab. The starting dose of pembrolizumab is the standard, approved dose and schedule and also the dose used in combination with epacadostat in Phase 3.

If the starting doses of the triplet combination of INCB001158, epacadostat, and pembrolizumab are tolerable (eg, none of the first 3 evaluable subjects experiences a DLT), the INCB001158 dose will be escalated in subsequent cohorts, while keeping the epacadostat and pembrolizumab doses constant, until one of the stopping rules, described above, is met.

If the starting doses of INCB001158, epacadostat 100 mg BID, and pembrolizumab 200 mg Q3W are not tolerable, then an additional cohort will be enrolled at a reduced dose of either INCB001158 or epacadostat, depending on which one is deemed most likely to have caused the intolerability, upon agreement between the medical monitor and the study investigators (ie, Dose Level -1A or -1B).

Dose Levels for Phase 1: INCB001158 + Epacadostat + Pembrolizumab, Based on INCB001158 Starting Dose of 50 mg BID

Dose Level	INCB001158	Epacadostat	Pembrolizumab
-1B[a]	50 mg PO BID	50 mg PO BID	200 mg IV Q3W
-1A[b]	25 mg PO BID	100 mg PO BID	200 mg IV Q3W
1	**50 mg PO BID**	**100 mg PO BID**	**200 mg IV Q3W**
2	75 mg PO BID	100 mg PO BID	200 mg IV Q3W
3	100 mg PO BID	100 mg PO BID	200 mg IV Q3W
4	150 mg PO BID	100 mg PO BID	200 mg IV Q3W

[a] -1 dose level to be used if unacceptable toxicity is observed at Dose Level 1 and is deemed to be due to epacadostat
[b] -1 dose level to be used if unacceptable toxicity is observed at Dose Level 1 and is deemed to be due to INCB001158.

Dose Levels for Phase 1: INCB001158 + Epacadostat + Pembrolizumab, Based on INCB001158 Starting Dose of 75 mg BID

Dose Level	INCB001158	Epacadostat	Pembrolizumab
-1B[a]	75 mg PO BID	50 mg PO BID	200 mg IV Q3W
-1A[b]	50 mg PO BID	100 mg PO BID	200 mg IV Q3W
1	**75 mg PO BID**	**100 mg PO BID**	**200 mg IV Q3W**
2	100 mg PO BID	100 mg PO BID	200 mg IV Q3W
3	150 mg PO BID	100 mg PO BID	200 mg IV Q3W

[a] -1 dose level to be used if unacceptable toxicity is observed at Dose Level 1 and is deemed to be due to epacadostat
[b] -1 dose level to be used if unacceptable toxicity is observed at Dose Level 1 and is deemed to be due to INCB001158.

A PAD will be defined as a dose at or below the monotherapy MTD at which at least half of the subjects (and at least 2 subjects in total) enrolled at a particular dose level achieve a trough (C_{min}) plasma concentration of INCB001158 at steady state of ≥1 µM, which is equivalent to the IC_{90} for arginase 1. This definition may be modified based on emerging data from the INCB 01158-101 first-in-human study, upon agreement between the medical monitor and the study investigators. The MTD, if reached, is the maximum tested dose of INCB001158, such that no more than 33% of the subjects receiving the triplet combination experience a DLT during the first 6 weeks on study drug.

After completing the dose escalation per the BOIN rules, one of the INCB001158 dose levels that is pharmacologically active (ie, a PAD) and tolerable in combination with epacadostat 100 mg BID or lower and pembrolizumab 200 mg Q3W (ie, MTD or lower) will be selected, and that triplet combination will be the RP2D. The doublet RP2D would consist of the same doses of INCB001158 and epacadostat.

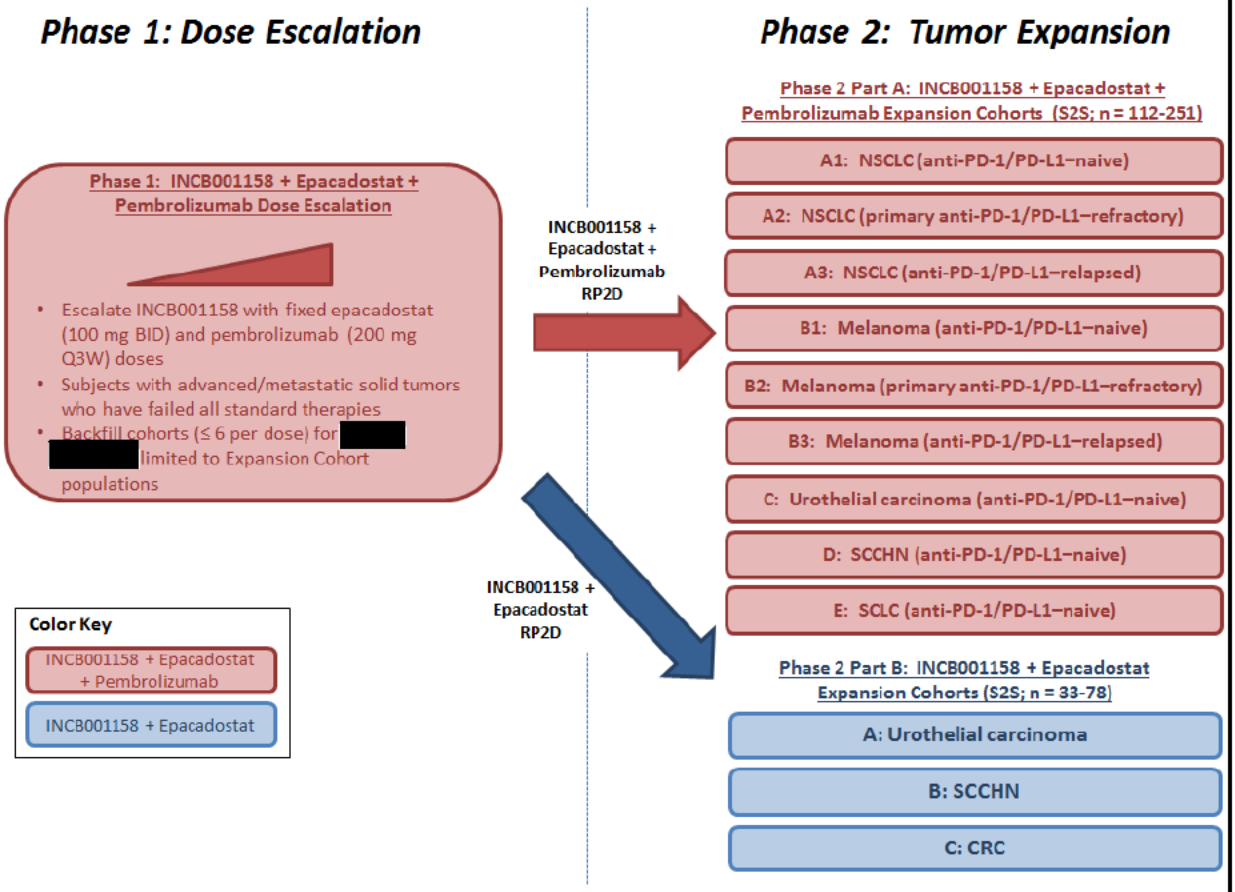
Note that if a dose level to be assigned as RP2D has fewer than 9 evaluable subjects in it, then the medical monitor and study investigators can consider adding subjects to a total of 9 before making the final RP2D decision.

At the discretion of the sponsor, up to a total of 6 additional "backfill" subjects may be enrolled at any tolerable dose level to further investigate safety [redacted].

Phase 2 – Tumor Expansion: In the tumor expansion parts (A and B), each tumor cohort will be assessed for the safety and tolerability of the RP2D of the respective combinations, as well as ORR using a Simon 2-stage design, to determine if the combinations have sufficient antitumor activity to warrant further testing in subsequent clinical studies. See Study Design figure for details of Phase 2 cohorts.

[redacted]

Study Design



Study Population: In Phase 1 (INCB001158 + epacadostat + pembrolizumab Dose Escalation), subjects with advanced or metastatic solid tumors who have failed all standard therapies, or who are intolerant to treatment will be enrolled. In Phase 2 Part A (INCB001158 + epacadostat + pembrolizumab Tumor Expansion), subjects with advanced or metastatic solid tumors that are either anti-programmed death-1 (PD-1)–receptor-naive (NSCLC, melanoma, urothelial carcinoma, SCCHN, and SCLC) or have received prior anti–PD-1 therapy (NSCLC and melanoma) will be enrolled. In Phase 2 Part B (INCB001158 + epacadostat Tumor Expansion), subjects with advanced or metastatic urothelial carcinoma who have progressed on prior standard therapy with a platinum-based regimen and a checkpoint inhibitor, subjects with advanced or metastatic CRC who have failed all standard therapies or who are intolerant to treatment, and subjects with metastatic or recurrent SCCHN not amenable to local therapy with curative intent who have had disease progression on prior treatment with a platinum-based therapy and an anti–PD-1 therapy will be enrolled.

Key Inclusion Criteria:

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

- Men and women, aged 18 or older.
- For Phase 1: Subjects with histologically or cytologically confirmed advanced or metastatic solid tumors that have failed prior standard therapy (disease progression; subject intolerance is also allowable). Note: There is no limit to the number of prior treatment regimens.

- For Phase 2 Part A Cohort A1 – Anti-PD-1/PD-L1–naive NSCLC:
  - Subjects with histologically or cytologically confirmed NSCLC, who have received no more than 2 prior systemic chemotherapy regimens for Stage IV disease (not including neoadjuvant and/or adjuvant therapy except as described below).
  - For subjects who have received 1 or 2 lines of prior systemic chemotherapy for Stage IV disease, 1 of the prior systemic regimens must include a platinum-based therapy. Subjects who have only received non–platinum-based regimens may be enrolled with medical monitor approval.
  - Tumors with driver mutations (epidermal growth factor receptor [EGFR] mutation–positive, anaplastic lymphoma kinase fusion oncogene–positive, proto-oncogene tyrosine-protein kinase ROS1–positive, or BRAF V600 mutant–positive) treated with a tyrosine kinase inhibitor are permitted and will not be considered a systemic chemotherapy regimen. However, subjects should have progressed on or be intolerant to the targeted therapy.
  - Maintenance or switch maintenance therapy after first- or second-line chemotherapy will be considered part of the prior systemic chemotherapy regimen and is acceptable.
  - Subjects who completed and progressed on a platinum-containing regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy within the 6 months before screening would be counted as 1 prior platinum-containing regimen and therefore would not require re-treatment with a platinum-containing regimen for Stage IV disease.
- For Phase 2 Part A Cohort A2 – Primary anti-PD-1/PD-L1–refractory NSCLC (primary refractory cohort):
  - Subjects with histologically or cytologically confirmed locally advanced unresectable or metastatic NSCLC.
  - Subjects with tumors with driver mutations (EGFR mutation–positive, anaplastic lymphoma kinase fusion oncogene–positive, proto-oncogene tyrosine-protein kinase ROS–positive, or BRAF V600 mutant–positive) should have progressed on or be intolerant to the targeted therapy.
  - Subjects must have received prior treatment with anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and have PD as their best response to treatment that is confirmed at least 4 weeks later (no less than 28 days).
    - Subjects must have received at least 2 doses of a prior anti–PD-1 or anti–PD-L1 agent.
  - Progressive disease must also be at least 12 weeks from first dose of anti–PD-1 or anti–PD-L1 therapy and confirmed 4 weeks (no less than 28 days) later.
- For Phase 2 Part A Cohort A3 – Anti-PD-1/PD-L1–relapsed NSCLC (relapsed cohort):
  - Subjects must have received prior anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and achieved either SD for at least 24 weeks or PR/CR, but later have confirmed PD (PD confirmed at least 4 weeks [no less than 28 days] later).
- For Phase 2 Part A Cohort B1 – Anti-PD-1/PD-L1–naive melanoma:
  - Subjects with histologically or cytologically confirmed unresectable Stage III or Stage IV melanoma, as per American Joint Committee on Cancer (AJCC) staging system, not amenable to local therapy.
  - Have documentation of V600-activating BRAF mutation status or consent to BRAF V600 mutation testing during the screening period.
  - Subjects must not have received more than 2 prior lines of systemic therapy for unresectable Stage III or Stage IV melanoma.
  - Ocular melanoma is excluded.
- For Phase 2 Part A Cohort B2 – Primary anti-PD-1/PD-L1–refractory melanoma (primary refractory cohort):
  - Subjects with histologically or cytologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging system, not amenable to local therapy.
  - Have documentation of V600-activating BRAF mutation status or consent to BRAF V600 mutation testing during the screening period.

- Subjects must have received prior treatment with anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and have PD as their best response to treatment that is confirmed at least 4 weeks later (no less than 28 days).
  - Subjects must have received at least 2 doses of a prior anti–PD-1 or anti–PD-L1 agent.
  - Progressive disease must also be at least 12 weeks from first dose of anti–PD-1 or anti–PD-L1 therapy and confirmed 4 weeks (no less than 28 days) later.
- Ocular melanoma is excluded.

- For Phase 2 Part A Cohort B3 – Anti-PD-1/PD-L1–relapsed melanoma (relapsed cohort):
  - Subjects must have received prior anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and achieved either SD for at least 24 weeks or PR/CR, but later have confirmed PD (PD confirmed at least 4 weeks [no less than 28 days] later).
- For Phase 2 Part A Cohort C – Anti-PD-1/PD-L1–naive urothelial carcinoma:
  - Subjects with histologically or cytologically confirmed, metastatic or inoperable locally advanced urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra that is transitional cell or mixed transitional/nontransitional (predominantly transitional) cell type.
  - Subjects must not have received more than 2 prior lines of systemic therapy for metastatic or inoperable locally advanced urothelial carcinoma.
  - For subjects who have received 1 or 2 lines of prior systemic therapy for metastatic or inoperable locally advanced urothelial carcinoma, 1 of the prior systemic regimens must include a platinum-based therapy. Subjects who have only received non–platinum-based regimens may be enrolled with medical monitor approval.
- For Phase 2 Part A Cohort D – Anti-PD-1/PD-L1–naive SCCHN:
  - Subjects with histologically or cytologically confirmed SCCHN not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy).
    - Carcinoma of the nasopharynx, salivary gland, or nonsquamous histologies are excluded.
  - Subjects must have received at least 1 prior platinum-based systemic chemotherapy regimen, and no more than 2 prior systemic chemotherapy regimens, including neoadjuvant and/or adjuvant therapy. Subjects who relapsed within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll.
- For Phase 2 Part A Cohort E – Anti-PD-1/PD-L1–naive SCLC:
  - Subjects with histologically or cytologically confirmed, advanced or metastatic SCLC with PD after at least 1 line of therapy that includes a platinum-based regimen in the first-line setting, and after no more than 2 prior lines of chemotherapy, and regardless of tumor PD-L1 status.
- For Phase 2 Part B Cohort A – Urothelial carcinoma:
  - Subjects with histologically or cytologically confirmed urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra that is transitional cell or mixed transitional/nontransitional (predominantly transitional) cell type.
  - Metastatic or inoperable locally advanced urothelial carcinoma that has progressed on prior standard therapy with a platinum-based regimen and a checkpoint inhibitor.
- For Phase 2 Part B Cohort B – SCCHN:
  - Subjects with histologically confirmed metastatic or recurrent SCCHN not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy).
  - Must have had disease progression on prior treatment with a platinum-based therapy and an anti–PD-1 therapy. Subjects who relapsed within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll.
  - Must have documented human papilloma virus status.
  - Carcinoma of the nasopharynx, salivary gland, or nonsquamous histologies are excluded.

- For Phase 2 Part B Cohort C – CRC:
  - Subjects with histologically or cytologically confirmed CRC that have failed prior standard therapy (disease progression; subject intolerance is also allowable).
  - Prior systemic regimens must include previously approved therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy (if no contraindication); and if negative for KRAS, NRAS, and BRAF mutations and no contraindication, an anti-EGFR therapy; and disease must have progressed after the last administration of approved therapy.
- Have the presence of at least 1 measurable lesion by computed tomography or magnetic resonance imaging per RECIST v1.1 as determined by the local site investigator/radiology assessment.
- [redacted]
- [redacted]
- ECOG performance status 0 to 1.
- Have resolution of all toxicities and any toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia). Subjects with ≤ Grade 2 neuropathy are an exception and may enroll.
- Adequate renal, hepatic, and hematologic functions as defined by laboratory parameters within ≤ 7 days before treatment initiation.
  - Absolute neutrophil count ≥ 1.5×10^9/L.
  - Platelets ≥ 100×10^9/L.
  - Hemoglobin ≥ 9 g/dL.
  - Measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine clearance) ≥ 50 mL/min.
  - Total bilirubin ≤ 1.5 × upper limit of normal (ULN) OR direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 × ULN.
  - Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) and alanine aminotransferase (serum glutamic-pyruvic transaminase) ≤ 2.5 × ULN.
  - International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 × ULN, unless subject is receiving anticoagulant therapy, in which case PT or INR must be within therapeutic range of intended use of anticoagulants.
  - Activated partial thromboplastin time ≤ 1.5 × ULN, unless subject is receiving anticoagulant therapy, in which case PTT must be within therapeutic range of intended use of anticoagulants.

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

- Participation in any other study in which receipt of an investigational study drug or device occurred within 2 weeks or 5 half-lives (whichever is longer) before first dose. For investigational agents with long half-lives (eg, 5 days), enrollment before the fifth half-life requires medical monitor approval.
- Has received a prior monoclonal antibody within 4 weeks or 5 half-lives (whichever is shorter) before administration of study drug.
  - EXCEPTION: No time off anti–PD-1 or anti–PD-L1 therapy is required.
  - EXCEPTION: Denosumab may be used.
- Phase 2 Part A Cohorts A1, B1, C, D, and E only: Has had prior therapy with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti–CTLA-4, anti-CD137, or any other antibody or drug specifically targeting checkpoint pathways.
  - EXCEPTION: Prior therapy with an anti–cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in the adjuvant setting is permitted.
- Phase 2 Part A Cohorts A2, A3, B2, and B3 only: Had any Grade 3/4 or any ocular toxicity while receiving prior anti–PD-1 therapy.
- Has had prior chemotherapy or targeted small molecule therapy within 2 weeks before administration of study treatment.
- Has had prior therapy with an IDO1 or arginase 1 inhibitor.
- Has received prior radiotherapy within 2 weeks of enrollment (except for radiation to central nervous system [CNS], which requires ≥ 4-week washout). Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
- Has had major surgery within 4 weeks before enrollment (C1D1).
- Has a known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 2 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the subject has been disease-free for > 1 year, after treatment with curative intent.
- Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dose regimens exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment.
- Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is not required unless mandated by the local health authority.
- Has known history of or is positive for hepatitis B (hepatitis B virus surface antigen [HBsAg] reactive) or hepatitis C (HCV RNA). Note: Testing must be performed to determine eligibility.
  - Hepatitis B virus DNA must be undetectable and HBsAg negative at screening visit.
  - Hepatitis C antibody testing is allowed for screening purposes in countries where HCV RNA is not part of standard of care. In these cases, HCV antibody positive patients will be excluded.
  - Subjects who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening visit.
- Phase 1 and Phase 2 Part A only: Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
- Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment, and any

neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases confirmed by repeat imaging (note that the repeat imaging should be performed during study screening), and have not required steroids for at least 14 days before study treatment.

- Subjects with evidence of cerebral edema will be excluded from participation. In addition, subjects will be excluded from participation in the study if it has been < 4 weeks since radiation therapy was delivered to the CNS.
- Has had a significant cardiac event within 6 months before Cycle 1 Day 1, including myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, or pulmonary embolism. Medically controlled arrhythmia is permitted.
- Has a history or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded (corrected by Fridericia or Bazett formula). In the event that a single QTc is > 480 milliseconds, the screening ECG may be repeated in triplicate, and the subject may enroll if the average QTc is < 480 milliseconds.
- Has received live vaccine within 30 days before the first dose of study treatment. 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 vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Has any history of serotonin syndrome after receiving serotonergic drugs.
- Concomitant therapy with valproic acid/valproate-containing therapies.
- Concomitant therapy with allopurinol and other xanthine oxidase inhibitors.
- Has received therapy with a monoamine oxidase inhibitor or UGT1A9 inhibitor within 21 days before starting treatment, or anticipates requiring one of these prohibited medications during the treatment phase.
- Has a known or suspected defect in the function of the urea cycle, including a known deficiency of carbamoyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase, N-acetyl glutamate synthetase, or arginase.
- Has a history of gastrointestinal condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) that may affect drug absorption.

INCB001158, Epacadostat, and Pembrolizumab Dosage, and Mode of Administration:

Drug	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period
INCB001158	25-150 mg	BID	Oral	Phase 1 and Phase 2 Part A: Daily until meets discontinuation criteria or for 35 cycles[a], whichever is sooner Phase 2 Part B: Daily until meets discontinuation criteria
Epacadostat	50-100 mg	BID	Oral	Phase 1 and Phase 2 Part A: Daily until meets discontinuation criteria or for 35 cycles[a], whichever is sooner Phase 2 Part B: Daily until meets discontinuation criteria
Pembrolizumab	200 mg	Every 3 weeks	IV infusion	Phase 1 and Phase 2 Part A: Day 1 of each cycle until meets discontinuation criteria or for up to 35 cycles[a], whichever is sooner

[a] A cycle length of 21 days.

The first on study imaging assessment should be performed at 9 weeks from the date of enrollment. Imaging then continues every 9 weeks.

Imaging should continue to be performed until PD is identified by the investigator, the start of new anticancer treatment, withdrawal of consent for imaging, or death, whichever occurs first. If the investigator elects to continue treatment [redacted] after initial radiographic PD, imaging should continue.

Partial response (PR) and CR should be confirmed by a repeat imaging assessment. The imaging for confirmation of response may be performed no earlier than 4 weeks after the first indication of a response or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated.

[redacted], disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site [redacted] Subjects who have confirmed disease progression [redacted] will discontinue the treatment, unless treatment beyond confirmed progression is approved by the medical monitor.

Study Schedule/Procedures:

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

Screening: Up to 21 days before enrollment. Screening will begin at the time that the subject signs the informed consent and will continue until the date that the subject is enrolled in the study (Cycle 1 Day 1).

Cycle 1: Day 1 and Days 8 and 15 (± 3 days).

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

Efficacy assessments: Every 9 weeks (± 7 days) starting on Cycle 4 Day 1.

End of treatment: Up to 5 days after withdrawal from study treatment.

Safety follow-up: 30 to 37 days after last dose of INCB001158 and epacadostat (all subjects); 90 to 97 days after last dose of INCB001158 and epacadostat (Phase 1 and Phase 2 Part A only).

[redacted]

Estimated Duration of Participation: In the triplet combination (INCB001158 + epacadostat + pembrolizumab) Phase 1 and Phase 2 Part A, subjects may continue on treatment for as long as they are receiving benefit and do not meet withdrawal criteria, for up to 35 cycles (approximately 2 years). In the doublet combination (INCB001158 + epacadostat) Phase 2 Part B, subjects may continue on treatment for as long as they are receiving benefit and do not meet withdrawal criteria.

Estimated Number of Subjects: With Protocol Amendment 2, up to 5 subjects will be enrolled in the dose-escalation (Phase 1), and no subjects will be enrolled in Phase 2.

Principal Coordinating Investigator: TBD

Statistical Methods:

Given that enrollment was terminated (Amendment 2) during the Phase 1 portion of the study, all efficacy analyses will now be only exploratory, and some planned tables and figures may be replaced with listings.

Sample Size Method: In Phase 1, a BOIN design will be used to determine the RP2D of the triplet combination of INCB001158, epacadostat, and pembrolizumab in 21-day treatment cycles in subjects

with advanced or metastatic solid tumors. The RP2D will then be further assessed in triplet tumor expansion cohorts in Phase 2 Part A. The equivalent INCB001158 + epacadostat doublet RP2D will be further assessed in doublet tumor expansion cohorts in Phase 2 Part B.

Each Simon 2-stage design will have a stopping rule to allow early termination of a particular tumor type within a treatment group at the end of Stage 1 if there is insufficient response observed, while enrolling enough subjects to predict possible target responses worthy of cohort expansion and potential further evaluation in future studies.

The proposed designs for each tumor type will be used for any planned Simon 2-stage design. Each Simon 2-stage design is set up to have a 1-sided Type I error of 0.1 and power of 80%. The response rates for each tumor type will be estimated with 95% confidence intervals.

Phase 2 Part A: Simon 2-Stage Design

Cohort	Background ORR	Target ORR	Alpha	Power	N for Stage 1	ORR to Proceed ≥ (r1 + 1) / n1[a]	N for Stage 2	ORR for Positive Cohort ≥ (r + 1) / n[a]
A1	30%	50%	0.1	80%	15	6/15	17	13/32
A2	2%	15%	0.1	80%	11	1/11	15	2/26
A3	15%	35%	0.1	80%	9	2/9	14	6/23
B1	56%	76%	0.1	80%	12	8/12	19	21/31
B2	2%	15%	0.1	80%	11	1/11	15	2/26
B3	15%	35%	0.1	80%	9	2/9	14	6/23
C	30%	50%	0.1	80%	15	6/15	17	13/32
D	39%	59%	0.1	80%	15	7/15	16	16/31
E	25%	45%	0.1	80%	15	5/15	12	10/27

[a] r1 = response rate at the end of Stage 1; n1 = sample size for Stage 1 only; r = overall response rate for combined Stage 1 and 2; n = sample size for combined Stage 1 and 2.

Phase 2 Part B: Simon 2-Stage Design

Cohort	Background ORR	Target ORR	Alpha	Power	N for Stage 1	ORR to Proceed ≥ (r1 + 1) / n1[a]	N for Stage 2	ORR for Positive Cohort ≥ (r + 1) / n[a]
A	2%	15%	0.1	80%	11	1/11	15	2/26
B	2%	15%	0.1	80%	11	1/11	15	2/26
C	2%	15%	0.1	80%	11	1/11	15	2/26

[a] r1 = response rate at the end of Stage 1; n1 = sample size for Stage 1 only; r = overall response rate for combined Stage 1 and 2; n = sample size for combined Stage 1 and 2.

Primary Analysis:

Objective response rate, defined as the percentage of subjects enrolled in Phase 2 Part A (plus subjects enrolled in Phase 1 who meet all of the inclusion and exclusion criteria for Phase 2 Part A) or Phase 2 Part B having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 will be summarized by treatment cohort.

Secondary Analysis:

The following efficacy analyses will be assessed for all subjects in each treatment combination:

- ORR defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 (Phase 1 only).
- DCR, defined as the percentage of subjects having CR, PR, or SD for at least 56 days, as determined by investigator assessment of radiographic disease as per RECIST v1.1.
- DoR, determined by radiographic disease assessment, defined as the time from earliest date of disease response until the earliest date of disease progression per RECIST v1.1, or death due to any cause, if occurring sooner than progression.
- PFS, defined as the time from date of first dose of study treatment until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1, or death due to any cause, if occurring sooner than progression.

The PK of INCB001158, epacadostat, and pembrolizumab, and the [redacted] will be summarized.

[redacted]

Interim Analysis:

In Phase 1, the BOIN design will be used to determine the RP2D of the combination of INCB001158, epacadostat, and pembrolizumab. Based on the algorithm of the BOIN design, a minimum of 3 evaluable subjects will be enrolled in each dose level with a maximum of 9 evaluable subjects in each dose level.

In Phase 2, the Simon 2-stage design will be applied for each tumor within a given treatment group. 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.

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LIST OF ABBREVIATIONS

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

Abbreviation	Definition
[redacted]	[redacted]
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
BID	twice daily
BOIN	Bayesian Optimal Interval
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DC	dendritic cell
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
HBsAg	hepatitis B virus surface antigen

Abbreviation	Definition
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
[redacted]	[redacted]
[redacted]	[redacted]
IDO1	indoleamine 2,3-dioxygenase 1
IEC	independent ethics committee
IFN-γ	interferon gamma
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
IN	Investigator Notification
INR	international normalized ratio
[redacted]	[redacted]
irAE	immune-related adverse event
IRB	institutional review board
[redacted]	[redacted]
IRT	Interactive Response Technology
[redacted]	[redacted]
[redacted]	[redacted]
LC/MS-MS	liquid chromatography tandem-mass spectrometry
LLC	Lewis lung carcinoma
MAOI	monoamine oxidase inhibitors
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NK	natural killer
NO	nitric oxide
NOS	nitric oxide synthase
NSAID	nonsteroidal antiinflammatory drug
NSCLC	non–small cell lung cancer

Abbreviation	Definition
ORR	objective response rate
[redacted]	[redacted]
PAD	pharmacologically active dose
PD	progressive disease
PD-1	programmed death-1 receptor
PD-L1	programmed death-1 receptor ligand
PFS	progression-free survival
PI	package insert
PK	pharmacokinetic
PO	*per os* (ie, orally administered)
PR	partial response
PT	prothrombin time
Q3W	once every 3 weeks
QD	once daily
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SNRI	selective serotonin/norepinephrine reuptake inhibitor
SPC	summary of product characteristics
SS	serotonin syndrome
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
T1DM	Type 1 diabetes mellitus
Treg	regulatory T cells
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 composed of diverse sets of cells designed to protect a host from pathogens while distinguishing from host and foreign antigens. This immune response is controlled by a series of checks and balances to allow for robust immune responses to pathogens while preventing either an excessive inflammatory event or an autoimmune response. Through immune surveillance, the immune system has been shown to recognize, attack, and destroy tumor cells (Wolchok and Saenger 2008). Detailed analysis of CD8+ T cells and the ratio of CD8+ Teffs/FoxP3+ Tregs seem to correlate with improved prognosis and long-term survival in many solid tumors (Nosho et al 2010, Chang et al 2014, Preston et al 2013). Although the immune system has been shown to recognize and reject a tumor, many tumors persist in evading immune surveillance or develop mechanisms of resistance.

These include expression of PD-L1, which can engage the inhibitory receptor PD-1 on activated T cells; the presence of the tryptophan-catabolizing enzyme IDO1, which exposes the exquisite sensitivity of T cells to tryptophan depletion and tryptophan metabolites; infiltration with FoxP3+ Treg, which can mediate extrinsic suppression of effector T-cell function; and the depletion of arginine in the tumor microenvironment by arginase-expressing MDSCs and neutrophils, which inhibits the proliferation and activation of cytotoxic T cells and NK cells. Therefore, agents that target these negative regulatory pathways and thereby allow the expansion of effector T cells present in the tumor may be beneficial in the clinic.

Targeting the immune system is a proven and effective approach for cancer therapies. FDA- and EMA-approved checkpoint inhibitors, including inhibitors of PD-1, pembrolizumab and nivolumab, allow for the immune response to continue proliferating in spite of inhibitory signals. Epacadostat is being developed in combination with PD-1 and PD-L1 inhibitors (see Section 1.2.2). Targeting arginase is another promising treatment approach and is the focus of this clinical study, in combination with IDO1 and PD-1 inhibition.

1.1.2. Inhibition of Arginase as a Target for Cancer

Two isoforms of arginase are found in the body. Arginase 1 (gene symbol: ARG1) is a cytoplasmic enzyme that is highly expressed in the liver and is a critical enzyme in the urea cycle. Arginase 1 is also expressed by granulocytic myeloid cells (MDSCs and neutrophils) and is localized in secretory granules within these cell types. A separate gene encodes arginase 2 (gene symbol: ARG2), a mitochondrial enzyme that is more widely expressed across cell types.

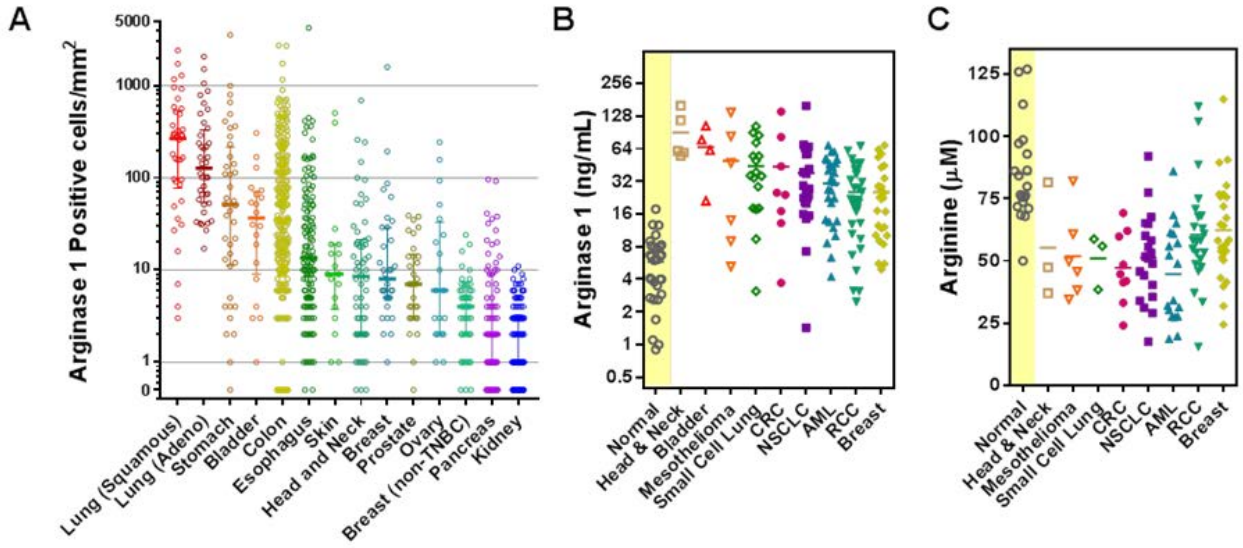
In cancer patients, arginase 1 in the tumor microenvironment is expressed by myeloid cells which release arginase from intracellular granules into the extracellular milieu following stimulation. Arginase is released from fully differentiated neutrophils/polymorphonuclear cells and/or from granulocytic MDSCs, which are immature neutrophils. These granulocytic cells degranulate and release arginase into the extracellular space when stimulated by factors produced by the tumor (eg, IL-8 and TNF-α), resulting in substantial depletion of the amino acid arginine, itself a critical factor in the proliferation and activation of cytotoxic T cells and NK cells.

Antitumor activity has been reported in mice when arginase is knocked out in the myeloid lineage in mice (Colegio et al 2014).

Immunohistochemical staining of tumor microarrays from multiple histotypes revealed that tumor cells themselves generally did not stain positive for arginase 1. Instead, large numbers of infiltrating polymorphonuclear cells containing arginase 1 were found across many histotypes with the greatest frequency in lung, colorectal, gastric, and bladder cancers (Figure 1 [A]). The positive arginase 1 IHC staining in tumor microarrays in this study was largely confined to polymorphonuclear cells based on morphology.

In addition to the high arginase 1 observed by IHC in tumor-infiltrating granulocytic myeloid cells, analysis of plasma from cancer patients across multiple histotypes demonstrated elevated arginase 1 protein levels and lower arginine levels compared with normal healthy control subjects (Figure 1 [B,C]). It has been hypothesized that arginase released from myeloid cells in the tumor microenvironment can be recovered in plasma, which may account for the elevated arginase 1 protein levels and lower arginine levels measured systemically.

Figure 1: Arginase and Arginine in Cancer Patients



[A] Frequency of arginase 1 expressing myeloid cells infiltrating human solid tumors. Arginase 1 protein was detected using a specific rabbit monoclonal antibody to human arginase 1. Digital quantification of arginase expression in myeloid cells was performed and the number of arginase 1–positive cells per mm^2 is plotted.
[B] Arginase protein and [C] arginine levels in plasma of cancer patients versus healthy subjects. Plasma from cancer patients and healthy normal volunteers were assayed for arginase 1 levels by ELISA and arginine levels by LC/MS-MS.

1.1.2.1. Activity of the Arginase 1 Inhibitor INCB001158 in Solid Tumors

INCB001158 (formerly known as CB-1158) is a potent, selective, and reversible inhibitor of human recombinant arginase 1 and arginase 2 (IC_{50} of 100 and 275 nM, respectively).

In cell-based assays, INCB001158 reversed the growth-suppressive effects of human neutrophils on human T cells when co-cultured *ex vivo* with an EC_{50} of 162 nM. Similarly, INCB001158 reversed inhibition of T-cell growth by patient-derived MDSCs with similar potency. In both cases, INCB001158 was able to antagonize the depletion of arginine mediated by neutrophils or

MDSCs in a dose-dependent manner. INCB001158 has no direct growth inhibitory or cytotoxic activity on tumor cells or on immune effector cells.

INCB001158 has single agent and combination activity in syngeneic tumor models. Oral BID administration of single agent INCB001158 produced a dose-dependent reduction in the growth of subcutaneously implanted LLC (lung) tumors. The efficacy of INCB001158 in LLC tumors is immune-mediated. When LLC tumors were grown in immunocompromised scid mice, there was no antitumor activity of INCB001158. The combinations of INCB001158 with anti–PD-L1 in the CT26 (colon) model and with epacadostat in the B16F10 (melanoma) model resulted in enhanced antitumor activity.

The safety and tolerability of INCB001158 in patients with advanced or metastatic solid tumors is being evaluated in the ongoing first-in-human Phase 1 study, INCB 01158-101 (formerly CX-1158-101). Early data from monotherapy dose-escalation cohorts (data cutoff: 24 APR 2017) showed that oral dosing of INCB001158 was well-tolerated at the first 3 doses tested (50, 100, and 150 mg BID); the steady-state trough levels of INCB001158 were above the IC_{90} for arginase inhibition at all dose levels, with 90% to 95% arginase inhibition and increases in plasma arginine, and there was preliminary evidence of peripheral immune modulation (Papadopoulos et al 2017).

Refer to the Investigator's Brochure for additional details of the INCB001158 preclinical experiments and updated data from the INCB 01158-101 clinical study (iIB).

1.1.3. Inhibition of PD-1 as a Target for Cancer

The PD-1 receptor-ligand interaction is a major pathway stimulated by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2; Talmadge et al 2007, Usubütün et al 1998). The mechanism by which PD-1 down modulates T-cell responses is similar to but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins (Hiraoka 2010, Nobili et al 2008). PD-1 has been shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, Tregs, and natural killer cells (Hodi and Dranoff 2010, Kloor 2009). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells as well as subsets of macrophages and DCs (Hillen et al 2008). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including nonhematopoietic tissues as well as in various tumors (Lee et al 2008, Leffers et al 2009, Nishimura et al 2000, Nobili et al 2008). Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.

PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues (Nobili et al 2008). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (Liotta et al 2010). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.1.3.1. Activity of PD-1/PD-L1 Inhibitors in Solid Tumors

A number of PD-1/PD-L1 checkpoint inhibitors have demonstrated activity in a variety of solid and liquid tumors:

- Pembrolizumab (Keytruda®) is a humanized IgG4-kappa monoclonal antibody that binds to PD-1 and is approved for certain patients with melanoma, NSCLC, SCCHN, urothelial carcinoma, classical Hodgkin lymphoma, and microsatellite instability-high cancer (Keytruda PI 2017, Keytruda SPC 2017).
- Nivolumab (Opdivo®) is a fully human IgG4 monoclonal antibody that also binds to PD-1 and is approved for certain patients with melanoma, NSCLC (both as monotherapy and in combination with ipilimumab), renal cell carcinoma, SCCHN, classical Hodgkin lymphoma, and urothelial carcinoma (Opdivo PI 2017, Opdivo SPC 2017).
- Atezolizumab (Tecentriq®) is an Fc-engineered, humanized, monoclonal antibody that binds to PD-L1 and is approved for certain patients with urothelial carcinoma and NSCLC (Tecentriq PI 2017).
- Durvalumab (Imfinzi®) is a human monoclonal antibody against PD-L1 and is approved for certain patients with urothelial carcinoma (Imfinzi PI 2017).
- Avelumab (Bavencio®) is a human monoclonal antibody against PD-L1 and is approved for certain patients with Merkel cell carcinoma (Bavencio PI 2017).

These data support the use of PD-1/PD-L1 inhibitors in a variety of solid tumors. However, the majority of patients do not derive a benefit as evidenced by the relatively low response rates, and there remains a high unmet medical need for more efficacious therapies. One approach being tried is to combine PD-1/PD-L1 inhibitors with other molecules, including those that can affect the tumor microenvironment. This is discussed in Section 1.1.5.

1.1.4. Inhibition of Indoleamine 2,3-Dioxygenase as a Target for Cancer

Recent interest has focused on the role of IDO1 as a mechanism of induction of tolerance to malignancy (Godin-Ethier et al 2011). IDO1 is a heme-containing monomeric oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N-formyl-kynurenine. Kynurenine can be subsequently metabolized through a series of enzymatic steps to nicotinamide adenine dinucleotide. IDO1 is the first rate-limiting enzyme in one of the breakdown pathways of tryptophan. In another pathway, tryptophan hydroxylase catalysis of tryptophan leads to the formation of serotonin and melatonin.

The expression and activity profiles of IDO1 are distinct from those of tryptophan dioxygenase, an enzyme predominantly expressed in liver that catalyzes the same enzymatic reaction as IDO1 and maintains proper tryptophan balance in response to dietary uptake. In contrast to tryptophan dioxygenase, IDO1 is expressed in a variety of tissues, with particularly high levels found in areas of contact with potential sources of immune challenge (eg, gut, respiratory tract, placenta, spleen), consistent with a role for regulating tryptophan metabolism in a local microenvironment (Mellor and Munn 2004). Within the immune system, IDO1 activity is specifically induced in cells such as DCs and macrophages at localized sites of inflammation (Mellor and Munn 2004).

IDO1-driven oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell–mediated responses by blocking T-cell activation and inducing T-cell apoptosis (Mellor et al 2003). Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects (Frumento et al 2002). IDO1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (Treg; Fallarino et al 2006). Because increased Treg activity has been shown to promote tumor growth and Treg depletion has been shown to allow an otherwise ineffectual antitumor immune response to occur (Zou 2006), IDO1 expansion of Tregs may provide an additional mechanism, whereby IDO1 could promote an immunosuppressive environment.

The biological relevance of IDO1 inhibition to immune tolerance was first demonstrated when it was shown that treating mice with a small molecule inhibitor of the IDO1 pathway, 1-methyl-tryptophan, could break the tolerogenic state that protects allogeneic concepti from the maternal immune system (Munn et al 1998). A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer (Mellor and Munn 2004). While IDO1 inhibition can exacerbate disease in models of autoimmune disorders (Mellor and Munn 2004), IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development (Mellor et al 2003), suggesting that IDO1 inhibition, in a therapeutic setting, may produce minimal side effects in subjects without pre-existing autoimmune conditions.

Within the context of cancer, there are several lines of evidence to suggest that IDO1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO1 activity can directly influence the ability of tumor-bearing animals to reject tumors (Uyttenhove et al 2003, Muller et al 2005). In addition, studies with 1-methyl-tryptophan, demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (eg, platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity (Muller et al 2005). Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T-cell–deficient animals, suggesting that the results may be the consequence of the disablement of immunosuppressive mechanisms that exist within the tumor microenvironment.

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in subjects with cancer, and IDO1 activation correlates with more extensive disease (Huang et al 2010, Weinlich et al 2007). IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types as well as by the DCs that localize to

the tumor draining lymph nodes (Uyttenhove et al 2003). Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced OS in subjects with melanoma, ovarian, colorectal, pancreatic, and bladder cancers (Brandacher et al 2006, Ino et al 2006, Nakamura et al 2007, Okamoto et al 2005, Witkiewicz et al 2008).

Together, these results suggest that the IDO1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance. Small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat advanced malignancies either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

1.1.5. Combinations of Immunotherapies for Cancer

Blockade of immune inhibitory pathways is emerging as an important therapeutic modality for the treatment of cancer as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/PD-L1. Ipilimumab, a fully human, IgG1 monoclonal antibody blocking CTLA-4, improved OS in patients with advanced melanoma (Hodi and Dranoff 2010). Nivolumab, a fully human IgG4 antibody blocking PD-1, produced durable overall responses in patients with melanoma, renal cell cancer, and NSCLC (Hamid et al 2013, Topalian et al 2012, and Wolchok et al 2013). Although these single agents have antitumor activity, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect (Quezada and Peggs 2013).

For example, CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone (Curran et al 2010, Selby et al 2013). This was demonstrated in clinical trials evaluating patients with metastatic melanoma, and the combination of nivolumab and ipilimumab has since been approved by regulatory authorities for melanoma, and this combination continues to be investigated in a number of additional tumor types.

1.1.5.1. Combined Inhibition of PD-1 and IDO1 as a Target for Cancer

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] Targeting PD-1 assumes that the T cells are essentially exhausted (and thus tolerant of the tumor), and that this exhaustion may be reversed by blocking PD-1 signaling. Targeting IDO will concurrently decrease infiltration of regulatory CD4+ cells and immune-suppressive cytokines. [redacted] Gangadhar et al 2016, Gangadhar et al 2017, Hamid et al 2017a, Hamid et al 2017b, Smith et al 2017, eIB). In addition, the combination of epacadostat and an anti–PD-1 agent has a favorable safety profile, with irAEs, Grade 3/4 AEs, and treatment discontinuation rates that are

low and similar to monotherapy anti–PD-1 therapy (Hamid et al 2017a, eIB). Further, early data with another small-molecule IDO1 inhibitor, GDC-0919, in combination with the PD-L1 inhibitor atezolizumab showed preliminary efficacy in a heterogeneous patient population of advanced or metastatic cancer patients during dose escalation (Burris et al 2017).

1.1.5.2. Combined Inhibition of PD-1, IDO1, and Arginase 1 as a Target for Cancer

Tumor-infiltrating MDSCs are the most common mediator of immunosuppression in tumors. MDSC cells represent a heterogeneous population that comprises both cells of granulocytic (G-MDSC) and monocytic (M-MDSC) origin, which display an equal immunosuppressive activity in tumors (Di Mitri et al 2015). As described in Section 1.1.2, G-MDSCs exert their immunosuppressive effect via arginase 1 which they release into the extracellular space. In addition, IDO1 promotes immunosuppressive cells such as M-MDSCs (Holmgaard et al 2015). [redacted] These nonoverlapping, complementary mechanisms, when added to a PD-1 inhibitor, may provide additional antitumor activity compared with dual inhibition of IDO1 and PD-1. This may also be important in overcoming adaptive resistance that develops during anti–PD-1 therapy.

Two recent studies suggest that the immunosuppressive effect of MDSCs may be important in tumors that are refractory or resistant to PD-1/PD-L1 inhibition. Firstly, in anti–PD-1 treated, recurrent/metastatic SCCHN patients, constitutive resistance to PD-1 checkpoint blockade in patients with inflamed tumors (high expression of a 6-gene IFN-γ signature) was associated with expression of GM-CSF and MDSC markers (Seiwert et al 2017). Secondly, in a study of mostly pretreated Stage IIIB/IV NSCLC patients, a distinct 'immunologically cold' subset of tumors with high expression of STAT3 or ARG1 and low expression of an IFN-γ signature was identified (Streicher et al 2017). [redacted]. *Note:* The combination of INCB001158 and a PD-1 inhibitor (pembrolizumab) will be tested in the ongoing INCB 01158-101 study.

In addition, there is recent evidence in mice that arginase 1 may control IDO expression in DCs, suggesting that arginase 1 and IDO1 cooperate in conferring long-term, immunosuppressive effects to DCs (Mondanelli et al 2017). [redacted].

It is possible that dual inhibition of G-MDSCs and M-MDSCs alone may be effective in treating advanced or metastatic cancer, but it may also be that this dual inhibition would be more effective at improving anticancer effect of PD-1 inhibitors.

1.2. Study Rationale

1.2.1. Rationale for Combining INCB001158 With Epacadostat in Solid Tumors

As described in Section 1.1, combined inhibition of arginase 1 and IDO1 may be effective through dual inhibition of both types of MDSCs found in tumors, to fully abrogate the myeloid immunosuppressive tumor microenvironment. [redacted].

1.2.2. Rationale for Combining INCB001158 With Epacadostat and Pembrolizumab in Solid Tumors

While inhibition of the PD-1 checkpoint has been effective in treating several solid tumors, there are still a large proportion of patients who either are refractory to PD-1 inhibition or have become resistant to treatment. Hence, there is a clear unmet medical need to deepen or lengthen responses to PD-1 inhibitors or to overcome resistance (primary or acquired). As described in Section 1.1, IDO1 inhibition with epacadostat appears to lead to higher response and disease-control rates over and above that demonstrated with single agent PD-1 blockade in several tumor types. By also inhibiting arginase 1, with INCB001158, this could further increase response and DCRs and DoR by providing broad inhibition of both immunosuppressive MDSC cell types and by potentially making "cold" tumors responsive to PD-1 inhibition. Also, as the combination of epacadostat and anti–PD-1 therapy has a favorable safety profile, this is a regimen to build on, especially with a molecule such as INCB001158 that also has a favorable safety profile. [redacted]

1.2.3. Rationale for the Study Population

1.2.3.1. Phase 1: Dose Escalation of INCB001158 + Epacadostat + Pembrolizumab

In the Phase 1 part of this study, the safety and tolerability of INCB001158 in combination with epacadostat and pembrolizumab will be evaluated in cancer patients. Because it is not known whether INCB001158 will alter the toxicity profile of epacadostat and pembrolizumab, only subjects with metastatic disease or advanced disease who have failed prior standard therapy (disease progression; subject intolerance is also allowable) will be enrolled.

1.2.3.2. Phase 2 Part A: Tumor Expansion of INCB001158 + Epacadostat + Pembrolizumab

In Phase 2 Part A, patient populations were selected for whom epacadostat and pembrolizumab (NSCLC, melanoma, urothelial carcinoma, and SCCHN) or pembrolizumab alone (SCLC) have shown antitumor activity and for whom there is high infiltration with arginase 1-positive cells (see Section 1.1.2), such that by adding an arginase 1 inhibitor, added benefit may be observed.

In Cohorts A1 (NSCLC), B1 (melanoma), C (urothelial carcinoma), and D (SCCHN), the populations are consistent with those from the INCB 24360-202 study, where the combination of epacadostat and pembrolizumab has demonstrated antitumor activity (see Section 1.1.5.1). This includes being naive to anti–PD-1 or anti–PD-L1 therapy or any other drug targeting the checkpoint pathways and having had no more than 2 prior lines of systemic therapy for metastatic or advanced disease. By using populations consistent with INCB 24360-202, and by using the same doses of epacadostat and pembrolizumab, the INCB 24360-202 data will provide a baseline to assess the effect of adding INCB001158 to these 2 therapies.

In Cohort E (SCLC) the population is broadly consistent with the SCLC cohort in the KEYNOTE-028 study, where pembrolizumab demonstrated an ORR of 33.3% (Ott et al 2016),

with 2 key modifications. Firstly, in Cohort E, subjects may have had no more than 2 prior lines of systemic therapy for metastatic or advanced disease, whereas approximately a third of SCLC patients in KEYNOTE-028 had received ≥ 3 previous lines of therapy. Secondly, while KEYNOTE-028 enrolled only PD-L1–positive patients (≥1%), Cohort E will not select based on tumor PD-L1 status. This is based on the results from the CheckMate 032 study in an unselected population of patients with recurrent SCLC, where responses with nivolumab were observed regardless of PD-L1 status (Hellman et al 2017). Therefore, the KEYNOTE-028 data will only provide a rough baseline to assess the effect of adding INCB001158 and epacadostat to pembrolizumab.

In Cohorts A2 and A3 (NSCLC) and B2 and B3 (melanoma), subjects will not be naive to anti–PD-1 or anti–PD-L1 therapy or any other drug targeting the checkpoint pathways. Instead they will have had documented radiological disease progression while receiving an anti–PD-1 or anti–PD-L1 agent in a previous line of therapy. In Cohorts A2 and B2, the subjects will be primary refractory to anti–PD-1 or anti–PD-L1 therapy; in Cohorts A3 and B3, the subjects will be anti–PD-1/anti–PD-L1 relapsed. This will allow an evaluation of whether INCB001158, in combination with epacadostat, can make these tumors responsive to anti–PD-1 therapy again and is based on the high arginase 1 expression observed in a distinct 'immunologically cold' subset of tumors (low IFN-γ signature expression; see Section 1.1.5.2), plus the [redacted] dual inhibition of G-MDSCs and M-MDSCs by INCB001158 and epacadostat, respectively.

1.2.3.3. Phase 2 Part B: Tumor Expansion of INCB001158 + Epacadostat

In Phase 2 Part B, 3 tumor types (urothelial carcinoma, SCCHN, and CRC) were selected that have high infiltration with arginase 1–positive cells (see Section 1.1.2), such that treatment with an arginase 1 inhibitor may be effective. In addition, the [redacted] dual inhibition of G-MDSCs and M-MDSCs by INCB001158 and epacadostat, respectively, may fully abrogate the myeloid immunosuppressive tumor microenvironment (see Section 1.1.5.2).

Because it is unknown whether INCB001158 in combination with epacadostat will be active, only subjects with metastatic disease or advanced disease that is not amenable to local therapy will be enrolled. Further, only subjects for whom there are no available therapies that have been shown to provide clinical benefit (eg, OS benefit) will be enrolled.

1.2.4. Rationale for the Dose and Schedule of INCB001158

The starting dose of INCB001158 in the Phase 1 dose-escalation portion of the proposed study will be at least 2 dose levels below the highest dose of INCB001158 that is shown to be tolerable as a monotherapy in the INCB 01158-101 study, but no lower than 50 mg BID.

As described in Section 1.3.1, INCB001158 has the potential to disrupt the hepatic urea cycle via inhibition of its constituent arginase. This can be measured via urinary orotic acid, which is used as a sensitive assay to identify defects in the urea cycle. Elevations of urinary orotic acid are not necessarily associated with toxicity, and in this study, dose-limiting events of urea cycle inhibition (eg, an increase in fasted urinary orotic acid to > 10 × ULN or any urinary orotic acid value to > 40 × ULN, or symptomatic hyperammonemia) are included in the assessment of tolerability in this study (see also Section 5.4.2 for definitions of DLTs and dose-limiting events).

In Study INCB 01158-101, as of the 21 JUL 2017 data cutoff, there were no DLTs or dose-limiting events at the 50 mg BID (n = 8), 75 mg BID (n = 7), and 100 mg BID (n = 8) dose levels, and there were no DLTs but 2 asymptomatic dose-limiting events of elevated urinary orotic acid ≥ 5 × ULN at the 150 mg BID (n = 3) dose level. Given that such elevations of urinary orotic acid are an indication of inhibition of the urea cycle, albeit asymptomatically, and given that relatively small increases in INCB001158 doses in rats resulted in dramatic increases in urinary orotic acid levels (> 1000-fold) and toxicity (refer to the iIB), it was decided a cautious approach was warranted and the starting dose was set at least 2 dose levels below the maximum tolerated and tested dose from Study INCB 01158-101.

In addition, dose escalation of INCB001158 in this study may go no higher than the maximum tolerated and tested monotherapy dose identified in the INCB 01158-101 study.

The criteria for the selection of the RP2D of INCB001158 plus epacadostat and pembrolizumab, and the RP2D of INCB001158 plus epacadostat are described in Section 4.1.1.

1.2.5. Rationale for the Dose of Epacadostat

In the Phase 1 dose escalation, the epacadostat dose will be kept constant at 100 mg BID, because it has been shown to be active and tolerable in several epacadostat combination clinical studies, including with pembrolizumab (eIB, Gangadhar et al 2017, Hamid et al 2017a, Hamid et al 2017b, Smith et al 2017), and it is the dose selected or use in combination with pembrolizumab in Phase 3 (eg, NCT02752074).

If unacceptable toxicity is observed at Dose Level 1 and is deemed to be due to epacadostat, a lower dose of epacadostat (50 mg BID) may be tested (see Section 4.1.1).

The selection of the RP2D of INCB001158 plus epacadostat and pembrolizumab, and the RP2D of INCB001158 plus epacadostat is described in Section 4.1.1.

1.2.6. Rationale for the Dose of Pembrolizumab

In the Phase 1 dose escalation, the dose of pembrolizumab will be kept constant at 200 mg Q3W, which is the approved dose and schedule (Keytruda PI 2017, Keytruda SPC 2017) and also the dose being used in combination with epacadostat in Phase 3 studies, such as INCB 24360-301 in metastatic melanoma (NCT02752074).

The criteria for the selection of the RP2D of INCB001158 plus epacadostat and pembrolizumab are described in Section 4.1.1.

1.2.7. Rationale for the Study Endpoints

1.2.7.1. Primary Endpoints

The primary safety endpoint will assess AEs, clinical laboratory assessments, physical examination results, and 12-lead ECG results to determine the RP2D of INCB001158 in combination with epacadostat ± pembrolizumab in Phase 1.

The primary efficacy endpoint will evaluate the ORR of INCB001158 in combination with epacadostat ± pembrolizumab by RECIST v1.1 in Phase 2. This is a standard endpoint for assessing the antitumor activity of immunotherapies and has been used for epacadostat and

pembrolizumab in previous studies, including INCB 24360-202. RECIST v1.1 is the accepted version by regulators such as the FDA.

1.2.7.2. Secondary Endpoints

The safety and tolerability of the RP2D of INCB001158 in combination with epacadostat ± pembrolizumab will be further assessed in Phase 2.

Each antitumor activity endpoint (ORR [Phase 1 only], DCR, DoR, and PFS) will be assessed by RECIST v1.1.

The PK of the 3 study treatments will be assessed using the same standard PK parameters that have been used to evaluate each of the 3 treatments as monotherapy and in the epacadostat plus pembrolizumab doublet.

[redacted]

1.3. Potential Risks and Benefits of the Treatment Regimen

1.3.1. Risks for INCB001158

INCB001158 is a potent and selective inhibitor of arginase 1 and arginase 2. Arginase 1 is primarily expressed in granulocytic myeloid cell granules, where it is excreted extracellularly and depletes extracellular arginine levels, and in liver hepatocytes, where it functions intracellularly as part of the urea cycle. It has been shown that INCB001158 is approximately 1000-fold more potent at inhibition of extracellular arginase 1 than intracellular arginase 1 that is engaged in the urea cycle. This is primarily due to poor penetration of INCB001158 across cell membranes and the "enzymatic channeling" phenomenon, whereby the enzymes of the urea cycle are grouped within the cell to transfer intermediates efficiently between themselves and restrict access of exogenous arginine or INCB001158 to urea cycle enzymes (Cheung et al 1989). Arginase 2 is primarily expressed in the mitochondria of many other tissues, including the gut and kidney. The functions of arginase 2 in these tissues include regulation of systemic arginine concentration, regulation of the production of downstream products (eg, proline, polyamines), and regulation of arginine availability for NO synthesis. Inhibition of arginase 2 is thought to result in elevations in systemic arginine levels, which may contribute to the therapeutic effect. Elevated arginine (up to ~100-fold above baseline) has been well-tolerated in humans following intravenous administration. Ten-fold elevations in plasma arginine (to a mean concentration of 822 μM) was associated with no change in systolic or diastolic blood pressure, and a 100-fold increase in arginine was associated with mild reductions in systolic and diastolic blood pressure (~9 mmHg for each; Mehta et al 1996, Bode-Böger et al 1998).

The results of the GLP-compliant rat and monkey toxicity studies are described in the INCB001158 IB (iIB). The low- and mid-dose levels were well-tolerated, with no adverse findings and the mid-dose being considered the no-observed-adverse-effect level in both species. INCB001158 exposures at the mid-dose level were > 16-fold above the projected human efficacious exposure and were associated with robust pharmacodynamic effects (eg, elevated plasma arginine) with no significant toxicities noted.

1.3.1.1. Potential Urea Cycle Toxicity

As detailed in the INCB001158 IB (iIB), high doses of INCB001158 that resulted in significant morbidity and mortality in mice, rats, and monkeys achieved exposures over 19-fold above the projected human efficacious exposure. In the nonclinical animal studies, the toxicity at the high doses was associated with evidence of hepatic urea cycle inhibition, including an elevation in liver arginine concentration, an increase in plasma ammonia concentration, a decrease in BUN concentration, and an increase in urinary orotic acid levels. Of particular interest, urinary orotic acid was elevated by > 1000-fold in rats at the high dose following a single dose, before any signs of toxicity. Smaller elevations in urinary orotic acid were also measured in some animals at the well-tolerated mid-dose level. Elevations of urinary orotic acid have also been observed in cancer patients administered at the highest tested dose of 150 mg BID in the first-in-human INCB 01158-101 study. Refer to the INCB001158 IB (iIB) and Section 1.2.4 for the latest INCB 01158-101 data plus the rationale for the thresholds of orotic acid (Section 5.4.2) to be used in this study.

Several measures of potential toxicity related to urea cycle inhibition will be evaluated in this study (see Table 14, Table 15, and Table 16). In particular, urinary orotic acid, plasma (venous) ammonia, and BUN will be measured on Day 1 and at regular intervals in the dose escalation portion of the study (Phase 1).

- Orotic acid – When the urea cycle is disrupted, the urea cycle substrate carbamoyl phosphate accumulates and is diverted into the pyrimidine synthesis pathway, producing substantial quantities of the pyrimidine precursor orotic acid. The elevated orotic acid is rapidly cleared in the urine and is used as a sensitive assay to identify defects in the urea cycle either due to inborn errors or toxic or therapeutic inhibition.
- Ammonia – Urea cycle inhibition can result in large elevations in ammonia, which can lead to CNS toxicity. Inhibition of arginase, the last step in the urea cycle, does not tend to cause dramatic elevations in ammonia, but they are possible and will be evaluated as ammonia is the primary mechanism of acute toxicity associated with urea cycle inhibition. Because plasma ammonia can be quite variable, elevations in plasma ammonia should be confirmed, particularly in asymptomatic patients.
- BUN – Blood urea nitrogen is a measure of plasma urea and can be reduced in the setting of urea cycle inhibition. Because BUN is also affected by other factors (eg, protein consumption, fluid status/dehydration), it is not an ideal biomarker of urea cycle function. However, clear evidence of significant reduction in plasma BUN would be consistent with sustained inhibition of the hepatic urea cycle and should be avoided.

1.3.1.2. Immune-Related Adverse Events

It is not known to what extent arginine depletion is operative in normal tissues or in noncancer inflammatory states. However, because arginase-mediated depletion of arginine is an immunosuppressive mechanism, irAEs may be associated with the restoration of local arginine by INCB001158 treatment. Although preclinical toxicity studies have not demonstrated any evidence of increased inflammation or autoimmunity, these models tend to be poor predictors of the safety profile of immune-oncology agents in humans. Experience with other immuno-oncology agents that target endogenous immunosuppressive mechanisms has demonstrated that irAEs can affect any organ or tissue, but most frequently occur in the skin (rash), gastrointestinal system (diarrhea/colitis), liver (hepatitis), lungs (pneumonitis), endocrine system (endocrinopathies due to inflammation of the pituitary, thyroid, and adrenals), and kidneys (nephritis).

Documentation of the immune-mediated nature of toxicities (eg, through demonstration of immune infiltration in biopsy tissue) will be of great value, and an effort should be made in cases of severe or prolonged potential irAEs to provide evidence of the role of the immune system. Management of irAEs will follow the general approach that has been used for other immuno-oncology agents, including 1) withholding study drug for events of moderate or worse severity (Grade $\geq$ 2) and 2) the use of immunosuppressive corticosteroids for more severe irAEs (Grade $\geq$ 3) or prolonged irAEs (lasting > 2 weeks with minimal or no improvement despite withholding study drug). High-dose steroids may be used for particularly severe irAEs or irAEs that fail to respond to initial oral steroids within 3 to 4 days. Nonsteroid immunosuppressive agents may also be employed for steroid-refractory irAEs.

1.3.1.3. Alterations in Hemodynamic Status

Although preclinical toxicity studies have not identified this as a toxicity signal, reductions in blood pressure leading to orthostatic hypotension, presyncope, or syncope are possible due to increased production of NO in response to the increased availability of circulating arginine, a key substrate for the NO-producing NOS enzymes. This is considered an unlikely toxicity for INCB001158 based on the absence of preclinical evidence of hypotension and the tolerability of very high levels of arginine when administered intravenously to humans, including the absence of an effect on blood pressure in individuals with a 10-fold mean increase of plasma arginine (Mehta et al 1996, Bode-Böger et al 1998). There has been no preclinical evidence of altered hemodynamic status in any preclinical studies of INCB001158, and no clinical evidence to date in the INCB 01158-101 study (iIB). In order to identify modest changes in hemodynamic status, blood pressure will be monitored in this study as part of the standard vital signs.

1.3.1.4. Clinical Experience

The INCB 01158-101 first-in-human study is ongoing. See Section 1.1.2.1 for early data from this study and the INCB001158 IB (iIB) and Section 1.2.4 for more recent data. Urinary orotic acid will continue to be studied in all clinical studies, to understand the role of food and the effects of extended exposure to INCB001158 and to combinations of INCB001158 with other molecules.

1.3.2. Risks for Epacadostat

Study INCB 24360-101 was a Phase 1, multicenter, open-label, dose-escalation study in subjects with refractory solid tumors that used a 3 + 3 design to determine the safety and tolerability, PK, and pharmacodynamics of escalating oral doses of epacadostat. Subjects were administered doses of epacadostat ranging from 50 mg QD to 700 mg BID. Of the 52 subjects treated, 8 subjects (15.4%) had an AE leading to death. Of these 8 subjects, the cause of death was disease progression in 7 subjects and hypoxia in the remaining subject. During the study, 25 subjects (48.1%) had an SAE. The most frequently reported SAEs were disease progression (4 subjects, 7.7%), abdominal pain, nausea, and hypoxia (3 subjects each, 5.8%). Treatment-emergent AEs were reported in all subjects. Fatigue was the most frequently reported TEAE (36 subjects, 69.2%). Two DLTs occurred: 1 DLT of radiation pneumonitis at the 300 mg BID dose level and 1 DLT of fatigue at the 400 mg BID dose level. An MTD was not determined.

A potential concern 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). Preclinical data suggest that SS is unlikely after treatment with either epacadostat alone or in combination with MAOIs such as linezolid (Zhang 2016). As of 27 FEB 2017, 2 of 958 subjects treated across the epacadostat program have reported nonserious SS or symptoms of SS; both episodes were mild in severity and resolved.

1.3.3. Risks for Pembrolizumab

Pembrolizumab (KEYTRUDA®) is a PD-1–blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma, metastatic NSCLC, recurrent or metastatic SCCHN, refractory classical Hodgkin lymphoma, locally advanced or metastatic urothelial carcinoma, and microsatellite instability-high cancer (Keytruda PI 2017, Keytruda SPC 2017).

Due to the mechanism of action of pembrolizumab, immune adverse reactions have been seen when used as monotherapy. Infusion-related reactions are also possible following administration of pembrolizumab. Guidance for the management of immune-related AEs and infusion-related reactions is in the Protocol.

Additional details regarding specific benefits and risks for subjects participating in this clinical study may be found in the accompanying Investigator's Brochure (pIB) and Informed Consent documents.

1.3.4. Risks for the Combination of INCB001158, Epacadostat, and Pembrolizumab

Prior to this study, the triplet combination of INCB001158 plus epacadostat and pembrolizumab had not been tested in humans. However, the doublet combination of pembrolizumab and epacadostat is being assessed in an ongoing Phase 1/2 study (INCB 24360-202), and the doublet of INCB001158 and pembrolizumab is being assessed in the first-in-human INCB 01158-101 study.

In the Phase 2 cohort-expansion part of the epacadostat plus pembrolizumab combination study (INCB 24360-202), safety data are available on 294 cancer subjects, of whom 273 had solid tumors and 21 had diffuse large B-cell lymphoma (Hamid et al 2017a). All subjects were dosed at epacadostat 100 mg BID and pembrolizumab 200 mg Q3W. The most frequently reported (≥ 10%) treatment-related AEs of any grade were fatigue (29%), rash (17%; including the preferred terms rash, rash generalized, rash macular, rash maculopapular, and rash pruritic), nausea (11%), and pruritus (10%). Treatment-related AEs ≥ Grade 3 occurring in more than 3 subjects were lipase increased (12 subjects, 4%), rash (9 subjects, 3%), fatigue, diarrhea, and amylase increased (4 subjects [1%] each). Treatment-related AEs leading to treatment discontinuations occurred in 11 subjects (4%); the most common were arthralgia and rash (2 subjects each). From the INCB 24360-202 study, epacadostat 100 mg BID plus pembrolizumab 200 mg Q3W was selected as a well-tolerated combination dose for further assessment in Phase 3. The same doses of epacadostat and pembrolizumab will also be used in the triplet combination in this INCB 01158-202 study.

By adding INCB001158, with its additional mechanism of inhibiting immunosuppression in the tumor microenvironment, there is the potential to cause more frequent, more severe, and/or new immune-related toxicities as compared with the doublet of epacadostat plus pembrolizumab. However, no immune-related toxicities have been observed to date in the ongoing INCB 01158-101 study (see iIB).

1.3.5. Benefits for the Combination of INCB001158, Epacadostat, and Pembrolizumab

As described in Section 1.2.2, inhibition of arginase 1, using INCB001158, could further increase ORR, DCR, and DoR observed in multiple solid tumors with epacadostat and pembrolizumab by providing broad inhibition of both immunosuppressive MDSC cell types and by potentially making "cold" tumors responsive to PD-1 inhibition. It is hypothesized that this additional benefit will not come at the cost of additional toxicity (see Section 1.3.4).

1.3.6. Risks for the Combination of INCB001158 and Epacadostat

As described in Section 1.1.5.2, INCB001158 and epacadostat have nonoverlapping mechanisms, and to date, the toxicities of each monotherapy have also been nonoverlapping. However, as the combination of INCB001158 and epacadostat has the potential to fully abrogate the myeloid immunosuppressive tumor microenvironment, there is the potential to cause more frequent, more severe, and/or new immune-related toxicities than epacadostat alone.

1.3.7. Benefits for the Combination of INCB001158 and Epacadostat

[redacted]. As described in Section 1.2.1, combined inhibition of arginase 1 and IDO1 may be effective through dual inhibition of both types of MDSC found in tumors, to fully abrogate the myeloid immunosuppressive tumor microenvironment. It is hypothesized that the potential benefit associated with combining INCB001158 with epacadostat will not come at the cost of additional toxicity (see Section 1.3.6).

2. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1 only: To assess the safety and tolerability, and to determine the RP2D of INCB001158 in combination with epacadostat ± pembrolizumab.	Safety, tolerability, DLTs, and RP2D of INCB001158 in combination with epacadostat ± pembrolizumab, as assessed by AEs, clinical laboratory assessments, physical examination results, and 12-lead ECG results.
Phase 2 only: To evaluate the ORR of INCB001158 in combination with epacadostat ± pembrolizumab.	ORR, defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1.
Secondary	
Phase 2 only: To assess the safety, tolerability, and RP2D of INCB001158 in combination with epacadostat ± pembrolizumab.	Safety, tolerability, and RP2D of INCB001158 in combination with epacadostat ± pembrolizumab, as assessed by AEs, clinical laboratory assessments, physical examination results, and 12-lead ECG results.
To evaluate the antitumor effect of INCB001158 in combination with epacadostat ± pembrolizumab by RECIST v1.1.	• ORR, defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 (Phase 1 only). • DCR, defined as the percentage of subjects having CR, PR, or SD for at least 56 days, as determined by investigator assessment of radiographic disease as per RECIST v1.1. • DoR, determined by radiographic disease assessment, defined as the time from earliest date of disease response until the earliest date of disease progression per RECIST v1.1, or death due to any cause, if occurring sooner than progression. • PFS, defined as the time from date of first dose of study treatment until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1, or death due to any cause, if occurring sooner than progression.
To determine the PK of each of INCB001158 and epacadostat in subjects treated with INCB001158 in combination with epacadostat ± pembrolizumab.	The PK of INCB001158 and epacadostat will be assessed by summarizing C_{max}, t_{max}, C_{min}, $AUC_{0\text{-}t}$, and Cl/F.

Table 1: Study Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

3. SUBJECT ELIGIBILITY

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

3.1. Subject Inclusion Criteria

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

1. Men and women, aged 18 or older.
2. For Phase 1: Subjects with histologically or cytologically confirmed advanced or metastatic solid tumors that have failed prior standard therapy (disease progression; subject intolerance is also allowable). *Note*: There is no limit to the number of prior treatment regimens.
3. For Phase 2 Part A Cohort A1 – Anti-PD-1/PD-L1–naive NSCLC (see cohort numbering in Section 4):
    a. Subjects with histologically or cytologically confirmed NSCLC, who have received no more than 2 prior systemic chemotherapy regimens for Stage IV disease (not including neoadjuvant and/or adjuvant therapy except as described below).
    b. For subjects who have received 1 or 2 lines of prior systemic chemotherapy for Stage IV disease, 1 of the prior systemic regimens must include a platinum-based therapy. Subjects who have only received non–platinum-based regimens may be enrolled with medical monitor approval.
    c. Tumors with driver mutations (EGFR mutation–positive, anaplastic lymphoma kinase fusion oncogene–positive, proto-oncogene tyrosine-protein kinase ROS1–positive, or BRAF V600 mutant–positive) treated with a tyrosine kinase inhibitor are permitted and will not be considered a systemic chemotherapy regimen. However, subjects should have progressed on or be intolerant to the targeted therapy.
    d. Maintenance or switch maintenance therapy after first- or second-line chemotherapy will be considered part of the prior systemic chemotherapy regimen and is acceptable.
    e. Subjects who completed and progressed on a platinum-containing regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy within the 6 months before screening would be counted as 1 prior platinum-containing regimen and therefore would not require re-treatment with a platinum-containing regimen for Stage IV disease.
4. For Phase 2 Part A Cohort A2 – Primary anti-PD-1/PD-L1–refractory NSCLC (primary refractory cohort):
    a. Subjects with histologically or cytologically confirmed locally advanced unresectable or metastatic NSCLC.
    b. Subjects with tumors with driver mutations (EGFR mutation–positive, anaplastic lymphoma kinase fusion oncogene–positive, proto-oncogene tyrosine-protein kinase ROS–positive, or BRAF V600 mutant–positive) should have progressed on or be intolerant to the targeted therapy.

c. Subjects must have received prior treatment with anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and have PD as their best response to treatment that is confirmed at least 4 weeks later (no less than 28 days).

   – Subjects must have received at least 2 doses of a prior anti–PD-1 or anti–PD-L1 agent.

   – Progressive disease must also be at least 12 weeks from first dose of anti–PD-1 or anti–PD-L1 therapy and confirmed 4 weeks (no less than 28 days) later.

5. For Phase 2 Part A Cohort A3 – Anti-PD-1/PD-L1–relapsed NSCLC (relapsed cohort):

   a. Subjects must have received prior anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and achieved either SD for at least 24 weeks or PR/CR, but later have confirmed PD (PD confirmed at least 4 weeks [no less than 28 days] later).

6. For Phase 2 Part A Cohort B1 – Anti-PD-1/PD-L1–naive melanoma:

   a. Subjects with histologically or cytologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging system, not amenable to local therapy.
   b. Have documentation of V600-activating BRAF mutation status or consent to BRAF V600 mutation testing during the screening period.
   c. Subjects must not have received more than 2 prior lines of systemic therapy for unresectable Stage III or Stage IV melanoma.
   d. Ocular melanoma is excluded.

7. For Phase 2 Part A Cohort B2 – Primary anti-PD-1/PD-L1–refractory melanoma (primary refractory cohort):

   a. Subjects with histologically or cytologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging system, not amenable to local therapy.
   b. Have documentation of V600-activating BRAF mutation status or consent to BRAF V600 mutation testing during the screening period.
   c. Subjects must have received prior treatment with anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and have PD as their best response to treatment that is confirmed at least 4 weeks later (no less than 28 days).

      – Subjects must have received at least 2 doses of a prior anti–PD-1 or anti–PD-L1 agent.

      – Progressive disease must also be at least 12 weeks from first dose of anti–PD-1 or anti–PD-L1 therapy and confirmed 4 weeks (no less than 28 days) later.

   d. Ocular melanoma is excluded.

8. For Phase 2 Part A Cohort B3 – Anti-PD-1/PD-L1–relapsed melanoma (relapsed cohort):
    a. Subjects must have received prior anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and achieved either SD for at least 24 weeks or PR/CR, but later have confirmed PD (PD confirmed at least 4 weeks [no less than 28 days] later).
9. For Phase 2 Part A Cohort C – Anti-PD-1/PD-L1–naive urothelial carcinoma:
    a. Subjects with histologically or cytologically confirmed, metastatic or inoperable locally advanced urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra that is transitional cell or mixed transitional/nontransitional (predominantly transitional) cell type.
    b. Subjects must not have received more than 2 prior lines of systemic therapy for metastatic or inoperable locally advanced urothelial carcinoma.
    c. For subjects who have received 1 or 2 lines of prior systemic therapy for metastatic or inoperable locally advanced urothelial carcinoma, 1 of the prior systemic regimens must include a platinum-based therapy. Subjects who have only received non–platinum-based regimens may be enrolled with medical monitor approval.
10. For Phase 2 Part A Cohort D – Anti-PD-1/PD-L1–naive SCCHN:
    a. Subjects with histologically or cytologically confirmed SCCHN not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy).
    b. Carcinoma of the nasopharynx, salivary gland, or nonsquamous histologies are excluded.
    c. Subjects must have received at least 1 prior platinum-based systemic chemotherapy regimen, and no more than 2 prior systemic chemotherapy regimens, including neoadjuvant and/or adjuvant therapy. Subjects who relapsed within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll.
11. For Phase 2 Part A Cohort E – Anti-PD-1/PD-L1–naive SCLC:
    a. Subjects with histologically or cytologically confirmed, advanced or metastatic SCLC with PD after at least 1 line of therapy that includes a platinum-based regimen in the first-line setting, and after no more than 2 prior lines of chemotherapy, and regardless of tumor PD-L1 status.
12. For Phase 2 Part B Cohort A – Urothelial carcinoma:
    a. Subjects with histologically or cytologically confirmed urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra that is transitional cell or mixed transitional/nontransitional (predominantly transitional) cell type.
    b. Metastatic or inoperable locally advanced urothelial carcinoma that has progressed on prior standard therapy with a platinum-based regimen and a checkpoint inhibitor.

13. For Phase 2 Part B Cohort B – SCCHN:
    a. Subjects with histologically confirmed metastatic or recurrent SCCHN not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy).
    b. Must have had disease progression on prior treatment with a platinum-based therapy and an anti–PD-1 therapy. Subjects who relapsed within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll.
    c. Must have documented human papilloma virus status.
    d. Carcinoma of the nasopharynx, salivary gland, or nonsquamous histologies are excluded.
14. For Phase 2 Part B Cohort C – CRC:
    a. Subjects with histologically or cytologically confirmed CRC that have failed prior standard therapy (disease progression; subject intolerance is also allowable).
    b. Prior systemic regimens must include previously approved therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy (if no contraindication); and if negative for KRAS, NRAS, and BRAF mutations and no contraindication, an anti-EGFR therapy; and disease must have progressed after the last administration of approved therapy.
15. Have the presence of at least 1 measurable lesion by CT or MRI per RECIST v1.1 as determined by the local site investigator/radiology assessment.
    a. If subjects have only 1 measurable lesion per RECIST v1.1, any biopsy specimen should be obtained from the nontarget lesion or archival tissue.
    b. If subjects have only 1 measurable lesion per RECIST v1.1, this lesion should not have been in the field of prior irradiation unless there is documented progression of the lesion.

[redacted]

18. Life expectancy > 12 weeks.
19. ECOG performance status 0 to 1.
20. Have resolution of all toxicities and any toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia). Subjects with ≤ Grade 2 neuropathy are an exception and may enroll.
21. Adequate renal, hepatic, and hematologic functions as defined by laboratory parameters within ≤ 7 days before treatment initiation.
    a. Absolute neutrophil count ≥ 1.5×10^9/L.
    b. Platelets ≥ 100×10^9/L.
    c. Hemoglobin ≥ 9 g/dL.
    d. Measured or calculated CrCl (glomerular filtration rate can also be used in place of CrCl) ≥ 50 mL/min.
       Note: Creatinine clearance should be calculated per institutional standard.
    e. Total bilirubin ≤ 1.5 × ULN **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 × ULN.
       – If there is no institutional normal range available for the direct bilirubin, the direct bilirubin should be < 40% of the total bilirubin.
       – In no case can total bilirubin exceed 3.0 × ULN.
    f. AST (SGOT) and ALT (SGPT) ≤ 2.5 × ULN.
    g. INR or PT ≤ 1.5 × ULN, unless subject is receiving anticoagulant therapy, in which case PT or INR must be within therapeutic range of intended use of anticoagulants.
    h. aPTT ≤ 1.5 × ULN, unless subject is receiving anticoagulant therapy, in which case PTT must be within therapeutic range of intended use of anticoagulants.
22. Does not require recurrent paracentesis for management of ascites or thoracentesis for management of pleural effusion, and does not have a shunt to manage ascites or pleural effusion.
23. Albumin > 3.0 g/dL.

24. 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 and at least 50 years of age.)
    b. Woman of childbearing potential who has a negative serum pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up (Phase 2 Part B only) or until 120 days after last dose of study treatment (Phase 1 and Phase 2 Part A only). Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
    c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up (Phase 2 Part B only) or until 120 days after last dose of study treatment (Phase 1 and Phase 2 Part A only). Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

3.2. Subject Exclusion Criteria

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

1. Participation in any other study in which receipt of an investigational study drug or device occurred within 2 weeks or 5 half-lives (whichever is longer) before first dose. For investigational agents with long half-lives (eg, 5 days), enrollment before the fifth half-life requires medical monitor approval.
2. Has received a prior monoclonal antibody within 4 weeks or 5 half-lives (whichever is shorter) before administration of study drug.
    a. *Exception*: No time off anti–PD-1 or anti–PD-L1 therapy is required.
    b. *Exception*: Denosumab may be used.
3. Phase 2 Part A Cohorts A1, B1, C, D, and E only: Has had prior therapy with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti–CTLA-4, anti-CD137, or any other antibody or drug specifically targeting checkpoint pathways.
    a. *Exception*: Prior therapy with an anti–CTLA-4 in the adjuvant setting is permitted.
4. Phase 2 Part A Cohorts A2, A3, B2, and B3 only: Had any Grade 3/4 or any ocular toxicity while receiving prior anti–PD-1 therapy.
5. Has had prior chemotherapy or targeted small molecule therapy within 2 weeks before administration of study treatment.
6. Has had prior therapy with an IDO1 or arginase 1 inhibitor.
7. Has received prior radiotherapy within 2 weeks of enrollment (except for radiation to CNS, which requires ≥ 4-week washout). Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.

8. Has had major surgery within 4 weeks before enrollment (C1D1).
9. Has a known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 2 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the subject has been disease-free for > 1 year, after treatment with curative intent.
10. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dose regimens exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment.
11. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
12. Has a known history of HIV infection. HIV testing is not required unless mandated by the local health authority.
13. Has known history of or is positive for hepatitis B (HBsAg reactive) or hepatitis C (HCV RNA). *Note*: Testing must be performed to determine eligibility.
    a. HBV DNA must be undetectable and HBsAg negative at screening visit.
    b. Hepatitis C antibody testing is allowed for screening purposes in countries where HCV RNA is not part of standard of care. In these cases, HCV antibody positive patients will be excluded.
    c. Subjects who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening visit.
14. Phase 1 and Phase 2 Part A only: Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
15. Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment, and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases confirmed by repeat imaging (note that the repeat imaging should be performed during study screening), and have not required steroids for at least 14 days before study treatment.
    a. Subjects with evidence of cerebral edema will be excluded from participation. In addition, subjects will be excluded from participation in the study if it has been < 4 weeks since radiation therapy was delivered to the CNS.
16. Has had a significant cardiac event within 6 months before Cycle 1 Day 1, including myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, or pulmonary embolism. Medically controlled arrhythmia is permitted.

17. Has a history or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded (corrected by Fridericia or Bazett formula). In the event that a single QTc is > 480 milliseconds, the screening ECG may be repeated in triplicate, and the subject may enroll if the average QTc is < 480 milliseconds.
18. Has received live vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
19. Has any history of SS after receiving serotonergic drugs.
20. Concomitant therapy with valproic acid/valproate-containing therapies.
21. Concomitant therapy with allopurinol and other xanthine oxidase inhibitors.
22. Has received therapy with a MAOI or UGT1A9 inhibitor within 21 days before starting treatment, or anticipates requiring one of these prohibited medications during the treatment phase. Examples of medications in these classes are found in Section 5.6.3.
23. Current use of any prohibited medication as described in Section 5.6.3.
24. Has a known or suspected defect in the function of the urea cycle, including a known deficiency of carbamoyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase, N-acetyl glutamate synthetase, or arginase.
25. Has a history of gastrointestinal condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) that may affect drug absorption.
26. Unable to receive medications PO.
27. Has known hypersensitivity ≥ Grade 3, or severe reaction, to study treatments or any of their excipients.
28. Pregnant or breastfeeding.
29. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 1/2 study, with Phase 1 being a dose-escalation of the triplet combination of INCB001158 plus epacadostat and pembrolizumab, and with Phase 2 consisting of tumor expansion cohorts to study the RP2D of the triplet combination of INCB001158 plus epacadostat and pembrolizumab in Part A and the RP2D of the doublet combination of INCB001158 plus epacadostat in Part B. Figure 2 shows a schematic of the study design.

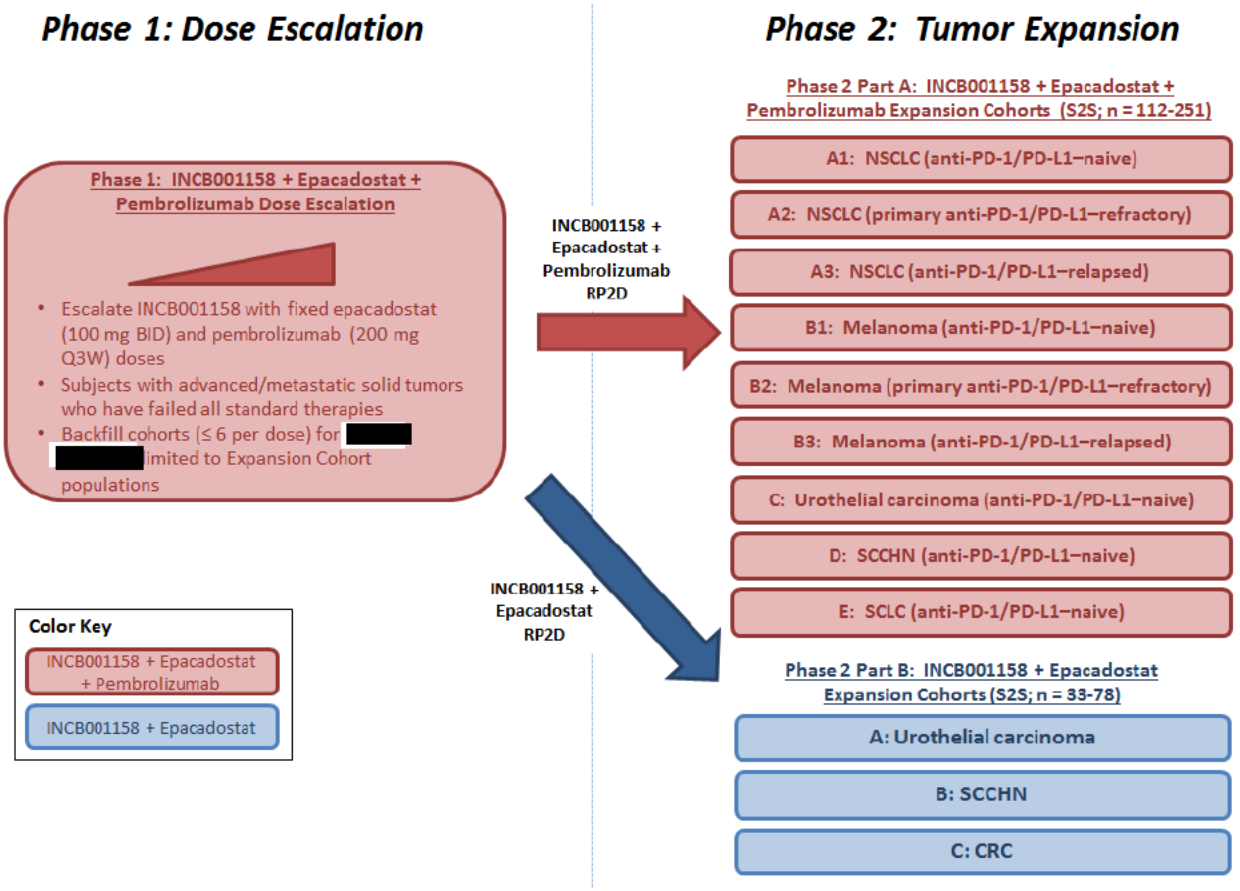
Subjects with advanced or metastatic solid tumors will be enrolled in Phase 1. Subjects with select advanced or metastatic solid tumors will be enrolled in Phase 2 Parts A (NSCLC, melanoma, urothelial carcinoma, SCCHN, and SCLC) and B (urothelial carcinoma, SCCHN, and CRC).

See Section 4.1.1 for full details of the triplet dose escalation (Phase 1), Sections 4.1.2 and 4.1.3 for full details of tumor expansion (Phase 2 Parts A and B, respectively), and Section 5.2 for full study drug administration information.

The definition of DLTs is provided in Section 5.4.2.

Continuous evaluation of toxicity events will be performed in the expansion cohorts. If the cumulative incidence of Grade ≥ 3 immune-related AEs is > 40% after 10 subjects are enrolled in a specific expansion cohort within Phase 2, further enrollment in that cohort will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determines the appropriate course of action. If an expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower dose level.

Figure 2: Study Design



4.1.1. Phase 1: Dose Escalation of INCB001158 + Epacadostat + Pembrolizumab

In this study, the RP2D of both the triplet (INCB001158 + epacadostat + pembrolizumab) and doublet (INCB001158 + epacadostat) will be determined from the dose escalation of the triplet combination in Phase 1. The INCB001158 dose will be escalated while keeping the epacadostat (100 mg BID) and pembrolizumab (200 mg Q3W) doses fixed at the levels used to study this doublet in Phase 3 (NCT02752074; eIB). INCB001158 is not expected to have overlapping toxicity with either of these molecules, based on their respective mechanisms and on the available safety data from the first-in-human study, INCB 01158-101 (iIB), and the epacadostat + pembrolizumab INCB 24360-202 Phase 2 study (Hamid et al 2017a). In the ongoing INCB 01158-101 study, INCB001158 doses have been identified that are pharmacologically active and well-tolerated (Papadopoulos et al 2017). Thus, it is hypothesized that when INCB001158 is escalated with the Phase 3 doses of epacadostat plus pembrolizumab, an RP2D will be identified based on an INCB001158 PAD and before an MTD is reached. In that case, the INCB001158 and epacadostat doses in the triplet RP2D would be appropriate to also use as the RP2D for the INCB001158 + epacadostat doublet in Phase 2 Part B. Hence, no separate dose escalation of INCB001158 with epacadostat 100 mg BID will be conducted in this study.

An open-label, BOIN design (Liu and Yuan 2015) will be used to determine the RP2D of the triplet combination of INCB001158, epacadostat, and pembrolizumab in 21-day treatment cycles in subjects with advanced or metastatic solid tumors. Given the target DLT rate of 33% for the

INCB001158 plus epacadostat and pembrolizumab combination, the dose escalation and de-escalation rules are shown in Table 2. The BOIN design also includes an elimination rule. When ≥ 3 subjects have been treated, if the probability that the estimated toxicity rate that is above the target DLT rate is > 95% at a certain dose level, then this dose level and higher dose levels are assumed too toxic and will be eliminated. If the lowest dose level is eliminated, the whole dose escalation will be terminated. Table 2 (in the bottom row) provides the elimination rules. Based on this algorithm, a minimum of 3 evaluable subjects and a maximum of 9 evaluable subjects will be enrolled at each tested dose level. The dose escalation will continue, based on the rules in Table 2, until the rules require at least 1 of the following:

- Enrollment of additional subjects in a cohort that already has 9 evaluable subjects, or
- Dose escalation to a dose level that has already been eliminated, or
- Dose escalation above the maximum allowable dose level identified in the INCB 01158-101 study (see Section 1.2.4).

At that point, the dose escalation will be stopped.

Table 2: Dose Escalation, De-Escalation, and Elimination Boundaries for Target DLT Rate = 33% in Phase 1

	The Number of Subjects Treated at the Current Dose								
Action	1	2	3	4	5	6	7	8	9[a]
Escalate if # of DLTs ≤	NA	NA	0	1	1	1	1	2	2
De-escalate if # of DLTs ≥	1	1	2	2	2	3	3	4	4
Elimination if # of DLTs ≥	NA	NA	3	3	4	4	5	5	6

DLT = dose-limiting toxicity; NA = not applicable.

[a] If 9 evaluable subjects are enrolled in a cohort and 3 of those subjects experience a DLT, then the medical monitor and the investigators will review the entirety of the data and decide whether to dose-escalate, dose–de-escalate, or to stop at that dose level.

Dose escalation will begin with starting doses of INCB001158 at least 2 dose levels below the maximum tolerated and tested dose from the INCB 01158-101 study (likely to be 50 mg BID or 75 mg BID – see Table 3 and Table 4, respectively. If the starting dose is not one of those 2 dose levels, then a revised dose escalation table will be provided to sites. However, the starting doses of epacadostat (100 mg PO BID continuous dose administration) and pembrolizumab (200 mg IV Q3W) will not be changed. Epacadostat 100 mg BID was selected as the starting dose because it has been shown to be active and tolerable in several epacadostat combination clinical studies, including with pembrolizumab (eIB, Gangadhar et al 2017, Hamid et al 2017a, Hamid et al 2017b, Smith et al 2017). The starting dose of pembrolizumab is the standard, approved dose and schedule (Keytruda PI, Keytruda SPC) and also the dose used in combination with epacadostat in Phase 3.

If the starting doses of the triplet combination of INCB001158, epacadostat, and pembrolizumab are tolerable (eg, none of the first 3 evaluable subjects experiences a DLT; see Section 5.4.2),

then the INCB001158 dose will be escalated in subsequent cohorts, while keeping the epacadostat and pembrolizumab doses constant, until one of the stopping rules (described above and in Table 2) is met.

If the starting doses of INCB001158, epacadostat 100 mg BID, and pembrolizumab 200 mg Q3W are not tolerable, then an additional cohort will be enrolled at a reduced dose of either INCB001158 or epacadostat, depending on which one is deemed most likely to have caused the intolerability, upon agreement between the medical monitor and the study investigators (ie, Dose Level -1A or -1B; see Table 3 and Table 4).

A PAD will be defined as a dose at or below the monotherapy MTD at which at least half of the subjects (and at least 2 subjects in total) enrolled at a particular dose level achieve a trough (C_{min}) plasma concentration of INCB001158 at steady state of ≥1 μM, which is equivalent to the IC_{90} for arginase 1. This definition may be modified based on emerging data from the INCB 01158-101 first-in-human study, upon agreement between the medical monitor and the study investigators. The MTD, if reached, is the maximum tested dose of INCB001158, such that no more than 33% of the subjects receiving the triplet combination experience a DLT during the first 6 weeks on study drug.

Dose interruptions and/or modifications may be implemented based on toxicity. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation is not permitted.

After completing the dose escalation per the BOIN rules, one of the INCB001158 dose levels that is pharmacologically active (ie, a PAD) and tolerable in combination with epacadostat 100 mg BID or lower and pembrolizumab 200 mg Q3W (ie, MTD or lower) will be selected, and that triplet combination will be the RP2D. The doublet RP2D would consist of the same doses of INCB001158 and epacadostat.

Note that if a dose level to be assigned as RP2D has fewer than 9 evaluable subjects in it, then the medical monitor and study investigators can consider adding subjects to a total of 9 before making the final RP2D decision.

The safety and tolerability of the triplet RP2D will be further assessed in 9 tumor expansion cohorts in Phase 2 Part A (see Section 4.1.2), and the safety and tolerability of the doublet RP2D will be further assessed in 3 tumor expansion cohorts in Phase 2 Part B (see Section 4.1.3).

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

Table 3: Dose Levels for Phase 1: INCB001158 + Epacadostat + Pembrolizumab, Based on INCB001158 Starting Dose of 50 mg BID

Dose Level	INCB001158	Epacadostat	Pembrolizumab
-1B[a]	50 mg PO BID	50 mg PO BID	200 mg IV Q3W
-1A[b]	25 mg PO BID	100 mg PO BID	200 mg IV Q3W
1	**50 mg PO BID**	**100 mg PO BID**	**200 mg IV Q3W**
2	75 mg PO BID	100 mg PO BID	200 mg IV Q3W
3	100 mg PO BID	100 mg PO BID	200 mg IV Q3W
4	150 mg PO BID	100 mg PO BID	200 mg IV Q3W

[a] -1 dose level to be used if unacceptable toxicity is observed at Dose Level 1 and is deemed to be due to epacadostat.
[b] -1 dose level to be used if unacceptable toxicity is observed at Dose Level 1 and is deemed to be due to INCB001158.

Table 4: Dose Levels for Phase 1: INCB001158 + Epacadostat + Pembrolizumab, Based on INCB001158 Starting Dose of 75 mg BID

Dose Level	INCB001158	Epacadostat	Pembrolizumab
-1B[a]	75 mg PO BID	50 mg PO BID	200 mg IV Q3W
-1A[b]	50 mg PO BID	100 mg PO BID	200 mg IV Q3W
1	**75 mg PO BID**	**100 mg PO BID**	**200 mg IV Q3W**
2	100 mg PO BID	100 mg PO BID	200 mg IV Q3W
3	150 mg PO BID	100 mg PO BID	200 mg IV Q3W

[a] -1 dose level to be used if unacceptable toxicity is observed at Dose Level 1 and is deemed to be due to epacadostat.
[b] -1 dose level to be used if unacceptable toxicity is observed at Dose Level 1 and is deemed to be due to INCB001158.

At the discretion of the sponsor, up to a total of 6 additional "backfill" subjects may be enrolled at any tolerable dose level to further investigate safety [redacted].

4.1.2. Phase 2 Part A: Tumor Expansion of INCB001158 + Epacadostat + Pembrolizumab

The RP2D of the triplet combination of INCB001158, epacadostat, and pembrolizumab identified in Phase 1 will be further assessed in Phase 2 Part A in the following 9 tumor expansion cohorts, 5 of which include only anti-PD-1/PD-L1–naive subjects, and 4 of which include only subjects who have received an anti–PD-1 or anti–PD-L1 agent in a recent line of therapy:

- Cohort A1: Subjects with anti-PD-1/PD-L1–naive NSCLC who have received no more than 2 prior systemic chemotherapy regimens for Stage IV disease, one of which must include a platinum-based therapy (see Inclusion Criterion 3 for more details). In a similar population in the INCB 24360-202 study, the ORR for epacadostat + pembrolizumab was 39% (Gangadhar et al 2017). However, in this study, a slightly lower ORR of 30% will be used as the background ORR.
- Cohort A2: Subjects with locally advanced unresectable or metastatic NSCLC who received prior treatment with anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and have PD as their best response to treatment that is confirmed at least 4 weeks later (see Inclusion Criterion 4 for more details). This population is expected to be refractory to further anti–PD-1/anti–PD-L1 treatment. This will be known as the primary anti–PD-1/anti–PD-L1 refractory cohort (primary refractory).
- Cohort A3: Subjects with locally advanced unresectable or metastatic NSCLC who have received prior anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and achieved either SD for at least 24 weeks or PR/CR but later have confirmed PD (PD confirmed at least 4 weeks later). See Inclusion Criterion 5 for more details. This will be known as the anti-PD-1/PD-L1–relapsed cohort (relapsed).
- Cohort B1: Subjects with anti-PD-1/PD-L1–naive melanoma who have received no more than 2 prior lines of systemic therapy for unresectable Stage III or Stage IV disease (see Inclusion Criterion 6 for more details). In a similar population in the INCB 24360-202 study, the ORR for epacadostat + pembrolizumab was 56% (Gangadhar et al 2016).
- Cohort B2: Subjects with unresectable Stage III or Stage IV melanoma who received prior treatment with anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and have PD as their best response to treatment that is confirmed at least 4 weeks later (see Inclusion Criterion 7 for more details). This population is expected to be refractory to further anti–PD-1/anti–PD-L1 treatment. This will be known as the primary anti-PD-1/PD-L1–refractory cohort (primary refractory).

- Cohort B3: Subjects with unresectable Stage III or Stage IV melanoma who have received prior anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and achieved either SD for at least 24 weeks or PR/CR, but later have confirmed PD (PD confirmed at least 4 weeks later). See Inclusion Criterion 8 for more details. This will be known as the anti-PD-1/PD-L1–relapsed cohort (relapsed).
- Cohort C: Subjects with PD(L)1-naive urothelial carcinoma who have received no more than 2 prior lines of systemic chemotherapy regimens for metastatic or inoperable locally advanced disease, one of which must include a platinum-based therapy (see Inclusion Criterion 7 for more details). In a similar population in the INCB 24360-202 study, the ORR for epacadostat + pembrolizumab was 38% (first and second line) and 25% (third line and beyond; Smith et al 2017).
- Cohort D: Subjects with PD(L)1-naive SCCHN not amenable to local therapy with curative intent, who have received at least 1 prior platinum-based systemic chemotherapy regimen, and no more than 2 prior systemic chemotherapy regimens (see Inclusion Criterion 8 for more details). In a similar population in the INCB 24360-202 study, the ORR for epacadostat + pembrolizumab was 39% (Hamid et al 2017b).
- Cohort E: Subjects with PD(L)1-naive, advanced or metastatic SCLC who have received at least 1 line of therapy that includes a platinum-based regimen in the first-line setting, and no more than 2 prior lines of chemotherapy (see Inclusion Criterion 9 for more details). In a broadly similar PD-L1–unselected population in the CheckMate 032 study, the ORR for nivolumab was 11%, whereas the ORR in a PD-L1–positive population treated with pembrolizumab was 33% (Hellman et al 2017, Ott et al 2016; see also Section 1.2.3.2). However, the sample sizes were small in each study, so these differences in ORR observed with pembrolizumab and nivolumab may not pan out in larger studies. For the purposes of this study, the baseline ORR was selected based on the average ORR of the 2 anti–PD-1 agents and allowing for some theoretical additive activity from epacadostat. Of note, epacadostat has not been studied in combination with an anti–PD-1 agent.

In each cohort, the ORR of the triplet combination will be assessed using a Simon 2-stage design (see Table 5), to determine whether the combination has sufficient antitumor activity to warrant further testing in subsequent clinical studies. The basis for the background ORR selected for each cohort is described above.

Note that the sponsor may evaluate fewer expansion cohorts or some cohorts in sequence, at their discretion.

If, at the time of completion of enrollment in Stage 1, it is not known whether the target ORR to proceed to Stage 2 will be met, then enrollment will be paused until and unless the ORR to proceed has been met.

Table 5: Phase 2 Part A: Simon 2-Stage Design

Cohort	Background ORR	Target ORR	Alpha	Power	N for Stage 1	ORR to Proceed ≥ (r1 + 1) / n1[a]	N for Stage 2	ORR for Positive Cohort ≥ (r + 1) / n[a]
A1	30%	50%	0.1	80%	15	6/15	17	13/32
A2	2%	15%	0.1	80%	11	1/11	15	2/26
A3	15%	35%	0.1	80%	9	2/9	14	6/23
B1	56%	76%	0.1	80%	12	8/12	19	21/31
B2	2%	15%	0.1	80%	11	1/11	15	2/26
B3	15%	35%	0.1	80%	9	2/9	14	6/23
C	30%	50%	0.1	80%	15	6/15	17	13/32
D	39%	59%	0.1	80%	15	7/15	16	16/31
E	25%	45%	0.1	80%	15	5/15	12	10/27

[a] r1 = response rate at the end of Stage 1; n1 = sample size for Stage 1 only; r = overall response rate for combined Stage 1 and 2; n = sample size for combined Stage 1 and 2.

[redacted]

4.1.3. Phase 2 Part B: Tumor Expansion of INCB001158 + Epacadostat

The RP2D of INCB001158 and epacadostat identified in Phase 1 will be assessed in Phase 2 Part B, in the following 3 tumor expansion cohorts:

- Cohort A: Subjects with metastatic or inoperable locally advanced urothelial carcinoma who have had disease progression on prior standard therapy with a platinum-based regimen and a checkpoint inhibitor (see Inclusion Criterion 12 for more details).
- Cohort B: Subjects with metastatic or recurrent SCCHN not amenable to local therapy with curative intent, who had disease progression on prior treatment with a platinum-based therapy and an anti–PD-1 therapy (see Inclusion Criterion 13 for more details).
- Cohort C: Subjects with CRC who have failed prior standard therapy (see Inclusion Criterion 14 for more details).

In each cohort, the ORR of the doublet combination will be assessed using a Simon 2-stage design (see Table 6), to determine whether the combination has sufficient antitumor activity to warrant further testing in subsequent clinical studies. Neither study drug has demonstrated antitumor activity as monotherapy in patients with advanced or metastatic cancer (refer to iIB and eIB), so the assumed background ORR of 2% is based on the doublet also not having antitumor activity. The target ORR of 15% represents an active doublet.

If, at the time of completion of enrollment in Stage 1, it is not known whether the target ORR to proceed to Stage 2 will be met, then enrollment will be paused until and unless the ORR to proceed has been met.

Table 6: Phase 2 Part B: Simon 2-Stage Design

Cohort	Background ORR	Target ORR	Alpha	Power	N for Stage 1	ORR to Proceed ≥ (r1 + 1) / n1[a]	N for Stage 2	ORR for Positive Cohort ≥ (r + 1) / n[a]
A	2%	15%	0.1	80%	11	1/11	15	2/26
B	2%	15%	0.1	80%	11	1/11	15	2/26
C	2%	15%	0.1	80%	11	1/11	15	2/26

[a] r1 = response rate at the end of Stage 1; n1 = sample size for Stage 1 only; r = overall response rate for combined Stage 1 and 2; n = sample size for combined Stage 1 and 2.

[redacted]

4.2. Measures Taken to Avoid Bias

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

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Under Protocol Amendment 2, up to 5 subjects will be enrolled in the dose-escalation (Phase 1) part. No subjects will be enrolled in Phase 2.

It is planned to have 4 sites during Phase 1.

4.3.2. Replacement of Subjects

During dose escalation in Phase 1, up to 4 subjects per cohort will be enrolled at a time, with the aim of obtaining at least 3 subjects who are evaluable for DLTs (see Section 5.4.2 for definition). If fewer than 3 subjects are evaluable, additional subjects will be enrolled until there are 3 evaluable subjects.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, subject study participation, including screening and post-treatment follow-up is expected to average approximately 12 to 18 months per individual subject. Note that the treatment period will last as long as subjects are deriving benefit, are tolerating the regimen and do not meet withdrawal criteria.

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 [redacted] been lost to follow-up, or have withdrawn consent for further follow-up. It is anticipated that the study duration will be approximately 3 years.

If there are ≤ 5 subjects on study for more than 6 months, a database lock of the study may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study treatment and be seen by the investigator per the study assessments in Section 6. 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 institutional review board (IRB)/independent ethics committee (IEC) in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively or if required by regulatory decision. 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.

4.6.1. Protocol Amendment (Version) 2

As of this Protocol Amendment (Version) 2, enrollment of subjects into any part of Study INCB 01158-202 is halted. This is based on the results from the ECHO-301/KEYNOTE-252 melanoma clinical study (Long et al 2018). In an interim analysis, the study did not meet the prespecified endpoint of improvement in progression-free survival for the combination of pembrolizumab and epacadostat compared with pembrolizumab and placebo. The overall survival endpoint was also not expected to reach statistical significance. There were no safety concerns with the treatment (pembrolizumab + epacadostat) arm compared with the control (pembrolizumab + placebo) arm.

Given the outcome of study ECHO-301/KEYNOTE-252, the changes to the INCB 01158-202 study design are summarized below:

- The ongoing Phase 1 portion (dose escalation and safety evaluation of INCB001158 in combination with epacadostat and pembrolizumab) will stop further enrollment, except for patients who have consented and are in screening as of 08 MAY 2018. These subjects will be permitted to enroll if eligibility is determined as outlined per the Protocol.
- The Phase 1 backfill cohorts and the Phase 2 portion of the study (Part A – tumor expansion of INCB001158 + epacadostat + pembrolizumab and Part B – tumor expansion of INCB001158 + epacadostat) will not be opened.
- Ongoing Phase 1 subjects may continue treatment with INCB001158 + epacadostat + pembrolizumab as long as, per the Protocol, they are deriving clinical benefit, tolerating the treatment, and do not meet any withdrawal criteria.

Sections of the Protocol relating to the parts of the study that will no longer be conducted are now not applicable and should be ignored.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

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

5.1.2. Randomization and Blinding

Not applicable, as this is an open-label study.

5.2. Study Drugs and Other Study Treatments

Study treatment is defined as any investigational treatment(s) or marketed product(s) intended to be administered to a study subject according to the study Protocol. There are 3 investigational study treatments in this study – INCB001158, epacadostat, and pembrolizumab (Table 7). INCB001158 is also referred to as the study drug in this Protocol. Although pembrolizumab is approved and marketed in various indications (see Section 1.1.3.1), it is investigational in this study in combination with INCB001158 and epacadostat.

Table 7: Study Drug and Other Study Treatments

Drug	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period
INCB001158	25-150 mg[a]	BID	Oral	Phase 1 and Phase 2 Part A: Daily until meets discontinuation criteria or for 35 cycles[b], whichever is sooner Phase 2 Part B: Daily until meets discontinuation criteria
Epacadostat	50-100 mg[a]	BID	Oral	Phase 1 and Phase 2 Part A: Daily until meets discontinuation criteria or for 35 cycles[b], whichever is sooner Phase 2 Part B: Daily until meets discontinuation criteria
Pembrolizumab	200 mg	Every 3 weeks	IV infusion	Phase 1 and Phase 2 Part A: Day 1 of each cycle until meets discontinuation criteria or for up to 35 cycles[b], whichever is sooner

[a] See Section 4.1.1 for details of dose levels of INCB001158 and epacadostat during the Phase 1 dose escalation.
[b] A cycle length of 21 days.

5.2.1. INCB001158

5.2.1.1. Description and Administration

INCB001158 will be administered orally using a capsule (25 mg or 100 mg per capsule) formulation. INCB001158 will be administered only to subjects who have signed and dated an ICF. INCB001158 will be administered on Days 1 through 21 of each 21-day cycle and should be taken orally using the number of capsules directed in the Pharmacy Manual. The starting dose will depend on which phase of the study the subject is in. In Phase 1, the starting dose will be based on which dose level cohort the subject is in; in Phase 2, the starting dose will be the RP2D identified in Phase 1. INCB001158 dosing will not be adjusted for body weight or surface area.

In Phase 1 and Phase 2 Part A, INCB001158 and epacadostat will be given daily in combination with pembrolizumab for up to 35 cycles, as long as disease progression has not occurred and criteria for treatment discontinuation have not been met.

In Phase 2 Part B, INCB001158 and epacadostat will be given daily for as long as disease progression has not occurred and criteria for treatment discontinuation have not been met.

5.2.1.2. Supply, Packaging, and Labeling

INCB001158 will be provided to sites by Incyte. The contents of the label will be in accordance with all applicable regulatory requirements.

INCB001158 will be supplied as 25 mg or 100 mg capsules packaged in blister cards. No preparation is required. All capsule excipients comply with the requirements of the applicable compendial monographs (Ph Eur, USP/NF; refer to iIB).

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

Blister cards of INCB001158 capsules should be stored at room temperature, 15°C to 30°C (59°F to 86°F).

5.2.1.4. Instruction to Subjects for Handling Study Drug (INCB001158)

The subject must be instructed in the handling of study drug as follows:

- To store the study drug at room temperature.
- To only remove from the study drug blister card the number of capsules needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses.

- To take study drug at approximately the same times each day without respect to food (except on Protocol-defined clinic days, when the subject should fast for at least 8 hours before taking study drug; see Section 7.6.5.2) and with a full glass of water. The second dose on any given day should be taken approximately 12 hours after the first dose.
- Subjects who vomit their INCB001158 dose should be instructed NOT to make up that dose and to report the frequency of vomiting occurrences associated with study drug administration to the site. Subjects who report ≥ 3 incidences of vomiting associated with study drug administration will have a blood sample drawn for an unscheduled PK analysis.
- To keep study drug in a safe place and out of reach of children.
- To bring all used and unused study drug blister cards to the site at each visit.
- Missed doses of INCB001158 should be skipped. If a subject forgets to take a dose of study drug and he/she is outside of the allotted window period (± 6 h), then he/she should be instructed to skip that dose and NOT to take extra study drug at their next administration.
- On Protocol-defined clinic days (see Table 14) subjects should be instructed NOT to take their morning dose of INCB001158 at home. The morning dose must be administered at the clinical site after all predose procedures have been performed. The time of dose administration will be recorded in the clinic. The evening doses will be self-administered by the subject after all postdose activities have been completed.

5.2.2. Epacadostat

Epacadostat 25 mg or 100 mg tablets will be self-administered orally BID. All BID doses will be taken morning and evening, approximately 12 hours apart without respect to food. If a dose is missed by more than 4 hours, that dose should be skipped and should be resumed at the scheduled time. Dose reductions or interruptions may be required for safety, see Section 5.4.

5.2.2.1. Description and Administration

Epacadostat 25 mg or 100 mg tablets will be self-administered orally BID. All BID doses will be taken morning and evening, at the same time as the INCB001158 dose, approximately 12 hours apart, without respect to food. If a dose is missed by more than 4 hours, that dose should be skipped and should be resumed at the next scheduled time. Dose reductions or interruptions may be required for safety; see Section 5.4. Subjects will hold the morning dose of epacadostat for each clinic visit; study medication will be administered in the clinic.

In Phase 1 and Phase 2 Part A, epacadostat may be taken in combination with INCB001158 and pembrolizumab for up to 35 cycles as long as disease progression has not occurred and criteria for treatment discontinuation have not been met.

In Phase 2 Part B, epacadostat and INCB001158 will be given daily for as long as disease progression has not occurred and criteria for treatment discontinuation have not been met.

5.2.2.2. Supply, Packaging, and Labeling

Epacadostat will be provided to sites by Incyte. The contents of the label will be in accordance with all applicable regulatory requirements.

Epacadostat will be supplied as 25 mg and 100 mg tablets packaged in high-density polyethylene bottles. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph Eur, USP/NF; refer to eIB).

5.2.2.3. Storage

Bottles of tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F).

5.2.2.4. Instruction to Subjects for Handling Epacadostat

The subject must be instructed in the handling of epacadostat study treatment as follows:

- To store the study treatment at room temperature.
- To only remove from the study treatment bottle/kit the number of tablets needed at the time of administration.
- To make every effort to take doses on schedule.
- To report any missed doses.
- Subjects who vomit their epacadostat dose should be instructed NOT to make up that dose and to report the frequency of vomiting occurrences associated with study drug administration to the site. Subjects who report ≥ 3 incidences of vomiting associated with epacadostat administration will have a blood sample drawn for an unscheduled PK analysis.
- To keep study treatment in a safe place and out of reach of children.
- To bring all used and unused study treatment kits to the site at each visit.
- If a dose is missed by more than 4 hours, that dose should be skipped, and the next scheduled dose should be administered at the usual time.

5.2.3. Pembrolizumab

5.2.3.1. Description and Administration

Study treatment with pembrolizumab (Phase 1 and Phase 2 Part A only) should be administered on Day 1 of each cycle after all procedures/assessments have been completed. All study treatments will be administered on an outpatient basis.

Study treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for Cycle 1 Day 1, where there is no window.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion, to start directly after the AM doses of INCB001158 and epacadostat. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of

infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

Pembrolizumab in combination with INCB001158 and epacadostat may be taken for up to 35 cycles as long as disease progression has not occurred.

5.2.3.2. Supply, Packaging, and Labeling

Pembrolizumab is supplied either as 50 mg lyophilized powder for reconstitution in single-use vials or as 25 mg/mL sterile solution for infusion in 4 mL vials. The Pharmacy Manual contains specific instructions for pembrolizumab, for reconstitution of the lyophilized powder, preparation of the infusion fluid, and administration.

5.2.3.3. Storage

Vials of pembrolizumab must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) in the original carton to protect them from light. Do not freeze. Do not shake.

5.3. Treatment Compliance

Compliance with all study-related treatments should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB001158 and epacadostat will be calculated by the sponsor based on the drug accountability documented in the patient diaries and by the site staff and will be monitored by the sponsor/designee (capsule/tablet counts). Subjects will be instructed to bring all study treatments with them to the study visits from Cycle 2 Day 1 onwards, in order for site personnel to conduct capsule/tablet counts to assess study treatment accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

Pembrolizumab is administered as an IV infusion by site personnel. Receipt of infusions will be documented by the site staff and monitored by the sponsor/designee.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Selections and modifications to the study treatment regimen are planned for dose-escalation cohorts in Phase 1. Dose interruptions and modifications also may occur for individual study subjects. The identification of DLTs will define the doses used in planned cohorts (see Section 4.1.1). Further, the occurrence of DLTs and other toxicities (related or unrelated to study treatment) will guide decisions for treatment interruptions and discontinuation for individual subjects. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation will not be permitted.

5.4.1.1. INCB001158

For subjects in Phase 1, dose reductions of INCB001158 will be permitted during the first 2 cycles (first 42 days) only if a subject experiences a DLT or a toxicity that may herald a DLT. If a subject experiences a DLT, treatment continuation at a lower dose of INCB001158 will be permitted as long as the toxicity has returned to ≤ Grade 1 or baseline within 28 days. When

INCB001158 is held or discontinued, epacadostat and pembrolizumab therapy may be continued, at the investigator's discretion. Upon recovery, subjects may restart at 1 INCB001158 dose level lower. Subjects who do not recover within 28 days will not be eligible for resumption of study treatment without approval from the medical monitor. After Cycle 2, dose reductions or interruptions for AEs may take place at any time at the discretion of the investigator in consultation with the medical monitor. See also Table 9.

5.4.1.2. Epacadostat

Doses of epacadostat may need to be decreased because of toxicity, or interrupted and restarted with recovery of laboratory values or AEs. See also Table 9.

5.4.1.3. Pembrolizumab

In Phase 1 and Phase 2 Part A, pembrolizumab may be interrupted, but no dose modifications are permitted. In all cases where pembrolizumab dosing is held, dosing for INCB001158 and epacadostat must also be held. However, if either or both of INCB001158 and epacadostat is/are discontinued due to drug-related AEs, subjects are allowed to continue to receive the other study treatments. See also Table 9.

5.4.2. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose in Phase 1

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 8 occurring up to and including Day 42, except those with a clear alternative explanation (eg, disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. All DLTs will be assessed by the investigator using CTCAE v4.03 criteria. Subjects who receive at least 63 of 84 doses (≥ 75%) for each of INCB001158 and epacadostat at the level assigned plus at least 2 doses of pembrolizumab or who have a DLT, will be considered evaluable for determining tolerability of the dose. Subjects who do not meet these criteria may be replaced to obtain sufficient evaluable subjects to be able to assess that dose level using the BOIN design, as outlined in Table 2.

Clear evidence of urea cycle inhibition (eg, an increase in fasting urinary orotic acid to > 10 × ULN, any orotic acid value of > 40 × ULN, or symptomatic hyperammonemia) would also be considered a dose-limiting event and will be treated the same as a DLT with regard to the dose escalation rules and definition of the MTD described in Section 4.1.1. Refer to the INCB001158 IB (iIB) for an explanation of these orotic acid thresholds.

Individual subject dose reductions for INCB001158 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 INCB001158, decisions will be made based on events that are observed from the first day of study treatment administration through and including the final day of Cycle 2 (Day 42). A lower MTD may subsequently be determined based on relevant toxicities that become evident after Day 42.

If a subject experiences a DLT that is considered life-threatening, permanently discontinue all 3 study treatments. If a subject experiences a DLT that is not considered life-threatening, interrupt all 3 study treatments, and follow the management guidelines in Table 9.

Table 8: Definition of Dose-Limiting Toxicity

Toxicity
Nonhematologic
• Any ≥ Grade 3 nonhematologic toxicity EXCEPT: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Asymptomatic changes in amylase, lipase, or lipid profiles. – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions).
Hematologic
• Grade 3 thrombocytopenia with bleeding. • Grade 4 thrombocytopenia. • Febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.5°C). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 7 days after interrupting study treatment. • Grade 4 anemia.
Immune-related toxicity
• ≥ Grade 2 ocular irAEs will be considered a DLT. • Grade 3 irAEs that do not improve to baseline or at least Grade 1 in < 5 days with appropriate care or with corticosteroid therapy will be considered a DLT. Exception: Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require systemic steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab or 14 days, whichever is longer. • Grade 4 irAEs will be considered a DLT regardless of duration. • ≥ Grade 2 pneumonitis.
General
• The inability to receive ≥ 75% of INCB001158 and/or epacadostat doses and/or 2 doses of pembrolizumab during the DLT-evaluation period (42 days) due to a drug-related AE will be considered a DLT. • Any other AE that is felt to be treatment-limiting in the medical opinions of the principal investigator and the medical monitor may be considered a DLT.

ANC = absolute neutrophil count.
Note: Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination will not be considered a DLT.

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

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

5.4.4. Follow-Up of Dose-Limiting Toxicities

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

5.4.5. Procedures for Cohort Review and Dose Escalation

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

5.4.6. Dose Modifications for Immune-Related AEs and AEs Related to Urea-Cycle Inhibition

As described in Section 1.3.1, INCB001158 has the potential to cause toxicity related to inhibition of arginase 1 in the hepatic urea cycle. Table 9 provides guidance for INCB001158 dose modifications and subject management if there is evidence of urea cycle inhibition.

Dose modification and toxicity management for irAEs associated with INCB001158, epacadostat, and/or pembrolizumab should be managed as follows.

Adverse events (both nonserious and serious) associated with INCB001158, epacadostat, and/or pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, adequate evaluation should be ensured to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue INCB001158, epacadostat, and/or pembrolizumab and administer corticosteroids.

Table 9 summarizes the AE dose modification actions for INCB001158, epacadostat, and/or pembrolizumab. For subjects enrolled in Phase 2 Part B and receiving only INCB001158 and epacadostat, the pembrolizumab details in this table should be ignored. Of note, when indicated by Table 9 to mitigate irAEs, the dose of INCB001158 must be reduced using the dose levels outlined in Table 3, and the dose of epacadostat must be reduced using the dose levels outlined in Table 10. Once reduced, re-escalation of INCB001158 and epacadostat is not permitted.

Table 9: Dose Modification and Toxicity Management Guidelines for Adverse Events in Subjects Receiving INCB001158 and Epacadostat ± Pembrolizumab

Adverse Event	Toxicity Grade or Conditions (CTCAE v4.03)	Study Medication	Action Taken With Study Medication	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Evidence of urea cycle inhibition	• Fasting urinary orotic acid > 2 × and < 10 × ULN • Any urinary orotic acid > 2 × and < 40 × ULN	INCB001158	Continue.	None.	Retest fasting urinary orotic acid 1 week later. If the fasting level is still abnormal, withhold INCB001158 and retest every week until fasting urinary orotic acid is ≤ 2 × ULN, then consider restarting (at a lower dose) in consultation with medical monitor.
		Epacadostat	Continue.		
		Pembrolizumab[a]	Continue.		
	• Ammonia 2 × ULN and 2 × baseline (repeated measurements or with symptoms) • Fasting urinary orotic acid > 10 × ULN • Any urinary orotic acid > 40 × ULN • BUN < 50% LLN	INCB001158	Withhold. Consider restarting (at a lower dose) in consultation with medical monitor.	See Section 5.4.8 for management of hyperammonemia.	
		Epacadostat	Continue.		
		Pembrolizumab[a]	Continue.		

Table 9: Dose Modification and Toxicity Management Guidelines for Adverse Events in Subjects Receiving INCB001158 and Epacadostat ± Pembrolizumab (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v4.03)	Study Medication	Action Taken With Study Medication	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Pneumonitis	Grade 2	INCB001158	Withhold until Grade 0-1. Restart at full dose.	Administer corticosteroids (initial dose of 1-2 mg/kg per day of prednisone or equivalent) followed by taper.	• Monitor subjects for signs and symptoms of pneumonitis. • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
		Epacadostat	Withhold until Grade 0-1. Related: Reduce by 1 dose level. Not related: Same dose level.		
		Pembrolizumab[a]	Withhold until Grade 0-1.		
	Grade 3 or 4, or recurrent Grade 2	INCB001158	Withhold until Grade 0-1. Consider re-challenge with monotherapy at next dose level lower.		
		Epacadostat	Permanently discontinue.		
		Pembrolizumab[a]	Permanently discontinue.		

Table 9: Dose Modification and Toxicity Management Guidelines for Adverse Events in Subjects Receiving INCB001158 and Epacadostat ± Pembrolizumab (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v4.03)	Study Medication	Action Taken With Study Medication	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Diarrhea/colitis	Grade 2 or 3	INCB001158	Withhold until Grade 0-1. Grade 2: Re-start at same dose level. Grade 3: Restart at next dose level lower.	Administer corticosteroids (initial dose of 1-2 mg/kg per day of prednisone or equivalent) followed by taper.	• Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
		Epacadostat	Withhold until Grade 0-1. Related: Reduce by 1 dose level. Not Related: Same dose level.		
		Pembrolizumab[a]	Withhold until Grade 0-1.		
	Grade 4	INCB001158	Withhold until Grade 0-1. Consider re-challenge with monotherapy at next dose level lower.		
		Epacadostat	Permanently discontinue.		
		Pembrolizumab[a]	Permanently discontinue.		

Table 9: Dose Modification and Toxicity Management Guidelines for Adverse Events in Subjects Receiving INCB001158 and Epacadostat ± Pembrolizumab (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v4.03)	Study Medication	Action Taken With Study Medication	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
AST/ALT elevation or Increased bilirubin[b]	Grade 2	INCB001158	Withhold until Grade 0-1. Re-start at same dose level.	Administer corticosteroids (initial dose of 0.5-1 mg/kg of prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently) until liver enzyme value returns to baseline or is stable.
		Epacadostat	Withhold until Grade 0-1. Related: Reduce by 1 dose level. Not related: Same dose level.		
		Pembrolizumab[a]	Withhold until Grade 0-1.		
	Grade 3 or 4	INCB001158	Withhold until Grade 0-1. Consider re-challenge with monotherapy at next dose level lower.	Administer corticosteroids (initial dose of 1-2 mg/kg of prednisone or equivalent) followed by taper.	
		Epacadostat	Permanently discontinue.		
		Pembrolizumab[a]	Permanently discontinue.		
Type 1 diabetes mellitus (T1DM) or Hyperglycemia[c]	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	INCB001158	Withhold until Grade 0-1. Grade 2: Re-start at same dose level. Grade 3: Restart at next dose level lower.	• Initiate insulin replacement therapy for subjects with T1DM. • Administer antihyperglycemic in subjects with hyperglycemia.	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
		Epacadostat	Withhold until Grade 0-1. Related: Reduce by 1 dose level. Not related: Same dose level.		
		Pembrolizumab[a]	Withhold until Grade 0-1.		

Table 9: Dose Modification and Toxicity Management Guidelines for Adverse Events in Subjects Receiving INCB001158 and Epacadostat ± Pembrolizumab (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v4.03)	Study Medication	Action Taken With Study Medication	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Hypophysitis	Grade 2	INCB001158	Withhold until Grade 0-1. Restart at same dose level.	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
		Epacadostat	Withhold until Grade 0-1. Related: Reduce by 1 dose level. Not related: Same dose level.		
		Pembrolizumab[a]	Withhold until Grade 0-1.		
	Grade 3 or 4	INCB001158	Withhold until Grade 0-1. Grade 3: Re-start at same dose level. Grade 4: Consider re-challenge with monotherapy at next dose level lower.		
		Epacadostat	Withhold until Grade 0-1 or permanently discontinue.[d] Related: Reduce by 1 dose level. Not related: Same dose level.		
		Pembrolizumab[a]	Withhold until Grade 0-1 or permanently discontinue.[d]		

Table 9: Dose Modification and Toxicity Management Guidelines for Adverse Events in Subjects Receiving INCB001158 and Epacadostat ± Pembrolizumab (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v4.03)	Study Medication	Action Taken With Study Medication	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Hyperthyroidism[c]	Grade 2	INCB001158	Continue.	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
		Epacadostat	Continue.		
		Pembrolizumab	Continue.		
	Grade 3 or 4	INCB001158	Withhold until Grade 0-1. Consider re-challenge at next dose level lower.		
		Epacadostat	Withhold until Grade 0-1 or permanently discontinue.[d] Related: Reduce by 1 dose level. Not related: Same dose level.		
		Pembrolizumab[a]	Withhold until Grade 0-1 or permanently discontinue.[d]		
Hypothyroidism[c]	Grade 2-4	INCB001158	Continue.	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.
		Epacadostat	Continue.		
		Pembrolizumab[a]	Continue.		

Table 9: Dose Modification and Toxicity Management Guidelines for Adverse Events in Subjects Receiving INCB001158 and Epacadostat ± Pembrolizumab (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v4.03)	Study Medication	Action Taken With Study Medication	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Nephritis and Renal dysfunction	Grade 2	INCB001158	Withhold until Grade 0-1. Restart at same dose level.	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
		Epacadostat	Withhold until Grade 0-1. Related: Reduce by 1 dose level. Not Related: Same dose level.		
		Pembrolizumab[a]	Withhold until Grade 0-1.		
	Grade 3 or 4	INCB001158	Withhold until Grade 0-1. Grade 3: Restart at same dose level. Grade 4: Consider re-challenge with monotherapy at next dose level lower.		
		Epacadostat	Permanently discontinue.		
		Pembrolizumab[a]	Permanently discontinue.		

Table 9: Dose Modification and Toxicity Management Guidelines for Adverse Events in Subjects Receiving INCB001158 and Epacadostat ± Pembrolizumab (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v4.03)	Study Medication	Action Taken With Study Medication	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Rash	1 or 2	INCB001158	Continue.	Manage with topical steroids with or without drug interruption.	
		Epacadostat	Continue.		
		Pembrolizumab[a]	Continue.		
	3[e]	INCB001158	Withhold until Grade 0-1. Re-start at same dose level.	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	If toxicity does not resolve within 12 weeks of last dose, or cannot taper below 10 mg or less of prednisone or equivalent within 12 weeks, must permanently discontinue. Restart epacadostat at same dose if rash is mild and assessed as Grade 3 based only on body surface area and resolves without oral steroids. If oral steroids are required, or rash is severe, decrease by 1 dose level once resolved to Grade 0-1.
		Epacadostat	Withhold until Grade 0-1. Related: Reduce by 1 dose level. Not related: Same dose level.		
		Pembrolizumab[a]	Withhold until Grade 0-1.		
	4	INCB001158	Withhold until Grade 0-1. Consider re-challenge with monotherapy at next dose level lower.	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
		Epacadostat	Permanently discontinue.		
		Pembrolizumab[a]	Permanently discontinue.		

Table 9: Dose Modification and Toxicity Management Guidelines for Adverse Events in Subjects Receiving INCB001158 and Epacadostat ± Pembrolizumab (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v4.03)	Study Medication	Action Taken With Study Medication	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Asymptomatic[f] Amylase or Lipase increased	3	INCB001158	May continue treatment with medical monitor approval.		Permanently discontinue if clinical signs and symptoms of pancreatitis develop (abdominal pain, nausea, vomiting). If toxicity does not resolve within 12 weeks of last dose after an interruption, must permanently discontinue unless approved by the medical monitor to continue. If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study treatment administration dosing may continue with medical monitor approval.
		Epacadostat	May continue treatment with medical monitor approval.		
		Pembrolizumab[a]	May continue treatment with medical monitor approval.		
	4	INCB001158	Withhold until Grade 0-1. Restart at same dose level.		
		Epacadostat	Withhold until toxicity resolves to Grade 0-1. Related: Reduce by 1 dose level. Not related: Same dose level.		
		Pembrolizumab[a]	Withhold until toxicity resolves to Grade 0-1.		

Table 9: Dose Modification and Toxicity Management Guidelines for Adverse Events in Subjects Receiving INCB001158 and Epacadostat ± Pembrolizumab (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAE v4.03)	Study Medication	Action Taken With Study Medication	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
All other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	INCB001158	Withhold until Grade 0-1. Consider re-challenge at next dose level lower.	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.
		Epacadostat	Withhold until Grade 0-1 Related: Reduce by 1 dose level. Not related: Same dose level.		
		Pembrolizumab[a]	Withhold until Grade 0-1.		
	Grade 4 or recurrent Grade 3	INCB001158	Withhold until Grade 0-1. Consider re-challenge with monotherapy at next dose level lower.		
		Epacadostat	Permanently discontinue.		
		Pembrolizumab[a]	Permanently discontinue.		

General Instructions:

1. Corticosteroid taper should be initiated upon AE improving to ≤ Grade 1 and continue to taper over at least 4 weeks.
2. For situations where INCB001158, epacadostat, and pembrolizumab have been withheld, INCB001158, epacadostat, and pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Epacadostat and pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. Continuation of INCB001158 may be considered in consultation with the medical monitor.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Abbreviations: AEs = adverse events; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; irAE = infusion-related adverse events; T1DM = Type 1 diabetes mellitus.

[a] Only applies to subjects in Phase 1 and Phase 2 Part A. Subjects in Phase 2 Part B will not receive pembrolizumab.

[b] Subjects with radiographically documented liver metastases should withhold at > 5 × ULN.

[c] For subjects with Grade 3 or 4 immune-related endocrinopathy where withholding of INCB001158, epacadostat, and pembrolizumab is required, INCB001158, epacadostat, and pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

[d] Withhold OR permanently discontinue INCB001158, epacadostat and pembrolizumab at the discretion of the investigator.

[e] Subjects with Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require systemic steroids, and resolves to Grade 1 within 14 days does not have to hold study medication

[f] If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study treatment administration dosing may continue (with or without dose reduction) with medical monitor approval.

Table 10: Dose Level Adjustments of Epacadostat

Starting Dose of Epacadostat	Dose Level -1	Dose Level -2
	First reduction of epacadostat	Second reduction of epacadostat
100 mg BID	50 mg BID	25 mg BID

Dose Level -2 is the lowest dose of epacadostat in this Protocol. If a subject is at Dose Level -2 and is instructed by Table 9 to further reduce epacadostat by 1 level, the investigator may choose to continue at Dose Level -2 when the AE has resolved to Grade 0 or 1 or to discontinue epacadostat. Refer to Section 5.2.2 for details.

5.4.7. Procedures for Subjects Exhibiting Serotonin Syndrome

As noted in Section 1.3.2, there is a rare chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger SS, when administered alone or 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 (Section 5.6.3).

Selective serotonin reuptake inhibitors and SNRIs are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of SS (summarized in Table 11) should be evaluated in the context of possible comorbid conditions as well.

The following procedures will be implemented if subjects exhibit the signs/symptoms of SS, including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt all study treatment 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 etiologies other than SS are excluded, INCB001158 and pembrolizumab administration may be resumed unless other AE management guidelines apply for the specific event.
- If subject chooses to remain in the study, restart treatment with epacadostat after the SSRI or SNRI has been discontinued, no sooner than 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 dosing 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. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.
- If a subject had experienced moderate or severe unconfounded SS in the opinion of the investigator, without concomitant SSRI or SNRI usage, or serotonergic concomitant medications, only INCB001158 and pembrolizumab administration may be resumed; epacadostat treatment should be permanently discontinued.

Table 11: Signs and Symptoms of Serotonin Syndrome

Seriousness	Autonomic signs	Neurological signs	Mental status	Other
Mild	Afebrile or low-grade fever Tachycardia Mydriasis Diaphoresis or shivering	Intermittent tremor Akathisia Myoclonus Mild hyperreflexia	Restlessness Anxiety	
Moderate	Increased tachycardia Fever (up to 41°C) Diarrhea with hyperactive bowel sounds Diaphoresis with normal skin color	Hyperreflexia Inducible clonus Ocular clonus (slow continuous lateral eye movements) Myoclonus	Easily startled Increased confusion Agitation and hypervigilance	Rhabdomyolysis Metabolic acidosis Renal failure Disseminated intravascular coagulopathy (secondary to hyperthermia)
Severe	Temperature often more than 41 °C (secondary to increased tone)	Increased muscle tone (lower limb > upper) Spontaneous clonus Substantial myoclonus or hyperreflexia	Delirium Coma	As above

Source: Boyer and Shannon 2005.

5.4.8. Supportive Care Guidelines for Management of Hyperammonemia

Subjects should be monitored for elevated venous plasma ammonia. Asymptomatic clinically significant drug-related elevations in ammonia (eg, a repeatable elevation in ammonia > 2 × ULN AND > 2 × baseline) should be managed by interrupting INCB001158 and monitoring to resolution. For symptomatic elevations (ie, significant ammonia elevation associated with nausea, vomiting, severe anorexia, mental status changes, seizure, or other symptoms associated with hyperammonemia), subjects should be admitted for management according to the local institutional protocol for hyperammonemia, including 1) sending appropriate labs (ammonia [on ice, measured immediately], plasma amino acid profile, liver chemistry tests, electrolytes, bicarbonate, BUN, creatinine, glucose, and urine orotic acid), 2) IV hydration with dextrose-containing fluids, 3) discontinuation of protein intake, 4) implementing therapy to reduce ammonia levels (oral lactulose/lactitol, IV Ammonul®), and 5) identifying and treating any potential triggers (eg, discontinue corticosteroids, treat infections).

5.4.9. Infusion Reaction Dose Modifications

Pembrolizumab may cause severe or life-threatening infusion-reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 12.

Table 12: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None.
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (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. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further treatment with pembrolizumab.**	Subject may be premedicated 1.5 h (± 30 min) before infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Table 12: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines (Continued)

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 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: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further treatment with pembrolizumab.**	No subsequent dosing.
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v4.03 at http://ctep.cancer.gov.		

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAID = nonsteroidal antiinflammatory drug; PO = oral.

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

- Occurrence of an AE that is related to treatment with the study treatment that, in the judgment of the investigator or the medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- An AE requiring more than 2 dose reductions of INCB001158 or epacadostat.
- Persistent AE requiring a delay of therapy for more than 4 weeks unless a greater delay has been approved by the sponsor, or persistent irAEs (described in Table 9) requiring a delay of therapy for more than 12 weeks.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

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

- The subject becomes pregnant.
- Consent is withdrawn. Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled. Note: Consent withdrawn means that the subject can no longer be followed and no additional data can be collected. Subjects may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity (see Sections 5.4.6, 5.4.9, and 5.4.10). Subjects with unacceptable toxicities must be withdrawn from study treatment but will continue in the follow-up period of the study (see Section 6.4).
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- Confirmed radiographic progression of disease per RECIST v1.1 (see Section 7.7.1.2). A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved (see Sections 7.7.1.2 and 7.7.1.5).

  Note: For unconfirmed progression see Section 7.7.1.2.
- If, during the course of the study, a subject is found not to have met eligibility criteria (see Section 3), the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study treatment administration 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 a follow-up visit. These visits are described in Section 6. 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 must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the eCRF and IRT.
- Subjects must be followed for safety until the time of the follow-up visit or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, 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.
- [redacted]

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

5.6. Concomitant Medications

All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 21 days before the first dose of study treatment and 30 days after the last dose of study treatment, or until the subject begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs as defined in Section 8. Concomitant treatments/procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

5.6.1. Permitted Medications

All treatments that are not excluded in the Protocol and 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 medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage frequency, route, and date will also be included on the eCRF.

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms. Surgery for tumor control is not permitted during the study. Palliative radiotherapy is permitted to a limited number of lesions if considered medically necessary by the treating physician as long as the lesions are NOT a RECIST v1.1-defined target lesion. Study therapy should be held during the course of palliative radiotherapy and should be

resumed no earlier than the next scheduled administration of study therapy. The specifics of the radiation treatment, including the location, will be recorded.

Note: The use of bisphosphonates and denosumab are permitted in this study.

5.6.2. Restricted Medications and Measures

Use of coumarin-based anticoagulants (eg, warfarin) is discouraged. Low-dose warfarin (1 mg) is acceptable; however, doses that increase the INR are discouraged and may require dose modification. If an alternative to coumarin-based anticoagulants cannot be used, investigators should follow the guidelines in Table 13 and either closely monitor or closely monitor and reduce the subject's dose of coumarin-based anticoagulant upon initiating therapy with epacadostat. The INR should be monitored weekly for the first 4 weeks after initiation of therapy and upon discontinuation of epacadostat.

Table 13: Warfarin Dose Adjustment Recommendation When Initiating Concurrent Epacadostat Treatment

	Epacadostat Dose
Stable INR	**≤ 100 mg BID**
INR ≤ 2.5	Close INR monitoring
INR > 2.5	Close INR monitoring

5.6.3. Prohibited Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy 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 medical monitor, and the subject.

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this Protocol.
- Immunotherapy not specified in this Protocol.
- Investigational agents other than INCB001158, epacadostat, and pembrolizumab.
- Oncologic surgery for tumor control.
- Radiation therapy for disease control.
  - *Note*: Radiation therapy to symptomatic lesions or to the brain may be allowed at the investigator's discretion, provided the lesions were not previously defined by the site as target lesions.

- 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, chickenpox, yellow fever, nasal seasonal flu, nasal H1N1 flu, rabies, BCG, and typhoid.
- Except for erythropoietin or darbepoetin alpha (Aranesp®), use of growth factors (ie, G-CSF, GM-CSF, etc.) is not permitted in the first treatment cycle unless the subject experiences a hematologic DLT.
- Concomitant treatment with valproic acid/valproate-containing therapies is not permitted as hyperammonemia is a well-described toxicity of valproic acid, particularly at high exposures, potentially through inhibition of the urea cycle (Verrotti et al 2002, Wadzinski et al 2007).
- Concomitant treatment with allopurinol or other xanthine oxidase inhibitors is not allowed. Xanthine oxidase inhibitors (eg, allopurinol) cause an accumulation of orotic acid in the urine, which would confound the assessment of safety in these subjects.
- Any MAOI or drug associated with significant MAO inhibitory activity agents is prohibited from 21 days before starting study treatment through 2 weeks after the final dose of epacadostat has been taken. See Appendix C for prohibited medications associated with MAO inhibition.
- Any UGT1A9 inhibitor, including, but not limited to acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid, glycyrrhizin, imatinib, imipramine, ketoconazole (systemic), linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.
- Prolonged therapy with systemic glucocorticoids (> 7 days) for any purpose other than to modulate symptoms from an AE, SAE, or event of clinical interest, or for use as a premedication for chemotherapy or in participants with a known history of an IV contrast allergy administered as part of CT radiography. Brief, limited use of systemic corticosteroids (≤ 7 days) are permitted where such use is considered standard of care (eg, for COPD exacerbation).
  - Replacement doses of steroids (eg, prednisone 5 to 7.5 mg daily) are permitted while on study, as is the use of local steroids.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from treatment but continue in study for assessment of disease status and survival.

The exclusion criteria describe other medications that are prohibited in this study.

There are no prohibited therapies during the post-treatment follow-up period.

6. STUDY ASSESSMENTS

All clinical assessments will be performed as indicated in Table 14, and all laboratory assessments will be performed as indicated in Table 15. Table 16 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.

Table 14: Schedule of Clinical Assessments

Procedure	Protocol Section	Screening	Treatment (21-Day Cycles)				EOT	Follow-Up				Notes
			Cycle 1			Other Cycles		Safety		Disease Status	[redacted]	
		Days -21 to -1	D1	D8 ±3d	D15 ±3d	D1 ±3d	EOT +5d	30-37d After Last Dose of INCB001158 and Epacadostat	90-97d After Last Dose of INCB001158 and Epacadostat (Phase 1 and Phase 2 Part A Only)	Q9W ±7d After Discon.	[redacted]	
ADMINISTRATIVE PROCEDURES												
Informed consent	7.1	X										
Review inclusion and exclusion criteria	3	X	X									
Demography and medical history	7.3	X										
Prior/concomitant medications	7.4	X	X	X	X	X	X	X	X			
STUDY TREATMENT ADMINISTRATION												
Dispensing INCB001158 and epacadostat study treatments	5.2.1 5.2.2 7.2		X			X						
Administer INCB001158 at site	5.2.1		X	X	X	X						Subject to withhold AM dose of INCB001158 study drug on days it will be administered at the site.
Administer epacadostat at site	5.2.2		X	X	X	X						Subject to withhold AM dose of epacadostat on days it will be administered at the site.
Administer pembrolizumab at site	5.2.3		X			X						Phase 1 and Phase 2 Part A only; infusion to start directly after the AM doses of INCB001158 and epacadostat.
Assess study treatment compliance	5.3					X	X					

Table 14: Schedule of Clinical Assessments (Continued)

Procedure	Protocol Section	Screening	Treatment (21-Day Cycles)				EOT	Follow-Up				Notes
			Cycle 1			Other Cycles		Safety		Disease Status	[redacted]	
		Days -21 to -1	D1	D8 ±3d	D15 ±3d	D1 ±3d	+5d	30-37d After Last Dose of INCB001158 and Epacadostat	90-97d After Last Dose of INCB001158 and Epacadostat (Phase 1 and Phase 2 Part A Only)	Q9W ±7d After Discon.	[redacted]	
CLINICAL PROCEDURES AND ASSESSMENTS												
Physical examination/body weight, height	7.6.2	X*	X	X	X	X	X	X	X			* Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only.
Vital signs	7.6.3	X	X	X	X	X	X	X	X			
12-lead ECG	7.6.4	X	X*			X*	X					* On C1D1 and C2D1 only, predose and 2 to 4 hours after morning dose.
ECOG status	7.8.1	X	X	X	X	X	X	X	X			
Radiographic tumor assessments (CT or MRI)	7.7.1	X				X*	X**			X**		* **Nine weeks** (±7 days) after Cycle 1 Day 1, then every 9 weeks (±7 days) after that. ** For subjects who discontinue study treatment without documented PD, every effort should be made to continue tumor imaging using the same imaging schedule used while on treatment until the start of new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first. If a prior scan was obtained within 4 weeks before the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue study treatment without confirmed disease progression, a radiological evaluation should be repeated at the time of treatment discontinuation (ie, date of discontinuation ± 4-week window).

Table 14: Schedule of Clinical Assessments (Continued)

Procedure	Protocol Section	Screening	Treatment (21-Day Cycles)					Follow-Up				Notes
			Cycle 1			Other Cycles		Safety		Disease Status	[redacted]	
		Days -21 to -1	D1	D8 ±3d	D15 ±3d	D1 ±3d	EOT +5d	30-37d After Last Dose of INCB001158 and Epacadostat	90-97d After Last Dose of INCB001158 and Epacadostat (Phase 1 and Phase 2 Part A Only)	Q9W ±7d After Discon.	[redacted]	
Review AEs	7.6.1	X	X	X	X	X	X	X	X			
Post-treatment anticancer therapy status	7.5						X	X	X	X	X	
[redacted]	[redacted]											

Table 15: Schedule of Laboratory Assessments

	Protocol Section	Screening	Treatment (21-Day Cycles)				EOT +5d	Safety Follow-Up		Notes
			Cycle 1			Other Cycles				
		Days -21 to -1	D1	D8 ±3d	D15 ±3d	D1 ±3d		30-37d After Last Dose of INCB001158 and Epacadostat	90-97d After Last Dose of INCB001158 and Epacadostat (Phase 1 and Phase 2 Part A only)	
Local laboratory tests										
Chemistries	7.6.5	X	X*	X	X	X	X	X	X	* Does not need to be repeated if the screening sample was obtained within 7 days before C1D1 unless a clinically significant change is suspected.
Hematology	7.6.5	X	X*	X	X	X	X	X	X	* Does not need to be repeated if the screening sample was obtained within 7 days before C1D1 unless a clinically significant change is suspected.
Lipid panel	7.6.5	X	X*	X	X	X	X	X	X	* Does not need to be repeated if the screening sample was obtained within 7 days before C1D1 unless a clinically significant change is suspected.
Coagulation panel	7.6.5	X					X			If a Coumadin®-based anticoagulant is given, monitor INR weekly for the first 4 weeks after initiation of therapy and upon discontinuation of epacadostat.
HIV and hepatitis B and C screening	7.6.5.5	X								
Urinalysis	7.6.5.1	X	X*			X	X			* Does not need to be repeated if the screening sample was obtained within 7 days before C1D1 unless a clinically significant change is suspected.
Thyroid panel: TSH, FT4, FT3/T3	7.6.5	X*				X*				* Perform within 7 days before Cycle 1, then every 2nd cycle (Cycles 2, 4, 6, 8, etc). May use central lab only if local lab is not capable.

Table 15: Schedule of Laboratory Assessments (Continued)

	Protocol Section	Screening	Treatment (21-Day Cycles)				EOT +5d	Safety Follow-Up		Notes
			Cycle 1			Other Cycles				
		Days -21 to -1	D1	D8 ±3d	D15 ±3d	D1 ±3d		30-37d After Last Dose of INCB001158 and Epacadostat	90-97d After Last Dose of INCB001158 and Epacadostat (Phase 1 and Phase 2 Part A only)	
Blood sample for plasma ammonia	7.6.5.3	X								
Pregnancy test	7.6.5.4	X						X*	X**	All female subjects of childbearing potential. * Phase 2 Part B only. ** Phase 1 and Phase 2 Part A only.
Central laboratory tests										
Urine sample for orotic acid	7.6.5.2		X*	X*/**	X*	X*				* See Table 17 for sample timings. Additional samples may be collected as clinically indicated. ** Phase 1 only.
Blood sample for PK of INCB001158/ epacadostat	7.9.1		X*			X*				* See Table 20 and Table 21 for extensive and sparse sample timings, respectively. Samples will be drawn on C1D1 and C2D1 only.
Blood sample for PK and [redacted] testing of pembrolizumab (Phase 1 and Phase 2 Part A only)	7.9.1		X*			X*				* Collect on C1D1 predose and C6D1 predose, as noted in Table 22.
[redacted]										

Table 15: Schedule of Laboratory Assessments (Continued)

	Protocol Section	Screening	Treatment (21-Day Cycles)				EOT	Safety Follow-Up		Notes
			Cycle 1			Other Cycles				
		Days -21 to -1	D1	D8 ±3d	D15 ±3d	D1 ±3d	+5d	30-37d After Last Dose of INCB001158 and Epacadostat	90-97d After Last Dose of INCB001158 and Epacadostat (Phase 1 and Phase 2 Part A only)	
[redacted]										
Baseline tumor biopsy/archival tissue collection*	7.10	X*								* Only for subjects enrolled in Phase 1 dose-escalation cohorts, [redacted]

Table 16: Laboratory Tests: Required Analytes

Serum Chemistries	Hematology	Urinalysis With Microscopic Examination	Hepatitis and HIV Screening
Albumin Alkaline phosphatase ALT [redacted] Ammonia Amylase [redacted] AST Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose [redacted] Lactate dehydrogenase Lipase [redacted] Phosphate Potassium Sodium Thyroid panel: TSH, FT4, FT3/T3 Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid	Complete blood count, including: Hemoglobin Hematocrit Platelet count Red blood cell count White blood cell count Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for: WBC differential laboratory results: Lymphocytes Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Orotic acid[a] Protein Urobilinogen **Lipid Panel** Total cholesterol Triglycerides LDL HDL **Coagulation** PT PTT INR	HBsAg HBV-DNA HCV antibody HCV-RNA HIV RNA (if required by local regulations) **Pregnancy Testing** A urine or serum pregnancy test will be required for all women of childbearing potential.

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.
[a] Tests to be conducted by central laboratory. All other tests will be conducted by a local laboratory where possible.

6.1. Screening

Screening is the interval between signing the ICF and the day the subject is enrolled in the study (Cycle 1 Day 1). Sites are requested to register the subject in the IRT system on the same day of the ICF signature. Refer to the IRT manual for detailed instructions. Screening procedures have to be completed within 21 days after signing the ICF, and preferably within 14 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 21 days of Cycle 1 Day 1). All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of study treatment. 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 treatment assignment 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.

Refer to the Cohort Management plan for the description of the slots management in Phase 1 Dose Escalation.

6.2. Treatment

The treatment period begins on the day the subject receives the first dose of study treatment (Cycle 1 Day 1), as assigned in the IRT system, through the point at which the investigator determines the subject will be permanently discontinued from study treatment. Cycle 1 Day 1 must be no more than 21 days after the subject has signed the ICF. Dates for subsequent study visits will be determined based on this day and should occur within 3 days (±) of the scheduled date unless delayed for safety reasons. At Cycle 1 Day 1, results from screening visit evaluations should be reviewed to determine whether the subject continues to meet the eligibility requirements, as specified in the Protocol.

Subjects will have regularly scheduled study visits as outlined in Table 14 and Table 15, and toxicities will be monitored continuously and will be graded using the NCI CTCAE v4.03 criteria.

6.3. End of Treatment

When the subject permanently discontinues all 3 study treatments, as outlined in Section 5.5, 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 EOT visit may occur up to 5 days after receiving the final dose of study treatment. The subject should be encouraged to return for the safety follow-up visit.

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visits, which should occur 30 to 37 days (all subjects) and 90 to 97 days (Phase 1 and Phase 2 Part A only) after the final dose of study treatments. Adverse events and SAEs must be reported up until the date of the follow-up visits, 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 the subject cannot return to the site for the safety follow-up visit (eg, lives far away), the subject should be contacted by telephone for assessment of AEs and SAEs. Sites should document this contact in the source.

If a subject is scheduled to begin a new anticancer therapy before the end of the 90- to 97-day safety follow-up period, the safety follow-up visit should be performed before new anticancer therapy is started. Once new anticancer therapy has been initiated, the subject will move into the survival follow-up period.

6.4.2. Disease Status Follow-Up

Subjects who discontinue all 3 study treatments for a reason other than disease progression will move into the disease status follow-up period and should be assessed every 9 weeks ± 7 days by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until:

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

[redacted]

6.5. End of Study

The end of the study will occur when all subjects have completed the last study follow-up visit or have discontinued study treatment and have completed applicable follow-up assessments.

Additionally, subjects will be considered as having completed the study if they meet any of the following criteria:

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

6.6. Unscheduled Visits

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

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

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

7.2. Interactive Response Technology Procedure

The IRT will be contacted to obtain a subject ID number when a subject enters screening. Upon determining that the subject is eligible for study entry, the IRT will be contacted to obtain the treatment group and cohort assignment. Additionally, the IRT will be contacted to update the subject's disposition and for study treatment resupply. Refer to the IRT manual for detailed instructions.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

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

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history will be collected at screening. Details regarding the subject's malignancy under study including date of diagnosis, initial and current cancer stage, tumor histology, relevant disease characteristics (including any available data on tumor PD-L1 and MSI status), and prior treatments including systemic, radiation, and surgical procedures will be recorded.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. Any medication received or procedure performed within 21 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, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF. See Section 5.6 for details regarding restricted and prohibited medications.

7.5. Post-Treatment Anticancer Therapy Status

The investigator or qualified designee will review all new anticancer therapy initiated after the last dose of study treatment. If a subject initiates a new anticancer therapy before the 30-day or 90-day (Phase 1 and Phase 2 Part A only) safety follow-up visit, the safety follow-up visit should occur before the first dose of the new anticancer therapy.

7.6. Safety Assessments

7.6.1. Adverse Events

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

7.6.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

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

7.6.2.1. Comprehensive Physical Examination

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

7.6.2.2. Targeted Physical Examination

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

7.6.3. Vital Signs

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

7.6.4. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest. Timed triplicate ECGs (separated by 5 minutes) will be performed.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study 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.

7.6.5. Laboratory Assessments

A certified laboratory local to the study site and subject will perform most of the clinical laboratory assessments for safety (ie, chemistries, hematology assessments, coagulation panel, thyroid panel, lipid panel, 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 15. Table 16 lists the specific laboratory analytes required for each test. Some additional tests (ie, [redacted], plus urinary orotic acid; see Table 16) will be conducted by one or more central laboratories, on the days indicated in Table 15.

Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Laboratory samples collected on study Day 1 must be performed before study 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.

[redacted]

7.6.5.2. Urinalysis

In addition to the standard urinalysis outlined in Table 16, urinary orotic acid levels will be assessed (see Table 17), as a marker of urea cycle inhibition, a potential side effect of INCB001158 (see Section 1.3.1). Subjects must fast at least 8 hours before each clinic visit and void their bladder in the morning before providing the predose urine sample at the clinic, as outlined in Table 17.

[redacted]

Table 17: Sample Collection Times for Urine Assessments of Orotic Acid

Study Visit[a]	Time
C1D1	Predose and 6 h (± 1 h) postdose
C1D8[b]	Predose
C1D15	Predose and 6 h (± 1 h) postdose
C2D1 and D1 of all subsequent cycles	Predose

[a] Additional samples may be collected as clinically indicated.
[b] The C1D8 sample will not be collected for subjects enrolled in Phase 2.

7.6.5.3. Plasma Ammonia

Plasma ammonia levels are to be tested during screening. If above the ULN, repeat the sample to confirm the value. If the subject experiences an elevation in urine orotic acid (> 10 × ULN fasted; or > 40 × ULN any value) while on study treatment or during the follow-up period, monitor plasma ammonia levels each time the urine orotic acid is tested, at least until orotic acid levels have returned to normal, at the investigator's and medical monitor's discretion.

7.6.5.4. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and must be within 72 hours before the first dose of study treatment. A serum pregnancy test should also be repeated at the 30-day (Phase 2 Part B only) or 90-day (Phase 1 and Phase 2 Part A only) safety follow-up visit. Pregnancy testing is not required if a subject is going to hospice. Urine pregnancy tests will be conducted as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a urine test was positive, 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.

7.6.5.5. Hepatitis and HIV Screening Tests

Hepatitis and HIV screening assessments will be performed at the screening visit (Table 15) to rule out hepatitis and HIV infection, respectively; required analytes are shown in Table 16. Generally, hepatitis and HIV 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.

Note: HIV testing is not required unless mandated by the local health authority.

7.7. Efficacy Assessments

7.7.1. Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, MRI may be used when CT with iodinated contrast is contraindicated or when local practice mandates it. Magnetic resonance imaging is the strongly preferred modality for imaging the brain. The same imaging modality (ideally the same scanner) and the use of contrast should be used in a subject throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Subject eligibility will be determined using local assessment (investigator assessment) based on RECIST v1.1. All scheduled images for all study subjects will be assessed by the investigator.

7.7.1.1. Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 21 days before Cycle 1 Day 1. The site study team must review screening images to confirm the subject has measurable disease per RECIST v1.1.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 21 days before Cycle 1 Day 1.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, that is, without evidence of progression by imaging (confirmed by MRI or CT imaging, whichever was used at prior imaging) for at least 4 weeks before the first dose of study treatment. Any neurologic symptoms must have returned to baseline, subjects must have no evidence of new or enlarging brain metastases, and subjects must not have used steroids for brain metastases for at least 14 days before initiating study treatment as per investigator assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability. Subjects with evidence of cerebral edema will also be excluded from participation. In addition, subjects will be excluded from participation in the study if it has been < 4 weeks since radiation therapy was delivered to the CNS.

7.7.1.2. Tumor Imaging During the Study

The first on study imaging assessment should be performed at 9 weeks (63 days ± 7 days) from the date of enrollment. Imaging then continues every 9 weeks (63 days ± 7 days). This equates to an imaging schedule occurring after Weeks 9, 18, 27, 36, 45, etc. Imaging timing should follow calendar days and should not be adjusted for delays in cycle dosing.

Imaging should continue to be performed until PD is identified by the investigator, the start of new anticancer treatment, withdrawal of consent for imaging, or death, whichever occurs first. If the investigator elects to continue treatment [redacted] after initial radiographic PD, imaging should continue.

Partial response and CR should be confirmed by a repeat imaging assessment. The imaging for confirmation of response may be performed no earlier than 4 weeks after the first indication of a response and no later than at the next scheduled scan (ie, 9 weeks ± 7 days later), whichever is clinically indicated. Subjects will then return to the regular imaging schedule, starting with the next scheduled imaging timepoint. Subjects who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging timepoint.

[redacted] disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site [redacted], provided they have met the conditions detailed in Section 7.7.1.5. Subjects who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging timepoint if clinically stable. Subjects who have confirmed

disease progression [redacted] will discontinue the treatment, unless treatment beyond confirmed progression is approved by the medical monitor, as detailed in Section 7.7.1.5.

7.7.1.3. End of Treatment and Follow-Up Imaging

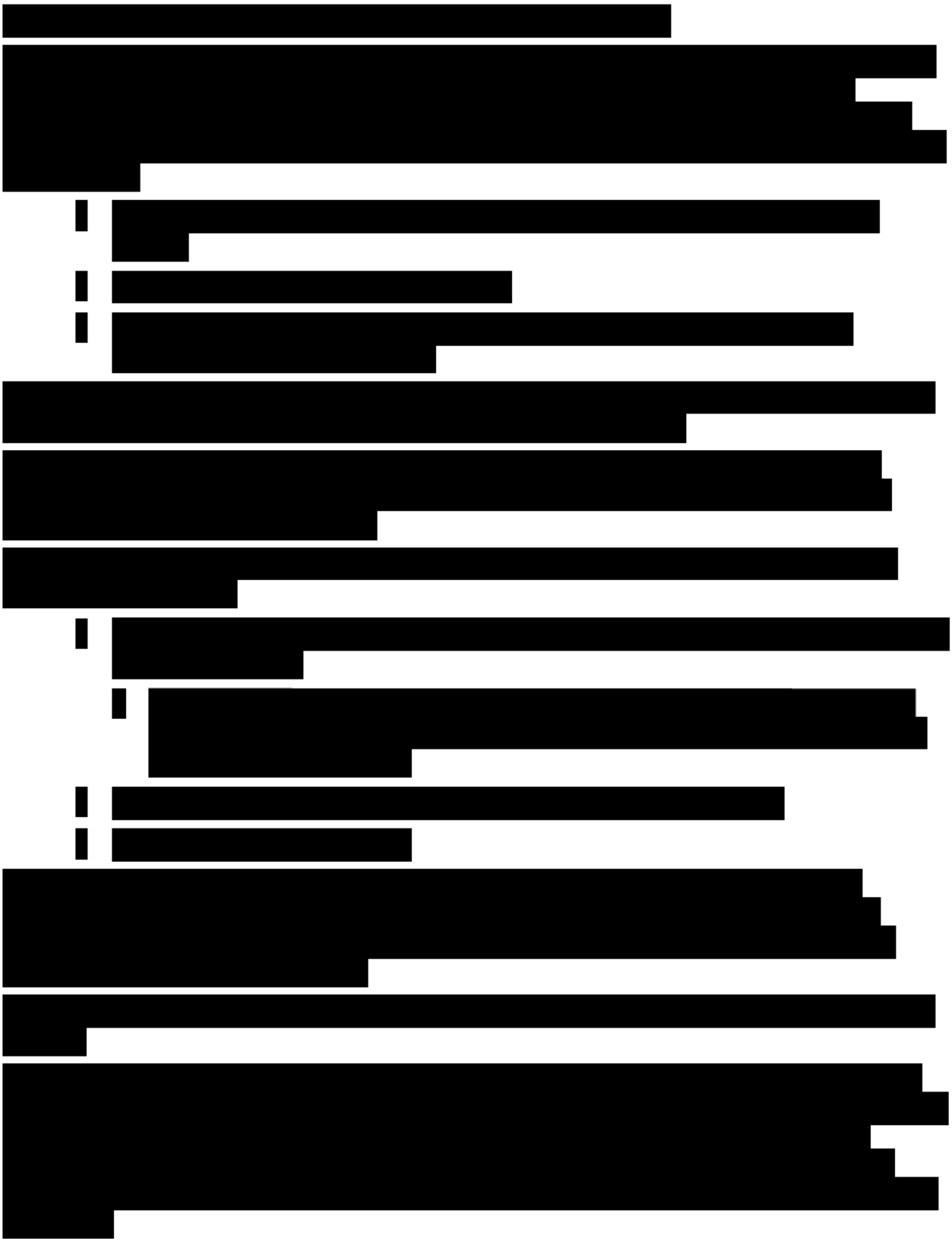
In subjects who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4-week window). If a previous imaging was obtained within 4 weeks before the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For subjects who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement [redacted]

In subjects who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment until the start of new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first. For these subjects, the next imaging would occur at the discontinuation visit. If previous imaging was obtained within 4 weeks before the date of discontinuation, then imaging at treatment discontinuation is not mandatory. The next imaging would then occur every 9 weeks subsequently. Once imaging is complete (eg, radiographic PD, new antineoplastic therapy), the subject enters [redacted]

7.7.1.4. RECIST v1.1 Assessment of Disease

RECIST v1.1 will be applied as the primary measure for assessment of tumor response and as a basis for all Protocol guidelines related to disease status (eg, discontinuation of study treatment).

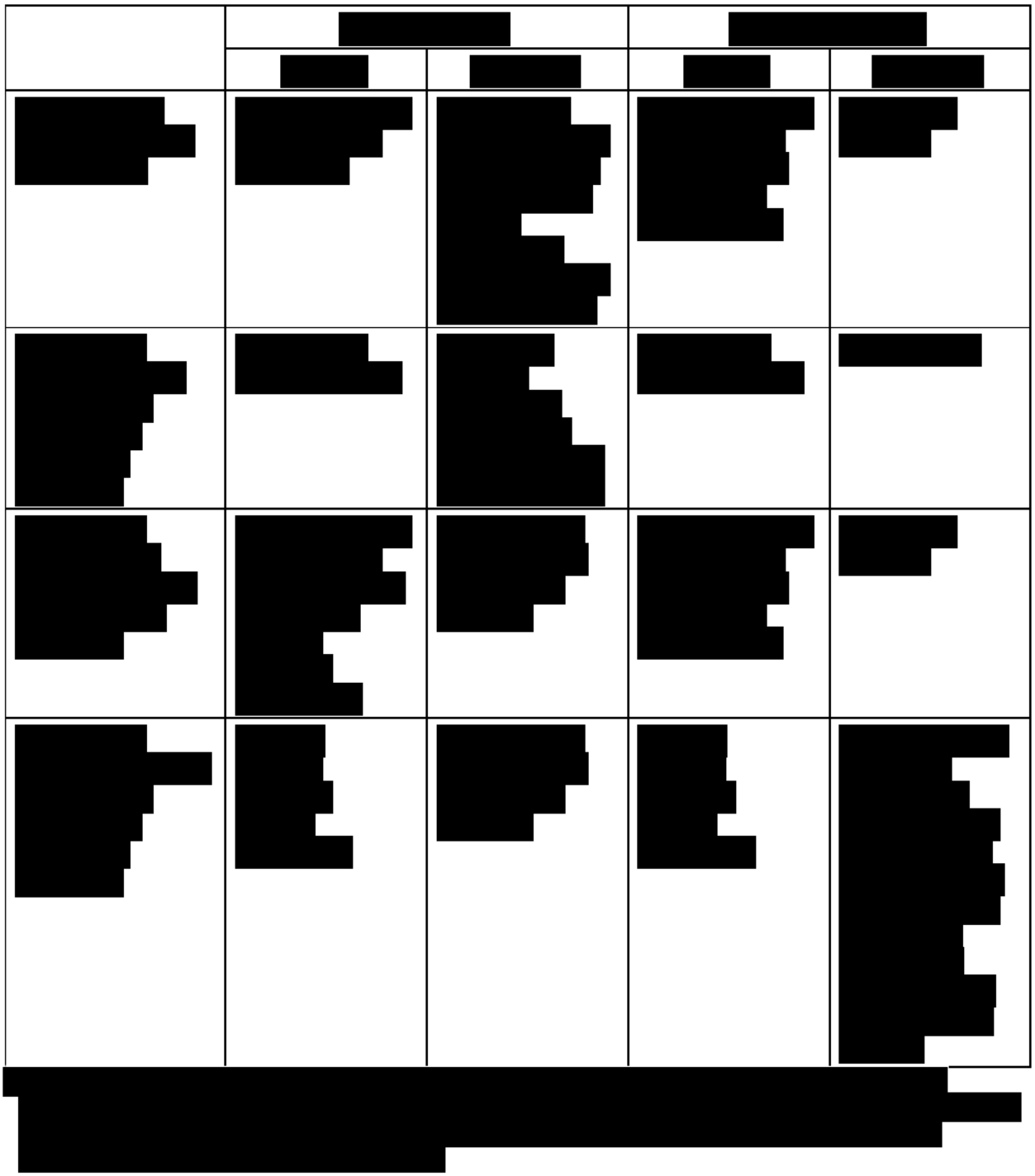
[redacted]



[redacted]

[redacted]

[redacted]



[redacted]

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 14 according to the criteria in Table 19.

Table 19: 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

7.9.1. Blood Sample Collection

Subjects will arrive at the clinic having fasted at least 8 hours and having withheld their morning doses of INCB001158 and epacadostat. Pharmacokinetic samples will be obtained at the visits indicated in Table 20, Table 21, and Table 22. [redacted] The pembrolizumab PK [redacted] samples will only be analyzed if there is a concern that pembrolizumab is not as active as expected. [redacted] After the predose (**predose is defined as within 24 hours before administration of pembrolizumab [Phase 1 and Phase 2 Part A only] and before administration of the morning dose of INCB001158 and epacadostat [all phases and parts]**) PK sample is drawn, subjects will take the morning doses of INCB001158 and epacadostat and, in Phase 1 and Phase 2 Part A only, then begin infusion of pembrolizumab. The exact date and time of the PK and [redacted] blood draws will be recorded in the eCRF along with the date and time of the last dose of study treatment preceding the blood draw. Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Sample collection times and windows for INCB001158, epacadostat, and pembrolizumab are shown in Table 20, Table 21, and Table 22, respectively.

Extensive PK sampling will be performed in the first 12 subjects enrolled in Phase 2 Part B, to test for any potential drug-drug interaction between INCB001158 and epacadostat (see Table 20). Sparse PK sampling will be performed in all other subjects (see Table 21 and Table 22).

Table 20: Extensive Sample Collection Time Windows for Pharmacokinetic Assessments for INCB001158 and Epacadostat in First 12 Subjects Enrolled in Phase 2 Part B

Study Visit	Timing of Sample Relative to INCB001158 and Epacadostat Administration						
C1D1	Predose	0.5 h ± 10 min	1 h ± 10 min	2 h ± 30 min	4 h ± 30 min	6 h ± 30 min	8 to 10 h
C2D1	Predose	0.5 h ± 10 min	1 h ± 10 min	2 h ± 30 min	4 h ± 30 min	6 h ± 30 min	8 to 10 h

Table 21: Sparse Sample Collection Time Windows for Pharmacokinetic Assessments for INCB001158 and Epacadostat in Phase 1 and Phase 2 Part A and the Thirteenth Subject Onwards Enrolled in Phase 2 Part B

Study Visit	Timing of Sample Relative to INCB001158 and Epacadostat Administration		
C1D1	Predose	1 h ± 10 min	4 h ± 30 min
C2D1	Predose	2 h ± 30 min	6 to 10 h

Table 22: Sample Collection Time Windows for Pharmacokinetic [redacted] Assessments for Pembrolizumab in Phase 1 and Phase 2 Part A

Study Visit	Timing of Sample Relative to Pembrolizumab Administration
C1D1	Predose within 24 hours before administration of pembrolizumab and before the morning doses of INCB001158 and epacadostat.
C6D1	Predose within 24 hours before administration of pembrolizumab and before the morning doses of INCB001158 and epacadostat.

7.9.2. Bioanalytical Methodology and Analysis

The plasma samples will be analyzed for INCB001158 and epacadostat by using a validated LC/MS-MS assay. These samples will be analyzed by the sponsor or its designee.

The plasma samples will be analyzed for pembrolizumab PK and [redacted] by a validated LC/MS-MS assay. These samples will be analyzed by the sponsor or its designee.

[redacted]

[redacted]

[redacted]

7.11. Other Study Procedures

7.11.1. Distribution of Subject Reminder Cards and Subject Diaries

Subjects will be provided with a reminder card at each visit, containing the following reminders:

- The date/time of the next visit;
- Not to take their morning doses of INCB001158 and epacadostat before visiting the clinic on those days, as they will take them after blood draws have been completed for safety evaluation;
- To fast for at least 8 hours before the next clinic visit, and to void their bladder in the morning before providing the predose urine sample at the clinic, as outlined in Table 17.

Subjects will also be provided with diaries to record dates, times, and doses of INCB001158 and epacadostat that they take between clinic visits.

[redacted]

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

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

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 90 days (Phase 1 and Phase 2 Part A only) or 30 days (Phase 2 Part B only) 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. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

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	Fatal

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). Relatedness will be assessed for each of INCB001158, epacadostat (all Phases and Parts) and pembrolizumab (Phase 1 and Phase 2 Part A only).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study treatment(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

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

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

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study treatment(s), 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[s]) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

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

8.3. Serious Adverse Events

8.3.1. Definitions

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

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

- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study treatment(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 90 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 90 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(s).

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatments. Relatedness will be assessed for each of INCB001158, epacadostat (all Phases and Parts) and pembrolizumab (Phase 1 and Phase 2 Part A only).

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment(s): 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(s) 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 IBs for the study treatments (new occurrence) and is thought to be related to at least 1 of the study treatments, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

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

- The study treatments 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 of each study treatment 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. Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For this study, an overdose of each study treatment is defined as follows:

- INCB001158: A dose that is higher than the dose that subject has been intended to receive, which could be either the originally assigned dose (if not subsequently modified) or a modified dose (eg, following a dose reduction).
- Epacadostat: A dose > 1000 mg.
- Pembrolizumab: A dose ≥ 1000 mg (5 times the dose).

No specific information is available on the treatment of overdose of INCB001158, pembrolizumab, or epacadostat. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE(s) is associated with ("results from") the overdose of study therapies, then the AE(s) is reported as an SAE, even if no other seriousness criteria are met.

All reports of overdose must be reported within 24 hours to the sponsor either by electronic media or paper.

8.7. Warnings and Precautions

Special warnings or precautions for the INCB001158 study drug and for epacadostat and pembrolizumab, derived from safety information collected by the sponsor or its designee, are presented in the Investigator's Brochure (iIB, eIB, pIB). Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). Any important new safety information should be discussed with the subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.8. Data Monitoring Committee

Not applicable. However, continuous evaluation of toxicity events will be performed throughout the study by the sponsor with study investigators, in order to review cohort-specific data and overall safety data, to agree on dose escalation/de-escalation in Phase 1, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions. The representatives from the sponsor will include the medical monitor, the Pharmacovigilance physician, and the Clinical Research Scientist, or designees thereof. See Sections 4.1 and 4.1.1 for further details.

8.9. Events of Clinical Interest

Selected nonserious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such in the eCRF and reported to the sponsor within 24 hours either by electronic media or paper. Sponsor contact information can be found in the Investigator Study File Binder (or equivalent). Events of Clinical Interest for this study include the following:

1. An overdose of study treatment, as defined in Section 8.6, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT laboratory value that is ≥ 3 × ULN and an elevated total bilirubin laboratory value that is ≥ 2 × ULN and, at the same time, an alkaline phosphatase laboratory value that is < 2 × ULN, as determined by way of Protocol-specified laboratory testing or unscheduled laboratory testing.

   Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).
3. Serotonin syndrome – see Section 1.3.2 and Section 5.4.7.

8.10. Product Complaints

The sponsor collects product complaints on study treatment(s) 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

Given that enrollment was terminated per Protocol Amendment (Version) 2 during the Phase 1 portion of the study, all efficacy analyses will now be only exploratory, and some planned tables and figures may be replaced with listings.

9.1. Study Populations

The full analysis set includes all subjects enrolled in the study who received at least 1 dose of study treatment (INCB001158, epacadostat, or pembrolizumab). This population will be used in the analyses of demographic, baseline, safety, study treatment administration, and efficacy data.

The DLT evaluable population is defined in Section 5.4.2 and includes subjects who receive at least 63 of 84 doses (≥ 75%) of INCB001158 and epacadostat plus at least 2 doses of pembrolizumab at the level assigned who or have a DLT. This population will be used for determining tolerability of the dose.

The PK evaluable population includes subjects who received at least 1 dose of study treatment (INCB001158, epacadostat, or pembrolizumab) and had at least 1 postdose PK sample collected and analyzed. [redacted]

9.2. Selection of Sample Size

9.2.1. Sample Size for Phase 1

In Phase 1, the BOIN design will be used to determine the RP2D of the combination of INCB001158, epacadostat, and pembrolizumab, in 21-day treatment cycles in subjects with advanced or metastatic solid tumors. The details of the dose escalation, de-escalation, and elimination boundaries according to the BOIN design are provided in Section 4.1.1.

9.2.2. Sample Size for Phase 2

Phase 2 will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the recommended dose of INCB001158 in combination with epacadostat ± pembrolizumab, as part of dose expansion cohorts in Part A (INCB001158 plus epacadostat and pembrolizumab) and Part B (INCB001158 and epacadostat). 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 5 and Table 6. Each Simon 2-stage design will have a stopping rule to allow early termination of a particular tumor type within the given treatment group at the end of Stage 1 if there is insufficient response observed, while enrolling enough subjects to predict possible target responses worthy of cohort expansion and potential 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.

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 RP2D of INCB001158 in combination with

epacadostat ± pembrolizumab, within the corresponding tumor type and treatment group 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 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, then the drug will be declared nonpromising for that cohort. The detailed calculations for each tumor type-specific cohort are based on a 1-sided Type I error of 0.1 and power of 80%.

9.3. Level of Significance

For the primary efficacy endpoint, the 1-sided Type I error will be controlled at 0.1 for each individual cohort expansion. Of note, this level of significance does not account for the multiple expansion cohorts. For other endpoints, CIs will be reported at a 95% confidence level.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

Objective response rate, defined as the percentage of subjects enrolled in Phase 2 Part A or Phase 2 Part B having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 will be summarized by treatment cohort.

For the hypothesis tests in the Simon 2-stage design, the null response rate is p_0% and alternative response rate is p_1%, where p_0 and p_1 are specific to the tumor type and are determined from historical response rates.

9.4.1.2. Secondary Efficacy Analyses

The following efficacy analyses will be assessed for all subjects in each treatment combination:

- ORR, defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 (Phase 1 only).
- DCR, defined as the percentage of subjects having CR, PR, or SD for at least 56 days, as determined by investigator assessment of radiographic disease as per RECIST v1.1.
- DoR, determined by radiographic disease assessment, defined as the time from earliest date of disease response until the earliest date of disease progression per RECIST v1.1, or death due to any cause, if occurring sooner than progression.
- PFS, defined as the time from date of first dose of study treatment until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1, or death due to any cause, if occurring sooner than progression.

[redacted]

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study 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 for all events and AEs of special interest, including irAEs and potential inhibition of the urea cycle (urinary orotic acid and plasma ammonia and BUN). Severity of AEs will be based on the NCI CTCAE v4.03 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship to one of the study treatments will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to one of the study treatments, the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.2.2. Clinical Laboratory Tests

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

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

- Number and percentage of subjects with worst postbaseline CTCAE grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.

- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

9.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 23), 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 23: Criteria for Clinically Notable Vital Sign Abnormalities

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

9.4.2.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (Table 24). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 24: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 480 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms

QTcF = Fridericia correction.

9.4.3. Pharmacokinetic Analysis

The PK parameters of C_{max}, t_{max}, C_{min}, AUC_{0-t}, and Cl/F (INCB001158 and epacadostat) for the first twelve subjects enrolled in Phase 2 Part B will be calculated from the plasma concentrations of INCB001158 and epacadostat using standard noncompartmental (model independent) PK methods. Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin®. Nominal times will be used in all cases, except when the difference between the actual time and nominal time is > 15 minutes for samples collected ≤ 4 hours after administration and > 30 minutes for samples collected > 4 hours after administration; in these cases, actual time will be used for PK analysis.

See Appendix B for a detailed list and description of the PK parameters.

In addition, for all subjects, the plasma concentrations of INCB001158, epacadostat, and, if needed, pembrolizumab will be analyzed by standard population PK methods using appropriate software (eg, NONMEM).

[redacted]

9.5. Interim Analysis

9.5.1. Interim Analysis for the BOIN Design

In Phase 1, the BOIN design will be used to determine the RP2D of the combination of INCB001158, epacadostat, and pembrolizumab. For the design parameters, let δ denote the target DLT rate, δ_1 denote the highest toxicity probability below the MTD so that dose escalation is required, and δ_2 denote the lowest toxicity probability deemed overly toxic so that dose de-escalation is required. We assume that $\delta_1 = 0.6\,\delta$ and $\delta_2 = 1.4\,\delta$. Also, to avoid assigning too many subjects to an overly toxic dose, we use the dose elimination rule when implementing the BOIN design. If $p_r(p_j > \delta | m_j, n_j) > 0.95$ and $n_j \geq 3$, dose levels j and higher are eliminated from the study, and the dose escalation is terminated if the lowest dose level is eliminated, where p_j represents the toxicity rate, δ represents the target DLT rate, n_j represents the total subjects who have been treated, and m_j represents the subjects who have experienced toxicity at dose level j. Section 4.1.1 Table 2 (in the bottom row) provides the elimination boundaries for the target DLT rate of 33%. For example, when the number of subjects treated at the current dose $n_j = 4$, we will eliminate that dose and higher doses if 3 or more subjects experience toxicity.

Based on the algorithm of the BOIN design, a minimum of 3 evaluable subjects will be enrolled in each dose level with a maximum of 9 evaluable subjects in each dose level.

9.5.2. Interim Analysis for the Simon 2-Stage Design

In Phase 2, the Simon 2-stage design will be applied for each tumor within a given treatment group (see Sections 4.1.2 Table 5 and 4.1.3 Table 6). During Stage 1, n_1 evaluable subjects treated at the recommended dose and schedule will be enrolled, and if r_1 or fewer responses are observed, then the cohort will be discontinued. As discussed in Section 9.2.2, the Simon 2-stage designs for each tumor type have design parameters determined by historical response rates and will have different sample sizes and different futility rules, depending on the historical response rate. The probability of early termination for Stage 1 is summarized in Table 25.

Table 25: Probability of Early Termination for Simon 2-Stage Design in Phase 2

Cohort (Tumor Type)	p_0	p_1	Probability of Early Termination	
			Under H_0	Under H_A
Part A				
A1	30%	50%	0.7216	0.1509
A2	2%	15%	0.8007	0.1673
A3	15%	35%	0.5995	0.1211
B1	56%	76%	0.6704	0.1377
B2	2%	15%	0.8007	0.1673
B3	15%	35%	0.5995	0.1211
C	30%	50%	0.7216	0.1509
D	39%	59%	0.6405	0.1095
E	25%	45%	0.6865	0.1204
Part B				
A, B, C	2%	15%	0.8007	0.1673

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 Treatments

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 treatments to the study site.
- Inventory of study treatments at the site.
- Subject use of the study treatments including pill or unit counts from each supply dispensed.
- Return of study treatments 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 treatments. 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 treatment 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 treatment 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 treatment is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

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

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

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

10.4. Data Privacy and Confidentiality of Study Records

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

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

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

10.5. Financial Disclosure

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

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

10.6. Publication Policy

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

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

Such methods include:

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

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
Source: CTFG 2014.

APPENDIX B. PHARMACOKINETIC ANALYTICAL PARAMETERS

C_{ave}	Average steady-state plasma concentration ($AUC_{0\text{-}12h}$/12h or $AUC_{0\text{-}24h}$/24h)
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration during the dosing interval
T_{max}	Time to maximum plasma concentration
$AUC_{0\text{-}t}$	Area under the single-dose plasma concentration-time curve from Hour 0 to the last quantifiable measurable plasma concentration, calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
$AUC_{0\text{-}\tau}$ (ie, $AUC_{0\text{-}12h}$ or $AUC_{0\text{-}24h}$)	Area under the steady-state plasma concentration-time curve over 1 dosing interval (ie, from Hour 0 to 12 for BID administration or from Hour 0 to 24 for QD administration), calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
λ_z	Apparent terminal phase disposition rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{½}$	Apparent plasma terminal phase disposition half-life (whenever possible), where $t_{½} = (\ln 2) / \lambda_z$
Cl/F	Oral dose clearance
V_z/F	Apparent oral dose volume of distribution
Fluctuation	Steady-state fluctuation ($[C_{max} - C_{min}]/C_{ave}$)

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin®. Additional details of analyses will be described in the statistical analysis plan.

APPENDIX C. PROHIBITED MONOAMINE OXIDASE INHIBITORS

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	

APPENDIX D. PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment (Version) 1:	27 OCT 2017
Amendment (Version) 2:	01 JUN 2018

Amendment 2 (Version 2 dated 01 JUN 2018)

The main reason for the Amendment is to halt enrollment into the study, based on emergent data from the ECHO-301/KEYNOTE-252 melanoma clinical study in which an interim analysis revealed that the study did not meet the prespecified endpoint of improvement in progression-free survival for the combination of pembrolizumab and epacadostat compared with pembrolizumab and placebo (Long et al 2018).

In addition, this amendment includes some corrected errors and a few updates based on new information (updated epacadostat safety information and the defined INCB001158 starting dose).

This amendment includes the changes to the Protocol INCB 01158-202 Amendment (Version) 1 (27 OCT 2017) summarized below.

1. **Synopsis; Section 4.3, Number of Subjects**

   Description of change: The estimated number of subjects to be enrolled and number of study sites in this study has been updated.

   Rationale for change: The early termination of enrollment will limit the number of subjects to be enrolled.

2. **Synopsis; Section 4.6.1, Protocol Amendment 2**

   Description of change: All further enrollment into this study was halted. Subjects who have consented and are in screening as of 08 MAY 2018 are permitted to enroll if eligibility is determined per Section 3, and subjects currently on treatment may continue as long as they are deriving clinical benefit, tolerating the treatment, and do not meet any withdrawal criteria. Phase 1 backfill cohorts and Phase 2 will not be opened.

   Rationale for change: The premise of this study was based on epacadostat + pembrolizumab having greater antitumor activity than pembrolizumab alone. However, because the ECHO-301/KEYNOTE-252 melanoma clinical study did not meet the prespecified endpoint of improvement in progression-free survival for the combination of pembrolizumab + epacadostat compared with pembrolizumab + placebo, it was decided to close all further enrollment into the INCB 01158-202 study.

3. **Synopsis; Section 9, Statistics**

   Description of change: All efficacy analyses will now only be exploratory; some planned tables and figures may be replaced by listings.

   Rationale for change: Due to enrollment into this study halting during the Phase 1 portion, there will not be sufficient efficacy data to warrant carrying out the planned efficacy analyses and producing all of the planned tables. Instead, efficacy analyses will now be exploratory, and tables will be replaced with listings as appropriate.

4. **Section 1.3.2, Risks for Epacadostat; Section 5.4.7, Procedures for Subjects Exhibiting Serotonin Syndrome**

   Description of change: Language regarding serotonin syndrome was updated.

   Rationale for change: Language was revised based on updated data from epacadostat studies.

5. **Section 5.2.3.2, Pembrolizumab Supply, Packaging, and Labeling**

   Description of change: Added an alternative pharmaceutical form in which the study treatment pembrolizumab could be provided, namely 50 mg lyophilized powder for reconstitution in single-use vials.

   Rationale for change: Pembrolizumab may be supplied in this form at some sites.

6. **Section 5.4.10, Criteria for Permanent Discontinuation of Study Treatment**

   Description of change: One of the definitions of "unacceptable toxicity" was changed from "An AE requiring more than 2 dose reductions of INCB001158 (and no lower than 50 mg BID) or epacadostat" to "An AE requiring more than 2 dose reductions of INCB001158 or epacadostat."

   Rationale for change: The restriction of "no lower than 50 mg BID" was an error.

7. **Section 6, Study Assessments (Table 14, Schedule of Clinical Assessments)**

   Description of change: Changed the section reference from 0 to 3 in the "Review inclusion and exclusion criteria" row.

   Rationale for change: Correction.

8. **Section 6, Study Assessments (Table 15, Schedule of Laboratory Assessments); Section 7.10.1, Timing of Assessments;** [redacted]

   Description of change: Changed the type of sample from [redacted].

   Rationale for change: Correction.

9. **Section 7.6.1, Adverse Events; Section 8, Safety Monitoring and Reporting; Section 10.2, Accountability, Handling, and Disposal of Study Treatments**

   Description of change: All mentions of safety monitoring and reporting, accountability, handling, and disposal related to "study drug" have been changed to "study treatment" or "study treatments."

   Rationale for change: The safety monitoring and reporting, accountability, handling, and disposal relates to any or all of the 3 study treatments, not just the INCB001158 study drug.

10. **Section 8.9, Events of Clinical Interest**

    Description of change: Serotonin syndrome was added to the list of Events of Clinical Interest.

    Rationale for change: The epacadostat clinical program now requires events of serotonin syndrome to be reported to the sponsor within 24 hours.

Amendment 1 (Version 1 dated 27 OCT 2017)

Overall Rationale for the Amendment: To address comments from FDA.

This amendment includes the changes to the Protocol INCB 01158-202 (02 OCT 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 1.2.3.1, Phase 1: Dose Escalation of INCB00158-202 + Epacadostat + Pembrolizumab; Section 3.1, Subject Inclusion Criteria**

   Description of change: Revised the eligibility criteria so that subjects who refuse standard-of-care treatment are not eligible.

   Rationale for change: FDA request.

2. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 4.1.3, Phase 2 Part B: Tumor Expansion of INCB001158 + Epacadostat**

   Description of change: Revised the eligibility criteria for Phase 2 Part B Cohort A (urothelial carcinoma) to require progression of disease after treatment with a platinum-based regimen and a checkpoint inhibitor.

   Rationale for change: FDA request.

3. **Synopsis, Section 3.1 Subject Inclusion Criteria; Section 4.1.3, Phase 2 Part B: Tumor Expansion of INCB001158 + Epacadostat**

   Description of change: Revised the eligibility criteria for Phase 2 Part B Cohort B (SCCHN) to require progression of disease after prior treatment with a platinum-based therapy and a PD-1 inhibitor.

   Rationale for change: FDA request.

4. **Section 5.4.2 Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose in Phase 1**

   Description of change: Revised to specify that subjects who experienced a DLT that is considered life-threatening must permanently discontinue all 3 study treatments. For DLTs that are not life-threatening, all 3 treatments should be interrupted and then restarted following the management guidelines in Table 9.

   Rationale for change: FDA request. Relevant details were missing.

5. **Section 5.4.6, Dose Modifications for Immune-Related AEs and AEs Related to Urea-Cycle Inhibition**

   Description of change: Revised Table 9 to include the action that will be taken if fasting urinary orotic acid after 1 week of the initial one is abnormal.

   Rationale for change: FDA request. Relevant details were missing.

6. **Section 5.4.10, Criteria for Permanent Discontinuation of Study Treatment**

   Description of change: Specified that only irAEs might require a 12-week treatment interruption, and that for all other AEs permanent discontinuation of study treatments would be required after 4 weeks.

   Rationale for change: FDA request. Provides important clarification.

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

Signature Manifest

Document Number: IC-DEV-PROT-AMEND-0351 **Revision:** 0

Title: INCB 01158-202 Protocol Amendment 2

All dates and times are in Eastern Standard Time.

01158-202 Protocol Amend 2

Approval and Release

Name/Signature	Title	Date	Meaning/Reason
[redacted]	[redacted]	05 Jun 2018, 10:02:55 AM	Approved
[redacted]	[redacted]	05 Jun 2018, 10:14:11 AM	Approved
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[redacted]	[redacted]	05 Jun 2018, 12:21:28 PM	Approved