Official Title:	**Safety, Pharmacokinetics, and Pharmacodynamics of Escalating Oral Doses of the Arginase Inhibitor INCB001158 (Formerly Known as CB1158) as a Single Agent and in Combination With Immune Checkpoint Therapy in Patients With Advanced/Metastatic Solid Tumors**
NCT Number:	NCT02903914
Document Date:	Clinical Study Protocol Amendment 2–US 3: 10 November 2020

Title	Safety, Pharmacokinetics, and Pharmacodynamics of Escalating Oral Doses of the Arginase Inhibitor INCB001158 (formerly known as CB-1158) as a Single Agent and in Combination with Immune Checkpoint Therapy in Patients with Advanced/Metastatic Solid Tumors
Protocol Number	INCB 01158-101 (formerly known as CX-1158-101)
IND Number	128080
EudraCT number	2017-002903-82
Sponsor	Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803
Date/Version	10 NOV 2020/Amendment 2-US 3

Confidentiality Statement

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 01158-101 Protocol Amendment 2-US 3 (dated 10 NOV 2020) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

SYNOPSIS

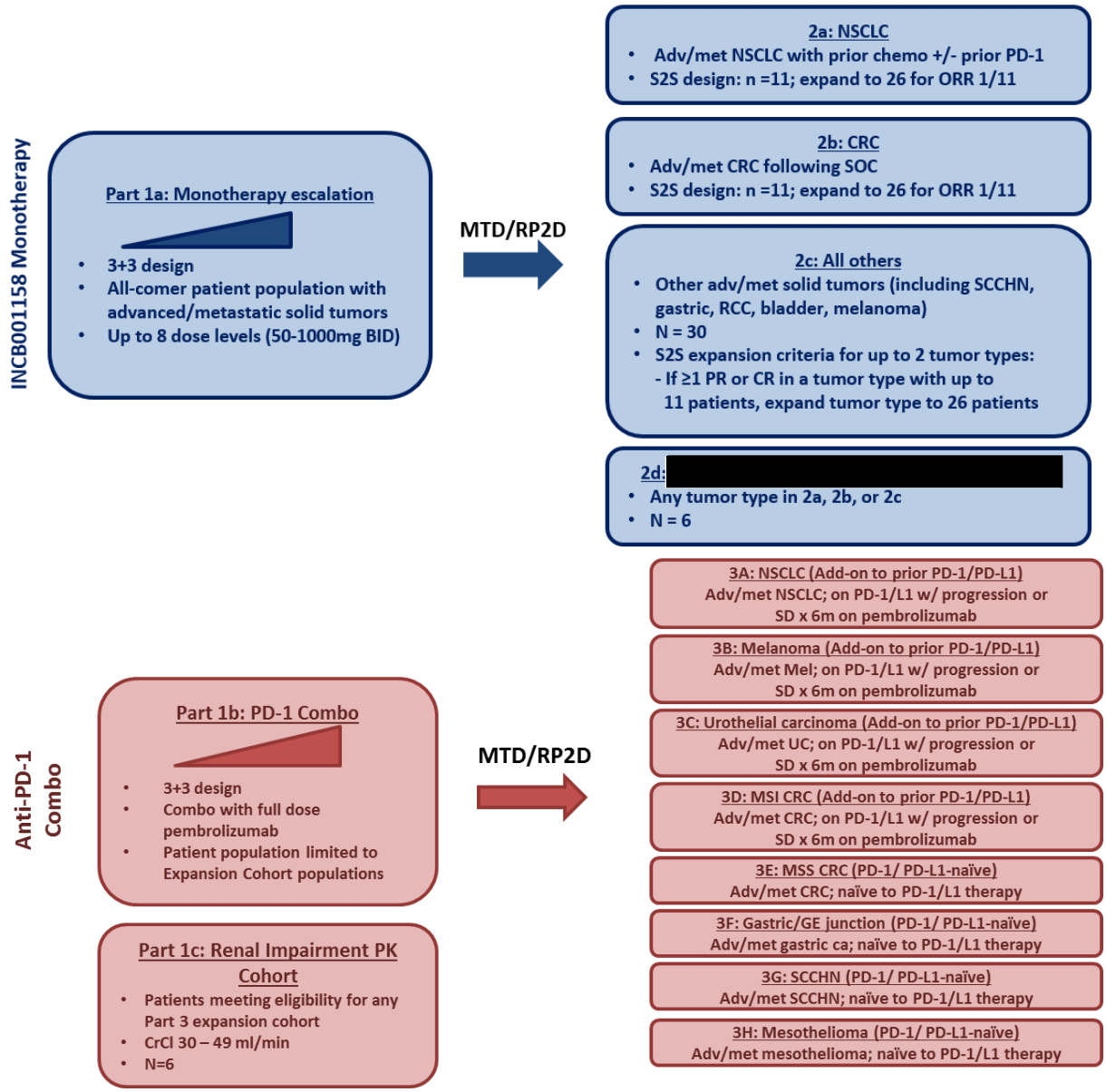
Name of Investigational Product: INCB001158	
Title of Study: Safety, Pharmacokinetics, and Pharmacodynamics of Escalating Oral Doses of the Arginase Inhibitor INCB001158 as a Single Agent and in Combination with Immune Checkpoint Therapy in Patients with Advanced/Metastatic Solid Tumors.	
Protocol Number: INCB 01158-101	**Study Phase:** 1
Indication: Part 1a (monotherapy dose escalation): all advanced/metastatic solid tumors. Parts 1b and 1c (pembrolizumab combination dose escalation): all patient populations included in Part 3. Part 2 (monotherapy expansion cohorts): advanced/metastatic non-small cell lung cancer (NSCLC), advanced/metastatic colorectal cancer (CRC), advanced/metastatic tumors including gastric cancer, cancer of the gastroesophageal junction (GEJ), urothelial cell cancer (UCC), renal cell cancer (RCC), melanoma, or squamous cell carcinoma of the head and neck (SCCHN) or other advanced/metastatic solid tumors (e.g., those demonstrated or expected to have high infiltration with arginase-positive cells) may be allowed based on the discretion of the Medical Monitor. Part 3 (pembrolizumab combination expansion cohorts): advanced/metastatic NSCLC, melanoma, UCC, microsatellite instability-high (MSI-H) CRC, microsatellite stable (MSS) CRC, advanced/metastatic Gastric/GEJ cancer, SCCHN and malignant pleural mesothelioma.	

Primary Objectives	***Primary Endpoints***
Parts 1a and 2	
To evaluate the safety and tolerability of INCB001158 for patients with advanced/metastatic and/or treatment-refractory solid tumors	Adverse events (AEs) and changes in laboratory values, vital signs, and physical examinations
Parts 1b, 1c, and 3	
To evaluate the safety and tolerability of INCB001158 in combination with pembrolizumab in patients with advanced/metastatic and/or treatment-refractory solid tumors	AEs and changes in laboratory values, vital signs and physical examinations
Secondary Objectives	***Secondary Endpoints***
Parts 1a and 2	
To select the Recommended Phase 2 Dose (RP2D) of INCB001158 for patients with advanced/metastatic solid tumors	Based on an evaluation of AEs, pharmacokinetics (PK), pharmacodynamics and evidence of clinical activity
Parts 1b and 3	
To select the RP2D of INCB001158 in combination with pembrolizumab for patients with advanced/metastatic solid tumors	Based on an evaluation of AEs, PK, pharmacodynamics and evidence of clinical activity
Parts 1a, 1b, 1c, 2, and 3	
To evaluate the anti-tumor effect of INCB001158 as monotherapy and in combination with pembrolizumab for patients with advanced/metastatic solid tumors	Assessed by standard RECIST v1.1 criteria (except for pleural mesothelioma, which will be evaluated using modified RECIST criteria) [overall response rate (ORR), best overall response (BOR), duration of response (DOR), and progression-free survival (PFS)]
Determine PK of INCB001158 alone and in combination with pembrolizumab	C_{max}, T_{max}, AUC_t, AUC_{0-12} and CL/F in patients with CrCl 30-49 mL/min (Part 1c only) or CrCl $\geq$ 50 mL/min (Parts 1a, 1b, 2, and 3)
[redacted]	

Overall Study Design

Phase 1 open-label, non-randomized study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and anti-tumor activity of the arginase inhibitor INCB001158, evaluated both as monotherapy and in combination with the immune checkpoint inhibitor pembrolizumab, an anti-programmed cell death protein-1 (anti-PD-1) agent.

The study design is illustrated in the following schematic:



Part 1a Dose Escalation

This is a standard 3+3 dose escalation of single agent INCB001158 in patients with advanced/metastatic solid tumors. A minimum of three eligible solid tumor patients will be assigned to each dose level during the Dose Escalation period. The starting dose of 50 mg BID was selected for the monotherapy dose escalation on the basis of GLP-compliant preclinical toxicity studies. The dose escalation schedule outlined below will be followed, which is based on the standard Modified Fibonacci design. Real-time PK and pharmacodynamic assessment will be performed on samples taken during dose escalation.

Part 1b Dose Escalation

The decision to initiate the evaluation of the safety of INCB001158 in combination with pembrolizumab (Part 1b) will be made on the basis of PK, pharmacodynamic and safety data from patients enrolled in the monotherapy dose escalation (Part 1a) and/or monotherapy expansion cohorts (Part 2). Part 1b may be opened if one of the following is achieved at a dose level that is confirmed to be at or below the monotherapy MTD:

- At least half of the patients (minimum of two patients) enrolled at a particular dose level achieve a trough (C_{min}) plasma concentration of INCB001158 at steady state of ≥ 1 μM, OR
- At least half of the patients (minimum of two patients) at a particular dose level achieve a 2.5-fold increase in fasting plasma arginine at Cycle 1 Day 15 predose relative to their baseline (Cycle 1 Day 1 predose) value.

When the PK or PD requirement has been satisfied in Part 1a or Part 2 as defined above, the final decision to open Part 1b will be made by agreement between the Medical Monitor and the Study Investigators.

Part 1b is a standard 3+3 dose escalation design. Upon opening Part 1b, a minimum of 3 patients will receive pembrolizumab (200 mg IV Q3W) in combination with INCB001158. Enrollment in Part 1b is limited to patients with tumor types that would be eligible for the Expansion Cohorts in Part 3. In Part 1b, the starting dose of INCB001158 will be 50 mg BID, which is 2 dose levels below the recommended monotherapy Phase 2 dose of 100 mg BID identified in Part 1a of this study. Dose escalation will proceed according to the Dose Escalation Schedule that is being employed in Part 1a in the table below. A dose level shall not be enrolled in Part 1b until it has been demonstrated to be at or below the monotherapy MTD in Part 1a.

INCB001158 Dose Levels			
Cohort	**BID Dose (mg)**	**% Increase**	**N**
-1	25	- 50%	3 – 6
1*	50	-	3 – 6
1.5	75	50%	3 – 6
2	100	33%	3 – 6
3	150	50%	3 – 6
4	225	50%	3 – 6
5	300	33%	3 – 6
6	400	33%	3 – 6
7	500	25%	3 – 6
8	600	20%	3 – 6

*starting dose level

Part 1c Renal Impairment Cohort

At US sites only, Cohort 1c will enroll 6 patients who have moderately impaired renal function (defined as CrCl 30-49 mL/min calculated by the Cockcroft-Gault formula) AND meet eligibility criteria for any of the combination expansion cohorts (3a through 3h). Based on population PK modeling, a dose of 50 mg BID in patients with CrCl 30-49 mL/min is predicted to achieve INCB001158 AUC/C_{min} values to fall within the known safe exposure range corresponding to doses at or below the established RP2D of 100 mg BID. Therefore, 6 patients meeting eligibility criteria for Parts 3a through 3h will be enrolled at a reduced dose of 50 mg BID in order to obtain full PK, PD, and safety data. All data collected during the first cycle (21 days) will be evaluated, along with the population PK modeling data, to determine the INCB001158 dose in patients with moderately impaired renal function that most closely approximates the PK parameters of the RP2D of 100 mg BID in patients with normal renal function. Patients who do not complete all planned PK assessments or have treatment discontinuation or interruptions during the first 21 days of dosing will be replaced until 6 evaluable patients have been accrued to the cohort. Efficacy evaluable patients in Cohort 1c who achieve the target exposure leading to continuous inhibition of extracellular arginase 1 by > 90% (C_{min} of $\geq$ 1 μM) and/or an elevation of fasting plasma arginine of $\geq$ 2.5-fold at Cycle 1 Day 15 predose relative to baseline will be counted towards their respective Part 3 expansion cohorts, provided these have not fully enrolled at the time data from these patients become available.

Dose Escalation Rules and Definition of Maximally Tolerated Dose (MTD)

Dose limiting toxicities (DLTs) observed in the first 28 days of dosing for monotherapy dose escalation (Part 1a) or the first 42 days of dosing for combination dose escalation (Part 1b) will be used to determine escalation to the next dose level. The study is using a traditional 3+3 design and the dose escalation rules are as follows:

- An initial cohort of 3 patients is enrolled.
- If 0/3 patients develops a DLT, escalation to the next dose will occur.
- If 1/3 patients develops a DLT:
    - Another 3 patients will be enrolled at this dose level.
        - If 0 of the 3 new patients develops a DLT (for a total of 1/6 patients with a DLT at this dose level), escalation to the next dose level will occur.
        - If $\geq$1 of the 3 new patients develops a DLT (for a total of $\geq$ 2/6 patients with a DLT at this dose level), the dose escalation stage of the trial will be terminated, and the dose directly below the current dose will be considered the MTD.
- If $\geq$ 2/3 patients develop a DLT, the dose escalation stage of the trial will be terminated, and the dose directly below the current dose will be considered the MTD.

If a dose level below 1000 mg BID is selected as the MTD on the basis of only 2 DLTs and subsequent clinical data [e.g., in the expansion cohort(s)] demonstrate that the rate of AEs that qualify as DLTs at that dose level is < 10% in > 10 patients, re-escalation to the next dose level previously associated with DLTs may be considered. If re-escalation occurs, up to 6 additional patients may be enrolled and the dose level may be considered tolerable if the overall DLT rate for that dose level is $\leq$ 25%.

Part 2 Single Agent Cohort Expansion

Following completion of monotherapy Dose Escalation and selection of the RP2D for INCB001158 in Part 1a, the following cohorts of patients will be enrolled to receive single agent INCB001158 at the RP2D.

- Cohort 2a will enroll patients with advanced NSCLC. Enrollment to this cohort will follow a Simon 2-stage design where the observed clinical activity in the first 11 patients will determine whether additional patients will be enrolled for a total of 26 patients.

- Cohort 2b will enroll patients with advanced/metastatic colorectal cancer. Enrollment to this cohort will follow a Simon 2-stage design where the observed clinical activity in the first 11 patients will determine whether additional patients will be enrolled for a total of 26 patients.
- Cohort 2c will initially enroll 30 patients with various other tumor types expected to have high infiltration with arginase positive cells. Up to 2 tumor types in Cohort 2c may then be expanded based on a Simon 2-stage design, if the observed clinical activity (1 or more PR or CR in a tumor type with up to 11 patients) supports enrollment of additional patients for a total of 26 patients per tumor type.
- Cohort 2d will enroll patients at US sites only who meet eligibility criteria for any of the monotherapy expansion cohorts (2a, 2b, or 2c). [redacted]

Part 3 Combination Cohort Expansion

Upon selection of the RP2D for INCB001158 in combination with pembrolizumab in Part 1b, cohorts of specific patients will be enrolled to receive INCB001158 in combination with pembrolizumab at the RP2D to further evaluate safety and identify an early signal of clinical activity.

Study Population

Part 1a (monotherapy dose escalation): all advanced/metastatic solid tumors.

Parts 1b and 1c (pembrolizumab combination dose escalation): all patient populations included in Part 3.

Part 2 (monotherapy expansion cohorts): advanced/metastatic NSCLC, advanced/metastatic CRC, advanced/metastatic tumors including gastric cancer, cancer of the GEJ, UCC, RCC, melanoma, or SCCHN or other advanced/metastatic solid tumors (e.g., those demonstrated or expected to have high infiltration with arginase-positive cells) may be allowed based on the discretion of the Medical Monitor.

Part 3: advanced/metastatic NSCLC, melanoma, UCC, microsatellite instability-high (MSI-H) CRC, microsatellite stable (MSS) CRC, advanced/metastatic Gastric/GEJ cancer, SCCHN and malignant pleural mesothelioma.

Key Inclusion Criteria

1. Age ≥ 18 years
2. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1
3. Adequate organ function as indicated by the laboratory values in
    - Absolute neutrophil count (ANC) ≥ 1.500/mcL
    - Platelets ≥ 100,000/mcL
    - Hemoglobin ≥ 9 g/dL
    - CrCl ≥ 50 mL/min (calculated using the Cockcroft-Gault formula), except for Cohort 1c, which will enroll patients with creatinine clearance 30-49 mL/min (calculated using the Cockcroft-Gault formula).
    - Serum total bilirubin OR Direct bilirubin (for patients with Gilbert Syndrome and total bilirubin levels > 1.5 ULN) ≤ 1.5 X ULN OR ≤ ULN
    - AST (SGOT) and ALT (SGPT) ≤ 2.5 X ULN
    - International Normalized Ratio (INR) or Prothrombin Time (PT) ≤ 1.5 X ULN- Does not apply to patients receiving therapeutic anticoagulation

4. Measurable Disease: At least one tumor lesion/lymph node that meets the RECIST v1.1 criteria for being "measurable."
   Resolution of all treatment-related toxicities, except alopecia, anemia, or endocrinopathies managed by hormone replacement, from any previous cancer therapy to ≤ Grade 1 or to values within those required for eligibility on this study prior to the first dose of study treatment.

Part 1: Inclusion Criteria Specific to the Dose Escalation

Part 1a: Inclusion Criteria Specific to the Monotherapy Dose Escalation

1. Histologically or cytologically proven diagnosis of any locally advanced or metastatic solid tumor not amenable to local therapy in patients who have disease progression after treatment with all available therapies known to confer clinical benefit

Part 1b: Inclusion Criteria Specific to the PD-1 Combination Dose Escalation

1. Histologically or cytologically proven diagnosis of advanced/metastatic NSCLC (squamous or non-squamous), mesothelioma, gastric/GEJ cancer, MSS CRC, MSI-H CRC, UCC, melanoma or SCCHN in patients who have disease progression after treatment with all available therapies known to confer clinical benefit. Patients that have not received prior anti-PD-1 therapies are allowed.

Part 1c: Inclusion Criteria Specific to the PD-1 Combination Moderately Renally Impaired Cohort

1. Criteria for any of Cohorts 3a to 3h.

Part 2: Inclusion Criteria Specific to Monotherapy Cohort Expansion

Part 2a: Inclusion Criteria Specific to the Monotherapy NSCLC Cohort

1. Histologically or cytologically proven diagnosis of advanced/metastatic NSCLC (squamous or non-squamous) in patients who have disease progression after treatment with all available therapies known to confer clinical benefit

Part 2b: Inclusion Criteria Specific to the Monotherapy CRC Cohort

1. Histologically or cytologically proven diagnosis of advanced/metastatic CRC in patients who have disease progression after treatment with all available therapies known to confer clinical benefit

Part 2c: Inclusion Criteria Specific to the Monotherapy in Other Tumors

1. Histologically or cytologically proven diagnosis of advanced/metastatic tumors including gastric cancer, cancer of the GEJ, UCC, RCC, melanoma, or SCCHN in patients who have disease progression after treatment with all available therapies known to confer clinical benefit. Other advanced/metastatic solid tumors (e.g., those demonstrated or expected to have high infiltration with arginase-positive cells) may be allowed based on the discretion of the Medical Monitor.

Part 2d: [redacted]

1. Meets the criteria for any of Parts 2a, 2b, or 2c.

[redacted].

Part 3: Inclusion Criteria Specific to the PD-1 Combination Cohort Expansion

Part 3a: Non-small cell lung cancer (NSCLC) – PD/SD on anti-PD-1/PD-L1 therapy

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic NSCLC that does not harbor an activating EGFR or ALK mutation
2. Prior progression on or after platinum-based chemotherapy or refused/ineligible to receive platinum-based chemotherapy.

3. Received an anti-PD-1/PD-L1 agent in a prior line of therapy for advanced/metastatic disease and EITHER:

a. Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks) while receiving anti-PD-1/PD-L1 therapy in the most recent line of therapy, OR
b. Had documented stable disease (per Investigator assessment) for ≥ 24 weeks while receiving pembrolizumab therapy in the most recent line of therapy

Part 3b: Melanoma – PD/SD on anti-PD-1/PD-L1 therapy

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic melanoma
2. Received an anti-PD-1/PD-L1 agent in the most recent prior line of therapy for advanced/metastatic disease and EITHER:
    a. Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks) while receiving anti-PD-1/PD-L1 therapy in the most recent line of therapy, OR
    b. Had documented stable disease (per Investigator assessment) for ≥ 24 weeks while receiving pembrolizumab therapy in the most recent line of therapy

Part 3c: Urothelial cell carcinoma (UCC) – PD/SD on anti-PD-1/PD-L1 therapy

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic UCC
2. Received an anti-PD-1/PD-L1 agent in the most recent prior line of therapy for advanced/metastatic disease and EITHER:
    a. Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks) while receiving anti-PD-1/PD-L1 therapy in the most recent line of therapy, OR
    b. Had documented stable disease (per Investigator assessment) for ≥ 24 weeks while receiving pembrolizumab therapy in the most recent line of therapy

Part 3d: Mismatch repair deficient and/or microsatellite instability-high (MSI-H) colorectal cancer (CRC) – PD/SD on anti-PD-1/PD-L1 therapy

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic CRC demonstrated to be mismatch repair deficient or microsatellite instability-high.
2. Received an anti-PD-1/PD-L1 agent in the most recent prior line of therapy for advanced/metastatic disease and EITHER:
    a. Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks) while receiving anti-PD-1/PD-L1 therapy in the most recent line of therapy, OR
    b. Had documented stable disease (per Investigator assessment) for ≥ 24 weeks while receiving pembrolizumab therapy in the most recent line of therapy

Part 3e: Microsatellite stable (MSS) colorectal cancer (CRC) – Checkpoint inhibitor naive

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic CRC demonstrated to lack mismatch repair deficiency and microsatellite instability (low or high).
2. Received at least one prior fluoropyrimidine-containing systemic therapy for advanced/metastatic CRC
3. Has not received prior anti-PD-1/PD-L1, anti-CTLA4, or other checkpoint inhibitor or immune co-stimulator (e.g., anti-OX-40, anti-41BB, etc.)

Part 3f: Gastric/gastro-esophageal (GE) junction cancer – Checkpoint inhibitor naive

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic gastric or GEJ cancer
2. Received at least two prior systemic therapies for advanced/metastatic disease; prior regimens must have included a platinum and a fluoropyrimidine
3. Human epidermal growth factor receptor 2 (HER-2/neu) negative, or, if HER2/neu positive, must have previously received treatment with trastuzumab
4. Has not received prior anti-PD-1/PD-L1, anti-CTLA4, or other checkpoint inhibitor or immune co-stimulator (e.g., anti-OX-40, anti-41BB, etc.)

Part 3g: Squamous cell carcinoma of the head and neck (SCCHN) – Checkpoint inhibitor naive

1. Histological or cytological diagnosis of recurrent or metastatic SCCHN
2. Had disease progression EITHER:
    a. While receiving or after platinum-containing chemotherapy administered for recurrent or metastatic SCCHN, OR
    b. Following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy.
3. Has not received prior anti-PD-1/PD-L1, anti-CTLA4, or other checkpoint inhibitor or immune co-stimulator (e.g., anti-OX-40, anti-41BB, etc.).

Part 3h: Mesothelioma – Checkpoint inhibitor naive

1. Histological or cytological diagnosis of locally advanced incurable or metastatic malignant pleural mesothelioma
2. Has failed or was unable to received standard therapy for malignant pleural mesothelioma
3. Has not received prior anti-PD-1/PD-L1, anti-CTLA4, or other checkpoint inhibitor or immune co-stimulator (e.g., anti-OX-40, anti-41BB, etc.)

Key Exclusion Criteria

1. Any other current or previous malignancy within the past three years except a) adequately treated basal cell or squamous cell skin cancer, b) carcinoma *in situ* of the cervix, c) prostate cancer with stable prostate specific antigen (PSA) levels for 3 years, d) or other neoplasm that, in the opinion of the Principal Investigator and with the agreement of the Medical Monitor, will not interfere with study-specific endpoints.
2. Cytotoxic chemotherapy, tyrosine kinase inhibitor (or other targeted anti-cancer agent), radiation therapy, or hormonal therapy within 14 days or 5 half-lives, whichever is longer, prior to Cycle 1 Day 1 (42 days for nitrosoureas or mitomycin C).
3. Immunotherapy or biological therapy (e.g., monoclonal antibodies) within 21 days prior to Cycle 1 Day 1
    - EXCEPTION: Washout of anti-PD-1 therapy is NOT required in Part 1b Dose Escalation or the Part 3 Expansion Cohorts.
4. Treatment with an unapproved investigational therapeutic agent within 21 days (or 5 half-lives for small molecule agents) prior to Cycle 1 Day 1
    - EXCEPTION: Washout of anti-PD-1 therapy is NOT required in Part 1b Dose Escalation or the Part 3 Expansion Cohorts.
5. Has a diagnosis of immunodeficiency or any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other systemic immunosuppressive medications within 14 days prior to the first dose of study treatment. Inhaled steroids and adrenal replacement steroid doses $\leq$ 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
6. Concomitant therapy with valproic acid/valproate-containing therapies.
7. Concomitant therapy with allopurinol and other xanthine oxidase inhibitors.
8. Exclusion criterion deleted in Protocol Amendment 2-EU.

9. Patients with symptomatic ascites or pleural effusion requiring intermittent paracentesis or thoracocentesis. A patient who is clinically stable following treatment for these conditions (including therapeutic thoraco- or para-centesis) is eligible.
10. Unable to receive medications *per os* (PO)
11. Unstable/inadequate cardiac function:
    - Myocardial infarction or symptomatic ischemia within the last 6 months
    - Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded; 1st degree AV block or asymptomatic LAFB/RBBB are eligible)
    - Congestive heart failure (New York Heart Association class III to IV)
12. 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.
13. Major surgery within 2 months prior to first dose of study treatment.
14. Infection requiring parenteral antibiotics, antivirals, or antifungals within two weeks prior to first dose of study treatment.
15. Patient is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C.
16. Refractory nausea and vomiting, uncontrolled diarrhea, malabsorption, significant small bowel resection or gastric bypass surgery, use of feeding tubes or other situation that may preclude adequate absorption
17. Serious psychiatric or medical conditions that could interfere with treatment or protocol-related procedures
18. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Note: Patients with brain metastases or CNS disease are permitted, but must have completed treatment and either (1) have no evidence of active CNS disease for at least 4 weeks prior to the first dose *OR* (2) have stable CNS lesions, defined as not requiring intrathecal chemotherapy for at least 6 weeks or systemic steroid treatment to prevent CNS complications for at least 3 weeks prior to first dose. Patients with CNS disease must also have a Screening head CT or MRI demonstrating stable disease compared to their most recent CNS evaluation. This exception does not apply to patients with carcinomatous meningitis who are excluded regardless of clinical stability.
19. Patients in whom oral and/or IV fluid hydration are contraindicated
20. Patients who are pregnant or lactating
21. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the Patient's participation for the full duration of the trial, or is not in the best interest of the Patient to participate, in the opinion of the treating investigator.
23. Has had an allogeneic tissue/solid organ transplant.

Disease-specific Exclusion Criteria

Part 1b AND Part 3

1. Intolerance to prior anti-PD-1/PD-L1 therapy including 1) discontinuation due to immune-related toxicity or, 2) immune-related toxicities that that required intensive or prolonged immunosuppression (including, high-dose IV corticosteroids, > 2 mo of immunosuppressive corticosteroids (i.e., equivalent of >10mg oral prednisone daily) or the addition of potent immunosuppression to corticosteroids (e.g., mycophenolate mofetil/CellCept or infliximab) to manage.
2. Prior severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients or prior severe hypersensitivity reaction to any other monoclonal antibody (mAb).
3. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
4. Has a history of interstitial lung disease.
5. Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 2 weeks prior to study Day 1.
6. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. 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.

Part 3

Part 3a: NSCLC

1. Documented activating mutations in EGFR or ALK.

Dosage and Mode of Administration

INCB001158

Study drug (INCB001158) will be taken orally using a capsule or tablet formulation in dose strengths of 25 mg or 100 mg. INCB001158 will be administered only to patients who have signed and dated an Informed Consent Form.

Patients in Part 1a and 2: INCB001158 will be taken on Days 1 through 28 of each 28-day cycle and should be taken orally using the number of capsules/tablets directed in the Pharmacy Manual.

Patients in Part 1b, 1c, and 3: INCB001158 will be taken on Days 1 through 21 of each 21-day cycle and should be taken orally using the number of capsules/tablets directed in the Pharmacy Manual.

Pembrolizumab

Pembrolizumab will be administered on day 1 of each 3-week treatment cycle after all procedures and assessments have been completed as detailed on the schedule of assessment. A 200 mg dose of pembrolizumab will be administered as an IV infusion over 30 minutes. The 200 mg Q3W dose and schedule is an approved dose in the United States and EU member states. Once the pembrolizumab infusion is complete, patients will be instructed to take their morning dose of INCB001158.

Study Schedule/Procedures

Patients 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 Patient signs the informed consent and will continue until the date that the Patient is enrolled in the study (Cycle 1 Day 1).

Part 1a **Cycle 1:** Day 1, Day 2, Day 8, Day 15, and Day 22 (± 2 days); **Cycle 2:** Day 1 and Day 8 (± 5 days).

Part 2 **Cycle 1:** Day 1, Day 8, Day 15, and Day 22 (± 2 days).

Parts 1b, 1c, and 3 **Cycle 1:** Day 1, Day 8, and Day 15 (± 2 days).

All other treatment cycles: Day 1 (± 5 days).
Part 1a and 2 Efficacy assessments: Every 8 weeks (± 7 days).
Part 1b, 1c, and 3 Efficacy assessments: Every 9 weeks (± 7 days).
End of treatment: The End of Treatment (EOT) visit must occur within 28 days of study treatment discontinuation and prior to initiation of any new anti-cancer therapy/regimen.

Safety follow-up

30 days (+ 7 days) (all patients) and 90 days (+ 7 days) (Parts 1b and 3 only) after end of study treatment.

Disease follow-up

Patients who discontinue study treatment for reasons other than disease progression will continue to be assessed for their disease status during the follow-up phase and should continue to have tumor assessments every 8 weeks (monotherapy) or 9 weeks (pembrolizumab combination) until a new cancer therapy is started, disease progression, death, or the end of the study.

Estimated Duration of Participation

Up to 21 days for screening, then continuous treatment in consecutive 28 day cycles for Part 1a and 2 and 21-day cycles for Part 1b and 3 as long as patients are receiving benefit, are tolerating the regimen and do not meet any criteria for discontinuation of study treatment, and 30 and 90 days for safety follow-up. Study participation, including post-treatment follow-up, is expected to average approximately 24 months per individual Patient.

Estimated Number of Patients

Up to 582 Patients may be enrolled in the study.
Part 1a Dose Escalation – Up to 108 evaluable Patients.
Part 1b Dose Escalation – Up to 108 evaluable Patients.
Part 1c Moderate Renal Impairment Cohort – Up to 6 evaluable Patients.
Part 2 Expansion (Simon 2-Stage) – Approximately 58 to 138 evaluable Patients.
Part 3 Expansion (Simon 2-Stage) – Approximately 90 to 222 evaluable Patients.

Principal Coordinating Investigator

TBD

Statistical Methods

Sample Size Method

The primary objective is to determine a dose level of INCB001158, as monotherapy and in combination with pembrolizumab, for which the rate of DLTs is less than 33%. Up to approximately 108 patients are planned for single agent dose escalation (Part 1a) and up to 108 patients for combination dose escalation (Part 1b).

Part 1c is intended to enroll the minimum number of patients required to generate sufficient PK data for a descriptive comparison of Day 1 and steady state (Day 8, Day 15) exposures between patients with moderate renal impairment (CrCl 30-49 mL/min) and normal renal function (CrCl > 50 mL/min). Accordingly, the sample size of 6 PK-evaluable patients for Cohort 1c is not based on a predefined statistical analysis.

In Parts 2a, 2b, and 3, the sample size for each tumor type within a treatment group will be guided by the Simon 2-stage design. Part 2c is designed to investigate the potential for clinical activity in a variety of tumor types. The sample size for the initial 30 patients was not based on a predefined statistical analysis. The sample size for each tumor type in any subsequent expansion of Cohort 2c will be guided by a Simon 2-stage design.

[redacted]

[redacted]

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 patients to predict possible target responses worthy of cohort expansion and potentially 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.

Part 2 and 3: Simon 2-Stage Design-Expansion Cohorts

Cohort	p0 Background ORR (%)	p1 Target ORR (%)	α	Power (%)	n1 for Stage 1 (r1)	n2 (n - n1) for Stage 2	Total n (r2)
2a	2%	15%	0.1	80	11 (0)	15	26 (1)
2b	2%	15%	0.1	80	11 (0)	15	26 (1)
2c expansion	2%	15%	0.1	80	11 (0)	15	26 (1)
3a	2%	15%	0.1	80	11 (0)	15	26 (1)
3b	2%	15%	0.1	80	11 (0)	15	26 (1)
3c	2%	15%	0.1	80	11(0)	15	26 (1)
3d	2%	15%	0.1	80	11 (0)	15	26 (1)
3e	2%	15%	0.1	80	11 (0)	15	26 (1)
3f	10%	25%	0.1	80	13 (1)	21	34 (5)
3g	20%	40%	0.1	80	12 (2)	13	25 (7)
3h	13%	30%	0.1	80	10 (1)	23	33 (6)

Primary Analysis

The following safety analyses will be assessed for all Patients in each treatment combination:

Adverse events (AEs) and changes in laboratory values, vital signs, and physical examinations.

Secondary Analyses

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

- Based on an evaluation of AEs, pharmacokinetics (PK), pharmacodynamics and evidence of clinical activity.
- Assessed by standard RECIST v1.1 criteria (except for pleural mesothelioma, which will be evaluated using modified RECIST criteria) [overall response rate (ORR), best overall response (BOR), duration of response (DOR), and progression-free survival (PFS)]
- Non-compartmental method of analysis will be used to analyze the plasma concentration of INCB001158

[redacted]

- [redacted]
- [redacted]
- [redacted]

Interim Analysis

With the exception of the analyses at the end of Stage 1 of each Simon 2-stage design, no formal interim analysis is planned; however, safety data will be examined on an ongoing basis to ensure safety of the study patients and compliance with the trial dose escalation and expansion rules.

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1.0 SAFETY REPORTING CONTACT

Incyte TelerX
SAE Reporting Details (to be used for submitting the SAE forms):

Safety Fax: [redacted]

Email: [redacted]

2.0 LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ARG1	Arginase 1 gene signature
ARG2	Arginase 2 gene signature
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
HCG	Human chorionic gonadotropin
BID	Twice daily
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
Cl-	Chloride
CL_{cr}	Creatinine clearance
CL/F	Apparent oral dose clearance
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CR	Complete remission
CRC	Colorectal Cancer
CTA	Clinical Trial Agreement
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP450	Cytochrome P450
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
g/dL	Grams per deciliter
GDPR	General Data Protection Regulation

Abbreviation or Term[1]	Definition/Explanation
GEJ	Gastroesophageal Junction
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
G-MDSC	Granulocytic Myeloid Derived Suppressor Cells
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HCO_3^-	Bicarbonate
hERG	Human Ether-à-Go-Go Related Gene
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose (non-rodents)
HPLC	High-performance liquid chromatography
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
iRECIST	Modified RECIST 1.1 for immune-based therapeutics
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LLC	Lewis Lung Carcinoma
mAb	Monoclonal Antibody
MDSC	Myeloid Derived Suppressor Cells
µL/mcL	Microliter
MedRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MDSC	Myeloid Derived Suppressor Cells
MSI-H	Microsatellite Instability- High
MSS	Microsatellite Stable
MTD	Maximum tolerated dose
NO	Nitric Oxide
NOAEL	No Observable Adverse Event Level
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OTC	Ornithine transcarbamylase
PD	Progressive Disease

Abbreviation or Term[1]	Definition/Explanation
PD-1	Programmed cell death protein-1
PD-L1	Programmed death ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PSA	Prostate specific antigen
PT	Prothrombin time
aPTT	Activated Partial thromboplastin time
QTcF	Corrected QT interval, Fridericia's formula
RBC	Red Blood Cell
RCC	Renal Cell Cancer
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of Care
STD_{10}	Severely toxic dose in 10% of animals (rodents)
T_{max}	Time of maximum observed concentration
TEAE	Treatment-emergent adverse event
UCC	Urothelial Cell Cancer
UCD	Urea cycle gene defect
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
WBC	White blood cell

1 All of these abbreviations may or may not be used in protocol.

CORE PROTOCOL

3.0 OBJECTIVES

Primary Objectives	***Primary Endpoints***
Parts 1a and 2	
To evaluate the safety and tolerability of INCB001158 for patients with advanced/metastatic and/or treatment-refractory solid tumors	Adverse events (AEs) and changes in laboratory values, vital signs, and physical examinations
Parts 1b, 1c, and 3	
To evaluate the safety and tolerability of INCB001158 in combination with pembrolizumab in patients with advanced/metastatic and/or treatment-refractory solid tumors	AEs and changes in laboratory values, vital signs and physical examinations
Secondary Objectives	***Secondary Endpoints***
Parts 1a and 2	
To select the Recommended Phase 2 Dose (RP2D) of INCB001158 for patients with advanced/metastatic solid tumors	Based on an evaluation of AEs, pharmacokinetics (PK), pharmacodynamics and evidence of clinical activity
Parts 1b and 3	
To select the RP2D of INCB001158 in combination with pembrolizumab for patients with advanced/metastatic solid tumors	Based on an evaluation of AEs, PK, pharmacodynamics and evidence of clinical activity
Parts 1a, 1b, 1c, 2, and 3	
To evaluate the anti-tumor effect of INCB001158 as monotherapy and in combination with pembrolizumab for patients with advanced/metastatic solid tumors	Assessed by standard RECIST v1.1 criteria (except for pleural mesothelioma, which will be evaluated using modified RECIST criteria) [overall response rate (ORR), best overall response (BOR), duration of response (DOR), and progression-free survival (PFS)]
Determine PK of INCB001158 alone and in combination with pembrolizumab	C_{max}, T_{max}, AUC_t, AUC_{0-12} and CL/F in patients with CrCl 30-49 mL/min (Part 1c only) or CrCl ≥ 50 mL/min (Parts 1a, 1b, 2, and 3)

4.0 POTENTIAL RISKS AND BENEFITS OF THE TREATMENT REGIMEN

4.1 Potential Risks of INCB001158 Monotherapy and its Combination with Pembrolizumab

The potential risks of INCB001158, pembrolizumab and the combination of INCB001158 with pembrolizumab are outlined in detail in Section 12.1 of the protocol.

4.2 Potential Benefit of INCB001158 and its Combination with Pembrolizumab

Since INCB001158 is an experimental therapy, it is not known if it will be of benefit to patients. Based on what is known about the expression of Arginase in cancers and the immunosuppressive effect of Arginase, though the depletion of arginine, it is hypothesized that the inhibition of Arginase will result in an increase in local and systemic arginine levels, which may reverse Arginase-induced immunosuppression. By reversing immunosuppression, an anti-tumor immune response may reactivated in patients, either as a monotherapy or in combination with anti-PD-1 therapy (e.g., pembrolizumab).

5.0 STUDY DESIGN

Protocol INCB 01158-101 is a Phase 1 open-label study of the arginase inhibitor INCB001158 given as monotherapy and in combination with the immune checkpoint inhibitor pembrolizumab, an anti-programmed cell death protein-1 (anti-PD-1) agent.

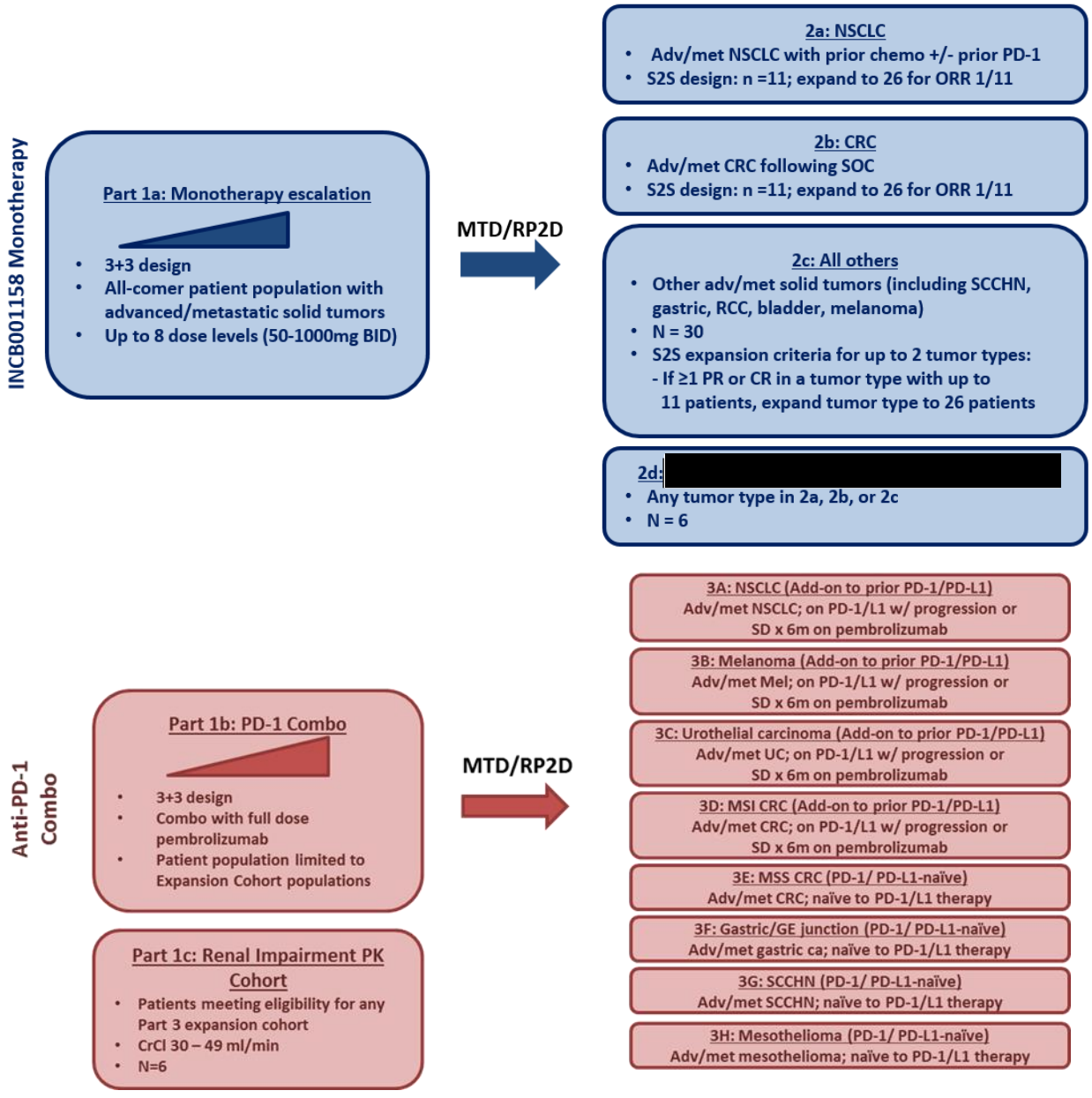


Figure 5.0-1: Study design.

5.1 Part 1. Dose Escalation

Part 1a of this Phase 1 study will begin with a standard, open-label, 3+3 dose-escalating design of single agent INCB001158 in patients with advanced/metastatic solid tumors. Dose escalation will continue until identification of a maximum tolerated dose (MTD) or to a planned maximum daily dose of 2000 mg orally [i.e., 1000 mg twice daily (BID)]. Dose escalation may continue beyond 2000 mg daily based on emerging clinical data. Escalation will be limited by a maximum pharmacokinetic (PK) threshold based on the exposure at the highest well tolerated doses in GLP-compliant toxicity studies (see Section 10.2.2 for further details).

After achieving a predefined threshold PK target exposure of INCB001158 and/or clear evidence of pharmacodynamic activity (i.e., elevated plasma arginine) during single agent escalation of INCB001158, the safety and tolerability of INCB001158 will be evaluated in combination with the anti-PD-1 agent pembrolizumab in a separate dose escalation (Part 1b). Pembrolizumab will be administered at the dose of 200 mg intravenously (IV) every 3 weeks. Only dose levels of INCB001158 that have already been demonstrated to be safe as a monotherapy will be tested in combination with pembrolizumab.

Part 1a. INCB001158 Monotherapy Dose Escalation

Sequential dose escalation of single agent INCB001158 will take place in patients with advanced/metastatic solid tumors. A minimum of three eligible solid tumor patients will be assigned to each dose level during the Dose Escalation period.

Dose escalation plan: The starting dose of 50 mg BID was selected for the monotherapy dose escalation on the basis of GLP-compliant preclinical toxicity studies (see Section 10.2.1). The dose escalation schedule outlined in Table 5.1-1 will be followed, which is based on the standard Modified Fibonacci design. Real-time PK and pharmacodynamic assessment will be performed on samples taken during dose escalation.

Table 5.1-1: Dose Escalation Schedule for Monotherapy and PD-1 Combination

INCB001158 Dose Levels			
Cohort	**BID Dose (mg)**	**% Increase**	**N**
-1	25	- 50%	3 – 6
1*	50	-	3 – 6
1.5	75	50%	3 – 6
2	100	33%	3 – 6
3	150	50%	3 – 6
4	225	50%	3 – 6
5	300	33%	3 – 6
6	400	33%	3 – 6
7	500	25%	3 – 6
8	600	20%	3 – 6

*starting dose level

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

Intermediate dose levels that are between those listed in Table 5.1-1 may be investigated if the safety, PK, or pharmacodynamic data warrant. If that were to occur, the dose escalation rules in Section 5.1.1 would apply.

Part 1b. INCB001158 Dose Escalation in Combination with Pembrolizumab

The decision to initiate the evaluation of the safety of INCB001158 in combination with pembrolizumab (Part 1b) will be made on the basis of PK, pharmacodynamic and safety data (see Section 10.2.1) from patients enrolled in the monotherapy dose escalation (Part 1a) and/or monotherapy expansion cohorts (Part 2). Part 1b may be opened if one of the following is achieved at a dose level that is confirmed to be at or below the monotherapy MTD:

1. At least half of the patients (minimum of two patients) enrolled at a particular dose level achieve a trough (C_{min}) plasma concentration of INCB001158 at steady state of ≥ 1 μM, OR
2. At least half of the patients (minimum of two patients) at a particular dose level achieve a 2.5-fold increase in fasting plasma arginine at Cycle 1 Day 15 predose relative to their baseline (Cycle 1 Day 1 predose) value.

When the PK or PD requirement has been satisfied in Part 1a or Part 2 as defined above, the final decision to open Part 1b will be made by agreement between the Medical Monitor and the Study Investigators.

Upon opening Part 1b, a minimum of 3 patients will receive pembrolizumab (200 mg IV Q3W) in combination with INCB001158. Enrollment in Part 1b is limited to patients that would be eligible for the Expansion Cohorts in Part 3. In Part 1b, the starting dose of INCB001158 will be 50 mg BID, which is 2 dose levels below the recommended monotherapy Phase 2 dose of 100 mg BID identified in Part 1a of this study. Dose escalation will proceed according to the Dose Escalation Schedule that is being employed in Part 1a (Table 5.1-1). A dose level shall not be enrolled in Part 1b until it has been demonstrated to be at or below the monotherapy MTD in Part 1a.

Part 1c. INCB001158 in Combination with Pembrolizumab in Patients with Moderately Impaired Renal Function

At US sites only, Cohort 1c will enroll 6 patients who have moderately impaired renal function (defined as CrCl 30-49 mL/min calculated by the Cockcroft-Gault formula) AND meet eligibility criteria for any of the combination expansion cohorts (3a through 3h). The safety of INCB001158 in combination with pembrolizumab was fully characterized with a comprehensive dose escalation in patients with CrCl $\geq$ 50 mL/min. Additionally, pembrolizumab did not have

any effect on the PK of INCB001158. Therefore, Cohort 1c will evaluate a reduced dose of INCB001158 50 mg BID (determined using population PK modeling) in combination with pembrolizumab in order to determine a pharmacodynamically active dose in patients with moderately impaired renal function.

Based on population PK modeling, a dose of INCB01158 50 mg BID in patients with CrCl 30 to 49 mL/min is predicted to achieve INCB001158 AUC/C_{min} values to fall within the known safe exposure range corresponding to doses at the established RP2D of 100 mg BID (see Section 10.2). Six patients meeting eligibility criteria for Parts 3a through 3h will be enrolled at the reduced dose of 50 mg BID to obtain full PK, PD (see Attachment 2C), and safety data. All data collected during the first cycle (21 days) will be evaluated, along with the population PK modeling data, to determine the INCB001158 dose in patients with moderately impaired renal function that most closely approximates the PK parameters of the RP2D of 100 mg BID in patients with normal renal function and specifically meets the following PK and PD criteria:

- At least half of the patients (minimum of 2 patients) achieve the target exposure leading to continuous inhibition of extracellular arginase 1 by > 90% (a trough [C_{min}] plasma concentration of INCB001158 at steady state of ≥ 1 μM), AND/OR
- At least half of the patients (minimum of 2 patients) achieve a 2.5-fold increase in fasting plasma arginine at Cycle 1 Day 15 predose relative to their baseline (Cycle 1 Day 1 predose) value.

Population PK modeling showed a highly predictable, linear, inverse relationship between CrCl and AUC, C_{max}, and half-life for INCB001158 (see Section 10.2.2.1). Therefore, if the PK-PD criteria specified above are not met at the 50 mg BID dose, population PK modeling will be used to determine whether a lower dose (25 mg BID) or a previously evaluated intermediate dose (75 mg BID) would more closely approximate PK parameters for the established RP2D of 100 mg BID. Cohort 1c patients who do not complete all planned PK assessments or have treatment discontinuation or interruptions during the first 21 days of dosing will be replaced until 6 evaluable patients have been accrued to the cohort. Patients meeting the pre-specified PK and PD criteria will be counted towards the Simon 2-stage efficacy assessment in their respective Part 3 expansion cohorts, provided these have not fully enrolled at the time data from these patients become available.

5.1.1 Dose Escalation Rules and Definition of Maximally Tolerated Dose (MTD)

Dose limiting toxicities (DLTs) observed in the first 28 days of dosing for monotherapy dose escalation (Part 1a) or the first 42 days of dosing for combination dose escalation (Part 1b) will be used to determine escalation to the next dose level. The study is using a traditional 3+3 design and the dose escalation rules are as follows:

- An initial cohort of 3 patients is enrolled.
- If 0/3 patients develops a DLT, escalation to the next dose will occur.
- If 1/3 patients develops a DLT:
    - Another 3 patients will be enrolled at this dose level.
        - If 0 of the 3 new patients develops a DLT (for a total of 1/6 patients with a DLT at this dose level), escalation to the next dose level will occur.
        - If ≥ 1 of the 3 new patients develops a DLT (for a total of ≥ 2/6 patients with a DLT at this dose level), the dose escalation stage of the trial will be terminated, and the dose directly below the current dose will be considered the MTD.
- If ≥ 2/3 patients develop a DLT, the dose escalation stage of the trial will be terminated, and the dose directly below the current dose will be considered the MTD.

If a dose level below 1000 mg BID is selected as the MTD on the basis of only 2 DLTs and subsequent clinical data [e.g., in the expansion cohort(s)] demonstrate that the rate of AEs that qualify as DLTs at that dose level is < 10% in > 10 patients, re-escalation to the next dose level previously associated with DLTs may be considered. If re-escalation occurs, up to 6 additional patients may be enrolled and the dose level may be considered tolerable if the overall DLT rate for that dose level is ≤ 25%.

5.1.2 Dose-Limiting Toxicity

During dose escalation, patients must receive at least 75% of the planned INCB001158 administrations (Parts 1a and 1b) and two doses of pembrolizumab (Part 1b only) in the DLT evaluation window to be considered evaluable for DLT, unless the patient has a DLT or has the study treatment held for an adverse event (AE) that may herald a DLT. The DLT evaluation window will be the first 28 days (Part 1a) or the first 42 days (Part 1b) on study, starting from Cycle 1 Day 1 (C1D1). Patients who discontinue the study during the DLT evaluation window prior to receiving the requisite study treatment administrations for reasons that include, but are not limited to, clinical/radiographic progression, voluntary withdrawal, or complications that the

Principal Investigator considers secondary to the patient's malignancy will not be considered evaluable for DLT and will be replaced. In addition to DLTs, a pharmacokinetic threshold of 100 μg*hr/mL is included as a dose-limiting event. This is an exposure that was well tolerated in preclinical species and exceeds the expected efficacious exposure by 14-fold.

During Part 1b, it is likely that Grade 3 AEs associated with pembrolizumab administration will occur and, given the small sample size of cohorts, this could occur by chance in 2 of 6 patients, the usual threshold for unacceptable toxicity. It will be important to differentiate between immune-related adverse events (irAEs) expected from pembrolizumab toxicity as opposed to an increase in frequency or a worsening of severity of irAEs as an indicator of unacceptable toxicity related to the combination. Dose escalation cohorts can be expanded up to 12 patients if DLTs occur that are expected pembrolizumab-related irAEs per the pembrolizumab product label.

The Common Terminology Criteria for Adverse Events (CTCAE v4.03) will be used to identify and classify toxicities arising during the study. The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the Investigator to be related (possibly or probably) to administration of either or both study treatment(s):

<u>Non- Hematologic DLTs:</u>

- Any ≥ Grade 4 non-hematological toxicity
- Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care with the exception of:
    - Grade 3 fatigue lasting ≤ 7 days
    - Grade 3 rash that resolves to ≤ Grade 1 within 3 weeks
    - Grade 3 tumor flare (defined as local pain, irritation or rash localized at sites of known or suspected tumor)
    - Grade 3 irAE that resolves to Grade 1 with corticosteroid therapy in ≤ 3 weeks (Part 1b ONLY)
    - A transient (resolves within 6 hr of onset) Grade 3 infusion-related AE (Part 1b ONLY)
- Any clinically meaningful Grade 3 non-hematologic laboratory value if:
    - Medical intervention (other than electrolyte repletion) is required to treat the patient, OR
    - The abnormality leads to hospitalization, OR
    - The abnormality persists for > 1 week.

Hematologic DLTs:

- Grade ≥ 3 febrile neutropenia (ANC < 1.0 x 10^9/L with either a single temperature ≥ 38.3ºC or a sustained temperature of ≥ 38ºC for more than 1 hr)
- Grade 4 neutropenia lasting > 7 days
- Grade 4 anemia
- Grade 4 thrombocytopenia (< 25.0 x 10^9/L)
- Grade 3 thrombocytopenia resulting in clinically significant bleeding or requiring platelet transfusion
- Any other ≥ Grade 3 hematologic toxicity

In addition to the DLTs defined above, clear evidence of urea cycle inhibition (e.g., an increase in fasting urinary orotic acid (OA) to ≥ 10X the ULN, any OA value of > 40X ULN (fasting or non-fasting) or symptomatic hyperammonemia) would also be considered a dose-limiting event and will be monitored closely (see below for urinary OA rationale). Finally, achieving a maximum exposure threshold of an $AUC_{0\text{-}12hr}$ that exceeds 100 µg*hr/mL in one patient will limit dose escalation. This exposure is approaching the top of the exposures that were well tolerated in preclinical GLP toxicology studies. Exposure in excess of this threshold will be treated the same as a DLT with regard to the dose escalation rules and definition of the MTD described in Section 5.1.1.

The inability to receive ≥ 75% of INCB001158 doses and/or 2 doses of pembrolizumab during the DLT-evaluation period (28 days in Part 1a and 42 days in Part 1b) due to a drug-related AE will be considered a DLT. In addition, 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. In general, patients who experience a DLT will not receive further treatment with the study treatments. Patients with toxicities that meet the DLT definition but are rapidly reversible (≤ Grade 1 within 3 weeks) may be continued on study with Investigator and Medical Monitor agreement.

Rationale for urinary orotic acid threshold

Urinary OA is being monitored in this study as a sensitive biomarker of hepatic urea cycle inhibition. Substantial elevations (generally to 100-800X the upper limit of normal) occur in patients with inherited defects in enzymes of the urea cycle. A similar magnitude of OA elevation (~1000X) was noted in animals that received doses associated with toxicity in

preclinical safety studies, although notable elevations in urinary OA were also noted in some animals treated at the NOAEL (Figure 10.1-6).

Due to the limited availability of data describing the clinical sequelae associated with modest (5-100X ULN) elevations of urinary OA, a threshold of 5X the ULN was selected to provide clear evidence of urea cycle inhibition. Importantly, elevations in urinary OA are not considered a toxicity but, rather, serve as a biomarker of urea cycle function. In addition to urinary OA, patients are also monitored for sustained elevations in ammonia or significant reductions in plasma blood urea nitrogen (BUN) as signs of clinically significant effects on the urea cycle. There has been no evidence of clinically significant urea cycle inhibition to date. However, as described in Section 10.1.9, transient, reversible elevations in urinary OA have occurred in two patients enrolled at the 150 mg dose level. These elevations were as high as 11.6 and 9.3 µmol/mmol creatinine (7.7X and 6.2X the ULN, respectively) in the two patients when evaluated predose (fasting). When tested 6 hr postdose (non-fasted), one of the two patients had elevated values, which were as high as 131 µmol/mmol creatinine (87.3X ULN). As described in Section 10.1.9, these patients were asymptomatic and had no laboratory evidence of clinically significant urea cycle inhibition.

Since this protocol was first written, additional literature sources have been identified in which elevation of urinary OA have been studied in healthy people who are carriers of a single urea cycle gene defect (UCD). In one study, 24 individuals that were carriers of a single defective gene for ornithine transcarbamylase (OTC) were studied (Nagasaka 2013). These individuals were considered healthy without clinical evidence of urea cycle dysfunction. Fasting urinary OA was elevated in all of these individuals, with a mean level of 11 µmol/mmol creatinine that ranged from 5 to 23 µmol/mmol creatinine. In addition, other studies in similar populations of healthy individuals with a known or presumed single defective urea cycle gene have demonstrated that urinary OA elevates significantly following a meal (due to the increased processing of ammonia by the liver following a protein meal), as compared to normal individuals with a fully intact urea cycle in whom there is a minimal change in urinary OA following a meal. Following a meal, the urinary OA in these healthy UCD carriers rose as high as 62 µmol/mmol creatinine (Goldstein 1974).

Based on the clinical experience to date with INCB001158 and the more extensive literature evidence of elevations in urinary OA in healthy UCD, the management of elevated urinary OA

has been updated in the protocol. Given the variability of urinary OA following a meal in healthy UCD carriers, separate thresholds have been defined for fasting patients (i.e., patients tested predose) versus those that have eaten (i.e., patients tested 6 hr postdose). In addition, since urinary OA elevations may be variable and have not been associated with evidence of clinically significant urea cycle inhibition, re-testing of urinary OA while the patient continues to receive INCB001158 is recommended in patients that have no evidence of clinically significant urea cycle inhibition (i.e., asymptomatic, plasma ammonia/BUN without significant change from baseline) in order to confirm that the elevation was not spurious. For elevations of urinary OA of > 15 µmol/mmol creatinine (>10X ULN) in fasting patients, dose reduction is recommended. This value is within the range of urinary OA elevations that are were seen in the cohort of 24 healthy UCD carriers tested while fasting in Nagasaka *et al* (2013). For patients that are not fasting, higher elevations can be expected, based on the elevations in UCD carriers following a meal. Therefore, for elevations of urinary OA of > 60 µmol/mmol creatinine (40X ULN) at any time, dose reduction is recommended.

In summary, there has been no evidence of clinically significant inhibition of the urea cycle to date. Two patients have had asymptomatic transient elevations in urinary OA, a sensitive biomarker of hepatic urea cycle inhibition, that were not associated with changes in plasma ammonia or BUN, but were dose reduced based on the original protocol defined urinary OA threshold of 5X ULN. Based on this clinical experience and a more extensive evaluation of the published data in healthy carriers of UCD genes, the approach to managing INCB001158 study drug in response to elevations in urinary OA has been changed in the current amendment. All of these data and the current management approach have been reviewed by an external clinical expert in the management of patients with UCD [redacted].

5.1.3 Definition of Recommended Phase 2 Dose (RP2D)

The RP2D for INCB001158 both as monotherapy and in combination with pembrolizumab will be selected on the basis of emerging safety, PK and pharmacodynamic data and will not exceed the maximally tolerated dose (MTD). The RP2D will either be the MTD or a lower dose if PK, pharmacodynamic, tolerability and efficacy data suggest that maximal efficacy is likely achieved at a dose below the MTD, particularly if the lower dose is associated with an improved safety profile.

5.2 Part 2. Single Agent Cohort Expansion

Following completion of monotherapy Dose Escalation and selection of the RP2D for INCB001158 in Part 1a, the following cohorts of patients will be enrolled to receive single agent INCB001158 at the RP2D.

Part 2a: Monotherapy Cohort Expansion in NSCLC patients

This expansion cohort will enroll patients with advanced/metastatic non-small cell lung cancer (NSCLC) that lack activating mutations in either the EGFR or ALK oncogenes and have received, declined, or are ineligible for standard of care (SOC) therapies. A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.02 versus the alternative that ORR ≥ 0.15. A minimum of 11 patients with advanced/metastatic NSCLC will receive INCB001158 in Stage 1 of the expansion. If at least 1 of the 11 response-evaluable patients responds (PR or better) at a single time point in Stage 1, then an additional 15 evaluable patients (for a total of 26 response-evaluable patients) will be enrolled in Stage 2.

Part 2b: Monotherapy Cohort Expansion in CRC patients

This expansion cohort will enroll patients with advanced/metastatic colorectal cancer (CRC) that have received, declined, or are ineligible for SOC therapies. A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.02 versus the alternative that ORR ≥ 0.15. A minimum of 11 CRC patients will receive INCB001158 in Stage 1 of the expansion. If at least 1 of the 11 response-evaluable patients responds (PR or better) at a single time point in Stage 1, then an additional 15 evaluable patients (for a total of 26 response-evaluable patients) will be enrolled in Stage 2.

Part 2c: Monotherapy Cohort Expansion in Patients with Other Cancer Types Likely to have High Granulocytic MDSCs or Neutrophils

Many tumor types have infiltrating granulocytic myeloid-derived suppressor cells (G-MDSCs) or neutrophils. This expansion cohort will enroll patients with a variety of advanced/metastatic cancers that have received, declined, or are ineligible for SOC therapies that are among tumor types that have been demonstrated to have infiltrating G-MDSCs or neutrophils, including squamous cell carcinoma of the head and neck (SCCHN), renal cell cancer (RCC), gastric or gastroesophageal junction (GEJ) cancer, urothelial cell cancer (UCC), and melanoma. Other tumor types may be enrolled with approval from the Sponsor and the Medical Monitor. A maximum of 30 patients will be enrolled initially in this cohort, with no more than 11 patients for any particular tumor type. Up to 2 tumor types in Cohort 2c may then be expanded based on a Simon 2-stage design, if the observed clinical activity (1 or more PR or CR in a tumor type with up to 11 patients) supports enrollment of additional patients for a total of 26 patients per tumor type.

Part 2d: [redacted]

Cohort 2d will enroll patients at US sites only who meet eligibility criteria for any of the monotherapy expansion cohorts (2a, 2b, or 2c). [redacted]

Cohort 2d patients may be counted towards the total number of patients planned in cohorts 2a, 2b, and 2c (if these have not fully accrued by the time cohort 2d opens).

[redacted]

Additional solid tumor cohorts may be added to Part 2 by protocol amendment based upon emerging preclinical data and/or observations of clinical benefit.

5.3 Part 3. Combination Cohort Expansion

Upon selection of the RP2D for INCB001158 in combination with pembrolizumab in Part 1b, cohorts of specific patients will be enrolled to receive INCB001158 in combination with pembrolizumab at the RP2D to further evaluate safety and identify an early signal of clinical activity.

Part 3a: INCB001158 in combination with pembrolizumab in patients with NSCLC that lacks activating mutations in EGFR or ALK and would be unlikely to have an objective response to monotherapy pembrolizumab.

This cohort will enroll patients with advanced/metastatic NSCLC that does not harbor activating mutations in the EGFR or ALK oncogenes and are considered unlikely to have an objective response to monotherapy pembrolizumab, as defined by having either:

1. Disease progression on an anti-PD-1/PD-L1 therapy in the immediate prior line of therapy (confirmed progression per iRECIST criteria preferred), OR
2. Ongoing prolonged stable disease (> 24 weeks) on pembrolizumab therapy in the immediate prior line of therapy

EGFR-mutant and ALK-mutant NSCLC patients have been excluded because they are reported to be less responsive to anti-PD-1 therapy (Borghaei 2015). [redacted]

[redacted]

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.02 versus the alternative that ORR ≥ 0.15. A total of 11 response-evaluable patients will be enrolled in Stage 1. If at least 1 patient responds (PR or better) out of 11 response-evaluable patients, then an additional 15 evaluable patients will be enrolled in Stage 2 (total of 26 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 2 patients must demonstrate a response (PR or better) to reject the null hypothesis.

Part 3b: INCB001158 in combination with pembrolizumab in patients with melanoma with disease progression or prolonged stable disease while receiving an anti-PD-1/PD-L1 agent in the immediate prior line of therapy.

This cohort will enroll patients with advanced/metastatic melanoma that are considered unlikely to have an objective response to monotherapy pembrolizumab, as defined by having:

1. Disease progression on an anti-PD-1/PD-L1 therapy in the immediate prior line of therapy (confirmed progression per iRECIST criteria preferred), OR
2. Ongoing prolonged stable disease (> 24 weeks) on pembrolizumab therapy in the immediate prior line of therapy

The primary endpoint will be ORR. Predose and postdose biopsies will be collected from patients enrolled to this cohort (unless it is not considered to be safe or otherwise is not feasible) until approximately 5 evaluable paired specimens are collected. Predose biopsies will be collected for all other patients, if feasible. [redacted]

[redacted]

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.02 versus the alternative that ORR ≥ 0.15. A total of 11 response-evaluable patients will be enrolled in Stage 1. If at least 1 patient responds (PR or better) out of 11 response-evaluable patients, then an additional 15 evaluable patients will be enrolled in Stage 2 (total of 26 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 2 patients must demonstrate a response (PR or better) to reject the null hypothesis.

Part 3c: INCB001158 in combination with pembrolizumab in patients with urothelial cell carcinoma (UCC) that would be unlikely to have an objective response to monotherapy pembrolizumab

This cohort will enroll patients with advanced/metastatic UCC that are considered unlikely to have an objective response to monotherapy pembrolizumab, as defined by having:

1. Disease progression on an anti-PD-1/PD-L1 therapy in the immediate prior line of therapy (confirmed progression per iRECIST criteria preferred), OR
2. Ongoing prolonged stable disease (> 24 weeks) on pembrolizumab therapy in the immediate prior line of therapy

The primary endpoint will be ORR. Predose and postdose biopsies will be collected from patients enrolled to this cohort (unless it is not considered to be safe or otherwise is not feasible) until approximately 5 evaluable paired specimens are collected. Predose biopsies will be collected for all other patients, if feasible. [redacted]

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.02 versus the alternative that ORR ≥ 0.15. A total of 11 response-evaluable patients will be enrolled in Stage 1. If at least 1 patient responds (PR or better) out of 11 response-evaluable patients, then an additional 15 evaluable patients will be enrolled in Stage 2 (total of 26 response-evaluable

patients). If Stages 1 and 2 are completed, a minimum of 2 patients must demonstrate a response (PR or better) to reject the null hypothesis

Part 3d: INCB001158 in combination with pembrolizumab in patients with microsatellite instability-high (MSI-H) CRC that would be unlikely to have an objective response to monotherapy pembrolizumab

This cohort will enroll advanced/metastatic CRC patients with documented microsatellite instability that are considered unlikely to have an objective response to monotherapy pembrolizumab, as defined by having either:

1. Disease progression on an anti-PD-1/PD-L1 therapy in the immediate prior line of therapy (confirmed progression per iRECIST criteria preferred), OR
2. Ongoing prolonged stable disease (>24 weeks) on pembrolizumab therapy in the immediate prior line of therapy

The primary endpoint will be ORR. Predose and postdose biopsies will be collected from patients enrolled to this cohort (unless it is not considered to be safe or otherwise is not feasible) until approximately 5 valuable paired specimens are collected. Predose biopsies will be collected for all other patients, if feasible. [redacted]

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.02 versus the alternative that ORR ≥ 0.15. A total of 11 response-evaluable patients will be enrolled in Stage 1. If at least 1 patient responds (PR or better) out of 11 response-evaluable patients, then an additional 15 evaluable patients will be enrolled in Stage 2 (total of 26 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 2 patients must demonstrate a response (PR or better) to reject the null hypothesis.

Part 3e: INCB001158 in combination with pembrolizumab in patients with microsatellite stable (MSS) CRC.

This cohort will enroll advanced/metastatic CRC patients that are documented MSS that have received at least one prior line of 5-FU-containing systemic therapy in the advanced/metastatic setting. Patients having received prior therapy with anti-PD-1/PD-L1, anti-CTLA4 or any other agent that specifically targets an immune checkpoint or co-stimulation pathway will be excluded.

The primary endpoint will be ORR. Predose and postdose biopsies will be collected from patients enrolled to this cohort (unless it is not considered to be safe or otherwise is not feasible) until approximately 5 evaluable paired specimens are collected. Predose biopsies will be collected for all other patients, if feasible. [redacted]

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.02 versus the alternative that ORR ≥ 0.15. A total of 11 response-evaluable patients will be enrolled in Stage 1. If at least 1 patient responds (PR or better) out of 11 response-evaluable patients, then an additional 15 evaluable patients will be enrolled in Stage 2 (total of 26 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 2 patients must demonstrate a response (PR or better) to reject the null hypothesis

Part 3f: INCB001158 in combination with pembrolizumab in PD-1/PD-L1 naïve patients with Gastric/GEJ cancer.

This cohort will enroll patients with advanced/metastatic gastric/GEJ cancer that have never received prior therapy with anti-PD-1/PD-L1, anti-CTLA4 or any other agent that specifically targets an immune checkpoint or co-stimulation pathway.

All patients will have testing for microsatellite stability performed on tumor tissue, either archival or a fresh biopsy. It is expected that ~80-90% of patients will have MSS gastric cancer

(Kim 2013). The primary endpoint will be ORR in patients with MSS disease, since historical data suggests a low ORR in response to anti-PD-1 therapy (Topalian 2012, Brahmer 2010). Patients with MSI will also be followed but will not be considered for the primary endpoint for this cohort. Predose and postdose biopsies will be collected from patients enrolled to this cohort (unless it is not considered to be safe or otherwise is not feasible) until approximately 5 evaluable paired specimens are collected. Predose biopsies will be collected for all other patients, if feasible. [redacted]

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.10 versus the alternative that ORR ≥ 0.25. A total of 13 response-evaluable MSS patients will be enrolled in Stage 1. If at least 2 patients respond (PR or better) out of 13 response-evaluable MSS patients, then an additional 21 evaluable MSS patients will be enrolled in Stage 2 (total of 34 response-evaluable MSS patients). If Stages 1 and 2 are completed, a minimum of 6 MSS patients must demonstrate a response (PR or better) to reject the null hypothesis

Part 3g: INCB001158 in combination with pembrolizumab in PD-1/PD-L1 naïve patients with SCCHN

This cohort will enroll patients with SCCHN that have received no more than one prior therapy in the advanced/metastatic setting and have never received prior therapy with anti-PD-1/PD-L1, anti-CTLA4 or any other agent that specifically targets an immune checkpoint or co-stimulation pathway.

The primary endpoint will be ORR. Predose and postdose biopsies will be collected from patients enrolled to this cohort (unless it is not considered to be safe or otherwise is not feasible) until approximately 5 evaluable paired specimens are collected. Predose biopsies will be collected for all other patients, if feasible. [redacted]

[redacted]

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.20 versus the alternative that ORR ≥ 0.40. A total of 12 response-evaluable patients will be enrolled in Stage 1. If at least 3 patients respond (PR or better) out of 12 response-evaluable patients, then an additional 13 evaluable patients will be enrolled in Stage 2 (total of 25 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 8 patients must demonstrate a response (PR or better) to reject the null hypothesis

Part 3h: INCB001158 in combination with pembrolizumab in patients with malignant pleural mesothelioma.

This cohort will enroll patients with advanced/metastatic malignant pleural mesothelioma that have received or were unable to receive standard front-line systemic therapy but have never received prior therapy with anti-PD-1/PD-L1, anti-CTLA4 or any other agent that specifically targets an immune checkpoint or co-stimulation pathway.

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.13 versus the alternative that ORR ≥ 0.30. A total of 10 response-evaluable patients will be enrolled in Stage 1. If at least 2 patients respond (PR or better) out of 10 response-evaluable patients, then an additional 23 evaluable patients will be enrolled in Stage 2 (total of 33 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 7 patients must demonstrate a response (PR or better) to reject the null hypothesis

Additional solid tumor cohorts may be added to Part 3 by protocol amendment based upon preclinical data, anti-tumor observations in Parts 1 and 2, and observations of clinical benefit. Up to 5 additional paired biopsies may be obtained in any cohort for which enrollment in Stage 2 is opened.

6.0 SAMPLE SIZE

Approximately 216 patients are planned for recruitment to the monotherapy and combination Dose Escalation cohorts. Approximately 148 patients are planned for recruitment in Stage 1 monotherapy and combination Expansion Cohorts. The number of patients may be increased in Stage 2 in each Expansion Cohort based upon observed anti-tumor activity. Assuming full enrollment of the Dose Escalation cohorts, including backfill patients (i.e., 12 patients per dose level for monotherapy and combination), and positive results in all Expansion Cohorts, up to 582 evaluable patients would be enrolled. Approximate recruitment estimates for Dose Escalation and each Expansion Cohort is shown in Table 6.0-1.

Table 6.0-1: Table of Sample Size Estimates

	Approximate N	
Part 1a. Monotherapy Dose Escalation	up to 108	
Part 1b. Combination Dose Escalation	up to 108	
Part 1c. Combination in Patients with Moderately Impaired Renal Function	6 (evaluable patients will be counted towards Part 3 cohorts)	
Dose Escalation Total	**up to 222**	
	Stage 1	Stage 2
Part 2. Monotherapy Cohort Expansion		
2a. NSCLC	11	15
2b. CRC	11	15
2c. Assorted tumor types	30	30-50
2d. [redacted]	6	N/A
Monotherapy Expansion Cohorts (Total)	**58**	**60-80**
Part 3. Combination Cohort Expansion		
3a. NSCLC Prior Checkpoint	11	15
3b. Melanoma	11	15
3c. Urothelial carcinoma (prior PD-1/PD-L1)	11	15
3d. CRC (MSI-H) (prior PD-1/PD-L1)	11	15
3e. MSS CRC (PD-1/PD-L1 naïve)	11	15
3f. Gastric/GEJ (PD-1/PD-L1 naïve)	13	21
3g. SCCHN (PD-1/PD-L1 naïve)	12	13
3h. Mesothelioma (PD-1/PD-L1 naïve)	10	23
Combination Expansion Cohorts (Total)	**90**	**132**

7.0 INCLUSION/EXCLUSION CRITERIA

7.1 Inclusion Criteria

1. Patients must have a histological or cytological diagnosis of metastatic cancer or locally advanced cancer that is not amenable to local therapy. Additional criteria specific to different Parts/Cohorts of the study are provided below.
2. Ability to provide written informed consent in accordance with federal, local, and institutional guidelines
3. Age ≥ 18 years
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1
5. Life Expectancy of at least 3 months
6. Adequate organ function as indicated by the laboratory values in Table 7.1-1

Table 7.1-1: Laboratory Values for Inclusion

Test	Value
Absolute neutrophil count (ANC)	≥ 1,500/mcL
Platelets	≥ 100,000/mcL
Hemoglobin	≥ 9 g/dL
CrCl	All except Part 1c: ≥ 50 mL/min (calculated using the Cockcroft-Gault formula) Part 1c only: 30-49 mL/min (calculated using the Cockcroft-Gault formula)
Serum total bilirubin OR Direct bilirubin (for patients with Gilbert Syndrome and total bilirubin levels > 1.5 ULN)	≤ 1.5 X ULN OR ≤ ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 X ULN*

* Does not apply to patients receiving therapeutic anticoagulation

7. Measurable Disease: At least one tumor lesion/lymph node that meets the RECIST v1.1 criteria for being "measurable."
8. 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 > 45 years of age.)

b. Woman of childbearing potential who has a negative serum pregnancy test within three days before the first dose of study treatment and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up (for patients receiving INCB001158 monotherapy) and until 120 days following the last dose of pembrolizumab. Permitted methods that are at least 99% effective in preventing pregnancy should be continued until 120 days after discontinuing should be communicated to the patient 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 (3 months following the last dose of study treatment). Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the patient and their understanding confirmed.

9. Resolution of all treatment-related toxicities, except alopecia, anemia, or endocrinopathies managed by hormone replacement, from any previous cancer therapy to ≤ Grade 1 or to values within those required for eligibility on this study prior to the first dose of study treatment. Patients with long-lasting sequelae from prior anti-cancer therapy that have been demonstrated to be stable for > 3 mo may be allowed if the Investigator and Medical Monitor determine that this will not compromise patient safety or interfere with the interpretation of the safety profile of INCB001158.

Part 1: Inclusion Criteria Specific to the Dose Escalation

Part 1a: Inclusion Criteria Specific to the Monotherapy Dose Escalation

1. Histologically or cytologically proven diagnosis of any locally advanced or metastatic solid tumor not amenable to local therapy in patients who have disease progression after treatment with all available therapies known to confer clinical benefit

Part 1b: Inclusion Criteria Specific to the PD-1 Combination Dose Escalation

1. Histologically or cytologically proven diagnosis of advanced/metastatic NSCLC (squamous or non-squamous), mesothelioma, gastric/GEJ cancer, MSS CRC, MSI-H CRC, UCC, melanoma or SCCHN in patients who have disease progression after treatment with all available therapies known to confer clinical benefit. Patients that have not received prior anti-PD-1 therapies are allowed.

Part 1c: Inclusion Criteria Specific to the PD-1 Combination Moderately Renally Impaired Cohort

1. Criteria for any of Cohorts 3a to 3h.

Part 2: Inclusion Criteria Specific to Monotherapy Cohort Expansion

Part 2a: Inclusion Criteria Specific to the Monotherapy NSCLC Cohort

1. Histologically or cytologically proven diagnosis of advanced/metastatic NSCLC (squamous or non-squamous) in patients who have disease progression after treatment with all available therapies known to confer clinical benefit

Part 2b: Inclusion Criteria Specific to the Monotherapy CRC Cohort

1. Histologically or cytologically proven diagnosis of advanced/metastatic CRC in patients who have disease progression after treatment with all available therapies known to confer clinical benefit

Part 2c: Inclusion Criteria Specific to the Monotherapy in Other Tumors

1. Histologically or cytologically proven diagnosis of advanced/metastatic tumors including gastric cancer, cancer of the GEJ, UCC, RCC, melanoma, or SCCHN in patients who have disease progression after treatment with all available therapies known to confer clinical benefit. Other advanced/metastatic solid tumors (e.g., those demonstrated or expected to have high infiltration with arginase-positive cells) may be allowed based on the discretion of the Medical Monitor.

Part 2d: [redacted]

1. Meets the criteria for any of Parts 2a, 2b, or 2c.
2. [redacted]

Part 3: Inclusion Criteria Specific to the PD-1 Combination Cohort Expansion

Part 3a: Non-small cell lung cancer (NSCLC) – PD/SD on anti-PD-1/PD-L1 therapy

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic NSCLC that does not harbor an activating EGFR or ALK mutation
2. Prior progression on or after platinum-based chemotherapy or refused/ineligible to receive platinum-based chemotherapy.
3. Received an anti-PD-1/PD-L1 agent in a prior line of therapy for advanced/metastatic disease and EITHER:
    a. Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks) while receiving anti-PD-1/PD-L1 therapy in the most recent line of therapy, OR
    b. Had documented stable disease (per Investigator assessment) for ≥ 24 weeks while receiving pembrolizumab therapy in the most recent line of therapy

Part 3b: Melanoma – PD/SD on anti-PD-1/PD-L1 therapy

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic melanoma
2. Received an anti-PD-1/PD-L1 agent in the most recent prior line of therapy for advanced/metastatic disease and EITHER:
    a. Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks) while receiving anti-PD-1/PD-L1 therapy in the most recent line of therapy, OR
    b. Had documented stable disease (per Investigator assessment) for ≥ 24 weeks while receiving pembrolizumab therapy in the most recent line of therapy

Part 3c: Urothelial cell carcinoma (UCC) – PD/SD on anti-PD-1/PD-L1 therapy

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic UCC
2. Received an anti-PD-1/PD-L1 agent in the most recent prior line of therapy for advanced/metastatic disease and EITHER:
    a. Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks) while receiving anti-PD-1/PD-L1 therapy in the most recent line of therapy, OR
    b. Had documented stable disease (per Investigator assessment) for ≥ 24 weeks while receiving pembrolizumab therapy in the most recent line of therapy

Part 3d: Mismatch repair deficient and/or microsatellite instability-high (MSI-H) colorectal cancer (CRC) – PD/SD on anti-PD-1/PD-L1 therapy

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic CRC demonstrated to be mismatch repair deficient or microsatellite instability-high.
2. Received an anti-PD-1/PD-L1 agent in the most recent prior line of therapy for advanced/metastatic disease and EITHER:
    a. Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks) while receiving anti-PD-1/PD-L1 therapy in the most recent line of therapy, OR
    b. Had documented stable disease (per Investigator assessment) for ≥ 24 weeks while receiving pembrolizumab therapy in the most recent line of therapy

Part 3e: Microsatellite stable (MSS) colorectal cancer (CRC) – Checkpoint inhibitor naive

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic CRC demonstrated to lack mismatch repair deficiency and microsatellite instability (low or high).
2. Received at least one prior fluoropyrimidine-containing systemic therapy for advanced/metastatic CRC

3. Has not received prior anti-PD-1/PD-L1, anti-CTLA4, or other checkpoint inhibitor or immune co-stimulator (e.g., anti-OX-40, anti-41BB, etc.)

Part 3f: Gastric/gastro-esophageal (GE) junction cancer – Checkpoint inhibitor naive

1. Histological or cytological diagnosis of locally advanced unresectable or metastatic gastric or GEJ cancer
2. Received at least two prior systemic therapies for advanced/metastatic disease; prior regimens must have included a platinum and a fluoropyrimidine
3. Human epidermal growth factor receptor 2 (HER-2/neu) negative, or, if HER2/neu positive, must have previously received treatment with trastuzumab
4. Has not received prior anti-PD-1/PD-L1, anti-CTLA4, or other checkpoint inhibitor or immune co-stimulator (e.g., anti-OX-40, anti-41BB, etc.)

Part 3g: Squamous cell carcinoma of the head and neck (SCCHN) – Checkpoint inhibitor naive

1. Histological or cytological diagnosis of recurrent or metastatic SCCHN
2. Had disease progression EITHER:
    a. While receiving or after platinum-containing chemotherapy administered for recurrent or metastatic SCCHN, OR
    b. Following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy.
3. Has not received prior anti-PD-1/PD-L1, anti-CTLA4, or other checkpoint inhibitor or immune co-stimulator (e.g., anti-OX-40, anti-41BB, etc.).

Part 3h: Mesothelioma – Checkpoint inhibitor naive

1. Histological or cytological diagnosis of locally advanced incurable or metastatic malignant pleural mesothelioma
2. Has failed or was unable to received standard therapy for malignant pleural mesothelioma
3. Has not received prior anti-PD-1/PD-L1, anti-CTLA4, or other checkpoint inhibitor or immune co-stimulator (e.g., anti-OX-40, anti-41BB, etc.)

7.2 Exclusion Criteria

1. Any other current or previous malignancy within the past three years except a) adequately treated basal cell or squamous cell skin cancer, b) carcinoma *in situ* of the cervix, c) prostate cancer with stable prostate specific antigen (PSA) levels for 3 years, d) or other neoplasm that, in the opinion of the Principal Investigator and with the agreement of the Medical Monitor, will not interfere with study-specific endpoints.
2. Cytotoxic chemotherapy, tyrosine kinase inhibitor (or other targeted anti-cancer agent), radiation therapy, or hormonal therapy within 14 days or 5 half-lives, whichever is longer, prior to Cycle 1 Day 1 (42 days for nitrosoureas or mitomycin C).

3. Immunotherapy or biological therapy (e.g., monoclonal antibodies) within 21 days prior to Cycle 1 Day 1
    - EXCEPTION: Washout of anti-PD-1 therapy is NOT required in Part 1b Dose Escalation or the Part 3 Expansion Cohorts.
4. Treatment with an unapproved investigational therapeutic agent within 21 days (or 5 half-lives for small molecule agents) prior to Cycle 1 Day 1
    - EXCEPTION: Washout of anti-PD-1 therapy is NOT required in Part 1b Dose Escalation or the Part 3 Expansion Cohorts.
5. Has a diagnosis of immunodeficiency or any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other systemic immunosuppressive medications within 14 days prior to the first dose of study treatment. Inhaled steroids and adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
6. Concomitant therapy with valproic acid/valproate-containing therapies.
7. Concomitant therapy with allopurinol and other xanthine oxidase inhibitors
8. Exclusion criterion deleted in Protocol Amendment 2-EU.
9. Patients with symptomatic ascites or pleural effusion requiring intermittent paracentesis or thoracocentesis. A patient who is clinically stable following treatment for these conditions (including therapeutic thoraco- or para-centesis) is eligible.
10. Unable to receive medications *per os* (PO)
11. Unstable/inadequate cardiac function:
    - Myocardial infarction or symptomatic ischemia within the last 6 months
    - Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded; 1st degree AV block or asymptomatic LAFB/RBBB are eligible)
    - Congestive heart failure (New York Heart Association class III to IV)
12. 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.
13. Major surgery within 2 months prior to first dose of study treatment.
14. Infection requiring parenteral antibiotics, antivirals, or antifungals within two weeks prior to first dose of study treatment.
15. Patient is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C.
16. Refractory nausea and vomiting, uncontrolled diarrhea, malabsorption, significant small bowel resection or gastric bypass surgery, use of feeding tubes or other situation that may preclude adequate absorption
17. Serious psychiatric or medical conditions that could interfere with treatment or protocol-related procedures
18. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

Note: Patients with brain metastases or CNS disease are permitted, but must have completed treatment and either (1) have no evidence of active CNS disease for at least 4 weeks prior to the first dose *OR* (2) have stable CNS lesions, defined as not requiring intrathecal chemotherapy for at least 6 weeks or systemic steroid treatment to prevent CNS complications for at least 3 weeks prior to first dose. Patients with CNS disease must also have a Screening head CT or MRI demonstrating stable disease compared to their most recent CNS evaluation. This exception does not apply to patients with carcinomatous meningitis who are excluded regardless of clinical stability.

19. Patients in whom oral and/or IV fluid hydration are contraindicated
20. Patients who are pregnant or lactating
21. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
23. Has had an allogeneic tissue/solid organ transplant.

Disease-specific Exclusion Criteria*:*

Part 1b AND Part 3

1. Intolerance to prior anti-PD-1/PD-L1 therapy including 1) discontinuation due to immune-related toxicity or, 2) immune-related toxicities that that required intensive or prolonged immunosuppression (including, high-dose IV corticosteroids, > 2 mo of immunosuppressive corticosteroids (i.e., equivalent of >10mg oral prednisone daily) or the addition of potent immunosuppression to corticosteroids (e.g., mycophenolate mofetil/CellCept or infliximab) to manage.
2. Prior severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients or prior severe hypersensitivity reaction to any other monoclonal antibody (mAb).
3. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
4. Has a history of interstitial lung disease.
5. Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 2 weeks prior to study Day 1.

6. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. 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.

Part 3

Part 3a: NSCLC

1. Documented activating mutations in EGFR or ALK.

8.0 RADIOLOGICAL TUMOR ASSESSMENTS

As part of Protocol Amendment 2-US 3, dated 10 NOV 2020, the irRECIST endpoints have been removed. This Section refers to the radiological tumor assessments before Protocol Amendment 2-US 3.

All patients will be evaluated for tumor response *both* according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (see Attachment 4) [in mesothelioma patients, modified RECIST criteria for pleural mesothelioma (Byrne 2004, Attachment 5)] *and* according to the immune-related response criteria using unidimensional measurements (irRECIST; Perrone 2016, see Attachment 6). The irRECIST guidelines are based on RECIST, immune-related response criteria and the findings in Nishino (2013) as described below. Although the primary endpoint for analysis of clinical activity is RECIST v1.1, patient management will follow the principles and guidelines that are specifically outlined in the irRECIST criteria (Attachment 6). On-study assessments by irRECIST take into account the observation that some patients with solid tumors can have a transient tumor flare in the first few months after start of immunotherapy with subsequent disease response. Clinical decisions will be based on the interpretation of the Investigator at the site treating the patient in real time using the irRECIST criteria. RECIST imaging analyses will be performed by the local radiologists and images may be collected and held in order to enable future independent image analysis.

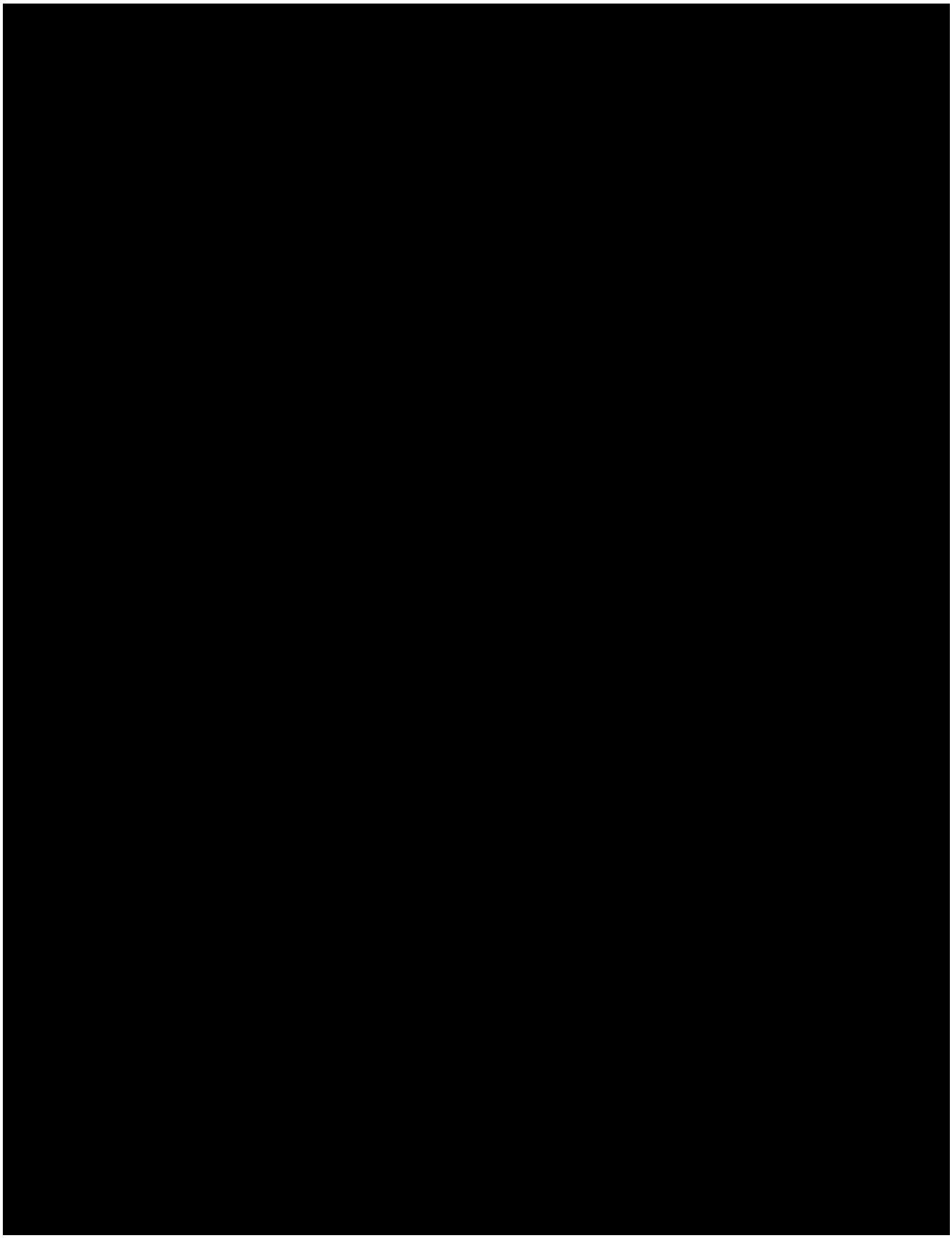
If imaging shows progressive disease per RECIST v1.1, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until imaging is repeated approximately 4 weeks later in order to confirm PD, as described in the irRECIST recommendations (see Attachment 6).

Patients that are deemed clinically unstable or who have biopsy-proven new metastatic lesions are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. At a minimum, patients must meet the following criteria for continued treatment on study after disease progression is identified at a tumor assessment:

- Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status

- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

In general, if repeat imaging confirms PD as described in Attachment 6, patients will be discontinued from study therapy. However, if a patient has confirmed radiographic progression, but the patient is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue study treatment may be considered following consultation with the Medical Monitor. If repeat imaging does not confirm PD, treatment with study treatments will continue/resume and the next imaging studies will be conducted every 8 weeks for parts 1a and 2 or every 9 weeks for parts 1b and 3 as previously scheduled. In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging.



PROTOCOL DETAILS

10.0 BACKGROUND AND RATIONALE

10.1 Background

10.1.1 Immunosuppressive Myeloid Cells and Arginase

Solid tumors have been shown to have moderate to extensive infiltration of immunosuppressive myeloid cells (Solito 2014). Myeloid Derived Suppressor Cells (MDSCs) and neutrophils are present in multiple solid tumors and correlate with poor outcome (Gentles 2015). Both granulocytic MDSCs and neutrophils contain the enzyme arginase within secretory granules. Upon stimulation by factors within the tumor microenvironment [e.g., Interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNF-α)], arginase is released into the tumor microenvironment via degranulation 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 2014). INCB001158 is a small molecule inhibitor of arginase that is able to restore the local tumor concentration of arginine, resulting in the re-activation of quiescent T- and NK-cells. INCB001158 has no direct growth inhibitory or cytotoxic activity on tumor cells or on immune effector cells.

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. INCB001158 is a competitive inhibitor of both recombinant human arginase 1 and arginase 2 with IC_{50}s of approximately 100 and 275 nM, respectively.

10.1.2 Arginase 1 Expression in Cancer Patients

In cancer patients, arginase 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 (PMNs) 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 (e.g., IL-8, TNF-α).

Immunohistochemical (IHC) 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 10.1-1). 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 to normal healthy control patients (Figure 10.1-1[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.

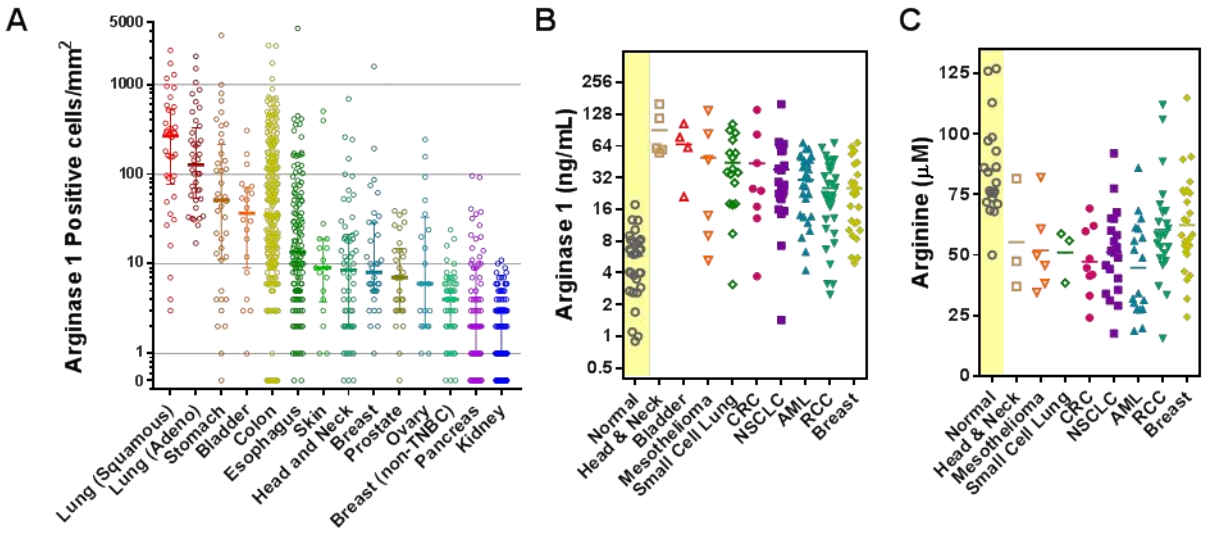


Figure 10.1-1: Arginase and arginine in cancer patients.

[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 volunteers. Plasma from cancer patients and healthy normal volunteers were assayed for arginase 1 levels by ELISA and arginine levels by LC/MS-MS.

10.1.3 Selectivity of INCB001158

INCB001158 is a potent, selective, and reversible inhibitor of human recombinant arginase 1 and 2 (IC_{50}'s of 100 and 275 nM, respectively). INCB001158 is also able to inhibit the elevated arginase activity present in the plasma of renal cancer patients with a similar potency. To assess selectivity, the compound was evaluated as an inhibitor of radioligand binding to a panel of 87 receptors and ion channels screened at a high concentration of 50 µM, well above the estimated 2–3 µM C_{max} of INCB001158 in humans at the projected efficacious dose.

Two targets showed > 50% binding in these assays. The enzyme cholinesterase showed 59% binding inhibition at 50 µM, although there were no clinical observations in mice, rats, or monkeys consistent with cholinesterase inhibition *in vivo* despite achieving a C_{max} of > 100 µM in mice and rats and > 80 µM in monkeys. There was also 63% inhibition of ligand binding to the dopamine transporter at 50 µM. It should be noted that INCB001158 has limited brain penetration as measured in mice and rats.

No inhibition of the arginine-utilizing nitric oxide synthase family of enzymes (eNOS, iNOS, and nNOS) was measured at 50 µM INCB001158 and no inhibition was seen in a panel of 5 serine proteases at the same concentration.

10.1.4 Activity of INCB001158 in Cell-Based Assays

Activated T-cells and NK-cells require the amino acid arginine to proliferate. Arginine is metabolized in the tumor environment by arginase that has been secreted from MDSCs and neutrophils (Munder 2005). Arginine depletion leads to a suppression of T-cell and NK-cell proliferation thereby blunting the anti-tumor immune response.

INCB001158 had no direct anti-proliferative activity on cell lines in culture, including human HepG2 or murine Lewis Lung Carcinoma (LLC) cell lines. Furthermore, INCB001158 did not inhibit the growth rate of normal human T-cells or NK-cells that were isolated and stimulated in culture. However, INCB001158 did reverse the growth suppressive effects of human neutrophils on human T-cells when co-cultured *ex vivo* with an EC50 of 162 nM as shown in Figure 10.1-2. 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 fashion.

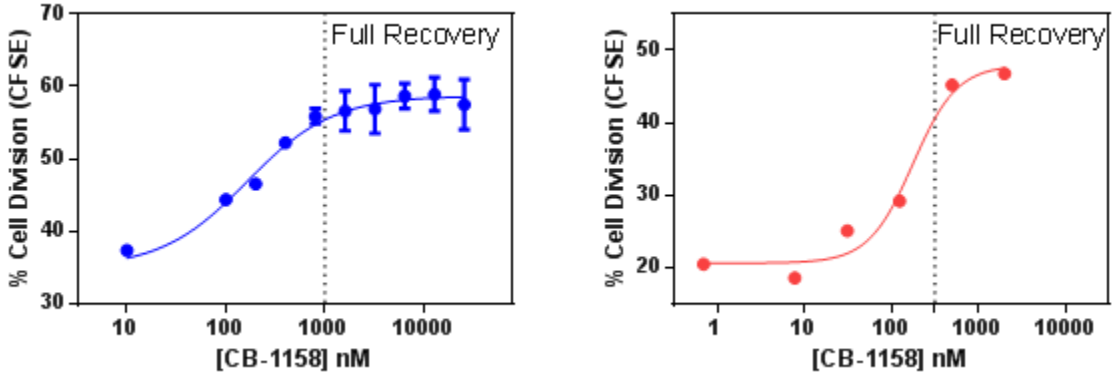


Figure 10.1-2: Inhibition of the immunosuppressive effect of neutrophils and MDSCs on T-cells *ex vivo*.

Left panel: Normal human neutrophils were co-cultured with normal human T-cells ex vivo in the presence of increasing concentrations of INCB001158. Right panel: Conditioned media from patient-derived MDSCs generated in the presence of increasing concentrations of INCB001158 was added to a culture of normal human T-cells ex vivo in the presence of increasing concentrations of INCB001158.

10.1.5 Immunosuppression by Arginase in Mice Versus Humans

Arginase is an immunosuppressive enzyme in mice and humans that limits the availability of extracellular arginine to T-cells in the tumor microenvironment. MDSCs participate in the immunosuppressive process in both species; however, the biology of MDSCs is fundamentally different between mice and humans. In mice, arginase and the arginine transporter are upregulated in MDSCs, leading to rapid uptake of arginine from the extracellular milieu and subsequent cleavage by arginase intracellularly. In contrast, in humans, arginine is cleaved by extracellular arginase *secreted* by MDSCs and neutrophils. INCB001158 inhibition of cellular arginase in mouse MDSCs is limited by poor cellular penetration. Thus, the anti-tumor efficacy of INCB001158 in mouse syngeneic tumor models requires higher doses than those anticipated for efficacy in humans and may in large part be mediated by the ability of INCB001158 to elevate systemic arginine levels, a pharmacodynamic effect.

10.1.6 Pharmacodynamics of INCB001158 in Tumors and Tissues in Mice

The tumor distribution and pharmacodynamic effects of INCB001158 were evaluated in mice bearing subcutaneously-implanted murine Lewis Lung Carcinoma (LLC) tumors 2 hr after treatment with a single dose or 2 hr after the last of five doses administered on a twice daily (BID) schedule. Plasma and tumor concentrations of both INCB001158 and the pharmacodynamic marker arginine were determined in these studies (Figure 10.1-3). Significant exposure to INCB001158 in plasma and tumors was observed after a single dose that was moderately higher after five doses on the BID schedule. With 250 mg/kg dosing, the concentration of arginine in plasma increased about 3-fold 2 hr after a single oral dose and almost 8-fold 2 hr after five doses on a BID schedule. INCB001158 accumulated approximately 2-fold in tumors following a BID schedule, while arginine in tumors increased by more than 3-fold. Studies looking at arginine and INCB001158 levels in plasma and tumors after BID dosing for 14 days showed similar levels of both INCB001158 and arginine indicating steady-state was reached within 3 days.

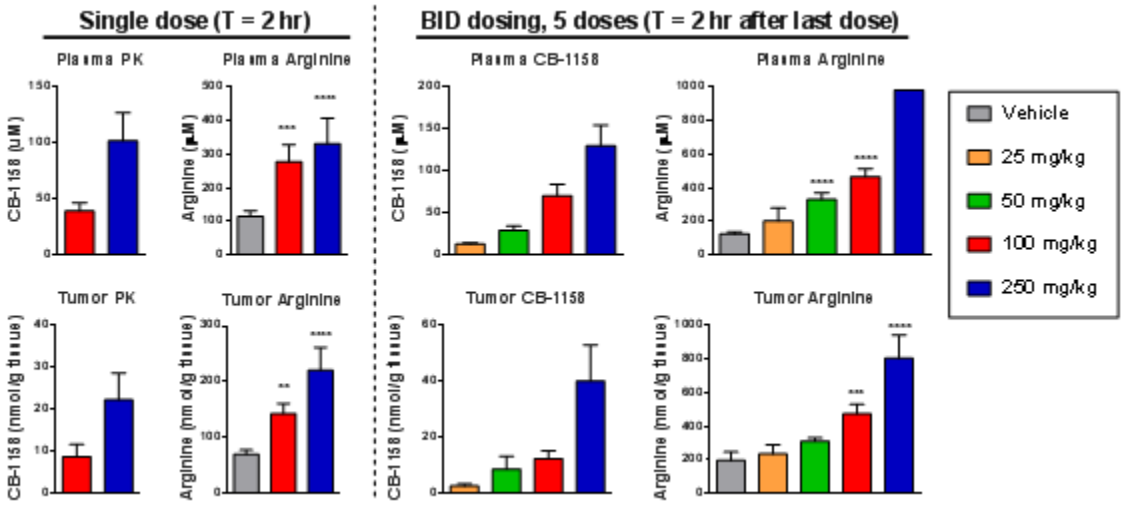


Figure 10.1-3: Tumor PK and pharmacodynamics of INCB001158.

INCB001158 was administered as a single dose or as five consecutive doses on a BID schedule to female C57.Bl/6 mice implanted with the mouse LLC tumors (N = 10). 2 hr after a single dose, or 2 hr after the last dose BID, INCB001158 and arginine concentrations were measured in plasma and tumor. **p<0.01, ***p<0.001, ****p<0.0001 vs. vehicle control (T-test)

10.1.7 Efficacy of INCB001158 in Tumor-Bearing Syngeneic Mice

Oral BID administration of single agent INCB001158 produced a dose-dependent reduction in the growth of subcutaneously implanted LLC tumors with significant activity at doses as low as 10 mg/kg (Figure 10.1-4[A]). A dose-related systemic increase in the plasma concentration of arginine correlated with this efficacy (Figure 10.1-4[B]). The efficacy of INCB001158 in LLC tumors is immune-mediated. When LLC tumors were grown in immuno-compromised scid mice, there was no anti-tumor activity of INCB001158; furthermore, depleting antibodies that target $CD8^+$ T-cells or NK-cells partially reverse the effect of INCB001158 in immune-competent animals (Figure 10.1-4[C,D]). Changes in tumor growth rate in the mouse LLC model were associated with increases in $CD8^+$ T cells within the tumor (Figure 10.1-4[E]), consistent with an immune stimulatory mechanism of action.

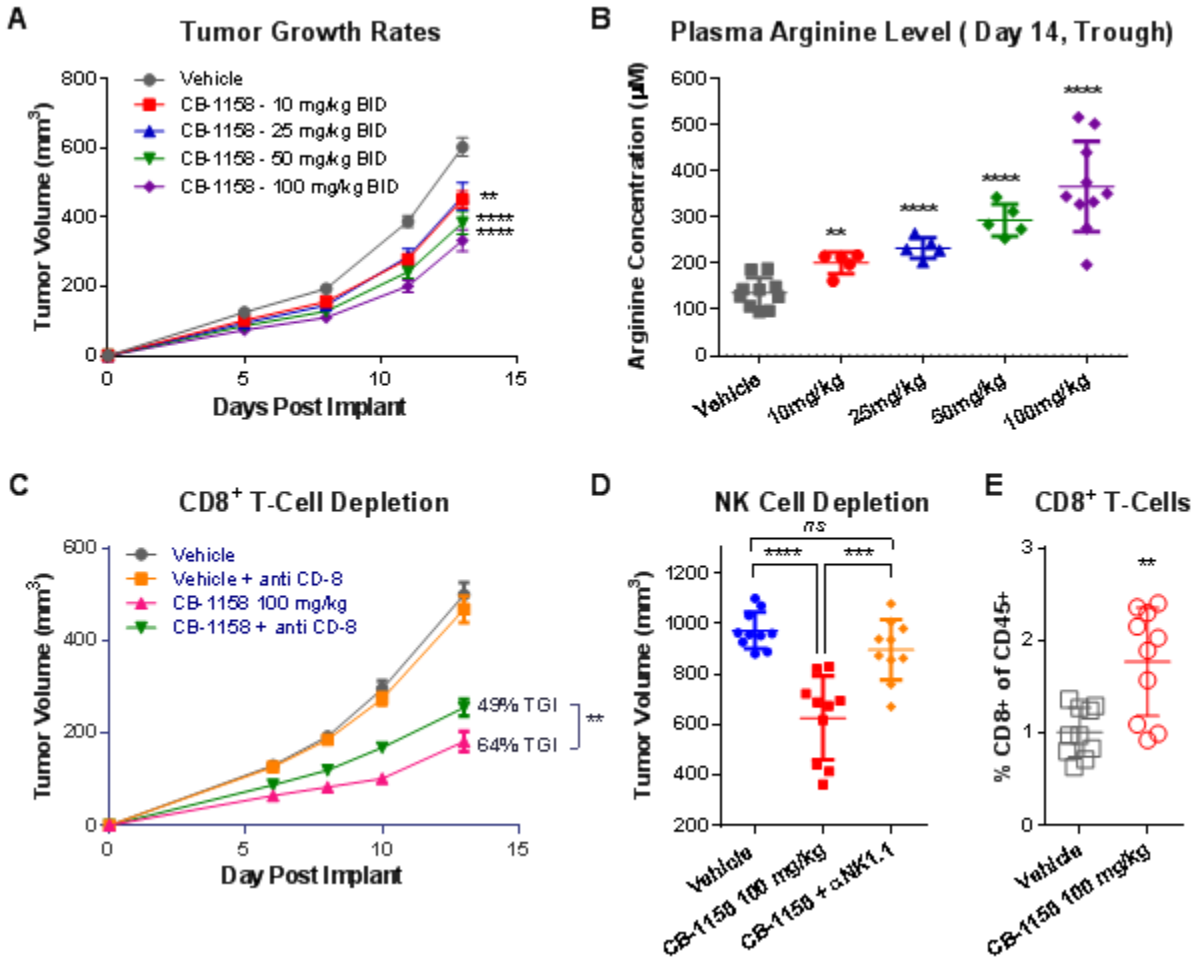


Figure 10.1-4: Inhibition of LLC tumor growth and pharmacodynamic effects *in vivo*.

Immunocompetent C57Bl.6 mice were implanted subcutaneously with LLC tumor cells and treated orally with 10 to 100 mg/kg INCB001158 BID. A) Dose-dependent reduction in growth rate of mouse LLC tumors. B) Plasma arginine concentration on Day 14, approximately 16 hr after the final dose of INCB001158. C) Partial abrogation of the efficacy of INCB001158 by depletion of CD-8$^+$ T-cells and D) Significant abrogation of INCB001158 efficacy by depletion of NK-cells from mice. E) Increase in CD45$^+$/CD8$^+$ T-cells in LLC tumors following oral BID dosing of INCB001158 BID for 14-days as determined by flow cytometry. **p<0.01, ***p<0.01, ****p<0.0001 vs. control (T-test).

Single agent INCB001158 also had activity in the B16.F10 murine melanoma model (Figure 10.1-5). Importantly, the combination of INCB001158 with anti-PD-L1 resulted in enhanced anti-tumor activity in the B16 model.

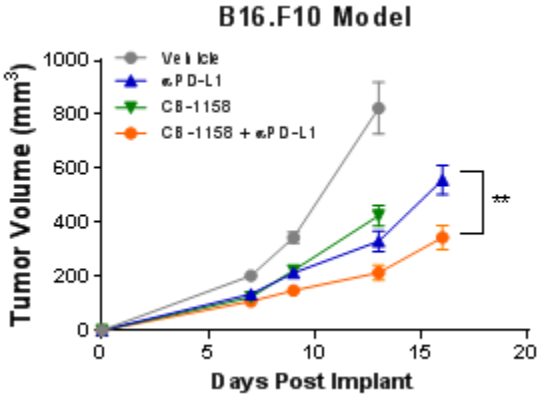


Figure 10.1-5: Inhibition of B16 melanoma tumor growth *in vivo*.

Immunocompetent C57Bl.6 mice were implanted subcutaneously with B16.F10 tumor cells were implanted subcutaneously in immunocompetent C57Bl.6 mice and treated with either 1) vehicle (water) orally twice daily; 2) 100 mg/kg INCB001158 orally BID beginning on Day 1; 3) 5 mg/kg αPD L1 (clone 10F.9G2) intraperitoneally (IP) on Days 3, 5, 7, 9, 11, and 13; or 4) a combination of INCB001158 and αPD-L1. **p<0.01 vs. αPD-L1 alone.

10.1.8 Nonclinical Toxicity Testing of INCB001158

INCB001158 is well tolerated in all species at doses that produce robust pharmacodynamic effects. There is a substantial safety margin of ≥ 16-fold from the projected clinical efficacious exposure (AUC and C_{max}) to the exposures that were well tolerated in the GLP toxicology studies in rats and monkeys.

Very high doses and exposures can result in the on-target toxicity of urea cycle inhibition associated with morbidity. The strongest evidence of urea cycle toxicity was identified in non-GLP studies in mice, where a thorough time course of plasma and liver arginine could be monitored along with plasma ammonia. Animals receiving very high doses of INCB001158 that caused mortality, showed dose-related increases in the plasma concentration of arginine and ammonia, large increases in liver arginine, and reduced serum BUN. These findings occurred at exposures > 45-fold and > 150-fold over the AUC and C_{max} projected to be needed to achieve efficacy in humans, respectively.

A dose of 500 mg/kg BID (1000 mg/kg/day) in the rat 28-day GLP toxicity study, produced a steady-state peak exposure (C_{max}) of > 62 µg/mL (216 µM) and an $AUC_{o\text{-}\tau}$ of > 283 µg*hr/mL, > 78-fold and > 40-fold above the projected human efficacious exposure, respectively. This dose resulted in mortality in 29% of rats that was associated with clear evidence of urea cycle

inhibition including a large elevation in liver arginine, elevated plasma ammonia and sporadic decreases in BUN. Additionally, modest increases (< 2-fold) in alanine (ALT) and aspartate aminotransferase (AST) as well as slight to moderate atrophy of the bone marrow, slight to moderate cytoplasmic clearing of the pars distalis of the pituitary gland, and non-adverse minimal to moderate hepatocellular cytoplasmic vacuolation were observed in the high dose animals, all of which were reversible following a two-week non-dosing recovery period. The dose of 150 mg BID (300 mg/kg/day) in rats did not result in adverse findings over 28 days and therefore was considered the NOAEL. The AUC and C_{max} in rats at steady-state at the NOAEL are expected to be at least 16- and 30-fold, respectively, over those projected to be efficacious in humans. Minimal histological findings were observed in the liver (vacuolation) and pituitary gland (cytoplasmic clearing) of rats receiving 300 mg/kg/day INCB001158 that were not considered adverse and were fully reversible following a two-week non-dosing recovery period. In the 28-day GLP toxicity study in cynomolgus monkeys, INCB001158 dosing at 150 mg/kg BID (300 mg/kg/day) resulted in morbidity in one female monkey. Findings in this animal were consistent with urea cycle inhibition with ~120-fold increase in liver arginine. A dose of 300 mg/kg/day in male monkeys was generally well-tolerated, as was a dose of 200 mg/kg/day in female monkeys. Findings in surviving high-dose animals included reversible ~2-fold elevations in ALT and AST correlating with minimal centrilobular hepatocyte degeneration, as well as modest decreases in total protein and albumin. At the high dose, the steady-state C_{max} was > 23 µg/mL (80 µM) and the AUC was > 137 µg*hr/mL, over 29-fold and 19-fold above the projected human efficacious exposure, respectively. A dose level of 50 mg/kg BID (100 mg/kg/day) in male and female monkeys did not result in any adverse findings and was considered the NOAEL. The dose level of 100 mg/kg BID (200 mg/kg/day) was considered the Highest Non-Severely Toxic Dose (HNSTD). The AUC and C_{max} in monkeys at steady-state at this dose are expected to be at least 16- and 24 fold, respectively, above the exposure predicted to be efficacious in humans.

A Functional Observational Battery and Locomotor Assessment were incorporated into the rat GLP toxicity study to evaluate any potential CNS effects. There were no findings in either evaluation that were attributed to INCB001158. In the GLP cynomolgus monkey study, ECG and blood pressure were monitored. There were no findings associated with INCB001158

treatment, consistent with minimal findings in a human ether-à-go-go (hERG) patch-clamp assay, wherein 50 µM INCB001158 inhibited the hERG potassium channel by less than 1%. Orotic acid (OA) is a marker of urea cycle inhibition that accumulates in the urine in patients with urea cycle defects. In rats, a single dose of 500 mg/kg (the dose that produced significant toxicity during the second week of BID dosing in the GLP toxicity study) produced a dramatic increase in urine OA (> 1000-fold; Figure 10.1-6). Notably, in one rat receiving the NOAEL dose of 150 mg/kg an increase in OA of ~100-fold was observed. Thus, urine OA is a sensitive surrogate marker for urea cycle inhibition and will be monitored closely in patients on the Phase 1 clinical study.

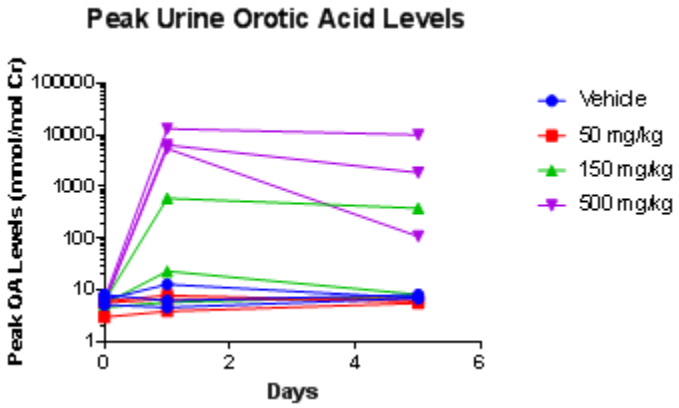


Figure 10.1-6: Peak urine orotic acid levels in rats.

Rats were dosed with INCB001158 orally twice daily for 5-days. Urine OA was measured via LC/MS/MS and normalized to urine creatinine.

INCB001158 did not induce a mutagenic response in a GLP Ames assay at concentrations up to 5000 µg/plate.

Additional information on the GLP and non-GLP evaluation of toxicity in animals can be found in the Investigator's Brochure for INCB001158.

10.1.9 Previous Human Experience

As of 23 May 2018, the Phase 1 clinical trial INCB 01158-101, previously referred to as CX-1158-101, is enrolling solid tumor patients to receive INCB001158 on a BID schedule as single agent and in combination with pembrolizumab. The recommended phase 2 dose (RP2D) for single agent INCB001158 was declared as 100 mg BID, and enrollment to the monotherapy expansion cohorts is ongoing. The combination of INCB001158 with pembrolizumab is

undergoing evaluation in dose escalation. Eighty patients have been enrolled to the study, 29 to monotherapy dose escalation, 30 across monotherapy dose expansions, and 21 to combination dose escalation. The preliminary PK, PD, and safety data from this ongoing study are reported below. Please note that this is an ongoing study and, as such, the clinical data are not fully clean and subject to change. Please see the Investigator's Brochure for additional information.

10.1.10 Pharmacokinetics of INCB001158

Administration of INCB001158 to solid tumor patients resulted in pharmacologically active exposure beginning with the first dose of 50 mg. The first three dose escalation cohorts enrolled patients at doses of 50, 100, and 150 mg BID. The pharmacokinetic data available as of 26 June 2017 are shown in Figure 10.1-7 and PK parameters are provided in Table 10.1-1. The half- life ($t_{1/2}$) of INCB001158 was approximately 6 hr and the C_{max} ranged from approximately 3–10 µM and occurred at approximately 4 hr after dosing. The minimum target for continuous exposure of INCB001158 based on preclinical efficacy data was approximately 1.0 µM and the steady state C_{min} (trough concentration) at 50, 100, and 150 mg BID was well above this target.

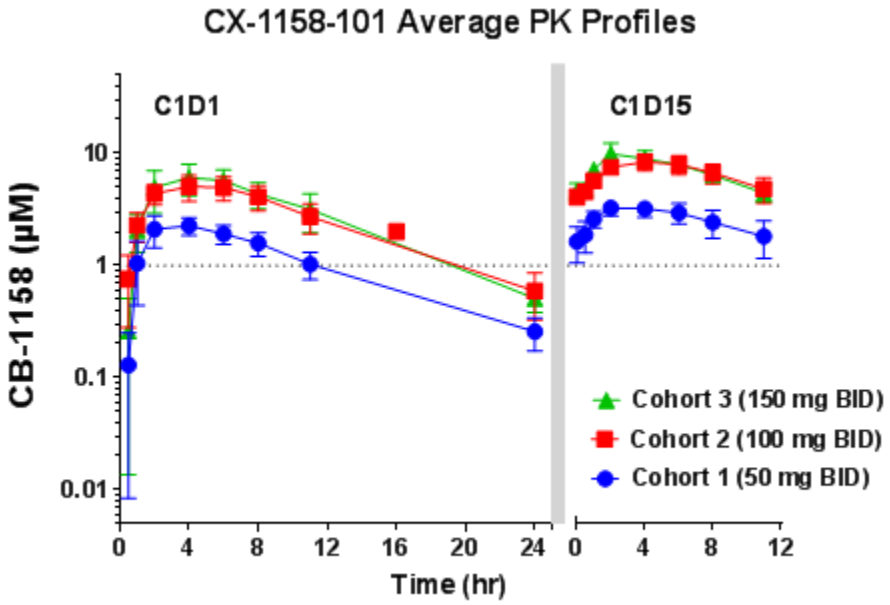


Figure 10.1-7: PK profile of INCB001158 in patients enrolled in the Phase 1 study.

Data from patients receiving 50 (N = 4), 100 (N = 4) and 150 (N = 3) mg BID are plotted. On C1D1, patients received a single dose of INCB001158 and plasma samples were collected through 12-16 hr on D1 and prior to the first BID dose on C1D2 (24 hr). A second PK profile was collected through 12 hr on C1D15 at steady state. The horizontal line indicates the target concentration for continuous exposure of INCB001158 to achieve 90% inhibition of arginase enzyme.

Table 10.1-1: PK Parameters from Phase 1 Patients

Cohort	$T_{1/2}$ (C1D1) (hr)	C_{max} (C1D15) (µM)	C_{min} (C1D15) (µM)	AUC_t (C1D15) (µM*hr)
50 mg BID	6.2 ± 1.0	3.3 ± 0.5	1.6 ± 0.6	30.2 ± 6.5
100 mg BID	6.0 ± 0.6	8.4 ± 1.4	4.1 ± 0.5	80.6 ± 12.2
150 mg BID	5.0 ± 0.5	9.9 ± 2.4	4.4 ± 0.8	85.5 ± 7.6

Note: Values represent the mean ± SD.

10.1.11 Pharmacodynamics of INCB001158

The pharmacodynamic activity of INCB001158 was determined by direct measurement of arginine concentration and arginase activity in plasma. Comparing to healthy volunteers, the cancer patients enrolled in this trial had reduced median plasma arginine concentration and elevated level of arginase protein in predose samples on C1D1 (Figure 10.1-8, Panels A and C). Plasma arginine levels increased in all patients on study. With the exception of two patients at 50 mg BID, all patients on study had increases of more than 50% in plasma arginine level, and even the two patients had further elevations at later time points (Figure 10.1-8, Panel B). These elevations in plasma arginine brought the plasma arginine of all patients into or above the normal range of plasma arginine concentration. Further, direct measurement of plasma arginase activity demonstrated >90% inhibition at 6h hours post-dose on C1D1, which was sustained predose on C1D15 (Figure 10.1-8, Panel D).

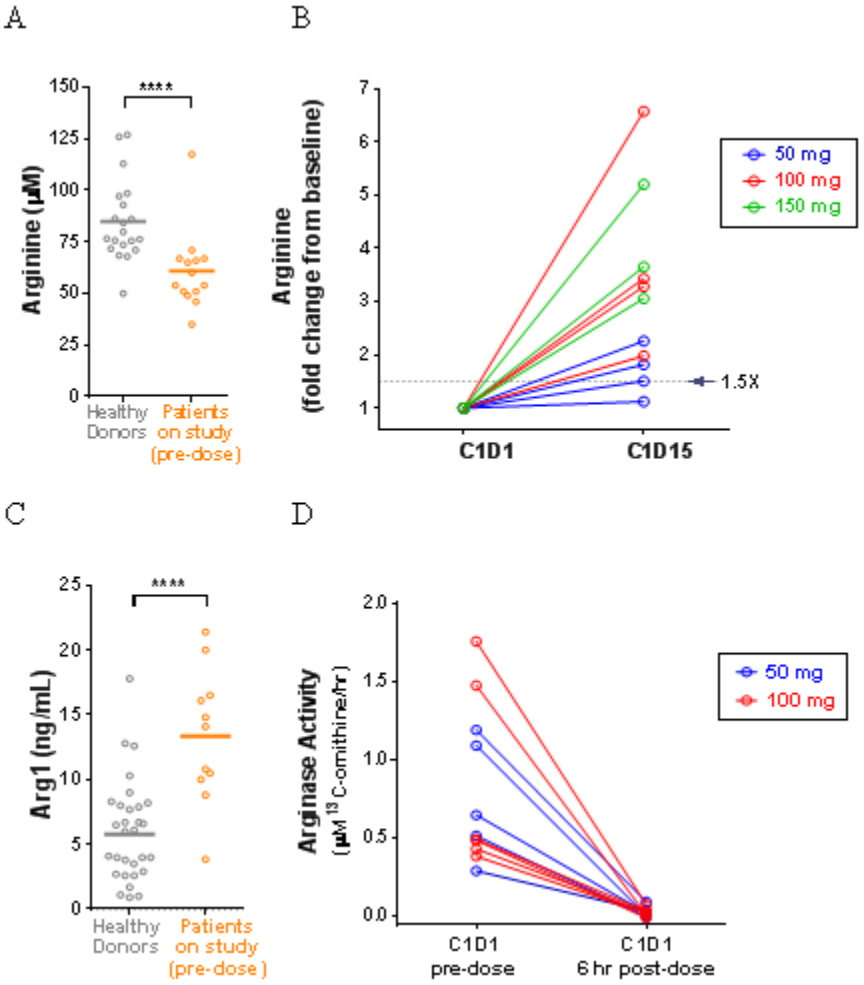


Figure 10.1-8: Plasma arginine and arginase in Phase 1 patients.

Panel A. On C1D1 prior to dosing, patients had a plasma arginine concentration that was significantly reduced compared with reference data from healthy volunteers (collected separately). Panel B. On C1D15, plasma arginine increase had reached > 1.5-fold compared with predose on C1D1 in most patients on study in 11 pts tested (n=4 at 50 mg, 4 at 100 mg and 3 at 150 mg). Panel C. Arginase protein levels in plasma were found to be elevated relative to healthy volunteers. Panel D. On C1D15, plasma arginase activity was reduced to < 10% in all 11 pts tested (n=5 at 50 mg and 6 at 100 mg). Arginine concentration in plasma was measured by amino acid analysis. Arginase protein was measured by ELISA and arginase activity was measured by incubating plasma with ^{13}C-arginine and detecting formation of ^{13}C ornithine by LC/MS-MS.

10.1.12 Safety of Single Agent INCB001158

The preliminary safety profile of INCB001158 has been evaluated during dose escalation from 50 to 150 mg BID. INCB001158 has been well tolerated at all doses tested. The rate of treatment-related adverse events has been low (40% of pts), all of which have been mild to moderate (Grade 1/2) and only one of which (fatigue) has occurred in as many as 2 patients. No treatment-related serious adverse events (SAEs) or adverse events of Grade ≥ 3 have occurred. Treatment-emergent Grade ≥ 3 adverse events have occurred in 6 patients, all of which have been considered unrelated or unlikely related to study drug, and have generally been related to underlying disease. Dose interruptions/reductions due to drug-related events have occurred in 2 patients, both due to asymptomatic elevations in urinary OA (see below) in patients enrolled at the 150 mg dose level.

Table 10.1-2: INCB001158-Related Treatment-Emergent Adverse Events by Preferred Term

	Number (%) of Patients (N=23)	
Adverse Event Preferred Term	**All Grades**	**≥ Grade 3**
Patients with Any INCB001158-Related Treatment-Emergent Adverse Event	18 (78.3%)	6 (26.1%)
Constipation	6 (26.1%)	0 (0.0%)
Abdominal pain	5 (21.7%)	2 (8.7%)
Anaemia	4 (17.4%)	1 (4.3%)
Back pain	4 (17.4%)	1 (4.3%)
Oedema peripheral	4 (17.4%)	0 (0.0%)
Pyrexia	4 (17.4%)	0 (0.0%)
Fatigue	3 (13.0%)	0 (0.0%)
Nausea	3 (13.0%)	0 (0.0%)
Cough	2 (8.7%)	0 (0.0%)
Diarrhoea	2 (8.7%)	0 (0.0%)
Dizziness	2 (8.7%)	0 (0.0%)
Dyspnoea	2 (8.7%)	0 (0.0%)
Peripheral sensory neuropathy	2 (8.7%)	0 (0.0%)
Acute kidney injury	1 (4.3%)	0 (0.0%)

Table 10.1-2: INCB001158-Related Treatment-Emergent Adverse Events by Preferred Term (Continued)

	Number (%) of Patients (N=23)	
Adverse Event Preferred Term	**All Grades**	**≥ Grade 3**
Alanine aminotransferase increased	1 (4.3%)	0 (0.0%)
Anxiety	1 (4.3%)	0 (0.0%)
Appetite disorder	1 (4.3%)	0 (0.0%)
Arthralgia	1 (4.3%)	0 (0.0%)
Ataxia	1 (4.3%)	0 (0.0%)
Blood creatinine increased	1 (4.3%)	0 (0.0%)
Bone pain	1 (4.3%)	0 (0.0%)
Carpal tunnel syndrome	1 (4.3%)	0 (0.0%)
Cellulitis	1 (4.3%)	1 (4.3%)
Conjunctivitis	1 (4.3%)	0 (0.0%)
Decreased appetite	1 (4.3%)	0 (0.0%)
Dry skin	1 (4.3%)	0 (0.0%)
Ear pain	1 (4.3%)	0 (0.0%)
Embolism	1 (4.3%)	0 (0.0%)

Effects on hepatic urea cycle function

Urinary OA is being monitored as a sensitive biomarker of urea cycle inhibition in the liver. (Hepatic urea cycle inhibition leads to the accumulation of carbamoyl phosphate, which is metabolized via the pyrimidine synthesis pathway leading the synthesis and urinary excretion of OA). Substantial elevations (generally to 100-800X the upper limit of normal) occur in patients with inherited defects in enzymes of the urea cycle. A similar magnitude of urinary OA elevation (~1000X) was noted in animals that received doses of INCB001158 that were associated with toxicity in preclinical safety studies, although notable elevations in urinary OA were also noted in some animals treated at the NOAEL.

Due to the limited availability of data describing the clinical sequelae associated with modest (5-100X ULN) elevations of urinary OA, a conservative threshold of 5X the ULN was used to provide evidence of urea cycle inhibition. Importantly, elevations in OA are not considered a toxicity but, rather, function as a biomarker of urea cycle function. In addition to urinary OA,

patients were also monitored for sustained elevations in ammonia or significant reductions in plasma blood urea nitrogen (BUN) as evidence of clinically significant effects on the urea cycle. There has been no evidence of clinically significant urea cycle inhibition to date. Although normal variability of plasma ammonia and BUN has been seen, no dose related trends or significant outliers have been noted (Tables 10.1-3 and 10.1-4). In addition, no symptoms associated with clinically significant urea cycle inhibition (e.g., unexplained anorexia, nausea, vomiting, mental status changes, etc.) have been noted.

Table 10.1-3: Plasma Ammonia Levels by Visit Day*

Dose Level (mg BID)	N	Baseline	C1D8	C1D15	C1D22	C2D1	C2D8
50	6-8***	20 ± 15	18 ± 11	24 ± 23	18 ± 11	45 ± 52	36 ± 44
100	3-7***	20 ± 12	17 ± 8	16 ± 8	16 ± 5.3	52 ± 66	18 ± 8.0
150**	3***	41 ± 23	30 ± 14	35 ± 13	36 ± 26	29 ± 19	25 ± 6.1

* Plasma ammonia units in µM (mean ± SD). Baseline values are C1D1 predose values. ULN at the labs where these labs were processed ranged from X to X.
**One patient at the 150 mg BID dose level was dose-reduced to 100 mg BID at C1D22 following a dose interruption of 4 days.
***Data not available for all patients at all time points.

Table 10.1-4: Blood Urea Nitrogen Levels by Visit Day*

Dose Level (mg BID)	N	Baseline	C1D8	C1D15	C1D22	C2D1	C2D8
50	6-8***	13 ± 4	14 ± 4	14 ± 4	13 ± 3	11 ± 3	12 ± 3
100	5-8***	17 ± 7	14 ± 4	15 ± 6	15 ± 5	17 ± 6	18 ± 3
150**	3***	13 ± 3	10 ± 1	10 ± 2	11 ± 2	10 ± 0	10 ± 2

* BUN units in mg/dL (mean ± SD). Baseline values are either the C1D1 predose measurement or the last measurement obtained prior to the first dose of INCB001158. JAMA reference range for BUN is 8-23 mg/dL).
**One patient at the 150 mg BID dose level was dose-reduced to 100 mg BID at C1D22 following a dose interruption of 4 days.
*** Data not available for all patients at all time points.

No significant changes in OA were identified in patients enrolled at the 50 or 100 mg BID dose levels (Table 10.1-5). However, 2 of 3 patients enrolled at the 150 mg BID dose level experienced elevations in urinary OA.

Table 10.1-5: Predose Orotic Acid Levels by Visit Day*

Dose Level (mg BID)	N	Baseline	C1D8	C1D15	C1D22	C2D1	C2D8
		Absolute Change (% Change from Baseline)					
50	6-8***	0.8 ± 0.3	0.7 ± 0.2 (-12.5%)	0.5 ± 0.2 (-37.5%)	0.6 ± 0.4 (-25.0%)	0.6 ± 0.5 (-25.0%)	0.6 ± 0.4 (-25.0%)
100	4-8***	0.7 ± 0.3	0.7 ± 0.4 (0.0%)	0.7 ± 0.4 (0.0%)	0.7 ± 0.2 (0.0%)	0.5 ± 0.5 (-28.6%)	0.5 ± 0.3 (-28.6%)
150**	2-3***	0.6 ± 0.3	0.6 ± 0.5 -(0.0%)	4.5 ± 6.2 (650%)	0.5 ± 0.2 (-16.7%)	0.7 ± 0.1 (16.7%)	3.5 ± 5.0 (480%)

*Orotic acid units in µmol OA/mmol creatinine (mean ± SD). Baseline values are C1D1 predose values. Laboratory reference range is 0.2 to 1.5 µmol OA/mmol creatinine.
**One patient at the 150 mg BID dose level was dose-reduced to 100 mg BID at C1D22 following a dose interruption of 4 days.
*** Data not available for all patients at all time points.

In one patient at the 150 mg BID dose level, the fasting predose urinary OA on C1D15 was 11.6 µmol/mmol creatinine (7.7X ULN) and the postdose (non-fasting) level was 47 µmol/mmol creatinine (31.3x ULN). This patient was asymptomatic without any significant changes in ammonia or BUN from baseline and the OA returned to baseline within 2 days of withholding the INCB001158 dose. After dose reduction to 100 mg, the predose OA values were normal after 2 and 3 weeks of additional dosing. However, despite the patient remaining asymptomatic, postdose elevations were noted at these two time points (27.4 and 131.6 µmol/mmol creatinine, respectively), so the patient was dose reduced further to the 50 mg dose level, after which no further elevations were noted. A second patient at the 150 mg dose level had elevated urinary OA predose on C2D8 (9.3 µmol/mmol creatinine; 6.2X ULN). This patient also remained asymptomatic and had no significant changes from baseline in plasma ammonia or BUN. After a 2-day interruption of study drug, the dose was reduced to 100 mg and no subsequent elevations in urinary OA were noted.

In summary, there has been no evidence of clinically significant inhibition of the urea cycle to date. Two patients have had asymptomatic elevations in urinary OA, a sensitive biomarker of

hepatic urea cycle inhibition, that were not associated with changes in plasma ammonia or BUN, but were dose reduced based on a protocol defined urinary OA threshold of 5X ULN. Both patients were able to continue on study drug at the reduced dose without subsequent elevations in OA.

10.2 Rationale for Study Design

10.2.1 Rationale for Starting Dose

The starting dose for monotherapy dose escalation will be 50 mg BID. This dose was selected based on the results of the GLP-compliant preclinical toxicology studies conducted in rats and cynomolgus monkeys. This dose is approximately one-thirty-sixth ($1/36^{th}$) of the No Observable Adverse Effect Level (NOAEL) and one-forty-eight ($1/48^{th}$) of the highest non-severely toxic dose (HNSTD) in monkeys. Monkeys were selected as the most appropriate species for starting dose selection based on 1) the greater genetic and, presumably, physiological similarity to humans and 2) the fact that they were more sensitive (as defined by plasma exposure associated with toxicity) to the toxic effects of INCB001158. A conservative starting dose was selected relative to the FDA S9 Guidance of one sixth ($1/6^{th}$) the HNSTD in non-rodent species; the bioavailability in monkeys (20%) was lower than in other species tested and plasma exposures could under-represent exposures that will be achieved in humans.

This study will also evaluate the safety, tolerability, and efficacy of INCB001158 in combination with the FDA-approved anti-PD-1 agent pembrolizumab. The decision to open the anti-PD-1 combination dose escalation is dependent on achieving either the target exposure that will lead to continuous inhibition of extracellular arginase 1 by > 90% (C_{min} of $\geq$ 1μM) and/or an elevation of plasma arginine to levels that correlated with *in vivo* activity in preclinical models (2.5-fold elevation from baseline in plasma arginine). The starting dose of INCB001158 that will be used in combination with full dose pembrolizumab will be 50 mg BID, which is 2 dose levels below the recommended monotherapy Phase 2 dose of 100 mg BID identified in Part 1a of this study.

10.2.2 Rationale for Dose Escalation Strategy

The dose escalation for this study will follow standard Modified Fibonacci dose escalation schedule for both monotherapy and the pembrolizumab combination (see Table 5.1-1). As described in Section 5.1, the selection of this dose escalation schedule was guided by the

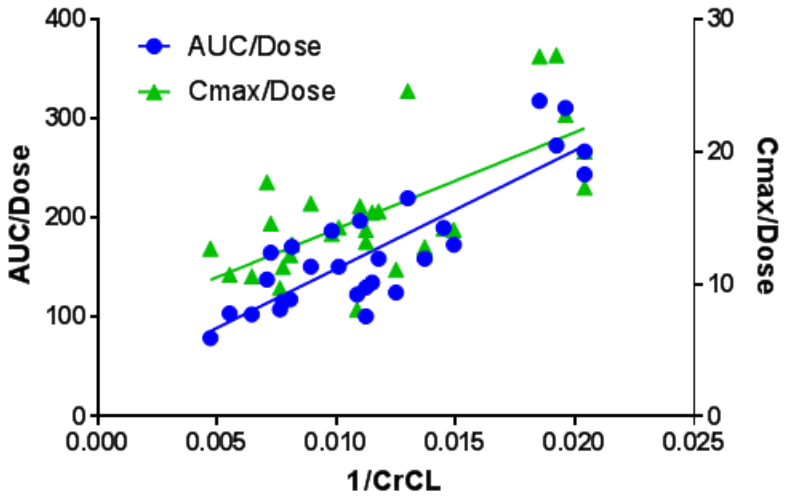
safety/tolerability of INCB001158 as well as the PK and pharmacodynamic data generated in the first two dose levels of the dose escalation.

10.2.2.1 Rationale for Dose in Patients with Moderately Impaired Renal Function

A considerable proportion of patients with the tumor types being evaluated in this study have moderately impaired renal function (defined as CrCl 30-49 mL/min) due to multiple factors including underlying disease, prior treatments and procedures, or baseline chronic renal insufficiency. Prior to Protocol Amendment 2-US 2, such patients were excluded from this study, even though they may well benefit from INCB001158 treatment. However, since the primary mechanism of elimination of INCB001158 is thought to be renal clearance, patients with impaired renal function may need a lower dose of INCB001158 to achieve exposure similar to patients with normal renal function. To test this hypothesis, population PK modeling was used to determine and evaluate a reduced dose of INCB001158 in patients with moderately impaired renal function defined as CrCl 30-49 mL/min as calculated by the Cockcroft-Gault formula.
The safety of INCB001158 alone and in combination with pembrolizumab has been well-characterized in the dose escalation Parts 1a and 1b (refer to the iIB). The MTD was not reached across 4 dose levels in monotherapy (50, 75, 100, and 150 mg BID) and 3 dose levels in combination with pembrolizumab (50, 75, and 100 mg BID). Pharmacokinetic data for INCB001158 in combination with pembrolizumab were similar to that of INCB001158 monotherapy, which was expected, since pembrolizumab was not predicted to have any effect on INCB001158 exposure. Additionally, moderate renal impairment (GFR < 60 and ≥ mL/min/1.73 m^2) has no clinically important effect on the clearance of pembrolizumab (refer to the pIB). The minimum target for continuous exposure of INCB001158 based on preclinical efficacy data is approximately 1.0 μM. As monotherapy, INCB001158 had steady-state C_{min} (trough concentration) well above this target at all dose levels evaluated (50, 75, 100, and 150 mg BID), indicating strong target inhibition. Pharmacokinetic data from the 50 and 75 mg BID dose levels in combination dose escalation also showed steady state C_{min} > 1 μM with no differences in the overall exposure range between patients in monotherapy and combination at steady state.
The overall safety profile across 3 INCB001158 dose levels evaluated in combination with pembrolizumab was favorable, with no DLTs or Grade 3 treatment-related AEs at the maximum

dose level of INCB001158 100 mg BID. INCB001158 PK and PD in combination with pembrolizumab were similar to that of INCB001158 monotherapy, with similar exposures at equivalent doses and strong target inhibition, as indicated by increases in plasma arginine. The RP2D for INCB001158 alone and in combination with pembrolizumab was declared as 100 mg BID. Therefore, evaluation of INCB001158 in patients with moderate renal impairment will be done in combination with pembrolizumab, since pembrolizumab did not have any effect on INCB001158 exposure.

In order to determine the appropriate dose in patients with moderate renal impairment (defined as CrCl 30-49 mL/min), population PK modeling was performed, incorporating full PK data from patients enrolled to the already completed dose escalation parts in patients with CrCl $\geq$ 50 mL/min. The PK data showed that INCB001158 AUC, C_{max}, and half-life inversely correlated with CrCl across all tested doses, as expected (Figure 10.2-1). Based on the strongly inverse linear relationship between CrCl and AUC, extrapolation of the data to CrCl values below 50 mL/min indicated that a dose of 50 mg BID in patients with CrCl 30 to 49 mL/min predicted INCB001158 AUC values to fall within the known safe exposure range corresponding to doses at or below the established RP2D of 100 mg BID (Table 10.2-1).



	AUC/Dose	Cmax/Dose
R square	0.7262	0.4597

Figure 10.2-1: Plot of INCB001158 CrCl versus AUC or C_{max} in patients treated with INCB001158 alone or in combination with pembrolizumab, from Parts 1a and 1b.

Table 10.2-1: Projected Human INCB001158 Steady-State AUCs During 1 Dose Interval at 50, 75, 100, and 150 mg for Patients with Different Creatinine Clearances Ranging from 15 to 200 mL/min

CrCl (mL/min)	AUC (50 mg)	AUC (75 mg)	AUC (100 mg)	AUC (150 mg)
15	41,210	61,815	82,420	123,630
20	31,283	46,924	62,565	93,848
30	21,355	32,033	42,710	64,065
40	16,391	24,587	32,783	49,174
50	13,413	20,120	26,826	40,239
60	11,428	17,141	22,855	34,283
70	10,009	15,014	20,019	30,028
80	8,946	13,418	17,891	26,837
90	8,118	12,178	16,237	24,355
100	7,457	11,185	14,913	22,370
110	6,915	10,373	13,830	20,745
120	6,464	9,696	12,928	19,391
130	6,082	9,123	12,164	18,246
140	5,755	8,632	11,509	17,264
150	5,471	8,207	10,942	16,413
200	4,478	6,717	8,957	13,435

10.2.3 Rationale for Patient Populations

10.2.3.1 Monotherapy

This is a Phase 1 study evaluating the safety and tolerability of INCB001158 in cancer patients. Since it unknown whether INCB001158 is efficacious, only patients with metastatic disease or advanced disease that is not amenable to local therapy will be enrolled. Further, only patients for whom there are no available therapies that have been shown to provide clinical benefit (e.g., overall survival benefit) will be enrolled. In order to maximize the potential for identifying clinical benefit, the expansion cohorts will enroll tumor types that have been previously shown to have significant infiltration with MDSCs and/or $Arg1^+$ cells. Two monotherapy expansion cohorts identify specific patient populations, NSCLC (Part 2a) and CRC (Part 2b), both of which have high infiltration with $Arg1^+$ cells (see Section 10.1.2) and have a large unmet need. An additional expansion cohort (Part 2c) allows a broader group of patient to be enrolled consisting of tumor types that also have high infiltration of $Arg1^+$ granulocytic MDSCs and PMNs (by

internal data or published accounts), in order to identify a preliminary signal of activity that can be subsequently followed up with a dedicated expansion cohort (or a separate clinical study).

10.2.3.2 Combination with Anti-PD-1 (Pembrolizumab)

As of the date when this amendment was authored, the anti-PD-1 agent pembrolizumab has been approved for the treatment of metastatic melanoma, NSCLC, SCCHN, urothelial carcinoma, and solid tumors that are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). Despite the impressive activity observed for this and other anti-PD-1/PD-L1 agents, a majority of patients with these diseases do not achieve an objective response to these agents and there is a recognized need for combination agents to either expand the population that benefits or amplifies the activity that they provide (Melero 2015).

Eight patient populations are eligible to enroll into expansion cohorts, including advanced/metastatic NSCLC (Part 3a), advanced/metastatic melanoma (Part 3b) advanced/metastatic UCC (Part 3c), advanced/metastatic MSI-H CRC (Part 3d), advanced/metastatic MSS CRC (Part 3e), advanced/metastatic gastric /GEJ (Part 3f), advanced/metastatic SCCHN (Part 3g), and advanced/metastatic malignant pleural mesothelioma (Part 3h). Since a primary objective of the expansion cohorts is to identify a signal of clinical activity of INCB001158 in combination with pembrolizumab, some of these cohorts will enroll patients that are unlikely to respond to monotherapy pembrolizumab because they either 1) had disease progression (even after an objective response) in the immediate prior line of therapy, OR 2) had prolonged stable disease (≥ 24 weeks) in the immediate prior line of therapy. The attribution of evidence of clinical activity (e.g., objective responses) to INCB001158 in this population can be made more confidently given the low likelihood of a response to monotherapy anti-PD-1 therapy. In addition to these "add-on" cohorts, other cohorts will enroll patients that have never received prior checkpoint inhibitor therapy. There are generally two reasons to include these cohorts: 1) to identify activity in patient populations that are known to be unresponsive to PD-1 therapy (e.g., MSS CRC) and 2) to identify activity of the INCB001158/pembrolizumab combination that could be missed in pembrolizumab-refractory patients.

All expansion cohorts target tumor types that have a significant proportion of patients with Arg+ infiltrating cells within tumor samples (as presented in Section 10.1) and/or elevated plasma arginase (along with depleted plasma arginine) which may contribute to immune suppression.

11.0 PROCEDURES

All patients must sign an IRB/IEC-approved informed consent prior to starting any protocol-specific procedures, including screening procedures. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. Patients must also meet the inclusion and exclusion criteria to be enrolled in the study.

11.1 Screening Period

11.1.1 Prior Treatment

Reasonable efforts will be made during the screening period to determine all prior therapeutic treatments received by the patient. All previous cancer treatments, including systemic therapies, radiation, and/or surgical procedures, should be recorded on the patients' electronic case report forms (eCRFs).

For some patients progressing on pembrolizumab in Parts 3a, 3b, 3c, and 3d, computerized tomography (CT) or magnetic resonance imaging (MRI) scans and/ or radiology reports may be requested for tumor evaluations during the course of prior pembrolizumab or other anti-PD-1 therapy in order to document the status of stable disease and/or progressive disease.

11.1.2 Concomitant Treatment

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor, and the patient.

11.1.2.1 Acceptable Concomitant Medications

Concomitant treatment with other therapies is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study treatments. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an adverse event), the treatment must be recorded on the appropriate eCRF, including the reason for treatment, name of the drug, dosage, route, and start and stop dates of administration.

For patients receiving INCB001158 in combination with pembrolizumab (Parts 1b and 3): In patients that are currently receiving pembrolizumab (Parts 3a, 3b, 3c, and 3d) as part of their prior line of therapy, pembrolizumab should be administered continuously, if possible (i.e., there is no need to discontinue or pause pembrolizumab dosing).

11.1.2.2 Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational therapeutic agents other than the study treatments, INCB001158 and pembrolizumab
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with Sponsor. The patient must have clear measurable disease outside the radiated field.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
  - Note: Inhaled steroids are allowed for management of asthma.
- Except for erythropoietin or darbepoetin alpha (Aranesp®), use of growth factors (i.e., G-CSF, GM-CSF, etc.) is not permitted in the first treatment cycle unless the patient 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 2002; Wadzinski 2007).
- Concomitant treatment with allopurinol or other xanthine oxidase inhibitors is not allowed during the monotherapy dose escalation of INCB001158 (Part 1a). Xanthine oxidase inhibitors cause an accumulation of OA in the urine, which would confound the assessment of safety in these patients.

11.1.3 Screening Evaluation

The following screening assessments must be performed **within 21 days** before study treatment administration on C1D1 according to the Attachment 1 [with the exception of imaging (CT/MRI); scans performed within 28 days of study treatment administration on C1D1 are acceptable]. Procedures listed below that are performed as part of the normal standard of care and within 21 days prior to C1D1 may be used for screening purposes:

- Sign and date an IRB/IEC-approved Informed Consent Form (ICF) before any study-specific (i.e., non-standard of care) screening procedures are performed
- Demographic information including date of birth, sex, and ethnic origin
- Medical history including review of prior cancer treatments
- Review of concomitant medications
- ECOG performance evaluation
- Complete physical examination including weight (kg) and height (cm)
- Vital signs and weight

- Standard duplicate 12-lead ECG with corrected QT interval by Fridericia's Formula (QTcF)
- Clinical laboratory evaluation (hematology, coagulation, serum chemistry, and urinalysis); see Attachment 3.
- Serum or urine pregnancy test. This is only required for females of child-bearing potential and must be negative within 3 days prior to C1D1.
- Radiographic evaluation of tumor burden (e.g., diagnostic CT or MRI). Scans performed within 28 days prior to C1D1 will be accepted and do not need to be repeated. See Attachment 1 and Attachment 2. Note: For this study, evaluation of tumor burden must be based on a diagnostic CT or MRI. 1-3 scans prior to the start of study and redacted scan reports will also be collected and sent to a central reader for exploratory evaluation.
- Fresh tumor biopsies: Predose tumor biopsies are required for some patients enrolled in this study. If fresh biopsies are not available at predose, archival tumor tissues, if available, collected within 3 months prior to screening are required. See Table 11.8-1 for additional details. Coagulation tests must be performed and evaluated within 24 hr prior to all biopsy procedures.

A patient who meets all of the inclusion criteria will enter the study. Screen failures will be marked in the electronic data capture (EDC) system.

11.2 Study Procedures

Screening physical exam, urinalysis, serum chemistry, coagulation, and hematology that occurred *within 3 days* prior to C1D1 do not need to be repeated unless a clinically significant change in the interim is suspected.

Patients in Part 1A should be instructed to fast overnight (> 8 hours prior to their clinic visit) on Cycle 1:D1, D8, D15, and D22, C2D1, C2D8, and on Day 1 of all subsequent cycles. Patients in Parts 1B and 3 should be instructed to fast overnight (> 8 hours prior to their clinic visit) on Cycle 1: D1, D8 and D15, and on Day 1 of all subsequent cycles. Patients in Part 2 should be instructed to fast overnight (> 8 hours prior to their visit) on C1D1, D8, D15, and D22, and on Day 1 of all subsequent cycles. All patients on study should be instructed to void their bladders upon waking.

On these days, patients will undergo the pre-dose assessments, and receive the INCB001158 dose in the clinic. Recommendations on meals can be found in the Meal Recommendations section of the Study Reference Manual. The evening dose will be self-administered by the patient after all post-dose activities have been completed.

A detailed breakdown of the visit schedule and sample collection time points can be found in Attachments 1A and 1B.

11.2.1 Cycle 1

During Cycle 1, patients will undergo the following procedures:

- AE Monitoring
- Recording of concomitant medications
- Vital signs and weight
- Symptom-directed physical exam
- ECOG Performance status evaluation
- Clinical laboratory evaluation (hematology, coagulation, serum chemistry, ammonia, and urinalysis)
- Plasma sample collection for PK [redacted] analysis (Attachment 2)
- [redacted]
- Urine sample for measurement of urine orotic acid levels
- Duplicate ECG with QTcF between 2-4 hr post-dose
- Administration of INCB001158.
- Part 1b and Part 3 patients will also receive pembrolizumab administration in the clinic on Day 1 of each 21-day cycle.

11.2.1.1 Part 1a and 1c Only: Cycle 1 Day 1 and Day 15

Patients in Parts 1a and 1c will have a full pharmacokinetic (PK) and pharmacodynamic evaluation on Cycle 1 Day 1 following a single dose of INCB001158. Dosing on the BID schedule will commence on Cycle 1 Day 2.

On Cycle 1 Day 1 and Day 15, patients will arrive at the clinic in a fasted state and will take their assigned dose of INCB001158 after predose assessments have been collected. Blood for PK and pharmacodynamic evaluation will be taken according to the schedule in Attachment 2. Once predose assessments have been completed, patients will take INCB001158 with a full glass of

water. Patients can eat breakfast 2 hours after taking INCB001158. **In Part 1a and 1c only, no second dose of drug will be provided on Cycle 1 Day 1.**

11.2.2 Cycle 2 and All Subsequent Cycles

A detailed breakdown of the visit schedule and sample collection time points for Cycle 2 and subsequent cycles can be found in Attachments 1 and 2. Patients will return to the clinic and undergo the following procedures:

- AE monitoring
- Recording of concomitant medications
- Vital signs and weight
- Symptom-directed physical exam
- Clinical laboratory values (hematology, coagulation, serum chemistry, ammonia, and urinalysis)
- Urine sample for measurement of urine orotic acid levels
- ECOG performance status evaluation
- [redacted]
- [redacted]
- Administration of INCB001158.
- Part 1b and Part 3 patients will also receive pembrolizumab administration in the clinic on Days 1 of each 21-day cycle.
- A postdose tumor biopsy will be obtained from all patients who have consented to the tumor biopsy and for patients enrolled in the backfill cohorts. Coagulation tests must be performed and evaluated within 24 hr prior to all biopsy procedures.
- Radiographic evaluation (e.g., diagnostic CT or MRI) of tumor burden will occur approximately every 8 weeks (Parts 1a and 2) or every 9 weeks (Parts 1b and 3). The same method of evaluation should be used throughout the course of the study. The scans and redacted reports will be collected and sent to a central reader for exploratory evaluation.

11.2.2.1 Part 1a Only: Cycle 2 Days 1-8

Patients in Part 1a will participate in a food effect assessment. During Cycle 2 Day 1 through Day 7, patients will be taking their INCB001158 dose with food. Recommendations on meals

can be found in the Meal Recommendations section of the Study Reference Manual. On Cycle 2 Day 8, patients will arrive at the clinic in a fasted state and will be provided breakfast in the clinic. Patients will take their assigned dose of INCB001158 immediately after eating breakfast. Blood for PK and pharmacodynamic evaluation will be taken over 8 hours, according to the schedule in Attachment 2.

11.2.2.2 Part 2d Only

[redacted]

11.3 Other Schedules and Procedures

For Study Parts 1a and 2, radiographic evaluation of tumor burden (e.g., diagnostic CT/MRI) will occur at Screening and approximately every 8 weeks after study initiation, or more frequently as clinically indicated.

For Study Parts 1b and 3, radiographic evaluation of tumor burden (e.g., diagnostic CT/MRI) will occur at Screening and approximately every 9 weeks after study initiation, or more frequently as clinically indicated.

Optional tumor biopsies may be obtained at variable time points as advised by the Investigator and Medical Monitor and agreed by the patient.

During study treatment, urine pregnancy tests will be performed locally as medically indicated, or per country-specific requirement. If a urine pregnancy test is positive, then the results should be confirmed with a serum pregnancy test.

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

11.4 End of Treatment (EOT)

The End of Treatment (EOT) visit must occur within 28 days of treatment discontinuation and prior to initiation of any new anti-cancer therapy/regimen. All patients discontinuing study treatment for any reason should undergo the following EOT procedures:

- AE monitoring
- Recording of concomitant medications
- Vital signs and weight
- Complete physical examination
- ECOG performance status evaluation
- Clinical laboratory values (hematology, coagulation, serum chemistry and urinalysis)
- Urine pregnancy test for women of child-bearing potential
- Duplicate 12-lead ECG with QTcF
- Radiographic evaluation (e.g., diagnostic CT or MRI) of tumor burden. Patients who discontinue from study due to objective findings of progressive disease during an on-treatment evaluation do not need to have repeat scans. CT or MRI is required for all patients who have not had at least 1 post-baseline image.

11.5 Follow-Up

11.5.1 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 patients) and 90 to 97 days (Parts 1b and 3 only) after the final dose of study treatments.

Adverse events (all patients) and SAEs (Parts 1a and 2 only) must be reported up until the date of the 30-day follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

Serious adverse events (Parts 1b and 3 only) must be reported up until the date of the 90-day follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

Reasonable efforts should be made to have the patient return for the follow-up visits and report any AEs that may occur during this period. If the patient cannot return to the site for the safety follow-up visit (eg, lives far away), the patient should be contacted by telephone for assessment of AEs and SAEs. Sites should document this contact in the source.

If a patient is scheduled to begin a new anticancer therapy before the end of the 90-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 patient will have completed the follow-up period.

11.5.2 Disease Status Follow-Up

Patients who discontinue study treatment for reasons other than disease progression will continue to be assessed for their disease status during the follow-up phase and should continue to have tumor assessments every 8 weeks (monotherapy) or 9 weeks (pembrolizumab combination) until a new cancer therapy is started, disease progression, death, withdrawal of consent, or the end of the study.

11.6 Screen Failures

Patients who sign an informed consent form, are not assigned to a treatment, and do not receive either INCB001158 or pembrolizumab are defined as screen failures. For all screen failures, the Investigator will enter the screening number, patient initials, and reason(s) for screen failure into the electronic data capture (EDC) system. These data will also be retained in the Investigator's study files and can be printed by the site in log format at the end of the study.

11.7 Safety Evaluation

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, duplicate 12-lead ECGs (including QTcF intervals), and clinical laboratory test results.

More frequent safety evaluations may be performed if clinically indicated or at the discretion of the Investigator. All AEs will be recorded from the time the patient receives the first dose of study treatment up to 28 days after the last dose.

11.7.1 Physical Examination

Complete physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner) at Screening and End of Treatment. Symptom-directed physical

exam are required as clinically indicated. Please refer to the Schedule of Study Assessments (Attachment 1).

11.7.2 Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) will be obtained in the sitting position. All patients should be sitting for 3-5 min prior to obtaining vital signs. Orthostatic vital signs will be measured on Cycle 1 days 1 and 15 at predose and 4 hrs post dose during the dose escalation (Part 1a). Due to the absence of an effect on orthostatic vital signs, orthostatic vital signs will only be required for patients enrolled in Part 1a. If effects on blood pressure are eventually noted, additional orthostatic vital sign monitoring will be re-introduced in Parts 1b, 2 and 3.

In Parts 1b and 3, on the day of pembrolizumab infusion, vital signs will be obtained pre-infusion, 15 minutes after the start of the infusion, at the end of the infusion, and 15 minutes after completion of the infusion. Vital signs should be collected ± 5 minutes from the scheduled times noted above.

11.7.3 Electrocardiograms

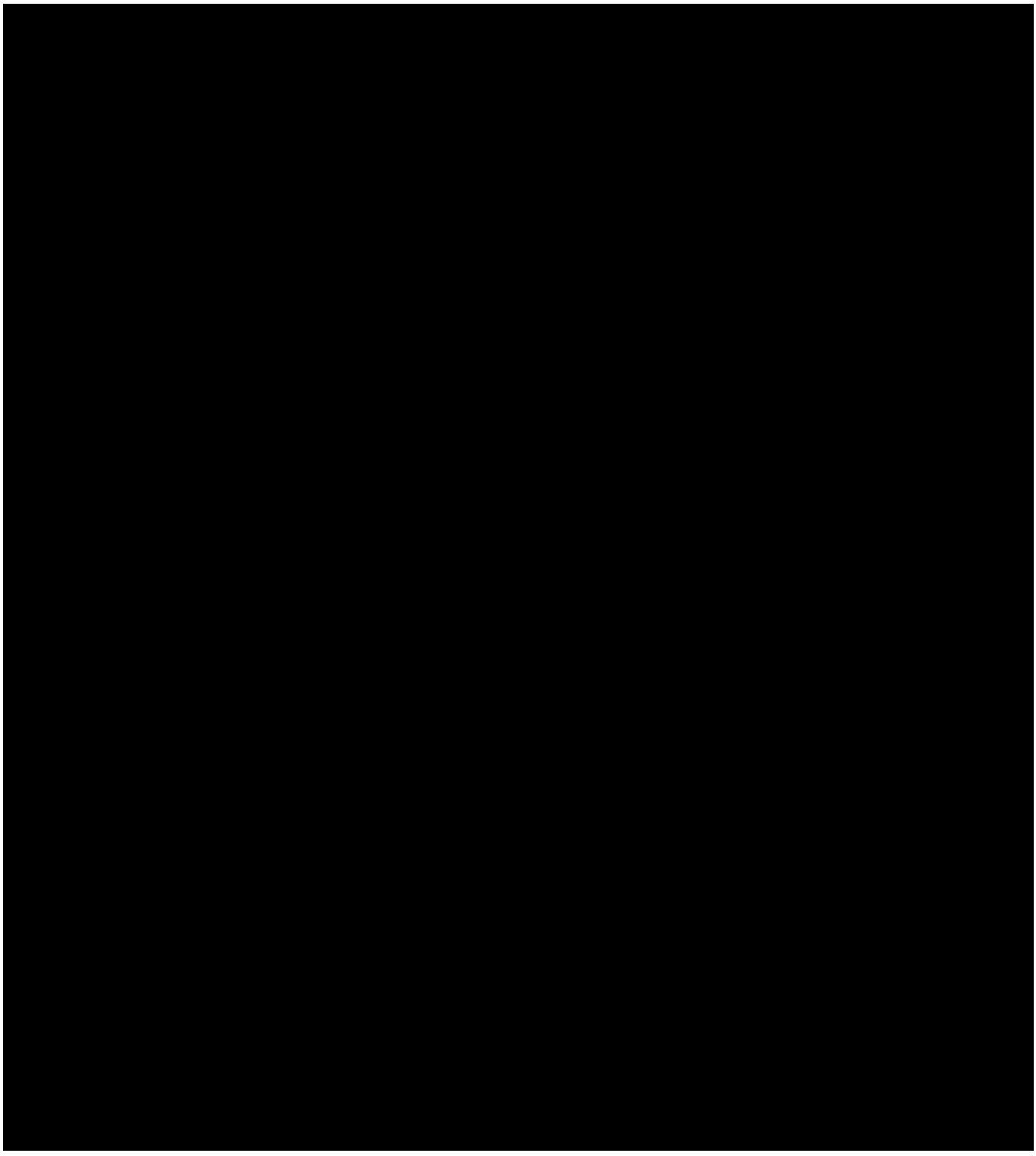
Patients should rest in the supine position for at least 5 min before each 12-lead ECG recording is started. Duplicate ECG recordings must be performed using a standard, high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements. The average of values will used for Inclusion/Exclusion and AE reporting purposes.

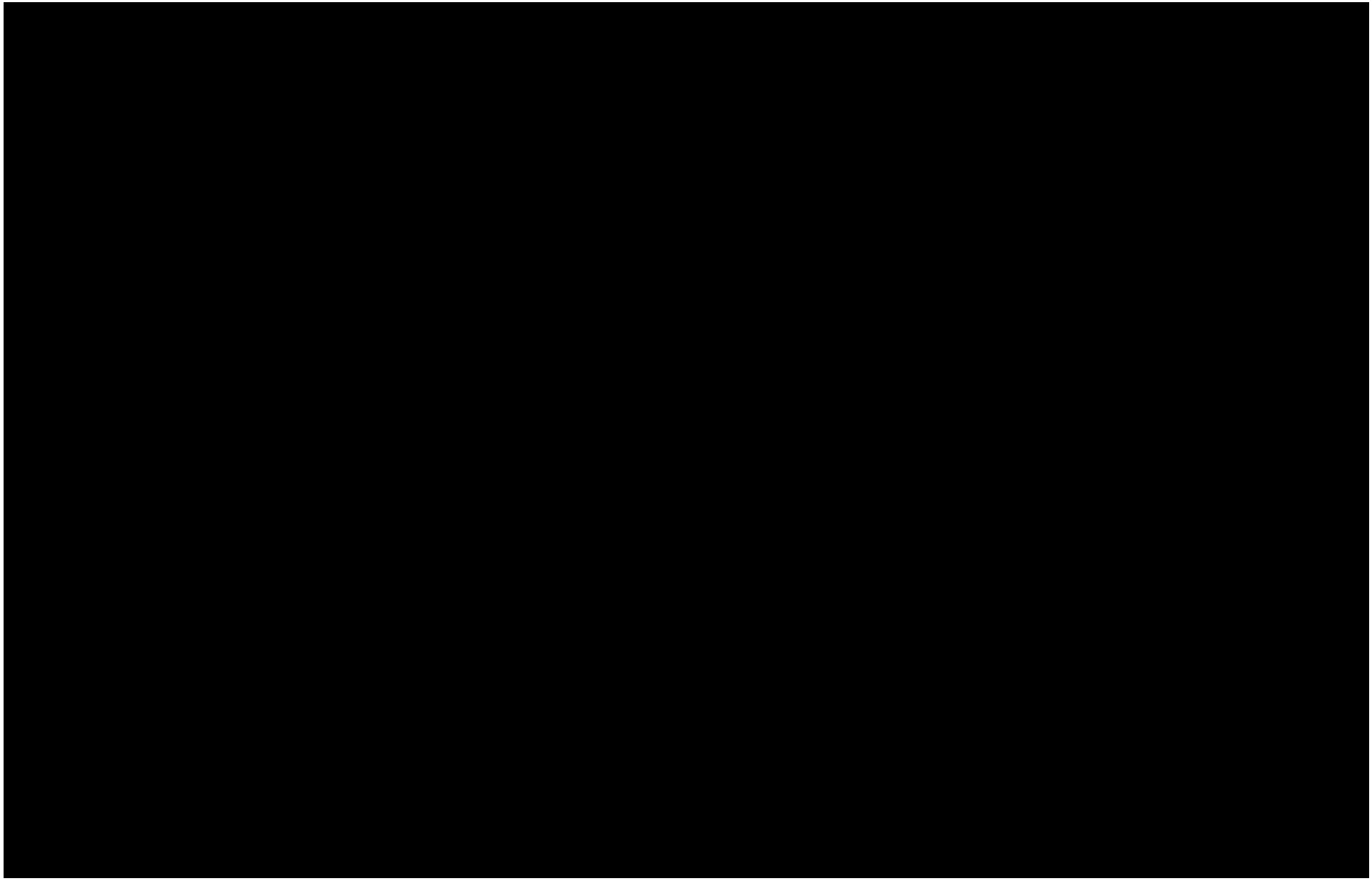
For safety monitoring purposes, the ECG must be reviewed, signed, and dated promptly by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate eCRF. The Investigator is responsible for providing the interpretation of all ECGs. The results will include heart rate (HR), R-R interval (RR), PR interval, QRS interval, QT interval, and QTcF interval. The corrected QT interval will be corrected for respiratory rate according to the following formula:

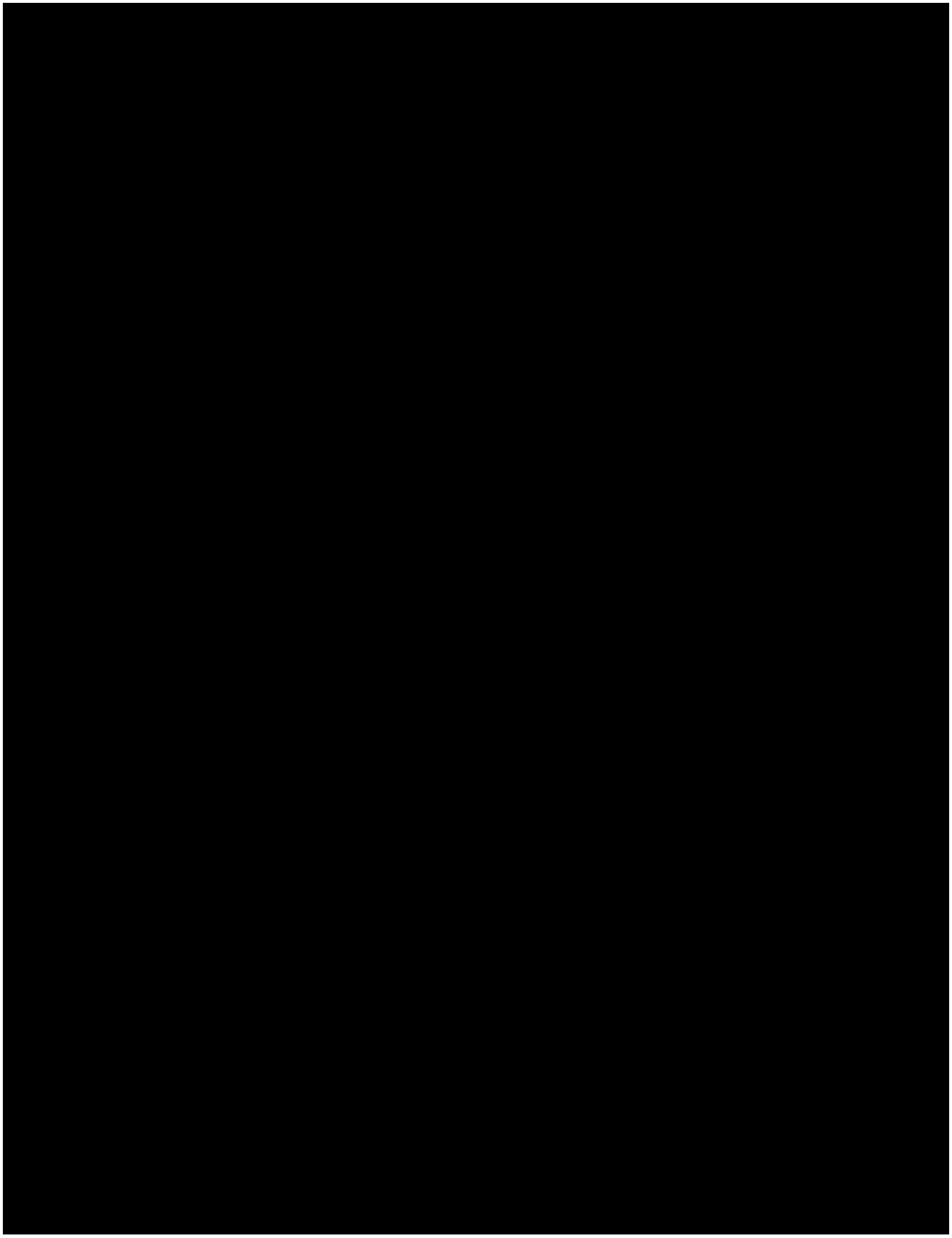
$$\text{Fridericia's formula: } QTcF = QT/RR^{0.33}$$

11.7.4 Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the Schedule of Study Assessment (Attachment 1A and 1B).







[redacted]

11.9 Pharmacokinetic Evaluation

11.9.1 Blood Collection

Plasma PK samples will be used to measure concentrations of INCB001158. [redacted] Blood samples for PK analysis should be collected at the requested time (Attachment 2). The exact actual time of collection must be noted in the source documents and eCRFs.

11.9.2 Intensive PK Sampling

Patients enrolled in Parts 1a and 1c will participate in the intensive PK sampling schedule. Plasma PK samples will be collected on Cycle 1, Days 1 and 15 at pre-dose and post-dose at 0.5, 1, 2, 4, 6, 8, and 12 hr.

In addition, patients assigned to the intensive PK group in Part 1a only will participate in an assessment of the effect of food on INCB001158 PK. On Cycle 2 Days 1 through 7, patients will take their INCB001158 doses immediately following a meal. On Cycle 2, Day 8, patients will arrive at the clinic fasted. The pre-dose assessments will be completed and the patient will take INCB001158 immediately after eating a modest breakfast. PK samples will be drawn at 0.5, 1, 2, 4, 6, and 8 hr after taking the morning dose. The evening dose will be taken per protocol 12 hr after the morning dose. Refer to the PK [redacted] Sampling Schedule (Attachment 2) for time points and blood volumes to be collected.

11.9.3 Sparse PK Sampling

Patients that are not part of the intensive PK group will have PK samples collected on Cycle 1 Days 1 and 15, and on Day 1 of Cycles 2, 3, and 4. Refer to the PK [redacted] Sampling Schedule (Attachment 2) for time points and blood volumes to be collected.

[redacted]

11.9.5 Bioanalytical Methodology

The plasma samples will be analyzed for INCB001158 by using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method of appropriate specificity and sensitivity according to Good Laboratory Practices (GLPs). PK samples taken on Cycle 1 Day 1 in Part 1a will be analyzed and results will be available prior to enrollment of patients on the subsequent dose escalation cohort.

12.0 POTENTIAL TOXICITIES, DOSE MODIFICATION AND MANAGEMENT OF TOXICITIES

12.1 Potential Toxicities

12.1.1 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 ~1000-fold more potent at inhibition of extracellular arginase 1 than intracellular arginase 1 that is engaged in the urea cycle, primarily due to poor penetration of INCB001158 across cell membranes and the "enzymatic channeling" phenomenon (Cheung 1989) that restricts access of exogenous arginine or INCB001158 to urea cycle enzymes. Arginase 2 is primarily expressed in the mitochondria of many other tissues, including the gut and in kidney. The functions of Arginase 2 in these tissues include regulation of systemic arginine concentration, regulation of the production of downstream products (e.g., proline, polyamines) and regulation of arginine availability for nitric oxide 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 1996, Bode-Böger 1998).

The results of the GLP-compliant rat and monkey toxicity studies are presented in Section 10.1.8. The low- and mid-dose levels were well tolerated with no adverse findings and the mid-dose being considered the NOAEL 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 (e.g., elevated plasma arginine) with no significant toxicities noted.

Potential Urea Cycle Toxicity

As detailed in Section 10.1.8, 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 or 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 OA levels. Of particular interest, urinary OA was elevated by > 1,000-fold in rats at the high dose following a single dose, prior to any signs of toxicity. Smaller elevations in urinary OA were also measured in some animals at the well-tolerated mid-dose level.

Several measures of potential toxicity related to urea cycle inhibition will be evaluated in this study (see Attachments 1 and 2). In particular, urinary OA, plasma (venous) ammonia and BUN will be measured on Day 1 and at regular intervals in the dose escalation portion of the study (Part 1a).

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 OA. The elevated OA 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 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. Since 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. Since it is also effected by other factors (e.g., 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.

Immune-related AEs (irAEs)

It is not known to what extent arginine depletion is operative in normal tissues or in non-cancer inflammatory states. However, since 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 (e.g., 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 treatment for events of moderate or worse severity (Grade ≥ 2) and 2) the use of immunosuppressive corticosteroids for more severe irAEs (Grade ≥ 3) or prolonged irAEs (lasting > two weeks with minimal or no improvement despite withholding study treatment). High dose steroids may be used for particularly severe irAEs or irAEs that fail to respond to initial oral steroids within 3-4 days. Non-steroid immunosuppressive agents may also be employed for steroid-refractory irAEs.

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 nitric oxide (NO) in response to the increased availability of circulating arginine, a key substrate for the NO-producing Nitric Oxide Synthase (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 1996, Bode-Böger 1998) There has been no preclinical evidence of altered hemodynamic status in any preclinical studies of INCB001158. In order to identify modest changes in hemodynamic status, frequent monitoring of blood pressure and careful assessment of orthostatic hypotension will be monitored in addition to standard vital signs as part of this study.

12.1.2 Pembrolizumab (Patients Enrolled in Parts 1b, 1c, and 3)

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure.
The safety profile of pembrolizumab is fully described in the pembrolizumab Label/Investigator's Brochure and primarily consists of immune-related adverse events (ir-AEs) due to activation and proliferation of T-cells. Ir-AEs 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). The management of these toxicities is described in the pembrolizumab Label/Investigator's Brochure but generally includes holding drug for moderate (Grade 2) toxicities and using systemic immunosuppression for severe (Grade 3/4) or prolonged moderate (> 1 week) toxicities. Additional immunosuppression (e.g., anti-TNFα therapy, infliximab) may be used if IV steroids are ineffective.

12.1.2.1 INCB001158 + Pembrolizumab Combination

The safety and tolerability of INCB001158 + pembrolizumab is not known. A primary objective of the current study is to evaluate the safety and tolerability of the combination of pembrolizumab and INCB001158. Preclinical studies of the combination of an anti-PD-1 agent and INCB001158 have been performed in mice for the purpose of evaluating the anti-tumor activity of the combination. In these experiments, the combination of anti-PD-1 and INCB001158 appeared to be well tolerated, but an extensive safety evaluation was not performed.

12.1.3 Dose Modifications and Toxicity Management

The expected toxicity risks for INCB001158 based on preclinical toxicity study data are summarized above. In general, management of AEs related to INCB001158 includes

withholding the medication for moderate to severe toxicities and providing the appropriate supportive care.

The safety and tolerability profile of pembrolizumab is well defined and outlined in the pembrolizumab Label/Investigator's Brochure. Ir-AEs are defined as those that occur while receiving pembrolizumab, require immunosuppression and have no clear alternate etiology. Guidelines for the management of ir-AEs and study treatment dosing are provided below. In general, for moderate to severe ir-AEs, pembrolizumab should be withheld or permanently discontinued and, depending on the nature of the AE, it should be managed with high-dose corticosteroids and hormone-replacement therapy, if necessary. Upon improvement to Grade 1 or less, a corticosteroid taper should be initiated and continued over at least 1 month. Restarting pembrolizumab may be considered after completion of corticosteroid taper based on the severity of the event. In some cases, the natural history of AEs associated with immunotherapy can differ from and be more severe than AEs caused by agents belonging to other therapeutic classes. Early recognition and management may mitigate severe toxicity. Evaluation and management guidelines for the following types of ir-AEs are provided in the pembrolizumab Label/Investigator's Brochure: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, rash and encephalitis.

For patients in the Dose Escalation Phase, dose reductions of INCB001158 will be permitted during Cycle 1 (first 28 days) *only if a patient experiences DLT or a toxicity that may herald a DLT*. If a patient 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 and pembrolizumab therapy can be continued. Upon recovery, patients may restart at one INCB001158 dose level lower. Patients who do not recover within 28 days will not be eligible for resumption of study treatment without approval from the Medical Monitor. After Cycle 1, dose reductions or interruptions for adverse events may take place at any time at the discretion of the Principal Investigator in consultation with the Medical Monitor.

12.1.3.1 Dose Modification Guidelines

Patients will be monitored continuously for AEs while on study. Treatment modifications (e.g., dose delay) will be based on specific laboratory and AE criteria.

INCB001158: Guidelines for AE management and dose modifications of INCB001158 due to AEs are provided in Table 12.1-1. These guidelines are based on the clinical experience with

INCB001158 to date. These guidelines are intended primarily for toxicities that are not easily managed with routine supportive care. For example, alopecia does not require dose modification, nor does Grade 2 nausea/vomiting that is easily managed with anti-emetics.
INCB001158/pembrolizumab combination: Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs are reversible and can be managed with interruptions of pembrolizumab and administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 12.1-2. Management of irAES occurring on combination therapy should follow dose interruption/modification guidelines for INCB001158 and pembrolizumab outlined in Tables 12.1-1 and 12.1-2, respectively.
These parameters are only guidelines and are not intended to supersede the clinical judgment of the treating physician. Investigators should err on the side of caution in the setting of potential ir-AEs. Investigators should contact the Medical Monitor if 1) a dose modification is planned, 2) systemic immunosuppression is required (NB: if immediate systemic immunosuppression is required, please DO NOT delay the start of immunosuppressive therapy in order to speak with the Medical Monitor), or 3) there is a preference to deviate from the guidelines for the management of AEs or dose modifications. Holding of the study treatment and study discontinuation for both non-hematological and hematological toxicities will be based on the Principal Investigator's judgment following discussion with the Medical Monitor.

12.1.3.2 Resumption of Study Treatment

For both INCB001158 and pembrolizumab, treatment may be delayed for up to 4 weeks from the last dose. Delays longer than 4 weeks are allowed only in cases where a prolonged steroid taper is required to manage drug-related AEs or, in some cases, if the delay was due to a

non-drug-related cause. Prior to re-initiating treatment in a patient with a dosing interruption lasting > 4 weeks, the Medical Monitor must be consulted. Treatment compliance will be monitored by drug accountability as well as the patient's medical record and eCRF.

Upon withholding study treatments for adverse events, the study treatments may be restarted when the AE has returned to ≤ Grade 1. For patients that require a steroid taper, pembrolizumab should not be restarted until the steroid taper is complete. In cases in which a particular toxicity is clearly related to only one of the two study treatments, the study treatment that is not involved in causing the AE may be restarted prior to a return to ≤ Grade 1. If INCB001158 is restarted after permanent discontinuation of pembrolizumab, INCB001158 should be permanently discontinued for a ≥ Grade 3 recurrence of the AE that resulted in pembrolizumab discontinuation.

Table 12.1-1: INCB001158 Dose Modification Guidelines for Adverse Events in Patients Receiving INCB001158 (All Parts)

Adverse Reaction	Severity	Management	Study Drug Dose Modification
Evidence of urea cycle inhibition	• Fasting urinary orotic acid > 2 X and ≤ 10 X ULN • Any urinary orotic acid > 2 X and ≤ 40 X ULN	• Re-test fasting urinary orotic acid 1 week later.	• None.
	• Ammonia 2 X ULN and 2 X baseline (repeated measurements or with symptoms) • Fasting urinary orotic acid > 10 X ULN • Any urinary orotic acid > 40 X ULN • BUN < 50% LLN	• See Section 12.1.3.3 for management of hyperammonemia.	• Interrupt study drug. • Consider restarting (at a lower dose) in consultation with Medical Monitor.
Study drug-related creatinine increase[1] (patients with CrCl 30-49 mL/min at baseline)	Grade 2 (> 1.5-3.0 X baseline)	Weekly testing of serum creatinine during interruption of study drug.	• Interrupt study drug. • 1st event: Restart at same dose upon resolution to ≤ Grade 1. • 2nd event: Restart at 25 mg BID upon resolution to ≤ Grade 1.
	Grade 3 (> 3.0 baseline) or 4 (dialysis indicated)	Weekly testing of serum creatinine during interruption of study drug.	• Interrupt study drug and do weekly serum creatinine testing and urinalysis until serum creatinine returns to ≤ Grade 1. Restart study drug at 25 mg BID. • If after 4 weeks the serum creatinine has not recovered to ≤ Grade 1, permanently discontinue study drug. • If after restarting study drug the toxicity reoccurs, permanently discontinue study drug.

Table 12.1-1: INCB001158 Dose Modification Guidelines for Adverse Events in Patients Receiving INCB001158 (All Parts) (Continued)

Adverse Reaction	Severity	Management	Study Drug Dose Modification
Study drug-related creatinine increase[1] (patients with CrCl > 50 mL/min at baseline)	Grade 2 (> 1.5-3.0 X baseline OR > 1.5-3.0 X ULN)	Weekly testing of serum creatinine during interruption of study drug.	• Interrupt study drug. • 1st event: Restart at same dose upon resolution to ≤ Grade 1. • 2nd event: Restart at 25 mg BID upon resolution to≤ Grade 1.
	Grade 3 (> 3.0 baseline; > 3.0-6.0 X ULN) or 4 (> 6.0 X ULN)	Weekly testing of serum creatinine during interruption of study drug.	• Interrupt study drug and do weekly serum creatinine testing and urinalysis until serum creatinine returns to ≤ Grade 1. Restart study drug at 25 mg BID. • If after 4 weeks the serum creatinine has not recovered to ≤ Grade 1, permanently discontinue study drug. • If after restarting study drug the toxicity reoccurs, permanently discontinue study drug.
Suspected immune-related adverse event (irAE) including: • Colitis • Pneumonitis • Dermatitis • Hepatitis • Hypophysitis • Adrenal insufficiency • Type I diabetes mellitus • Nephritis	Grade 1	• Symptomatic therapy, as appropriate	No change
	Grade 2	• If > 5 days, 0.5 to 1 mg/kg/day prednisone. If worsening or no improvement, increase to 1 to 2 mg/kg/day prednisone equiv. and consider IV.	• Interrupt study drug. • 1st event: Restart at same dose upon resolution to ≤ Grade 1. • 2nd event: Restart one dose level lower for second event of the same AE.
	Grade 3	• 1 to 2 mg/kg/day prednisone equiv. Consider IV.	• Interrupt study drug. • 1st event: Consider restarting at next lower dose level upon resolution to ≤ Grade 1. • 2nd event: Permanently discontinue.
	Grade 4	• 1 to 2 mg/kg/day prednisone equiv. Consider IV.	• Permanently discontinue.

Table 12.1-1: INCB001158 Dose Modification Guidelines for Adverse Events in Patients Receiving INCB001158 (All Parts) (Continued)

Adverse Reaction	Severity	Management	Study Drug Dose Modification
All others	Grade 1	Symptomatic therapy, as appropriate.	No change.
	Grade 2	Symptomatic therapy, as appropriate.	• Interrupt study drug. • 1st event: Restart at same dose upon resolution to ≤ Grade 1. • 2nd event: Restart one dose level lower for second event of the same AE.
	Grade 3	Symptomatic therapy, as appropriate.	• Interrupt study drug. • 1st event: Consider restarting at next lower dose level upon resolution to ≤ Grade 1. • 2nd event: Permanently discontinue.
	Grade 4	Symptomatic therapy, as appropriate.	• Permanently discontinue.

[1] For creatinine increases that are unrelated to study drug (e.g. obstructive uropathy) INCB001158 may be continued at a dose appropriate for the new CrCl (as calculated by the Cockcroft-Gault formula) as follows:

- CrCl > 50 mL/min: Continue INCB001158 at 100 mg BID.
- CrCl 30-49 mL/min: Reduce INCB001158 to 50 mg BID.
- CrCl < 30 mL/min: Hold INCB001158 and restart once CrCl > 30 mL/min as specified above.

Table 12.1-2: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab (Parts 1b, 1c, and 3)

General instructions

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	**Toxicity Grade (CTCAE V4.0)**	**Action With Pembrolizumab**	**Corticosteroid and/or Other Therapies**	**Monitoring and Follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants 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) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Table 12.1-2: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab (Parts 1b, 1c, and 3) (Continued)

irAEs	Toxicity Grade (CTCAE V4.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders

Table 12.1-2: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab (Parts 1b, 1c, and 3) (Continued)

irAEs	Toxicity Grade (CTCAE V4.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: > 3.0 - 5.0 × ULN if baseline normal; > 3.0 - 5.0 × baseline, if baseline abnormal; bilirubin: > 1.5 - 3.0 × ULN if baseline normal; > 1.5 - 3.0 × baseline if baseline abnormal

[b] AST/ALT: > 5.0 to 20.0 × ULN, if baseline normal; > 5.0 - 20.0 × baseline, if baseline abnormal; bilirubin: > 3.0 - 10.0 × ULN if baseline normal; > 3.0 - 10.0 × baseline if baseline abnormal

[c] AST/ALT: > 20.0 × ULN, if baseline normal; > 20.0 × baseline, if baseline abnormal; bilirubin: > 10.0 × ULN if baseline normal; > 10.0 × baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

12.1.3.3 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Guidelines outlined below should be used in conjunction with information provided in the pembrolizumab product label:

Hyperammonemia: Patients should be monitored for elevated venous plasma ammonia. Asymptomatic clinically significant drug-related elevations in ammonia (e.g., a repeatable elevation in ammonia > 2x ULN AND > 2x baseline) should managed by interrupting INCB001158 study drug and monitoring to resolution. For symptomatic elevations (i.e., significant ammonia elevation associated with nausea, vomiting, severe anorexia, mental status changes, seizure, or other symptoms associated with hyperammonemia), patients should be admitted for management according to the local institutional protocol for hyperammonemia, including 1) sending appropriate labs [ammonia (on ice, measured STAT), plasma amino acid profile, LFTs, electrolytes, bicarb, 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/lacitol, IV Ammonul), and 5) identifying and treating any potential triggers (e.g., discontinue corticosteroids, treat infections, etc).

Diarrhea: Patients should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. In patients with severe enterocolitis, treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. In patients that do not respond to high dose steroids with 72 hr, consider initiation of additional immunosuppressive therapy (e.g., infliximab). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

In addition, patients with severe enterocolitis that are receiving INCB001158 monotherapy will have INCB001158 permanently discontinued, whereas, for patients receiving INCB001158/pembrolizumab combination, pembrolizumab will be permanently discontinued and INCB001158 will be withheld. Restarting INCB001158 may be considered in INCB001158/pembrolizumab combination patients if enterocolitis is not a toxicity associated with monotherapy INCB001158.

In patients with moderate enterocolitis, pembrolizumab should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with INCB001158 and pembrolizumab, see Table 12.1-2.

All patients who experience diarrhea 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.

Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. Since nausea/vomiting can be a symptom of hyperammonemia, there should be a low threshold to test plasma ammonia levels for patients with nausea, vomiting, or new onset anorexia.

Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.

Neutropenia: Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. Idiopathic thrombocytopenic purpura (ITP) should be ruled out before initiation of platelet transfusion.

Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

Immune-related adverse events: Patients who develop a Grade 2 or higher irAE (e.g., colitis, skin rash, hepatitis, uveitis, hypo- or hyperthyroidism, hypophysitis, or any other), should be discussed immediately with the Medical Monitor. Depending on the type and severity of an irAE, oral or IV treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition. For severe immune-mediated adverse events that do not respond to high dose IV steroids within 72 hours, consider initiation of additional immunosuppressive therapy (e.g., infliximab for non-hepatic toxicities or mycophenolate mofentil for immune-mediated hepatotoxicity).

Dose modification and toxicity management of infusion reactions related to pembrolizumab: 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 for pembrolizumab-associated infusion reactions are provided in Table 12.1-3.

Table 12.1-3: 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 patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**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 patient 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 (e.g., from 100 mL/hr. to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.**	Patient may be premedicated 1.5 hr (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator 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 patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Patient is permanently discontinued from further study drug treatment.	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 Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov.		

12.2 Dose Adjustments, Infusion Delays, and Missed Doses

Missed doses of INCB001158 should be skipped. If a patient forgets to take a dose of INCB001158 study drug and he/she is outside of the allotted window period (± 6 hr), he/she should be instructed to skip that dose and NOT to take extra INCB001158 study drug at their next administration.

In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed, and subsequent visits will follow every 2 weeks (the infusion at the original schedule visit will be considered a missed dose). Patients with infusion delays > 35 days should discontinue from the study unless approved by the Medical Monitor in settings where benefit/ risk may justify continued study therapy.

12.3 Discontinuation of Treatment and Withdrawal of Patients

The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, adverse events, disease progression, patient request, Investigator decision, protocol violation, patient noncompliance, and study termination by the Sponsor.

When a patient discontinues or is withdrawn, the Investigator or designee will notify the Sponsor (or designee) and should perform all End of Treatment and follow up procedures as indicated in the Schedule of Study Assessments (Attachment 1) after discontinuation of study treatment. The Investigator or designee must document in the source if the patient withdrew consent from treatment/ study procedure only or from treatment/ study procedures and from further contact.

13.0 STUDY DRUG 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 2 investigational study treatments in this study – INCB001158 and pembrolizumab. INCB001158 is also referred to as the study drug in this Protocol. Although pembrolizumab is approved and marketed in various indications, it is investigational in this study in combination with INCB001158.

13.1 Study Treatment Administration

INCB001158

Study drug (INCB001158) needs to be taken orally as capsule or tablet (25 mg or 100 mg per capsule or tablet) formulation. INCB001158 will be administered only to patients who have signed and dated an Informed Consent Form. Patients in Part 1a and 2: INCB001158 needs to be taken on Days 1 through 28 of each 28-day cycle and should be taken orally using the number of capsules or tablets directed in the Pharmacy Manual. [redacted] Patients in Part 1b and 3: INCB001158 needs to be taken on Days 1 through 21 of each 21-day cycle and should be taken orally using the number of capsules or tablets directed in the Pharmacy Manual. INCB001158 dosing will not be adjusted for body weight or surface area. Patients will continue to receive INCB001158 until disease progression (per irRECIST), intolerable toxicity, patient withdraws consent, or the Investigator determines that it is not in the patient's best interest to remain on study.

The study drug should be taken by the patient at approximately the same times each day on an empty stomach with a full glass of water. The first dose should be taken at least 2 hr before breakfast. The evening dose of INCB001158 will be taken approximately 12 hr later and at least 2 hr before or 1 hr after eating a meal. The effect of food is being evaluated in Part 1a during monotherapy dose escalation. If it is demonstrated that improved bioavailability can be achieved by taking INCB001158 with food, then patients thenceforth will take the drug with breakfast and dinner.

On PK days (see Attachment 1) patients 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 pre-dose procedures have been performed. The time of dosing will be recorded in the clinic.

The evening doses will be self-administered by the patient after all post-dose activities have been complete.

Patients enrolled in the pembrolizumab combination cohorts (Part1b and Part 3) will have all pre-dose procedures performed prior to receiving pembrolizumab. Once the pembrolizumab infusion is complete, patients should be instructed to take their morning dose of INCB001158. Breakfast should not be eaten until at least 2 hr after taking INCB001158. The time of dosing will be recorded in the clinic. The evening dose of INCB001158 will be taken by the patient as usual. On non-PK collection days, patients will take INCB001158 per their usual administration schedule.

Patients 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. Patients who report ≥ 3 incidences of vomiting associated with study drug administration will have a blood sample drawn for an unscheduled PK analysis.

Pembrolizumab

Pembrolizumab will be administered on day 1 of each 3-week treatment cycle after all procedures and assessments have been completed as detailed on the schedule of assessment. Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. 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 between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min). Patients will continue to receive pembrolizumab until disease progression (per irRECIST), intolerable toxicity, patient withdraws consent, or the Investigator determines that is not in the patient's best interest to remain on study. The maximum duration of pembrolizumab treatment on study will be up to 35 doses (approximately 2 years).

Pembrolizumab (Keytruda®) is supplied either as a 50 mg, lyophilized powder in single-use vials for reconstitution or as a 25 mg/mL sterile solution for infusion in 4 mL vials. The dose recently approved in the United States and several other countries for treatment of melanoma patients is 2 mg/kg Q3W. Please refer to the pembrolizumab Label/Investigator's Brochure for specific instructions on pembrolizumab administration.

13.2 Packaging and Labeling

INCB001158 capsules and tablets (25 and 100 mg) are manufactured, packaged, and labeled according to current Good Manufacturing Practices (cGMP). All product labels will be in the local language and will comply with the legal requirements of each country. For additional information, please refer to the Pharmacy Manual.

Pembrolizumab is available either as 50 mg, lyophilized powder in single-use vials or as a 25 mg/mL sterile solution for infusion in 4 mL vials (3). The product label will be in the local language and will comply with the legal requirements of each country. For additional information, please refer to the pharmacy manual.

13.3 Storage and Stability

INCB001158

INCB001158 capsules and tablets will be stored at the clinical site, as indicated on the study drug label, i.e., room temperature, between 15ºC - 30ºC (59ºF - 86ºF).

Patients will be requested to store the study drug at the recommended storage conditions noted on the label, out of the reach of children.

Pembrolizumab

Pembrolizumab vials should be stored under refrigeration at 2°C - 8°C (36°F - 46°F). Protect from light by storing in the original package until time of use. Do not freeze or shake. For procedures for the proper handling, storage, preparation and administration of pembrolizumab, please refer to the Pembrolizumab Label/Investigator's Brochure.

13.4 INCB001158 Accountability, Reconciliation, and Return

On Day 1 of Cycle 1, patients will be provided with enough INCB001158 to last until their next clinic visit. For patients in Parts 1a and 2, patients will return on Day 1 of each cycle thereafter and will receive a 28-day supply of INCB001158; the number of capsules or tablets remaining from the previous visit will be counted and recorded.

For patients in Parts 1b and 3, patients will return on Day 1 of each cycle thereafter and will receive a 21-day supply of INCB001158; the number of capsules or tablets remaining from the previous visit will be counted and recorded.

The Investigator or designee must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to the Sponsor at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

If evidence of tampering is observed, notify the Sponsor and return the questionable INCB001158 shipment with the appropriate form to the contract distribution center. Returned and unused INCB001158 study drug may also be destroyed and documented at the investigative site in accordance with approved site/institution standard operating procedures.

13.5 Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the patient by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB001158 will be calculated by the sponsor based on the drug accountability documented by the site staff and will be monitored by the sponsor/designee (capsule/tablet counts). Patients will be instructed to bring all unused INCB001158 capsules/tablets 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. Missed doses of INCB001158 should be skipped. If a patient forgets to take a dose of study drug and he/she is outside of the allotted window period (± 6 hr), he/she should be instructed NOT to take extra study drug at their next administration.

14.0 MEASURES TO MINIMIZE/AVOID BIAS

Each patient will be assigned a unique number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients should be identified to the Sponsor only by their assigned number, initials (not required for EU), date of birth, and sex. The Investigator must maintain a patient master log.

15.0 STATISTICAL ANALYSIS

15.1 General Statistical Considerations

Protocol INCB 01158-101 is a Phase 1 multicenter, open-label study in patients with advanced and metastatic solid tumors.

Since this is an open-label clinical trial, descriptive statistics will be employed to analyze the data by tumor type and dose level. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented by tumor type as frequency counts and percentages, and time-to-event variables will be summarized by Kaplan-Meier plots, medians, and ranges.

The data will be tabulated and analyzed with respect to patient enrollment and disposition, demographic and baseline characteristics, prior and concomitant medications, efficacy, and safety measures. The efficacy analysis will be conducted on the Efficacy Evaluable Population, and the safety analysis will be performed on the Safety Population (see Section 15.3.1).

All confidence intervals will be constructed at the 95% confidence level. Data listings will be created to support each table and to present all data collected.

15.2 Sample Size and Power

Dose Escalation: The goal is to determine a dose level of INCB001158 for which the rate of DLTs is less than 33%. Up to approximately 108 patients are planned for single agent dose escalation (Part 1a) and 108 patients for combination dose escalation (Part 1b), both including backfill patients.

Dose Expansion: For Expansion Cohorts in Parts 2 and 3 (except the initial part of Cohort 2c), Simon's two-stage design (Simon 1989) will be used as outlined in Table 15.2-1 below. The null hypothesis that the true response rate is [p0] will be tested against a one-sided alternative. In the first stage, [n1] patients will be accrued. If there are [r1] or fewer responses in these [n1]

patients, the study will be stopped. Otherwise, [n - n1] additional patients will be accrued for a total of [n]. The null hypothesis will be rejected if [r2 + 1] or more responses are observed in [n] patients. This design yields a type I error rate of 0.1 and power of 80% when the true response rate is [p1].

Table 15.2-1: Summary of Sample Size and Power for Expansion Cohorts

Cohort	p0 Background ORR (%)	p1 Target ORR (%)	α	Power (%)	n1 for Stage 1 (r1)	n2 (n - n1) for Stage 2	Total n (r2)
2a	2%	15%	0.1	80	11 (0)	15	26 (1)
2b	2%	15%	0.1	80	11 (0)	15	26 (1)
2c expansion	2%	15%	0.1	80	11 (0)	15	26 (1)
3a	2%	15%	0.1	80	11 (0)	15	26 (1)
3b	2%	15%	0.1	80	11 (0)	15	26 (1)
3c	2%	15%	0.1	80	11 (0)	15	26 (1)
3d	2%	15%	0.1	80	11 (0)	15	26 (1)
3e	2%	15%	0.1	80	11 (0)	15	26 (1)
3f	10%	25%	0.1	80	13 (1)	21	34 (5)
3g	20%	40%	0.1	80	12 (2)	13	25 (7)
3h	13%	30%	0.1	80	10 (1)	23	33 (6)

Cohort 2c is designed to generate additional evidence of clinical activity in a variety of tumor types. The sample size for the initial 30 patients was not based on a predefined statistical analysis. The sample size for each tumor type in any subsequent expansion of Cohort 2c will be guided by a Simon 2-stage design.

[redacted]

Part 1c is intended to enroll the minimum number of patients required to generate sufficient PK data for a descriptive comparison of Day 1 and steady state (Day 8, Day 15) exposures between patients with moderate renal impairment (CrCl 30-49 mL/min) and normal renal function (CrCl

> 50 mL/min). Accordingly, the sample size of 6 PK-evaluable patients for Cohort 1c is not based on a predefined statistical analysis.

15.3 Analysis Populations

15.3.1 Safety Population

All patients who receive at least 1 dose of INCB001158 or pembrolizumab will be included in the analysis of safety, regardless of the duration of treatment.

AE and laboratory data from all patients in the safety population will be evaluated for safety. Patients from dose escalation will be combined with patients receiving the same dose and schedule from cohort expansion for safety evaluation. Patients with moderate renal impairment in Part 1c will be evaluated separately. Data will be tabulated to examine the frequency, organ systems affected, and relationship to study treatments. No formal interim analysis is planned; however, safety data will be examined on an ongoing basis to ensure safety of the study patients and compliance with the trial dose escalation and expansion rules.

15.3.2 DLT-Evaluable Populations in Dose Escalation

DLTs will be evaluated during dose escalation. Unless doses are missed in Cycle 1 due to drug-related AE(s), a patient must receive at least 75% of the planned INCB001158 doses (43 of 56 total doses) to be considered evaluable for DLT. If a patient received less than 43 doses of INCB001158 in the first 28 days of treatment for reasons other than a DLT, the patient will be considered non-evaluable for DLT and replaced. For patients in Part 1b and Part 3, patients must receive both doses of pembrolizumab in Cycle 1 in order to be evaluable for DLT.

Patients who discontinue the study prior to receiving the requisite study treatment administrations for reasons that include, but are not limited to, clinical/radiographic progression, voluntary withdrawal, or complications that the Principal Investigator considers secondary to the patient's malignancy will not be considered evaluable for DLT and will be replaced.

15.3.3 Efficacy Evaluable Populations

The Response Evaluable Population includes all patients who received at least 1 dose of study treatment (INCB001158 or pembrolizumab), completed a baseline scan, and met at least 1 of the following criteria:

- The patient had at least 1 post-baseline scan.

- The patient discontinued from study treatment for any reason except unrelated toxicity or death, or withdrawal of consent.

The PFS Evaluable Population includes all patients who received at least 1 dose of study treatment (INCB001158 or pembrolizumab).

Patients enrolled in the expansion cohorts who do not meet the requirements for the Response Evaluable Population will be considered non-evaluable for response and will be replaced.

15.4 Efficacy Analysis

Response to treatment will be evaluated using RECIST v1.1 for patients with solid tumors (except for mesothelioma; Eisenhauer 2009). For patients with pleural mesothelioma, response will be evaluated using the modified RECIST criteria for pleural mesothelioma (Byrne 2004, Attachment 5). Responses for patients with pericardial or peritoneal mesothelioma will be described based upon RECIST v1.1 for patients with measurable disease combined with clinical improvements.

The Kaplan-Meier method will be used to estimate the median Duration of Response (DOR) and Progression-Free Survival (PFS) for each treatment cohort in Dose Expansion (note: Dose Escalation patients of the same histology enrolled at the RP2D will be included in this analysis). Efficacy analyses will be performed on the Efficacy Evaluable Population. Additional efficacy analyses will also be performed on an expanded population that includes patients that lack post-treatment scans due to toxicity or death.

For each patient with objectively measurable disease, response to therapy, will be calculated using RECIST v1.1 and Modified RECIST for pleural mesothelioma (DOR, PFS, Best Overall Response [BOR], and Overall Response Rate[ORR]).

- DOR is defined as the number of days from the date of initial response (PR or better) to the date of first documented disease progression/relapse or death, whichever occurs first.
- PFS is defined as the number of days from the date of treatment initiation (i.e., C1D1) to the date of documented disease progression or death from any cause, whichever occurs first, and will be calculated for all patients. In the event that no disease progression or death is documented prior to study termination, analysis cutoff, or the start of confounding anticancer therapy, these endpoints will be censored at the date of last available tumor assessment.

- BOR is the best RECIST v1.1 /modified RECIST for pleural mesothelioma response recorded from the start of the study treatment until disease progression/recurrence.
- ORR is defined as the response of the proportion of efficacy evaluable patients with tumor size reduction from the time the start of treatment until documented tumor progression. ORR includes complete response (CR) and partial response (PR).

[redacted]

15.5 Safety Analysis

Safety variables to be analyzed by dose level and tumor type are AEs, laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), ECG, weight, and vital signs. Adverse event terms recorded on the eCRFs will be mapped to preferred terms using the most recent version of the Medical Dictionary for Drug Regulatory Activities (MedDRA®). All AEs will be summarized according to the system organ class and preferred term within the organ class. Adverse events will be tallied for overall frequency (number and percentage of patients), worst reported severity, and relationship to study treatment for each preferred term per patient. Serious adverse events will be similarly summarized. Listings of deaths, SAEs, and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided.

Laboratory variables will be examined using mean change in value from baseline to scheduled time points. The baseline value of a variable is defined as the last value obtained on or before the date and time of the first dose of INCB001158 or pembrolizumab.

ECG, weight, and vital signs will also be summarized by changes from baseline to scheduled time points using descriptive statistics.

15.6 Pharmacokinetic Analysis

For Part 1a- Dose Escalation PK samples, a noncompartmental method of analysis will be used to analyze the plasma concentrations of INCB001158. The maximum plasma concentration (C_{max}) and the time to attain the C_{max} (T_{max}) will be determined directly from the observed data. In Part 1a, full AUC ($AUC_{0\text{-}12\ hr}$) will be calculated on Days 1 and 15 in Cycle 1.

For Parts 1b, 2a, 2b, 2c, and 3, sparse sampling will be collected to confirm exposure and to explore population PK (see Attachment 1A and 1B).

For Part 1c, a noncompartmental method of analysis will be used to analyze the plasma concentrations of INCB001158. The log-transformed PK parameters will be compared between renally impaired patients (CrCl 30-49 mL/min) and patients with normal renal function (CrCl ≥ 50 mL/min) using an analysis of variance. The geometric mean relative bioavailability and 90% confidence intervals for INCB01158 C_{max} and AUC will be calculated using the intrapatient variability from the ANOVA model to assess the magnitude of the difference between the patients with normal renal function and those with moderate renal impairment.

[redacted]

15.7 Precautions

Although major adverse events are not anticipated, the Investigator must proceed with utmost caution. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected reaction. Patients must be selected carefully and closely monitored.

For a complete description of preclinical studies of INCB001158, please refer to the INCB001158 Investigator's Brochure. For a description of precautions with pembrolizumab, please refer to the Product Label.

16.0 SAFETY MONITORING AND REPORTING

16.1 Adverse Events

16.1.1 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).

16.1.2 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 up to 30 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. 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 16.3.2. 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 (all Parts) and pembrolizumab (Parts 1b and 3 only).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 16.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 16.3.2).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event form in the eCRF and the

treatment should be specified on the Prior and Concomitant Medications or Procedures form in the eCRF.

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

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

16.2 Laboratory Test Abnormalities

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

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 16.3.1. A dose modification for the laboratory abnormality may be required (see Section 12.1.3) and should not contribute to the designation of a laboratory test abnormality as an SAE.

16.3 Serious Adverse Events

16.3.1 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.

16.3.2 Reporting

For Parts 1a and 2, every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through 30 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.
For Parts 1b and 3, every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through 90 days after the last dose of study treatment, or within 30 days after the last dose of study treatment if 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 30 days [Parts 1a and 2 only] or 90 days [Parts 1b and 3 only] after the last dose of study treatment should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.
Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment. Relatedness will be assessed for each of INCB001158 (all Parts) and pembrolizumab (Parts 1b and 3 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: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.
Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form,

with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IBs for the study treatments (new occurrence) and is thought to be related to at least one 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.

16.4 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 patient during maternal or paternal exposure to study treatment(s), the following procedures should be followed in order to ensure subject safety:

- The study treatment implicated 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 patient, to determine whether it is in the patient'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.

16.5 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 patient 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).
- Pembrolizumab: A dose ≥ 1000 mg (5 times the dose).

No specific information is available on the treatment of overdose of INCB001158 or pembrolizumab. In the event of overdose, the patient 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 treatments, 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.

16.6 Warnings and Precautions

Special warnings or precautions for the INCB001158 study drug and for pembrolizumab, derived from safety information collected by the sponsor or its designee, are presented in the Investigator's Brochures (iIB, 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.

For guidance for potential DILI (drug induced liver injury), refer to the pembrolizumab label/Investigator's Brochure (pIB) and Attachment 7.

16.7 Product Complaints

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

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

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 16.1.2 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.

17.0 STUDY SUSPENSION, TERMINATION, AND COMPLETION

The Sponsor may suspend or terminate the study or any part of the study at any time for any reason. If the Investigator suspends or terminates the study, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide a detailed written explanation. The Investigator will also return all study treatments, containers, and other study materials to the Sponsor or designee, or destroy the materials at the investigative site. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations.

If at least 6 months elapsed since the last subject was enrolled in the study, and if there are no more than 10 subjects still on study treatment, a database lock of the study may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study treatment and be seen by the investigator per usual standard of care for this population. The investigator will be expected to monitor for and report any SAEs and pregnancies, as detailed in Section 16.0. No other data will be collected. The remaining subjects are considered to be on study until a discontinuation criterion is met.

18.0 INFORMED CONSENT

The Investigator will provide for the protection of the patients by following all applicable regulations. These regulations are available upon request from the Sponsor. The Informed Consent Form used during the informed consent process must be reviewed by the Sponsor and approved by the IRB/IEC. All patients must be consented per the requirements and recommendations in 21CFR50, 45CFR46, and ICH/ GCP E6.

The study begins when the first patient signs the informed consent form. The end of the study will occur when all patients have completed applicable follow-up assessments.

Before any procedures specified in the protocol are performed, a patient must:

- Be informed of all pertinent aspects of the study and all elements of informed consent
- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB/IEC approved Informed Consent Form

19.0 PROTOCOL AMENDMENTS

Any significant change in the study requires a protocol amendment. An Investigator must not make any changes to the study without IRB/IEC and Sponsor approval. All protocol amendments must be reviewed and approved following the same process as the original protocol.

20.0 QUALITY CONTROL AND ASSURANCE

The Sponsor or designee performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients in this study, Sponsor personnel and the Investigator review the protocol, the Investigator's Brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study. During these site visits, information recorded in the eCRFs is verified against source documents.

21.0 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

21.1 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 patients.
  - 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 patients' questions have been answered and the patients 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 patient. 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 patient 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 patients 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.

21.2 Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study treatments to the study site.
- Inventory of study treatments at the site.
- Patient use of the study treatments including capsule or unit counts from each supply dispensed.
- Return of the INCB001158 study drug to the investigator or designee by patients.

The study treatments must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the patients 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 study treatments and study patients. 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 treatments 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.

21.3 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 patient. 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 patient'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 by the study monitor in the Monitoring Visit report. 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.

21.4 Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Patient names will not be supplied to the sponsor or its designee. Only the patient number and patient's initials (patient's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the patient's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws. The patients 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.

21.5 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.

21.6 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.

Per the International Committee of Medical Journal Editors recommendations (ICMJE 2015), an author is generally considered to be anyone who provides substantive intellectual contributions to a published study. Specifically, authorship credit should be based on 1) substantial contributions to study conception and design, or acquisition, analysis and interpretation of data, and 2) drafting the article or revising it critically for important intellectual content, 3) final approval of the version to be published, and 4) agreement to be accountable for all aspects of the work to ensure its accuracy and integrity. All four conditions should be met.

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ATTACHMENT 1A: SCHEDULE OF STUDY ASSESSMENTS FOR PART 1A AND PART 2 (INCB001158 MONOTHERAPY)

Cycle Length = 28 Days

Visit	Screening	Cycle 1				Cycle 2+		End of Treatment	Follow-Up	
									Safety	Disease Status
	Day -21 to -1	Day 1 (-1 day) [1]	Day 2 (-1 day) [1,22]	Days 8 and 22 (± 2 days) [1]	Day 15 (± 2 days) [1]	Day 1 (± 5 days)[1,23]	Day 8 (Cycle 2 only) (± 5 days)[15,22]	Within 28 days post treatment discontin-uation	30-37 days after last dose of INCB001158	Q8W after discontin-uation
Written Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Demographics and Medical History	X									
Physical Examination[2]	X	X		X	X	X[3]	X	X	X	
Height	X									
Weight	X	X		X	X	X[3]	X	X	X	
Vital Signs	X	X		X	X	X	X	X	X	
Orthostatic Vital Signs[4]		X			X					
ECOG Performance Status	X	X				X[3]	X	X	X	
Duplicate 12-lead ECG with QTcF[5]	X	X[6]			X[6]			X		
Urinalysis	X	X[7]		X	X	X		X		
Serum Chemistry levels[8]	X	X[7]	X	X	X	X	X	X		
Hematology[8]	X	X[7]	X	X	X	X	X	X		
Pregnancy Test[9]	X	X						X		
Plasma Ammonia Levels[10, 21]		X	X	X	X	X	X			

Visit	Screening	Cycle 1				Cycle 2+		End of treatment	Follow-Up	
									Safety	Disease Status
	Day -21 to -1	Day 1 (-1 day) [1]	Day 2 (-1 day) [1,22]	Days 8 and 22 (± 2 days) [1]	Day 15 (± 2 days) [1]	Day 1 (± 5 days) [1,23]	Day 8 (Cycle 2 only) (± 5 days)[15,22]	Within 28 days post treatment discontin-uation	30-37 days after last dose of INCB001158	Q8W after discontin-uation
Urine Sample for Orotic Acid[11, 12, 21]		X	X	X	X	X	X			
Coagulation tests	X	X[7]		X	X	X	X	X		
Pharmacokinetic (PK) Assay[12, 21, 22]		X	X	X[21]	X	X	X			
Amino Acid Panel[12 ,21, 22]		X	X	X[21]	X	X	X			
[redacted]										
INCB001158 Dosing[13]		X[14]	X	X	X	X[15]	X[15]			
Radiographic Evaluation of Tumor Burden (diagnostic CT or MRI)[16]	X[17]					X[18]		X		X
[redacted]										
Adverse Events		X	X	X	X	X		X	X	
Concomitant Medications	X	X	X	X	X	X		X	X	
Post-treatment anticancer therapy status								X	X	X

Explanation of Superscripts

1. With approval from the sponsor, windows for cycles/ days may be modified due to holidays conflicting with the clinic schedules.
2. Complete physical exam is required at Screening and at End of Treatment. A symptom-directed physical exam can be done on all other visits. System exams are only required as clinically indicated.
3. Assessment to be completed on Day 1 of every cycle.
4. Phase 1a patients only: orthostatic vital signs to be performed on C1D1 and C1D15, predose and 4 hr postdose.
5. To be performed in duplicate within (2-5 minutes).
6. ECG to be performed 2-4 hr post-dose.
7. Does not need to be repeated if the Screening sample was obtained within 3 days prior to C1D1 unless a clinically significant change is suspected.

8. Serum chemistry, urinalysis, and hematology should be performed and reviewed before dosing. These labs may be performed up to 48 hours prior to the planned dosing. Any new ≥Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continue dosing. In the event of uncertainty, the medical monitor should be contacted.
9. Required of all females of child-bearing potential. Screen pregnancy test must occur within 3 days prior to C1D1. During study treatment, urine pregnancy tests will be performed locally as medically indicated or per country-specific requirement. See Section 11.3 for additional details.
10. Ammonia samples to be sent to local laboratory for analysis. See Attachments 2A, 2B, and 2D for additional details.
11. A fasting (of >8 hours) urine sample will be taken for the measurement of orotic acid on day one of every cycle or more frequently as clinically indicated. See Attachments 2A, 2B, and 2D for specific time points and volume to be taken.
12. Samples are sent to a central laboratory. See Attachments 2A, 2B, [redacted] for specific time points and volume of collection.
13. INCB001158 is given daily, BID. During PK days, the morning dose of INCB001158 will be administered during the clinic visit after all pre-dosing procedures, and pre-dose PK blood sampling, has occurred.
14. Patients in Part 1a only will receive a single dose of INCB001158 on C1D1.
15. Part 1a patients: During C2, D1 through D8, INCB001158 will be taken with food. The first dose will be taken in the morning right after eating a substantial breakfast and the second dose will be taken in the evening after eating dinner. Part 2 patients will not have C2D8 visit.
16. Whenever possible, imaging should be done at the same institution/facility and with the same modality that will be used to measure response during the patient's participation in the study. The redacted copies of the reports will be submitted and the scans must be sent to a reader for exploratory analyses. If available, 1-3 redacted scan reports for scans that occurred prior to screening will be requested.
17. Tumor assessments within 28 days prior to C1D1 will be accepted.
18. Completed approximately every 8 weeks per RECIST v1.1. Evaluations may occur more frequently as clinically indicated.

[redacted]

21. For patients in Part 2, on C1D8 and C1D22, PK and Amino Acid tests are NOT REQUIRED. Plasma Ammonia and Orotic Acid are required.
22. Part 2 patients will not have C1D2 and C2D8 visits.
23. Orotic acid and plasma ammonia samples will also be collected on Day 1 of every cycle after Cycle 4.

ATTACHMENT 1B: SCHEDULE OF STUDY ASSESSMENTS FOR PARTS 1B, 1C, AND 3 (INCB001158 + PEMBROLIZUMAB)

Cycle Length = 21 Days

Visit	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4+	End of Treatment	Follow-Up Safety	
	Day -21 to -1	Day 1	Day 8 (± 2 days) [1]	Day 15 (± 2 days) [1]	Day 1 (± 5 days) [1]	Day 1 (± 5 days) [1]	Day 1 (± 5 days) [1, 20]	Within 28 days post treatment discontin-uation	30-37 days after last dose of INCB001158 + pembrolizumab	90-97 days after last dose of INCB001158 + pembrolizumab
Written Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Demographics and Medical History	X									
Physical Examination[2]	X	X	X	X	X	X	X[3]	X	X	X
Height	X									
Weight	X	X	X	X	X	X	X[3]	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X			X	X	X[3]	X	X	X
Duplicate 12-lead ECG with QTcF[5]	X	X[6]		X[6]				X		
Urinalysis	X	X[7]			X	X	X	X		
Serum Chemistry levels[8]	X	X[7]	X	X	X	X	X	X		
Hematology[8]	X	X[7]	X	X	X	X	X	X		
Pregnancy Test[9]	X	X						X		

Visit	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4+	End of Treatment	Follow-Up		
									Safety		Disease Status
	Day-21 to -1	C1D1	C1D8 (± 2 days) [1]	Day 15 (± 2 days) [1]	Day 1 (± 5 days) [1]	Day 1 (± 5 days) [1]	Day 1 (± 5 days) [1, 20]	Within 28 days post treatment discontin-uation	30-37 days after last dose of INCB001158 + pembrolizumab	90-97 days after last dose of INCB001158 + pembrolizumab	Q9W after discontinuation
Plasma Ammonia Levels[10]		X	X	X	X	X	X				
Urine Sample for Orotic Acid[11, 12]		X	X	X	X	X	X				
Coagulation tests	X	X[7]	X	X	X	X	X	X			
Pharmacokinetic (PK) Assay[12]		X		X	X	X	X				
Amino Acid Panel[12]		X		X	X	X	X				
[redacted]											
Pembrolizumab Dosing[13]		X			X	X	X				
INCB001158 Dosing[14]		X	X	X	X	X	X				
Radiographic Evaluation of Tumor Burden (diagnostic CT or MRI)[15]	X[16]						X[17]	X			X
[redacted]											
Adverse Events		X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Post-treatment anticancer therapy status									X	X	X

Explanation of Superscripts

1. With approval from the sponsor, windows for cycles/ days may be modified due to holidays conflicting with the clinic schedules.
2. Complete physical exam is required at Screening and at End of Treatment. A symptom-directed physical exam can be done on all other visits. System exams are only required as clinically indicated.
3. Assessment to be completed on Day 1 of every cycle.
4. Vital sign measurements include temperature, pulse, respiratory rate, and resting systolic and diastolic blood pressure. On the day of pembrolizumab infusion, vital signs will be obtained pre-infusion, 15 min after the start of the infusion, at the end of the infusion, and 15 min after completion of the infusion. Vital signs should be collected ± 5 min from the scheduled times noted above.
5. To be performed in duplicate within (2-5 min).
6. ECG to be performed 2-4 hr post-dose.
7. Does not need to be repeated if the Screening sample was obtained within 3 days prior to C1D1 unless a clinically significant change is suspected.
8. Serum chemistry, urinalysis, and hematology should be performed and reviewed before dosing. These labs may be performed up to 48 hours prior to the planned dosing. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continue dosing. In the event of uncertainty, the medical monitor should be contacted.

9. Required of all females of child-bearing potential. Screen pregnancy test must occur within 3 days prior to C1D1. During study treatment, urine pregnancy tests will be performed locally as medically indicated or per country-specific requirement. See Section 11.3 for additional details.
10. Ammonia samples to be sent to local laboratory for analysis. See Attachment 2C for additional details.
11. A fasting of > 8hours urine sample will be taken for the measurement of orotic acid on day one of every cycle or more frequently as clinically indicated. See Attachment 2C for specific time points and volume to be taken.
12. Samples are sent to a central laboratory. See Attachment 2C for specific time points and volume of collection.
13. Patients enrolled in Parts 1b, 1c, and 3: Pembrolizumab dosing will take place on D1 of every cycle. Study treatment with pembrolizumab 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. Infusion of pembrolizumab precede INCB001158 dosing and PK analysis on C1D1 and day one of every cycle.
14. INCB001158 is given daily, BID. During PK days, the morning dose of INCB001158 will be administered during the clinic visit after all pre-dosing procedures, including pembrolizumab administration and pre-dose PK blood sampling, has occurred. INCB001158 will be taken within 5 minutes after pembrolizumab infusion.
15. Whenever possible, imaging should be done at the same institution/facility and with the same modality that will be used to measure response during the patient's participation in the study. The redacted copies of the reports will be submitted and the scans must be sent to a reader for exploratory analyses. If available, 1-3 redacted scan reports for scans that occurred prior to screening will be requested.
16. Tumor assessments within 28 days prior to C1D1 will be accepted.
17. Completed approximately every 9 weeks per RECIST v1.1 OR Modified RECIST for pleural mesothelioma. Evaluations may occur more frequently as clinically indicated.

[redacted]

20. Orotic acid and plasma ammonia samples will also be collected on day one of every cycle after Cycle 4.

ATTACHMENT 2A: PHARMACOKINETIC [redacted] SAMPLING SCHEDULE FOR PART 1A

Detailed instructions on sample collection and shipment can be found in the Laboratory manual.

	INTENSIVE SAMPLING PK GROUP: Part 1a Patients Only			[redacted]			
Study Day (C=cycle, D=Day)	**Time point [1]**	**PK [redacted]**	**Amino Acid Panel[4,9]**		**Urine sample for Orotic Acid[4, 5, 10]**	**Plasma Ammonia[5, 6]**	[redacted]
Screening							
C1, D1 & D15	Predose	3 mL	2 mL		2 mL	X	
C1, D1 & D15	0.5 hr	3 mL					
C1, D1 & D15	1 hr	3 mL					
C1, D1 & D15	2 hr	3 mL				X	
C1, D1 & D15	4 hr	3 mL					
C1, D1 & D15	6 hr	3 mL	2 mL		2 mL	X	
C1, D1 & D15	8 hr	3 mL					
C1, D1 & D15	12 hr	3 mL					
C1, D2	Predose	3 mL	2 mL		2 mL	X	
C1, D8	Predose	3 mL	2 mL		2 mL	X	
C1, D22	Predose	3 mL	2 mL		2 mL	X	
C2, D1	Predose	3 mL	2 mL		2 mL	X	
C2, D8	Predose	3 mL	2 mL		2 mL	X	
C2, D8	0.5 hr	3 mL					
C2, D8	1 hr	3 mL					
C2, D8	2 hr	3 mL				X	
C2, D8	4 hr	3 mL					
C2, D8	6 hr	3 mL	2 mL		2 mL	X	
C2, D8	8 hr	3 mL					
C3, D1	Predose	3 mL	2 mL		2 mL	X	
C4, D1	Predose	3 mL	2 mL		2 mL	X	
Total sample collected		63 mL blood	20 mL blood				

1. Where applicable, the collection window is ±15 minutes. Post dose time points for urine orotic acid collection window are ± 1 hour. The collection window for the C1D1 and C1D15 12 hr PK sample is ± 1 hr. The actual sample collection time will be entered in the EDC.

[redacted]

4. The sample collection time points may be modified if the data indicate that these samples are no longer necessary to ensure patient safety. Pre-dose orotic acid will be collected any time prior to patient's dosing. Where applicable, the post dose collection window is ± 1hr.
5. The sample collection time points may be modified if the data indicate that these samples are no longer necessary.
6. Plasma ammonia samples will be collected and sent to the sites local laboratory.
[redacted]
9. 2 mL blood will be collected in to one sodium heparin tube and processed for amino acid.
10. In addition to Orotic acid samples collected through Cycle 4 Day 1 (C4D1), samples will also be collected on day one of every cycle (example, C5D1, C6D1, etc).

ATTACHMENT 2B: PHARMACOKINETIC [redacted] SAMPLING SCHEDULE FOR PARTS 2A, 2B, AND 2C

Detailed instructions on sample collection and shipment can be found in the Laboratory manual.

	SPARSE SAMPLING PK GROUP: Patients in Parts 2a, 2b, and 2c			[redacted]			
Study Day (C=cycle, D=Day)	**Time point [1]**	**PK [redacted]**	**Amino Acid Panel[4,9]**		**Urine sample for Orotic Acid[4, 10]**	**Plasma Ammonia[4,5, 10]**	
Screening							
C1, D1	Predose	3 mL	2 mL		2 mL	X	
C1, D1	Postdose	3 mL[7]	2 mL[8]		2 mL[8]	X[8]	
C1, D8	Predose				2 mL	X	
C1, D15	Predose	3 mL	2 mL		2 mL	X	
C1, D15	Postdose	3 mL[7]	2 mL[8]		2 mL[8]	X[8]	
C1, D22	Predose				2 mL	X	
C2, D1	Predose	3 mL	2 mL		2 mL	X	
C3, D1	Predose	3 mL	2 mL		2 mL	X	
C4, D1	Predose	3 mL	2 mL		2mL	X	
Total sample collected		21 mL blood	14 mL blood				

1. Where applicable, the collection window is ±15 minutes. Post dose time points for urine orotic acid collection window are ± 1 hour. The actual sample collection time will be entered in the EDC.

[redacted]

4. The sample collection time points may be modified if the data indicate that these samples are no longer necessary to ensure patient safety. Pre-dose orotic acid will be collected any time prior to patient's dosing. Where applicable, the post dose collection window is ± 1hr.
5. Plasma ammonia samples will be collected and sent to the sites local laboratory.

[redacted]

7. The PK postdose sample will be collected 1-4 hours post dose.
8. The Orotic acid, amino acid, and ammonia samples will be collected 4-6 hours post dose.
9. 2 mL blood will be collected in to one sodium heparin tube and processed for amino acid
10. In addition to Orotic acid and plasma ammonia samples collected through Cycle 4 Day 1 (C4D1), samples will also be collected on Day 1 of every cycle (example, C5D1, C6D1, etc).

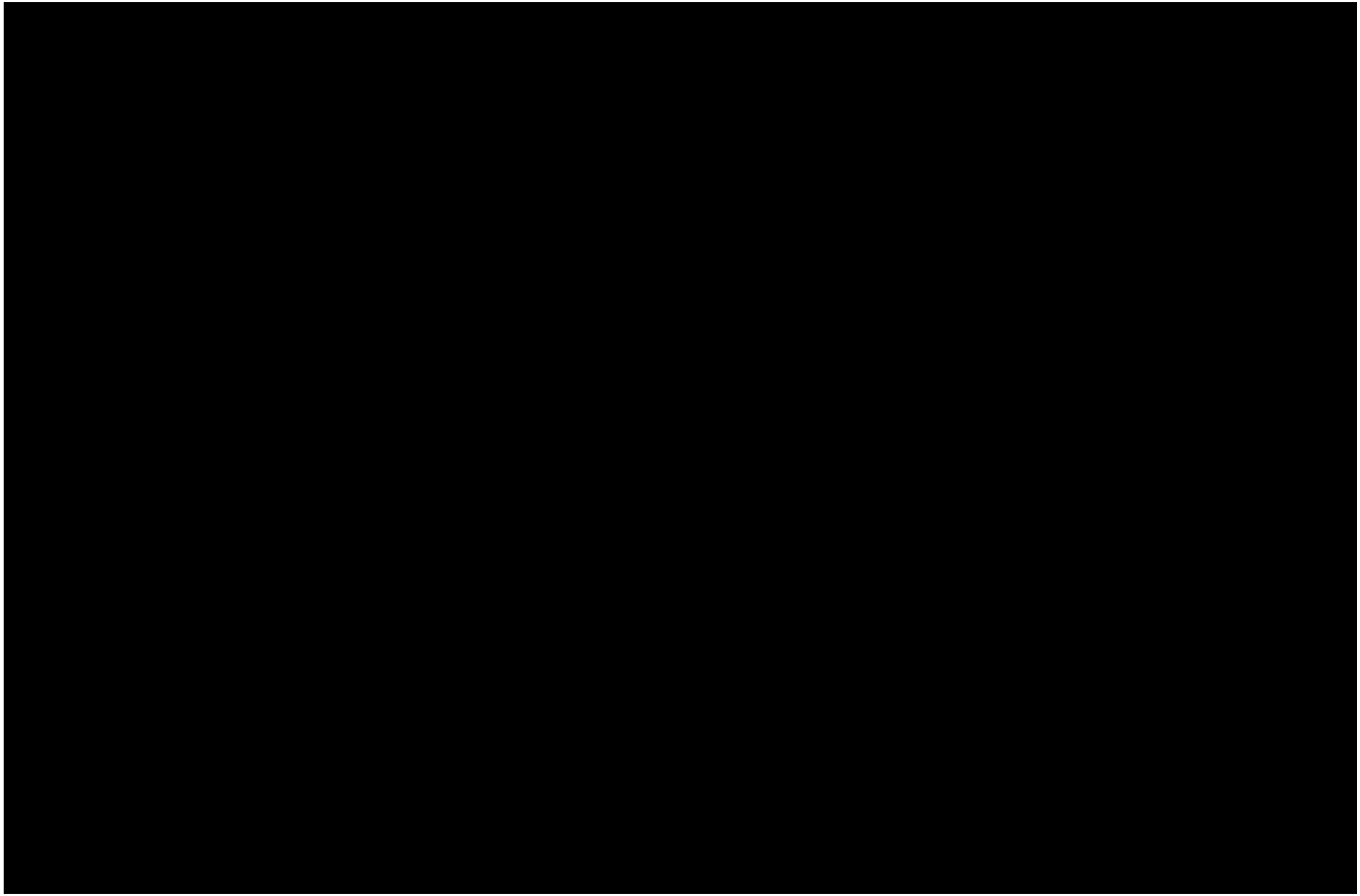
ATTACHMENT 2C: PHARMACOKINETIC [redacted] SAMPLING SCHEDULE FOR PARTS 1B, 1C, AND 3

Detailed instructions on sample collection and shipment can be found in the Laboratory manual.

	SPARSE SAMPLING PK GROUP: All patients in Part 1b and 3 ***Below are assessments for patients enrolled in Part 1b and 3***						
Study Day (C=cycle, D=Day)	**Time point [1]**	**PK/ [redacted]**	**Amino Acid Panel[4,9]**	[redacted]	**Urine sample for Orotic Acid[4, 10]**	**Plasma Ammonia[4,5,10]**	[redacted]
Screening							
C1, D1	Predose	3 mL	2 mL		2 mL	X	
C1, D1	Postdose	3 mL[7]	2 mL[8]		2 mL[8]	X[8]	
C1, D8	Predose				2mL	X	
C1, D15	Predose	3 mL	2 mL		2 mL	X	
C1, D15	Postdose	3 mL[7]	2 mL[8]		2 mL[8]	X[8]	
C2 D1	Predose	3 mL	2 mL		2 mL	X	
C3, D1	Predose	3 mL	2 mL		2 mL	X	
C4, D1	Predose	3 mL	2 mL		2 mL	X	
Total sample collected		21 mL blood	14 mL blood				

Study Day (C=cycle, D=Day)	PK/PD ASSESSMENTS FOR PART 1C *Below are assessments for patients enrolled in Part 1c*					
	Time point [1]	PK/ [redacted]	Amino Acid Panel[4,9]	[redacted]	Urine sample for Orotic Acid[4, 10]	Plasma Ammonia[4,5,10]
Screening						
C1, D1	Predose	3 mL	2 mL		2 mL	X
C1, D1	0.5 hr	3 mL				
C1, D1	1 hr	3 mL				
C1, D1	2 hr	3 mL				X
C1, D1	4 hr	3 mL				
C1, D1	6 hr	3 mL	2 mL		2 mL	X
C1, D1	8 hr	3 mL				
C1, D1	12 hr	3 mL				
C1, D8	Predose				2mL	X
C1, D15	Predose	3 mL	2 mL		2 mL	X
C1, D15	Postdose	3 mL[7]	2 mL[8]		2 mL [8]	X[8]
C2 D1	Predose	3 mL	2 mL		2 mL	X
C3, D1	Predose	3 mL	2 mL		2 mL	X
C4, D1	Predose	3 mL	2 mL		2 mL	X

1. Where applicable, the collection window is ±15 min. Post dose time points for urine orotic acid collection window are ± 1 hour. The actual sample collection time will be entered in the EDC.
[redacted]
4. The sample collection time points may be modified if the data indicate that these samples are no longer necessary to ensure patient safety. Pre-dose orotic acid will be collected any time prior to patient's dosing. Where applicable, the post dose collection window is ± 1 hr.
5. Plasma ammonia samples will be collected and sent to the sites local laboratory.
[redacted]
7. The PK postdose sample will be collected 1-4 hours post dose.
8. The Orotic acid, amino acid, and ammonia samples will be collected 4-6 hours post dose.
9. 2 mL blood will be collected in to one sodium heparin tube and processed for amino acid.
10. In addition to Orotic acid and plasma ammonia samples collected through Cycle 4 Day 1 (C4D1), samples will also be collected on day one of every cycle (example, C5D1, C6D1, etc).



ATTACHMENT 3: CLINICAL LABORATORY TESTS

Hematology (Peripheral Blood Sample):

- Hemoglobin and hematocrit
- RBC count
- White blood cell count with differential
- Platelet count

Coagulation Tests

- PT, aPTT and INR

Serum Chemistry-Full Metabolic Panel (Peripheral Blood Sample) with additional analytes

- Sodium
- Potassium
- Chloride
- CO2
- Magnesium
- Calcium
- Phosphorus
- Glucose1
- Blood urea nitrogen
- Amino acid analysis
- Ammonia (venous)
- Uric acid
- Total protein
- Albumin
- Total and direct bilirubin2
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (AP)
- Lactate dehydrogenase (LDH)
- Creatinine
- Thyroid Function Tests (TFTs) 3
- Carcinoembryonic antigen (CEA)4

[1] Fasting glucose (8-10 hour fast) is required on PK days only
[2] Direct bilirubin is only required if Total Bilirubin is above the upper limit of normal.
[3] Thyroid functioning will be monitored by measuring thyroid stimulating hormone (TSH) only, with a full panel run if there is an abnormal TSH result or if thyroid dysfunction is suspected
[4] Only in CRC patients

Pregnancy test (urine or serum β- HCG): Women of child-bearing potential

Urinalysis

ATTACHMENT 4: RECIST CRITERIA VERSION 1.1

Source: Eisenhauer et al 2009

Sponsor's Note: INCB001158, may affect glucose metabolism in both normal and tumor tissues. Preclinical data suggest that glucose uptake may increase with arginase inhibition in sensitive tissues, reflecting the pharmacodynamics effects of INCB001158. False positive interpretations of progressive disease with FDG-PET scans may occur. Therefore, all FDG-PET findings suggestive of progressive disease should be confirmed by dedicated anatomic imaging (CT or MRI) for this study.

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions will be categorized measurable or non-measurable as follows.

Measurable tumor lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable tumor lesions

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, **with identifiable soft tissue components**, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. For this protocol, these tumor lesions will be considered non-measurable lesions.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. Still, non-contrast CT is preferred over chest X-ray.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

If prior to enrolment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) will be used to evaluate the patient at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, **if not, the patient should be considered not evaluable from that point forward**.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of ‘target’ and ‘non-target’ lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression.’ In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <)

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease: **In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.** A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) For the purposes of this study, progressive disease *should not* be made solely on FDG-PET findings because the mechanism of the study drug, INCB001158, may affect glucose metabolism in both normal and tumor tissues. All FDG-PET findings suggestive of progressive disease should be confirmed by dedicated anatomic imaging (CT or MRI). The following modifications to RECIST v1.1 will be applied to this study:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. *Confirmation of the new lesion by CT or MRI scan is required per protocol.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new sign of disease confirmed by CT, this is PD
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal *CT scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

*reflects study-specific modification to RECIST v.1.1

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table A provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table B is to be used.

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Best overall response: All time points

The best overall response (Table C) will be determined by statistical programming once all the data for the patient are known.

Table A: Time Point Response: Patients with Targets (+/- Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.

Table B: Time Point Response: Patients with Non-Target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

1. Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.
[a] = 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table C: Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PRa
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

1. Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.
[a] = If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

Conditions that define 'early progression, early death, and non-evaluability are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

ATTACHMENT 5: MODIFIED RECIST CRITERIA FOR MALIGNANT PLEURAL MESOTHELIOMA

Source: modified from Byrne MJ and Nowak AK. 2004

Evaluation of malignant pleural mesothelioma will employ the RECIST v.1.1 criteria, but one of the organ site target measurements should reflect the typical mesothelial "rind" as one of the target measurements, as follows:

- Tumor thickness perpendicular to the chest wall or mediastinum will be measured in two positions at three separate levels on transverse CT scan cuts.
  - The transverse cuts must be at least 2 cm apart and related to anatomical landmarks for future assessments.
  - The pleural thickness must be at least 10 mm to be considered measurable.
- The sum of the six measurements defines a "pleural unidimensional measure", similar to the "longest unidimensional diameter" of a target tumor mass per RECIST.
- At disease reassessment, pleural thickness should be measured at the same positions and levels as the Screening/Baseline tumor evaluation.

Nodal, subcutaneous and other bidimensionally measurable lesions will be measured unidimensionally per the standard RECIST v 1.1 criteria.

Objective responses are defined using RECIST v.1.1 criteria:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)

Confirmation of a response requires a repeat observation at least 4 weeks apart.

ATTACHMENT 6: IMMUNE RELATED RECIST CRITERIA (BASED ON RECIST v1.1)

As part of Protocol Amendment 2-US 3, dated 10 NOV 2020, the irRECIST endpoints have been removed. However, this attachment, describing irRECIST, has been retained, as patient management at the time of PD will continue to follow irRECIST principles under Protocol Amendment 2-US 3.

Source: Perrone A. (Oral presentation at IO360 meeting, February 2016)

Immune-related RECIST (irRECIST) is derived from RECIST v1.1 conventions, as described in Attachment 4 and Eisenhauer et al 2009. The implementation of irRECIST (Perrone 2016) is identical to RECIST v1.1 until progressive disease (PD) is identified. Upon demonstration of PD (see Attachment 4) per RECIST v1.1, patients may remain on study per Investigator discretion, assuming the patient remains clinically stable, as defined in the protocol. Patients that remain on study will have an imaging disease assessment performed at least 4 weeks after the initial PD is demonstrated in order to confirm PD.

1 EVALUATION OF LESIONS

1.1 Evaluation of Target Lesions

Immune-related Complete Response (irCR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Immune-related Partial Response (irPR): At least a **30% decrease in the sum of diameters of target lesions** (i.e., Percentage Change in Tumor Burden)**,** taking as reference the baseline sum diameters.

Immune-related Progressive Disease (irPD): Same requirements for PD as standard RECIST v1.1, with exception that progressive disease must be confirmed. After demonstration of PD by standard RECIST v1.1 criteria, patients remain on study and are re-imaged after ≥4 weeks. Confirmation of target lesion PD is constituted by the following:

- Sum of linear diameters (SLD) reaches PD threshold of ≥ 20% increase from nadir OR
- SLD remains ≥20% increased above baseline (if already ≥ 20% increased at initial PD)

Immune-related Stable Disease (irSD): Neither sufficient shrinkage to qualify for irPR nor sufficient increase to qualify for irPD, taking as reference the smallest sum diameters while on study.

1.1.1 Special Notes on the Assessment of Target Lesions

1.1.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

1.1.1.2 Target Lesions that Become "Too Small to Measure"

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm. However, when such a lesion becomes difficult to assign an exact measure to then:

- if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be

assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

1.1.1.3 Target Lesions that Split or Coalesce on Treatment

- When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

1.2 Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Immune-related Complete Response (irCR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Immune-related Non-CR/Non-PD (ir-Non-CR/Non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. This also includes non-target lesions that demonstrated unequivocal progression at the initial demonstration of PD but then stabilized or regressed on subsequent scans.

Immune-related Progressive Disease (irPD): Unequivocal progression of existing non-target lesions on a disease assessment subsequent to initial demonstration of PD. Therefore, irPD by non-target lesions requires one of the following on a disease assessment ≥4 weeks after the initial demonstration of PD:

- New unequivocal progression OR
- Further unequivocal progression (if unequivocal progression present at initial PD)

1.3 New Lesions

The appearance of new lesions that occurs on a disease assessment subsequent to initial demonstration of PD. Therefore, irPD by new lesions requires one of the following on a disease assessment ≥4 weeks after the initial demonstration of PD:

- New lesions appear OR
- Additional new lesions appear or prior new lesions grow (if new lesions were present at initial PD)

1.4 Confirmation of Progressive Disease

As described above, irPD requires that an initial demonstration of PD is confirmed in a subsequent disease assessment performed ≥4 weeks after the initial demonstration of PD. The above section describes what constitutes irPD with respect to Target Lesions, Non-target Lesions and New Lesions. For the sake of clarity, the presence of ALL of the following ≥4 weeks after initial PD means that PD IS NOT confirmed:

Target lesions

- SLD is <20% increased from nadir

Non-target lesions

- No additional unequivocal progression from prior scan

New lesions

- No additional new lesions
- Any prior new lesions are stable or shrinking (qualitatively)

Clinical status

- Patient remains clinically stable

2 RESPONSE CRITERIA

2.1 Time Point Response

A response assessment should occur at each time point specified in the protocol.

- **Immune-related Complete Response (irCR)**: Complete disappearance of all tumor lesions (target and non-target), together with no new measurable or unmeasurable lesions, for at least 4 weeks from the date of documentation of irCR. All lymph nodes short axes must be < 10 mm.

- **Immune-related Partial Response (irPR)**: The sum of the linear diameters (SLD) of all target lesions is measured and captured as the sum of diameters at baseline. At each subsequent tumor assessment, the SLD of all target lesions is calculated. A decrease in SLD, relative to baseline SLD, of 30% or greater is considered an irPR, in the absence of irCR or irPD.

- **Immune-related Stable Disease (irSD)**: irSD is defined as the failure to meet criteria for irCR, irPR or irPD.

- **Immune-related Progressive Disease (irPD)**: It is recommended for patients that are clinically stable to confirm PD at the following tumor assessment. Any of the following will constitute progressive disease:

    - Overall ir-response of irPD (per Table 2.1) after confirmation of PD with disease assessment ≥4 weeks after initial demonstration of PD
    - PD per RECIST v1.1 in a patient that is not clinically stable enough to remain on study for confirmation

Table 2.1: irRECIST v1.1 Definitions

Target Lesion Response per RECIST v1.1	Non-target Lesion Response	New Lesions	Overall ir-response
CR	CR	• None, OR • Completely resolved	irCR
PR	ir-Non-CR/Non-PD	• None, OR • Stable/shrinking relative to first PD scan	irPR
SD	ir-Non-CR/Non-PD	• None, OR • Stable/shrinking relative to first PD scan	irSD
PD (with confirmation)	Any	Any	irPD
Any	Presence of unequivocal progression >4 weeks after initial PD scan	Any	
Any	Any	• Appearance of new lesions after initial PD scan	

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ir = immune-related.

2.2 Best overall response: All time points

Best Overall Response and Date of Progression Using irRECIST v1.1 (irBOR): The investigator will be asked to provide all responses on study and date(s) of progression, if applicable, and the best overall response will be calculated by the sponsor or designee based on the time point responses and tumor measurements provided by the investigator.

ATTACHMENT 7: GUIDANCE FOR POTENTIAL DILI (DRUG-INDUCED LIVER INJURY)

Evaluation algorithm for potential DILI if there are no other clinical reasons

Note: If clear etiology for the laboratory abnormalities has been confirmed, Stage 1 and 2 testing may not be required. In this case, consultation with the Sponsor is recommended.

Stage 1 work-up should be performed within 48-72 hours:

- ALT
- AST
- Bilirubin: total, direct, indirect
- Alkaline phosphatase (ALP)
- Prothrombin Time (PT)/international normalized ratio (INR)
- Creatine phosphokinase (CPK)
- Manual eosinophil count (if automated count was elevated)
- Toxicology screen for drugs of abuse (including ethanol) and for acetaminophen/paracetamol level should also be sent. Investigators may order additional toxicology tests as clinically indicated.
- Evaluate patient for the following signs and symptoms: fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash.
- Obtain the following additional history and assessment for associated risk/confounding factors:
  - ✓ More detailed history of symptoms and prior or concurrent illness
  - ✓ Aminotransferase values obtained prior to the study or administration of study medication
  - ✓ Alcohol consumption (recent and historical)
  - ✓ Acetaminophen (APAP)/paracetamol use
  - ✓ New prescription, concomitant, or non-prescription (including herbal and other dietary supplements) medications
  - ✓ Unusual foods (e.g. mushrooms) or special diets. Consumption of seasonal foods.
  - ✓ Recreational drug use
  - ✓ Prior history of liver injury or disease, including but not limited to Gilbert's syndrome, autoimmune disorders, cancer, Wilson's disease, NASH, alcoholic or infectious hepatitis, biliary tract disease, hypoxic/ischaemic hepatopathy
  - ✓ Obesity/abdominal adiposity (record weight, height, and waist circumference)
  - ✓ Occupational history and history of exposure to chemical agents or other environmental toxins
  - ✓ Recent travel (last three [3] years)
  - ✓ Transfusion history

- Perform the following required laboratory tests**:**
  - ✓ Albumin
  - ✓ Eosinophils (percentage and absolute; obtain manual count if automated count is elevated)

- ✓ Viral hepatitis serologies (obtain appropriate consent prior to testing, if required locally)
  - A (IgG, IgM)
  - B (HepBs Ag, Hep Bs Ab, Hep Bc Ab, Hep Be Ag)
  - C (RNA)
  - D (requires concomitant hepatitis B infection)
- ✓ Human Immunodeficiency Virus (HIV) testing (obtain appropriate consent prior to testing, if required locally)
- ✓ Evaluation for autoimmune hepatitis:
  - Serum gamma globulin levels/ serum protein electrophoresis
  - Antinuclear antibody (ANA)
  - Anti-mitochondrial antibody (if ALP or TBL >ULN)
- ✓ If AST/ALT ratio is greater than one (1) with suspicions of increased alcohol intake, perform the following:
  - Gamma-glutamyl transferase (GGT)

- Obtain a right upper quadrant ultrasound

Stage 2 work-up tests should be drawn within one (1) week of receiving the Stage 1 work-up results and the results of Stage 1 evaluation are negative.

Note: A specific test may be performed earlier if the investigator determines that the clinical presentation leads to a certain diagnosis.

Stage 2 work-up:

- Perform the following laboratory tests:
  - ✓ Genetic test for Gilbert's disease if there is a suspicious history. Ensure appropriate patient consent is obtained for this test.
  - ✓ Viral hepatitis E (IgG and IgM, obtain appropriate consent prior to testing, if required locally)
  - ✓ Anti-smooth muscle antibody
  - ✓ Anti-liver-kidney microsomal antibody
  - ✓ Anti-soluble liver antigen
  - ✓ Serologies for the following:
    - Cytomegalovirus (CMV) (IgG, IgM)
    - Epstein-Barr Virus (EBV) (IgG, IgM)
    - Herpes simplex
    - Toxoplasmosis
    - Varicella
    - Parvovirus

- ✓ Ceruloplasmin
- ✓ Serum alpha-1 anti trypsin
- ✓ Genetic test for hemochromatosis. Ensure appropriate patient consent is obtained for this test
- ✓ Iron Studies:
  - serum ferritin,
  - serum iron,
  - total iron binding capacity

- Consider referral to hepatologist/gastroenterologist
- Consider screen for celiac disease and cystic fibrosis if clinically indicated
- If laboratory tests or ultrasound evidence of biliary tract obstruction, consider obtaining Endoscopic Retrograde Cholangiopancreatography (ERCP) or Magnetic Resonance Cholangiopancreatography (MRCP)

If applicable, request copies of hospital discharge summaries, consultation reports, pathology reports, special studies (e.g. imaging or biopsy), etc.

ATTACHMENT 8: AMENDMENT 2 EXECUTIVE SUMMARY OF CHANGES

Amendment 2 of protocol INCB 01158-101 (formerly CX-1158-101) is being submitted in order to address four primary goals. First, the anti-PD-1 agent is being changed from nivolumab to pembrolizumab. Second, the patient populations in which the INCB001158/PD-1 combination is being studied are being expanded. Third, the management of urinary orotic acid values has been modified based on the clinical experience to date, a more extensive evaluation of the urea cycle defect literature and feedback from an expert in the management of urea cycle defects. On the basis of these data, the threshold of acceptable urinary orotic acid elevations has been redefined for patients that are fasting and non-fasting at the time of the assessment. [redacted] In addition to these primary goals of the Amendment, other minor changes have also been made to clarify protocol requirements.

The following important changes were implemented to protocol INCB 01158-101 (formerly known as CX-1158-101) under Amendment 2:

- **Throughout:** The investigational product identifier was changed from "CB 1158" to "INCB001158" and the protocol identifier was changed from "Protocol CX-1158-101" to "Protocol INCB 01158-101" to reflect the new partnership with Incyte Pharmaceuticals.
- **Added-** EudraCT number
- **Throughout:** The design of the study was changed. INCB001158 is now tested in combination with pembrolizumab instead of nivolumab. It is also tested as a monotherapy. In the appropriate sections "pembrolizumab" replaces "nivolumab," and instructions for administration of pembrolizumab are provided.
- [redacted]
- [redacted]
- **Sponsor Contact:** deleted contacts from the protocol except for safety reporting
- **Section 8.0, Study Design:** Added 6 cohorts to part 3 of the combination expansion.
- **Section 8.1, Table 8.1-1 Dose Escalation Schedule:** Added Cohort 1.5 with 75mg dose.
- **Section 8.1.2, Dose-Limiting Toxicity:** Increased fasting urinary orotic acid (OA) to ≥ 10X the ULN, any OA value of > 40X ULN (fasting or non-fasting). Added rationale for urinary orotic acid threshold.
- **Section 8.3, Part 3 Combination Cohort Expansion:** Revised criteria for entry into cohort 3b and created 6 new cohorts, with all cohorts investigating INCB001158 in combination with pembrolizumab; providing null hypotheses and primary endpoints for newly created cohorts.
    - Cohort 3b: patients with melanoma with disease progression or prolonged stable disease while receiving an anti-PD-1 agent in the immediate prior line of therapy

- Cohort 3c: patients with urothelial cell carcinoma (UCC) that would be unlikely to have an objective response to monotherapy pembrolizumab
- Cohort 3d: patients with microsatellite instability-high (MSI-H) CRC that would be unlikely to have an objective response to monotherapy pembrolizumab
- Cohort 3e: patients with microsatellite stable (MSS) CRC
- Cohort 3f: in PD-1/PD-L1 naïve patients with Gastric/GEJ cancer
- Cohort 3g: in PD-1/PD-L1 naïve patients with SCCHN
- Cohort 3h: patients with malignant pleural mesothelioma

- **Section 9.0, Sample Size:** The sample size estimates were revised for Cohorts in Part 2 Monotherapy Cohort Expansion and cohorts in Part 3 Combination Cohort Expansion (table 9.0-1).

- **Section 10.1, Inclusion Criteria:**

  - Parts 3a, b, c and d: Removed PD-L1 from prior therapies allowed in the most recent line of therapy. Add-on cohorts are restricted to patients that received PD-1 therapy in prior therapy
  - Revised criterion No. 8 to provide specific contraceptive requirements for women of nonchildbearing potential, women of childbearing potential, and men. Also clarified that female contraception to continue until 120 days beyond last dose
  - Revised inclusion criteria for patients with non-small cell lung cancer (NSCLC) and melanoma
  - Added exclusion criteria for patients with urothelial cell carcinoma (UCC); mismatch repair deficient and/or microsatellite instability-high (MSI-H) colorectal cancer (CRC); microsatellite stable (MSS) colorectal cancer (CRC); gastric/gastro-esophageal (GE) junction cancer; squamous cell carcinoma of the head and neck; and mesothelioma

- **Section 10.2, Disease-specific exclusion criteria:** Modified criterion with known active CNS and Part 3 so as to exclude all patients with NSCLC who have documented activating mutations in EGFR or ALK. Added criterion liver virus vaccination and history or evidence of any condition, therapy or laboratory abnormality that confound with trial results. Also added language to exclude pneumonitis in combination cohort.

- **Section 11.0, Radiological Tumor Assessments**: Specified that response criteria for patients with pleural mesothelioma is modified RECIST criteria and modified language if repeat imaging confirmed disease progression for patient receiving clinically meaningful benefit.

- **Section 13.1.9, Previous Human Experience:** Added data on pharmacokinetic, pharmacodynamic and safety to previous human experience on INCB001158 and the Effects on hepatic urea cycle function.

- **Section 13.2.2, Rationale for Dose Escalation Strategy:** Provides updated rationale for the dose escalation strategy.

- **Section 13.2.3.2, Combination with anti-PD-1 (Pembrolizumab):** Provides rationale for use of pembrolizumab in combination with INCB001158. Also updated approvals for pembrolizumab to include SCCHN and MSI/MMR cancers.

- **Section 14.1.2.2 Prohibited Concomitant Medications:** Updated to reflect the pembrolizumab con meds.

- **Section 14.2 Study procedures:** Clarified fasting to >8 hours.

- **Section 14.3 other Schedules and Procedures:** Clarified time for radiographic evaluation of tumor burden for part 1b and 3.

- **Section 14.6.2 Vital signs:** Clarified orthostatic vital signs collection requirement.

- **Section 15.1.2 Pembrolizumab:** Added standard pembrolizumab background information.

- **Section 15.1.2 (and elsewhere):** Added language to refer to pembrolizumab IB, as well as the product label, as a reference for the product safety profile.

- **Section 15.1.2.1:** Added “safety” to 1st sentence to read "The safety and tolerability of CB-1158 + pembrolizumab is not known."

- **Section 15.1.3.1 Dose modification guidelines:**

    - Provided a new table (15.1-2) that is based on the Merck table for the management of pembrolizumab. The table also includes information for the management of CB-1158. Please note that the Table is almost identical to the table that Incyte has used in their clinical combination studies with pembrolizumab, with the exception that CB-1158 (and unique AE’s such as urea cycle inhibition) has been included and epacadostat has been removed.
    - In Table 15.1-1, listed the most likely immune related AEs in the table.
    - In Table 15.1-2, included the individual immune related AEs.

- **Section 16.1 Test Article Administration:** Added text stating that the maximum duration of pembrolizumab treatment on study will be up to 35 doses (approximately 2 years).

- **Section 18.4, Efficacy Analysis:** An analysis that included patients that did not have a post-treatment scan due to toxicity or death.

- **Section 19.0 Adverse Events:** Added guidance for potential DILI(drug induced injury) in Attachment 7.

- **Section 19.1:** Added language regarding the definition and management of pembrolizumab overdose.

- **Section 19.2 Recording and Reporting:** Added language regarding reporting of pregnancy and lactation out to 120 days following study medication (or 30 days if new therapy is started).

- **Attachments:** The schedule of assessments was changed and additional schedules of assessments were added to reflect investigation of the combination of INCB001158 with pembrolizumab.

    - In Attachment 1A, Schedule of Study Assessments for Part 1A and 2 INCB001158 Monotherapy the collection of orotic acid was expanded to Day 1 of every cycle. Collection (note: under Amendment 1, this is entitled “Attachment 1A, Schedule of Study Assessments”).
    - Collection of orotic acid also occur Cycle 1 day 8 and on Day 1 of every cycle in also occurs in the Attachment 1b, Schedule of Assessments for Part 1b and Part 3 (INCB001158 + Pembrolizumab.
    - Modifications were modified to reflect current data and combination drug.

Important Note: A redline version of the document showing changes made from Amendment 1 to Amendment 2 is available upon request.

ATTACHMENT 9: AMENDMENT 2-EU EXECUTIVE SUMMARY OF CHANGES

The purpose of this amendment is to make additional changes and correct known inconsistencies in the protocol. The specific changes are as follows:

Synopsis: Updated the patient population for Part 2 to match the rest of the protocol.

Synopsis; Attachments 1A and 1B: Clarified scheduled visits for each study part.

Synopsis; Section 5 Study Design: Updated study design schema to reflect that for cohorts 3a, 3b, 3c, and 3d, subjects must have received an anti-PD-1/PD-L1 agent in the most recent prior line of therapy for advanced/metastatic disease. Previously subjects were required to have received an anti-PD-1 agent in the most recent prior line of therapy. The reason for the change is that anti-PD-1 and anti-PD-L1 agents target the same PD-1/PD-L1 interaction, and the effect of treatment with either type of agent is expected to be similar in these subjects.

Synopsis; Section 5.1 Part 1. Dose Escalation; Section 10.2.1 Rationale for Starting Dose: Added the starting dose of 50 mg BID for the dose escalation of INCB001158 plus pembrolizumab in Part 1b, as this has now been determined in Part 1a as 2 dose levels below the RP2D of 100 mg BID.

Synopsis; Section 7.1 Inclusion Criteria: Broadened exception for PT and INR inclusion cutoffs to include patients receiving therapeutic anticoagulation with drugs other than warfarin, as all of these drugs can affect PT and INR.

Synopsis; Section 7.1 Inclusion Criteria, Part 1b Dose Escalation Criteria: Removed reference to RCC and added mesothelioma, gastric/GEJ cancer, MSS CRC, MSI CRC, UCC, and SCCHN, to match the rest of the protocol.

Synopsis; Section 7.1 Inclusion Criteria, Part 3 Expansion: For Part 3a, corrected an inconsistency in bullet 2 to make consistent with exclusion of patients with EGFR or ALK mutations

For cohorts 3a, 3b, 3c, and 3d, specified that subjects must have received an anti-PD-1/PD-L1 agent in the most recent prior line of therapy for advanced/metastatic disease. Previously subjects were required to have received an anti-PD-1 agent in the most recent prior line of therapy. The reason for the change is that anti-PD-1 and anti-PD-L1 agents target the same PD-1/PD-L1 interaction, and the effect of treatment with either type of agent is expected to be similar in these subjects.

Synopsis; Section 7.2 Exclusion Criteria: Removed exclusion criterion #8 prohibiting patients with history of diverticulitis, intra-abdominal abscess, GI obstruction, and abdominal carcinomatosis from enrolling to the study. This exclusion criterion has been limiting on a number of occasions to date on this study, as it covers a lot of commonly occurring bowel pathology in patients, particularly those with GI malignancies. There is no known safety concern with allowing such patients onto this study.

Section 11.3.1 Distribution of Subject Reminder Cards and Subject Diaries; Section 13.4 INCB001158 Accountability, Reconciliation, and Return; Section 13.5 Study Treatment Compliance: Section 11.3.1 is new and describes subject reminder cards and diaries, which are being introduced in this study to facilitate drug compliance and the quantification of that compliance. Sections 13.4 and 13.5 describe how the subject diaries will be used and how compliance will be

assessed. Section 13.5 also now contains standard Incyte protocol template language for compliance assessment.

Section 11.2 Study Procedures: Corrected an inconsistency between this section and Attachments 2A, 2B, and 2C regarding when subjects in Parts 1a, 1b, 2, and 3 should come to the clinic fasted.

Section 11.6.2 Vital Signs; Attachment 1B: Clarified vital sign collection requirement.

[redacted]

Section 12.1.3.1 Dose Modification Guidelines: Clarified that guidelines for AE management for INCB001158 apply to subjects in all parts of the study, not just monotherapy. Added language providing additional guidance on pembrolizumab-related irAEs and further clarified which dose modification tables to follow for subjects treated with the combination of INCB001158 and pembrolizumab.

Table 12.1-1: INCB001158 Dose Modification Guidelines: Changed the title to specify that dose modification guidelines described in the table are for INCB001158 and apply to subjects in all parts of the study.

Table 12.1-2: Pembrolizumab Dose Modification Guidelines: Changed title to specify that dose modification and toxicity management guidelines described in the table are for irAEs associated with pembrolizumab and apply to subjects treated in the combination Parts 1b and 3 and revised the table accordingly.

Section 12.1.3.3: Supportive Care Guidelines: Added more detailed guidance on management of pembrolizumab-related infusion reactions, including addition of Table 12.1-3.

Section 13.0 Test Article/Study Drug: The section title was changed to "Study Drug and Other Study Treatments" and study drug was defined as INCB001158, and study treatments were defined as any mention of INCB001158 or pembrolizumab. This has been clarified throughout the protocol where INCB001158 and/or pembrolizumab are mentioned.

Section 13.1 Test Article Administration; Section 13.2, Packaging and Labeling: Clarified that the pembrolizumab drug product may also be provided to sites as a 100 mg/4 mL (25 mg/mL) sterile solution in a single-dose vial.

Section 16.0 Adverse Events: This section has been replaced with equivalent section from the Incyte protocol template (Safety Monitoring and Reporting), to align with other Incyte-sponsored studies. The new sub-sections are 16.1 Adverse Events, 16.2 Laboratory Test Abnormalities, 16.3 Serious Adverse Events, 16.4 Pregnancy, 16.5 Definition of an Overdose for this Protocol and Reporting of Overdose to the Sponsor, 16.6 Warnings and Precautions, and 16.7 Product Complaints.

Section 21.0 Direct Access, Data Handling, and Record Keeping; Section 22.0 Pre-Study Documentation; Section 23.0 Records Retention: These 3 sections have been replaced with a single section (21.0 Ethical Considerations and Administrative Procedures) taken from the Incyte protocol template. This covers the same topics as the former Sections 21.0, 22.0, and 23.0.

Attachments: Attachments 1A, 1B, 2A, 2B and 2C have time point discrepancies for Plasma Ammonia, Orotic Acid, PK, [redacted]:

- For patients in Part 1a, on C1D2, Plasma Ammonia, Orotic Acid, PK and Amino Acid are required.
- Patients in Part 2 will not have a C1D2 visit
- For patients in Part 2, on C1D8, PK and Amino Acid tests are NOT REQUIRED. Plasma Ammonia and Orotic Acid are required.
- For patients in Part 2, on C1D22, PK and Amino Acid tests are NOT REQUIRED. Plasma Ammonia and Orotic Acid are required.
- For patients in Part 1b and Part 3, on C1D8, Plasma Ammonia and Orotic Acid are required. PK and Amino Acid are NOT REQUIRED.
- Patients in Part 2 will not have a C2D8 visit
- In the Attachment 1B footnotes, the “Attachment 2” hyperlinks should direct to “Attachment 2C” which is the PK [redacted] schedule for Parts 1b and 3.
- In all parts, orotic acid and plasma ammonia samples will also be collected on Day 1 of every cycle after Cycle 4.

Attachment 3: Clinical Laboratory Tests - CEA was added to the table of "Serum Chemistry-Full Metabolic Panel (Peripheral Blood Sample) with additional analytes" as an additional analyte to test in CRC patients. CEA is a frequently elevated tumor marker in colon cancer that is routinely monitored during therapy and will be collected in all CRC patients enrolled to the study.

Throughout: "Package insert" (a US-specific term) was changed to "label" (more generic term) throughout as this protocol is now opening in EU.

Important Note: A redline version of the document showing changes made from Amendment 2 to Amendment 2-EU is available upon request.

ATTACHMENT 10: AMENDMENT 2-US EXECUTIVE SUMMARY OF CHANGES

Revisions from an EU-specific amendment (Amendment 2-EU, see Attachment 9) have also been incorporated in this US-specific amendment, with the exception of the item related to subject reminder cards and diaries.

Amendment 2-US of protocol INCB 01158-101 has the following main goals:

[redacted]

2. Expansion of the Monotherapy basket Cohort 2c
   Since monotherapy expansion Cohort 2c is a basket cohort enrolling multiple tumor types thought to have infiltration with arginase-expressing cells, the current protocol does not have a mechanism to further evaluate those tumor types in which INCB001158 monotherapy may show evidence of clinical activity. Therefore, this amendment allows the option to expand the monotherapy basket cohort to enroll additional patients with a specific tumor type from part 2c where INCB001158 shows meaningful clinical activity as a single agent.

The specific changes in Amendment 2-US are as follows:

[redacted]

Synopsis; Section 5.0: Overall Study Design:

- Updated section on Part 2 single agent cohort expansion to show expansion of Part 2c basket cohort and addition of Cohort 2d
- Corrected errors in sample sizes of Parts 3f and 3g expansion cohorts
- Updated study schematic to show expansion of Part 2c basket cohort and addition of cohort 2d [redacted].

Synopsis; Section 5.2 Study Design: Added subsections describing the designs and patient populations for the existing and new Part 2 cohorts.

Synopsis; Dosage and Mode of Administration: Specified that INCB001158 may be taken orally using a capsule or tablet formulation in dose strengths of 25 mg or 100 mg.

Synopsis: Study Schedule/Procedures: Organized study visit days by study part.

Synopsis; Section 6.0 Sample Size:

- Updated number of patients to be enrolled in Part 2 to account for expansion of Cohort 2c basket cohort and addition of Cohort 2d.
- Corrected the potential maximum number of evaluable patients who could be enrolled in dose escalation of INCB001158 monotherapy (Part 1a) and of the INCB001158 plus pembrolizumab combination (Part 1b), to account for all possible dose levels being needed and for up to 12 backfill patients being enrolled at each possible dose level.

Synopsis; Section 7.1 Inclusion Criteria: Added inclusion criteria specific to the newly added Cohort 2d.

Synopsis; Section 7.2 Exclusion Criteria: Added criterion to exclude patients who have had prior allogeneic tissue/solid organ transplant, as there is a risk for such patients developing graft-versus-host disease after receiving pembrolizumab.

Synopsis, Statistical Methods; Section 15.2 Sample Size and Power: Updated to describe sample sizes for expansion of Cohort 2c basket cohort and addition of Cohort 2d.

Section 5.1.2 Dose-Limiting Toxicity: Removed the exception to non-hematologic DLTs that required testing of serum amylase and lipase in the absence of symptoms of pancreatitis, as neither analyte is tested in this study.

Section 5.2 Part 2. Single Agent Cohort Expansion: Clarified that the assessment of ORR in the Simon 2-Stage is based on responses at single time points, and not requiring subsequent confirmation.

Section 10.1.9 Previous Human Experience: Updated the available data from this study, as of 23 May 2018. This includes the RP2D of INCB001158 monotherapy of 100 mg BID.

Section 10.1.10 Pharmacokinetics of INCB001158: Added a footnote to Table 10.1-1 (PK Parameters from Phase 1 Patients) to clarify that the values represent the mean ± SD.

Section 11.2; Study Procedures: Added subsection 11.2.2.2 specifying study procedures specific to Cohort 2d.

Section 11.3 Other Schedules and Procedures; Attachment 1A Schedule of Study Assessments for Part 1A and Part 2; Attachment 1B, Schedule of Study Assessments for Part 1B and Part 3: Added urine pregnancy tests during study treatment that will be performed locally as medically indicated or per country-specific requirement.

Synopsis; Section 11.5 Follow-Up; Attachment 1A Schedule of Study Assessments for Part 1A and Part 2; Attachment 1B, Schedule of Study Assessments for Part 1B and Part 3:

- Added new section (11.5) that explains the safety and disease follow-up procedures, which are already summarised in the Synopsis.
- Added these visits to the Schedules of Study Assessments.

[redacted]

Section 13.0; Study Drug and Other Study Treatments:

- Inserted that INCB001158 will be administered as capsules or tablets, where applicable.

Section 15.3.3; Efficacy Evaluable Populations: The Efficacy Evaluable Population has been split into 2 populations - Response Evaluable and PFS Evaluable Populations, and the definitions have been aligned with other Sponsor studies.

Synopsis; Section 15.4; Efficacy Analysis: All mention of survival follow-up and an overall survival analysis has been removed to align with the endpoints, which do not include overall survival.

[redacted]

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

ATTACHMENT 11: AMENDMENT 2-US 2 EXECUTIVE SUMMARY OF CHANGES

The purpose of this US-specific amendment is to add a cohort of patients with moderate renal impairment to determine the PK of INCB001158 50 mg BID (in combination with pembrolizumab), which is predicted by modelling to have comparable exposure to the RP2D of INCB001158 100 mg BID in patients with normal renal function. This cohort will be in a new sub-part of Part 1, namely Part 1c.

The specific changes are as follows:

Synopsis; Section 3.0 Objectives: Part 1c was added to the following objectives/endpoints: primary safety, secondary anti-tumor effect and PK, [redacted].

Synopsis; Section 5.0 Study Design: The study design figure was updated to include Part 1c.

Synopsis; Section 5.1 Part 1. Dose Escalation: A full description of the new renal impairment cohort (Part 1c) was added.

Synopsis; Section 6.0 Sample Size; Section 15.2 Sample Size and Power: Part 1c (6 patients) was added, and the total number of evaluable patients was updated accordingly. An explanation for the sample size of Part 1c was added.

Synopsis; Section 7.1 Inclusion Criteria: Inclusion criterion #6 was updated to include Part 1c patients with CrCl 30 to 49 mL/min. Also, inclusion criteria specific to Part 1c were added to the section for "Part 1: Inclusion Criteria Specific to the Dose Escalation".

Synopsis; Section 11.2.1.1 Part 1a and 1c Only: Cycle 1 Day 1 and Day 15; Section 11.8.1 Fresh Pre-Dose and Post-Dose Tumor Biopsies; Section 11.9.2 Intensive PK Sampling; Section 12.1.2 Pembrolizumab (Patients Enrolled in Parts 1b, 1c, and 3); Section 15.3.1 Safety Population; Section 15.6 Pharmacokinetic Analysis: Part 1c was added. The safety population was updated to state that patients with moderate renal impairment in Part 1c will be evaluated separately.

Section 10.2.2.1 Rationale for Dose in Patients with Moderately Impaired Renal Function: New section added.

Section 12.1.3.2 Resumption of Study Treatment: Dose modification guidelines were added to Table 12.1-1 for patients with moderately impaired renal function and patients with normal renal function who have AEs of study drug–related creatinine increase. Part 1c was added to the title of Table 12.1-2.

Section 21.4 Data Privacy and Confidentiality of Study Records: Language was updated to reflect recent changes in privacy laws.

Attachment 1B Schedule of Study Assessments for Parts 1b, 1c, and 3 (INCB001158 + Pembrolizumab): Title and footnotes of Attachment 1B were updated to include Part 1c.

Attachment 2C Pharmacokinetic [redacted] Sampling Schedule for Parts 1b, 1c, and 3: Part 1c schedule was added.

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

ATTACHMENT 12: AMENDMENT 2-US 3 EXECUTIVE SUMMARY OF CHANGES

For studies that have been ongoing beyond enrollment of the final subject where sufficient data have been collected to address the primary and secondary objectives, and only a limited number of subjects remain on study treatment, it is appropriate to discontinue protocol study assessments and data collection (except for SAEs and pregnancies) for these active subjects, while allowing them to continue receiving study treatment. The main purpose of this US-specific amendment is to introduce language that will allow such a switch to take place.

The specific changes are as follows:

Title page: Study execution responsibilities have been transferred from Calithera Biosciences, Inc. to the Sponsor, Incyte Corporation. The title page of the protocol has been updated to reflect this change.

Synopsis; List of Abbreviations; Section 3.0 Objectives; Section 8.0 Radiological Tumor Assessments; Section 15.4 Efficacy Analysis; Attachment 6 Immune-Related RECIST Criteria (Based on RECIST v1.1): The efficacy analyses will no longer include any of the irRECIST endpoints. Instead efficacy will be assessed solely by RECIST v1.1. Patient management beyond PD will continue to follow irRECIST guidelines.

Section 12.1.3 Dose Modifications and Toxicity Management: The dose modification guidelines for immune-related AEs associated with pembrolizumab (Table 12.1-2) have been updated to match the most recent guidelines from Merck.

Section 16.3.2 Reporting: The rules for reporting SAEs for subjects in Parts 1b and 3 have been updated to match the most recent guidelines from Merck. Site personnel must report SAEs that occur within 30 days after the last dose of study treatment if a subject receives a new anticancer therapy within that 30 day period.

Section 17.0 Study Suspension, Termination, and Completion: Language has been added to define criteria for discontinuing study assessments (except SAEs and pregnancies) for remaining active study subjects.

ATTACHMENT 13: ELECTRONIC SIGNATURE PAGE

Signature Page for VV-CLIN-000684 v3.0

Approval	[redacted] Approver 11-Nov-2020 17:21:13 GMT+0000
Approval	[redacted] Approver 11-Nov-2020 17:47:25 GMT+0000
Approval	[redacted] 11-Nov-2020 20:18:47 GMT+0000
Approval	[redacted] Approver 12-Nov-2020 14:20:12 GMT+0000
Approval	[redacted] Approver 12-Nov-2020 21:13:23 GMT+0000

Signature Page for VV-CLIN-000684 v3.0